Cochrane
Library

Cochrane Database of Systematic Reviews

Chlorpromazine versus penfluridol for schizophrenia (Review)

Nikvarz N, Vahedian M, Khalili N

Nikvarz N, Vahedian M, Khalili N.
Chlorpromazine versus penfluridol for schizophrenia.
Cochrane Database of Systematic Reviews 2017, Issue 9. Art. No.: CD011831.
DOI: [10.1002/14651858.CD011831.pub2](https://doi.org/10.1002/14651858.CD011831.pub2).

www.cochranelibrary.com

TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	5
Figure 1.	6
Figure 2.	7
OBJECTIVES	8
METHODS	8
RESULTS	13
Figure 3.	14
Figure 4.	15
Figure 5.	16
DISCUSSION	18
AUTHORS' CONCLUSIONS	20
ACKNOWLEDGEMENTS	20
REFERENCES	21
CHARACTERISTICS OF STUDIES	24
DATA AND ANALYSES	28
Analysis 1.1. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 1 Service utilisation: 1. Hospital readmission. .	30
Analysis 1.2. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 2 Adverse effects: 1a. General - needing antiparkinsonian medication.	31
Analysis 1.3. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 3 Adverse effects: 1b. General - need to reduce antipsychotic dose due to side effects.	31
Analysis 1.4. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 4 Adverse effects: 2a. Specific - extrapyramidal events (moderate or severe) - short term.	32
Analysis 1.5. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 5 Adverse effects: 2b. Specific - extrapyramidal events (moderate or severe) - medium term.	32
Analysis 1.6. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 6 Adverse effects: 2c. Specific - anticholinergic (moderate or severe) - short term.	34
Analysis 1.7. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 7 Adverse effects: 2d. Specific - anticholinergic (moderate or severe) - medium term.	34
Analysis 1.8. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 8 Adverse effects: 2e. Specific - central nervous system (moderate or severe) - short term.	35
Analysis 1.9. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 9 Adverse effects: 2f. Specific - central nervous system (moderate or severe) - medium term.	36
Analysis 1.10. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 10 Adverse effects: 2g. Specific - various other effects (moderate or severe) - short term.	36
Analysis 1.11. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 11 Adverse effects: 2h. Specific - various other effects (moderate or severe) - medium term.	37
Analysis 1.12. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 12 Leaving the study early: 1a. Any reason. ...	38
Analysis 1.13. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 13 Leaving the study early: 1b. Due to adverse events.	38
ADDITIONAL TABLES	39
HISTORY	40
CONTRIBUTIONS OF AUTHORS	40
DECLARATIONS OF INTEREST	40
SOURCES OF SUPPORT	41
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	41
INDEX TERMS	41

[Intervention Review]

Chlorpromazine versus penfluridol for schizophrenia

Naemeh Nikvarz¹, Mostafa Vahedian², Navid Khalili³¹Herbal and Traditional Medicines Research Center, Faculty of Pharmacy and Pharmaceutical Sciences, Kerman University of Medical Sciences, Kerman, Iran. ²Department of Biostatistics and Epidemiology, Kerman University of Medical Sciences, Kerman, Iran.³Department of Psychiatry, Kerman University of Medical Sciences, Kerman, Iran**Contact:** Navid Khalili, Department of Psychiatry, Kerman University of Medical Sciences, Shahid Beheshti Hospital, Jomhuri Eslami Blvd, Kerman, Iran. navidkhalili2000@yahoo.com.**Editorial group:** Cochrane Schizophrenia Group.**Publication status and date:** New, published in Issue 9, 2017.**Citation:** Nikvarz N, Vahedian M, Khalili N. Chlorpromazine versus penfluridol for schizophrenia. *Cochrane Database of Systematic Reviews* 2017, Issue 9. Art. No.: CD011831. DOI: [10.1002/14651858.CD011831.pub2](https://doi.org/10.1002/14651858.CD011831.pub2).

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

The efficacy of chlorpromazine, a benchmark antipsychotic, has not been fully assessed in direct comparison with different individual antipsychotics. Penfluridol is another old antipsychotic with a long half-life so one oral dose may last up to one week. This could confer advantage.

Objectives

To assess the clinical effects of chlorpromazine compared with penfluridol for adults with schizophrenia.

Search methods

On 31 March 2017, we searched the Cochrane Schizophrenia Group's Study-Based Register of Trials which is based on regular searches of CINAHL, BIOSIS, AMED, Embase, PubMed, MEDLINE, PsycINFO, and registries of clinical trials. There are no language, date, document type, or publication status limitations for inclusion of records in the register.

Selection criteria

We included all randomised clinical trials focusing on chlorpromazine versus penfluridol for adults with schizophrenia or related disorders. Outcomes of interest were death, service utilisation, global state, mental state, adverse effects and leaving the study early. We included trials meeting our selection criteria and reporting useable data.

Data collection and analysis

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

Main results

The review includes three studies with a total of 130 participants. Short-term results for hospital admissions showed no clear difference between chlorpromazine and penfluridol (1 RCT, $n = 29$, RR 0.19, 95% CI 0.01 to 3.60, *low-quality evidence*). No clear difference in the incidence of akathisia was found at medium term (2 RCTs, $n = 85$, RR 0.19, 95% CI 0.04 to 1.06, *low-quality evidence*), and similar numbers of participants - nearly half - from each treatment group left the study early (3 RCTs, $n = 130$, RR 1.21, 95% CI 0.83 to 1.77, *low-quality evidence*). The risk of needing additional antiparkinsonian medication was less in the chlorpromazine group (2 RCTs, $n = 74$, RR 0.70, 95% CI 0.51 to 0.95). No useable data reported clinically important change in global or mental state. No data were reported for relapse. No deaths were reported by the trials.

Chlorpromazine versus penfluridol for schizophrenia (Review)

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Authors' conclusions

Only three small studies provided data and the quality of reporting and evidence is low. Limited data indicate the efficacy and adverse effects profiles of chlorpromazine and penfluridol are generally similar. Penfluridol, however, may confer advantage by needing to be given only once per week. Firm conclusions are not possible without good-quality trials, and where these treatments are used, such trials are justified.

PLAIN LANGUAGE SUMMARY

Chlorpromazine versus penfluridol for schizophrenia

Review question

How effective is the antipsychotic chlorpromazine as a treatment for schizophrenia compared to penfluridol?

Background

Schizophrenia is serious mental disorder where people experience symptoms such as hallucinations and delusions, social withdrawal, decreased motivation and poor emotional response. The main treatment for schizophrenia is antipsychotic drugs. Chlorpromazine and penfluridol are widely used antipsychotics. However, different antipsychotics have different effects, and knowing the individual effects of different antipsychotics and what particular side effects they cause could help with deciding which antipsychotic to prescribe for an individual with schizophrenia. This review compares chlorpromazine with penfluridol and is one of a series of reviews comparing chlorpromazine directly with other antipsychotics.

Searching

The Information Specialist of Cochrane Schizophrenia searched their trials register in March, 2017 for trials that randomised adults with schizophrenia or related disorders to receive either chlorpromazine or penfluridol. Seven records were found and checked by the review authors

Evidence found

Only three randomised controlled trials, with a total of 130 participants met the review requirements and provided useable data. The quality of evidence available was low, no real difference was noted between chlorpromazine and penfluridol for hospital admissions, incidence of akathisia or numbers of participants leaving the study early. There were no deaths during the trials. We were unable to use the available data for global and mental state due to poor reporting, and no studies reported relapse data.

Conclusions

We can not make firm conclusions regarding the comparable effectiveness between chlorpromazine and penfluridol with such poor quality data - but penfluridol only needs to be given once per week - which could help the poor adherence to medication common with schizophrenia. Remarkably, for such old drugs, more trials that report high-quality data are needed.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Chlorpromazine versus Penfluridol for schizophrenia

Patient or population: patients with schizophrenia

Settings: hospital inpatients and outpatients

Intervention: Chlorpromazine versus penfluridol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk ³	Corresponding risk				
	Penfluridol	Chlorpromazine				
Service utilisation: hospital admission (short term)	150 per 1000	28 per 1000 (1 to 540)	RR 0.19 (0.01 to 3.60)	29 (1 study)	⊕⊕⊕⊖ low 1,2	
Global state: clinically important change in global state	See comment		Not estimable	0 (0)	See comment	No studies reported 'clinically important change in global state'. Change in global state was measure using global state scales but all data were presented without SD.
Global state: relapse	See comment		Not estimable	0 (0)	See comment	No studies reported this outcome.
Mental state: clinically important change in mental state	See comment		Not estimable	0 (0)	See comment	No studies reported 'clinically important change in mental state'. Change in mental state was measure using mental state scales but all data were presented without SD.
Adverse effect/event: clinically important extrapyramidal adverse events - akathisia (medium term)	200 per 1000	38 per 1000 (8 to 212)	RR 0.19 (0.04 to 1.06)	85 (2 studies)	⊕⊕⊕⊖ low 1,2	The same studies reported data for other extrapyramidal adverse events such as rigidity, tremor, dystonia and dyskinesia. There was no observable difference between chlorpromazine and penfluridol regarding any of these adverse effects.

Adverse effect/event: death	See comment		Not estimated	2 RCTs (0)	See comment	No deaths reported.
Leaving the study early: any reason (medium term)	400 per 1000	484 per 1000 (332 to 708)	RR 1.21 (0.83 to 1.77)	130 (3 studies)	⊕⊕⊕⊕ low 1,2	

*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; **SD:** standard deviation

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: downgraded by one level - study had an unclear risk of bias for random sequence generation and blinding of assessors.

² Serious risk of imprecision: downgraded by one level - studies had small sample sizes and number of events.

³ We have used the risk of an event in the penfluridol group within the trial/s the benchmark, rounding to nearest five for clarity of presentation in the table.

BACKGROUND

Description of the condition

Schizophrenia is a chronic disabling and relapsing mental illness with a worldwide lifetime prevalence of around 1% ([Almeida-Filho 1997](#); [Perala 2007](#)). A person with schizophrenia experiences formal thought disorder and some cognitive disturbances ([Fioravanti 2005](#); [Liddle 1987](#)). Symptoms can be divided into positive symptoms (such as delusions, hallucinations) and negative symptoms (such as poverty of speech, flattened affect, lack of pleasure, and lack of motivation) ([Crow 1980](#)). Although the symptoms of schizophrenia can be treated with antipsychotic medication, people often relapse. One of the main reasons of relapse in schizophrenia is poor compliance to drugs, often due to their adverse effects, or lack of insight to the disorder ([Lindstrom 2000](#)).

Description of the intervention

Antipsychotic drugs are the first-line treatment for symptoms of schizophrenia. Chlorpromazine is one of the essential antipsychotic drugs in the World Health Organization's list of essential drugs ([WHO 2015](#)). Chlorpromazine was introduced in the 1950s for the treatment of both acute and chronic psychoses, including schizophrenia and the manic phase of bipolar disorder, as well as amphetamine-induced psychoses. In early trials for schizophrenia, chlorpromazine in comparison with placebo showed efficacy in terms of clinical recovery, improvements

in social functioning, and preventing relapse. Chlorpromazine has long been recognised as a benchmark by which other antipsychotics have been evaluated ([Adams 2014](#)). Chlorpromazine has a wide range of effects on various parts of the body; in addition to extrapyramidal side effects, it has anticholinergic and antihistaminergic effects which cause other adverse effects. To name a few, dry mouth, blurred vision, urinary retention, restlessness, tremors, facial rigidity, shuffling gait and repetitive movements of the face and/or trunk are some of its common side effects ([Adams 2014](#)). Chlorpromazine as a phenothiazine is the first of drugs named neuroleptics; after its discovery, new phenothiazine derivatives have also been introduced ([Rees 1960](#)).

Penfluridol is a long-acting antipsychotic agent first synthesised in 1963. This drug is usually administered once weekly and can be considered as a depot medication ([Gerlach 1975](#)). It is a diphenylbutylpiperidine. Similar to chlorpromazine, the side effects of penfluridol are tardive dyskinesia, extrapyramidal symptoms and sedation ([Reynolds 1982](#)).

How the intervention might work

Both chlorpromazine and penfluridol are typical antipsychotic drugs. Chlorpromazine is a phenothiazine [Subclass: aliphatic side chain; Formula: 2-chloro-10-(3-dimethylaminopropyl) phenothiazine] ([Figure 1](#)). Trade names include Largactil, Hibernal, Megaphen, Solidon and Thorazine. Since it is a dopamine antagonist, its antipsychotic property affects particular areas of the brain.

Figure 1. Chlorpromazine structure

Penfluridol shows a relative antidopaminergic effect through the blocking of dopaminergic receptor membrane ([Gerlach 1975](#); [Janssen 1970](#)). It belongs to the diphenylbutylpiperidines ([Ionescu 1983](#); [van Praag 1971](#)) [Formula: 4-(p-chloro- β -trifluorom-tolyl)-1-[4,4-bis(pfluorophenyl) butyl]-4-piperidinol] ([Figure 2](#)). Trade names include Semap, Sémap and Flupidol. Pimozide is

the other drug in this class. Penfluridol is a tertiary amine and only slightly soluble in water ([Janssen 1970](#)). After absorption from the gastrointestinal tract, it deposits in fatty tissue from which it is gradually released, giving the prolonged duration of effects of penfluridol with its 70 hour half-life.

Figure 2. Penfluridol structure

Why it is important to do this review

Chlorpromazine is widely used for psychotic disorders in Africa, India and South-East Asia. Chlorpromazine is also usually a benchmark for evaluating other drugs (Adams 2005). This review is one of a series of reviews in order to evaluate chlorpromazine in comparison with other antipsychotics so that a full overview of

chlorpromazine's clinical efficacy can be completed (Table 1). There is a Cochrane systematic review of *Penfluridol for schizophrenia* (Soares 2006), however, the clinical profile of chlorpromazine compared with a long-acting antipsychotic such as penfluridol needs to be updated.

OBJECTIVES

To assess the clinical effects of chlorpromazine compared with penfluridol for adults with schizophrenia.

METHODS

Criteria for considering studies for this review

Types of studies

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

Types of participants

Adults, however defined, with schizophrenia or related disorders, including schizophreniform disorder and schizoaffective disorder again, by any means of diagnosis. We are interested in making sure that information is as relevant to the current care of people with schizophrenia as possible so proposed, if information was available, to clearly highlight the current clinical state (acute, early post-acute, partial remission, remission) as well as the stage (prodromal, first episode, early illness, persistent) and as to whether the studies primarily focused on people with particular problems (for example, negative symptoms, treatment-resistant illnesses).

Types of interventions

1. Chlorpromazine

Any dose and mode or pattern of administration.

2. Penfluridol

Any dose and mode or pattern of administration.

Types of outcome measures

We divided outcomes into short term (less than 12 weeks), medium term (12-52 weeks) and long term (over one year).

Primary outcomes

1. Service utilisation*

1.1 Hospital admission/readmission

2. Global state

2.1 Clinically important change in global state -as defined by each of the studies (short term)

3. Adverse effects

3.1 Clinically important extrapyramidal side effects - as defined by each of the studies

Secondary outcomes

1. Service utilisation

1.1 Days in hospital

2. Global state

2.1 Average endpoint/change score on global state scale

2.2 Relapse - as defined by each of the studies

3. Mental state

3.1 Clinically important change in negative symptoms - as defined by each of the studies

3.2 Average endpoint/change score on mental state scale

3.3 Average endpoint/change score in negative symptoms

4. Behaviour

4.1 Clinically important change in behaviour - as defined by each of the studies

4.2 Average endpoint/change score on behaviour scale

5. Adverse effects/events

5.1 General

5.1.1. Death-suicide/natural causes

5.1.2 At least one serious adverse effect/event

5.2 Specific (grouped by system-one expanded example given below)

5.2.1 Movement disorders

a. Any extrapyramidal side effects

b. Use of antiparkinson drugs

c. Clinically important extrapyramidal side effects-as defined by each of the studies

d. Average endpoint/change score on extrapyramidal side effects scale

5.2.2 Anticholinergic

5.2.3 Cardiovascular

5.2.4 Central nervous system

5.2.5 Gastrointestinal

5.2.6 Endocrine (e.g. amenorrhoea, galactorrhoea, hyperlipidaemia, hyperglycaemia, hyperinsulinaemia)

5.2.7 Haematology (e.g. haemogram, leucopenia, agranulocytosis/neutropenia)

5.2.8 Hepatic (e.g. abnormal transaminase, abnormal liver function)

5.2.9 Metabolic

5.2.10 Various other

6. Leaving the study early

6.1 For any reason

6.2 Due to adverse effects

7. Social functioning

7.1 Clinically important change in social functioning -as defined by each of the studies

7.2 Average endpoint/change score on social functioning scale

7.3 Employment status

8. Economic outcomes

9. Quality of life/satisfaction with care, for either recipients of care or carers

9.1 Clinically important change in quality of life/satisfaction-as defined by each of the studies

9.2 Average endpoint/change score on quality of life/satisfaction scale

10. Cognitive functioning

10.1 Clinically important change in cognitive functioning - as defined by each of the studies

10.2 Average endpoint/change score on cognitive functioning scale

* see [Differences between protocol and review](#)

'Summary of findings' table

We used the GRADE approach to interpret findings ([Schünemann 2011](#)); and used [GRADEpro GDT](#) to export data from our review to create a 'Summary of findings' table. This table provides outcome-specific information concerning the overall certainty 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 selected the following main outcomes for inclusion in the 'Summary of findings' table:

1. Service utilisation: Hospital admission
2. Global state: Clinically important change in global state-as defined by each of the studies (short term)
3. Global state: Relapse
4. Mental state: Clinically important change in mental state -as defined by each of the studies (short term)
5. Adverse effects: Clinically important extrapyramidal side effects - as defined by each of the studies
6. Adverse effects: Death
7. Leaving the study early

Search methods for identification of studies

Electronic searches

Cochrane Schizophrenia Group's Study-Based Register of Trials

On 17 August 2015 and 31 March 2017, the Information Specialist searched the register using the following search strategy:

(Chlorpromazine AND Penfluridol) in Intervention Field of STUDY

In such a study-based register, searching the major concept retrieves all the synonyms and relevant studies because all the studies have already been organised based on their interventions and linked to the relevant topics.

This register is compiled by systematic searches of major resources (including AMED, BIOSIS, CINAHL, Embase, MEDLINE, PsycINFO, PubMed, and registries of clinical trials) and their monthly updates, handsearches, grey literature, and conference proceedings (see [Group's Module](#)). There is no language, date, document type, or publication status limitations for inclusion of records into the register.

Searching other resources

1. Reference searching

We inspected the references of all included studies for further relevant studies.

2. Personal contact

We did not contact the manufacturers of penfluridol or chlorpromazine for additional data.

Data collection and analysis

Selection of studies

Review authors NN and NK independently inspected citations from the searches and identified relevant abstracts. MV independently re-inspected a random 20% sample to ensure reliability. Where disputes arose, we acquired the full-text report for more detailed scrutiny. NN and NK obtained and inspected the full reports of the abstracts meeting the review criteria. Again, MV re-inspected a random 20% of reports in order to ensure reliable selection. If it had not been possible to resolve disagreement by discussion, we would have attempted to contact the authors of the study for clarification.

Data extraction and management

1. Extraction

Review author MV extracted data from all included studies. In addition, to ensure reliability, NN independently extracted data from all included studies. There were no disagreements between review authors in terms of the extracted data. If required, we would have extracted data presented only in graphs and figures whenever possible, but would have only included the data if two review authors independently had the same results.

2. Management

2.1 Forms

We extracted data onto standard, pre-designed simple forms.

2.2 Scale-derived data

We would have included continuous data from rating scales only if:

1. the psychometric properties of the measuring instrument have been described in a peer-reviewed journal ([Marshall 2000](#));
2. the measuring instrument has not been written or modified by one of the trialists for that particular trial; and
3. the instrument should be a global assessment of an area of functioning and not sub-scores which are not, in themselves, validated or shown to be reliable. However there are exceptions; we would have included sub-scores from mental state scales measuring positive and negative symptoms of schizophrenia.

Ideally, the measuring instrument should either be i. a self-report or, ii. completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly; in 'Description of studies' in the Results section we would have noted whether or not this was the case.

2.3 Endpoint versus change data

There are advantages to 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 would have combined endpoint and change data in the analysis as we prefer to use mean differences (MD) rather than standardised mean differences (SMD) (Deeks 2011).

2.4 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we planned to apply the following standards to scale data.

For endpoint data from studies $N < 200$

1. If a scale started from the finite number zero, we would have subtracted the lowest possible value from the mean, and divided this by the standard deviation (SD). If this value was lower than 1, it would have strongly suggested a skew and we would have excluded such data. If this ratio was higher than 1 but below 2, there is a suggestion of skew. We would have entered such data and tested whether its inclusion or exclusion changed the results substantially. If these data did change the results we would have entered them as 'other data'. Finally, if the ratio was larger than 2, we would have included these data, because skew was less likely (Altman 1996; Higgins 2011).
2. If a scale starts from a positive value (such as the Positive and Negative Syndrome Scale (PANSS), which can have values from 30 to 210) (Kay 1986), the calculation described above can be modified to take the scale starting point into account. In these cases skew is present if $2 \text{ SD} > (S - S_{\min})$, where S is the mean score and ' $S_{\min}$ ' is the minimum score.

For change data

1. We would have entered change data as when continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not. We would have presented and entered change data into statistical analyses.

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

We would have made efforts to convert continuous 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 Positive and Negative Syndrome Scale (PANSS, Kay 1986), this could be considered as a clinically significant response (Leucht 2005a; Leucht 2005b). Had data based on these thresholds not been available, we would have 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 indicates a favourable outcome for chlorpromazine.

Assessment of risk of bias in included studies

MV and MV worked independently to assess risk of bias by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a) to assess trial quality. This set of criteria is based on evidence of associations between an overestimate of effect and high risk of bias of the article, such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

If the raters had disagreed, the final rating would have been made by consensus. If inadequate details of randomisation and other characteristics of trials were provided, we would have contacted authors of the studies in order to obtain additional information. We would have reported non-concurrence in quality assessment, and if disputes arose as to which category a trial was to be allocated, again, we would have resolved these by discussion.

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

2. Continuous data

There were no usable reported continuous data in the included studies.

Unit of analysis issues

1. Cluster trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice), but analysis and pooling of clustered data poses problems. Firstly, authors often fail to account for intraclass correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby P values are spuriously low, CIs unduly narrow, and statistical significance overestimated. This causes type I errors (Bland 1997; Gulliford 1999).

If we had included cluster-randomised trials and clustering had not been accounted for in primary studies, we would have presented data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. In subsequent versions of this review, we will seek to contact first authors of studies to obtain intra-class correlation coefficients (ICCs) for their clustered data and adjust for this by using accepted methods (Gulliford 1999). If clustering had been incorporated into the analysis of primary

studies, we would have presented these data as if from a non-cluster randomised study, but adjusted the data for the clustering effect.

We have sought statistical advice and have been advised that the binary data as presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the ICC [Design effect = $1 + (m - 1) \times \text{ICC}$] (Donner 2002). If the ICC was not reported we would have assumed it 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 be possible using the generic inverse variance technique.

2. Cross-over trials

A major concern of cross-over trials is the carry-over effect. It occurs if an effect (e.g. pharmacological, physiological or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence, on entry to the second phase the participants can differ systematically from their initial state, despite a wash-out phase. For the same reason, cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both effects are very likely in severe mental illness, if cross-over trials had been included, we would only have used data of the first phase of cross-over studies.

3. Studies with multiple treatment groups

Had a study involved more than two treatment arms, we would have presented the additional treatment arms in comparisons. If data were binary, we would simply have added and combined the data within the two-by-two table. If data were continuous, we would have combined data following the formula in section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If the additional treatment arms were not relevant, we would not have used these data.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up, data must lose credibility (Xia 2009). We chose that, for any particular outcome, should more than 50% of data be unaccounted for, we would not reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a study were lost, but the total loss was less than 50%, we would address this within the 'Summary of findings' table by down-rating quality. Finally, we also planned to downgrade quality within the 'Summary of findings' table should the loss be 25% to 50% in total.

2. Binary

In the case where attrition for a binary outcome was between 0% and 50% and where these data were not clearly described, we planned to present data on a 'once-randomised-always-analyse' basis (an intention-to-treat analysis (ITT)). Those leaving the study early would all have been assumed to have the same rates of negative outcome as those who completed. We would have used the rate of those who stayed in the study - in that particular arm of the trial - and applied this also to those who did not. We planned to undertake a sensitivity analysis to test how prone the

primary outcomes were to change when data only from people who completed the study to that point were compared to the intention-to-treat analysis using the above assumptions.

3. Continuous

3.1 Attrition

In cases 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 would have reproduced such data.

3.2 Standard deviations

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

3.3 Assumptions about participants who left the trials early or were lost to follow-up

Various methods are available to account for participants who leave the trials early or are lost to follow-up. Some trials just present the results of study completers, others use the method of last observation carried forward (LOCF), while more recently methods such as multiple imputation or mixed effects models for repeated measurements (MMRM) have become more of a standard. While the latter methods seem to be somewhat better than LOCF (Leon 2006), we feel that the high percentage of participants leaving the studies early and differences in the reasons for leaving the studies early between groups is often the core problem in randomised schizophrenia trials. We therefore decided we would not exclude studies based on the statistical approach used. However, we would preferably have used the more sophisticated approaches. For example, MMRM or multiple-imputation is preferred to LOCF and we would only present completer analyses if some kind of ITT data were not available at all. Moreover, we addressed this issue in the 'Risk of bias' tool.

Assessment of heterogeneity

1. Clinical heterogeneity

We considered all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We simply inspected all studies for clearly outlying people or situations which we had not predicted would arise. If such situations or participant groups had arisen, we would have discussed any issues.

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. If such methodological outliers had arisen, we would have discussed any issues.

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 χ^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 χ^2 test, or a confidence interval for I^2). We would have considered an I^2 estimate greater than or equal to around 50% accompanied by a statistically significant χ^2 statistic, as evidence of substantial levels of heterogeneity (Section 9.5.2, Deeks 2011). If substantial levels of heterogeneity had been found in the primary outcome, we would have explored reasons for heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in section 10.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011).

1. Protocol versus full study

We tried to locate protocols of included randomised trials. If the protocol was available, we compared outcomes in the protocol and in the published report. If the protocol was not available, we compared outcomes listed in the methods section of the trial report with actually reported results.

2. Funnel plot

We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We planned not to use funnel plots for outcomes where there were 10 or fewer studies, or where all studies were of similar size. In other cases, where funnel plots were possible, we would have 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 fixed model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary outcomes

No subgroup analysis was anticipated.

2. Investigation of heterogeneity

If inconsistency was high, we would have reported it. First, we would have investigated whether data had been entered correctly. Second, if data were correct, we would have visually inspected the graph and successively removed outlying studies to see if homogeneity was restored. For this review, we decided that should this occur with data contributing to the summary finding of no more than around 10% of the total weighting, we would present the data. If not, we would not pool these data, but discuss any issues. We know of no supporting research for this 10% cut-off but are investigating use of prediction intervals as an alternative to this unsatisfactory state.

If unanticipated clinical or methodological heterogeneity had been obvious we would simply have stated hypotheses regarding these for future reviews or versions of this review. We did not anticipate undertaking analyses relating to these.

Sensitivity analysis

If substantial differences had been noted in the direction or precision of effect estimates in any of the sensitivity analyses listed below, we would not have pooled data from the excluded trials with the other trials contributing to the outcome, but presented them separately as 'other data'.

1. Implication of randomisation

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

2. Assumptions for lost binary data

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

3. Risk of bias

For the primary outcome, we would have analysed the effects of excluding trials that were judged to be at high risk of bias across one or more of the domains of randomisation (see [Assessment of risk of bias in included studies](#)). If the exclusion of trials at high risk of bias had not substantially altered the direction of effect or the precision of the effect estimates, then we would have included data from these trials in the analysis.

4. Imputed values

If we had included cluster 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.

5. Fixed-effect or random-effects

We synthesised all data using a fixed-effect model. However, we also synthesised data for the primary outcome using a random-effects model to evaluate whether this altered the significance of

the results. If there had been a substantial difference, we would have reported this.

RESULTS

Description of studies

Please see [Characteristics of included studies](#) and [Characteristics of excluded studies](#).

Results of the search

Details of the search results are illustrated in the PRISMA table ([Figure 3](#)).

Figure 3. Study flow diagram.

In the original search we found seven reports that were potentially relevant. There were no duplicates. We inspected full text of these reports and then grouped these into trials where several reports referred to the same trial. After excluding two trials, we included three trials (five reports).

Included studies

1. Duration

Duration of studies ranged from 13 to 52 weeks. Results of [Chouinard 1977](#) were reported in three separate published articles. Two of them contain results of participants receiving the chlorpromazine or penfluridol for an inpatient phase of three weeks and the other has results of an outpatient follow-up phase which lasted 10 weeks. [Wang 1982](#) was a medium-term trial of 20 weeks and, finally, [Claghorn 1979](#) was for a total of 52 weeks.

2. Participants

A total of 130 people aged 19 to 60 years participated in the studies.

All participants were diagnosed with schizophrenia. Participants in [Chouinard 1977](#) were classified as paranoid or non-paranoid subtype based on the Diagnostic and Statistical Manual of Mental Disorders-II (DSM-II criteria). [Wang 1982](#) reported no criteria for diagnosis of schizophrenia. The diagnostic criteria for [Claghorn 1979](#) are not clear. All participants had a history of chronic schizophrenia with the people in the [Claghorn 1979](#) study being particularly unwell with a duration of illness in the decades and even the particular episode of illness being between eight and 10 years long.

Participants in [Wang 1982](#) were all males. [Claghorn 1979](#) and [Chouinard 1977](#) included both men and women.

3. Setting

[Chouinard 1977](#) had an inpatient setting for three weeks, followed by a 10-week outpatient phase. [Wang 1982](#) included both inpatients and outpatients. [Claghorn 1979](#), dealing with a group of very ill people, was conducted all in hospital.

4. Intervention

Both intervention drugs were administered orally.

4.1 Chlorpromazine

The starting dose and maximum doses of chlorpromazine in [Wang 1982](#) were 415 mg/day and 1050 mg/day, respectively. [Chouinard 1977](#) prescribed chlorpromazine at dose of 300 mg/day during the first week, 600 mg/day in the second week and 900 mg/day during the third week, and continued the last dose in the 10-week follow-

up phase (the mean dose was 650 mg/day). Although there were higher doses used, the final mean dose in [Claghorn 1979](#) settled at 300 mg/day.

4.2 Penfluridol

The initial dose, and maximum doses of penfluridol [Wang 1982](#) were 60 mg/week and 140 mg/week, respectively. [Chouinard 1977](#) prescribed penfluridol at single dose of 40 mg in the first week, 80 mg in the second week and 120 mg during the third week and continued the last dose in the 10-week follow-up phase (the mean dose was 102 mg/week). A similar regimen was adopted by [Claghorn 1979](#), with the final mean dose being 74 mg/week.

5. Outcomes and outcome scales

Studies reported dichotomous (binary) and continuous outcomes; however, all scale data were impossible to use as, either, means were presented without SD or attrition was over 50% (please see [Dealing with missing data](#)). No included study reported economic outcomes, and effects of interventions on quality of life, employment status or cognitive functioning.

Excluded studies

We excluded two studies. One was a quasi-randomised study ([Bao 1988](#)). We initially had excluded [Claghorn 1979](#) as less than 50% of people completed the entire course of the trial, but found that some adverse effects and the number actually leaving were reported on 100% of people; as a result, this study is now included. [Li 1987](#) also seemed to have high attrition, but in addition, the number of people in each group was not mentioned. Therefore we excluded this study.

Risk of bias in included studies

See [Figure 4](#) and [Figure 5](#).

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

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chouinard 1977	+	?	?	?	+	?	?
Claghorn 1979	+	?	?	?	?	-	?
Wang 1982	+	?	+	?	+	?	?

Allocation

None of the included studies described the methods used to generate random allocation, although [Claghorn 1979](#) used block randomisation. Having said that, the [Claghorn 1979](#) study, conscious of how allocation can still result in imbalanced groups, reported on differences in distribution of illness duration and sex. There was an implication from the writing in this study that the authors understood the randomisation procedure. We have no information from these old studies about allocation concealment.

Blinding

All three included trials used a double-blind design. [Chouinard 1977](#) had an unclear risk of bias as reports did not explain how they used a double-blind method and how successful their attempts at blinding were. [Claghorn 1979](#) used placebo tablets to mask that participants in one group really only got one active dose per week whereas those allocated to chlorpromazine were given active compound daily. [Wang 1982](#) described their method of blinding. In

this study all patients received identical appearing capsules on a special "blister pack" medication card allowing the patient to take the medication on a twice-a-day schedule. We rated [Wang 1982](#) as low risk of bias for performance bias as they had described the methods used to ensure blinding of participants and personnel.

Incomplete outcome data

This was not a major issue in two of the trials. [Claghorn 1979](#), however, had high attrition that was clearly described.

Selective reporting

We felt that both [Chouinard 1977](#) and [Wang 1982](#) carry at least an 'unclear' risk of bias for selective reporting as quite a few outcomes were not clearly reported. [Claghorn 1979](#), however, we thought, should be rated as 'high' risk as there was clear selective reporting of adverse effects. We recognise that when extensive investigations are undertaken this can generate a very long list of rare adverse effects that is cumbersome to reproduce in the published report.

With online storage of data this becomes less of a problem and we may be judging [Claghorn 1979](#) by standards of three decades beyond its publication. However, we think, even in 1979, inclusion of extensive lists of adverse effects was not rare and such a table would have been reassuring to the reader that rare but important effects had not been under-reported.

Other potential sources of bias

All three studies had an unclear risk of bias for other potential sources of bias.

Effects of interventions

See: [Summary of findings for the main comparison](#)

1. COMPARISON 1. Chlorpromazine versus penfluridol

1. Service utilisation: hospital readmission

We identified one short-term study ($n = 29$) reporting data for this outcome. We did not find evidence of a clear difference between chlorpromazine and penfluridol (risk ratio (RR) 0.19, 95% confidence interval (CI) 0.01 to 3.60, low-quality evidence; [Analysis 1.1](#)).

1.2 Adverse effects: 1a. General - needing antiparkinsonian medication

Short-term results from [Chouinard 1977](#) showed no observable difference between chlorpromazine and penfluridol for numbers of participants needing antiparkinsonian medication (1 RCT, $n = 33$, RR 0.82, 95% CI 0.46 to 1.46) and [Wang 1982](#) however found evidence that chlorpromazine had a favourable effect in the medium term (1 RCT, $n = 41$, RR 0.63, 95% CI 0.43 to 0.91). Overall, there was suggestion that use of chlorpromazine carried less risk of needing additional medication for movement disorder adverse effects (2 RCTs, $n = 74$, RR 0.70, 95% CI 0.51 to 0.95; [Analysis 1.2](#)).

1.3 Adverse effects: 1b. General - need to reduce antipsychotic dose due to adverse effects

Similar numbers of participants from each group needed a reduction in their antipsychotic dose to alleviate adverse effects (1 RCT, $n = 33$, RR 0.74, 95% CI 0.26 to 2.06; [Analysis 1.3](#)).

1.4 Adverse effects: 2a. Specific - extrapyramidal events (moderate or severe) - short term

[Chouinard 1977](#) assessed extrapyramidal adverse effects at three weeks. No incidences of akathisia, dyskinesia, dystonia or tremor were observed. Two participants receiving penfluridol experienced rigidity, while no rigidity occurred in the chlorpromazine group, however, these data do not show a substantial difference between chlorpromazine and penfluridol for this outcome (1 RCT, $n = 33$, RR 0.15, 95% CI 0.01 to 2.90; [Analysis 1.4](#)).

1.5 Adverse effects: 2b. Specific - extrapyramidal events (moderate or severe) - medium term

Overall, no differences between chlorpromazine and penfluridol were evident for extrapyramidal events ([Analysis 1.5](#)).

1.5.1 akathisia

Two studies reported data for akathisia, there was not a clear difference in effect between chlorpromazine and penfluridol (2 RCTs, $n = 85$, RR 0.19, 95% CI 0.04 to 1.06, low-quality evidence).

1.5.2 dyskinesia

Two studies reported data for dyskinesia, there was not a clear difference in effect between chlorpromazine and penfluridol (2 RCTs, $n = 85$, RR 0.97, 95% CI 0.14 to 6.52).

1.5.3 dystonia

One study reported data for dystonia, with one person from each group experiencing dystonia (1 RCT, $n = 29$, RR 0.93, 95% CI 0.06 to 13.54).

1.5.4 muscle spasm

One study ($n = 56$) reported data for muscle spasm, there was not a clear difference between chlorpromazine and penfluridol (RR 3.00, 95% CI 0.13 to 70.64).

1.5.5 rigidity

Two studies ($n = 70$) reported data for this outcome, there was not a clear difference in effect between chlorpromazine and penfluridol (RR 0.22, 95% CI 0.04 to 1.20).

1.5.6 tremor

Two studies ($n = 85$) reported data for this outcome, there was not a clear difference in effect between chlorpromazine and penfluridol (RR 0.70, 95% CI 0.14 to 3.43).

1.6 Adverse effects: 2c. Specific - anticholinergic (moderate or severe) - short term

One study provided data for anticholinergic effects. Overall, no differences between chlorpromazine and penfluridol were evident for anticholinergic adverse effects in the short term ([Analysis 1.6](#)).

1.6.1 constipation

Six people receiving chlorpromazine and one person receiving penfluridol experienced constipation (1 RCT, $n = 33$, RR 4.42, 95% CI 0.60 to 32.71).

1.6.2 dry mouth

Only one person in the chlorpromazine group experienced dry mouth (1 RCT, $n = 33$, RR 2.25, 95% CI 0.10 to 51.46).

1.6.3 increased salivation

One person receiving penfluridol experienced an increase in salivation (1 RCT, $n = 33$, RR 0.25, 95% CI 0.01 to 5.72).

1.7 Adverse effects: 2d. Specific - anticholinergic (moderate or severe) - medium term

Again, only one study reported data. Overall, no differences between chlorpromazine and penfluridol were evident for anticholinergic adverse effects in the medium term ([Analysis 1.7](#)).

1.7.1 blurred vision

No people receiving chlorpromazine and one receiving penfluridol experienced blurred vision (1 RCT, $n = 29$, RR 0.31, 95% CI 0.01 to 7.09).

1.7.2 constipation

Four people in the chlorpromazine group and one receiving penfluridol experienced constipation (1 RCT, $n = 29$, RR 3.73, 95% CI 0.47 to 29.49).

1.7.3 dry mouth

One person receiving chlorpromazine experienced dry mouth (1 RCT, $n = 29$, RR 2.81, 95% CI 0.12 to 63.83).

1.8 Adverse effects: 2e. Specific - central nervous system (moderate or severe) - short term

Data from one study found no differences between chlorpromazine and penfluridol were evident for anticholinergic adverse effects in the short term ([Analysis 1.8](#)).

1.8.1 agitation

One person receiving chlorpromazine became agitated in the short term (1 RCT, $n = 33$, RR 2.25, 95% CI 0.10 to 51.46).

1.8.2. drowsiness

Five people receiving chlorpromazine became drowsy (1 RCT, $n = 33$, RR 8.25, 95% CI 0.49 to 137.94).

1.8.3 dizziness

One participant in the chlorpromazine group and three in the penfluridol group experienced dizziness (1 RCT, $n = 33$, RR 0.25, 95% CI 0.03 to 2.12).

1.8.4 insomnia

One person receiving chlorpromazine experienced insomnia (1 RCT, $n = 33$, RR 2.25, 95% CI 0.10 to 51.46).

1.9 Adverse effects: 2f. Specific - central nervous system (moderate or severe) - medium term

Two studies reported central nervous system effects data for the medium term, there was no clear differences between the two treatments for specific central nervous system effects.

1.9.1 drowsiness

Two studies showed no evidence of a clear difference between the two treatments for drowsiness (2 RCTs, $n = 85$, RR 1.05, 95% CI 0.54 to 2.05).

1.9.2 dizziness

One study reported data for dizziness. One person in the chlorpromazine group and two in the penfluridol group experienced dizziness (1 RCT, $n = 29$, RR 0.47, 95% CI 0.05 to 4.60).

1.9.3 excitement

One study reported data for excitement. One person in the chlorpromazine group experienced excitement (1 RCT, $n = 29$, RR 2.81, 95% CI 0.12 to 63.83).

1.9.4 faintness

One study reported data for faintness. Two participants from each group experienced faintness (1 RCT, $n = 29$, RR 0.93, 95% CI 0.15 to 5.76).

1.9.5 insomnia

Two studies reported data for insomnia. There was evidence of a clear difference, favouring chlorpromazine (2 RCTs, $n = 85$, RR 0.17, 95% CI 0.03 to 0.93).

1.10 Adverse effects: 2g. Specific - various other effects (moderate or severe) - short term

Two studies provided data for various other effects. One reported on heartburn and the other reported on systemic allergic reaction. Chlorpromazine was no different in its effect compared to penfluridol for various other short-term effects ([Analysis 1.10](#)).

1.10.1 heartburn

One study ($n = 33$) provided data for heartburn. No one experienced heartburn in either group.

1.10.2 increased alkaline phosphatase, bilirubin, SGOT (serum glutamic oxaloacetic transaminase)

One study found no evidence of a difference between the two treatments (1 RCT, $n = 56$, RR 0.33 95% CI 0.01 to 7.85)

1.10.3 Systemic allergic reaction

One study provided data. Three people in the chlorpromazine group experienced systemic allergic reaction (1 RCT, $n = 33$, RR 5.25, 95% CI 0.29 to 94.14).

1.11 Adverse effects: 2h. Specific - various other effects (moderate or severe) - medium term

Various other adverse effects were measured in the medium term by one study. No clear difference was seen between the two treatments for any of these effects [Analysis 1.11](#).

1.11. 1 depression

(1 RCT, $n = 29$, RR 0.19, 95% CI 0.01 to 3.60).

1.11.2 decreased sexual drive

(1 RCT, $n = 29$, RR 0.47, 95% CI 0.05 to 4.60).

1.11.3 impotence

(1 RCT, $n = 29$, RR 2.81, 95% CI 0.12 to 63.83).

1.11.4 photosensitivity

(1 RCT, $n = 29$, RR 2.81, 95% CI 0.12 to 63.83).

1.11.5 poor appetite

(1 RCT, $n = 29$, RR 0.93, 95% CI 0.06 to 13.54).

1.12 Leaving the study early: 1a. Any reason

Pooled data from three studies showed no clear medium-term differences between penfluridol and chlorpromazine (3 RCTs, $n = 130$, RR 1.21, 95% CI 0.83 to 1.77, low-quality evidence; [Analysis 1.12](#)).

1.13 Leaving the study early: 1b. Due to adverse events

Two studies found no clear differences, in either short or medium term, when leaving early was due to adverse effects ([Analysis 1.13](#))

DISCUSSION

Summary of main results

The summary below shows the outcomes selected for the [Summary of findings for the main comparison](#) and addresses the main findings of this review.

1. Service utilisation: hospital readmission

There was only one study reporting two participants on penfluridol who were readmitted (due to depression). There was no clear differences between the drugs, but this important outcome was only reported in one tiny study ($n = 29$) and data quality have to be considered low. Best evidence highlights no difference, but the best evidence is poor.

2. Global state

This is not a difficult outcome to record. No study reported on a binary outcome and the continuous data-measured by Clinical Global Impression (CGI) were unusable (standard deviations of means were not reported in both included studies). No study reported on relapse as the other aspect of global state.

3. Mental state

There is, at least, consistency across outcomes. Again, no study reported on a binary outcome and the continuous data were unusable (standard deviations of means were not reported in both included studies). It is easy to unfairly judge pioneering studies of the past by standards of today, but we think it unlikely that the participants in these trials gave informed consent to have data squandered.

4. Adverse effects/events

4.1 Extrapyramidal adverse events-akathisia

We chose this medium-term outcome because two studies reported on it. Data quality were low, trials were very small (2 RCTs, $N = 85$) and results equivocal, but there was a suggestion that should studies have been larger, the chlorpromazine group would have experienced less akathisia. Penfluridol, with a relatively higher potency, would be expected to induce more extrapyramidal side effects than chlorpromazine. However, the small sample size and probable reporting bias could mean little difference between the two drugs regarding extrapyramidal adverse effects was observed.

4.2 Death

The lifetime incidence of suicide in people with schizophrenia is estimated to be 10% to 13% (Caldwell 1992). Sudden death as an adverse effect of antipsychotic drugs has been shown to have an incidence rate ratio of 1.99 (Manu 2011). There was no report of death in the short and small included studies. Of course this is an important effect/event but, in retrospect, it might not have been wise to present this in the 'Summary of findings' as we would always have been unlikely to detect this rare event.

5. Leaving the study early

Leaving the study early may be the result of a multitude of reasons including lack of efficacy, adverse effects or an unacceptable study design. All in all, similar numbers of participants left early from each treatment group, neither drug was worse or better than the other. Nearly half of those entered into the studies left or were withdrawn early. On one hand, this could reflect a real-world situation, attrition is often high, but there is the worry that these studies not convincingly reflecting care in routine practice, had any authority they had further eroded by loss to follow-up.

Overall completeness and applicability of evidence

1. Completeness

These are old, small and limited studies. Much data were wasted because of poor reporting and more were never recorded. These are two important drugs and we do not have anywhere near a complete picture of their comparative effects.

2. Applicability

Studies in this review included people in both outpatient and inpatient settings. People in the trials were often chronically unwell. This is an important group of people, but not inclusive of everyone with schizophrenia. Trials are also three to four decades old. In many places services have changed considerably in that time, in others, less so. What evidence we have is thin, and its applicability problematic.

Quality of the evidence

The quality of the current evidence is low, based on ratings generated though GRADE (Schünemann 2011). None of the studies reported how randomisation was achieved and only one trial described the method of allocation concealment. Although studies were reported as double-blinded, none clearly described whether assessors were blinded to the treatment groups. All scale data were reported as means without standard deviations for the main results. Most results were presented in the text with authors simply reporting that results were statistically significant or not, but they did not report statistical measures of probability (P values) or the confidence interval. 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 ' $P < 0.001$ '.

Potential biases in the review process

1. Adding the old to the new

We have found no time-related differences in studies within this review and no indication of 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 handsearching old files. Nevertheless, it may be difficult to avoid some bias from not identifying long-lost studies.

3. Failing to identify other language trials

We identified trials in other languages by searching specialist databases. This should have identified, for example, Chinese studies. However, there is always a danger of failing to identify studies and especially if published in languages other than English. It seems unlikely, however, that we have failed to find large important studies.

Agreements and disagreements with other studies or reviews

To our knowledge, there is no previous review specifically comparing chlorpromazine with penfluridol (Table 1). In another Cochrane study of penfluridol in schizophrenia, penfluridol has

been suggested to have no significant difference with any other typical antipsychotics in terms of global state, mental state, attrition, and requiring antiparkinsonian medication (Soares 2006). Compared with placebo, chlorpromazine has shown to improve global state and reduce relapse rate and attrition significantly (Adams 2005).

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia

Although limited data on global state or mental state are available in the included studies of this review, there was no report that chlorpromazine was less effective than penfluridol regarding these outcomes. Needing supplementary antiparkinsonian drugs might be less with chlorpromazine in the medium term.

2. For clinicians

There is the suggestion that chlorpromazine may cause less movement disorders than penfluridol, but data are too sparse to be sure. What very few data there are suggests little difference between the two drugs. Penfluridol, however, only needs to be given once per week. This is important and, if there were good data, this long half-life could be useful for some people.

3. For managers and policy makers

In situations where these two drugs are accessible, and prescribed, managers and policy makers may wish to encourage randomisation when there is clinical doubt as to which to use. In such a situation real-world randomisation could add much to our knowledge of these drugs.

Implications for research

1. General

We had to exclude Li 1987 due to the poor quality of data reporting, diminishing the already limited evidence-base (please refer to Characteristics of excluded studies for details). Nowadays, following CONSORT (Moher 2001) guidance for reporting of clinical trials would help increase the data available in this review.

2. Specific

Even though chlorpromazine has been used in the management of schizophrenia for many years, and penfluridol is also an old drug, high-quality evidence for comparative efficacy and safety is so limited that conducting a well-designed large controlled study is justified where these treatments are still used. We do realise that such studies take meticulous planning but studies reporting clear and routine data have great utility and we suggest a design in Table 2.

ACKNOWLEDGEMENTS

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

The search term was developed by the Information Specialist of the Cochrane Schizophrenia Group and the contact author of this protocol. Jun Xia from Systematic Review Solutions extracted data of Chinese studies. We would like to thank Jamie Majdi and Pippa Shaw for peer reviewing this version of the review.

Parts of this review were generated using RevMan HAL v 4.0. You can find more information about RevMan [here](#).

REFERENCES

References to studies included in this review

Chouinard 1977 {published data only}

Chouinard G, Annable L. Penfluridol in the treatment of newly admitted schizophrenic patients in a brief therapy unit. *American Journal of Psychiatry* 1976;**133**(7):850-3. [PUBMED: 937582]

Chouinard G, Annable L, Cooper S. Antiparkinsonian drug administration and plasma levels of penfluridol, a new long-acting neuroleptic. *Communications in Psychopharmacology* 1977;**1**(4):325-31. [PUBMED: 615695]

* Chouinard G, Annable L, Kolivakis TN. Penfluridol in the maintenance treatment of schizophrenic patients newly discharged from a brief therapy unit. *Journal of Clinical Pharmacology* 1977;**17**(2-3):162-7. [PUBMED: 833344]

Claghorn 1979 {published data only}

Claghorn JL, Mathew RJ, Mirabi M. Penfluridol: a long acting oral antipsychotic drug. *Journal of Clinical Psychiatry* 1979;**40**(2):107-9. [PUBMED: 368045]

Wang 1982 {published data only}

Wang RI, Larson C, Treul SJ. Study of penfluridol and chlorpromazine in the treatment of chronic schizophrenia. *Journal of Clinical Pharmacology* 1982;**22**(5-6):236-42. [PUBMED: 7107969]

References to studies excluded from this review

Bao 1988 {published data only}

Bao XQ. A double-blind study on the effect of clozapine, penfluridol and chlorpromazine in the treatment of schizophrenia. *Chinese Journal of Neurology and Psychiatry* 1988;**21**(5):274-6, 318. [PUBMED: 3069382]

Li 1987 {published data only}

Li Y. Application of NOSIE in the study of neuroleptic treatment. *Chinese Journal of Neurology and Psychiatry* 1987;**20**(6):325-7. [PUBMED: 3329087]

Additional references

Adams 2005

Adams CE, Rathbone J, Thornley B, Clarke M, Borrill J, Wahlbeck K, et al. Chlorpromazine for schizophrenia: a Cochrane systematic review of 50 years of randomised controlled trials. *BMC Medicine* 2005;**3**:15. [PUBMED: 16229742]

Adams 2014

Adams CE, Awad GA, Rathbone J, Thornley B, Soares-Weiser K. Chlorpromazine versus placebo for schizophrenia. *Cochrane Database of Systematic Reviews* 2014, Issue 1. [DOI: [10.1002/14651858.CD000284.pub3](https://doi.org/10.1002/14651858.CD000284.pub3); PUBMED: 24395698]

Ahmed 2010

Ahmed U, Jones H, Adams CE. Chlorpromazine for psychosis induced aggression or agitation. *Cochrane*

Database of Systematic Reviews 2010, Issue 4. [DOI: [10.1002/14651858.CD007445.pub2](https://doi.org/10.1002/14651858.CD007445.pub2); CD007445]

Almeida-Filho 1997

Almeida-Filho N, Mari J de J, Coutinho E, Franca JF, Fernandes J, Andreoli SB, et al. Brazilian multicentric study of psychiatric morbidity. Methodological features and prevalence estimates. *British Journal of Psychiatry* 1997;**171**(6):524-9. [PUBMED: 9519090]

Almerie 2007

Almerie MQ, Alkhateeb H, Essali A, Matar HE, Rezk E. Cessation of medication for people with schizophrenia already stable on chlorpromazine. *Cochrane Database of Systematic Reviews* 2007, Issue 1. [DOI: [10.1002/14651858.CD006329](https://doi.org/10.1002/14651858.CD006329); CD006329]

Altman 1996

Altman DG, Bland JM. Detecting skewness from summary information. *BMJ* 1996;**313**(7066):1200.

Bazrafshan 2015

Bazrafshan A, Zare M, Okhovati M, Shamsi Meimandi M. Acetophenazine versus chlorpromazine for schizophrenia. *Cochrane Database of Systematic Reviews* 2015, Issue 4. [DOI: [10.1002/14651858.CD011662](https://doi.org/10.1002/14651858.CD011662)]

Bland 1997

Bland JM. Statistics notes. Trials randomised in clusters. *BMJ* 1997;**315**:600.

Boissel 1999

Boissel JP, Cucherat M, Li W, Chatellier G, Gueyffier F, Buyse M, et al. The problem of therapeutic efficacy indices. 3. Comparison of the indices and their use [Aperçu sur la problématique des indices d'efficacité thérapeutique, 3: comparaison des indices et utilisation. Groupe d'Etude des Indices D'efficacité]. *Thérapie* 1999;**54**(4):405-11. [PUBMED: 10667106]

Caldwell 1992

Caldwell CB, Gottesman II. Schizophrenia--a high-risk factor for suicide: clues to risk reduction. *Suicide and Life-Threatening Behavior* 1992;**22**(4):479-93. [PUBMED: 1488792]

Crow 1980

Crow TJ. Molecular pathology of schizophrenia: more than one disease process?. *British Medical Journal* 1980;**280**(6207):66-8. [PUBMED: 6101544]

Deeks 2000

Deeks J. Issues in the selection for meta-analyses of binary data. 8th International Cochrane Colloquium; 2000 Oct 25-28; Cape Town. Cape Town: The Cochrane Collaboration, 2000.

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG, editor(s). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March

2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Divine 1992

Divine GW, Brown JT, Frazier LM. The unit of analysis error in studies about physicians' patient care behavior. *Journal of General Internal Medicine* 1992;**7**(6):623-9.

Donner 2002

Donner A, Klar N. Issues in the meta-analysis of cluster randomized trials. *Statistics in Medicine* 2002;**21**:2971-80.

Dudley 2009

Dudley K, Liu X, De Han S. Chlorpromazine dose for people with schizophrenia. *Cochrane Database of Systematic Reviews* 2017, Issue 4. [DOI: [10.1002/14651858.CD007778.pub2](https://doi.org/10.1002/14651858.CD007778.pub2); CD007778]

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629-34.

Elbourne 2002

Elbourne D, Altman DG, Higgins JPT, Curtina F, Worthington HV, Vaile A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140-9.

Eslami 2015

Eslami Shahrabaki M, Sharafkhani R, Dehnavieh R, Vali L. Chlorpromazine versus piperacetazine for schizophrenia. *Cochrane Database of Systematic Reviews* 2015, Issue 6. [DOI: [10.1002/14651858.CD011709](https://doi.org/10.1002/14651858.CD011709)]

Fioravanti 2005

Fioravanti M, Carlone O, Vitale B, Cinti ME, Clare L. A meta-analysis of cognitive deficits in adults with a diagnosis of schizophrenia. *Neuropsychology Review* 2005;**15**(2):73-95. [PUBMED: 16211467]

Furukawa 2006

Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. *Journal of Clinical Epidemiology* 2006;**59**(7):7-10.

Gerlach 1975

Gerlach J, Kramp P, Kristjansen P, Lauritsen B, Lohdord K, Munkvad I. Peroral and parenteral administration of long-acting neuroleptics: a double-blind study of penfluridol compared to flupenthixol decanoate in the treatment of schizophrenia. *Acta Psychiatrica Scandinavica* 1975;**52**(2):132-44. [PUBMED: 1096541]

Gulliford 1999

Gulliford MC. Components of variance and intraclass correlations for the design of community-based surveys and intervention studies: data from the Health Survey for England 1994. *American Journal of Epidemiology* 1999;**149**:876-83.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60.

Higgins 2011

Higgins JPT, Green S, editor(s). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S, editor(s), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Higgins 2011a

Higgins JPT, Altman DG, Sterne JAC, editor(s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Hutton 2009

Hutton JL. Number needed to treat and number needed to harm are not the best way to report and assess the results of randomised clinical trials. *British Journal of Haematology* 2009;**146**(1):27-30.

Ionescu 1983

Ionescu R, Tiberiu C, Miklos R, Angelescu C, Persiceanu AM. Penfluridol in the maintenance therapy of schizophrenia. *Neurologie et Psychiatrie* 1983;**21**(1):33-41. [PUBMED: 6342112]

Janssen 1970

Janssen PA, Niemegeers CJ, Schellekens KH, Lenaerts FM, Verbruggen FJ, Van Nueten JM, et al. The pharmacology of penfluridol (R 16341) a new potent and orally long-acting neuroleptic drug. *European Journal of Pharmacology* 1970;**11**(2):139-54. [PUBMED: 5447800]

Kay 1986

Kay SR, Opler LA, Fiszbein A. Positive and Negative Syndrome Scale (PANSS) Manual. North Tonawanda, NY: Multi-Health Systems, 1986.

Leon 2006

Leon AC, Mallinckrodt CH, Chuang-Stein C, Archibald DG, Archer GE, Chartier K. Attrition in randomized controlled clinical trials: methodological issues in psychopharmacology. *Biological Psychiatry* 2006;**59**(11):1001-5. [PUBMED: 16905632]

Leucht 2005a

Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel R. Clinical implications of brief psychiatric rating scale scores. *British Journal of Psychiatry* 2005;**187**:366-71. [PUBMED: 16199797]

Leucht 2005b

Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel RR. What does the PANSS mean?. *Schizophrenia Research* 2005;**79**(2-3):231-8. [PUBMED: 15982856]

Leucht 2008

Leucht C, Kitzmantel M, Kane J, Leucht S, Chua WLLC. Haloperidol versus chlorpromazine for schizophrenia. *Cochrane Database of Systematic Reviews* 2008, Issue 1. [DOI: [10.1002/14651858.CD004278.pub2](https://doi.org/10.1002/14651858.CD004278.pub2); CD004278]

Liddle 1987

Liddle PF. The symptoms of chronic schizophrenia. A re-examination of the positive-negative dichotomy. *British Journal of Psychiatry* 1987;**151**:145-51. [PUBMED: 3690102]

Lindstrom 2000

Lindstrom E, Bingeors K. Patient compliance with drug therapy in schizophrenia. Economic and clinical issues. *PharmacoEconomics* 2000;**18**(2):106-24. [PUBMED: 11067646]

Manu 2011

Manu P, Kane JM, Correll CU. Sudden deaths in psychiatric patients. *Journal of Clinical Psychiatry* 2011;**72**(7):936-41. [PUBMED: 21672496]

Marshall 2000

Marshall M, Lockwood A, Bradley C, Adams C, Joy C, Fenton M. Unpublished rating scales: a major source of bias in randomised controlled trials of treatments for schizophrenia. *British Journal of Psychiatry* 2000;**176**:249-52.

Moher 2001

Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. *BMC Medical Research Methodology* 2001;**1**:2. [PUBMED: 11336663]

Overall 1962

Overall JE, Gorham DR. The brief psychiatric rating scale. *Psychological Reports* 1962;**10**:799-812.

Perala 2007

Perala J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsa E, Pirkola S, et al. Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Archives of General Psychiatry* 2007;**64**(1):19-28. [PUBMED: 17199051]

Rees 1960

Rees L. Chlorpromazine and allied phenothiazine derivatives. *British Medical Journal* 1960;**2**(5197):522-5. [PUBMED: 14436902]

Reynolds 1982

Reynolds JEM. Penfluridol. Martindale: The Extra Pharmacopoeia. 28th Edition. London: The Pharmaceutical Press, 1982:1550.

Saha 2013

Saha KB, Bo L, Zhao S, Xia J, Sampson S, Zaman RU. Chlorpromazine versus atypical antipsychotic drugs for schizophrenia. *Cochrane Database of Systematic Reviews* 2016, Issue 4. [DOI: [10.1002/14651858.CD010631.pub2](https://doi.org/10.1002/14651858.CD010631.pub2)]

Schünemann 2011

Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In Higgins JPT, Green S editor(s), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Soares 2006

Soares BG, Silva de Lima M. Penfluridol for schizophrenia. *Cochrane Database of Systematic Reviews* 2006, Issue 2. [DOI: [10.1002/14651858.CD002923.pub2](https://doi.org/10.1002/14651858.CD002923.pub2); PUBMED: 16625563]

Sterne 2011

Sterne JAC, Egger M, Moher D, editor(s). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Intervention*. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Ukoumunne 1999

Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ. Methods for evaluating area-wide and organisation-based intervention in health and health care: a systematic review. *Health Technology Assessment* 1999;**3**(5):1-75.

van Praag 1971

van Praag HM, Schut T, Dols L, van Schilfgaarden R. Controlled trial of penfluridol in acute psychosis. *British Medical Journal* 1971;**4**(5789):710-3. [PUBMED: 4943034]

WHO 2015

World Health Organization. 19th WHO Essential Medicines List. www.who.int/medicines/publications/essentialmedicines/en/ (accessed prior to 25 May 2017).

Xia 2009

Xia J, Adams CE, Bhagat N, Bhagat V, Bhoopathi P, El-Sayeh H, et al. Loss to outcomes stakeholder survey: the LOSS study. *Psychiatric Bulletin* 2009;**33**(7):254-7.

Zare 2015

Zare M, Bazrafshan A. Chlorpromazine versus metiapine for schizophrenia. *Cochrane Database of Systematic Reviews* 2017, Issue 3. [DOI: [10.1002/14651858.CD011655.pub2](https://doi.org/10.1002/14651858.CD011655.pub2)]

References to other published versions of this review

Khalili 2005

Khalili N, Vahedian M, Nikvarz N, Piri M. Chlorpromazine versus penfluridol for schizophrenia. *Cochrane Database of Systematic Reviews* 2015, Issue 8. [DOI: [10.1002/14651858.CD011831](https://doi.org/10.1002/14651858.CD011831)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Chouinard 1977

Methods	Allocation: randomised. Blindness: double-blind. Location: inpatient and outpatient. Duration: 13 weeks (3 weeks inpatient, 10 weeks outpatient).
Participants	Diagnosis: schizophrenia (DSM-II). N = 33. Age: 19-60 years (mean 35.7 ± 12.6). Sex: 15M and 14F* . History: 15 participants had been hospitalised for less than a year.
Interventions	1. Chlorpromazine: oral - 300 mg/day the first week, 600 mg/day second week, and 900 mg/day third week. N = 19.** 2. Penfluridol: oral - 40 mg/day the first week, 80 mg/day second week, and 120 mg/day third week. N = 14.**
Outcomes	Adverse events: general (needing antiparkinson medication, reduction in antipsychotic dose due to side effects, specific (extrapyramidal and various other effects). Leaving the study early. Unable to use - Global state: average score/change CGI (no data). Need for additional medication: not outcome prespecified in protocol. Mental state: average score/change BPRS and IMPS (no SD).
Notes	* 4 participants left early during inpatient phase-not included in follow-up analyses at 13 weeks.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Subjects were assigned to one of two evaluating psychiatrists in such a way that each psychiatrist evaluated a group that included both male and female patients, permitting the examination of a possible sex effect. Individuals in each group were randomly assigned to one of the two drug treatments, penfluridol or chlorpromazine, which were administered under double-blind conditions".
Allocation concealment (selection bias)	Unclear risk	No description regarding allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double blind-no further details reported.

Chouinard 1977 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details about blinding of outcome assessment given "Assessment of symptoms was based on clinical interviews conducted by one of the two psychiatrists, the same psychiatrist always evaluating the same group of patients".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition low and clearly described.
Selective reporting (reporting bias)	Unclear risk	All outcomes reported, but poor reporting of scale data.
Other bias	Unclear risk	Source of funding not reported.

Claghorn 1979

Methods	Allocation: randomised. Blindness: double-blind. Location: inpatient. Duration: 52 weeks.
Participants	Diagnosis: schizophrenia. N = 56. Age: mean ~37 years. Sex: 32M, 24F. History: duration ill ~10 years, duration of present episode ~8 years.
Interventions	1. Chlorpromazine: oral-maximum 380 mg/day-initially , maximum 760 mg/day thereafter; final mean 300mg/day. N = 28. 2. Penfluridol: oral- maximum 80 mg/week-initially, maximum 160 mg/week thereafter; final mean 74 mg/week. N = 28. Both groups received antiparkinsonian medication, chloral hydrate as required.
Outcomes	Adverse events: any, central nervous system, hepatic-"increased alkaline phosphatase, bilirubin, SGOT". Leaving the study early. Unable to use - Adverse events: "aberrations in physical or laboratory data" (no data reported), systems other than central nervous system (some listed but stated to be "infrequent"-no numbers), physical examination, electrocardiograms, slit lamp tests, laboratory studies, vital signs (no data). Global state: CGI (> 50% loss to follow-up). Social functioning: ESF (> 50% loss to follow-up). Mental state: BPRS (> 50% loss to follow-up).
Notes	

Risk of bias
Chlorpromazine versus penfluridol for schizophrenia (Review)

Claghorn 1979 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	..."randomly assigned in blocks of 8 or 10".
Allocation concealment (selection bias)	Unclear risk	No description regarding allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as "double blind"-placebo tablet given to penfluridol group to cover non-drug days. No further details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details about blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition high but clearly described.
Selective reporting (reporting bias)	High risk	Adverse effects mostly reported if frequent (unclear how frequent), poor reporting of scale data.
Other bias	Unclear risk	Source of funding not reported.

Wang 1982

Methods	Allocation: randomised. Blindness: double blind. Location: inpatient. Duration: 20 weeks.
Participants	Diagnosis: schizophrenia. N = 41 (double-blind phase). Age: 20-60 years. Sex: all male. History: chronic schizophrenia for at least 18 months prior to the start of the study. Excluded: all participants were stabilised on penfluridol before the trial, participants who did not complete dose titration were excluded before randomisation.
Interventions	1. Chlorpromazine: oral (150 mg/day to 1050 mg/day). N = 20. 1. Penfluridol: oral (20 mg to 140 mg once a week). N = 21.
Outcomes	Adverse events: use of antiparkinson medication, extrapyramidal. Leaving the study early. Unable to use - Global state: average score/change CGI (no SD).

Chlorpromazine versus penfluridol for schizophrenia (Review)

Wang 1982 (Continued)

Use of additional antipsychotic: not outcome prespecified in protocol.
Mental state: average score/change BPRS (no SD).
Behaviour: average score/change NOSIE (no SD).
Social functioning: average score/change ESF (no SD).

Notes

Trial had a dose titration phase where all participants stabilised on penfluridol and a double-blind phase where participants randomised to continue penfluridol or switch to chlorpromazine, we only used data from the double-blind phase.

It is indicated in the paper that there were no statistical differences in scale-derived data, and that patients on penfluridol had more akathisia than patients on chlorpromazine, but no data presented.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"When the patients were stable, they were randomly assigned to a penfluridol or a chlorpromazine group".
Allocation concealment (selection bias)	Unclear risk	No details regarding allocation concealment given.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All patients received identical appearing capsules on a special "blister pack" medication card allowing the patient to take the medication on a twice-a-day schedule".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear if outcome assessor was blind-"The rating scales for evaluating efficacy were completed by the psychiatrist investigator".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition low and clearly described.
Selective reporting (reporting bias)	Unclear risk	All outcomes reported, but poor reporting of scale data.
Other bias	Unclear risk	No further details.

BPRS-Brief Psychiatric Rating Scale

CGI-Clinical Global Impression

ESF-Evaluation of Social Functioning

IMPS: Inpatient Multidimensional Psychiatric Scale

NOSIE-Nurse's Observation Scale for Inpatient Evaluation

SD: standard deviation

SGOT: serum glutamic oxaloacetic transaminase

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bao 1988	Allocation: quasi-randomised.
Li 1987	Allocation: randomised. Participants: people with schizophrenia.

Study	Reason for exclusion
	Intervention: penfluridol versus chlorpromazine versus clozapine.
	Outcome: all data unusable data as numbers allocated to each group not reported.

DATA AND ANALYSES

Comparison 1. CHLORPROMAZINE versus PENFLURIDOL

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Service utilisation: 1. Hospital readmission	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 3.60]
1.1 short term	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 3.60]
2 Adverse effects: 1a. General - needing antiparkinsonian medication	2	74	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.51, 0.95]
2.1 short term	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.46, 1.46]
2.2 medium term	1	41	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.43, 0.91]
3 Adverse effects: 1b. General - need to reduce antipsychotic dose due to side effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 medium term	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.26, 2.06]
4 Adverse effects: 2a. Specific - extrapyramidal events (moderate or severe) - short term	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 akathisia	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 dyskinesia	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 dystonia	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.4 rigidity	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 2.90]
4.5 tremor	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Adverse effects: 2b. Specific - extrapyramidal events (moderate or severe) - medium term	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 akathisia	2	85	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.04, 1.06]
5.2 dyskinesia	2	85	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.14, 6.52]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.3 dystonia	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.06, 13.54]
5.4 muscle spasm	1	56	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 70.64]
5.5 rigidity	2	70	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.04, 1.20]
5.6 tremor	2	85	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.14, 3.43]
6 Adverse effects: 2c. Specific - anticholinergic (moderate or severe) - short term	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 constipation	1	33	Risk Ratio (M-H, Fixed, 95% CI)	4.42 [0.60, 32.71]
6.2 dry mouth	1	33	Risk Ratio (M-H, Fixed, 95% CI)	2.25 [0.10, 51.46]
6.3 increased salivation	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.01, 5.72]
7 Adverse effects: 2d. Specific - anticholinergic (moderate or severe) - medium term	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 blurred vision	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.09]
7.2 constipation	1	29	Risk Ratio (M-H, Fixed, 95% CI)	3.73 [0.47, 29.49]
7.3 dry mouth	1	29	Risk Ratio (M-H, Fixed, 95% CI)	2.81 [0.12, 63.83]
8 Adverse effects: 2e. Specific - central nervous system (moderate or severe) - short term	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 agitation	1	33	Risk Ratio (M-H, Fixed, 95% CI)	2.25 [0.10, 51.46]
8.2 drowsiness	1	33	Risk Ratio (M-H, Fixed, 95% CI)	8.25 [0.49, 137.94]
8.3 dizziness	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.12]
8.4 insomnia	1	33	Risk Ratio (M-H, Fixed, 95% CI)	2.25 [0.10, 51.46]
9 Adverse effects: 2f. Specific - central nervous system (moderate or severe) - medium term	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 drowsiness	2	85	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.54, 2.05]
9.2 dizziness	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.05, 4.60]
9.3 excitement	1	29	Risk Ratio (M-H, Fixed, 95% CI)	2.81 [0.12, 63.83]
9.4 faintness	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.15, 5.76]
9.5 insomnia	2	85	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.03, 0.93]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Adverse effects: 2g. Specific - various other effects (moderate or severe) - short term	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 heartburn	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 increased alkaline phosphatase, bilirubin, SGOT	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.85]
10.3 systemic allergic reaction	1	33	Risk Ratio (M-H, Fixed, 95% CI)	5.25 [0.29, 94.14]
11 Adverse effects: 2h. Specific - various other effects (moderate or severe) - medium term	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 depression	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 3.60]
11.2 decreased sexual drive	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.05, 4.60]
11.3 impotence	1	29	Risk Ratio (M-H, Fixed, 95% CI)	2.81 [0.12, 63.83]
11.4 photosensitivity	1	29	Risk Ratio (M-H, Fixed, 95% CI)	2.81 [0.12, 63.83]
11.5 poor appetite	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.06, 13.54]
12 Leaving the study early: 1a. Any reason	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 medium term	3	130	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.83, 1.77]
13 Leaving the study early: 1b. Due to adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 short term	1	33	Risk Ratio (M-H, Fixed, 95% CI)	6.75 [0.39, 116.00]
13.2 medium term	2	74	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.72, 3.28]

Analysis 1.1. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 1 Service utilisation: 1. Hospital readmission.

Analysis 1.2. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 2 Adverse effects: 1a. General - needing antiparkinsonian medication.

Analysis 1.3. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 3 Adverse effects: 1b. General - need to reduce antipsychotic dose due to side effects.

Analysis 1.4. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 4 Adverse effects: 2a. Specific - extrapyramidal events (moderate or severe) - short term.

Analysis 1.5. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 5 Adverse effects: 2b. Specific - extrapyramidal events (moderate or severe) - medium term.

**Analysis 1.6. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 6
Adverse effects: 2c. Specific - anticholinergic (moderate or severe) - short term.**

**Analysis 1.7. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 7
Adverse effects: 2d. Specific - anticholinergic (moderate or severe) - medium term.**

Analysis 1.8. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 8 Adverse effects: 2e. Specific - central nervous system (moderate or severe) - short term.

Analysis 1.9. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 9 Adverse effects: 2f. Specific - central nervous system (moderate or severe) - medium term.

Analysis 1.10. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 10 Adverse effects: 2g. Specific - various other effects (moderate or severe) - short term.

Analysis 1.11. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 11 Adverse effects: 2h. Specific - various other effects (moderate or severe) - medium term.

Analysis 1.12. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 12 Leaving the study early: 1a. Any reason.

Analysis 1.13. Comparison 1 CHLORPROMAZINE versus PENFLURIDOL, Outcome 13 Leaving the study early: 1b. Due to adverse events.

ADDITIONAL TABLES

Table 1. Cochrane reviews on chlorpromazine for people with schizophrenia

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

Table 2. Suggested design of study

Methods	Allocation: randomised, fully explicit description of methods of randomisation and allocation concealment. Blinding: single-blind or double-blind, but tested. Setting: anywhere. Duration: follow-up to at least 52 weeks.
Participants	Diagnosis: schizophrenia. N = 300.* Age: adults. Sex: both.

Table 2. Suggested design of study *(Continued)*

Interventions	1. Chlorpromazine: oral-maximum around 400 mg/day. N = 150. 2. Penfluridol: oral-maximum around 80 mg/week. N = 150. Both groups could receive antiparkinsonian medication as required.
Outcomes	Service utilisation: Hospital admission, time to admission. Global state: Clinically significant response in global state, relapse. Mental state: Clinically significant response in mental state. Adverse effects: Clinically significant extrapyramidal side effects, death. Leaving the study early. Functioning: Employed, days working, in supportive relationship, healthy days. Economic outcomes.
Notes	* Powered to be able to identify a difference of ~ 20% between groups for primary outcome with adequate degree of certainty.

HISTORY

Protocol first published: Issue 8, 2015

Review first published: Issue 9, 2017

Date	Event	Description
31 March 2017	Amended	Search was updated and no new results were found.

CONTRIBUTIONS OF AUTHORS

Navid Khalili: Wrote the protocol, discussed allocation of responsibility for the tasks, selection of studies, data extraction, edited the Cochrane Schizophrenia Group template for the methods section, contributed in entering data in the Review Manager (RevMan) software, substantially contributed in writing and completing the primary draft of the manuscript and read and approved the final version of the review.

Mostafa Vahedian: Discussed allocation of responsibility for the tasks, selection of studies, data extraction, edited the Cochrane Schizophrenia Group template for the methods section, contributed in entering data in RevMan substantially contributed in writing and completing the primary draft of the manuscript and read and approved the final version of the review.

Naemeh Nikvarz: Discussed allocation of responsibility for the tasks, selection of studies, data extraction, contributed in entering data in RevMan and Grade profiler software, substantially contributed in writing and completing the primary draft of the manuscript and critically revised it and read and approved the final version of the review.

DECLARATIONS OF INTEREST

NK: No conflict of interest.

MV: No conflict of interest.

NN: No conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Kerman University of Medical Sciences, Kerman, Iran.

Employs lead author Naemeh Nikvarz and review author Navid Khalili. Review author Mostafa Vahedian is a student at this university.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have reworded and regrouped the outcomes to more closely reflect the latest Cochrane Schizophrenia Group's methods template. Originally, the outcome of the adverse event/effect of death was the first outcome on our preferred 'Summary of findings' list. This seemed to strike an unfortunate, unwanted and inaccurate emphasis and for the full review we reordered outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

Akathisia, Drug-Induced [epidemiology]; Antipsychotic Agents [adverse effects] [*therapeutic use]; Chlorpromazine [adverse effects] [*therapeutic use]; Length of Stay; Penfluridol [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Schizophrenia [*drug therapy]

MeSH check words

Adult; Humans