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Chlorpromazine for psychosis induced aggression or agitation (Review)

Ahmed U, Jones H, Adams CE

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Chlorpromazine for psychosis induced aggression or agitation.
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[Intervention Review]

Chlorpromazine for psychosis induced aggression or agitation

Uzair Ahmed[1], Hannah Jones[2], Clive E Adams[3]

[1]North Yorkshire and York PCT, York, UK. [2]Academic Unit of Psychiatry, Community Based Medicine, University of Bristol, Bristol, UK. [3]Cochrane Schizophrenia Group, University of Nottingham, Nottingham, UK

Contact address: Uzair Ahmed, North Yorkshire and York PCT, System House, Clifton Moor, Amy Johnson way, York, YO30 4XT, UK. dr_uz78@yahoo.com.

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ABSTRACT

Background

Agitated or violent behaviour constitutes 10% of all emergency psychiatric treatment. Some guidelines do not recommend the use of chlorpromazine for rapid tranquillisation but it is still often used for this purpose.

Objectives

To examine the effects of oral or intramuscular chlorpromazine for psychosis induced agitation or aggression.

Search methods

We searched the Cochrane Schizophrenia Group Trials Register (up to July 2009) which is based on regular searches of CINAHL, EMBASE, MEDLINE and PsycINFO.

Selection criteria

Randomised control trials or double blind trials (implying randomisation) comparing chlorpromazine with another drug or placebo for people who are thought to be acutely aggressive or agitated due to psychotic illness.

Data collection and analysis

We extracted data independently. For dichotomous data we calculated relative risks (RR) and their 95% confidence intervals (CI) on an intention-to-treat basis based on a fixed-effects model.

Main results

One study (total n=30) met the inclusion criteria. When compared with haloperidol (Man 1973) (1 RCT, n=30) people allocated chlorpromazine were no more likely to have one additional injection than those allocated haloperidol (RR 3.00 CI 0.13 to 68.26). This remained true for 2-4 injections (RR 0.90 CI 0.52 to 1.55) and for 5 or more injections (RR 0.75 CI 0.20 to 2.79). Two people allocated chlorpromazine had sudden, serious hypotension while no one allocated haloperidol had such an effect (RR 5.00 CI 0.26 to 96.13). No extrapyramidal symptoms were observed. One person allocated chlorpromazine developed status epilepticus (RR 3.00 CI 0.13 to 68.26).

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Authors' conclusions

Overall the quality of evidence is limited, poor and dated. Where drugs that have been better evaluated are available, it may be best to avoid use of chlorpromazine. Where chlorpromazine is used for acute aggression or where choices are limited, relevant trials are possible and urgently needed.

PLAIN LANGUAGE SUMMARY

Chlorpromazine for treating aggression or agitation due to psychosis

Chlorpromazine was the first medicine specifically developed to treat psychoses as it helps people to feel less anxious, tense or angry. This review systematically examines the evidence to see how effective chlorpromazine is at reducing aggression or agitation due to psychosis. From the evidence available, we are unable to draw any firm conclusion about using this medicine for this purpose. We found that chlorpromazine was just as effective at reducing aggression or agitation due to psychosis as similar medicines, but that it may be associated with more side effects than other medicines. Further research is needed to clarify whether chlorpromazine is effective at reducing psychosis induced aggression or agitation. Such research would be best carried out using carefully designed clinical trials.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

CHLORPROMAZINE compared to HALOPERIDOL for psychosis induced aggression or agitation

Patient or population: patients with psychosis induced aggression or agitation
Settings: in hospitals of over 30 years ago
Intervention: CHLORPROMAZINE
Comparison: HALOPERIDOL

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	HALOPERIDOL	CHLORPROMAZINE				
Global outcome: Number of additional injections - 2-4 injections	Study population		RR 0.9 (0.52 to 1.55)	30 (1 study)	⊕◯◯◯ very low[1,2]	
	667 per 1000	600 per 1000 (347 to 1000)				
	Medium risk population					
	667 per 1000	600 per 1000 (347 to 1000)				
Global outcome: Number of additional injections - 5 or more	Study population		RR 0.75 (0.2 to 2.79)	30 (1 study)	⊕◯◯◯ very low[1,2]	
	267 per 1000	200 per 1000 (53 to 745)				
	Medium risk population					
	267 per 1000	200 per 1000 (53 to 745)				
Adverse effects - cardio-vascular - hypotension	Study population		RR 5 (0.26 to 96.13)	30 (1 study)	⊕◯◯◯ very low[1,2]	Serious adverse event

	0 per 1000	**0 per 1000** (0 to 0)				
	Medium risk population					
	0 per 1000	**0 per 1000** (0 to 0)				
Adverse effects - movement disorders - extrapyramidal side effects	See comment	See comment	Not estimable	30 (1 study)	See comment	No events[3]
Adverse effects - seizures	**Study population**		**RR 3** (0.13 to 68.26)	30 (1 study)	⊕○○○ **very low**[1,2]	
	0 per 1000	**0 per 1000** (0 to 0)				
	Medium risk population					
	0 per 1000	**0 per 1000** (0 to 0)				
Leaving the study early	**Study population**		**RR 2** (0.2 to 19.78)	30 (1 study)	⊕○○○ **very low**[1,2]	
	67 per 1000	**134 per 1000** (13 to 1000)				
	Medium risk population					
	67 per 1000	**134 per 1000** (13 to 1000)				

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

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

[1] Randomisation not well described, blindness unlikely, selective reporting
[2] Small study
[3] Unusual not to experience any such effects, even in short term

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BACKGROUND

Description of the condition

Agitated or violent behaviour constitutes 10% of all emergency psychiatric treatment (Tardiff 1982). Overall, the prevalence of violence in people who have schizophrenia, major depression or manic/bipolar disorder is about 11 to 13%. An even higher percentage of people with alcoholism (25%) or substance misuse (35%) have, at some stage, presented with violence or aggression. Even when additional factors such as alcohol and drug use are taken into account, psychotic symptoms such as delusions or hallucinations are significantly and strongly associated with aggressive and violent behaviour (Swanson 1990).

Description of the intervention

In 1952, the discovery of the antipsychotic properties of chlorpromazine was termed as a "psychopharmacological revolution" for the practice of modern psychiatry (Lopez-Munez 2005, Turner 2007). Although the newer generation of antipsychotic drugs has, to a certain extent, taken its place, chlorpromazine is still in worldwide use. We found one relevant survey of clinicians' preferences for drug management of the acutely aggressive situation and chlorpromazine was the favoured drug of clinicians in Oxford, UK in 1994 (Cunnane 1994). UK guidelines do not recommend the use of chlorpromazine for rapid tranquillisation because it is a local irritant if given intramuscularly and, based on cohort and case control studies, there is said to be a risk of cardiovascular complications, in particular hypotension, especially in the doses required for rapid tranquillisation (NICE 2005). Despite this, chlorpromazine is still widely used because of its marked sedating effect and its ability to treat violent patients without causing stupor (BNF 2008). In many situations chlorpromazine may be the only choice available. Chlorpromazine remains one of three antipsychotic drugs on the World Health Organisation's Essential Medicine list .This list comprises of medication for the basic health care system, all of which must be designated safe, effective and cost effective for priority conditions (WHO 2007).

How the intervention might work

The discovery of neuroleptic drugs in 1952 provided a new strategy for seeking a biological basis of schizophrenia (Seaman 2004). Chlorpromazine is in the phenothiazine family of compounds and may work by its ability to block dopaminergic receptor in limbic forebrain. Beside this action it also blocks to different degrees adrenergic, dopamine reuptake, histaminic, muscarinic and serotonergic receptors (Kalyana 2006). It may be the antihistaminic effects that cause the sedation associated with use of chlorpromazine.

Chlorpromazine is mainly indicated for schizophrenia or other psychosis, mania, short-term adjunctive management of severe anxiety, psychomotor agitation, excitement and violent or dangerously impulsive behaviour (BNF 2008). Time to peak plasma levels is approximately three hours (oral) (Bazier 2007), either 15 to 30 minutes (Keltner 2001) or one to four hours (I/M) (Bazier 2007) (texts differ), and either ten minutes (Keltner 2001) or two to four hours (I/V) (Bazier 2007) (texts differ). Chlorpromazine and its metabolites are mainly excreted from body in urine with elimination half-life is approximately 16 to 30 hours (Kalyana 2006).

Why it is important to do this review

Mental health problems impose a significant burden in developing countries (Shah 2000). As about 1% of any population suffers from schizophrenia (Sartorius 1972) and around 80% of the world live in developing countries (CIA 2008), most care of people with serious mental illnesses such as schizophrenia must take place in these low and middle income country situations. There is no evidence that the prevalence of psychiatric emergencies differ across the globe and it seems reasonable to assume that most episodes of severe aggression and agitation in people with severe mental health problems will be taking place in the low and middle income countries. In many of these countries expensive antipsychotic drugs may be available, but they are generally not affordable (WPA 2003). Even in high income countries older and inexpensive managements, such as chlorpromazine, may be favoured (Cunnane 1994). In 2003, chlorpromazine was the most frequently prescribed of the first generation antipsychotic drug in the UK, at a time when the older group of antipsychotics accounted for 44% of all antipsychotic prescriptions (NHS 2008). We, however, know of no systematic reviews of the use of chlorpromazine in the emergency situation. This is one of a series of linked reviews (Table 1).

OBJECTIVES

To examine whether chlorpromazine oral or intramuscular is an effective treatment for psychosis induced agitation or aggression.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised control trials. We excluded quasi-randomised trials, such as those where allocation is undertaken on

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surname. If a trial was described as double blind, but it was implied it had been randomised, we included these trials in a sensitivity analysis. Randomised cross-over studies were eligible but only data up to the point of first cross-over were included because of the instability of the problem behaviours and the likely carryover effects of all treatments.

Types of participants

People currently within an aggressive episode thought to be due to psychotic illness. Should studies also have involved people with other diagnoses, such as drug or alcohol intoxication, organic problems including dementia, non-psychotic mental illnesses or learning disabilities, we included these as long as the proportion of the other groups do not exceed that for psychotic people.

Types of interventions

1. Chlorpromazine alone: given orally or intramuscular any dose compared with:
a. Other antipsychotic given orally or intramuscularly: any dose.
b. Benzodiazepine alone given orally or intramuscularly: any dose.
c. Anticonvulsant alone given orally or intramuscularly: any dose.
d. Placebo or no intervention.
2. Chlorpromazine: in combination with other drugs compared with:
a. Other intervention, or placebo or no intervention.

Types of outcome measures

All outcomes grouped by time: by 30 minutes, up to two hours, up to four hours, up to 24 hours and finally over 24 hours.

Primary outcomes

Not tranquil or asleep by up to 30 minutes (intramuscular - IM) or 60 minutes (orally)

Secondary outcomes

1. Tranquillisation or asleep
1.1 Not tranquil
1.2 Not asleep
1.3 Time to tranquillisation / sleep
1.4 Time to tranquillisation
1.5 Time to sleep
2. Death
3. Specific behaviours
3.1 Self-harm, including suicide
3.2 Injury to others
3.3 Aggression
3.3.1 Another episode of aggression by 24 hours
3.3.2 No clinically important change in aggression
3.3.3 No change in aggression
3.3.4 Average endpoint aggression score
3.3.5 Average change in aggression scores
4. Global outcomes
4.1 No overall improvement
4.2 Use of additional medication
4.3 Use of restraints/seclusion
4.4 Relapse - as defined by each study
4.5 Recurrence of violent incidents
4.6 Needing extra visits from the doctor
4.7 Refusing oral medication
4.8 Not accepting treatment
4.9 Average endpoint score
4.10 Average change score
4.11 Average dose of drug
5. Service outcomes
5.1 Duration of hospital stay
5.2 Re-admission
5.3 No clinically important engagement with services
5.4 No engagement with services
5.5 Average endpoint engagement score
5.6 Average change in engagement scores
6. Mental state
6.1 No clinically important change in general mental state
6.2 No change in general mental state
6.3 Average endpoint general mental state score
6.4 Average change in general mental state scores
7. Adverse effects
7.1 Clinically important general adverse effects
7.2 Any general adverse effects
7.3 Any serious, specific adverse effects
7.4 Average endpoint general adverse effect score
7.5 Average change in general adverse effect scores
7.6 No clinically important change in specific adverse effects
7.7 No change in specific adverse effects
7.8 Average endpoint specific adverse effects
7.9 Average change in specific adverse effects
8. Leaving the study early
8.1 For specific reasons
8.2 For general reasons
9. Satisfaction with treatment
9.1 Recipient of treatment not satisfied with treatment
9.2 Recipient of treatment average satisfaction score
9.3 Recipient of treatment average change in satisfaction scores
9.4 Informal treatment provider not satisfied with treatment
9.5 Informal treatment providers' average satisfaction score
9.6 Informal treatment providers' average change in satisfaction scores
9.7 Professional providers not satisfied with treatment
9.8 Professional providers' average satisfaction score
9.9 Professional providers' average change in satisfaction scores
10. Acceptance of treatment
10.1 Not accepting treatment

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10.2 Average endpoint acceptance score
10.3 Average change in acceptance scores
11. Quality of life
11.1 No clinically important change in quality of life
11.2 Not any change in quality of life
11.3 Average endpoint quality of life score
11.4 Average change in quality of life scores
11.5 No clinically important change in specific aspects of quality of life
11.6 No change in specific aspects of quality of life
11.7 Average endpoint specific aspects of quality of life
11.8 Average change in specific aspects of quality of life
12. Economic outcomes
12.1 Direct costs
12.2 Indirect costs

Search methods for identification of studies

Electronic searches

We searched the Cochrane Schizophrenia Group Trials Register (up to July 2009) using the phrase:
[((*anadep* or *chlora* or *chlorprom* or *(chlor p-z)* or *chromeda* or *cpz* or *elmarine* or *esmind* or *fenactil* or *hibanil* or *hibernal* or *klorazin* or *klorpro* or *largactil* or *megaphen* or *neurazin* or *plegomaz* or *procalm* or *proma* or *promexin* or *promosol* or *prozil* or *psychozin* or *psylactil* or *serazon* or *sonazin* or *thoradex* or *tranzine*) and (*aggress* or *violen* or *agitation* or *tranq*)) in title, abstract, index terms of REFERENCE]
This register is compiled by systematic searches of major databases, hand searches and conference proceedings (see Group Module).

Searching other resources

We also searched reference lists of included and excluded studies for additional relevant trials.

Data collection and analysis

Selection of studies

Authors UA, HJ and MG independently inspected citations identified from the searches. We identified 16 potentially relevant reports and discussed these with CEA. We then ordered 12 full papers for assessment.

Data extraction and management

1. Extraction
Authors UA and HJ independently extracted data from included studies. Again, any disagreement was discussed, decisions documented and, if necessary, authors of studies were contacted for clarification. With remaining problems CEA helped clarify issues and those final decisions were documented.
2. Management
Data were extracted onto standard, simple forms.
3. Scale-derived data
We included continuous data from rating scales only if the measuring instrument had been described in a peer-reviewed journal (Marshall 2000) and the instrument is either a self-report or completed by an independent rater or relative (not the therapist).

Assessment of risk of bias in included studies

Again working independently, UA and HJ assessed risk of bias using the tool described in the Cochrane Collaboration Handbook (Higgins 2008). This tool encourages consideration of how the sequence was generated, how allocation was concealed, the integrity of blinding at outcome, the completeness of outcome data, selective reporting and other biases. We would not have included studies where sequence generation was at high risk of bias or where allocation was clearly not concealed.
If disputes arose as to which category a trial has to be allocated, again, resolution was made by discussion, after working with the third reviewer (CEA).

Measures of treatment effect

1. Binary data
For binary outcomes we calculated a standard estimation of the fixed-effect risk ratio (RR) and its 95% confidence interval (CI). For statistically significant results we calculated the number needed to treat/harm statistic (NNT/H), and its 95% confidence interval (CI) using Visual Rx (http://www.nntonline.net/) taking account of the event rate in the control group.
2. Continuous data
2.1 Summary statistic
For continuous outcomes we estimated a fixed-effect weighted mean difference (WMD) between groups. We did not calculate effect size measures.
2.2 Endpoint versus change data
We preferred to use scale endpoint data, which typically cannot have negative values and is easier to interpret from a clinical point of view. Change data are often not ordinal and are very problematic to interpret. If endpoint data were unavailable, we used change data.
2.3 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 aim to apply the following standards

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

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, confidence intervals unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997, Gulliford 1999).

Where clustering is not accounted for in primary studies, we 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 intraclass correlation co-efficient of their clustered data and to adjust for this by using accepted methods (Gulliford 1999). Where clustering had been incorporated into the analysis of primary studies, we present these data as if from a non-cluster randomised study, but adjusted for the clustering effect.

We have sought statistical advice and have been advised that the binary data as presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the intraclass correlation co-efficient (ICC) [Design effect = 1+(m-1)*ICC] (Donner 2002). If the ICC was not reported it was assumed to be 0.1 (Ukoumunne 1999).

If cluster studies has been appropriately analysed taking into account intraclass correlation co-efficient and relevant data documented in the report, synthesis with other studies would have been possible using the generic inverse variance technique.

2. Cross-over trials

A major concern of cross-over trials is the carryover 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 schizophrenia, we will only use data of the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involved more than two treatment arms, if relevant, the additional treatment arms were presented in comparisons. Where the additional treatment arms were not relevant, these data were not reproduced.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow up data must lose credibility. We are forced to make a judgment where this is for the very short-term trials likely to be included in this review. Should more than 40% of data be unaccounted for by 24 hours we did not reproduce these data or use them within analyses.

2. Binary

In the case where attrition for a binary outcome is between 0 and 40% and outcomes of these people are described, we included these data as reported. Where these data were not clearly described, we assumed the worst primary outcome, and rates of adverse effects similar to those who did continue to have their data recorded.

3. Continuous

In the case where attrition for a continuous outcome is between 0 and 40% and completer-only data were reported, we have reproduced these.

Assessment of heterogeneity

1. Clinical heterogeneity

We considered all included studies without any comparison to judge clinical heterogeneity.

2. Statistical

2.1 Visual inspection

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

2.2 Employing the I-squared statistic

This provided an estimate of the percentage of inconsistency thought to be due to chance. I-squared estimate greater than or equal to 50% was interpreted as evidence of high levels of heterogeneity (Higgins 2002).

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 (Higgins 2008). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect

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small-study effects. We did not use funnel plots for outcomes where there were ten or fewer studies, or where all studies were of similar sizes. In other cases, where funnel plots were possible, we sought statistical advice in their interpretation.

Data synthesis

Where possible we employed a fixed-effect model for analyses. We understand that there is no closed argument for preference for use of fixed or random-effect models. The random-effect method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This does seem true to us, however, random-effect does put added weight onto the smaller of the studies - those trials that are most vulnerable to bias. For this reason we favour using fixed-effect models employing random-effect only when investigating heterogeneity.

Subgroup analysis and investigation of heterogeneity

If data are clearly heterogeneous we checked that data are correctly extracted and entered and that we had made no unit-of-analysis errors. If the high levels of heterogeneity remained we did not undertake a meta-analysis at this point for if there is considerable variation in results, and particularly if there is inconsistency in the direction of effect, it may be misleading to quote an average value for the intervention effect. We would have wanted to explore heterogeneity. We pre-specify no characteristics of studies that may be associated with heterogeneity except quality of trial method. If no clear association could be shown by sorting studies by quality of methods a random-effect meta-analysis was performed. Should another characteristic of the studies be highlighted by the investigation of heterogeneity, perhaps some clinical heterogeneity not hitherto predicted but plausible causes of heterogeneity, these post-hoc reasons will be discussed and the data analysed and presented. However, should the heterogeneity be substantially unaffected by use of random-effect meta-analysis and no other reasons for the heterogeneity be clear, the final data were presented without a meta-analysis.

Sensitivity analysis

If necessary, we analysed the effect of including studies with high attrition rates in a sensitivity analysis. We aimed to include trials in a sensitivity analysis if they are described as 'double-blind' but only implied randomisation. If we found no substantive differences within primary outcome when these high attrition and 'implied randomisation' studies were added to the overall results, we included them in the final analysis. However, if there was a substantive difference we only used clearly randomised trials and those with attrition lower than 50%.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

For substantive descriptions of studies please see the Characteristics of included studies and Characteristics of excluded studies.

Results of the search

The searches (original: June 2008; update: July 2009) yielded 118 references of potentially eligible studies. After checking titles and abstracts, 12 full text papers were obtained for a second assessment. After exclusion of eleven papers not meeting inclusion criteria (because of mainly non-randomised design, wrong investigational compounds or wrong population), one study was included in the present review (Man 1973).

Included studies

Details of the study that met the inclusion criteria (Man 1973) are provided in the Characteristics of included studies table.

1. Length of studies

The duration of the study was 3 days.

2. Participants

2.1 Clinical state

Participants presented with "acute psychotic symptoms or acute exacerbations of chronic illness" requiring rapid parenteral medication or were "agitated, assaultive psychotics".

2.2 Diagnosis

Participants had diagnoses of "manic-depression psychosis, manic type and acute uncontrollable schizophrenia of various types".

2.3. Exclusions

Exclusion criteria included people with acute or chronic brain syndromes, epilepsy, neuroses, drug addiction or personality disorders.

2.4 Age

Participants ranged from 18-56 years.

2.5 Sex

There were 15 male and 15 female participants.

3. Study size

30 participants were initially randomised, 27 participants completed the study.

4. Interventions

Intramuscular chlorpromazine was compared against intramuscular haloperidol.

5. Dosing

5.1 Chlorpromazine: 50mg intramuscular at 30 minutes interval until optimal levels reached.

5.2 Haloperidol: dose 5mg intramuscular at 30 minutes interval until optimal levels reached.

6. Leaving the study early

Two people allocated to chlorpromazine were removed from the study following severe hypotension. Both had received chlorpro-

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mazine during a prior admission and the trialists suggested that participants had been sensitised by chlorpromazine, hence the subsequent administration of chlorpromazine was described as an almost fatal hypotensive episode. These people, had they not been in a trial, and therefore having their blood pressure taken frequently, may have died. One person in the haloperidol arm was removed as they received medication not in agreement with the protocol.

7. Outcomes

Symptom scales for assessing treatment effects were used. Data obtained from these scales, however, were not useable. Reasons for exclusions of scale and other data are given under 'outcomes' in the Characteristics of included studies table. The outcomes that did have useable data for this review are listed below:

- Global state: number of injections
- Adverse effects: blood pressure, extrapyramidal effects, local irritation
- Leaving the study early

Excluded studies

Eleven studies did not meet all the inclusion criteria. Eight were excluded because it became clear that participants had not had an aggressive episode thought to be due to psychotic illness (Abse 1960, Claghorn 1967, Hanlon 1965, Schiele 1961, Somerville 1960, Talbot 1964, Van Wyk 1971, Wadzisz 1969). Two were excluded because participants were not randomised (Herrera 1988, Chen 2004). One study (Stabenau 1964) was excluded because outcomes did not focus on rapid tranquillisation. This was an unusual study in that people were aggressive at the point of randomisation but data were not recorded for the effects of the interventions (chlorpromazine vs thioridazine) for the very short term. Stabenau 1964 therefore did not fit with the focus of this review. Chen 2004 was close to being included in this review but was excluded on the basis that it was quasi-randomised. Chen 2004 compared chlorpromazine venoclysis (50-200mg until optimal levels reached, n=90) with haloperidol venoclysis (10-20mg until optimal levels reached, n=90) for people with schizophrenia and acute agitation for one week. There was no significant difference in overall 'improvement' between groups (6/90 did not improve on haloperidol, 9/90 did not improve on chlorpromazine). There were, however, many adverse effects experienced by people taking both medications. Five people taking chlorpromazine died while no participants taking haloperidol died.

1. Awaiting classification

No studies were classified as awaiting assessment.

2. Ongoing

No studies were classified as ongoing.

Risk of bias in included studies

Overall, we judge the risk of bias for the included study to be high and therefore it is likely that these studies over estimated any true positive effects and under estimated any negative effects, see (Figure 1).

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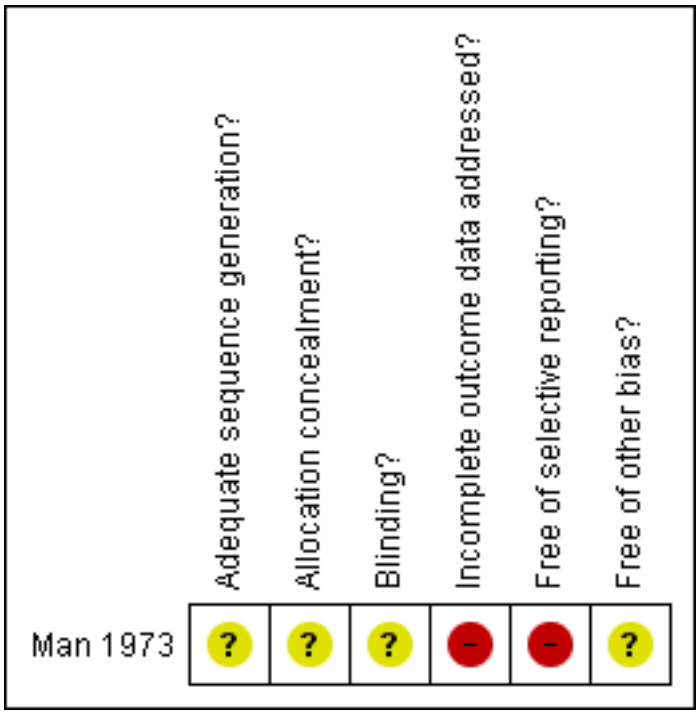
Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

The method of randomisation was not explicit and no other information was given on how randomisation and allocation concealment were undertaken.

Blinding

The study was conducted under double blind conditions but no details were given on how the process of blinding was accomplished.

Incomplete outcome data

A high risk of bias was found. Only participants who completed the study were included in the analyses there was no intention to treat analysis. The study also failed to report data for all outcomes for every participant; the number of participants described in the text is inconsistent with the number reported in tables.

Selective reporting

The study appears to have reported on all the measures they set out to use in as far as can be discerned from the published reports. We did not have access to the original protocols.

Other potential sources of bias

It is not clear how the study was funded.

Effects of interventions

See: **Summary of findings for the main comparison** CHLORPROMAZINE compared to HALOPERIDOL for psychosis induced aggression or agitation

CHLORPROMAZINE versus HALOPERIDOL

We identified one relevant small (n=30) study (Man 1973).

2.1 Global outcomes - number of additional injections

People allocated chlorpromazine were no more likely to have one additional injection than those allocated haloperidol (RR 3.00 CI 0.13 to 68.26). This remained true for 2-4 injections (RR 0.90 CI 0.52 to 1.55) and for 5 or more injections (RR 0.75 CI 0.20 to 2.79, Analysis 1.1).

2.2 Adverse effects

2.2.1 Cardiovascular - hypotension

Two people allocated chlorpromazine had sudden, near fatal episodes of hypotension while no one allocated haloperidol had such an effect. With few events in this small trial, confidence intervals were wide and the difference did not reach conventional levels of statistical significance (RR 5.00 CI 0.26 to 96.13, Analysis 1.2).

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2.2.2 Movement disorders - extrapyramidal adverse effects
Not estimable. No extrapyramidal symptoms were observed in any of the participants receiving haloperidol or chlorpromazine.
2.2.3 Seizures
One person allocated chlorpromazine developed status epilepticus which was controlled. People allocated chlorpromazine were not statistically significantly more likely to experience seizures than those allocated haloperidol (RR 3.00 CI 0.13 to 68.26, Analysis 1.2).
2.2.4 Local irritation
Not estimable. No local irritation was observed in participants allocated chlorpromazine or haloperidol.
2.3 Leaving the study early
People allocated chlorpromazine were no more likely to leave the study early than those allocated haloperidol (RR 2.00 CI 0.20 to 19.78, Analysis 1.3).

DISCUSSION

Summary of main results

CHLORPROMAZINE versus HALOPERIODOL
This study compared parental haloperidol with chlorpromazine in acutely psychotic people exhibiting severe agitation and hostility.
2.1 Global outcome
With the limited data available we found no difference between chlorpromazine and haloperidol for global outcomes of number of additional injections, or number of participants leaving the study early.
2.2 Adverse effects
We found no significant difference for extrapyramidal effects or local irritation at the site of injections. It is surprising that, despite the high incidence of extrapyramidal effects reported with the use of haloperidol (BNF 2008), this review found no extrapyramidal symptoms for people receiving either haloperidol or chlorpromazine whereas another review found movement disorders were significantly more frequent for those allocated haloperidol compared with people on longer term chlorpromazine (Leucht 2008). We are not clear why this should be so.
Two people allocated chlorpromazine suffered almost fatal hypotensive episodes and one developed status epilepticus. Haloperidol, therefore, does appear to be a safer drug but this impression is based on a single study which randomised just 30 people. There is, at the very least, a suggestion that whilst using parental chlorpromazine, there does need to be caution and people given this treatment do require close monitoring of blood pressure.

Overall completeness and applicability of evidence

1. Completeness
There was a very small sample size (15 people per arm). It is possible that we did not identify other small studies. Furthermore, method and data were reported with insufficient clarity to allow extraction of really reliable information. It would also be expected that there would be some movement disorder adverse effects from the use of haloperidol as another review has found this result (Leucht 2008), but none at all in the study relevant to this review (Man 1973). This study was undertaken over 35 years ago and is, therefore, being judged against the clinical trials standards of today (CONSORT) but, nevertheless, the reality is that incompleteness of data reporting seems likely.
2. Applicability
The study was undertaken in people who were not very clearly diagnosed, in an urgent situation in an old-fashioned hospital settings, with older drugs. Chlorpromazine and haloperidol are still used today (WHO Essential Drug List 2009). It is also common that the clinical situation precludes clear diagnoses at the time of administration and often people are in hospital when given these treatments. If the study had been methodologically stronger, and study size larger, despite being undertaken decades ago, treatment practice has not moved on so much as to make their findings inapplicable.

Quality of the evidence

This systematic review did not find any data from randomised controlled trials of sufficient methodological rigour or reported with sufficient quality to really assess the clinical effects of chlorpromazine in managing psychosis induced by agitation or aggression. Overall the trial was small and provided no information about core issues to assess study quality (such as randomisation, allocation concealment, blinding and completeness of outcome data). The extent to which a Cochrane review can draw conclusions about the effects of an intervention depends on whether the data and results from the included studies are valid. In particular, invalid studies may produce misleading results (Higgins 2008).

Potential biases in the review process

We are not aware of biases in the review process. We may have failed to identify small studies because of a degree of publishing bias (Egger 1997) operating in this review but do not think we would have not found large relevant studies. We did not contact authors of the included trials as they were completed over 35 years ago.

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Agreements and disagreements with other studies or reviews

We know of no other systematic review for the use of chlorpromazine for treating psychosis induced aggression or agitation.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia

Some clinical guidelines do not recommend the use of chlorpromazine, and, although this review has not found definitive evidence that chlorpromazine is any better or worse than haloperidol, there are some suggestions that adverse effects of chlorpromazine are potentially dangerous. There are no comparisons with any other drugs or techniques. The studies that do exist are pioneering but small and not very informative. People with schizophrenia may not have any opportunity to object to the use of chlorpromazine in the emergency situation. It would seem reasonable that in any advanced directive that a person could request to be given treatment with better evidence to support its use or to enter a study that will generate good quality evidence.

2. For clinicians

It is surprising how few studies have investigated the use of chlorpromazine for treating psychosis-induced aggression or agitation. The relevant study was performed over 35 years ago. The poor quality of the study precludes clear guidance. Where choices are limited chlorpromazine may be the only treatment available. If used, what few data there are suggest that, at the very least, close monitoring of blood pressure is indicated.

3. For policy makers

We are not convinced that the data in this review, and those from other similar reviews (Table 1) is strong enough for those compiling guidance to advice against using chlorpromazine. Data across many of these reviews is poor and dated. In situations where chlorpromazine is still used it could be justified to undertake treatment within a well designed study. Such studies need not be expensive and can be highly informative.

Implications for research

1. General

The included study we found was performed over 35 years ago. The studies of today are usually reported in more detail, thanks to the CONSORT statement (Consolidated Standards of Reporting Trials; CONSORT; Moher 2001). This is intended to improve reporting of randomised controlled trials, enabling readers to understand the design, conduct, analysis and interpretation, and to assess the validity of results. CONSORT emphasises that this can only be achieved through complete transparency from authors.

2. Specific

Large simple well-designed randomised trials are needed and are possible even in circumstances of routine care in grossly under funded clinical situations (Alexander 2004; Huf 2007; Raveendran 2007; TREC 2003). Large pragmatic randomised trials that measure simple outcomes such as 'tranquil', 'asleep', 'serious adverse effect', 'needing additional medication', 'further aggressive episodes' are required. See Table 2 for a suggested design for a study.

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

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Man 1973

Methods	Allocation: randomly assigned. Blindness: double. Duration: 3 days.
Participants	Diagnosis: manic-depression psychosis, acute schizophrenia. N=30. Age: range 18-56 years. Sex: 15 men, 15 women. History: acutely psychotic, exhibiting severe agitation, hostility, and mania. Excluded: epilepsy, neurosis, drug addiction, acute or chronic brain syndromes, personality disorders
Interventions	1. Chlorpromazine: dose 50mg intramuscular at 30 minutes interval until optimal levels reached. N=15. 2. Haloperidol: dose 5mg intramuscular at 30 minutes interval until optimal levels reached. N=15
Outcomes	Global state: number of additional injections. Adverse effects: blood pressure, extrapyramidal effects, local irritation. Leaving the study early. Unable to use - Mental state: BPRS (mean, no SD), Target Symptom Rating Scale (mean, no SD), number of injections (combined total BPRS and target symptom profile (mean, no SD)
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "conducted under double-blind conditions, each participant received either 5mg IM haloperidol or 50mg IM chlorpromazine" (p60) Implication of randomisation, not explicit. Did not describe the process of randomisation.
Allocation concealment?	Unclear	Implication of concealment but not explicit.
Blinding? All outcomes	Unclear	Quote: "conducted under double-blind conditions..." not tested

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Man 1973 (*Continued*)

Incomplete outcome data addressed? All outcomes	No	Those leaving early not included in analyses. Some measures were not completed for every person, number of participants described in text is inconsistent with number reported in tables One person (haloperidol group) excluded due to receiving medication at 6-hour intervals which was not in agreement with study protocol, 2 people (chlorpromazine group) excluded because they developed severe hypotensive reactions. Number in analysis = 27 (13 chlorpromazine, 14 haloperidol)
Free of selective reporting?	No	Outcomes listed in available paper are reported. Binary data clearly reported and usable, continuous data reported as mean without variance
Free of other bias?	Unclear	No clear interested funding.

BPRS - Brief Psychiatric Rating Scale
MACL - Mood Adjective Check List
MSCL -The Mental State Check List
WPRS - The Wittenborn Psychiatric Rating Scale

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

Study	Reason for exclusion
Abse 1960	Study 1 Allocation: randomised. Participants: people with schizophrenia, did not have psychosis-induced aggression or agitation. Interventions: reserpine versus powdered opium versus placebo Study 2 Allocation: randomised. Participants: people with schizophrenia, did not have psychosis-induced aggression or agitation. Interventions: chlorpromazine versus powdered opium versus placebo Results of two studies are added and placebo groups are reported as one, so no useable data
Chen 2004	Allocation: received medication according to order of family name, quasi-randomised

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(*Continued*)

Claghorn 1967	Allocation: randomised. Participants: men with schizophrenia, did not have psychosis induced aggression or agitation
Hanlon 1965	Allocation: randomised. Participants: people with schizophrenia, psychotic episode, neurosis and personality disorder, did not have psychosis induced aggression or agitation
Herrera 1988	Allocation: quasi randomised.
Schiele 1961	Allocation: randomised. Participants: men with chronic schizophrenia, did not have psychosis-induced aggression or agitation
Somerville 1960	Allocation: randomised. Participants: women with chronic schizophrenia, paraphrenic psychosis and manic depression, did not have psychosis induced aggression or agitation
Stabenau 1964	Allocation: randomised. Participants: those who were acutely ill with uncontrolled aggressive behaviour, severe anxiety, hyperactivity, schizophrenic thought disorder or delusional and hallucinatory states. Interventions: chlorpromazine versus thioridazine. Outcomes: none focused on rapid tranquillisation - long term follow up of people who had presented aggressive
Talbot 1964	Allocation: randomised. Participants: men with chronic schizophrenia, did not have psychosis induced aggression or agitation
Van Wyk 1971	Allocation: randomised. Participants: people with psychotic episode, did not have psychosis induced aggression or agitation
Wadzisz 1969	Allocation: randomised. Participants: women with schizophrenia, manic depressive psychosis and puerperal psychosis, did not have psychosis induced aggression or agitation

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DATA AND ANALYSES

Comparison 1. CHLORPROMAZINE vs HALOPERIDOL

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global outcome: number of additional injections	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 One additional injection	1	30	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 68.26]
1.2 Two - four injections	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.9 [0.52, 1.55]
1.3 Five or more injections	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.20, 2.79]
2 Adverse effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Cardiovascular - hypotension	1	30	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.26, 96.13]
2.2 Movement disorders - extrapyramidal adverse effects	1	30	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3 Seizures	1	30	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 68.26]
2.4 Local irritation	1	30	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Leaving the study early	1	30	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.20, 19.78]

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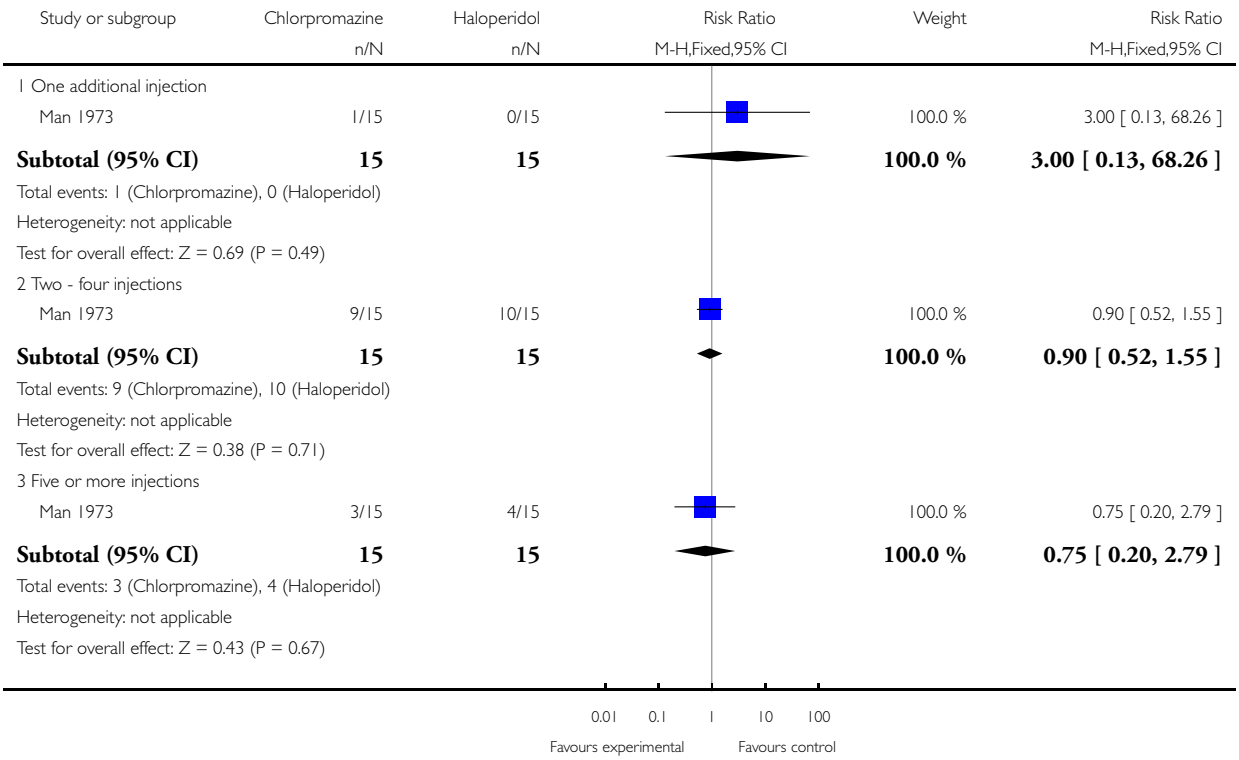
Analysis 1.1. Comparison 1 CHLORPROMAZINE vs HALOPERIDOL, Outcome 1 Global outcome: number of additional injections.

Review: Chlorpromazine for psychosis induced aggression or agitation

Comparison: 1 CHLORPROMAZINE vs HALOPERIDOL

Outcome: 1 Global outcome: number of additional injections



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Analysis 1.2. Comparison 1 CHLORPROMAZINE vs HALOPERIDOL, Outcome 2 Adverse effects.

Review: Chlorpromazine for psychosis induced aggression or agitation

Comparison: 1 CHLORPROMAZINE vs HALOPERIDOL

Outcome: 2 Adverse effects

Study or subgroup	Chlorpromazine n/N	Haloperidol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Cardiovascular - hypotension					
Man 1973	2/15	0/15		100.0 %	5.00 [0.26, 96.13]
Subtotal (95% CI)	**15**	**15**		**100.0 %**	**5.00 [0.26, 96.13]**
Total events: 2 (Chlorpromazine), 0 (Haloperidol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.07 (P = 0.29)					
2 Movement disorders - extrapyramidal adverse effects					
Man 1973	0/15	0/15			Not estimable
Subtotal (95% CI)	**15**	**15**			**Not estimable**
Total events: 0 (Chlorpromazine), 0 (Haloperidol)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Seizures					
Man 1973	1/15	0/15		100.0 %	3.00 [0.13, 68.26]
Subtotal (95% CI)	**15**	**15**		**100.0 %**	**3.00 [0.13, 68.26]**
Total events: 1 (Chlorpromazine), 0 (Haloperidol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
4 Local irritation					
Man 1973	0/15	0/15			Not estimable
Subtotal (95% CI)	**15**	**15**			**Not estimable**
Total events: 0 (Chlorpromazine), 0 (Haloperidol)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

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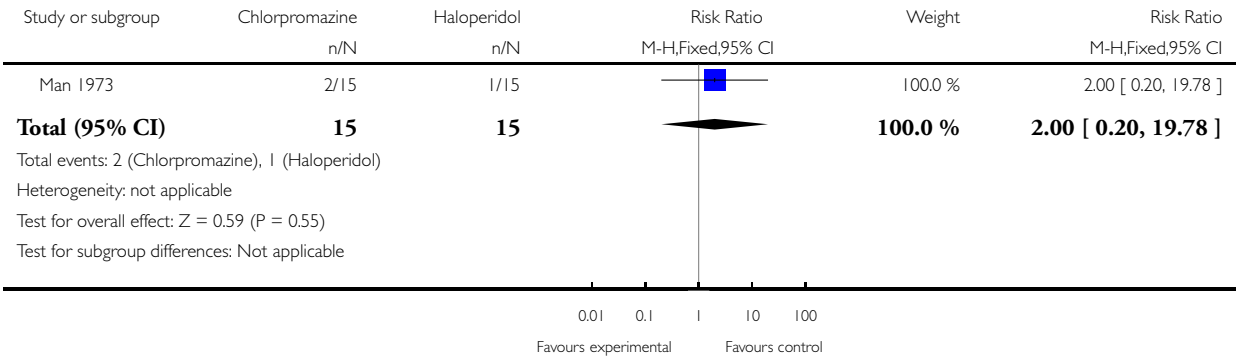
Analysis 1.3. Comparison 1 CHLORPROMAZINE vs HALOPERIDOL, Outcome 3 Leaving the study early.

Review: Chlorpromazine for psychosis induced aggression or agitation

Comparison: 1 CHLORPROMAZINE vs HALOPERIDOL

Outcome: 3 Leaving the study early



ADDITIONAL TABLES

Table 1. Other relevant Cochrane Reviews

Focus of review	Reference
Benzodiazepines	Volz 2007
Containment strategies	Muralidharan 2006
Haloperidol + promethazine	Huf 2009
Loxapine	Chakrabarti 2007
Olanzapine IM	Belgamwar 2005
Seclusion and restraint	Sailas 2000
Zuoclopenthixol acetate	Gibson 2004

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Table 2. Suggested design for a study

Methods	Allocation: randomised, clearly described. Blindness: double, described and tested. Duration: 2 weeks.
Participants	Diagnosis: thought to have psychoses. N= 300.* Age: any. Sex: both. History: acutely ill, aggressive.
Interventions	1. Chlorpromazine IM: dose flexible within recommended limits. N=150. 2. Haloperidol + promethazine IM: dose flexible within recommended limits. N=150
Outcomes	All outcomes are grouped by time: by 30 minutes, up to two hours, up to four hours, up to 24 hours and finally over 24 hours. Tranquillisation or asleep. Mortality. Specific behaviours - Self-harm, including suicide, Injury to others, aggression. Global outcomes - overall improvement, use of additional medication, use of restraints/seclusion. Service outcomes - duration of hospital stay, re-admission. Mental state - no clinically important change in general mental state. Adverse effects - clinically important adverse effects. Leaving the study early - why. Economic outcomes.
Notes	* Powered to be able to identify a difference of ~20% between groups for primary outcome with adequate degree of certainty

WHAT'S NEW

Last assessed as up-to-date: 15 March 2010.

Date	Event	Description
10 November 2010	Amended	Contact details updated.

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HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 4, 2010

Date	Event	Description
6 October 2010	Amended	Contact details updated.
4 August 2010	Amended	Contact details updated.
7 July 2010	Amended	Contact details updated.
14 April 2010	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

Uzair Ahmed - took the lead in the review, wrote the protocol, screened search results (2008 and 2009 searches), screened and retrieved papers against eligibility criteria, appraised quality of papers, extracted data from papers, entered data into RevMan and analysed data, interpreted data and wrote the review.

Hannah Jones - screened search results (2008 and 2009 searches), screened and retrieved papers against eligibility criteria, appraised quality of papers, extracted data from papers, entered data into RevMan and analysed data, interpreted data and wrote the review.

Clive E Adams - helped write the protocol, screened search results (2008 and 2009 searches), screened and retrieved papers against eligibility criteria, appraised quality of papers, extracted data from papers, entered data into RevMan and analysed data, interpreted data and wrote the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

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External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Aggression [*drug effects; psychology]; Antipsychotic Agents [*administration & dosage]; Chlorpromazine [*administration & dosage]; Haloperidol [administration & dosage]; Injections, Intramuscular; Psychomotor Agitation [*drug therapy]; Psychotic Disorders [*drug therapy; psychology]

MeSH check words

Humans

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