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Haloperidol dose for the acute phase of schizophrenia (Review)

Donnelly L, Rathbone J, Adams CE

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[Intervention Review]

Haloperidol dose for the acute phase of schizophrenia

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ABSTRACT

Background

Haloperidol is a benchmark, accessible antipsychotic drug against which the effects of newer treatments are gauged.

Objectives

To determine the best range of doses for haloperidol for the treatment of people acutely ill with schizophrenia.

Search methods

We searched the Cochrane Schizophrenia Group Trials Register (February 2010), which is based on regular searches of CINAHL, EMBASE, MEDLINE and PsycINFO.

Selection criteria

We selected studies if they involved people being treated for acute schizophrenia, randomised to two or more dose ranges of non-depot haloperidol, and if they reported clinically meaningful outcomes.

Data collection and analysis

For this update, we inspected all citations and independently re-inspected a sample of citations in order to ensure reliable selection. We resolved any disagreement by discussion, and where doubt remained, we acquired the full-text article for further inspection. We then ordered papers, and reliably re-inspected and quality assessed the full reports, and extracted data. For homogeneous dichotomous data, we calculated the risk ratio (RR) with 95% confidence intervals (CI) on an intention-to-treat (ITT) basis. We assumed that people who left the study early or were lost to follow-up had a negative outcome. We calculated mean differences (MD) for continuous outcomes that reported ITT, last observation carried forward (LOCF) data. We excluded data if loss to follow-up was greater than 50%.

Main results

We included 19 trials with 19 different randomised dose comparisons. No studies reported data on relapse rates or quality of life and only one compared low dose (> 1.5 to 3 mg/day) haloperidol to higher dose ranges. Using standard lower dose (> 3 to 7.5 mg/day) did not result in loss of efficacy (no clinically important improvement in global state, versus standard higher dose (> 7.5 to 15 mg/day, n = 48, 1 RCT, RR 1.09, 95% CI 0.7 to 1.8, *very-low-quality evidence*); versus high dose (> 15 to 35 mg/day, n = 81, 2 RCTs, RR 0.95, 95% CI 0.8 to 1.2, *very-low-quality evidence*). Doses of haloperidol in the range of > 3 to 7.5 mg/day had a lower rate of development of clinically significant extrapyramidal adverse effects than higher doses (clinically significant extrapyramidal adverse effects, versus

standard higher dose, n = 64, 2 RCTs, RR 0.12, 95% CI 0.01 to 2.1, *very-low-quality evidence*); versus high dose, n = 144, 3 RCTs, RR 0.59, 95% CI 0.5 to 0.8, very-low-quality evidence; versus very high dose (> 35 mg/day, n = 86, 2 RCTs, RR 0.70, 95% CI 0.5 to 1.1, *very-low-quality evidence*). None of the other comparisons between dose ranges yielded statistically significant differences, but several, particularly with lower dose ranges, were underpowered to detect clinically meaningful differences.

Authors' conclusions

Noresults were conclusive and all were based on small, short studies of limited quality. However, it would be understandable if clinicians were cautious in prescribing doses in excess of 7.5 mg/day of haloperidol to a person with uncomplicated acute schizophrenia, and if people with schizophrenia were equally reticent to take greater doses. Further research is needed regarding the efficacy and tolerability of the lower dose ranges, especially > 1.5 to 3 mg/day.

PLAIN LANGUAGE SUMMARY

Haloperidol dose for the acute phase of schizophrenia

Schizophrenia is a mental illness where the person often experiences both positive symptoms (such as hearing voices, seeing things and having strange beliefs) and negative symptoms (such as tiredness, apathy and loss of emotion). Antipsychotic drugs are used to treat schizophrenia. The antipsychotic drug, haloperidol, is one of the most frequently used drugs worldwide for people with schizophrenia.

The benefits of antipsychotic drugs, such as haloperidol, need to be weighed against their tendency for causing debilitating side effects (such as movement disorders, weight gain, lack of drive) and in some cases an increased likelihood of physical illnesses such as diabetes and heart disease. These debilitating side effects may mean that people stop taking their medication, which can lead to relapse and going into hospital. It is, therefore, important to find a tolerable and effective dose of haloperidol, which helps control the symptoms of schizophrenia but with fewer side effects.

The main aim of this review was to determine the best range of doses of haloperidol for the treatment of schizophrenia. Nineteen trials were included that compared varying doses of haloperidol. Despite over 30 years of trials, data on the effects of differing doses of haloperidol are sparse and poorly reported. This is especially so for the lower dose ranges generally used for the treatment of schizophrenia today. However, lower doses of haloperidol may be just as effective as higher doses but result in fewer side effects. This review also suggests that an important bias against haloperidol may exist in modern trials comparing new drugs with haloperidol. Results are not conclusive and are based on small, short studies of limited quality.

The authors of the review note that it would be understandable if psychiatrists were cautious about prescribing doses above 7.5 mg a day and if people with schizophrenia did not want to take higher dosages. Further research is needed to assess the tolerability and effectiveness of lower doses. Low doses of haloperidol may be just as good as higher doses, but with fewer side effects.

This plain language summary was written by a consumer, Benjamin Gray, Service User and Service User Expert. Rethink Mental Illness. Email: ben.gray@rethink.org.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

DOSES: 2. STANDARD LOWER DOSE (> 3 to 7.5 mg/day) versus OTHER DOSES for the acute phase of schizophrenia

Patient or population: people with the acute phase of schizophrenia
Settings: in hospital
Intervention: standard lower dose (> 3-7.5 mg/day) versus other doses

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	STANDARD LOWER DOSE (> 3-7.5 mg/day) vs. OTHER DOSES				
Leaving the study early (2-10 weeks) vs. standard higher dose (> 7.5-15 mg/day)	121 per 1000	15 per 1000 (1 to 257)	RR 0.12 (0.01 to 2.12)	64 (2 studies)	⊕○○○ very low[1,2,3]	
Leaving the study early (2-10 weeks) vs. high dose (> 15-35 mg/day)	Study population		RR 0.78 (0.47 to 1.28)	191 (4 studies)	⊕○○○ very low[2,4,5]	
	256 per 1000	200 per 1000 (120 to 328)				
	Medium risk population					
	212 per 1000	165 per 1000 (100 to 271)				
Global state: 1. No clinically significant response in global state (2-10 weeks) vs. standard higher dose (> 7.5-15 mg/day)	Study population		RR 1.09 (0.67 to 1.75)	48 (1 study)	⊕○○○ very low[1,6,7]	

	560 per 1000	**610 per 1000** (375 to 980)			
	Medium risk population				
	560 per 1000	**610 per 1000** (375 to 980)			
Global state: 1. No clinically significant response in global state (2-10 weeks) vs. high dose (> 15-35 mg/day)	**Study population**		**RR 0.95** (0.75 to 1.19)	81 (2 studies)	⊕○○○ **very low**[2,3,4]
	800 per 1000	**760 per 1000** (600 to 952)			
	Medium risk population				
	828 per 1000	**787 per 1000** (621 to 985)			
Adverse effects: 1. Clinically significant extrapyramidal side effects (2-10 weeks) vs. standard higher dose (> 7.5-15 mg/day)	**Study population**		**RR 0.12** (0.01 to 2.12)	64 (2 studies)	⊕○○○ **very low**[1,2,3]
	121 per 1000	**15 per 1000** (1 to 257)			
	Medium risk population				
	80 per 1000	**10 per 1000** (1 to 170)			
Adverse effects: 1. Clinically significant extrapyramidal side effects (2-10 weeks) vs. high dose (> 15-35 mg/day)	**Study population**		**RR 0.59** (0.45 to 0.78)	144 (3 studies)	⊕○○○ **very low**[2,4,8]
	769 per 1000	**454 per 1000** (346 to 600)			
	Medium risk population				

	760 per 1000	**448 per 1000** (342 to 593)			
Mental state/behaviour: clinically significant agitation (2-10 weeks)	**Study population**		**RR 0.93** (0.69 to 1.26)	65 (1 study)	⊕○○○ **very low**[1,6,7]
	750 per 1000	**698 per 1000** (517 to 945)			
	Medium risk population				
	750 per 1000	**698 per 1000** (517 to 945)			

*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] Limitations in design: rated as 'serious' - no trial described randomisation process or tested blinding.
[2] Imprecision: rated as 'serious' - very small trials.
[3] Publication bias: rated as 'serious' - two very small trials.
[4] Limitations in design: rated as 'serious' - no trial described randomisation process and only one tested blinding informally and found it to be ineffective.
[5] Publication bias: rated as 'serious' - four small trials.
[6] Imprecision: rated as 'serious' - single small trial.
[7] Publication bias: rated as 'serious' - single trial.
[8] Publication bias: rated as 'serious' - three very small trials.

BACKGROUND

Antipsychotic medications are a mainstay of treatment for people with acute schizophrenia. These compounds are beneficial in the short to medium term course of the illness. For example, in a review of 45 randomised studies involving the oldest neuroleptic, chlorpromazine, there was a clinically significant reduction in a person's symptoms over placebo after six months of treatment (10 RCTs, n = 1123, RR 0.76, 95% CI 0.7 to 0.8) (Thornley 2002). When haloperidol was compared with placebo, the findings were similar (8 RCTs, n = 313, RR 0.65, 95% CI 0.6 to 0.8) (Joy 2002). The value of these drugs for treating people with acute psychoses needs to be weighed against their tendency to induce significant adverse effects. In one chlorpromazine review, the risk of medication-related parkinsonism, such as tremor and stiffness, was significantly higher than placebo (10 RCTs, n = 1265, RR 2.0, 95% CI 1.5 to 2.7, NNTH 10, 95% CI 8 to 16) (Thornley 2002). This was also the case in one haloperidol review (4 RCTs, n = 165, RR 8.9, 95% CI 2.6 to 31, NNTH 3, 95% CI 2 to 5) (Joy 2002). Such adverse effects are a cause for concern to people with schizophrenia and their clinicians.

Intolerable effects can lead to the premature discontinuation of drugs and result in an increase in potentially damaging relapses of acute symptoms of schizophrenia (Hansen 1997; Marder 1998). Therefore, various means of minimising adverse effects have been sought (Bezchlibnyk 1994; De Oliveira 1996; Leucht 1999; McEvoy 1991). The focus of this review will be one specific means of avoiding adverse effects, the determination of a tolerable yet effective dose range of a specific drug. This is often termed the dose-response relationship (Miller 1997). We have also chosen to focus this review on a specific antipsychotic agent, haloperidol, which continues to be among the most frequently used drugs for people with schizophrenia worldwide (Baldessarini 1995; Johnson 1993; Kiivet 1995; Raschetti 1993; Williams 1999) and haloperidol remains a comparison agent of choice for clinical drug trials of novel agents (Awad 1993; Thornley 1998).

The development of the so-called second-generation antipsychotics has changed how schizophrenia is treated. Studies have shown these drugs to be a heterogeneous group (Davis 2003; Gardner 2005). Clozapine, amisulpride, risperidone and olanzapine antipsychotics are more efficacious than first-generation antipsychotics and produce a better functional recovery making them cost effective (Davis 2003). A lesser propensity to cause extrapyramidal side effects is another benefit of second-generation over first-generation drugs, but this must be balanced against metabolic, endocrine and cardiovascular effects (Gardner 2005).

Description of the condition

Schizophrenia is a chronic, relapsing mental illness and has a worldwide lifetime prevalence of about 1% irrespective of culture, social class and race. The acute phase of schizophrenia is the florid psychotic phase, during which the patient exhibits acute symptoms that can include positive symptoms (such as delusions, hallucinations, disorganised thinking and speech), or more profound negative symptoms (such as flattened affect, alogia and avolition), or both positive and negative symptoms. Twenty-five per cent of those who have experienced an episode of schizophrenia recover and the illness does not recur. Another 25% experience an unremitting illness. Fifty per cent do have a recurrent illness but with long episodes of considerable recovery from the positive symptoms. Current medication is effective in reducing positive symptoms, but negative symptoms are fairly resistant to treatment. In addition, drug treatments are associated with adverse effects and the overall cost of the illness to the individual, their carers and the community is considerable.

Description of the intervention

Haloperidol is a 'typical' or 'older-generation' antipsychotic. It is a butyrophenone derivative. It was discovered by Paul Janssen and developed by Janssen Pharmaceuticals in Belgium in 1958; however, it was not approved for use in the US until 1967. Haloperidol remains a widely used antipsychotic although the development of 'atypical' antipsychotic agents has seen a decrease in its use in developed countries. It is only one of three antipsychotic drugs on the World Health Organizations Essential Drug List (WHO 2011).

How the intervention might work

The mechanism of action of haloperidol is not entirely understood but it is thought that its high affinity for the D_2 subtype of dopamine receptor in the mesocortex and limbic systems of the brain is responsible for its efficacy in treating positive symptoms of schizophrenia. There is a marked tendency to produce extrapyramidal effects, which is thought to be due to its antidopaminergic action in the nigrostriatal pathways.
Haloperidol has relatively minor antihistamine and anticholinergic properties. It has strong sedative properties. The peripheral actions of haloperidol are thought to be responsible for its antiemetic properties and its potential to cause hyperprolactinaemia.

Why it is important to do this review

There are already important reviews that pool data on the combined dose-response relationship of various typical antipsychotic agents and that incorporate some data on haloperidol. One review proposed an optimum dosage range of 10 to 15 mg/day haloperidol or the equivalent of such a dose when using other antipsychotics (Baldessarini 1988). This review summarised randomised

controlled trial data combined with information from studies using other methodologies. Another systematic review looking at antipsychotic neuroleptic dose for maintenance management of people with schizophrenia employed systematic review techniques and examined data from randomised controlled trials up to June 1989 (Bollini 1994). The conclusion reached was that there was no benefit from using doses higher than 375 mg/day of chlorpromazine or the equivalent of such a dose when using other antipsychotics (about 7.5 mg/day of haloperidol).

There are several reasons for a study to complement this previous work. First, previous reviews need to be updated with data from more recent trials. Second, the use of conversion factors to pool data from studies of different antipsychotics is not based on rigorous evidence and different means of comparing drugs are currently in evolution (Awad 1993; Kane 1996; Kapur 1998). Thus, this review summarises data from trials investigating the dose-response relationship of haloperidol alone. Third, several new agents have been developed that are not significantly different from placebo with regard to important adverse effects such as parkinsonism (Leucht 1999). This has led to the recommendation of these agents as first-line treatments for acute schizophrenia (APA 1997; CPA 1998). Using the cost of mean clinical doses as a basis for comparison, these novel drugs have the drawback of being significantly more expensive than agents such as haloperidol (Awad 1999; Glazer 1998; Zito 1998). There is need for a systematic review to determine whether an optimum dosage of the less costly drugs may minimise adverse effects with no significant decrease in clinical efficacy. Finally, many trials of novel agents do not report a clear justification for the dose of reference drug that they choose. They have frequently used doses well in excess of the maximum levels recommended by Bollini 1994 and Baldessarini 1995. Using a higher dose of the reference drug, frequently haloperidol, may have biased results in favour of the novel agent due to differential attrition or the promotion of adverse effects in the control arm of the study (Awad 1993; Jadad 1999). An accurate estimate of a dose range for specific reference drugs that defines an optimum balance between adverse effects and efficacy is urgently needed to serve as a 'gold standard' for future comparative studies. Haloperidol continues to be used as a comparative agent in trials of novel antipsychotics such as lurasidone (Citrome 2011).

Once a decision had been made to undertake a review focusing on the dose-response of haloperidol, it was important for the review authors to define specific dose ranges to be used. The review authors selected dose ranges (> 0.25 to 1.5 mg/day, > 1.5 to 3 mg/day, > 3 to 7.5 mg/day, > 7.5 to 15 mg/day, > 15 to 35 mg/day and > 35 mg/day) that were considered to reflect patterns of clinical use (Baldessarini 1984; Reardon 1989), research using positron emission tomography (PET) studies (Kapur 1996; Kapur 1997; Kapur 1998), the findings of previous reviews (Baldessarini 1988; Bollini 1994; Leucht 1999), and the recommendations of treatment guidelines (Geddes 1999). This review also investigates only within-study comparisons - where one group of participants has been randomised to two or more dose ranges - and not cross-study comparisons. In cross-study comparisons, many variables, such as participant group or clinical setting, may be so radically different as to make comparison fraught with difficulty.

Having underlined the need to review a specific drug in predefined dose ranges using multiple dose studies only, the final major factor to discuss was duration of treatment. The review authors did not consider that pooling data where treatment can vary from less than 24 hours' duration to more than six months' duration was justifiable. It has been well established that the efficacy and rate of adverse effects with antipsychotic drugs vary depending on the treatment duration (Conley 1997; Kane 1996). Therefore, the review authors defined four treatment durations (3 days to < 2 weeks, 2 weeks to 10 weeks, > 10 weeks to 6 months, > 6 months) to reflect various findings on the course of treatment response (Garver 1984; Hogarty 1973; Hogarty 1974; Levy 1996; Lieberman 1993; Milton 1995).

Several factors may affect results of a review that uses data from trials conducted across a wide time span in many different settings. Variables such as participant age, sex and phase of illness, may substantially differ between studies and affect the size or even direction of outcomes. As diagnostic criteria for schizophrenia have varied over the years (Awad 1993), a sensitivity analysis for only the primary outcomes (see Types of outcome measures) was performed for whether formal diagnostic criteria were used or not. The review authors also performed sensitivity analysis for studies whose participants had schizophrenia defined as first episode or treatment resistant to determine if they differed in their treatment response from other people with schizophrenia.

OBJECTIVES

To determine the dose-response relationships for haloperidol, at a range of treatment durations, in the treatment of people with schizophrenia experiencing an acute phase of their illness.

It was also proposed to see if:

1. people whose illnesses were diagnosed using operational criteria, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD), differed in their treatment response from people with informally derived diagnoses;

2. people whose illness was defined as first episode or treatment resistant differed in their treatment response from other people with schizophrenia.

METHODS

Criteria for considering studies for this review

Types of studies

We included all relevant randomised controlled trials. We included any trials that were described as 'double-blind' where it was implied that the studies were randomised and the demographic details of each group were similar. We excluded quasi-randomised studies, such as those allocated by using alternate days of the week. The duration of studies included in this review needed to be a minimum of three days.

Types of participants

We included people with schizophrenia or similar serious, non-affective psychosis diagnosed by any criteria irrespective of gender, age, or race. If a trial included people with other mental illnesses, we accepted it for inclusion if greater than 50% of participants had serious functional psychotic illnesses such as schizophrenia, but we excluded studies if greater than 33% of people were experiencing an affective psychosis. We considered people to be in the acute phase of schizophrenia if they were experiencing an exacerbation in their baseline level of symptoms, or if they had active symptoms and were currently hospitalised. We excluded studies where greater than 50% of people were considered to be healthy, or were described as undergoing maintenance, or dose reduction treatment.

Types of interventions

Drug dosages

1. Haloperidol: dose greater than 0.25 mg/day to 1.5 mg/day (ultra low dose).
2. Haloperidol: dose greater than 1.5 mg/day to 3 mg/day (low dose).
3. Haloperidol: dose greater than 3 mg/day to 7.5 mg/day (standard lower dose).
4. Haloperidol: dose greater than 7.5 mg/day to 15 mg/day (standard higher dose).
5. Haloperidol: dose greater than 15 mg/day to 35 mg/day (high dose).
6. Haloperidol: dose greater than 35 mg/day (very high dose).

Plasma levels

1. Haloperidol: plasma level greater than 1.4 to 3.5 ng/mL (very low plasma levels).
2. Haloperidol: plasma level greater than 3.5 to 7 ng/mL (low plasma levels).
3. Haloperidol: plasma level greater than 7.0 to 16.5 ng/mL (medium plasma levels).
4. Haloperidol: plasma level greater than 16.5 ng/mL (high plasma levels).

We included any means of administration with the exception of depot.

Types of outcome measures

We divided outcomes into the following time periods:

- three days to less than two weeks;
- two weeks to 10 weeks *
- greater than 10 weeks to six months;
- greater than six months.

* (timescale for primary outcomes of interest)

If data on more than one time point within these time periods were available, we used the duration closest to the middle of the time period. For the greater than six months period, we used the longest available time period.

Primary outcomes

1. Leaving the study early

2. Clinical response

2.1 No clinically significant response in global state

3. Extrapyramidal adverse effects

3.1 No clinically significant extrapyramidal adverse effects

4. Behaviour

4.1 Clinically significant agitation

Secondary outcomes

1. Mortality, any cause

2. Clinical response

2.1 Mean score/change in global state
2.2 Clinically significant change in mental state
2.3 No clinically significant response in psychotic symptoms
2.4 Mean score/change in psychotic symptoms
2.5 No clinically significant response in positive symptoms
2.6 Mean score/change in positive symptoms
2.7 No clinically significant response in negative symptoms
2.8 Mean score/change in negative symptoms
2.9 Relapse

3. Extrapyramidal adverse effects

3.1 Use of any antiparkinsonism drugs
3.2 Mean score/change in extrapyramidal adverse effects
3.3 Tardive dyskinesia
3.4 Acute dystonia
3.5 Akathisia

4. Other adverse effects, general and specific

5. Hospital and service utilisation outcomes

5.1 Hospital admission
5.2 Mean change in days in hospital
5.3 Improvement in hospital status (e.g. change from formal to informal admission status, use of seclusion, level of observation)

6. Economic outcomes

6.1 Mean change in total cost of medical and mental health care
6.2 Total indirect and direct costs

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

7.1. No significant change in quality of life/satisfaction
7.2 Mean score/change in quality of life/satisfaction

8. Behaviour

8.1 Use of adjunctive medication for sedation
8.2 Aggression to self or others

9. Cognitive response

9.1 No clinically important change
9.2 No change, general and specific

Search methods for identification of studies

Electronic searches

1. Cochrane Schizophrenia Group Trials Register

The Trials Search Co-ordinator of the Cochrane Schizophrenia Group searched the Cochrane Schizophrenia Group Trials Register (February 2010) with the phrase:

[(*dosage-effect* or *dose-activity* or *dose-dependence* or *dose-effect* or *dose-rate* or *dose-response* or *dosage-scheme* or *drug-response* or *effective-dose* or *dose-finding* or *dose-calculation* or *therapeutic-equivalency* or *blood-level* or *blood-drug* or *serum-level* or *serum-drug* or *plasma-level* or *plasma-drug* or *high-dos* or *low-dos* or *medium-dos* or *standard-dos* or *middle-dos* or *maximum-dos* or *minimum-dos* or *threshold-dos*) AND (*haloperi* or *R-1625* or *haldol* or *alased* or *aloperidi* or *bioperido* or *buterid* or *ceree* or *dozic* or *duraperido* or *fortuna* or *serena* or *serenel* or *seviu* or *sigaperid* or *sylad* or *zafri*) in title abstract and index terms of reference) OR (*haloperidol* and dosage*) in intervention of STUDY]
Previous search strategies are shown in Appendix 1.

Searching other resources

1. Cited reference searching

We inspected the references of all identified trials for more studies. Each of the included studies was sought as a citation on the SCISEARCH database. We inspected reports of articles that had cited these studies in order to identify further trials.

2. Search of other Cochrane reviews

We reviewed the included studies of other Cochrane reviews involving haloperidol for potential inclusion.

3. Personal contact

We contacted the primary authors of all studies initially selected for inclusion, as well as the authors of Cochrane haloperidol reviews, in order to identify further relevant trials. We also contacted companies producing relevant compounds for copies of published, unpublished, and archived trials.

Data collection and analysis

For details of previous data collection and analysis methods see Appendix 2.

Selection of studies

For this update, one review author (LD) inspected all abstracts. LD used a random number generator program to select a sample of 10% of all abstracts. CEA then re-inspected this sample in order to allow selection to be reliable. We resolved any disagreement by discussion, or where there was still doubt, we acquired the full-text article for further inspection. We obtained full-text articles of relevant reports and two review authors (LD and CEA) independently decided whether they met the review criteria. We resolved any disagreement by discussion, and, when this was not possible, we sought further information from the study authors. We excluded studies that appeared to meet all inclusion criteria but had no extractable outcomes pending further information from the study authors.

Data extraction and management

1. Extraction

LD extracted data from all included studies. CEA independently extracted data from a sample to ensure reliability. Again, we resolved any disagreements by discussion. We extracted data presented in graphs and figures whenever possible, as well as that reported clearly in text.

2. Management

2.1 Forms

We extracted data onto standard forms.

2.2 Scale-derived data

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

2.3 Endpoint versus change data

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

2.4 Skewed data

Continuous data on outcomes in mental health trials are often not normally distributed. To avoid applying parametric tests to non-parametric data, we applied the following standards to all endpoint data derived from continuous measures. The criteria were used before inclusion: (a) standard deviations (SD) and means had to be obtainable; and, for finite scores, such as endpoint measures on rating scales, (b) the SD, when multiplied by two had to be less than the mean (as otherwise the mean was unlikely to be an appropriate measure of the centre of the distribution) (Altman 1996). If a scale started from a positive value (such as the Positive and Negative Syndrome Scale (PANSS), which can have values from 30 to 210), the calculation described above in (b) should be modified to take the scale starting point into account. In these cases, skew is present if 2 SD > (S - Smin), where S is the mean score and Smin is the minimum score.

Skewed endpoint data from studies with fewer than 200 participants were not shown graphically, but were added to 'Other data' tables and briefly commented on in the text. However, skewed endpoint data from larger studies ($\geq$ 200 participants) pose less of a problem and we entered the data for analysis.

For continuous mean change data (endpoint minus baseline), the situation is even more problematic. In the absence of individual patient data, it is impossible to know if change data are skewed. The Review Manager 5 meta-analyses of continuous data are based on the assumption that the data are, at least to a reasonable degree, normally distributed (RevMan 2011). Therefore, we included such data, unless endpoint data from the same scale were also reported.

2.5 Conversion of continuous to binary

Where possible, we attempted to convert outcome measures into binary data. This can be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It is generally assumed that if there is a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS) (Overall 1962) or the PANSS (Kay 1986), this could be considered a clinically significant response (Leucht 2005a; Leucht 2005b). For many people, especially those with chronic or severe illness, a less rigorous definition of important improvement (e.g. 25% on the BPRS) would be equally valid. If individual patient data were available, we used the 50% cut-off point for non-chronically ill people and a 25% cut-off point for those with chronic illness. If data based on these thresholds were not available, we used the primary cut-off presented by the original study authors.

2.6 Management of dose-response studies other than fixed-dose studies

We gave careful consideration to determining a methodology on how to combine studies that used alternate methods of dose allocation, for example plasma studies, neuroleptic threshold studies. We converted the thresholds for dosage groups into plasma thresholds using data from PET research (Kapur 1996). These indicated that a 2.1 mg oral dose was approximately equivalent to a 1 ng/mL plasma level. The thresholds for plasma dose ranges in nanograms per millilitre are outlined in Types of interventions. This approach was affirmed using data from another study (Volavka 1995), which reported both oral dose and plasma levels, and there was 100% correspondence between oral dose range allocation and plasma dose allocation using this method.

We classified treatment arms from neuroleptic threshold and other flexible-dose range studies in the same dose ranges as fixed-dose studies. The criteria used were the following: if the mean dose plus or minus the 50% confidence interval (CI) fell within the predefined fixed-dose range, or if at least 50% of people in a dose arm had received doses within the prespecified ranges, the flexible

treatment arm was considered equivalent to the corresponding fixed-dose treatment arm. If the dose range from a treatment arm met none of the criteria, then data related to that arm of the study were not extracted.

2.7 Management of co-interventions

We excluded studies that involved randomisation to combined treatments of neuroleptic with additional known psychoactive treatments. We did not exclude studies that allowed for use of other forms of intervention on an 'as needed' basis, or as part of routine clinical practice.

2.8 Management of multiple time periods

If data on more than one time point within prespecified time periods were available, we used the duration closest to the middle of the time period. For the greater than six-month period, we used the longest available time period.

2.9. Management of multiple doses

If data were available for more than one dose within the prespecified dosage ranges, we pooled the data from these two doses.

2.10 Clinically significant outcomes

Several outcomes were prefixed by the term 'clinically significant'. Wherever possible, we utilised the definition of the authors of the study to define this concept. Where the authors were not specific, we determined that any circumstance that would have led to a significant change in clinical management (e.g. intolerable adverse effects, use of adjunctive medication) was considered clinically significant. For continuous outcomes, we considered a 40% change to be clinically significant.

2.11 'Summary of findings' table

We used the GRADE approach to interpret findings (Schünemann 2011), and used GRADE profiler (GRADEPRO), to import data from Review Manager 5 (RevMan 2011) to create 'Summary of findings' tables. These tables provide outcome-specific information concerning the overall quality of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rated as important to patient care and decision making. We considered treatment with a standard lower dose (> 3 to 7.5 mg/day) versus other doses and selected the following main outcomes for inclusion in the 'Summary of findings' table:

1. Leaving the study early;
2. Clinical response;
2.1 No clinically significant response in global state;
3. Extrapyramidal adverse effects;
3.1 No clinically significant extrapyramidal adverse effects;
4. Behaviour;
4.1 Clinically significant agitation.

Assessment of risk of bias in included studies

We assessed risk of bias using the tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). 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.

If disputes arose as to which category a trial had to be allocated, we resolved them by discussion, after working with a third review author.

Earlier versions of this review used a different, less well-developed, means of categorising risk of bias (Waraich 2002; see Appendix 3).

Measures of treatment effect

1 Binary data

For binary outcomes, we calculated the risk ratio (RR) and its 95% CI based on the fixed-effect model. RR is more intuitive than odds ratios (OR) (Boissel 1999), and ORs tend to be interpreted as RRs by clinicians (Deeks 2000). This misinterpretation then leads to an overestimate of the impression of the effect. The number needed to treat for an additional beneficial outcome (NNTB) and number needed to treat for an additional harmful outcome (NNTH) 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' tables, where possible, we calculated illustrative comparative risks.

2. Continuous data

For continuous outcomes, estimated mean difference (MD) between groups. We preferred not to calculate effect size measures (standardised mean difference (SMD)). However, if scales of considerable similarity are used, we presumed there was a small difference in measurement, and we calculated effect size and transformed the effect back to the units of one or more of the specific instruments.

Unit of analysis issues

1. Cluster trials

Studies increasingly employ cluster randomisation (such as randomisation by clinician or practice), but analysis and pooling of clustered data poses problems. First, authors often do not account

for intraclass correlation (ICC) 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).
Where clustering had not been accounted for in primary studies, we presented the data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. In subsequent versions of this review, we will contact first authors of studies to obtain ICCs of their clustered data and to adjust for this using standard methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we will also present these data as if from a non-cluster randomised study, but adjusted for the clustering effect.
We have sought statistical advice and have been advised that the binary data as presented in a report should be divided by a design effect. This is calculated using the mean number of participants per cluster (m) and the ICC [Design effect = 1 + (m - 1) *ICC] (Donner 2002). If the ICC was not reported, we assumed it to be 0.1 (Ukoumunne 1999). If cluster studies had been appropriately analysed taking into account ICCs and relevant data documented in the report, we combined these with other studies using the generic inverse variance technique.

2. Cross-over design

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 washout phase. For the same reason, cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both effects are likely in schizophrenia, we only used data of the first phase of cross-over studies.

3. Studies with multiple treatment groups

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

Dealing with missing data

1. Leaving the study early

We excluded data from studies where more than 50% of participants in any group were lost to follow-up (this did not include the outcome of 'leaving the study early'), as such data were considered to be too prone to bias. In studies with less than 50% dropout rate, people leaving early were considered to have had a negative outcome, except for the event of death, and dropouts that were clearly attributable to clinical improvement. We analysed the impact of including studies with high attrition rates (25% to 50%) in a sensitivity analysis. If inclusion of data from this latter group resulted in a substantive change in the estimate of effect, we did not add their data to trials with less attrition, but presented them separately.

2. Management of deaths

When analysing loss of contacts in studies where deaths had occurred, the 'type' of death affected analysis. Deaths as a result of 'natural causes' were not counted as losses of contact and the number of deaths reduced the size of treatment or control groups. However, we counted suicides or suspicious deaths as loss to follow-up and their data were incorporated into the analysis.

Assessment of heterogeneity

First, we considered all the included studies within any comparison to judge for clinical heterogeneity. Then we visually inspected graphs to investigate the possibility of statistical heterogeneity. We supplemented this by using primarily the I^2 statistic. This provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. Where the I^2 estimate was greater than or equal to 50%, we interpreted this as indicating the presence of considerable levels of heterogeneity (Higgins 2003). If inconsistency remained high, and substantially altered the results, we did not add those studies responsible for heterogeneity to the main body of homogeneous trials. We summated the heterogeneous studies and presented them separately and reasons for heterogeneity investigated.

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. These are described in Section 10.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects (Egger 1997). We did not use funnel plots for outcomes where there were 10 or fewer studies, or where all studies were of similar sizes. In other cases, where funnel plots were possible, we sought statistical advice in their interpretation.

Data synthesis

Where possible we used a fixed-effect model for analyses. 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. However, this seems true to us, as random effects put added weight onto the smaller studies - those trials that are most vulnerable to bias.

Subgroup analysis and investigation of heterogeneity

When we found heterogeneous results, we investigated the reasons for this. Where heterogeneous data substantially altered the results and the reasons for the heterogeneity were identified, we did not summate these studies in the meta-analysis, but presented them separately and discussed them in the text.

Sensitivity analysis

LD and CEA selected trials that involved people whose illnesses were diagnosed using operational criteria. We also selected trials that involved people whose illnesses were defined as first episode or treatment resistant at the data extraction stage of the review.

RESULTS

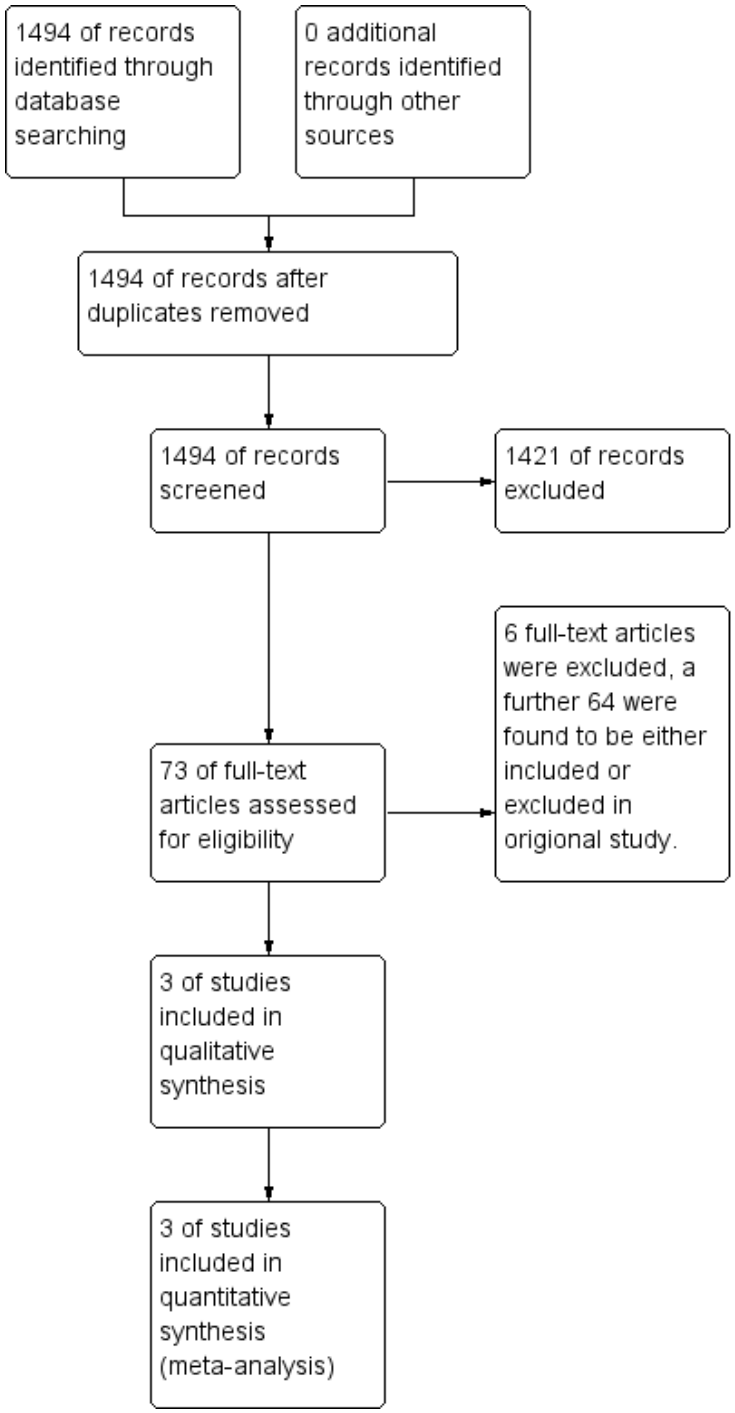
Description of studies

For substantive descriptions of studies see: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

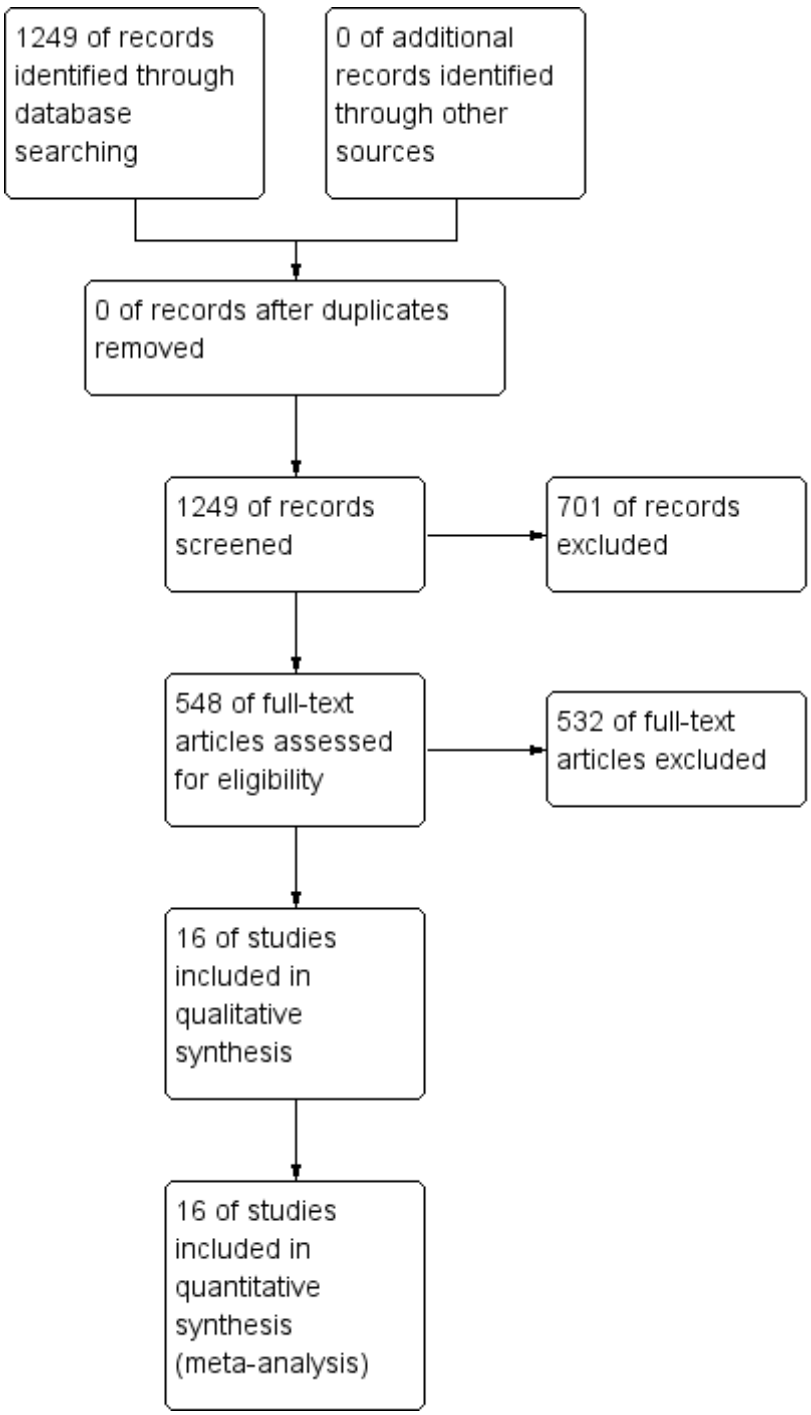
In this update, we identified 1494 citations in the search, and excluded 1421 because they were not controlled, not randomised or quasi-randomised, did not primarily involve people with schizophrenia, did not include acutely ill people, were not studies of antipsychotics, involved only one dose of medication, were comparing two doses of an antipsychotic drug but not haloperidol or were duplicate reports of the same trial. Thus, 73 studies remained for the final stage of inclusion/exclusion (Figure 1). CEA independently assessed a 10% random sample of the original 1494 citations for inclusion/exclusion. LD and CEA agreed on inclusion/exclusion for this 10% sample.

Figure 1. Study flow diagram (from results of 2010 search only).



Details of citations identified and subsequent processing in the original Waraich 2002 review are shown in Figure 2.

Figure 2. Study flow diagram (2002 review).



Included studies

See Appendix 4 for results of the original 2002 review.
We included three further studies following this update (Curtis 1995; Khanna 1997; Oosthuizen 2004), giving 19 studies in the review. The included studies dated between 1967 and 2004.

1. Length of studies

The longest study was 10 weeks (Liang 1987), the shortest was six days (Neborsky 1981). Most studies were between three and six weeks.

2. Participants

The largest study involved 132 people (Volavka 1992), the smallest (Simpson 1967) only 16 people. Only three of the included trials did not report stringent criteria for the diagnosis of schizophrenia (Curtis 1995; Donlon 1980; Simpson 1967). In the other studies, diagnoses were established by structured interviews or clinical examination by a psychiatrist and the diagnostic criteria applied included Research Diagnostic Criteria (RDC), ICD and DSM.
Although sometimes demographic data were missing, participants tended to be acutely ill men or women in their 20s or 30s. People had often been recently admitted to hospital, although some studies included acutely ill people who had been in hospital for months or years. Most studies involved people who had been ill before and for some time. One study used subjects with a first episode of psychosis (Oosthuizen 2004).

3. Interventions

Doses of haloperidol varied from a low of 1 mg/day (Kapur 2000) to a high of up to 100 mg/day (Donlon 1980). Doses were commonly fixed, perhaps preceded by a titration up to the final dose, and were given orally. The most common comparison (5/13) was standard higher dose (> 7.5 to 15 mg/day) versus high dose (> 15 to 35 mg/day).
One study had grouped participants in such a way that the control group straddled both our standard higher and high intervention group (Louza 1988). Four out of 19 randomised trials focused on plasma levels rather than dose.

4. Outcomes

All included studies, with the exception of Curtis 1995, reported 'leaving the study early' and most reported usable data on global state. Definitions of 'no clinically significant improvement' differed across studies. It was difficult to decide whether the results concerning clinical improvement were comparable. It seemed unlikely, however, that those judging improvement would have applied such dramatically differing criteria as to make summation inappropriate, especially given that analysis was restricted to randomised comparisons only. Further, if convergence of effects occurs despite differing methods, this may enhance the applicability of findings.
Mental state was reported in a form that was useful for this review in 11 of the included studies, and some adverse effects were clearly reported in 12 studies. All scale-derived data that we were able to present were from two studies (Oosthuizen 2004; Rifkin 1991).
We describe scales used by included studies to collect data.

4.1 Clinical Global Impression

Clinical Global Impression (CGI) is a rating instrument commonly used in studies on schizophrenia that enables clinicians to quantify severity of illness and overall clinical improvement during therapy. Generally, a seven-point scoring system is used, with low scores indicating decreased severity or greater recovery, or both (Guy 1976).

4.2 Schedule for Affective Disorders and Schizophrenia

Schedule for Affective Disorders and Schizophrenia (SADS) makes use of collateral information and past history. It rates symptoms at their highest level of severity over the previous week. Used serially, it provides a detailed record of the individual's progress. Greater scores indicate more severe symptoms (Endicott 1978).

4.3 Simpson and Angus Scale

Simpson and Angus Scale is a standard physical examination that measures parkinsonism. This scale is comprised of a 10-item rating scale, each item rated on a five-point scale with zero indicating the complete absence of condition and four indicating the presence of condition in extreme. Adding the items and dividing by 10 obtains the total score (Simpson 1970).

4.4 Calgary Depression Rating Scale

The Calgary Depression Rating Scale is the standard rating scale for measuring depression in people with schizophrenia. This is a semi-structured interview that scores nine items on a scale of absent, mild, moderate and severe (Addington 1990).

4.5 Positive and Negative Symptoms of Schizophrenia

PANSS is a relatively brief structured interview commonly used in the study of antipsychotic therapy. It rates positive and negative symptoms as defined by the American Psychiatric Association scoring one to seven on 30 different items. It constitutes four scales measuring positive and negative symptoms, their differential and general severity of illness (Kay 1986).

Excluded studies

We added a further six studies to the excluded studies section of the review following this update giving 22 studies. Several reported outcomes in such a way that made inclusion impossible. Either data did not have clear clinical implications, for example EEG recordings, or relevant clinical data were inadequately reported. Frequently, the numbers of participants in each group were not specified, means or SDs were not reported, or data were not reported from individual arms of cross-over studies.

Awaiting assessment

There are no studies currently awaiting assessment.

Ongoing

The review authors know of no ongoing studies.

Risk of bias in included studies

We used the tool for assessment of bias described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and a graphical overview can be seen in Figure 3 and Figure 4.

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

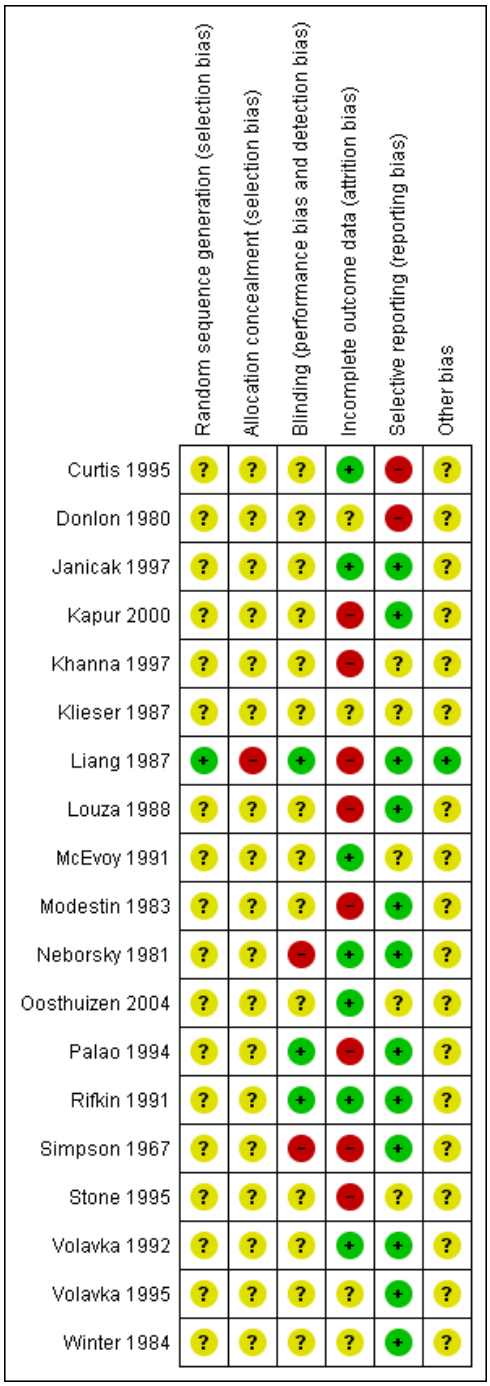
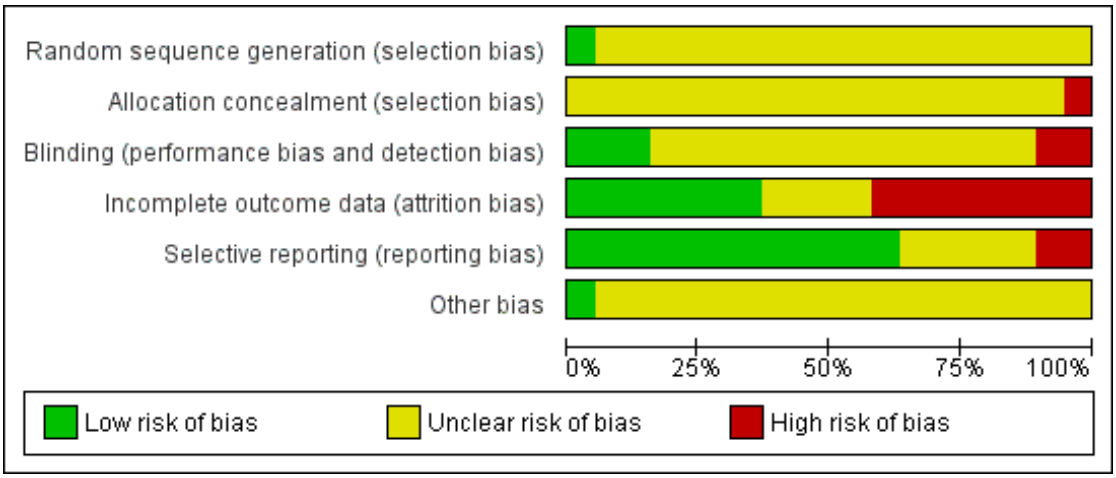


Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

The quality of randomisation in the studies was generally unclear. All studies were described as 'randomised'. Only one study described using random number tables to achieve randomisation (Liang 1987). Most studies simply reported randomisation and presented baseline data that were equivalent for the different comparator groups.

Blinding

All studies were reported as 'double-blind' with the exception of Curtis 1995. Several trials described using identical methods of dose delivery between groups. Only Simpson 1967 tested this by asking ward staff to guess the allocated treatment (91% of doctors and 89.5% of nurses were able to guess correctly).

Incomplete outcome data

The majority of studies described the numbers of people leaving early and reasons for leaving. Of the 19 studies, six described intention-to-treat analysis, nine described a 'per protocol' analysis and four did not report if dropout data were included in the analyses.

Selective reporting

The majority of the studies report a wide range of both statistically significant and non-significant outcomes but few reported all outcome measures. One paper presented only highly significant results (McEvoy 1991), and another did not report results from one treatment group (Curtis 1995).

Other potential sources of bias

We noted no obvious other sources of bias for this update.

Effects of interventions

See: **Summary of findings for the main comparison** STANDARD LOWER DOSE (> 3 to 7.5 mg/day) versus OTHER DOSES for the acute phase of schizophrenia

All the studies included in the review so far had outcomes assessed before 10 weeks, so no data could be presented for longer periods (greater than 10 weeks to six months, greater than six months). For several of the comparisons, the same data from a specific study were re-presented several times. For example, one study may have compared low-dose and high-dose haloperidol. Therefore, we considered it was appropriate to present these data in both comparison number 2, where low dose is the 'experimental intervention' and high the 'control' and comparison number 6, where the opposite applies.

We are aware that presenting the findings in this way does, at times, result in the repeating of results - but in reverse, for example

the low dose versus high dose is listed twice as it appears later as high dose versus low dose. This makes results long and repetitive - although because we are using the RR rather than OR the figures do change. It is feasible to restructure the review but to not repeat listings would have asked more of the reader. For this version we have left the structure of the review as it was originally (Waraich 2002), with each comparison containing all available data for that particular question (see Implications for research).

1. DOSES: 1. ULTRA LOW DOSE (> 0.25 to 1.5 mg/day) versus OTHER DOSES

We found one small (n = 26) study comparing ultra low dose with low dose (> 1.5 to 3 mg/day) (Kapur 2000).

1.1 Leaving the study early

We found no significant difference between study groups in rates of people leaving the study early (n = 26, 1 RCT, RR 0.29, 95% CI 0.03 to 2.4).

1.2 Global state

We found no significant difference between study groups (n = 26, 1 RCT, RR 1.89, 95% CI 0.9 to 3.9) though numerically there were more people who showed no significant response in the ultra low group (11/14 versus 5/12). Again, there was no significant difference between groups in use of adjunctive medication for sedation (Analysis 1.3).

1.3 Mental state/behaviour

There was no significant difference in frequency of clinically significant agitation between groups (Analysis 1.4).

1.4 Adverse effects

We found no significant difference in extrapyramidal side effect (EPSE) rates between groups (n = 26, 1 RCT, RR 0.51, 95% CI 0.15 to 1.7). We also found no significant difference in use of antiparkinsonism drugs between groups (n = 26, 1 RCT, RR 0.5, 95% CI 0.15 to 1.7).

2. DOSES: 2. LOW DOSE (> 1.5 to 3 mg/day) versus OTHER DOSES

We found one small study (n = 26) comparing low dose with ultra low dose (> 0.25 to 1.5 mg/day) (Kapur 2000). A further small study compared low dose with standard higher dose (> 7.5 to 15 mg/day) (Oosthuizen 2004).

2.1 Leaving the study early

We found few participants left before completion with no clear difference in acceptability between low dose and ultra low dose (n = 26, 1 RCT, RR 3.5, 95% CI 0.4 to 29).
We found there were numerically more dropouts in the standard higher dose (8/20) than the low dose (3/20) groups, but this difference was not statistically significant.

2.2 Global state

More people in the ultra low dose group showed no significant response during the study than in the low dose group. This did not reach conventional levels of statistical significance (n = 26, 1 RCT, RR 0.53, 95% CI 0.3 to 1.1). Use of adjunctive medication for sedation occurred less frequently in the ultra low dose group compared with low dose group, but again not to a statistically significant degree (n = 26, 1 RCT, RR 1.75, 95% CI 0.4 to 9). Mean dose of lorazepam was also similar between low and standard higher dose groups (Analysis 2.5), as was endpoint CGI scores (Analysis 2.4).

2.3 Mental state/behaviour

Clinically significant agitation was infrequent and no different in either low or ultra low groups (n = 26, 1 RCT, RR 1.75, 95% CI 0.4 to 9). Data comparing low dose with standard higher doses was presented as endpoint PANSS differential scores (Analysis 2.7; Analysis 2.9), CGI scores (Analysis 2.4), and Calgary Depression Rating Scale scores (Analysis 2.10), which were all highly skewed with the exception of the PANSS positive subscale, which showed no significant difference between groups (n = 40, 1 RCT, MD 0.8, 95% CI -4.1 to 5.7).

2.4 Adverse effects

EPAEs were less frequent for people allocated the ultra low dose compared to low dose, but not to a statistically significant degree (n = 26, 1 RCT, RR 1.94, 95% CI 0.6 to 6.5), as did use of antiparkinsonism drugs (n = 26, 1 RCT, RR 1.94, 95% CI 0.6 to 6.5).
Dystonic reactions (n = 40, 1 RCT, RR 0.33, 95% CI 0.1 to 1.5), dyskinesia (n = 40, 1 RCT, RR 0.2, 95% CI 0.01 to 3.9) and akathisia (n = 40, 1 RCT, RR 0.38, 95% CI 0.1 to 1.2) occurred more commonly in the standard higher dose group compared to the low dose group but the differences were not statistically significant. Mean dose of orphenadrine used in the standard higher dose group was significantly higher than in the low dose range, though data were skewed (Analysis 2.13). Similarly, prolactin levels at endpoint were significantly higher in the standard higher dose group though data were again skewed (Analysis 2.17).

3. DOSES: 3. STANDARD LOWER DOSE (> 3 mg to 7.5 mg/day) versus OTHER DOSES

3.1 Leaving the study early

Standard lower dose was more acceptable than standard higher dose (> 7.5 to 15 mg/day) (n = 64, 2 RCTs, RR 0.1, 95% CI 0.01 to 2.1). When the standard lower dose was compared with high dose (> 15 to 35 mg/day) the results did not conclusively show that the lower of the two doses was more acceptable. This did not reach a statistically significant level (n = 191, 4 RCTs, RR 0.78, 95% CI 0.5 to 1.3). There also was no discernible difference in the numbers leaving the groups early when the standard lower dose was compared with very high dose (> 35 mg/day) (n = 86, 2 RCTs, RR 0.7, 95% CI 0.3 to 1.6).

3.2 Global state

About the same numbers of people allocated to the standard lower dose group showed no clinically important improvement in global state compared with standard higher dose (n = 48, 1 RCT, RR 1.09, 95% CI 0.7 to 1.8) and with high dose (n = 81, 2 RCTs, RR 0.95, 95% CI 0.8 to 1.2). The need for sedative medication was evenly balanced between standard lower and standard higher dose groups (n = 238, 4 RCT, RR 0.99, 95% CI 0.8 to 1.2).

3.3 Mental state/behaviour

One small study (n = 65) reported on agitation (Volavka 1995). There was no difference for those allocated standard lower dose compared with high dose (RR 0.93, 95% CI 0.7 to 1.3).

3.4 Adverse effects

Adverse effects were measured by development of clinically significant EPSE and use of antiparkinsonism drugs.
Compared with standard higher dose, the standard lower dose was not shown to spare people clinically significant EPAEs (n = 64, 2 RCTs, RR 0.12, 95% CI 0.01 to 2.1). Compared with a high dose, people allocated the standard lower dose had fewer adverse effects (n = 144, 3 RCTs, RR 0.59, 95% CI 0.5 to 0.8, NNTH 3, 95% CI 2 to 6). When the same standard lower dose was compared with very high dose, however, this finding was not replicated (n = 86, 2 RCTs, RR 0.7, 95% CI 0.5 to 1.1).

4. DOSES: 4. STANDARD HIGHER DOSE (7.5 to 15 mg/day) versus OTHER DOSES

4.1 Mortality

Only one small study (n = 20), comparing standard higher dose with very high dose (> 35 mg/day), reported on death stating that none had occurred (Neborsky 1981).

4.2 Leaving the study early

Two studies comparing standard higher dose with very high dose reported early study attrition (between 3 and 14 days). There was no clear difference between groups (n = 83, 2 RCTs, RR 0.72, 95% CI 0.3 to 2). One study reported one participant leaving on day one or two (Louza 1988).
Several studies reported attrition between two and 10 weeks. There was no difference between the standard higher dose group and low dose (> 1.5 to 3 mg/day) (n = 40, 1 RCT, RR 2.67, 95% CI 0.8 to 8.6), standard lower dose (> 3 to 7.5 mg/day) (n = 64, 2 RCTs, RR 8.31, 95% CI 0.5 to 146), high dose (> 15 to 35 mg/day) (n = 188, 4 RCTs, RR 0.87, 95% CI 0.5 to 1.7), or very high dose (n = 74, 2 RCTs, RR 0.62, 95% CI 0.3 to 1.5).

4.3 Global state

One study comparing standard higher dose with very high dose reported early appraisal of global state (between 3 and 14 days). There was no clear difference between groups (n = 20, 1 RCT, RR 3.0, 95% CI 0.4 to 24).
A series of small trials, even when combined, showed no difference for the outcome of 'no significant global improvement' when standard higher dose was compared with standard lower dose (n = 48, 1 RCT, RR 1.09, 95% CI 0.7 to 1.7), high dose (n = 106, 2 RCTs, RR 1.33, 95% CI 0.9 to 2.1), or very high dose (n = 58, 1 RCT, RR 1.29, 95% CI 0.8 to 2).
Mean change scores were also equivocal. Numbers of people needing additional sedation not significantly when standard higher dose was compared with high dose (n = 58, 1 RCT, RR 1.0, 95% CI 0.5 to 2), or very high dose (n = 58, 1 RCT, RR 1.43, 95% CI 0.6 to 3).
One trial reported endpoint CGI scores (Analysis 4.9) and mean use of lorazepam (Analysis 4.10) in standard higher and low dose groups. The results were similar between groups and skewed.

4.4 Mental state/behaviour

Early appraisal of psychotic symptoms (between 3 and 14 days) was undertaken in the one study that compared standard higher dose with very high dose. There was no clear difference between groups (n = 20, 1 RCT, RR 3.0, 95% CI 0.4 to 24).
PANSS positive subscale endpoint score was not significantly different between standard higher and low dose groups (n = 40, 1 RCT, MD -0.8, 95% CI -5.56 to 3.96). PANSS general score (Analysis 4.13), PANSS negative subscale (Analysis 4.15) and Cal-

gary Depression Rating Scale (Analysis 4.16) were all similar between groups and skewed.
Rifkin 1991 reported on agitation between 2 and 10 weeks, but showed no differences between standard higher dose and high dose (n = 58, 1 RCT, RR 1.0, 95% CI 0.5 to 2), or very high dose (n = 58, 1 RCT, RR 1.43, 95% CI 0.6 to 3).

4.5 Adverse effects

Acute dystonia was no more common in those allocated standard higher dose than in people given very high dose (n = 63, 1 RCT, RR 0.69, 95% CI 0.4 to 1.2). Neither were clinically significant EPAEs clearly more common for people taking standard higher dose than those given standard lower dose (n = 64, 2 RCTs, RR 8.3, 95% CI 0.5 to 146). Mean change scores for EPAEs were also equivocal. Conversely, dystonic reaction (n = 40, 1 RCT, RR 3, 95% CI 0.7 to 13.1), dyskinesia (n = 40, 1 RCT, RR 5, 95% CI 0.3 to 98) and akathisia (n = 40, 1 RCT, RR 2.7, 95% CI 0.8 to 8.6) appeared more common in the standard higher dose group than the low dose group though not to a significant level.
Louza 1988 compared EPSE between standard higher dose versus high and very high doses combined but again, there was no significant difference (Analysis 4.21).
Mean values of orphenadrine used (Analysis 4.22) and endpoint prolactin levels (Analysis 4.25) were significantly higher in the standard higher dose group to the low dose group, though data were skewed.
Finally, only one study reported on postural hypertension (n = 63) but showed no difference between people taking standard higher dose compared with people taking very high dose (RR 0.7, 95% CI 0.03 to 16) (Donlon 1980).

5. DOSES: 5. HIGH DOSE (> 15 to 35 mg/day) versus OTHER DOSES

5.1 Leaving the study early

No differences were apparent when high dose was compared with standard lower dose (> 3 to 7.5 mg/day) (n = 191, 4 RCTs, RR 1.28, 95% CI 0.8 to 2.1), standard higher dose (> 7.5 to 15 mg/day) (n = 188, 4 RCTs, RR 1.16, 95% CI 0.6 to 2.2) and very high dose (> 35 mg/day) (n = 312, 5 RCTs, RR 1.04, 95% CI 0.7 to 1.6).

5.2 Global state

Even combination of several studies found no differences when high dose was compared with standard lower dose (n = 81, 2 RCTs, RR 1.06, 95% CI 0.8 to 1.3) and very high dose (n = 255, 4 RCTs, RR 0.92, 95% CI 0.8 to 1.1). Change scores also found no clear differences when high dose was compared with standard higher dose and very high dose . One study used the outcome of 'no psychotic symptoms' to compare high dose and standard lower dose but no people in either group met the description.
The risk of needing additional sedation was greater for people given high dose compared with standard lower dose (n = 144, 3 RCTs, RR 1.40, 95% CI 1.1 to 1.8, NNTH 3, 95% CI 2 to 6). No differences were apparent when high dose was compared with standard higher dose (n = 58, 1 RCT, RR 1.0, 95% CI 0.5 to 2), and very high dose (n = 115, 2 RCTs, RR 1.07, 95% CI 0.7 to 1.7). The use of sedatives at high dose compared to standard lower dose between 0 and 14 days specifically was not significant (n = 47, 1 RCT, RR 0.74, 95% CI 0.4 to 1.3), similarly between 2 and 10 weeks (n = 47, 1 RCT, RR 0.29, 95% CI 0.03 to 2.6).

5.3 Mental state/behaviour

For the outcome of 'no clinically important change in psychotic symptoms' there were no differences for those given high dose compared with people allocated to very high dose (n = 92, 1 RCT, RR 1.57, 95% CI 0.8 to 3.1).
Agitation was equally common for people given high dose versus standard lower dose (n = 65, 1 RCT, RR 1.08, 95% CI 0.8 to 1.5), standard higher dose (n = 58, 1 RCT, RR 1.0, 95% CI 0.5 to 2), or very high doses (n = 115, 2 RCTs, RR 1.07, 95% CI 0.7 to 1.7). Mean scores were also equivocal. Although sustained high doses of haloperidol are extensively used to treat agitation in acute phases of schizophrenia (Baldessarini 1988), there were no statistically significant differences between the dose ranges in studies that reported on this outcome. However, there are few studies that examine this outcome.
It should be emphasised that this review does not have any information regarding the benefits and tolerability of 'as needed' doses of antipsychotics. For this, readers should examine the findings from a complementary Cochrane review (Whicher 2002).

5.4 Adverse effects

High doses resulted in more EPAEs than standard lower doses (n = 144, 3 RCTs, RR 1.7, 95% CI 1.3 to 2.2, NNTH 3, 95% CI 2 to 6), but the same levels as very high doses (n = 114, 2 RCTs, RR 1.03, 95% CI 0.7 to 1.4). Change scores in ratings of EPAEs were, compared with standard higher dose and very high doses, equivocal and uninformative. More people allocated to high dose needed drugs to counter parkinsonism compared with standard lower dose (n = 144, 3 RCTs, RR 1.7, 95% CI 1.3 to 2.2, NNTH 3, 95% CI 2 to 6). Compared with very high doses people given high dose did not need more antiparkinsonism drugs (n = 114, 2 RCTs, RR 1.13, 95% CI 0.9 to 1.4). Akathisia was as common for people allocated to high dose as people allocated to very high dose (n = 57, 1 RCT, RR 0.71, 95% CI 0.4 to 1.4).
One study considered blurred vision in high and standard lower dose groups, but there was no significant difference between the groups.

6. DOSES: 6. VERY HIGH DOSE (> 35 mg/day) versus OTHER DOSES

6.1 Mortality

Only one small study (n = 20), comparing standard higher dose (> 7.5 to 15 mg/day) with very high dose, reported on death, stating that none had occurred (Neborsky 1981).

6.2 Leaving the study early

Two studies comparing very high dose with standard higher dose reported early study attrition (between 3 and 14 days). There was no clear difference between groups (n = 83, 2 RCTs, RR 1.4, 95% CI 0.5 to 4).

Several studies reported study attrition between 2 and 10 weeks. There was no clear difference between the very high dose group and standard lower dose (> 3 to 7.5 mg/day) (n = 86, 2 RCTs, RR 1.42, 95% CI 0.6 to 3.2), standard higher dose (n = 74, 2 RCTs, RR 1.62, 95% CI 0.7 to 4), or high dose (> 15 to 35 mg/day) (n = 312, 5 RCTs, RR 0.96, 95% CI 0.6 to 1.5).

6.3 Global state

One study comparing very high dose with standard higher dose reported early appraisal of global state (between 3 and 14 days). There was no clear difference between groups (n = 20, 1 RCT, RR 0.33, 95% CI 0.04 to 3).

For the outcome of 'no global improvement between 2 and 10 weeks', no clear differences were found when very high dose was compared with standard higher dose (n = 58, 1 RCT, RR 0.78, 95% CI 0.5 to 1.3), and high dose (n = 255, 4 RCTs, RR 1.09, 95% CI 0.9 to 1.3). Mean change scores comparing very high dose with standard higher dose and high dose were equally equivocal. The numbers of people needing additional sedation was not significantly different when very high dose was compared with standard higher dose (n = 58, 1 RCT, RR 0.7, 95% CI 0.3 to 1.6) or high dose (n = 115, 2 RCTs, RR 0.94, 95% CI 0.6 to 1.5).

6.4 Mental state/behaviour

Very high doses were no different to any other doses for various measures of mental state/behaviour. For the outcome of 'no clinically important change in psychotic symptoms between three days and two weeks,' very high doses were not significantly different to standard higher doses (n = 20, 1 RCT, RR 0.33, 95% CI 0.04 to 2.7). There was also no significant difference in changes in psychotic symptoms when very high dose were compared with high dose (n = 92, 1 RCT, RR 1.18, 95% CI 0.9 to 1.5). Mean change scores on rating of mental state were also equivocal for a comparison of very high dose versus high dose. Finally, agitation was equally common for people given very high dose when compared with both standard higher dose (n = 58, 1 RCT, RR 0.7, 95% CI 0.3 to 1.6) and high dose (n = 115, 2 RCTs, RR 0.94, 95% CI 0.6 to 1.5).

6.5 Adverse effects

Acute dystonia was as common for people allocated very high dose as for people given standard higher dose (n = 63, 1 RCT, RR 1.45, 95% CI 0.9 to 2.5). However, when compared with standard lower dose, very high doses did not cause more clinically significant EPAEs (n = 86, 2 RCTs, RR 1.42, 95% CI 0.9 to 2.2). When very high dose was compared with high dose, studies found no difference (n = 114, 2 RCTs, RR 0.97, 95% CI 0.7 to 1.4). Mean scores where very high dose was compared with standard higher dose or high dose, were equivocal and uninformative. Use of drugs to counter parkinsonism was as common for those allocated very high dose as for people given standard lower doses (n = 70, 1 RCT, RR 1.25, 95% CI 0.8 to 2) and high dose (n = 114, 2 RCTs, RR 0.89, 95% CI 0.7 to 1.1). Akathisia was common, but no more so for people taking very high dose compared with high dose (n = 57, 1 RCT, RR 1.4, 95% CI 0.7 to 2.7).

Finally, postural hypotension was not common and had the same risk of occurrence for people taking very high doses and those given standard higher dose (n = 63, 1 RCT, RR 1.43, 95% CI 0.1 to 34).

7. DOSES: 7. COMBINED HIGH AND VERY HIGH DOSES (> 15 mg/day) versus OTHER DOSES

7.1 Leaving the study early

One study compared doses above 15 mg/day with standard higher doses (> 7.5 to 15 mg/day). There was no significant difference between groups in either early attrition (1 to 2 days) or late (2 to 10 weeks) (Analysis 7.1).

7.2 Adverse effects

There was no significant difference in rates of EPSE between the combined high and very high group and the standard higher group (Analysis 7.1).

8. PLASMA LEVELS: 1. VERY LOW LEVELS (> 1.4 to 3.5 ng/mL) versus OTHER PLASMA LEVELS

8.1 Leaving the study early

Very low plasma levels (> 3.5 to 7 ng/mL) resulted in fewer people leaving the studies early when compared to medium plasma levels (> 7.0 to 16.5 ng/mL), but this did reach statistical significance (n = 128, 2 RCTs, RR 0.61, 95% CI 0.4 to 1.1). There was no clear

difference when very low plasma levels were compared with high levels (> 16.5 ng/mL) (n = 70, 1 RCT, RR 0.96, 95% CI 0.4 to 2.4).

8.2 Global state

One study monitored 'no clinically significant improvement in global state' (n = 65) and when very low plasma levels were compared with medium levels (> 7.0 to 16.5 ng/mL), the trialists found no difference (RR 0.8, 95% CI 0.3 to 1.9) (Volavka 1995).

8.3 Mental state/behaviour

One study looked at 'significant response in positive symptoms' between very low and medium plasma level but found no significant differences (Analysis 8.3).

8.4 Adverse effects

Very low plasma levels resulted in fewer clinically significant EPEAs than medium levels (n = 128, 2 RCTs, RR 0.63, 95% CI 0.5 to 0.8, NNTH 3, 95% CI 2 to 7). When the same very low levels were compared with high plasma levels, no clear differences were found (n = 70, 1 RCT, RR 0.8, 95% CI 0.5 to 1.2).

9. PLASMA LEVELS: 2. MEDIUM LEVELS (> 7.0 to 16.5 ng/mL) versus OTHER PLASMA LEVELS

9.1 Leaving the study early

Compared with very low plasma levels (> 1.4 to 3.5 ng/mL), medium levels did not promote study attrition (n = 128, 2 RCTs, RR 1.63, 95% CI 0.9 to 3). This also applied to comparisons with high plasma levels (> 16.5 ng/mL), although results were heterogeneous (n = 149, 2 RCTs, RR 1.1, 95% CI 0.6 to 2.1, heterogeneous P value = 0.074).

9.2 Global state

Medium plasma levels did not result in different rates of global improvement when compared with either very low plasma levels (n = 65, 1 RCT, RR 0.80, 95% CI 0.3 to 1.9) or high plasma levels (n = 92, 1 RCT, RR 1.57, 95% CI 0.8 to 3.1).

9.3 Mental state/behaviour

Two studies looked at significant response in positive symptoms between medium and low plasma levels and found no significant differences (Analysis 9.3).

9.4 Adverse effects

Clinically significant EPAEs were more common for those allocated to medium plasma levels compared with people in a very low plasma level group (n = 128, 2 RCTs, RR 1.59, 95% CI 1.2 to 2.1, NNTH 3, 95% CI 2 to 7). There was no clear difference for those in a medium plasma level group compared with a high level group (n = 59, 1 RCT, RR 1.28, 95% CI 0.9 to 1.8).

10. PLASMA LEVELS: 3. HIGH LEVELS (> 16.5 ng/mL) versus OTHER PLASMA LEVELS

10.1 Leaving the study early

Compared with both very low plasma levels (> 1.4 to 3.5 ng/mL), high plasma levels did not affect study attrition (n = 70, 1 RCT, RR 1.04, 95% CI 0.4 to 2.6), neither did medium levels (> 7 to 16.5 ng/mL) (n = 149, 2 RCTs, RR 0.91, 95% CI 0.5 to 1.7, heterogeneous P value = 0.074).

10.2 Global response

One small study (n = 92) reported that there was no difference for those allocated to high levels compared with medium plasma levels (RR 1.18, 95% CI 0.9 to 1.5).

10.3 Adverse effects

Over half of people given haloperidol, irrespective of plasma level, had significant EPAEs (high levels versus very low levels: n = 70, 1 RCT, RR 1.25, 95% CI 0.8 to 2; high levels versus medium levels: n = 59, 2 RCTs, RR 0.8, 95% CI 0.5 to 1.1).

11. Sensitivity analyses

There were no data to undertake analyses separately for people in their first episode of illness. As regards use of operational diagnostic criteria, only Curtis 1995, Donlon 1980 and Simpson 1967 did not use operational criteria that were clearly described. Where these trials contributed to outcomes in which meta-analysis had taken place, in no case did they alter the final result to an important extent. When these trials were the sole contributor to an outcome - for example Analysis 8.3 or Analysis 9.3 in the case of Curtis 1995 - removal of these data deleted the outcome as a whole. However, there is no evidence that trials using operational criteria to diagnose people with schizophrenia have substantially different results from trials that imply that such stipulated criteria were not employed. Finally we were not confident that trials specifically included people whose illness would be recognised as treatment resistant, and therefore we did not undertake a sensitivity analysis.

12. Publication bias

There was an insufficient number of trials per comparison (maximum of five trials) to conduct a valid funnel plot to examine for possible publication bias.

DISCUSSION

Summary of main results

1. DOSES: 1. ULTRA LOW DOSE (> 0.25 to 1.5 mg/day) versus OTHER DOSES

Kapur 2000 compared ultra low dose to low dose (> 1.5 to 3 mg/day) and found no differences in terms of leaving the study early (both treatments were very acceptable), global measures of outcome, mental state and adverse effects. For a study involving 26 people, it would have been surprising if any outcomes had suggested a clear difference in groups, but that several favoured the ultra low dose group, even if they did not reach conventional levels of statistical significance. This suggests that this question could be further investigated.

2. DOSES: 2. LOW DOSE (> 1.5 to 3 mg/day) versus OTHER DOSES

Oosthuizen 2004 compared low dose to standard higher dose (> 7.5 to 15 mg/day). Measures of efficacy of intervention such as PANSS and CGI were similar between groups, the Calgary Depression Rating Scale was also unequivocal as was lorazepam use for agitation. Some of the adverse effects measures - such as mean dose of orphenadrine used and mean prolactin level - were significantly higher in the high dose group (> 15 to 35 mg/day) suggesting better tolerability of low dose. Rates of attrition, dystonia, dyskinesia and akathisia all favoured use of a low dose though results for these measures were not statistically significant. This study involved 40 participants and was, therefore, underpowered to assess efficacy and tolerability in all areas adequately. No other studies investigated this comparison.

3. DOSES: 3. STANDARD LOWER DOSE (> 3 to 7.5 mg/day) versus OTHER DOSES

The standard lower dose was, generally, more acceptable than any of the higher doses, as measured in terms of leaving the study early (Summary of findings for the main comparison). However, no findings reached conventional levels of statistical significance but all comparisons involved small numbers (maximum 191). Considering the importance of this question, it would seem that more investigation is justified.

Standard lower dose was as effective, in terms of global state and mental state, as standard higher dose (> 7.5 to 15 mg/day) and high dose (> 15 to 35 mg/day), but again, the numbers involved in these comparisons were small (maximum 126). This lack of difference is striking given the tendency in clinical practice to increase the dose of people who do not respond, or to utilise high doses from the start of treatment. The finding is probably widely applicable, given that global improvement was defined in a variety of ways across studies. Considering the potential for the introduction of bias into these outcomes, this finding should only be considered as hypothesis-generating.

Standard lower dose consistently resulted in fewer people experiencing EPAEs, when compared with higher doses. In the comparison involving most people (n = 144), this did reach statistical significance with an NNTB of three. This is an important finding given the frequent use of the latter dose range in comparative trials of new antipsychotic agents and in clinical practice. It is also interesting to note that this finding had some preliminary evidence as early as 1967 (Simpson 1967). Unfortunately, this was not re-examined in a high-quality study until 1984 (Garver 1984), and was not reported appropriately in a study until 1991 (McEvoy 1991). Nevertheless, despite this favourable result for the standard lower dose, nearly half of the people given standard lower dose either experienced these distressing adverse effects or left the study early.

4. DOSES: 4. STANDARD HIGHER DOSE (7.5 to 15 mg/day) versus OTHER DOSES

All relevant studies were small and, even when combined, the totals amounted to no more than 188 people.

Standard higher dose did not result in people leaving the short studies early, when compared with standard lower dose (> 3 to 7.5 mg/day), high dose (> 15 to 35 mg/day) or very high dose (> 35 mg/day). There were also no clear differences for global state or mental state/behaviour. Most data were reported for the comparison of standard higher dose with high dose at 2 to 10 weeks (n = 106), for 'no clinically important improvement in global state'. Numbers in groups were evenly balanced, with more than one-third of participants not showing any important degree of improvement. The fact that there was no difference in response between dose groups may be suggestive that dose level is less important, for global state and mental state outcomes, than just taking the antipsychotic.

While no comparisons found differences in the few adverse effects reported, there were the suggestions, consistent with the other data in this review, that higher doses led to more adverse effects.

5. DOSES: 5. HIGH DOSE (> 15 to 35 mg/day) versus OTHER DOSES

These set of comparisons contain some of the highest numbers of participants in this review (maximum 312).

High dose haloperidol seems as acceptable, in terms of leaving these short studies early, as standard lower dose (> 3 to 7.5 mg/day) (n = 191), standard higher (> 7.5 to 15 mg/day) (n = 188) and very high doses (> 35 mg/day) (n = 312).

For outcomes relevant to mental state/behaviour, the numbers in each comparison were low and no differences were discernible. It does seem surprising that so little research reporting useful data has been undertaken in this key area.

Direct comparisons for measures of global state found no differences when high dose was compared with standard lower, standard higher dose and very high doses. The risk of needing additional sedation was greater for people given high dose compared with standard lower (n = 144, NNTH 3), but not with standard higher dose, and very high doses. This must be seen as an advantage of the standard lower dose compared with the high dose. High doses also resulted in more people experiencing EPAEs or needing drugs to counter parkinsonism compared with standard lower doses (n = 144, NNTH 3), but the same levels as very high doses (n = 134). Akathisia was as common for people allocated to high dose as people allocatedtovery high dose.

There is no evidence that a high dose is better than standard low for mental state/global state outcomes, and the findings favouring standard low dose for adverse effect outcomes is compelling.

6. DOSES: 6. VERY HIGH DOSE (> 35 mg/day) versus OTHER DOSES

Very high doses did not disproportionately cause people to leave studies before completion. Very high doses were as clinically effective for global state/mental state outcomes as standard higher dose (> 7.5 to 15 mg/day) (n = 58), and high dose (> 15 to 35 mg/day) (n = 255).

Several movement disorder adverse effects were not significantly more common for people given very high doses compared with high dose (n = 117), standard higher dose (n = 63) and even standard lower dose (> 3 to 7.5 mg/day) (n = 86). This is a somewhat surprising result considering the consistent findings thus far in this review - where higher doses of haloperidol do result in more adverse effects, and is difficult to explain.

7. DOSES: 7. COMBINED HIGH AND VERY HIGH DOSE (> 15 mg/day) versus OTHER DOSES

Louza 1988 found no differences in attrition rates or EPSE between more than 15 mg/day and standard higher dose (> 7.5 to 15 mg/day). This was a small, single study comparison (n = 20).

8. PLASMA LEVELS: 1. VERY LOW LEVELS (> 1.4 to 3.5 ng/mL) versus OTHER PLASMA LEVELS

Very low plasma levels (> 3.5 to 7 ng/mL) resulted in fewer people leaving the studies early when compared to medium plasma levels (> 7.0 to 16.5 ng/mL), but this did not quite reach conventional levels of statistical significance (n = 128). When compared with medium plasma levels, very low plasma levels were not clearly different for the outcome of 'no clinically significant improvement in global state' (n = 65). As regards adverse effects, however, very low plasma levels resulted in fewer clinically significant EPAEs than medium levels (n = 128, NNTH 3). This finding was not replicated when the very low levels were compared with high plasma levels (> 16.5 ng/mL), but this may have been because of the low power of this comparison (n = 70).

9. PLASMA LEVELS: 2. MEDIUM LEVELS (> 7.0 to 16.5 ng/mL) versus OTHER PLASMA LEVELS

Compared with very low plasma levels (> 1.4 to 3.5 ng/mL) (n = 128), and high plasma levels (> 16.5 ng/mL) (n = 149), medium levels did not clearly promote study attrition or encourage different rates of global improvement.

Clinically significant EPAEs were more common for those allocated to medium plasma levels compared with people in a very low plasma level group (n = 128, NNTH 3), but no different when compared with the high plasma level group (n = 59). This could have been a function of power and the consistent finding is that lower levels/doses of haloperidol do lead to fewer adverse effects.

10. PLASMA LEVELS: 3. HIGH LEVELS (> 16.5 ng/mL) versus OTHER PLASMA LEVELS

Compared with both very low plasma levels (> 1.4 to 3.5 ng/mL) (n = 70) high plasma levels did not clearly affect study attrition, or when compared with medium plasma levels (> 7 to 16.5 ng/mL) (n = 149). There was no difference for those allocated to high levels compared with medium plasma levels (n = 92) for global state outcomes, and no differences for adverse effects. However, over half of the participants given haloperidol, irrespective of plasma level, had significant EPAEs (versus very low plasma levels, n = 70; versus medium plasma levels, n = 59).

Even if the global and mental state changes do not seem greatly sensitive to dose, haloperidol is a common cause of adverse effects and the latter tend to be more common with higher dose/plasma level.

Overall completeness and applicability of evidence

This study benefited from extensive searches of the worldwide literature regarding haloperidol dosage. Some of the non-English studies may not have been included without such extensive searches (Klieser 1987; Liang 1987). Another major strength was that all comparisons were restricted to randomised studies of the same drug, which has not been the case with previous reviews (Baldessarini 1984; Bollini 1994). This should significantly reduce

the potential for bias introduced by using differing measures for the various outcomes studied.

A major weakness of this study was that for several outcomes there was either minimal or no data from high-quality randomised trials. This resulted in many findings being prone to type II errors (a masking of a real effect by wide CIs), and several important hypotheses being unanswered.

Quality of the evidence

The quality of included studies was generally poor, with authors not describing the randomisation process, allocation concealment and blinding (Figure 3; Figure 4). This could mean that even these few results are prone to biases and an overestimate of effect. Poor reporting of the process and outcomes of the trials was common. We excluded many studies due to a lack of information about the number of people randomised to various treatment arms.

The number and size of trials was particularly poor for the dose range of primary interest (low dose > 1.5 to 3 mg/day) and the lowest dose range (ultra low dose > 0.25 to 1.5 mg/day). Only one small study (n = 26) compared the lowest two groups (Kapur 2000), and no study compared the primary dose range of interest to the next highest dose range. One further study (n = 40) compared low dose and standard higher dose (> 7.5 to 15 mg/day) (Oosthuizen 2004).

Potential biases in the review process

While the authors made every effort to avoid publication bias, it remains possible that not all relevant studies have been identified as yet. The Cochrane Register of studies could still represent a biased sample of trials. However, we consider that a large unpublished trial in this area is implausible and that we are more likely to have overlooked other small studies.

We do not think that we have biased the review process by holding prior opinions and having seen past reviews. However, we have not tested this in undertaking the work.

Agreements and disagreements with other studies or reviews

A systematic review of randomised trials of the maintenance phase of schizophrenia reached a similar conclusion to that made in this review in 2002 (Waraich 2002), and by others even longer ago (Bollini 1994); they concluded that there is no benefit in administering doses higher than 375 mg/day of chlorpromazine or the equivalent of such a dose when using other antipsychotics (about 7.5 mg/day of haloperidol). Despite this, many studies have been conducted since using much higher doses than 7.5 mg/day of haloperidol (Kennedy 2002; Leucht 1999; Rosenheck 2003; Srisurapanont 2002).

AUTHORS' CONCLUSIONS

Implications for practice

Almost all data in this review were at modest to high risk of bias. All implications must be tempered with this consideration.

1. For clinicians

For people who are acutely ill, there is no evidence of an important drop off in efficacy as the dose of haloperidol declines; this is true to a dose range of > 0.25 to 1.5 mg/day. There are greater numbers of studies examining higher dose ranges and these suggest no clear evidence of advantages of doses greater than the > 3 to 7.5 mg/day range. There is no information on longer-term outcomes from haloperidol dose studies.

Doses above the > 3 to 7.5 mg/day range are associated with increased risk of extrapyramidal adverse effects and probably should be avoided, especially given there is no clear evidence for added efficacy. There are, unfortunately, no data that compare the standard lower dose range (> 3 to 7.5 mg/day) with the next lowest dose range (> 1.5 to 3 mg/day), so it is currently impossible to determine from randomised controlled trials whether there may be added benefit in using even lower dose in terms of the reduction of adverse effects. There are no data regarding long-term adverse effects, such as rates of tardive dyskinesia, in comparative haloperidol dose trials.

This review does not answer the question as to whether there is a dose of haloperidol that may be no different from placebo in terms of extrapyramidal adverse effects or tardive dyskinesia.

2. For people with schizophrenia

Generally, there are unlikely to be major benefits from a dose of haloperidol higher than > 3 to 7.5 mg/day for people with schizophrenia. This review cannot answer the question as to whether there may be modest benefits to higher doses, neither can it rule out major benefits of high doses in selected individuals. Doses higher than > 3 to 7.5 mg/day are, however, associated with more extrapyramidal adverse effects. The lowest effective dose of haloperidol during the non-acute phase of illness is still unknown. People with schizophrenia should note that lack of long-term data is also a problem with newer antipsychotic agents (Duggan 2002; Kennedy 2002; Leucht 1999; Srisurapanont 2002).

3. For policy makers

There are no data regarding the impact of varying dose ranges of haloperidol on health service utilisation and costs.

This review highlights the need for funding agencies, industry and drug regulatory authorities to collaborate to ensure that clinical trials utilise appropriate dose ranges when comparing new antipsychotic drugs to reference drugs. These agencies should commission

or access existing systematic reviews that closely examine dosage issues for reference drugs. They should then ensure that this information is used in the design of clinical trials at the planning stages. Such an intervention would be likely to decrease any real or perceived bias regarding the tolerability and efficacy of new drug agents in the future. This review cannot definitively answer the question as to whether there is a highly tolerable and efficacious dose range of haloperidol that might be an inexpensive equivalent to some of the newer antipsychotic agents. However, it does highlight the possibility that much of the added tolerability attributed to newer drugs is secondary to an inappropriate dosage of haloperidol as a comparator. This issue deserves to be considered when decisions regarding coverage of the new drugs on institutional formularies are being debated.

Implications for research

1. Importance of systematic reviews

This review clearly highlights the importance of systematic reviews for informing research activities. Had this systematic review been completed in 1991, there would have already been 16 studies (nine of these with completer data only - see Characteristics of excluded studies) that reported no significant benefit in randomisation to higher doses of haloperidol for people with acute schizophrenia. Four of these studies involved the standard lower dose range (> 3 to 7.5 mg/day); the earliest study was conducted in 1967. If these results had been incorporated into drug trials of new agents, we would probably have a much clearer idea of the comparative benefits of the newer agents than we do at present.

The issue here is not only the matter of publishing studies that address dosage issues, but is also the need for the dissemination of the results of these studies throughout clinical and research practice. Researchers need to work together with funding agencies, the pharmaceutical industry and drug regulatory authorities to ensure that future comparative trials make use of the most up-to-date and systematic dosage literature on reference antipsychotic drugs so that future trials are not prone to real or perceived bias related to inappropriate dose comparisons.

Cochrane systematic reviews of newer antipsychotic agents have identified six studies that compare new agents with doses of older antipsychotics equivalent to > 3 to 7.5 mg/day of haloperidol, and have a dropout rate of less than 50%. Three involve risperidone (Emsley 1995; Hoyberg 1993; Huttunen 1995), and three involve quetiapine (Kudo 1999; Murasaki 1999; Peuskens 1997). There are no such studies identified in Cochrane reviews involving ziprasidone or olanzapine (Bagnall 2002; Duggan 2002). While the tolerability to the new agents in these studies is generally somewhat higher than to the older drugs, it is much less so than in studies that have utilised high doses of haloperidol as a comparator. In all six studies, the point estimate for the efficacy of the new agent was lower than that of the reference older drug. Thus, the hypothesis that low-dose haloperidol is an inexpensive equivalent to new antipsychotic agents remains to be excluded.

2. The next update

We are aware that this review is repetitive and lists several sets of data twice. For the next update, we will consider only listing each set of data once and directing the reader to other comparisons when relevant. We will also consider using OR rather than RR. We would be interested in the opinion of readers on this point.

3. Future studies

Future antipsychotic dose range trials should closely examine outcomes that have been neglected. These include service utilisation, quality of life, satisfaction with treatment and agitation. The latter is particularly important as behavioural agitation may have different dose-response characteristics than other dimensions of symptoms of schizophrenia. This may partially explain the use of higher doses of neuroleptic agents. We do realise that trial design is something that is to be undertaken with great care and detail, but we suggest an outline for a study that would be most informative and address some of the questions currently unanswered (Table 1).
Although it would fall beyond the remit of this review, long-term data on the effects of haloperidol for relapse prevention is also needed. The question of long-term relapse rates has been given new impetus by the finding that many newer drugs dissociate very quickly from dopamine type 2 (D_2) receptors in the brain compared to drugs such as haloperidol (Kapur 2001). It would be useful to know whether treatment with low-dose haloperidol leads to lower relapse rates compared to new agents in people who take medication intermittently.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Curtis 1995

Methods	Allocation: randomised - no details available. Blindness: no details. Duration: not clear (time to desired haloperidol level or putative receptor occupancy level)
Participants	Diagnosis: schizophrenia (unclear diagnostic criteria). N = 53. Age: no details. Sex: no details. History: no details. Setting: no details.
Interventions	1. Haloperidol: dose to 50% Bromocriptine Growth Hormone Test* blockade level (mean plasma level < 0 ng/mL). N = 5 2. Haloperidol: dose to 100% Bromocriptine Growth Hormone Test blockade level (mean plasma level 1.5 ng/mL). N = 19.** 3. Haloperidol: plasma level 10 ng/mL (mean 9 ng/mL). N = 23 4. Placebo: N = 6.***
Outcomes	Mental state: clinically significant response (30% reduction in positive symptoms, criterion unclear) Unable to use: • Adverse effects: EPSE ratings and tardive dyskinesia (no data reported by dose).
Notes	* Bromocriptine Growth Hormone Test blockade used as neuroendocrine index of D_2 receptor occupancy for purpose of antipsychotic dose adjustment ** Trialists reported results of group 1 and 2 together. *** No data reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" - no details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported on all participants.

Curtis 1995 (*Continued*)

Selective reporting (reporting bias)	High risk	Results of different intervention groups combined, 1 intervention group not reported, outcomes (EPSE) not reported
Other bias	Unclear risk	None obvious.

Donlon 1980

Methods	Allocation: randomised - no details but baseline demographics similar. Blindness: double - no further details. Duration: 10 days.
Participants	Diagnosis: schizophrenia (no mention of standardised diagnostic criteria), CGI at least = 4. N = 63. Age: 18-45 years. Sex: 45 males, 18 females. History: newly admitted. Setting: hospital.
Interventions	1. Haloperidol: 5-day titration to dose 100 mg/day (mean: 90 mg). N = 20. 2. Haloperidol: 10-day titration to dose 100 mg/day (mean: 77 mg). N = 23. Both above groups combined into > 35 mg dose for analyses. 3. Haloperidol dose 10 mg/day fixed oral dose. n = 20.
Outcomes	Leaving the study early (between 3 and 14 days). Adverse effects: acute dystonia, postural hypotension (between 3 and 14 days) Unable to use: • Global state: CGI (no data presented by dose). • Mental state: BPRS (no data presented by dose).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised" - no details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double": each treatment group given 10 capsules daily (haloperidol + placebo)

Donlon 1980 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details of reasons for leaving early given but no details of how this was reflected in analysis
Selective reporting (reporting bias)	High risk	Continuous data not presented by dose.
Other bias	Unclear risk	None obvious.

Janicak 1997

Methods	Allocation: randomised. Allocation concealment: stated random and baseline demographics similar. Blindness: double. Duration: 2 weeks.
Participants	Diagnosis: schizophrenia or schizoaffective disorder (RDC). N = 95. Age: mean about 32 years. Sex: 47 males, 48 females. History: mean number of previous hospitalisations about 5. Setting: hospital.
Interventions	1. Haloperidol: plasma dose target 2 ng/mL. N = 38. 2. Haloperidol: plasma dose target 12 ng/mL. N = 25. 3. Haloperidol: plasma dose target 30 ng/mL. N = 32. Also oral dosing 3.3 mg/day vs. 25.8 mg/day vs. 50.8 mg/day.
Outcomes	Leaving the study early (2-10 weeks). Global state: use of adjunctive medication for sedation. Adverse effects: extrapyramidal side effects, use of antiparkinsonism drugs Unable to use: • Mental state: BPRS (no SD).
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Random assignment" - no details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double" - no further details.

Janicak 1997 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for leaving early reported; intention-to-treat analysis used
Selective reporting (reporting bias)	Low risk	Presents a wide range of statistically significant and non-significant outcomes
Other bias	Unclear risk	None obvious.

Kapur 2000

Methods	Allocation: randomised - no details but baseline demographics similar. Blindness: double - no further details. Duration: 2 weeks.
Participants	Diagnosis: schizophrenia or schizophreniform disorder (DSM-IV). N = 26. Age: mean 30 years (completers only). Sex: 17 males, 5 females (completers only). History: length of illness episode median 52 weeks (completers only). Setting: hospital and outpatient clinic.
Interventions	1. Haloperidol: 1 mg/day fixed oral dose. N = 14. 2. Haloperidol: 2.5 mg/day fixed oral dose. N = 12.
Outcomes	Leaving the study early. Global state: no clinically significant response, use of adjunctive sedatives Mental state and behaviour: clinically significant agitation. Adverse effects: EPSE, use of antiparkinsonism drugs, withdrawal due to EPSE Unable to use: • Global state: CGI score (completer data only). • Mental state: PANSS score (completer data only). • Adverse effects: Barnes Akathisia Scale, ESRS (completer data only).
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" - no details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double" raters blind to occupancy results.

Kapur 2000 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for leaving early reported; per-protocol analysis.
Selective reporting (reporting bias)	Low risk	Presents a wide range of statistically significant and non-significant outcomes
Other bias	Unclear risk	None obvious.

Khanna 1997

Methods	Allocation: randomised. Blindness: double. Duration: 6 weeks.
Participants	Diagnosis: acute and transient psychotic disorder (ICD-10). N = 47. Age: 17-55 years. Sex: male 22, female 18 (completers only). History: drug naive in this episode. Setting: psychiatric outpatients.
Interventions	1. Haloperidol: dose 5 mg/day. N = 25. 2. Haloperidol: dose 20 mg/day. N = 22.
Outcomes	Leaving the study early. Mental state/behaviour - no psychotic symptoms (2-10 weeks). Global state: use of adjunctive medication for sedation. Adverse effects: blurred vision. Unable to use: • Mental state: BPRS. • Adverse effects: haloperidol side effects checklist - no data reported.
Notes	Error in reporting, comparison of BPRS score in table 3 and 4 were identical but with columns reversed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" - no further details - no details but baseline demographics similar
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details except doses in both groups administered in identical capsules in single daily dose

Khanna 1997 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for leaving early reported; per-protocol analysis.
Selective reporting (reporting bias)	Unclear risk	Only most common side effects at days 7 and 42 reported.
Other bias	Unclear risk	None obvious.

Klieser 1987

Methods	Allocation: randomised - no details but baseline demographics similar. Blindness: double - no further details. Duration: 2 weeks.
Participants	Diagnosis: schizophrenia (ICD-9). N = 90. Age: mean about 32 years (completers only). Sex: 40 males, 47 females (completers only). History: mean duration ill about 4 years (completers only). Setting: hospital.
Interventions	1. Haloperidol: 10 mg/day fixed oral dose. N = 30. 2. Haloperidol: 20 mg/day fixed oral dose. N = 30. 3. Haloperidol: flexible dose mean 16.3 mg, SD 14.1 mg (data not extracted for this group as dose did not conform to defined dose ranges). N = 30
Outcomes	Leaving the study early. Unable to use: • Mental state: BPRS (completer data only). • Adverse effects: Simpson-Angus score (completer data only).
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomisation" - no details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double" - no further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Seems to be per-protocol analysis - but unclear.

Klieser 1987 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Not clear.
Other bias	Unclear risk	None obvious.

Liang 1987

Methods	Allocation: randomised - no details but baseline demographics similar. Blindness: double. Duration: 10 weeks.
Participants	Diagnosis: schizophrenia (ICD-9). N = 88. Age: mean 27 years. Sex: 32 males, 35 females. History: mean duration ill 3.5 years. Setting: hospital.
Interventions	1. Haloperidol: dose 0.15 mg/kg (mean 9.2 mg, SD 1.6 mg). N = 24 2. Haloperidol: dose 0.40 mg/kg (mean 23.0 mg, SD 3.8 mg). N = 24 3. Insulin coma therapy. N = 16 (completer). 4. Insulin coma therapy plus haloperidol dose 0.4 mg/kg (mean 20.4 mg, SD 3.8 mg). N = 11 (completer)
Outcomes	Leaving the study early. Global state: no clinically significant response in global state (unclear criterion) Unable to use: • Mental state: BPRS, PSE (completer data only).
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was undertaken with random number tables.
Allocation concealment (selection bias)	High risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind: participants, medical staff and assessors were all blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	People leaving early were excluded from final analysis.
Selective reporting (reporting bias)	Low risk	All measured outcomes reported.

Liang 1987 (*Continued*)

Other bias	Low risk	None obvious.

Louza 1988

Methods	Allocation: randomised - no details but baseline demographics similar Blindness: double. Duration: 6 weeks (4 weeks data extracted).
Participants	Diagnosis: schizophrenia or schizoaffective disorder (DSM-III and RDC) N = 20. Age: mean about 37 years. Sex: 11 males, 9 females. History: no details. Setting: hospital.
Interventions	1. Haloperidol: dose 0.15 mg/kg (range 7.8-14.9 mg). N = 10. 2. Haloperidol: dose 0.40 mg/kg (range 20.0-39.6 mg). N = 10
Outcomes	Leaving the study early. Adverse effects: clinically significant EPSE. Unable to use: • Global state: change/score BPRS (no means or SD). • Mental state: change/score BPRS (no means or SD). • Adverse effects: Simpson-Angus scale (no means or SD).
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised" - no details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double" - both haloperidol and adjunctive benzotropine administered in same way across groups
Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for leaving early reported Per-protocol analysis (excluded from analysis from time of leaving study)
Selective reporting (reporting bias)	Low risk	Presents a wide range of statistically significant and non-significant outcomes

Louza 1988 (*Continued*)

Other bias	Unclear risk	None obvious.

McEvoy 1991

Methods	Allocation: randomised - no details but baseline demographics similar. Blindness: double. Duration: 2 weeks.
Participants	Diagnosis: schizophrenia or schizoaffective disorder (RDC). N = 106 (N = 48 in randomised portion of study). Age: mean about 32 years. Sex: 57 males, 49 females. History: 30% neuroleptic naive. Setting: hospital and outpatient clinic (3 participants).
Interventions	1. Haloperidol neuroleptic threshold dose (mean 3.4 mg, SD 2.3 mg). N = 23. 2. Haloperidol 2.5 x neuroleptic threshold dose (mean 11.6 mg, SD 4.7 mg). N = 25
Outcomes	Leaving the study early (2-10 weeks). Global state: no clinically significant response (2-10 weeks) Adverse effects: clinically significant EPSE (2-10 weeks). Adverse effects: significant EPSE. Unable to use: • Mental state: BPRS (completer data only). • Adverse effects: EPSE (completer data only).
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomisation" - no details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for leaving early and exclusion reported; early termination data used in endpoint analysis
Selective reporting (reporting bias)	Unclear risk	Presents a wide range of statistically significant and non-significant outcomes; only highly significant (P value < 0.01) correla-

McEvoy 1991 (*Continued*)

		tions with outcome reported (*Psychopharmacology Bulletin*).
Other bias	Unclear risk	None obvious.

Modestin 1983

Methods	Allocation: randomised - no details but baseline demographics similar. Blindness: double. Duration: 3 weeks.
Participants	Diagnosis: schizophrenia (ICD-9). N = 57. Age: mean 38 years. Sex: 18 males, 23 women completed study. 16 who left early not reported. History: previous hospitalisations 29/57, mean duration ill 3.5 years. Setting: hospital.
Interventions	1. Haloperidol: flexible dose 5 mg tablets (mean 20 mg). N = 27. 2. Haloperidol: flexible dose 15 mg tablets (mean 58 mg). N = 30
Outcomes	Leaving the study early (2-10 weeks). Global state: no significant response (2-10 weeks), use adjunctive sedatives. Mental state/behaviour: significant agitation (2-10 weeks). Adverse effects: significant EPSE, use of any antiparkinsonism drugs, akathisia Unable to use: • Mental state: BPRS (no mean or SD). • Adverse effects: Simpson-Angus scale (no mean or SD).
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised" - no details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double": tablets in both groups identical in appearance.
Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for leaving early and withdrawal reported; per-protocol analysis

Modestin 1983 (*Continued*)

Selective reporting (reporting bias)	Low risk	Presents a wide range of statistically significant and non-significant outcomes
Other bias	Unclear risk	None obvious.

Neborsky 1981

Methods	Allocation: randomised - no details but baseline demographics similar. Blindness: double. Duration: 6 days.
Participants	Diagnosis: schizophrenia, acute paranoid reaction, manic-depressive illness-manic type (DSM-II). N = 20. Age: mean 22 years. Sex: 20 males. History: first episode 15/20. Setting: hospital.
Interventions	1. Haloperidol: 2 mg tablets, 1-8 tablets per day 1st 48 h then dose fixed at final flexible dose at 48 h and continued up to day 6 (> 50% received dose within > 7.5-15 mg/day range). N = 10. 2. Haloperidol: 10 mg tablets, 1-8 tablets per day 1st 48 h then dose fixed at final flexible dose at 48 h and continued up to day 6 (> 50% received dose within > 35 mg/day range) . N = 10
Outcomes	Mortality. Leaving the study early (3-14 days). Global state: no clinically significant response (3-14 days). Mental state/behaviour: no clinically significant response in psychotic symptoms (93-14 days) Unable to use: • Mental state: BPRS change/score (data skewed).
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised" - no details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	High risk	"Double": note differences in route and frequency of administration between groups

Neborsky 1981 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented on all participants (no-one left early).
Selective reporting (reporting bias)	Low risk	Presents a wide range of statistically significant and non-significant outcomes
Other bias	Unclear risk	None obvious.

Oosthuizen 2004

Methods	Allocation: randomised 1:1. No further details but baseline demographics similar Blindness: double. Duration: 6 weeks.
Participants	Diagnosis: schizophreniform disorder, schizophrenia or schizoaffective disorder DSM-IV N = 40 Age: 16-55 years. Sex: History: first episode psychosis, lifetime neuroleptic exposure $\leq$ 4 weeks Setting: inpatient and outpatient.
Interventions	1. Haloperidol: dose 2 mg/day. 2. Haloperidol: dose 8 mg/day (with a build-up of dose over first week)
Outcomes	Leaving the study early. Reduction in PANNS. Reduction in PANSS positive and general psychopathology subscale Reduction in PANSS negative subscale. Calgary Depression Rating Scale. ESRS total score. ESRS parkinsonism subscale. Dystonic reaction. Akathisia. Use of concomitant medication. Prolactin level.
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised" - no details
Allocation concealment (selection bias)	Unclear risk	No details

Oosthuizen 2004 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double". Doses given to both groups in a single identical capsule daily
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropout reported Intention-to-treat analysis - last observation carried forward
Selective reporting (reporting bias)	Unclear risk	ESRS and parkinsonism reported only as t values, degree of freedom and P values
Other bias	Unclear risk	None obvious.

Palao 1994

Methods	Allocation: randomised - no details but baseline demographics similar. Blindness: double. Duration: 3 weeks.
Participants	Diagnosis: schizophrenia (DSM-III-R). N = 22. Age: mean 29 years (completers). Sex: 6 males, 14 females (completers). History: mean duration ill 8.5 years (completers). Setting: hospital.
Interventions	1. Haloperidol: 10 mg/day fixed oral dose. N = 6. 2. Haloperidol: 20 mg/day fixed oral dose. N = 8. 3. Haloperidol: 30 mg/day fixed oral dose. N = 8. Groups 2 and 3 combined for data extraction.
Outcomes	Leaving the study early. Unable to use: • Mental state: BPRS, SANS, SAPS (completer data only). • Adverse effects: Simpson-Angus scale, use of antiparkinsonism drugs (completer data only).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised" - no details.
Allocation concealment (selection bias)	Unclear risk	No details.

Palao 1994 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind - assessing physicians, nursing staff and participants blinded to dose groups. Dose given to groups in identical oral solutions
Incomplete outcome data (attrition bias) All outcomes	High risk	Reason for dropouts reported. Per-protocol analysis.
Selective reporting (reporting bias)	Low risk	Presents a wide range of statistically significant and not significant outcomes
Other bias	Unclear risk	None obvious.

Rifkin 1991

Methods	Allocation: randomised - no details but baseline demographics similar. Blindness: double. Duration: 6 weeks.
Participants	Diagnosis: schizophrenia (DSM-III). N = 87. Age: mean about 34 years. Sex: 34 males, 33 females. History: mean hospitalisations about 5. Setting: hospital.
Interventions	1. Haloperidol: 10 mg/day fixed oral dose. N = 29. 2. Haloperidol: 30 mg/day fixed oral dose. N = 29. 3. Haloperidol: 80 mg/day fixed oral dose. N = 29.
Outcomes	Leaving study early (2-10 weeks). Global state: mean change CGI score, use of adjunctive sedatives, no clinically significant response. Mental state/behaviour: mean change SADS score, clinically significant agitation (2-10 weeks). Adverse effects: mean change EPSE score.
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised - no details given.
Allocation concealment (selection bias)	Unclear risk	No details.

Rifkin 1991 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Double - participants, stall and raters blind to groups. Doses administered in 8 study tablets to all participants across study groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts and exclusions reported. Both per-protocol and survival analysis reported.
Selective reporting (reporting bias)	Low risk	Presents a wide range of statistically significant and not significant outcomes
Other bias	Unclear risk	None obvious.

Simpson 1967

Methods	Allocation: randomised - no details but baseline demographics similar. Blindness: double. Duration: 8 weeks.
Participants	Diagnosis: schizophrenia (no diagnostic criteria specified). N = 16. Age: mean about 37 years. Sex: 16 males. History: mean duration ill 12 years. Setting: hospital.
Interventions	1. Haloperidol: dose 6 mg/day. N = 8. 2. Haloperidol: dose 30 mg/day. N = 8. 3. Placebo. N = 8 (not extracted).
Outcomes	Leaving the study early. Global state: no significant change in global state, use of adjunctive sedation. Adverse effects: significant EPSE, use of any antiparkinsonism drugs Unable to use: • Mental state: IMPS scale, PRP scale (no SD).
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised" - no details.
Allocation concealment (selection bias)	Unclear risk	No details.

Simpson 1967 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	"Double" - participants in all study groups received identical tablet regimens; 91% ward doctors and 89.5% ward nurses correctly guessed which participants were taking active medication
Incomplete outcome data (attrition bias) All outcomes	High risk	Result available for only 7 of 8 in placebo group, no explanation given
Selective reporting (reporting bias)	Low risk	Presents a wide range of statistically significant and not significant outcomes
Other bias	Unclear risk	None obvious.

Stone 1995

Methods	Allocation: randomised - no details but baseline demographics similar. Blindness: double. Duration: 2 weeks.
Participants	Diagnosis: schizophrenia (DSM-III). N = 24. Age: mean 27 years. Sex: 11 males, 13 females. History: mean duration ill about 5 years. Setting: hospital.
Interventions	1. Haloperidol: 4 mg/day oral fixed dose. N = 8. 2. Haloperidol: 10 mg/day oral fixed dose. N = 8. 3. Haloperidol: 40 mg/day oral fixed dose. N = 8.
Outcomes	Leaving the study early. Adverse effects: significant EPSE. Unable to use: • Mental state: BPRS (maximum response data only, data highly skewed).
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised" - no details
Allocation concealment (selection bias)	Unclear risk	No details

Stone 1995 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double" - no further details
Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for withdrawal reported Per-protocol analysis
Selective reporting (reporting bias)	Unclear risk	Not clear.
Other bias	Unclear risk	None obvious.

Volavka 1992

Methods	Allocation: randomised - no details but baseline demographics similar. Blindness: double. Duration: 6 weeks.
Participants	Diagnosis: schizophrenia or schizoaffective disorder (RDC). N = 132. Age: mean 33 years. Sex: 97 males, 35 females. History: mean number of previous hospitalisations 7. Setting: hospital.
Interventions	1. Haloperidol: plasma dose 2-13 ng/mL (data not extracted due to non-overlap with predefined ranges). 2. Haloperidol: plasma dose 13.1-24 ng/mL (15-35 mg oral dose). N = 45. 3. Haloperidol: plasma dose 24.1-35 ng/mL (> 35 mg oral dose). N = 47
Outcomes	Leaving the study early (2-10 weeks). Global state: no clinically significant change global state, clinically significant EPSE (2-10 weeks). Mental state/behaviour: no clinically important change in psychotic symptoms Adverse effects: clinically significant EPSE. Unable to use: • Mental state: BPRS (completers only). • Adverse effects: significant EPSE (completers only), use of antiparkinsonism drugs (completers only), Simpson-Angus score (completers only).
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised" - no details.

Volavka 1992 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Sample attrition fully reported. Endpoint analysis included last observation carried forward data on all subjects observed beyond week 2
Selective reporting (reporting bias)	Low risk	Presents a wide range of statistically significant and not significant outcomes
Other bias	Unclear risk	None obvious.

Volavka 1995

Methods	Allocation: randomised - no details but baseline demographics similar. Blindness: double. Duration: 3 weeks.
Participants	Diagnosis: schizophrenia or schizoaffective disorder (DSM-III-R). N = 65. Age: mean 34 years (completers only). Sex: 43 males, 11 females (completers only). History: mean number of previous hospitalisations 15 (completers only). Setting: hospital.
Interventions	1. Haloperidol: plasma dose target 2 ng/mL. N = 33. 2. Haloperidol: plasma dose target 10 ng/mL. N = 32.
Outcomes	Leaving the study early. Global state: no significant response, significant response, use of adjunctive sedative. Mental state: clinically significant agitation. Adverse effects: significant EPSE, use of any antiparkinsonism drugs Unable to use: • Mental state: BPRS score (completers only). • Adverse effects: Simpson-Angus score (completers only).
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised" - no details.

Volavka 1995 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double" but with principal investigator, delegates and nominated psychiatrist in each centre not blind to allow dose adjustments according to monitoring of plasma haloperidol levels
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Sample attrition fully reported though it is not clear how this was accounted for in analysis
Selective reporting (reporting bias)	Low risk	Presents a wide range of statistically significant and not significant outcomes
Other bias	Unclear risk	None obvious.

Winter 1984

Methods	Allocation: randomised - pills sent by manufacturer suggest concealed list but mean ages differ by 8 years. Blindness: double. Duration: 3 weeks.
Participants	Diagnosis: schizophrenia (ICD-9). N = 48. Age: mean 35 years (completers only). Sex: 16 males, 24 females (completers only). History: mean length of illness 4 years (completers only). Setting: hospital.
Interventions	1. Haloperidol: 16 mg/day liquid formulation fixed dose. N = 24. 2. Haloperidol: 80 mg/day liquid formulation fixed dose. N = 24
Outcomes	Leaving the study early. Global state: no clinically significant improvement in global state Unable to use: • Mental state: AMDP Scale score (not validated scale, no SD).
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Assigned randomly" by authors

Winter 1984 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No details
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double" - manufacturers controlled distribution of tablets to participants identified by numbers, tablets then administered by ward doctors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No reports of dropout given
Selective reporting (reporting bias)	Low risk	Presents a wide range of statistically significant and not significant outcomes
Other bias	Unclear risk	None obvious.

AMDP: Association for Methodology and Documentation in Psychiatry;
BPRS - Brief Psychiatric Rating Scale; CGI: Clinical Global Impression; DSM - II/III/IV: Diagnostic Statistical Manual version 2/3/4; EPSE: extrapyramidal side effects; ESRS: Extrapyramidal Symptom Rating Scale; ICD: International Classification of Diseases; IMPS: Inpatient Multidimensional Psychiatric Scale; PANSS: Positive and Negative Symptom Scale; PRP: Psychotic Reaction Profile; PSE: Present State Examination; RDC: Research Diagnostic Criteria; SADS: Schedule for Affective Disorders and Schizophrenia; SANS: Schedule for Negative Symptoms; SAPS: Schedule for Positive Symptoms; SD: standard deviation.

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

Study	Reason for exclusion
Bjorndal 1980	Allocation: randomised. Participants: people with schizophrenia. Interventions: haloperidol dose mean 15, 103 mg/day (completers only). Outcomes: no usable data - unclear how many originally randomised to groups Authors contacted 1 March 2002, no reply.
Boyer 1987	Allocation: randomised. Participants: people with schizophrenia. Interventions: amisulpride vs. haloperidol, not different doses of haloperidol
Coryell 1990	Allocation: randomised. Participants: people with schizophrenia. Interventions: haloperidol dose mean 33.0, 40.0 mg/day (completers only). Outcomes: no usable data - unclear how many originally randomised to groups Authors contacted 1 March 2002, no reply.

(*Continued*)

Coryell 1998	Allocation: randomised. Participants: people with schizophrenia. Interventions: haloperidol dose mean 24.8, 36.8 mg/day (completers only). Outcomes: no usable data - unclear how many originally randomised to groups Authors contacted 1 March 2002, no reply.
Davis 1985	Allocation: randomised. Participants: people with schizophrenia. Interventions: haloperidol dose 15, 60 mg/day (first 5 days of study only). Outcomes: no usable data - unclear how many originally randomised to groups Authors contacted 1 March 2002, no reply.
Dubin 1985	Allocation: randomised. Participants: people with schizophrenia. Interventions: haloperidol dose 5, 10, 25 mg/day. Outcomes: no usable data - unclear how many originally randomised to groups Authors contacted 1 March 2002, no reply.
Dutoit 1995	Allocation: randomised. Participants: people with schizophrenia. Interventions: haloperidol dose 6, 10, 15 mg/day. Outcomes: no usable data - unclear how many originally randomised to groups Authors contacted 1 March 2002, no reply.
Garver 1984	Allocation: randomised. Participants: people with schizophrenia. Interventions: haloperidol dose 6, 12, 24 mg/day. Outcomes: no usable data - unclear how many originally randomised to groups Authors contacted 1 March 2002, no reply.
Garver 1985	Allocation: randomised. Participants: people with schizophrenia. Interventions: haloperidol 6, 12 or 24 mg/day. Outcomes: no usable data - unclear how many originally randomised to groups
Gerlach 1985a	Allocation: randomised. Participants: people with chronic schizophrenia. Interventions: dogmatil vs. haloperidol, not comparing haloperidol doses
Hirschowitz 1997	Allocation: randomised. Participants: people with schizophrenia. Interventions: haloperidol dose mean 3.2, 6.5, 14.0 mg/day (completers only). Outcomes: no usable data - unclear how many originally randomised to groups Authors contacted 1 March 2002, no reply.
Levin 1996	Allocation: randomised. Participants: people with schizophrenia. Interventions: haloperidol dose mean 1.6, 4.7, 10.0 mg/day (completers only).

(*Continued*)

	Outcomes: no usable data - unclear how many originally randomised to groups Authors contacted 1 March 2002, no reply.
Ortega-Soto 1993	Allocation: randomised. Participants: people with acute schizophrenia. Interventions: individually determined threshold dose for parkinsonism plus haloperidol 20 mg/day or placebo. Unclear what dose range participants randomised to
Ortega-Soto 1994	Allocation: randomised. Participants: people with schizophrenia. Interventions: haloperidol dose mean 3.4, 23.9 mg/day (completers only). Outcomes: no usable data - unclear how many originally randomised to groups Authors contacted 1 March 2002, no reply.
Reschke 1974	Allocation: randomised, no details but baseline demographics similar. Participants: people with schizophrenia. Interventions: haloperidol 1, 2 and 5 mg vs. chlorpromazine 25 mg intramuscular as needed every 30 minutes vs. placebo - unclear how many doses received in each group
Santos 1989	Allocation: randomised. Participants: people with schizophrenia. Interventions: haloperidol dose 15, 20, 30 mg/day. Outcomes: no usable data - unclear how many originally randomised to groups Authors contacted 1 March 2002, no reply.
Sim 1989	Allocation: randomised. Participants: people with schizophrenia. Interventions: haloperidol dose 12, 30, 60 mg/day. Outcomes: no usable data - reported as "no significant differences", so excluded. Authors contacted 1 March 2002, no reply.
Smith 1984	Allocation: randomised. Participants: people with schizophrenia. Interventions: haloperidol dose 10, 25 mg/day. Outcomes: no usable data - unclear how many originally randomised to groups Authors contacted 1 March 2002, no reply.
Smith 1987	Allocation: randomised. Participants: people with schizophrenia. Interventions: haloperidol dose 8, 40 mg/day. Outcomes: no usable data - unclear how many originally randomised to groups Authors contacted 1 March 2002, no reply.
Van Putten 1990	Allocation: quasi-randomised, by day of the week, and baseline demographics not similar
Volavka 2000	Allocation: randomised. Participants: people with schizophrenia. Interventions: haloperidol plasma levels 8-12 ng/mL and > 15 ng/mL Outcomes: unclear how many participants randomised to experimental and control groups

(*Continued*)

Zimbroff 1997	Allocation: randomised. Participants: people with schizophrenia. Interventions: haloperidol dose 4, 8, 16 mg/day, sertindole dose 12, 20, 24 mg/day. Outcomes: leaving the study early: > 50% dropout rate therefore study excluded Authors contacted 1 March 2002, no reply.

DATA AND ANALYSES

Comparison 1. DOSES: 1. ULTRA LOW DOSE (> 0.25 to 1.5 mg/day) versus OTHER DOSES

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early (2-10 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 versus low dose (> 1.5-3 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Global state: no clinically significant response in global state (2-10 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 versus low dose (>1.5-3 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Global state: use of adjunctive medication for sedation (2-10 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 versus low dose (> 1.5-3 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Mental state/behaviour: clinically significant agitation (2-10 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 versus low dose (1.5-3 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Adverse effects: clinically significant EPSE (2-10 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 versus low dose (> 1.5-3 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Adverse effects: use of antiparkinsonism drugs (2-10 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 versus low dose (> 1.5-3 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. DOSES: 1. LOW DOSE (> 1.5 to 3 mg) versus OTHER DOSES

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early (2-10 weeks)	2	66	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.28, 1.74]
1.1 versus ultra low doses (> 0.25-1.5 mg/day)	1	26	Risk Ratio (M-H, Fixed, 95% CI)	3.5 [0.42, 29.39]
1.2 versus standard higher group (> 7.5-15 mg/day)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.12, 1.21]

2 Global state: 1. No clinically significant response in global state (2-10 weeks)	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 versus ultra low doses (> 0.25-1.5 mg/day)	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Global state: 2. Use of adjunctive medication for sedation (2-10 weeks)	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 versus ultra low doses (> 0.25-1.5 mg/day)	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Global state: 3. CGI score at endpoint (skewed data)		Other data	No numeric data
4.1 versus standard higher dose (7.5-15 mg/day)		Other data	No numeric data
5 Global state: 4. Mean dose of lorazepam (skewed data)		Other data	No numeric data
5.1 versus standard higher dose (> 7.5-15 mg/day)		Other data	No numeric data
6 Mental state/behaviour: 1. Clinically significant agitation (2-10 weeks)	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 versus ultra low doses (> 0.25-1.5 mg/day)	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Mental State/behaviour: 2. PANNS general endpoint score (skewed data)		Other data	No numeric data
7.1 versus standard higher dose (> 7.5-15 mg/day)		Other data	No numeric data
8 Mental state/behaviour: 3. PANSS positive endpoint score	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 versus standard higher dose (> 7.5-15 mg/day)	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Mental state/behaviour: 4. PANNS negative endpoint score (skewed data)		Other data	No numeric data
9.1 versus standard higher dose (> 7.5-15 mg/day)		Other data	No numeric data
10 Mental state/behaviour: 5. Calgary Depression Rating Scale endpoint score (skewed data)		Other data	No numeric data
10.1 versus standard higher dose (> 7.5-15 mg/day)		Other data	No numeric data
11 Adverse effects: 1. Clinically significant extrapyramidal side effects (2-10 weeks)	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.1 versus ultra low doses (> 0.25-1.5 mg/day)	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Adverse effects: 2a. Use of any antiparkinsonism drugs (2-10 weeks)	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

12.1 versus ultra low doses (> 0.25-1.5 mg/day)	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Adverse effects: 2b. Mean dose of orphenadrine (skewed data)		Other data	No numeric data
13.1 versus standard higher dose (>7.5-15mg/day)		Other data	No numeric data
14 Adverse effects: 3. Dystonic reaction (duration unclear)	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
14.1 versus standard higher dose (> 7.5-15 mg)	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Adverse effects: 4. Dyskinesia (duration unclear)	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
15.1 versus standard higher dose (> 7.5-15 mg/day)	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Adverse effects: 5. Akathisia (duration unclear)	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
16.1 versus standard higher dose (> 7.5-15 mg/day)	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Adverse effects: 6. Prolactin at endpoint (skewed data)		Other data	No numeric data
17.1 versus standard higher dose (> 7.5-15 mg/day)		Other data	No numeric data

Comparison 3. DOSES: 2. STANDARD LOWER DOSE (> 3 to 7.5 mg) versus OTHER DOSES

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early (2-10 weeks)	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 versus standard higher dose (> 7.5-15 mg/day)	2	64	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.01, 2.12]
1.2 versus high dose (> 15-35 mg/day)	4	191	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.47, 1.28]
1.3 versus very high dose (> 35 mg/day)	2	86	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.31, 1.60]
2 Global state: 1. No clinically significant response in global state (2-10 weeks)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 versus standard higher dose (> 7.5-15 mg/day)	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.67, 1.75]
2.2 versus high dose (> 15-35 mg/day)	2	81	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.75, 1.19]
3 Global state: 2. Use of adjunctive medication for sedation	4	238	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.79, 1.24]
3.1 versus high dose (> 15-35 mg/day) - less than 2 weeks	3	126	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.70, 1.33]

3.2 versus high dose (> 15-35 mg/day) - (2-10 weeks)	2	112	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.75, 1.40]
4 Mental state/behaviour: clinically significant agitation (2-10 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 versus high dose (> 15-35 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Mental state/behaviour: no psychotic symptoms (2-10 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 versus high dose (> 15-35 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Adverse effects: 1. Clinically significant extrapyramidal side effects (2-10 weeks)	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 versus standard higher dose (> 7.5-15 mg/day)	2	64	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.01, 2.12]
6.2 versus high dose (> 15-35 mg/day)	3	144	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.45, 0.78]
6.3 versus very high dose (> 35 mg/day)	2	86	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.45, 1.09]
7 Adverse effects: 2. Use of any antiparkinsonism drugs (2-10 weeks)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 versus high dose (> 15-35 mg/day)	3	144	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.45, 0.78]
7.2 versus very high dose (> 35 mg/day)	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.51, 1.24]
8 Adverse effects: 3. Specific adverse effects-blurred vision (< 2 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 versus high dose (> 15-35 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 4. DOSES: 3. STANDARD HIGHER DOSE (7.5 to 15 mg) versus OTHER DOSES

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality (3 days-2 weeks)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 versus very high dose (> 35 mg/day)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Leaving the study early (day 1-2)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 versus high to very high dose range	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Leaving the study early: 1. By between 3 and 14 days	2	83	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.26, 1.95]
3.1 versus very high dose (> 35 mg/day)	2	83	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.26, 1.95]

4 Leaving the study early: 2. By between 2 and 10 weeks	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 versus low dose (> 1.5-3 mg/day)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [0.82, 8.62]
4.2 versus standard lower dose (> 3-7.5 mg/day)	2	64	Risk Ratio (M-H, Fixed, 95% CI)	8.31 [0.47, 146.32]
4.3 versus high dose (> 15-35 mg/day)	4	188	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.45, 1.65]
4.4 versus very high dose (> 35 mg/day)	2	74	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.26, 1.49]
4.5 versus high and very high dose (> 15 mg/day)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.12, 2.14]
5 Global state: 1. No clinically significant response (3 days-2 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 versus very high dose (> 35 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Global state: 2. No clinically significant response in global state (2-10 weeks)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 versus standard lower dose (> 3-7.5 mg/day)	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.57, 1.48]
6.2 versus high dose (>15-35mg/day)	2	106	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.86, 2.07]
6.3 versus very high dose (> 35 mg/day)	1	58	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.80, 2.06]
7 Global state: 3. Mean change CGI	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 versus high dose (> 15-35 mg/day)	1	58	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.80, 0.20]
7.2 versus very high dose (> 35 mg/day)	1	58	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-0.86, 0.06]
8 Global state: 4. Use of adjunctive medication for sedation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 versus high dose (> 15-35 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 versus very high dose (> 35 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Global state: 5. CGI score at endpoint (skewed data)			Other data	No numeric data
9.1 versus low dose (> 1.5-3 mg/day)			Other data	No numeric data
10 Global state: 6. Mean dose of lorazepam (skewed data)			Other data	No numeric data
10.1 versus low dose (> 1.5-3 mg/day)			Other data	No numeric data
11 Mental state/behaviour: 1. No clinically significant response in psychotic symptoms (3 days-2 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

11.1 versus very high doses (> 35 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Mental state/behaviour: 2. Clinically significant agitation (2-10 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
12.1 versus high dose (> 15-35 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 versus very high dose (> 35 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Mental State/behaviour: 3. PANNS general endpoint score (skewed data)			Other data	No numeric data
13.1 versus low dose (> 1.5-3 mg/day)			Other data	No numeric data
14 Mental state/behaviour: 3. PANSS positive endpoint score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14.1 versus low dose (> 1.5-3 mg)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Mental state/behaviour: 4. PANNS negative endpoint score (skewed data)			Other data	No numeric data
15.1 versus low dose (> 1.5-3 mg/day)			Other data	No numeric data
16 Mental state/behaviour: 5. Calgary Depression Rating Scale endpoint score (skewed data)			Other data	No numeric data
16.1 versus low dose (> 1.5-3 mg/day)			Other data	No numeric data
17 Adverse effects: 1. Acute dystonia (3 days-2 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
17.1 versus very high dose (> 35 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Adverse effects: dystonic reaction (duration unclear)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
18.1 versus low dose (> 1.5-3 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Adverse effects: dyskinesia (duration unclear)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
19.1 versus low dose (> 1.5-3 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20 Adverse effects: akathisia (duration unclear)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
20.1 versus low dose (> 1.5-3 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 Adverse effects: 2a. Clinically significant extrapyramidal side effects (2-10 weeks)	3	84	Risk Ratio (M-H, Fixed, 95% CI)	2.11 [0.49, 9.07]
21.1 versus standard lower dose (> 3-7.5 mg/day)	2	64	Risk Ratio (M-H, Fixed, 95% CI)	8.31 [0.47, 146.32]

21.2 versus high and very high dose (> 15 mg/day)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 4.67]
22 Adverse effects: 2b. Mean dose of orphenadrine (skewed data)			Other data	No numeric data
22.1 versus low dose (> 1.5-3 mg/day)			Other data	No numeric data
23 Adverse effects: 3. Mean score/ change in EPS	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
23.1 versus high dose (> 15-35 mg/day)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
23.2 versus very high dose (> 35 mg/day)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
24 Adverse effects: 4. Postural hypotension (3 days-2 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
24.1 versus very high dose (> 35 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25 Adverse effects: 6. Prolactin at endpoint (skewed data)			Other data	No numeric data
25.1 versus low dose (> 1.5-3 mg/day)			Other data	No numeric data

Comparison 5. DOSES: 4. HIGH DOSE (> 15 to 35 mg/day) versus OTHER DOSES

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early (2-10 weeks)	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 versus standard lower dose (> 3-7.5 mg/day)	4	191	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.78, 2.12]
1.2 versus standard higher dose (> 7.5-15 mg/day)	4	188	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.60, 2.21]
1.3 versus very high dose (> 35 mg/day)	5	312	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.68, 1.60]
2 Global state: 1. No clinically significant response in global state (2-10 weeks)	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 versus standard lower dose (> 3-7.5 mg/day)	2	81	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.84, 1.33]
2.2 versus standard higher dose (> 7.5-15 mg/day)	2	106	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.48, 1.17]
2.3 versus very high dose (> 35 mg/day)	4	255	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.75, 1.12]
3 Global state: 2. Mean change CGI	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 versus standard higher dose (> 7.5-15 mg/day)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

3.2 versus very high dose (> 35 mg/day)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Global state: 3a. Use of adjunctive medication for sedation	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 versus standard lower dose (> 3-7.5 mg/day)	3	144	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.07, 1.83]
4.2 versus standard higher dose (> 7.5-15 mg/day)	1	58	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.49, 2.03]
4.3 versus very high dose (> 35 mg/day)	2	115	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.67, 1.69]
5 Global state: 3b. Use of adjunctive medication for sedation (< 2 weeks).	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 versus standard lower dose (> 3-7.5 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Global state: 3c. Use of adjunctive medication for sedation (2-10 weeks).	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 versus standard lower dose (> 3-7.5 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Mental state/behaviour 1: No psychotic symptoms (2-10 weeks)	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.1 versus standard lower dose (> 3-7.5 mg/day)	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Mental state/behaviour: 2. No clinically important change in psychotic symptoms	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 versus very high dose (> 35 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Mental state/behaviour: 3. Clinically significant agitation (2-10 weeks)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 versus standard lower dose (> 3-7.5 mg/day)	1	65	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.80, 1.45]
9.2 versus standard higher dose (> 7.5-15 mg/day)	1	58	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.49, 2.03]
9.3 versus very high dose (> 35 mg/day)	2	115	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.67, 1.69]
10 Mental state/behaviour: 4. Mean score - SADS mean score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 versus standard higher dose (> 7.5-15 mg/day)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 versus very high dose (> 35 mg/day)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Adverse effects: 1. Clinically significant extrapyramidal side effects (2-10 weeks)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 versus standard lower dose (> 3-7.5 mg/day)	3	144	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [1.29, 2.23]

11.2 versus very high dose (> 35 mg/day)	2	114	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.74, 1.43]
12 Adverse effects: 2. Mean score/ change in EPS on Simpson Angus scale	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.1 versus standard higher dose (> 7.5-15 mg/day)	1	58	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-1.41, 1.21]
12.2 versus very high (> 35 mg/day)	1	58	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.73, 1.13]
13 Adverse effects: 3. Use of any antiparkinsonism drugs (2-10 weeks)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 versus standard lower dose (> 3-7.5 mg/day)	3	144	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [1.29, 2.23]
13.2 versus high dose (> 35 mg/day)	2	114	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.94, 1.35]
14 Adverse effects: 4. Akathisia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
14.1 versus very high dose (> 35 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Adverse effects: 3. Specific adverse effects-blurred vision (< 2 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
15.1 versus standard lower dose (> 3-7.5 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 6. DOSES: 5. VERY HIGH DOSE (> 35 mg/day) versus OTHER DOSES

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (3 days-2 weeks)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 versus standard higher dose (> 7.5-15 mg/day)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Leaving the study early: 1. By between 3 and 14 days	2	83	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.51, 3.79]
2.1 versus standard higher dose (> 7.5-15 mg/day)	2	83	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.51, 3.79]
3 Leaving the study early: 2. By between 2 and 10 weeks	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 versus standard lower dose (> 3-7.5 mg/day)	2	86	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.62, 3.24]
3.2 versus standard higher dose (> 7.5-15 mg/day)	2	74	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.67, 3.89]
3.3 versus high dose (> 15-35 mg/day)	5	312	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.63, 1.48]
4 Global state: 1. No clinically significant response (3 days-2 weeks)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 2.69]

4.1 versus standard higher dose (> 7.5-15 mg/day)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 2.69]
5 Global state: 2. No clinically significant response (2-10 weeks)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 versus standard higher dose (> 7.5-15 mg/day)	1	58	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.49, 1.25]
5.2 versus high dose (> 15-35 mg/day)	4	255	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.89, 1.33]
6 Global state: 3. Mean change CGI	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 versus standard higher dose (> 7.5-15 mg/day)	1	58	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.06, 0.86]
6.2 versus high dose (> 15-35 mg/day)	1	58	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.40, 0.60]
7 Global state: 4. Use of adjunctive medication for sedation	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 versus standard higher dose (> 7.5-15 mg/day)	1	58	Risk Ratio (M-H, Fixed, 95% CI)	0.7 [0.31, 1.59]
7.2 versus high dose (> 15-35 mg/day)	2	115	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.59, 1.48]
8 Mental state/behaviour: 1. No clinically significant response in psychotic symptoms (3 days-2 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 versus standard higher doses (> 7.5-15 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Mental state/behaviour: 2. No clinically important change in psychotic symptoms	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 versus high dose (> 15-35 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Mental state/behaviour: 3. Mean score SADS mean score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 versus high dose (> 15-35 mg/day)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Mental state/behaviour: 4. Clinically significant agitation (2-10 weeks)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 versus standard higher dose (> 7.5-15 mg/day)	1	58	Risk Ratio (M-H, Fixed, 95% CI)	0.7 [0.31, 1.59]
11.2 versus high dose (> 15-35 mg/day)	2	115	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.59, 1.48]
12 Adverse effects: 1. Acute dystonia (3 days-2 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
12.1 versus standard higher dose (> 7.5-15 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Adverse effects: 2. Clinically significant extrapyramidal side effects (2-10 weeks)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

13.1 versus standard lower dose (> 3-7.5 mg/day)	2	86	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.91, 2.21]
13.2 versus high dose (> 15-35 mg/day)	2	114	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.70, 1.35]
14 Adverse effects: 3. Mean score/change in EPS Simpson Angus Scale	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14.1 versus standard higher dose (> 7.5-15 mg/day)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 versus high dose (> 15-35 mg/day)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Adverse effects: 4. Use of any antiparkinsonism drugs (2-10 weeks)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 versus standard lower dose (> 3-7.5 mg/day)	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.81, 1.95]
15.2 versus high dose (> 15-35 mg/day)	2	114	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.74, 1.06]
16 Adverse effects: 5. Akathisia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
16.1 versus high dose (> 15-35 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Adverse effects: 6. Postural hypotension (3 days-2 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
17.1 versus standard higher dose (> 7.5-15 mg/day)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 7. DOSES: 6. HIGH AND VERY HIGH DOSES (> 15 mg/day) versus OTHER DOSES

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 versus standard higher dose (> 7.5-15 mg/day)	1	60	Odds Ratio (M-H, Fixed, 95% CI)	1.58 [0.42, 6.02]
1.1 Leaving the study early (day 1-2)	1	20	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.01, 8.33]
1.2 Leaving the study early (2-10 weeks)	1	20	Odds Ratio (M-H, Fixed, 95% CI)	2.67 [0.36, 19.71]
1.3 Adverse effects: clinically significant EPSE	1	20	Odds Ratio (M-H, Fixed, 95% CI)	2.25 [0.17, 29.77]

Comparison 8. PLASMA LEVELS: 1. VERY LOW LEVELS (> 1.4 to 3.5 ng/mL) versus OTHER PLASMA LEVELS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early (2-10 weeks)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 versus medium plasma levels (> 7.0-16.5 ng/mL)	2	128	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.35, 1.06]
1.2 versus high plasma levels (> 16.5 ng/mL)	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.39, 2.36]
2 Global state: clinically significant response in global state (2-10 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 versus medium plasma levels (> 7.0-16.5 ng/mL)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Mental state: clinically significant response in mental state, positive symptoms (unclear duration)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 versus medium plasma levels (> 7.0-16.5 ng/mL)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Adverse effects: clinically significant extrapyramidal side effects (2-10 weeks)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 versus medium plasma levels (> 7.0-16.5 ng/mL)	2	128	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.48, 0.83]
4.2 versus high plasma levels (> 16.5 ng/mL)	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.51, 1.24]

Comparison 9. PLASMA LEVELS: 2. MEDIUM LEVELS (> 7.0 to 16.5 ng/mL) versus OTHER PLASMA LEVELS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early (2-10 weeks)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 versus very low plasma levels (> 1.4-3.5 ng/mL)	2	128	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [0.95, 2.82]
1.2 versus high plasma levels (> 16.5 ng/mL)	2	149	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.58, 2.07]
2 Global state: no clinically significant response in global state (2-10 weeks)	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 versus very low plasma levels (> 1.4-3.5 ng/mL)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

2.2 versus high plasma levels (16.5 ng/mL)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Mental state: clinically significant response in mental state, positive symptoms (duration unclear)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 versus very low plasma levels (> 1.4-3.5 ng/mL)	2	112	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.51, 1.96]
4 Adverse effects: clinically significant extrapyramidal side effects (2-10 weeks)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 versus very low levels (> 1. 4-3.5 ng/mL)	2	128	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.21, 2.09]
4.2 versus high plasma levels (> 16.5 ng/mL)	2	59	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.89, 1.84]

Comparison 10. PLASMA LEVELS: 3. HIGH LEVELS (> 16.5 ng/mL) versus OTHER PLASMA LEVELS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early (2-10 weeks)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 versus very low plasma levels (> 1.40-3.5 ng/mL)	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.42, 2.55]
1.2 versus medium plasma levels (> 7.0-16.5 ng/mL)	2	149	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.48, 1.72]
2 Global state: no clinically significant response in global state (2-10 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 versus medium plasma levels (> 7.0-16.5 ng/mL)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Adverse effects: clinically significant extrapyramidal side effects (2-10 weeks)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 versus very low plasma level (> 1.40-3.5 ng/mL)	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.81, 1.95]
3.2 versus medium plasma level (> 7.0-16.5 ng/mL)	2	59	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.54, 1.12]

ADDITIONAL TABLES

Table 1. Suggested design for a trial

Methods	Allocation: randomised, clearly described, concealed. Blindness: double, described and tested. Duration: 8 weeks.
Participants	Diagnosis: schizophrenia. N = 450.* Age: any. Sex: both. History: acutely unwell.
Interventions	1. Haloperidol 1 mg/day. N = 150. 2. Haloperidol 2.5 mg/day. N = 150. 3. Haloperidol 5 mg/day. N = 150.
Outcomes	Leaving the study early - reason. Clinical response - no clinically significant response in global state Extrapyramidal side effects - no clinically significant extrapyramidal side effects, use of anticholinergic medication Behaviour - agitation, aggression, self harm. Service utilisation - admission, duration of stay. Quality of life - no clinically significant change in quality of life measure Satisfaction with treatment.
Notes	* Powered to be able to identify a difference of about 20% between groups for primary outcome with adequate degree of certainty

WHAT'S NEW

Last assessed as up-to-date: 2 February 2010.

Date	Event	Description
3 April 2013	New citation required and conclusions have changed	Conclusions changed after results from new trials assessed.
7 September 2012	New search has been performed	Substantial update with new trials and summary of findings.

HISTORY

Protocol first published: Issue 1, 2000

Review first published: Issue 3, 2002

Date	Event	Description
25 May 2002	Amended	Minor update.
30 September 1999	Amended	Reformatted.

CONTRIBUTIONS OF AUTHORS

Lorna Donnelly - formulation of protocol, conducting searches, inclusion/exclusion of studies, data extraction, results/conclusions, ongoing maintenance of review.

John Rathbone - help with data extraction for previous versions of the review.

Clive Adams - formulation of protocol, inclusion/exclusion of studies, data extraction, results/conclusions, ongoing maintenance of review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Norfolk and Suffolk Foundation Trust, UK.
- MHECCU, Department of Psychiatry, University of British Columbia, Canada.
- Iberoamerican Cochrane Centre, Spain.
- University of Nottingham, UK.

External sources

- No external sources of support provided, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the secondary outcome measures authors added clinically significant change in mental state as a subgroup in clinical response.

NOTES

Review original title: Haloperidol dose for exacerbation of schizophrenia

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Antipsychotic Agents [*administration & dosage]; Haloperidol [*administration & dosage]; Randomized Controlled Trials as Topic; Schizophrenia [*drug therapy]

MeSH check words

Humans