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Adams CE, Bergman H, Irving CB, Lawrie S

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[Intervention Review]

Haloperidol versus placebo for schizophrenia

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ABSTRACT

Background

Haloperidol was developed in the late 1950s for use in the field of anaesthesia. Research subsequently demonstrated effects on hallucinations, delusions, aggressiveness, impulsiveness and states of excitement and led to the introduction of haloperidol as an antipsychotic.

Objectives

To evaluate the clinical effects of haloperidol for the management of schizophrenia and other similar serious mental illnesses compared with placebo.

Search methods

Initially, we electronically searched the databases of Biological Abstracts (1985-1998), CINAHL (1982-1998), *The Cochrane Library* (1998, Issue 4), The Cochrane Schizophrenia Group's Register (December 1998), EMBASE (1980-1998), MEDLINE (1966-1998), PsycLIT (1974-1998), and SCISEARCH. We also checked references of all identified studies for further trial citations and contacted the authors of trials and pharmaceutical companies for further information and archive material.

For the 2012 update, on 15 May 2012, we searched the Cochrane Schizophrenia Group's Trials Register.

Selection criteria

We included all relevant randomised controlled trials comparing the use of haloperidol (any oral dose) with placebo for those with schizophrenia or other similar serious, non-affective psychotic illnesses (however diagnosed). Our main outcomes of interest were death, loss to follow-up, clinical and social response, relapse and severity of adverse effects.

Data collection and analysis

We evaluated data independently and extracted, re-inspected and quality assessed the data. We analysed dichotomous data using risk ratio (RR) and calculated their 95% confidence intervals (CI). For continuous data, we calculated mean differences (MD). We excluded continuous data if loss to follow-up was greater than 50% and inspected data for heterogeneity. We used a fixed-effect model for all analyses. For the 2012 update, we assessed risk of bias of included studies and used the GRADE approach to create a 'Summary of findings' table.

Main results

Twenty-five trials randomising 4651 people are now included in this review. We chose seven main outcomes of interest for the 'Summary of findings' table. More people allocated haloperidol improved in the first six weeks of treatment than those given placebo (4 RCTs n = 472, RR 0.67 CI 0.56 to 0.80, *moderate quality evidence*). A further eight trials also found a difference favouring haloperidol across the six weeks to six months period (8 RCTs n = 307 RR 0.67 CI 0.58 to 0.78, *moderate quality evidence*). Relapse data from two trials favoured haloperidol at < 52 weeks but the evidence was *very low quality* (2 RCTs n = 70, RR 0.69 CI 0.55 to 0.86). *Moderate quality evidence* showed about half of those entering studies failed to complete the short trials (six weeks to six months), although, at up to six weeks, 16 studies found a difference that marginally favoured haloperidol (n = 1812, RR 0.87 CI 0.80 to 0.95). Adverse effect data does, nevertheless, support clinical impression that haloperidol is a potent cause of movement disorders, at least in the short term. *Moderate quality evidence* indicates that haloperidol caused parkinsonism (5 RCTs n = 485, RR 5.48 CI 2.68 to 11.22), akathisia (6 RCTs n = 695, RR 3.66 CI 2.24 to 5.97, and acute dystonia (5 RCTs n = 471, RR 11.49 CI 3.23 to 10.85). Discharge from hospital was equivocal between groups (1 RCT n = 33, RR 0.85 CI 0.47 to 1.52, *very low quality evidence*). Data were not reported for death and patient satisfaction.

Authors' conclusions

Haloperidol is a potent antipsychotic drug but has a high propensity to cause adverse effects. Where there is no treatment option, use of haloperidol to counter the damaging and potentially dangerous consequences of untreated schizophrenia is justified. However, where a choice of drug is available, people with schizophrenia and clinicians may wish to prescribe an alternative antipsychotic with less likelihood of adverse effects such as parkinsonism, akathisia and acute dystonias. Haloperidol should be less favoured as a control drug for randomised trials of new antipsychotics.

PLAIN LANGUAGE SUMMARY

Haloperidol versus placebo for schizophrenia

Haloperidol was first developed in the late 1950s. Research subsequently showed its therapeutic effects on the symptoms of schizophrenia, such as hearing voices and seeing things (hallucinations), having strange beliefs (delusions), aggressiveness, impulsiveness and states of excitement. This led to the introduction of haloperidol as one of the first antipsychotic drugs. Antipsychotic drugs are the main treatment for the symptoms of schizophrenia. Despite the introduction of newer antipsychotic drugs (second generation or 'atypical' drugs), haloperidol remains in widespread use and is the benchmark for judging the effectiveness of newer antipsychotic drugs.

The aim of this review was to evaluate the effects of haloperidol for schizophrenia and other similar serious mental illnesses compared with 'dummy' or no treatment (placebo). A new search for trials was carried out in May 2012 and the review now includes 25 studies with a total of 4651 people. Review authors rated the quality of evidence reported in the trials for seven main outcomes (global state, death, discharge from hospital, relapse, leaving the study early, adverse effects and satisfaction with treatment). For global state, leaving the study early and adverse effects the reviewers rated the evidence as moderate quality, however, relapse and discharge from hospital were rated to be very low quality evidence. There were no data available for death and satisfaction with treatment.

Based on moderate quality evidence, haloperidol was found to be better than placebo in treating schizophrenia. More people given haloperidol improved in the first six weeks of treatment than those given placebo. However, a significant number of people on haloperidol suffered from side effects, including muscle stiffness, uncontrollable shaking, tremors, sleepiness and restlessness.

Authors concluded that haloperidol is a potent and effective antipsychotic for treating the symptoms of schizophrenia but has the potential to cause debilitating side effects. People with schizophrenia and psychiatrists may wish to prescribe a newer antipsychotic drug with fewer side effects.

Finally, a large proportion of other information and data in the trials were poor and badly reported, meaning that better studies are required. Many people, from both groups left the trials early. This suggests that the design and running of the trials was poor and perhaps not acceptable to people. In light of these findings, it is perhaps surprising that haloperidol is a benchmark antipsychotic in widespread use for treating schizophrenia. It is also surprising that haloperidol is widely used as a comparison for new medication. Haloperidol is an effective antipsychotic drug but has serious and debilitating side effects.

Benjamin Gray, Service User and Service User Expert, Rethink Mental Illness.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

HALOPERIDOL versus PLACEBO for schizophrenia

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

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	HALOPERIDOL versus PLACEBO				
Death - suicide and natural causes	See comment	See comment	Not estimable	0 (0)	See comment	No studies reported on this outcome.
Overall improvement: No marked global improvement Rated by clinician Follow-up: >6-24 weeks	**841 per 1000**	**564 per 1000** (488 to 656)	**RR 0.67** (0.58 to 0.78)	307 (8 studies)	⊕⊕⊕◯ **moderate**[1]	Another four trials reported on this outcome at up to six weeks follow-up, and one trial at > 6-24 weeks follow-up using a nurse-rated scale, both sub-analyses showed significant results in favour of haloperidol
Not discharged from hospital Follow-up: > 6-24 weeks	**625 per 1000**	**531 per 1000** (294 to 950)	**RR 0.85** (0.47 to 1.52)	33 (1 study)	⊕◯◯◯ **very low**[2,3,4]	
Relapse Follow-up: <52 weeks	**1000 per 1000**	**690 per 1000** (550 to 860)	**RR 0.69** (0.55 to 0.86)	70 (2 studies)	⊕◯◯◯ **very low**[3,5,6]	

Leaving the study early Follow-up: > 6-24 weeks	**134 per 1000**	**72 per 1000** (39 to 134)	**RR 0.54** (0.29 to 1)	304 (8 studies)	⊕⊕⊕○ **moderate**[1]	Another 16 trials reported on this outcome at up to six weeks follow-up showing a significant result in favour of haloperidol. One trial at < 52 weeks follow-up showed no difference between haloperidol and placebo
Satisfaction with treatment	See comment	See comment	Not estimable	0 (0)	See comment	No studies reported on this outcome.
Adverse effects: Movement disorders - parkinsonism Follow-up: 3 weeks to 3 months	**28 per 1000**	**154 per 1000** (75 to 315)	**RR 5.48** (2.68 to 11.22)	485 (5 studies)	⊕⊕⊕○ **moderate**[7]	Several studies also reported on other, specific movement disorders: there was a significant result favouring placebo for akathisia, dystonia, needing anti-Parkinson medication, rigidity and tremor; there was no difference between haloperidol and placebo for tardive dyskinesia, oculogyric crises, teeth grinding and 'thick' speech

*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] Seven out of the eight included studies had an unclear risk of bias for random sequence generation and for allocation concealment. Blinding of participants and personnel was unclear in four studies and blinding of assessors was unclear in six. Two studies had an unclear risk of bias for incomplete outcome data. One study had a high risk of other bias as they were funded by industry and three an unclear risk of bias as the drugs were provided by a pharmaceutical company.

[2] The included study had an unclear risk of bias for random sequence generation, allocation concealment, and blinding of outcome assessors.

[3] The total number of participants and events were very low.

[4] Only one out of the 25 included studies reported on this outcome.

[5] The two included studies had an unclear risk of bias for random sequence generation, allocation concealment, and for blinding of outcome assessors. One study had a high risk of bias for incomplete outcome data, the other an unclear risk of bias.

[6] Only two out of the 25 included studies reported on this outcome.

[7] Four out of the five included studies had an unclear risk of bias for random sequence generation, and all five studies had an unclear risk of bias for allocation concealment. Blinding of participants and personnel was unclear in two studies and blinding of assessors was unclear in four. One study had a high risk of bias for incomplete outcome data, and two for other bias as they were funded by industry or the drugs were provided by a pharmaceutical company.

BACKGROUND

Description of the condition

Schizophrenia affects about 1% of the world's population, irrespective of race, gender, social class or country of origin (Jablensky 1992). Central to the treatment of this disabling mental illness are antipsychotic drugs, the earliest of which, chlorpromazine and haloperidol, were formulated and introduced in the 1950's. This introduction caused a revolution in the care of those with serious mental illnesses (Awad 1997; Dally 1967). Despite the formulation of a newer generation of atypical antipsychotics, chlorpromazine and haloperidol are still the most frequently prescribed antipsychotic drugs world-wide (Ayd 1978; Carpenter 1994; Waddington 1997).

Description of the intervention

Haloperidol was developed in the late 1950s for use in the field of anaesthesia and was initially used to prevent surgical shock. Research subsequently demonstrated its beneficial effect on hallucinations, delusions, aggressiveness, impulsiveness and states of excitement (Ayd 1972; Ayd 1978; Settle 1983). These findings led to the introduction of haloperidol as an antipsychotic. Hailed as a breakthrough, it was considered to be the most potent antipsychotic known, effective for a wide range of psychotic disorders, and in addition, appeared to keep side effects to a minimum (Settle 1983). Since its introduction, clinical experience has suggested that haloperidol is indeed an effective antipsychotic, particularly beneficial for those who are experiencing acute hallucinations and delusions.

How the intervention might work

Antipsychotic drugs block, to a greater or lesser extent, the transmission of dopamine, which is implicated in the cause of schizophrenia, in the brain (Willner 1997). The action of these drugs is not specific and unwanted blockade can occur. This produces a wide range of side effects including lethargy, sedation, dry mouth, blurred vision, constipation, weight gain, and stiffness. Haloperidol has a higher potency dopamine blockade compared to most other antipsychotics, therefore, low-dose haloperidol can be used to achieve an antipsychotic effect. This keeps the sort of adverse effects described above to a minimum. Haloperidol's high potency for dopamine blockade, however, means that it may cause more disorders of movement and expression (parkinsonism), involuntary and perhaps irreversible movements (dyskinesia), overwhelming feelings of restlessness (akathisia) and dangerous disturbances of the body's temperature and blood pressure regulatory systems (neuroleptic malignant syndrome) (Settle 1983).

Despite these recent concerns, research in general has consistently found haloperidol to be an effective, well tolerated antipsychotic that produces minimal side effects (Ayd 1972; Ayd 1978; Settle 1983). Consequently, in accordance with the recommendations of drug regulatory authorities, such as the Food and Drug Administration (FDA) of the United States of America, haloperidol is increasingly used as a comparator drug in clinical trials (Settle 1983; Thornley 1998). To an even greater extent than chlorpromazine, haloperidol remains the benchmark by which all other antipsychotics are measured.

Why it is important to do this review

Haloperidol's efficacy as an antipsychotic seems to vary. Some research suggests factors such as drug dose, administration of antiparkinson medication, recipient's age, sex, and individual physiology may all change efficacies (Ayd 1972; Ayd 1978; Settle 1983). More recently there has been increasing concern and debate surrounding the long-term use of haloperidol and the subsequent development of serious adverse side effects (Settle 1983).

OBJECTIVES

To evaluate the clinical effects of haloperidol for the management of schizophrenia and other similar serious mental illnesses compared with placebo.

METHODS

Criteria for considering studies for this review

Types of studies

We included all relevant randomised controlled trials. We included trials that implied randomisation, i.e. the trial was described as 'double-blind' and the participants' demographic details in each group were similar. We excluded quasi-randomised studies, such as those allocating by using alternate days of the week.

Types of participants

We included anyone with schizophrenia or similar serious, non-affective psychosis diagnosed by any criteria, irrespective of gender, age or race. We accepted a trial including people with less serious mental illnesses if the majority of participants suffered from serious functional psychotic illnesses, such as schizophrenia.

Types of interventions

1. Haloperidol: any oral dose.*
2. Placebo: active or inactive.

* Depot administration of haloperidol has been evaluated in another Cochrane Review (Quraishi 1999), and if trials relevant to this comparison were found we sent these to the contact author of this review. A systematic review of haloperidol, one dose versus another, has also been published (Donnelly 2013) and relevant studies were also supplied to this review author.

Types of outcome measures

We also grouped outcomes into immediate (up to six weeks), short (six weeks to six months), medium (six months to one year), and long (over one year) term.

Primary outcomes

1. Death - suicide and natural causes

2. Global state

2.1 Overall improvement
2.2 Relapse - as defined by each study
2.3 Hospital discharge

3. Satisfaction with treatment

4. Behaviour

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

Secondary outcomes

1. Global state

1.1 Duration of hospital stay
1.2 Re-admission
1.3 Leaving the study early

2. Mental state

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

3. Behaviour

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

4. Adverse effects

4.1 General
4.2 Specific
4.2.1 Movement disorders
4.2.2 Other CNS
4.2.3 Cardiovascular effects
4.2.4 Others

5. Economic

5.1 Cost of care

6. ,Summary of findings, table

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

1. Death - suicide and natural causes.
2. Overall improvement.
3. Not discharged from hospital.
4. Relapse.
5. Leaving the study early
6. Satisfaction with treatment - participant/carer.
7. Adverse effects: Movement disorders - parkinsonism.

Search methods for identification of studies

Electronic searches

For details of the search terms and previous searches see Appendix 1

Cochrane Schizophrenia Group Trials Register (May 2012)

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

Searching other resources

1. Reference searching

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

2. Personal contact

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

Data collection and analysis

Methods used in data collection and analysis for this 2012 update are set out below; for previous methods, please see Appendix 2.

Selection of studies

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

Data extraction and management

1. Extraction

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

2. Management

2.1 Forms

We extracted data onto standard, simple forms, created in a web-based software (DistillerSR).

2.2 Scale-derived data

We included continuous data from rating scales only if:
a) the psychometric properties of the measuring instrument have been described in a peer-reviewed journal (Marshall 2000); and
b) the measuring instrument has not been written or modified by one of the trialists for that particular trial.

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

2.3 Endpoint versus change data

There are advantages of both endpoint and change data. Change data can remove a component of between-person variability from the analysis. On the other hand, calculation of change needs two assessments (baseline and endpoint), which can be difficult in unstable and difficult to measure conditions such as schizophrenia. We decided primarily to use endpoint data, and only use change data if the former were not available. We combined endpoint and change data in the analysis as we used mean differences (MD) rather than standardised mean differences throughout (Higgins 2011, Chapter 9.4.5.2).

2.4 Skewed data

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

2.5 Common measure

To facilitate comparison between trials, we intended to convert variables that can be reported in different metrics, such as days in hospital (mean days per year, per week or per month) to a common metric (e.g. mean days per month).

2.6 Conversion of continuous to binary

Where possible, we made efforts to convert outcome measures to dichotomous data. This can be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It is generally assumed that if there is a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS, Overall 1962) or the PANSS (Kay 1986), this could be considered as a clinically significant response (Leucht 2005; Leucht 2005a). If data based on these thresholds were not available, we used the primary cut-off presented by the original authors.

2.7 Direction of graphs

Where possible, we entered data in such a way that the area to the left of the line of no effect indicated a favourable outcome for haloperidol.

Assessment of risk of bias in included studies

For this 2012 update, two members of the Enhance Reviews team worked independently by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to assess trial quality for the new included studies and all previously included studies. This new set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

Where inadequate details of randomisation and other characteristics of trials were provided, we did not contact authors of the studies in order to obtain additional information.

We have noted the level of risk of bias in both the text of the review and in the Summary of findings for the main comparison.

Measures of treatment effect

1. Binary data

For binary outcomes we calculated a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI). It has been shown that RR is more intuitive (Boissel 1999) than odds ratios and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000).

2. Continuous data

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

Unit of analysis issues

1. Cluster trials

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

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

For adjustment for clustering a posteriori, the binary data as presented in a report are 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 is not reported, it will be assumed to be 0.1 (Ukoumunne 1999). If cluster studies have been appropriately analysed taking into account ICCs and relevant data documented in the report, synthesis with other studies will be possible using the generic inverse variance technique.

2. Cross-over trials

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

3. Studies with multiple treatment groups

Where a study involves more than two treatment arms, if relevant, we presented the additional treatment arms in comparisons. If data were binary, we simply added these and combined within the two-by-two table. If data were continuous, we combined data following the formula in section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systemic reviews of Interventions* (Higgins

2011). Where the additional treatment arms were not relevant, we did not reproduce these data.

Dealing with missing data

1. Overall loss of credibility

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

2. Binary

In the case where attrition for a binary outcome was between 0% and 50% and where these data were not clearly described, we presented data on a 'once-randomised-always-analyse' basis (an intention-to-treat analysis). Those leaving the study early were all assumed to have the same rates of negative outcome as those who completed, with the exception of the outcome of death and adverse effects. For these outcomes, the rate of those who stayed in the study - in that particular arm of the trial - were used for those who did not. We undertook a sensitivity analysis to test how prone the primary outcomes were to change when 'completer' data only were, compared to the intention-to-treat analysis using the above assumptions.

3. Continuous

3.1 Attrition

In the case where attrition for a continuous outcome was between 0% and 50% and completer-only data were reported, we reproduced these.

3.2 Standard deviations

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

3.3 Last observation carried forward

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

Assessment of heterogeneity

1. Clinical heterogeneity

We considered all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We simply inspected all studies for clearly outlying people or situations which we had not predicted would arise. When such situations or participant groups arose, we fully discussed these.

2. Methodological heterogeneity

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

3. Statistical heterogeneity

3.1 Visual inspection

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

3.2 Employing the I^2 statistic

We investigated heterogeneity between studies by considering the I^2 method alongside the Chi^2 P value. The I^2 provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 depends on i. magnitude and direction of effects and ii. strength

of evidence for heterogeneity (e.g. a P value from Chi^2 test, or a confidence interval for I^2). An I^2 estimate greater than or equal to around 50% accompanied by a statistically significant Chi^2 statistic was interpreted as evidence of substantial levels of heterogeneity (Higgins 2011). When substantial levels of heterogeneity were found in the primary outcome, we explored reasons for heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

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

Data synthesis

We understand that there is no closed argument for preference for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us and the random-effects model takes into account differences between studies even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the random-effects model: it puts added weight onto small studies which often are the most biased ones. Depending on the direction of effect, these studies can either inflate or deflate the effect size. We chose the fixed-effect model for all analyses. The reader is, however, able to choose to inspect the data using the random-effects model.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses - only primary outcomes

1.1 Clinical state, stage or problem

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

- male versus female participants;
- under 18 years of age versus 18-65 years old, versus older than 65 years;
- acute versus chronic phase of illness;
- low dose (≤ 5 mg/day) versus medium to high dose (> 5 mg/day), or as defined by each study;
- use of anti-Parkinson medication versus no use of anti-Parkinson medication;
- people diagnosed according to any operational criteria versus those who have not been diagnosed using operational criteria.

2. Investigation of heterogeneity

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

Sensitivity analysis

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

1. Implication of randomisation

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

2. Assumptions for lost binary data

Where assumptions had to be made regarding people lost to follow-up (see Dealing with missing data), we compared the findings of the primary outcomes when we use our assumption/s and when we used data only from people who completed the study to that point. A sensitivity analysis was undertaken to test how prone results were to change when completer-only data only were compared to the imputed data using the above assumption. If there was a substantial difference, we reported results and discussed them, but continued to employ our assumption.

3. Risk of bias

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

or the precision of the effect estimates, then we included data from these trials in the analysis.

4. Imputed values

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

RESULTS

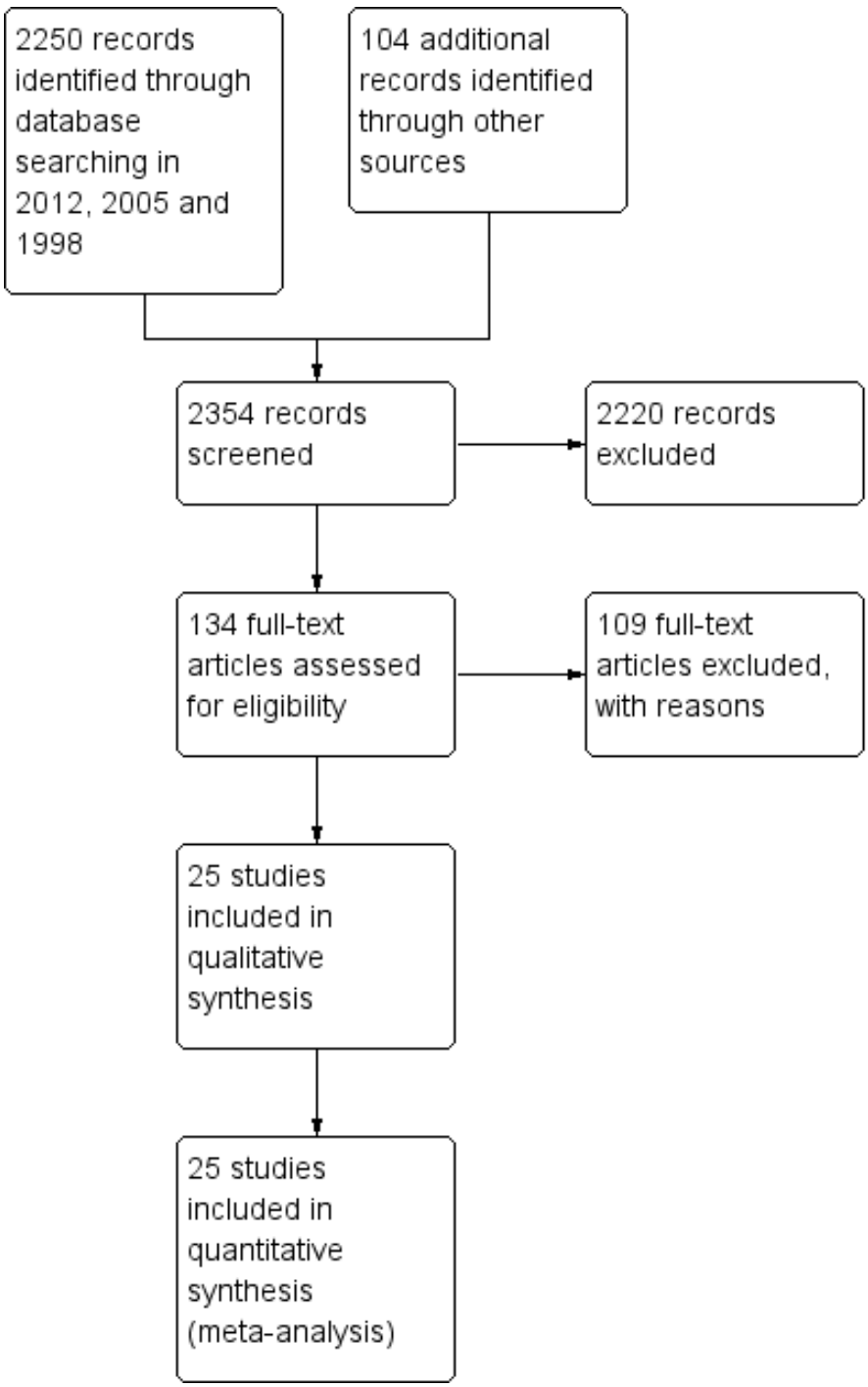
Description of studies

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

Results of the search

From the 2012 search, we added five new trials (Garcia 2009; Kane 2010; Meltzer 2004; NCT00044044 2002; Potkin 2008) to the included studies, taking the total number of included studies to 25. Previous searches in 2005 and 1998 produced 2161 references; in addition to our own search, Dr Jo Wood, at Janseen-Cilag UK Limited, kindly carried out a search of an in-house databases and provided a further 104 possible references. A total of 2250 references have now been screened and 134 full texts retrieved for further inspection (See Figure 1).

Figure 1. Study flow diagram.



Included studies

1. Methods

Most included studies had a parallel design, and four studies were cross-over trials (Howard 1974; Nishikawa 1982; Spencer 1992; Vichaiya 1971). All studies were either stated or described as being randomised.

2. Length of trials

Schizophrenia is often chronic, and, in some cases, lifelong. This review categorised data into 'immediate' (up to six weeks), 'short-term' (six weeks to six months), 'medium-term' (six months to one year) and 'long -term' (over one year) follow-up. Not one of the studies presented usable data on 'long-term' follow-up, only two (Nishikawa 1982; Nishikawa 1984) had a follow-up of one year. Eight studies lasted for less than six weeks and the other 15 studies presented data that fell into the 'short-term' category. A placebo wash-out or a medication-free period preceded treatment in all but six trials.

3. Participants

Fifteen studies included people with schizophrenia diagnosed by DSM-III, DSM-III-R or DSM-IV criteria. The other 10 studies included people with schizophrenia, but did not describe the means of diagnosis. Nishikawa 1982 and Nishikawa 1984 included people who were stable and in remission. Other studies also included a few people with other mental illnesses such as neurosis (Durost 1964) and major depressive disorder (Klieser 1989), in addition to people with schizophrenia. In these studies, only data for those suffering from schizophrenia were used. The majority of participants were hospitalised and chronically ill. Eight studies specifically stated that participants were currently acutely ill. Only one study included people who were under 18 years old (Spencer 1992) and none included people who were over 65 years of age. Most trials were of mixed sex. Howard 1974 and Vichaiya 1971 included only women, while Simpson 1967 and Bechelli 1983 included only men. Only Borison 1989 did not describe the sex of participants.

4. Setting

Trials mainly took place in inpatient settings. Two trials were conducted in outpatient settings (Nishikawa 1982 and Nishikawa 1984), and three in a mixture of inpatient and outpatient settings (Beasley 1996; Howard 1974; Kane 2010). Eleven studies were multi-centre (Arvanitis 1997; Beasley 1996; Borison 1989; Chouinard 1993; Garcia 2009; Kane 2002; Kane 2010; Marder 1994; Meltzer 2004; NCT00044044 2002; Potkin 2008).

5. Study size

The included studies involved 4651 participants. The largest trial (Potkin 2008) randomised 621 people (although this review only uses data for the haloperidol (n = 124) and placebo groups (n = 127)), while the smallest study included only 12 participants (Spencer 1992). Seven of the 25 studies randomised fewer than 50 people and 11 were greater than 100. Nine of these randomised over 300 participants (Arvanitis 1997; Beasley 1996; Garcia 2009; Kane 2002; Kane 2010; Marder 1994; Meltzer 2004; NCT00044044 2002; Potkin 2008).

6. Interventions

A wide range of doses of haloperidol was used in the trials. The smallest doses were given in Spencer 1992 who used a range of 0.5 to 10 mg/day for children under 12 years of age and the greatest in Howard 1974 (doses up to 200 mg/day). Most studies used doses in the range of 4 mg/day to 20 mg/day. The majority of trials adjusted the dose according to need with only seven studies appearing to give a fixed dose throughout the trial (Garcia 2009; Kane 2010; Klieser 1989; Marder 1994; Potkin 2008; Simpson 1967; Vichaiya 1971). Most trials randomised to other drugs in addition to placebo. The other comparators included amitriptyline, asenapine, blonanserin, chlorpromazine, clopenthixol, diazepam, iloperidone, imipramine, loxapine, lurasidone, olanzapine, quetiapine, risperidone, thioridazine, thiothixene, trazodone and one trial (Meltzer 2004) also evaluated four receptor antagonists (5-$HT_{2A/2C}$, NK_3, CB_1 and NTS_1 antagonists). Only six studies had the single comparison of haloperidol with placebo (Bechelli 1983; Durost 1964; Garry 1962; Jann 1997; Spencer 1992; Vichaiya 1971). Of these Vichaiya 1971 and Spencer 1992 were cross-over trials. Fourteen studies stated that they used other medications to alleviate adverse effects or behaviour as required. These drugs included benztropine mesylate, biperiden, chloral hydrate, lorazepam, nitrazepam, paraldehyde, procyclidine, sodium amytal and trihexyphenidyl.

7. Outcomes

7.1 Missing outcomes

None of the studies evaluated patient or staff satisfaction. Death, suicide or self-harm was also not mentioned in any study. Outcomes such as employment status, living status and community

burden were not investigated in the included studies, nor were economic outcomes such as cost of care.

7.2 Scales

Twenty different instruments were used to collect data. Although all of the scales used were validated through peer review, only seven collected continuous data useful to this review. Details of the scales are shown below. Reasons for exclusion of data from the other instruments are given in the Characteristics of included studies. Frequently, despite using a scale, no data were presented, or means were reported without a variance.

7.2.1 Mental state

i. Brief Psychiatric Rating Scale - BPRS (Overall 1962)
This is used to assess the severity of abnormal mental state. The original scale has 16 items, but a revised 18-item scale is commonly used. Each item is defined on a seven-point scale varying from 'not present' to 'extremely severe', scoring from zero to six or one to seven. Scores can range from zero to 126, with high scores indicating more severe symptoms. Bechelli 1983, Borison 1992a, Jann 1997 and Klieser 1989 reported data from this scale.
ii. Calgary Depression Scale - CDS (Addington 1990)
The CDS is a nine-item special purpose scale designed to measure depression in patients with chronic schizophrenia. Each item is rated from zero - absent to three -severe. Kane 2010 reported data from this scale.
iii. Positive and Negative Syndrome Scale - PANSS (Kay 1986)
This schizophrenia scale has 30 items, each of which can be defined on a seven-point scoring system varying from one (absent) to seven (extreme). This scale can be divided into three sub-scales for measuring the severity of general psychopathology, positive symptoms (PANSS-P), and negative symptoms (PANSS-N). A low score indicates lesser severity. Garcia 2009 and Kane 2010 reported data from this scale.

7.2.2 Global state

i. Clinical Global Impression - CGI (Guy 1976)
A rating instrument commonly used in studies on schizophrenia that enables clinicians to quantify severity of illness and overall clinical improvement. A seven-point scoring system is usually used with low scores indicating decreased severity and/or greater recovery. Garcia 2009 and Kane 2010 reported data from this scale.

7.2.3 Adverse effects

i. Simpson-Angus Scale - SAS (Simpson 1970)
This scale was employed to measure extrapyramidal symptoms. The 10-item SAS is used to evaluate the presence and severity of parkinsonian symptomatology and other extrapyramidal effects. Higher scores reflect more adverse effects. This scale was used by Kane 2010.
ii. Barnes Akathisia Scale - BAS (Barnes 1989)
This is a 12-item scale consisting of a standardised examination followed by questions rating the orofacial, extremity and trunk movements, as well as three global measurements. Each of these 10 items can be scored from zero (none) to four (severe). Two additional items assess the dental status. The BAS ranges from zero to 40, with higher scores indicating greater severity. This scale was used by Kane 2010.
iii. Abnormal Involuntary Movement Scale - AIMS (Guy 1976)
This is a 12-item clinician-rated scale to assess severity of dyskinesias (specifically, orofacial movements and extremity and truncal movements) in patients taking neuroleptic medications. Items are scored on a scale of zero (none) to four (severe) basis; the scale provides a total score (items one through seven) or item eight can be used in isolation as an indication of overall severity of symptoms. This scale was used by Kane 2010.

Ongoing trials

As far as we are aware, there are currently no ongoing trials evaluating oral haloperidol versus placebo.

Studies awaiting assessment

There are currently no studies awaiting assessment.

Excluded studies

Of the 109 excluded studies, we excluded 24 because they were not randomised and/or allocation was unclear. We excluded another nine because the participants were not suffering from schizophrenia. We excluded 31 because they compared haloperidol with another antipsychotic without a placebo group. We excluded seven studies because they administered haloperidol by intramuscular injection, not orally. We excluded five more studies because they were withdrawal trials. In these trials, people stable on haloperidol were randomised to placebo or to continue their usual dose of haloperidol. As this review is, at present, focusing on instigation studies of haloperidol, we excluded these trials. We eventually excluded a further 22 studies because all outcome data were impossible to use. Seven of these were only published as conference proceedings and information was not available in the short abstract. We have contacted the authors of these studies for additional data and this data may be included in later versions of this review. We excluded one cross-over study (Rees 1965) as no data were provided for the first arm of the trial. Three studies had losses to follow-up greater than 50%, but data could not be added

for leaving the study early: Zimbroff 1997 only reported the total number of losses, not per treatment group; Browne 1988 allowed people who had relapsed to re-enter the study under single-blind conditions; and North America 1997 combines data from several centres, which combined has greater than 50% loss, instead data from publications of specific centres have been included (Chouinard 1993; Marder 1994). The other six either reported data incorrectly. We had to exclude Pool 1976 and Price 1987 because they replaced people who withdrew from the trial with people whom they did not randomise and presented outcomes that included data from these non-random additions.

Risk of bias in included studies

See also 'Risk of bias' tables in Characteristics of included studies, and Figure 2 and Figure 3.

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

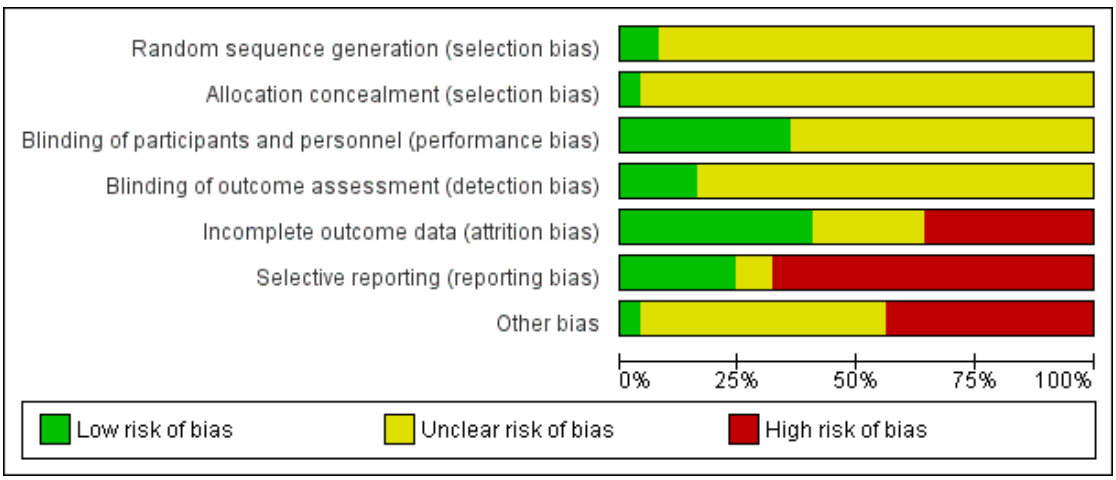
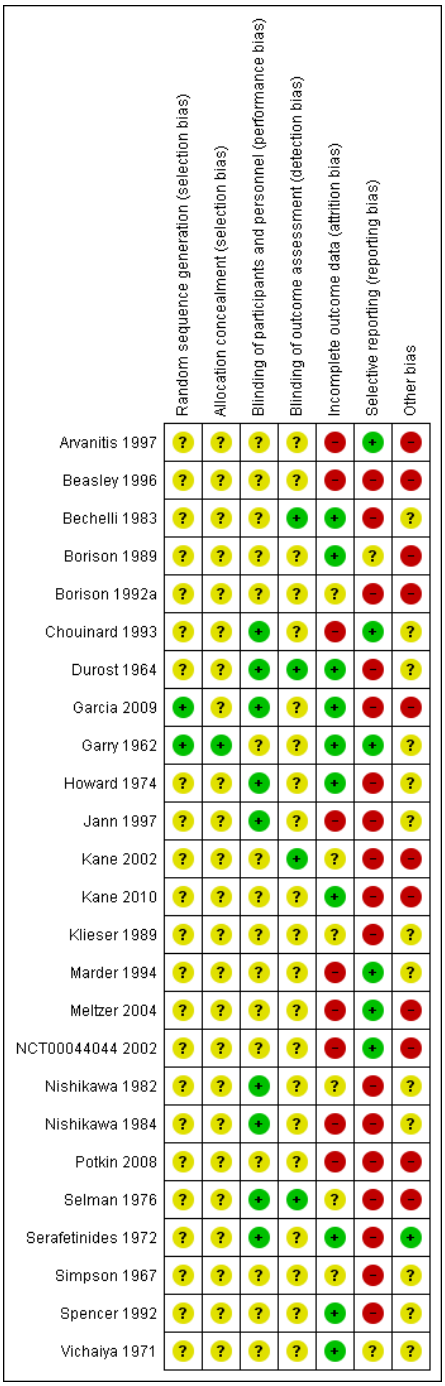


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All included studies were reported as randomised. A few studies mentioned the use of 'randomised blind schedules' (Borison 1989; Klieser 1989) and/or patient codes (Bechelli 1983; Spencer 1992; Simpson 1967) but it was not stated how these were generated or used. We therefore categorised these studies as unclear risk of bias. Only two studies reported method of generation of randomisation sequence and were rated low risk of bias (Garcia 2009 and Garry 1962).

Only one study (Garry 1962) reported method of allocation concealment and was rated low risk of bias, whereas the other studies did not provide any details and were rated unclear risk of bias for allocation concealment.

Blinding

All studies were reported to be double-blind although this was difficult to maintain due to the appearance of characteristic adverse side effects when administering haloperidol. Some trials tried to overcome this by masking some of the side effects with antiparkinson medication. Nine studies were rated low risk of bias for blinding of participants and personnel, most of these specifically stated blindness was achieved through use of identical capsules and/or bottles of medication (Chouinard 1993, Garcia 2009, Howard 1974, Jann 1997, Nishikawa 1982, Nishikawa 1984, Serafetinides 1972, Selman 1976), but no trial tested whether their attempts at blinding had been successful. Only four studies described outcome assessors as being blinded to treatment and were rated low risk of bias (Bechelli 1983, Durost 1964, Kane 2002 and Selman 1976). The remaining studies were of unclear risk of bias as no information on blinding of outcome assessors was provided.

Incomplete outcome data

Ten studies were rated as low risk of bias for incomplete outcome data and six studies had an unclear risk of bias. Nine studies were rated as high risk of bias, for seven of these it was due to more than 50% of losses to follow-up (Arvanitis 1997; Beasley 1996; Chouinard 1993; Marder 1994; Meltzer 2004; NCT00044044 2002; Potkin 2008). For these studies only the outcome 'Leaving the study early' was collected for the review, see Dealing with missing data.

Selective reporting

Six studies were of low risk of bias with regard to selective reporting, and two were unclear. The remaining 17 studies were of high risk of bias, mainly due to poor data reporting. Overall, there were very little data that were possible to use from the 25 included trials. Continuous data were particularly problematic. Many studies presented findings without standard deviations or any other measure of variance, in graphs, in percentiles or by inexact P values. 'P' values are commonly used as a measure of association between intervention and outcomes instead of showing the strength of the association. Further, many pre-planned outcomes were not reported at all.

Other potential sources of bias

Eleven trials were subject to other biases as they were either partly or fully funded by the pharmaceutical industry. Only one study was of low risk of bias for other potential sources of bias (Serafetinides 1972) and the remaining 13 had an unclear risk of bias, three of which had the drugs used in the trials provided by the pharmaceutical industry.

Effects of interventions

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

1. Comparison: HALOPERIDOL versus PLACEBO

We grouped outcomes as immediate (up to six weeks), short (six weeks to six months), medium (six months to one year) and long term (over one year). We used risk ratios (RR) for dichotomous data and mean differences (MD) for continuous data, with their respective 95% confidence intervals (CIs) throughout.

1.1 Death - suicide or natural causes

None of the 25 included studies reported on this outcome.

1.2 Global state

1.2.1 Overall improvement

Results favoured haloperidol (Analysis 1.1). Four trials found that a marked improvement was significantly more likely at up to six weeks with haloperidol (n = 472, RR 0.67 CI 0.56 to 0.80) compared with placebo. Results were heterogenous (I^2 = 72%); when the data are analysed using random-effects, the result remains significant (RR 0.59 CI 0.39 to 0.89). This heterogeneity is explored in the results of subgroup analyses (Analysis 1.21; Analysis 1.22), and in sensitivity analysis (Analysis 1.23). We found, when splitting the studies by low dose and medium to high dose, the heterogeneity was removed (see subgroup analysis section 2.4, Analysis 1.21).

A further eight trials also found a significant difference favouring haloperidol across the six weeks to six months period (n = 307, RR 0.67 CI 0.58 to 0.78). Serafetinides 1972 reported results for 'nurse-rated' global improvement across this time period, as opposed to the other 'clinician-rated' trials, and found similar results favouring haloperidol (n = 28, RR 0.59 CI 0.37 to 0.92). Garcia 2009 and Kane 2010 reported average change at six weeks on the CGI-S scale (Analysis 1.2). Results favoured haloperidol (n = 353, MD -0.49 CI -0.73 to -0.25).

1.2.2 Hospital discharge

Only one study, Howard 1974 reported usable data on hospitalisation-related outcomes. This small trial found no difference between haloperidol and placebo for not being discharged from hospital between six weeks and six months (1 RCT n = 33; Analysis 1.3).

1.2.3 Relapse

Only two studies reported on relapse. Nishikawa 1982 and Nishikawa 1984 found that once a person's illness was stable and in remission, if haloperidol was started, it was more likely to keep people in remission than placebo (n = 70, RR 0.69 CI 0.55 to 0.86; Analysis 1.4).

1.2.4 Leaving the study early

Sixteen studies with up to six weeks follow-up, found that people allocated to haloperidol were more likely to remain in the study than participants receiving placebo (n = 1812, RR 0.87 CI 0.80 to 0.95). At six weeks to six months follow-up, results were equivocal (8 RCTs n = 304), as they were for Nishikawa 1984 at one year follow-up (n = 50; Analysis 1.5).

We did not identify any studies reporting on re-admission or satisfaction with treatment.

1.3 Mental state

Only six studies had useable data on mental state outcomes.

1.3.1 Overall improvement

No significant difference was found at up to six weeks follow-up by Borison 1992a when measuring clinical improvement by reduction in BPRS scores by at least 20% (n = 24; Analysis 1.6).

1.3.2 General symptoms

The result from three studies showed a significant difference favouring haloperidol for the average BPRS score at six weeks (n = 108, MD -9.76 CI -14.60 to -4.93; Analysis 1.7), but with significant heterogeneity (I^2 = 81.9). Removing the study with results that were causing this heterogeneity, as judged by visual inspection (Klieser 1989, which reported average change data, whereas the other two studies, Bechelli 1983 and Jann 1997, reported average and point data), eliminates this heterogeneity. However, it is unclear what the reason for heterogeneity is because there are only three, small studies included. Finally, for average change at six weeks on the PANSS total scale, data from Garcia 2009 favoured haloperidol (n = 119, MD -15.58 CI -23.92 to -7.24; Analysis 1.8).

1.3.3 Positive symptoms

Garcia 2009 and Kane 2010 found an improvement in symptoms favouring haloperidol on the PANSS positive scale average change scores at six weeks (n = 353, MD -3.29 CI -4.70 to -1.89; Analysis 1.9). Results were heterogenous (I^2 = 83%) and there was no obviously outlying study out of the two. When the results are analyses using random-effects, the results remain significant (MD -3.97 CI -7.72 to -0.23).

1.3.4 Negative symptoms

Similarly, the same two studies found an improvement in symptoms on the PANSS negative scale average change scores at six weeks favouring haloperidol (n = 353, MD -1.18 CI -2.32 to -0.04; Analysis 1.10).

1.3.5 Mood

Kane 2010 found no significant difference for depression between haloperidol and placebo on the CDS average change scores (n = 234; Analysis 1.11).

1.4 Behaviour

None of the 25 included studies reported on behaviour outcomes such as social functioning, employment status or violent incidents.

1.5 Adverse effects

1.5.1 Movement disorders

Haloperidol causes various extrapyramidal adverse effects (Analysis 1.12), such as akathisia (6 RCTs n = 695, RR 3.66 CI 2.24 to 5.97), dystonia (5 RCT n = 471, RR 11.49 CI 3.23 to 40.85), parkinsonism (5 RCTs n = 485, RR 5.48 CI 2.68 to 11.22), rigidity (5 RCTs n = 461, RR 4.98 CI 2.74 to 9.05), and tremor (5 RCTs n = 447, RR 3.93 CI 1.96 to 7.91). Further, haloperidol increases the need for anti-Parkinson medication (4 RCTs n = 480, RR 3.23 CI 2.20 to 4.72). However, data from the small study Selman 1976 (n = 33) found no difference between placebo and haloperidol groups for teeth grinding or 'thick' speech. A further

two studies found no difference for oculogyric crises (2 RCTs n = 83).
Garcia 2009 and Howard 1974 found no evidence that haloperidol causes tardive dyskinesia or dyskinesia (2 RCTs n = 157; Analysis 1.13).
Kane 2010 provided data measuring movement disorder average change scores on three different scales (Analysis 1.14). No difference was found on the AIMS scale (1 RCT n = 231), whereas placebo was favoured on the BAS (1 RCT n = 231, MD 0.31 CI 0.10 to 0.52) and SAS (n = 231, MD 1.48 CI 0.76 to 2.20) scales.

1.5.2 Other central nervous system (CNS) effects

Selman 1976 and Kane 2002 found haloperidol appeared more likely to produce blurred vision than placebo (2 RCTs, n = 240, RR 3.96 CI 1.21 to 12.93). Selman 1976 (n = 33) found no clear differences between haloperidol and placebo for confusion or dry mouth. Kane 2010 found no difference between groups for sedation (n = 238; see Analysis 1.15).

1.5.3 Cardiovascular effects

Three studies were unable to demonstrate clear differences between groups for incidences of low blood pressure (3 RCTs, n = 245), and Borison 1989 also found no effect for raised blood pressure (1 RCT n = 16). Similarly, Garcia 2009 (n = 124) found no difference between haloperidol and placebo for bradycardia (See Analysis 1.16).

1.5.4 Other adverse effects

Seven studies found haloperidol more likely to induce sleepiness than placebo (7 RCTs, n = 686, RR 3.09 CI 1.51 to 6.31). Kane 2002 and Kane 2010 found haloperidol more likely to cause weight gain (2 RCTs, n = 441, RR 4.89 CI 1.41 to 16.95).
No significant differences between haloperidol and placebo groups were found for the following adverse effects: agitation (2 RCTs n = 362), anxiety (2 RCTs n = 362), drooling (3 RCTs n = 207), facial oedema (1 RCT n = 33), headache (4 RCTs n = 593), infection (1 RCT n = 24), insomnia (4 RCTs n = 629), nausea/vomiting (2 RCTs n = 231), oral hypoaesthesia (1 RCT n = 238), perspiration (2 RCTs n = 93), or weight loss (3 RCTs n = 385). (See Analysis 1.17).

1.6 Economic outcomes

None of the 25 included studies reported on economic outcomes such as cost of care.

2. Subgroup analyses

2.1 Gender: men versus women

Most studies included both men and women but did not report results separated by gender. The only primary outcome where results are available for comparison is 'Global state: Overall improvement: No marked global improvement, > 6-24 weeks' (Analysis 1.18). Howard 1974 and Vichaiya 1971 included only women, whereas, Simpson 1967 only men. Results were equally significant for both subgroups (P = 0.20).

2.2 Age: adult (18-65 years) versus child (< 18 years)

All studies, except Spencer 1992, which included only children, included adult participants. For 'Global state: Overall improvement: No marked global improvement, > 6-24 weeks' (Analysis 1.19) there were no differences between subgroups (P = 0.07).

2.3 Phase of illness: acute versus chronic

Again, only 'Global state: Overall improvement: No marked global improvement, > 6-24 weeks' had sufficient data for a comparison to be made among the primary outcomes (Analysis 1.20). There were no differences between subgroups (P = 0.58).

2.4 Dose: low dose ($\leq$ 5 mg/day) versus medium to high dose (> 5 mg/day), or as defined by each study

Heterogeneity (I^2 = 72%) was observed for 'Global state: Overall improvement: No marked global improvement, up to six weeks' (Analysis 1.1). When splitting the studies by dose, the heterogeneity was removed, and results from low dose Kane 2010 show no statistically significant difference between haloperidol and placebo, whereas medium to high dose Bechelli 1983, Garcia 2009 and Selman 1976 favour haloperidol (P = 0.003; Analysis 1.21). For 'Global state: Overall improvement: No marked global improvement, > 6-24 weeks' results were equally significant for both subgroups (P = 1.00).

2.5 Anti-Parkinson drugs: administration of any anti-Parkinson drug (any dose) versus administration of haloperidol alone.

We could not perform this subgroup analysis as data for primary outcomes were only available from studies where anti-Parkinson medication was allowed.

2.6 Diagnosis of schizophrenia: operational criteria versus non-operational diagnoses

The heterogeneity of 'Global state: Overall improvement: No marked global improvement, up to six weeks' (Analysis 1.1) does not diminish or disappear with this subgroup analysis (Analysis 1.22), and no differences between subgroups were observed (P = 0.90). Similarly, there were no differences between subgroups for 'Global state: Overall improvement: No marked global improvement, > 6-24 weeks' (P = 0.07) or for 'Global state: Relapse' (P = 0.59).

3. Sensitivity analyses

3.1 Implications for randomisation

All included studies either described the method of randomisation or stated that the study was randomised. Had there been studies implying randomisation without stating or describing, we would have performed this sensitivity analysis.

3.2 Assumptions for lost binary data

For 'Global state: Overall improvement: No marked global improvement, up to 6 weeks' one study (Garcia 2009) used LOCF assumptions about missing data. When this study was removed from the analysis the results remained significant (Analysis 1.23), and heterogeneity from the pooled analysis (Analysis 1.1) remains.

3.2 Risk of bias

No studies were judged to be at high risk of bias across one or more of the domains of randomisation and therefore no sensitivity analysis was undertaken.

3.4 Imputed values

Had we included any cluster-randomised trials, we would have undertaken a sensitivity analysis to assess the effects of including data from trials where we used imputed values for ICC in calculating the design effect in cluster-randomised trials.

3.5 On dishonest researchers

It has come to our attention that Dr Richard Borison and Dr Bruce Diamond have been convicted of theft, making false statements and violations of state racketeering law in the USA. At this point, it seems that crimes were to do with criminal diversion of funds, rather than falsifying study data (http://www.the-scientist.com/?articles.view/articleNo/19152/title/Notebook/). Nevertheless, we temporarily removed studies with either of these authors from the analyses to see if this made a substantive difference to the findings. Arvanitis 1997 only provided data for leaving the study early. Borison 1989 and Borison 1992a also reported on this outcome but also presented usable data on mental state (< 20% reduction in BPRS), and a range of adverse effects. In every case, where data from these trials are added to those of others, removal of the studies never resulted in substantive changes in the findings. For example, most data are available for the outcome of leaving the study early. With all trials included, the results favour the haloperidol group (16 RCTs n = 1812, RR 0.87 CI 0.80 to 0.95; Analysis 1.5). Removing the three studies results in no change. Where difficulties arise is where Borison 1989 or Borison 1992a report unique outcomes. In these cases, of course, removal of the study results in the deletion of the complete outcome. This applies to the outcome of < 20% reduction in BPRS (Analysis 1.6), and the adverse effects of high blood pressure (Analysis 1.16) and infection (Analysis 1.17) (see Potential biases in the review process).

4. Reporting biases (publication bias)

Only one outcome in this review lent itself to producing a funnel plot, i.e. had more than 10 included studies; 'Global state: Leaving the study early, up to six weeks'. The funnel plot was symmetrical for this outcome.

DISCUSSION

Summary of main results

Twenty-five trials enrolling 4651 participants met the inclusion criteria. The summary below reflects the outcomes chosen for Summary of findings for the main comparison, and considered the main findings of this review that can support evidence-based decision making.

1. Overall global improvement

Moderate quality evidence indicates that the efficacy of haloperidol for improving global state is 33% for both up to six weeks follow-up and for six weeks to six months follow-up. In the clinical environment haloperidol is clearly a valuable antipsychotic. However, there were no studies that reported on this outcome beyond six months.

2. Hospital discharge

Only one, small study (Howard 1974), reported on discharge from hospital and no significant differences were observed.

3. Relapse

Results from two small studies (Nishikawa 1982 and Nishikawa 1984) show that haloperidol reduced the number of participants experiencing a relapse by 31% from six months to one year follow-up. Based solely on this very low quality evidence, we cannot say whether haloperidol prevents relapses in real, clinical settings.

4. Leaving the study early

Just less than half those allocated haloperidol and just over half of those given placebo did not complete the six-week studies. Although the result does favour haloperidol, this is a shocking loss of data and much greater than is seen in the companion review, 'Chlorpromazine versus placebo for schizophrenia' (Adams 2007). There is no suggestion that this attrition, much greater than would be expected in normal clinical practice, has changed over three decades of trials. Clearly the trial design is either unacceptable to participants or is asking researchers to withdraw participants for reasons that are not apparent to those reading the final reports. In any event this is not acceptable.

5. Mental state

We expected more data on the specific symptoms of schizophrenia. One set of mental state data were presented in a study undertaken by dishonest researchers (Borison 1992a), where no differences were observed between haloperidol and placebo. Results from change data on the BPRS scale from Klieser 1989 also showed no differences. On the other hand, Bechelli 1983 and Jann 1997 (n = 72) found a significant difference, favouring haloperidol, by approximately 12 points on the BPRS at six weeks. Garcia 2009 (n = 119) and Kane 2010 (n = 234) reported data from the PANSS; they found significant results favouring haloperidol on the total (by 15.6 points), positive (by 3.3 points) and negative (by 1.2 points) subscales. We are unsure whether these are clinically significant findings.

6. Adverse effects

Use of haloperidol has long been associated with movement disorders, and trial-derived data would seem to fit with clinical experience. Evidence from this review indicate that haloperidol causes different extrapyramidal symptoms (EPS) such as akathisia, dystonia, parkinsonism, rigidity and tremor, and more people given haloperidol needed anti-Parkinson medication than those given placebo. On the other hand, there was no evidence that haloperidol causes other EPS such as oculogyric crises, teeth grinding, or 'thick' speech. There were so few long-term data that rates of tardive dyskinesia were difficult to quantify with confidence. Although not noted as being a sedating antipsychotic, haloperidol does commonly induce sleepiness. Also, people given haloperidol tend to gain weight.

7. Subgroup analyses

The power to detect a real difference between studies in any one of the subgroup analyses was very low. The only statistically significant difference was for low versus medium to high dose for the outcome 'Global state: Overall improvement: No marked global improvement, up to six weeks'. Pooled results for this outcome had high heterogeneity (I^2 = 72%); this heterogeneity disappeared when trials were split into subgroups of low and medium to high dose haloperidol. For low dose (4 mg/day), Kane 2010 did not observe any difference in global improvement between haloperidol and placebo, whereas for medium to high doses (> 5 mg/day), Bechelli 1983, Garcia 2009 and Selman 1976 found that haloperidol was 52% more effective than placebo.

Overall completeness and applicability of evidence

Completeness

Given that haloperidol is so widely used in routine practice across the world, and is a common control drug for randomised trials of new compounds, readers may have expected more data; certainly we did. We were especially surprised not to find a single study that reported on deaths. In addition, no study reported on satisfaction with treatment, cost of care or behavioural outcomes. Also, only one study reported on hospitalisation and only two on relapse. If further data from randomised trials become available, this review will be updated and might report results with greater confidence. Nevertheless, to date, this systematic review represents a rare attempt to quantify the effects of this potent antipsychotic in some clinically meaningful terms.

Applicability

The 25 included studies in this review included many people who would be recognisable in everyday practice. There were those with strictly diagnosed illness and those whose illness was diagnosed using less rigorous criteria; the results of the subgroup analyses on diagnostic rigour (see Effects of interventions, section 2.6) support the assertion that the results are widely applicable. However, most studies were undertaken in hospital, whereas the great majority of people with schizophrenia are in the community, and thus, generalising to treatment in community settings could be problematic. In addition, the dose of haloperidol in 68% of the included studies was high (10-200 mg/day), see Characteristics of included studies, and one of the subgroup analyses on dose revealed a difference between low- and medium- to high-dose haloperidol (see Effects of interventions section 2.4) suggesting results may not be fully applicable to any haloperidol dose.

Finally, most studies were conducted in Europe and North America, therefore, results may not be applicable to Africa, Asia, Australia or South America.

Quality of the evidence

The quality of the evidence is moderate to very low based on GRADE (Schünemann 2008). Overall, outcomes with a small number of participants were rated very low quality, and other outcomes moderate quality. None were rated high quality as most studies had an overall unclear to high risk of bias. The great majority of studies did not report the method of randomisation, and only one trial described the method of allocation concealment. Although all studies were reported to be double-blind, it was not clearly described in most trials. Thirty-six per cent out of the included studies were rated as high risk of bias for incomplete outcome reporting, mainly due to very high losses to follow-up. Data presentation was poor, with most scale data rendered unusable (see Characteristics of included studies). Studies failed to report variances, reported only P values, or did not report the result at all. In this way a lot of potentially informative data were lost. Consequently, 68% of the trials were rated as high risk of selective reporting bias. With closer adherence to the CONSORT statement (Begg 1996), data reporting should improve, although it should be noted that some of the most recent trials (Garcia 2009 and Kane 2002) still failed to present standard deviations for some or all of their continuous data.

Potential biases in the review process

1. Failing to identify old trials

We identified trials by meticulous searching, including Janssen-Cilag UK helping the original search. Despite this, it is reasonable to assume that no data set is complete for haloperidol, one of the oldest antipsychotic drugs. Nevertheless, we do not feel that we have omitted very many highly influential studies.

2. Under-reporting of trial methodology

As can be seen in Figure 2, most trials were rated unclear risk of bias for randomisation generation, allocation concealment and blinding. This was because the trial reports did not specify the methods adequately. Consequently, we downgraded the quality of the evidence in the Summary of findings for the main comparison, and by doing so we may have introduced bias.

3. Sensitivity analyses on dishonest researchers

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

Agreements and disagreements with other studies or reviews

We know of two systematic reviews of randomised controlled trials that evaluate haloperidol versus placebo for schizophrenia: i. Gao 2008 systematically reviewed extrapyramidal side effects and, similar to our results, found that there was a higher risk of developing akathisia and overall EPS with haloperidol compared with placebo; ii. Klemp 2011 reviewed the clinical efficacy and adverse effects of four atypical antipsychotics compared with haloperidol and placebo, and in agreement with our results found that haloperidol had a significantly better antipsychotic effect than placebo, and that haloperidol induces weight gain and EPS compared with placebo.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia

Even with this limited data set it can be seen that haloperidol is a potent antipsychotic drug but has a high propensity to cause adverse effects. The addition of new data further strengthens this observation. Given the choice, people with schizophrenia may wish to switch to another antipsychotic with less likelihood of causing parkinsonism, akathisia and acute dystonias.

2. For clinicians

Haloperidol remains a benchmark for modern treatments. This review supports and, perhaps for the first time, objectively quantifies evidence of clinical experience. Clinicians with little choice of treatment should be reassured that the evidence for haloperidol's antipsychotic effect is borne out by trials and that it should remain as one useful treatment option. Where several antipsychotics are available to a clinician, the comparative effects, including adverse effects of each antipsychotic, should be carefully considered.

3. For managers and policy makers

Haloperidol is inexpensive and effective. Initial cost savings could be offset by the consequences of adverse effects, which may include poor compliance with medication. It is important that a person with schizophrenia is treated for their illness. Policy makers must take into account the evidence as presented in this review and formulate humane, culturally sensitive, policy optimising a persons' chance of maintaining recovery.

Implications for research

1. General

More well designed, conducted and reported randomised trials would probably have allowed this review to be more authoritative and comprehensive. Much data were lost due to poor reporting, even in some of the most recent studies.

2. Specific

It is unfortunate to have to mention that there is still scope for better designed, conducted and reported randomised trials on the absolute effects of haloperidol after nearly five decades of research. Although such trials might be of academic interest, we recognise that new placebo-controlled studies are unlikely. However, using haloperidol as the control drug in randomised controlled trials evaluating new antipsychotics is likely to continue to be common practice. Haloperidol is an effective antipsychotic. However, with such common, marked, and unacceptable adverse effects, any comparison with almost any other antipsychotic is going to suggest that the experimental compound has a more favourable adverse effect profile. Haloperidol should be less favoured as a control drug.

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Irving CB, Adams CE, Lawrie S. Haloperidol versus placebo for schizophrenia. *Cochrane Database of*

Systematic Reviews 2006, Issue 4. [DOI: 10.1002/14651858.CD003082.pub2]

Joy 2001

Joy CB, Adams CE, Lawrie SM. Haloperidol versus placebo for schizophrenia. *Cochrane Database of Systematic Reviews* 2001, Issue 2. [DOI: 10.1002/14651858.CD003082]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Arvanitis 1997

Methods	Allocation: random assignment. Blindness: double-blind. Duration: 6 weeks (preceded by a 7-day single blind placebo washout). Location: multicentre. Design: parallel. Setting: inpatients. Country: USA and Canada. Consent: written.
Participants	Diagnosis: (DSM-III-R) schizophrenia. N = 361. History: sub/chronic hospitalised, currently experiencing acute exacerbation of psychotic symptoms. Sex: 76% M, 24% F. Age: 18 - 64 years (mean ~ 37 years). Exclusions: BPRS score < 27, CGI score < 4, history of seizures, other significant medical condition, participation in other drug trial within 30 days, use of depot antipsychotics within 1 dosing interval, pregnancy, placebo responders, non completion of dose escalation
Interventions	1. Haloperidol: fixed dose (FD) 12 mg/day, increased day 1-14. N = 52 2. Placebo. N = 51. 3. Quetiapine: (FD) 75 mg/day, increased day 1-14. N = 53. 4. Quetiapine: (FD) 150 mg/day, increased day 1-14. N = 48. 5. Quetiapine: (FD) 300 mg/day, increased day 1-14. N = 52. 6. Quetiapine: (FD) 600 mg/day, increased day 1-14. N = 51. 7. Quetiapine: (FD) 750 mg/day, increased day 1-14. N = 54. Chloral hydrate, lorazepam, benztropine mesylate as required
Outcomes	Leaving the study early. Unable to use - Global effect: improved/not improved, CGI (> 50% loss). Dose response (> 50% loss). Time to response (> 50% loss). Mental state: BPRS, SANS (> 50% loss). Adverse events: AIMS, SAS, other various observed effects (> 50% loss)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Arvanitis 1997 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"Randomised" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind"; "[Blood] samples were shipped to the sponsor and analysed". No further details reported
Incomplete outcome data (attrition bias) All outcomes	High risk	"Of all patients evaluated, 149 (41%) completed 6 weeks of treatment. Lack of efficacy was the primary reason for withdrawal and was seen most often in the placebo group". No further details reported
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	High risk	Supported by a grant from Zeneca Pharmaceuticals.

Beasley 1996

Methods	Allocation: random assignment. Blindness: double-blind. Duration: 6 weeks (preceded by a 4-7 day single blind placebo washout). Location: multicentre. Design: parallel. Setting: inpatients and outpatients. Country: USA. Consent: written.
Participants	Diagnosis: (DSM-III-R) schizophrenia. N = 335. History: currently suffering from acute exacerbation of symptoms. Sex: 88% M, 12% F. Age: 18 - 65 years. Exclusions: other serious physical or neurological disorder/condition, substance abuse within 3 months of study, abnormal lab results, placebo responders
Interventions	1. Haloperidol: dose 10, 15 or 20 mg/day; initial dose 15 mg/day, adjusted accordingly thereafter. N = 69. 2. Placebo. N = 68. 3. Olanzapine: dose 2.5, 5 or 7.5 mg/day; initial dose 5 mg/day, adjusted accordingly thereafter. N = 65.

	4. Olanzapine: dose 7.5, 10 or 12.5 mg/day; initial dose 10 mg/day, adjusted accordingly thereafter. N = 64. 5. Olanzapine: dose 12.5, 15 or 17.5 mg/day; initial dose 15 mg/day, adjusted accordingly thereafter. N = 69. Lorazepam, benztropine mesylate as required.
Outcomes	Leaving the study early. Unable to use - Global effect: CGI, PGI (> 50% loss). Hospitalisation: admission/discharge, days in hospital (> 50% loss). Dose response (> 50% loss). Mental state: BPRS, SANS (> 50% loss). Adverse events: SAS, AIMS, BAS, other observed effects (> 50% loss). Compliance (> 50% loss).
Notes	Data only taken from the initial 'acute phase' trial.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up ranged from 51% - 68% in the five treatment arms
Selective reporting (reporting bias)	High risk	Patient Global Impression (PGI) assessed but not reported.
Other bias	High risk	Source of funding from industry "From the Psychopharmacology Division, Lilly Research Laboratories, Eli Lilly and Company"

Bechelli 1983

Methods	Allocation: random assignment. Blindness: double-blind. Duration: 21 days (preceded by 3 days stabilisation with chlorpromazine and haloperidol followed by 2 day washout). Location: hospital. Design: parallel. Setting: inpatients. Country: Brazil. Consent: not stated.
Participants	Diagnosis: (ICD-9) schizophrenia. N = 90. History: recently admitted to hospital, currently acute. Sex: male. Age: mean ~ 29 years. Exclusions: substance abuse, other clinically significant medical or neurological pathologies
Interventions	1. Haloperidol: dose 5 - 20 mg/day. N = 30. 2. Placebo: N = 31. 3. Pipotiazine: dose 10 - 40 mg/day. N = 29. Biperiden and trihexyphenidyl as required on day 1 - 3 only.
Outcomes	Adverse event: various observed effects. Global effect: improved/not improved. Leaving the study early. Mental state: BPRS.
Notes	If, after entering the trial, participants showed improvement they could be discharged from hospital. If, however, they were readmitted due to relapse they could then re-enter the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were assigned to 3 groups of 30 each in a random and probabilistic manner, after stratification", no further details reported
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Blinding of outcome assessment (detection bias)	Low risk	"The assessments were always performed by the same investigator in a double-blind

Bechelli 1983 (*Continued*)

All outcomes		trial. Only at the end of the study after the data were analysed were the patient group assignments identified"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Five patients ran away between the 6th and 27th day of the study. Three belonged to the pipotiazine group, 1 belonged to the haloperidol group, and 1 to the placebo group". "These patients were excluded from the analysis"
Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Unclear risk	Source of funding not reported.

Borison 1989

Methods	Allocation: random assignment. Blindness: double-blind. Duration: 6 weeks (preceded by a 7 day single blind placebo wash out). Location: not stated. Design: parallel. Setting: not reported. Country: not reported. Consent: written.
Participants	Diagnosis: (DSM-III) schizophrenia. N = 32. History: not stated. Sex: not stated. Age: 18 - 60 years. Exclusions: unstable physical health.
Interventions	1. Haloperidol: dose 15 - 75 mg/day. N = 8. 2. Placebo. N = 8. 3. Tiospirone: dose 45 - 225 mg/day. N = 8. 4. Thioridazine: dose 150 - 750 mg/day. N = 8. Chloral hydrate as required.
Outcomes	Adverse events: various observed effects, use of antiparkinson medication. Leaving the study early. Unable to use - Mental state: BPRS (no SD).
Notes	
Risk of bias	

Borison 1989 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...subjects were assigned on a randomized blind schedule to treatment" no further details reported
Allocation concealment (selection bias)	Unclear risk	"...subjects were assigned on a randomized blind schedule to treatment" no further details reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double- blind" no further details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up or missing data were balanced across intervention groups, with similar reasons for missing data. "...three placebo-treated patients were terminated prior to study completion due to lack of efficacy. Two patients receiving haloperidol terminated early due to positive response and the desire to leave the hospital, and one patient in the haloperidol treatment group was terminated for administrative reasons. The only patient who left the study prematurely due to an apparent adverse reaction was one receiving placebo, who developed chest pain and electrocardiographic changes"
Selective reporting (reporting bias)	Unclear risk	Study does not state in methods which outcomes will be measured, and/or no protocol available
Other bias	High risk	Researchers currently imprisoned for research fraud.

Borison 1992a

Methods	Allocation: random assignment. Blindness: double-blind. Duration: 7 weeks (preceded by a 7-day single blind placebo washout). Location: multicentre, part of larger trial. Design: parallel. Setting: inpatients. Country: not reported. Consent: written.
Participants	Diagnosis: (DSM-III-R) schizophrenia. N = 36. History: chronic. Sex: 97% M, 3% F. Age: ~ 31-52 years. Exclusions: substance abuse, other clinically significant medical or neurological pathologies, women of child bearing capacity
Interventions	1. Haloperidol: dose 4-20 mg/day, dose adjusted as required days 1-18. N = 12. 2. Placebo. N = 12. 3. Risperidone: dose 2-10 mg/day, dose adjusted as required days 1-18. N = 12. Lorazepam, sodium amytal, chloral hydrate, benztropine or trihexyphenidyl as required
Outcomes	Adverse events: various observed effects. Leaving study early. Mental state: no clinical improvement (< 20% reduction in BPRS score) Unable to use - Adverse events: AIMS (no data), ESRS (no SD). Global effect: CGI (no SD). Mental state: BPRS, SANS (no SD).
Notes	Participants already part of larger multicentre trial. May be part of North American Trial.

Risk of bias

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

Borison 1992a (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details reported.
Selective reporting (reporting bias)	High risk	Several outcomes not fully reported (BPRS, CGI, SANS, or ESRS)
Other bias	High risk	Source of funding not reported. Richard Borison, MD, former psychiatry chief at the Augusta Veterans Affairs medical center and Medical College of Georgia, was sentenced to 15 years in prison for a $10 million clinical trial fraud

Chouinard 1993

Methods	Allocation: random assignment. Blindness: double-blind. Duration: 8 weeks (preceded by a 7-day single blind placebo washout). Location: multicentre. Design: parallel. Setting: inpatients. Country: Canada. Consent: written.
Participants	Diagnosis: (DSM-III-R) schizophrenia. N = 135. History: chronic, hospitalised. Sex: 71% M, 29% F. Age: mean ~ 37 years. Exclusions: other clinically significant neurological or psychical disorder, substance abuse, pregnancy, placebo responders
Interventions	1. Haloperidol: dose 20 mg/day, initial dose 2 mg/day increased in fixed increments day 2-7. N=21. 2. Placebo. N = 22. 3. Risperidone: dose 2 mg/day 4. Risperidone: dose 6 mg/day, initial dose 2 mg/day increased in fixed increments day 2-4. 5. Risperidone: dose 10 mg/day, initial dose 2 mg/day, increased in fixed increments day 2-5. 6. Risperidone: dose 16 mg/day, initial dose 2 mg/day, increased in fixed increments day 2-7. Chloral hydrate, benzodiazepine, biperiden or procyclidine as required
Outcomes	Leaving the study early. Unable to use - Global effect: CGI (> 50% loss). Level of medication required (> 50% loss).

Chouinard 1993 (*Continued*)

	Mental state: BPRS, GPS, PANSS (> 50% loss). Adverse events: ESRS, various observed effects (UKU), use of antiparkinson medication (> 50% loss). Cost of treatment (> 50% loss).
Notes	Part of North American Trial.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind", "Study medication was administered under double-blind conditions as identical tablets of risperidone, haloperidol and placebo"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind", "Assessment of symptoms was based on clinical interviews conducted by a psychiatrist". No further details reported
Incomplete outcome data (attrition bias) All outcomes	High risk	A total of 65 participants (48.1%) left the study early: 16 (72.7%) from the placebo group and 13 (61.9%) from the haloperidol group "Statistical analyses of efficacy and safety parameters were conducted according to the intent-to-treat analysis principle"
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	Unclear risk	Source of funding not reported.

Durost 1964

Methods	Allocation: random assignment. Duration: 10 days - 3 months (mean 3 weeks). Location: hospital. Design: parallel. Setting: inpatients. Country: not reported. Consent: unknown.
Participants	Diagnosis: schizophrenia (40%), neurosis (60%).* N = 84 (schizophrenia 34, neurosis 50). History: unknown. Sex: 60% M, 40% F. Age: mean ~ 39 years. Exclusions: unknown.
Interventions	1. Haloperidol: dose 2-25 mg/day, mean 6 mg/day. N = 19. 2. Placebo. N = 15.
Outcomes	Global effect: improved/not improved. Leaving the study early. Unable to use - Adverse events: various observed effects (no data).
Notes	* use only data for those suffering from schizophrenia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...all drugs were given at random" no further details reported
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"...'pharmacotherapeutically blind unit,' that is, in a hospital service where all drugs were given at random and used without the service team (made up of one intern, two assistant residents, one resident, one psychologist, two to four nurses, one social worker and one occupational therapist) knowing what drugs were being investigated."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The assessment of the patients (and the drugs) was a result of the pooling of the opinions of the different members of the team."

Durost 1964 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no drop-outs from the study.
Selective reporting (reporting bias)	High risk	Details on side effects were not fully reported although "Side effects were relatively numerous and disturbing to the patients."
Other bias	Unclear risk	"Haloperidol was generously supplied by G. D. Searle & Co."

Garcia 2009

Methods	Allocation: randomised. Blinding: double-blind. Duration: 6 weeks. Design: parallel. Setting: inpatient. Country: USA, Bulgaria, the Czech Republic and Russia. Consent: written.
Participants	Diagnosis: schizophrenia DSM-4. N = 307. Age: 18-65 (Mean 38.1, SD 11.1). Sex: M 183, F 124. History: acute exacerbation of illness, hospitalised for < 2 weeks at screening due to the exacerbation. PANSS score of at least 70. Exclusions: patients improving > 20% in the PANSS total score or 1 point in the CGI-S scale at baseline compared with screening; resistant to antipsychotic treatment; DSM-IV-TR-defined substance abuse/dependency within the preceding 3 months (or a positive urine drug test); treated with depot antipsychotics, unless the last injection was administered within greater than one treatment cycle before study entry;clinically significant or currently relevant illness or those judged by the investigator to be at serious suicidal risk
Interventions	1. Blonanserin: dose 2.5 mg/day. N = 61. 2. Blonanserin: dose 5 mg/day. N = 58. 3. Blonanserin: dose 10 mg/day. N = 64. 4. Haloperidol: dose 10 mg/day. N = 60. 5. Placebo. N = 64.
Outcomes	Leaving the study early Global state: No overall improvement (< 20% reduction in PANSS-total score) Mental state: PANSS-total score, mean change from baseline at 6 weeks Mental state: PANSS-positive score, mean change from baseline at 6 weeks Mental state: PANSS-negative score, mean change from baseline at 6 weeks Global state: CGI-S, mean change from baseline at 6 weeks Adverse effects: Extrapyramidal symptoms (akathisia, dyskinesia, dystonia, parkinsonism, rigidity, tremor)

	Adverse effects: Cardiovascular (bradycardia) Adverse effects: Other (insomnia, drooling, headache, weight loss, agitation, anxiety, sleepiness) Unusable data (no measurement of variance reported) - Adverse effects: Extrapyramidal symptoms: SAS, BAS and AIMS scales	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization of medication was performed using a computer-generated schedule"
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind", "...blinding was ensured by over-encapsulating all capsules to ensure the same appearance"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind", no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up or missing data were balanced across intervention groups, with similar reasons for missing data. Missing data have been imputed using appropriate methods (intention-to-treat analysis)
Selective reporting (reporting bias)	High risk	Not all of the study's pre-specified primary outcomes have been reported (BPRS, UKU assessments)
Other bias	High risk	"Laboratorios Almirall SA provided financial support for performing the study and Dainippon Sumitomo Pharma Co., Ltd funded the preparation of this manuscript. Drs Garcia, Robert and Peris are employees of Laboratorios Aimirall SA. H. Nakamura, Dr Sato and Y. Terazawa are employees of Dainippon Sumitomo Pharma Co. , Ltd. Drs Garcia and Peris have received stock options from Laboratorios Almirall SA."

Garry 1962

Methods	Allocation: random assignment. Blindness: double-blind. Duration: 12 weeks (preceded by a 2-week medication free period). Location: not stated. Design: parallel. Setting: inpatients. Country: not stated. Consent: not stated.
Participants	Diagnosis: schizophrenia. N = 52. History: chronic, hospitalised. Sex: 62% M, 38% F. Age: mean ~ 46 years. Exclusions: not stated.
Interventions	1. Haloperidol: dose 0.75 - 4.5 mg/day, increased day 1 - 42. N = 26. 2. Placebo. N=26.
Outcomes	Adverse events: various observed effects* Global effect: improved/not improved. Leaving the study early.
Notes	*Adverse effects reported for haloperidol group only, reviewers assumed that placebo group had no adverse effects

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants "were divided into two groups on the basis of a list of random numbers supplied by the drug company"
Allocation concealment (selection bias)	Low risk	Central allocation "Our pharmacist allotted the patients from an alphabetical list supplied by us"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Two patients were withdrawn from the trial, one had a recurrence of a skin rash (he was eventually found to be on the placebo)

Garry 1962 (*Continued*)

		and the other was found to have early pulmonary tuberculosis on routine chest X-ray. We were finally left with 50 patients (25 on drug and 25 on controls) who completed the trial"
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	Unclear risk	Messrs. G. D. Searle and Co. Ltd. supplied the haloperidol and control tablets

Howard 1974

Methods	Allocation: random assignment. Blindness: double-blind. Duration: max 12 weeks (preceded by a 14 day placebo washout). Location: hospital. Design: parallel and cross-over. Setting: inpatients and outpatients. Country: USA. Consent: not stated.
Participants	Diagnosis: schizophrenia (80%). N = 49. History: treatment resistant, hospitalised. Sex: female. Age: 25 - 65 years. Exclusions: other serious physical or neurological disorder, pregnancy, severe hyposensitivity to haloperidol or thiothixene, placebo responders
Interventions	1. Haloperidol: dose < 200 mg/day. N = 17. 2. Placebo. N = 16. 3. Thiothixene: dose < 200 mg/day. N = 16.
Outcomes	Global effect: improved/not improved. Hospital discharge. Leaving the study early. Adverse events: various observed effects. Unable to use - Behaviour: NOSIE (no SD). Mental state: BPRS (no mean, no SD), MSC (data given only for those remaining in hospital)
Notes	

Risk of bias

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

Howard 1974 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"the patients were randomly assigned" no further details reported
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The study medications were prepared in identical appearing capsules"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up were balanced across intervention groups, with similar reasons for missing data
Selective reporting (reporting bias)	High risk	All outcomes were not fully reported (no SD s were reported for BPRS and NOSIE)
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists (does not report source of funding)

Jann 1997

Methods	Allocation: random assignment. Blindness: unsure. Duration: 6 weeks. Location: not stated. Design: parallel. Setting: inpatients. Country: not reported. Consent: written.
Participants	Diagnosis: (DSM-III-R) schizophrenia. N = 36. History: not stated. Sex: not stated. Age: ~ 25 - 43 years. Exclusions: not stated.
Interventions	1. Haloperidol: dose up to 75 mg/day, dose individually adjusted weekly. N = 18. 2. Placebo. N = 18. Lorazepam or chloral hydrate as required.

Jann 1997 (*Continued*)

Outcomes	Adverse events: various observed effects. Leaving the study early. Mental state: BPRS. Unable to use - Adverse events: AIMS (no data).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Identical looking capsules" were used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	"Only 8 patients in the placebo group completed the 6-week study". "For the haloperidol group, 12 patients completed the study"
Selective reporting (reporting bias)	High risk	All pre-stated outcomes were not reported (no data reported for the AIMS scale)
Other bias	Unclear risk	Source of funding not reported.

Kane 2002

Methods	Allocation: random. Blindness: double-blind. Duration: 4 weeks. Location: hospital, multicentre. Design: parallel. Setting: inpatients. Country: USA. Consent: given.

Kane 2002 (*Continued*)

Participants	Diagnosis: (DSM-IV) schizophrenia or schizoaffective disorder. N = 414*. History: acute relapse, hospitalised. Age: 18 - 65 years. Sex: 70% M, 30% F. Exclusions: other psychiatric disorder, history of violence or self-harm
Interventions	1. Aripiprazole: dose 15 mg/day. N = 102. 2. Aripiprazole: dose 30 mg/day. N = 102. 3. Haloperidol: dose 10 mg/day. N = 104. 4. Placebo. N = 106. lozepam for anxiety or insomnia
Outcomes	Leaving the study early. Adverse events: various observed effects. Unable to use: Global effect: CGI (no SD). Mental state: BPRS, PANSS (no SD).
Notes	Data taken from haloperidol and placebo groups only. Data provided for some outcomes have only 103 people in haloperidol group and 104 in placebo group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" no further information reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The same rater conducted the assessment throughout the study and was blinded to the patient's treatment"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of losses and reasons for leaving the study similar across groups. "Analysis of efficacy parameters was performed on an intention-to-treat basis using data obtained from each patient's last visit (i.e. last observation carried forward analysis at week 4" "Of the 414 randomised patients, 248 competed the 4-week study period"

Kane 2002 (*Continued*)

Selective reporting (reporting bias)	High risk	All pre-stated outcomes were not fully reported (SDs were not reported for PANSS, BPRS, CGI, AIMS, SAS and BAS scales, weight and serum prolactin levels)
Other bias	High risk	Sponsored by Otsuka Pharmaceutical Co. Ltd (Tokyo, Japan) and Bristol-Meyers Squibb Company (Princeton, NJ)

Kane 2010

Methods	Allocation: randomised. Blinding: double-blind. Duration: 6 weeks. Design: parallel. Setting: inpatients and outpatients*. Country: 43 centres (United States, 17 sites; Russia, 11 sites; India, 7 sites; Romania, 7 sites; Canada, 1 site) Consent: written.
Participants	Diagnosis: schizophrenia, DSM-IV. N = 458. Age: 37 to 40 years. Sex: M 270, F 188. History: acute exacerbation of psychotic symptoms. Exclusions: a clinically significant medical condition or abnormal laboratory or physical examination ndings; diagnosis of residual-type schizophrenia, schizoaffective disorder, or coexisting psychiatric disorder coded on Axis I; current or past substance abuse; 20% or higher decrease in PANSS total score from screening to baseline; known allergy or sensitivity to haloperidol; imminent risk of self-harm or harm to others; previous participation in an asenapine trial
Interventions	1. Asenapine: dose 5 mg/day. N = 114. 2. Asenapine: dose 10 mg/day. N = 106. 3. Placebo. N = 123. 4. Haloperidol: dose 4 mg/day. N = 115.
Outcomes	Leaving the study early Global state: no overall improvement (no CGI-I score of 1 [very much improved] or 2 [much improved]) (also measured as < 30% reduction in PANSS total score, not used) Mental state: PANSS subscale scores (positive, negative), mean change from baseline at 6 weeks Global state: CGI-S and CGI-I, mean change from baseline at 6 weeks Mental state: Calgary Depression Scale for Schizophrenia (CDSS), mean change from baseline at 6 weeks Adverse effects: Extrapyramidal symptoms (SAS, BAS and AIMS scales), mean change from baseline at 6 weeks Adverse effects: Extrapyramidal symptoms (parkinsonism, akathisia, dystonia, rigidity)

	Adverse effects: Other (insomnia, oral hypoaesthesia, sleepiness, agitation, headache, anxiety, weight loss, weight gain) Adverse effects: Autonomic (sedation) Use of anti-Parkinson medication Unable to use (measurements of variance not reported) - PANSS total score mean change from baseline to day 42 (primary outcome) Modied International Suicide Prevention Trial (InterSePT) Scale for Suicidal Thinking Readiness to Discharge Questionnaire (RDQ)
Notes	*Patients were hospitalised for at least 2 weeks.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomized", no further details provided.
Allocation concealment (selection bias)	Unclear risk	"Randomized", no further details provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind", no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Safety assessments were made using data from the treated population (all patients who received >1 dose of study medication); efcacy analyses were based on data from the intent-to-treat (ITT) population (treated patients who had >1 postbaseline PANSS assessment)"
Selective reporting (reporting bias)	High risk	Not all pre-specified outcomes were reported fully.
Other bias	High risk	"funded by Schering-Plough Corporation, now Merck & Co, Inc"

Klieser 1989

Methods	Allocation: random assignment. Blindness: double-blind. Duration: 3 weeks. Location: hospital. Design: parallel. Setting: inpatients. Country: not reported. Consent: not stated.
Participants	Diagnosis: schizophrenia (63%), major depressive disorder (37%). N = 120. History: chronic, hospitalised. Sex: 41% M, 59% F. Age: mean ~ 43 years. Exclusions: not stated.
Interventions	1. Haloperidol: dose 20 mg/day. N = 20*. 2. Placebo. N = 16. 3. Trazodone: dose 400 mg/day. N = 17. 4. Amitriptyline: dose 150 mg/day. N = 22. Biperiden as required.
Outcomes	Leaving the study early Mental state: BPRS.
Notes	*number of people with schizophrenia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of losses from each treatment group and reasons for loss to follow-up not reported. "Fourteen patients left the study on day 3, 19 patients left on day 7, and 6 patients left on day 14"

Klieser 1989 (*Continued*)

Selective reporting (reporting bias)	High risk	Not all expected outcomes were reported.
Other bias	Unclear risk	Source of funding not reported.

Marder 1994

Methods	Allocation: random assignment. Blindness: double-blind. Duration: 8 weeks (preceded by 1 week placebo wash out). Location: multicentre. Design: parallel. Setting: inpatients. Country: USA. Consent: given.
Participants	Diagnosis: (DSM-III-R) schizophrenia. N = 388. History: hospitalised, chronic. Sex: 89% M, 11% F. Age: mean ~37 years. Exclusions: physically unhealthy, schizoaffective disorder.
Interventions	1. Haloperidol: dose 20 mg/day. N = 66. 2. Placebo: N = 66. 3. Risperidone: dose 2 mg/day. N = 63. 4. Risperidone: dose 6 mg/day. N = 64. 5. Risperidone: dose 10 mg/day. N = 65. 6. Risperidone: dose 16 mg/day. N = 64. Lorazepam or chloral hydrate as required.
Outcomes	Leaving the study early Unable to use - Global state: CGI (> 50% loss). Mental state: PANSS (> 50% loss). Adverse events: EPS, UKU scale (> 50% loss).
Notes	Part of 'North America 1997'.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"...randomization was in blocks of 12" no further details reported
Allocation concealment (selection bias)	Unclear risk	No information reported.

Marder 1994 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	"early termination in 53% of the patients. ..62 % of the placebo patients; and 38% of patients receiving haloperidol...Both observed case and last observation carried forward (or end point) analyses were performed"
Selective reporting (reporting bias)	Low risk	All expected outcomes are reported.
Other bias	Unclear risk	Source of funding from a pharmaceutical company "Supported by a grant from the Janssen Research Foundation"

Meltzer 2004

Methods	Allocation: randomised. Blinding: double-blind. Duration: 6 weeks. Design: parallel. Setting: inpatients up to day 15 after randomisation. Country: USA. Consent: written.
Participants	Diagnosis: schizophrenia and schizoaffective disorder DSM-IV. N = 481. Age: 18-64 (range 35.4-37.5). Sex: M 355, F 126. History: hospitalised at baseline; a total score on the PANSS greater than 65 at screening and baseline, a minimum severity of illness score of 4 (moderately ill) on the CGI at screening and baseline. Exclusions: patients with other axis I DSM-IV diagnoses; patients considered by the investigator to have been non-responsive to treatment with at least two different classes of antipsychotic medications; patients with any clinically significant medical illnesses; patients with clinical laboratory or ECG abnormalities; patients with evidence of current substance abuse or dependence; patients who were a danger to themselves or others
Interventions	1. Haloperidol: dose 10 mg/day. N = 98. 2. Placebo. N = 98. 3. 5-HT2A/2C antagonist: dose 5 mg/day. N = 70. 4. NK3 antagonist: dose 200 mg/day. N = 67.

	5. CB1 antagonist: dose 20 mg/day. N = 69. 6. NTS1 antagonist: dose 180 mg/day. N = 63.
Outcomes	Leaving the study early* Unable to use (losses to follow-up > 50%) - Mental state: PANSS (total, positive, negative, general), mean change from baseline at 6 weeks BPRS (total), mean change from baseline at 6 weeks Global state: CGI-I, mean endpoint score at 6 weeks Global state: CGI-S, mean change from baseline at 6 weeks Mental state: Calgary Depression Scale (CDS), mean change from baseline at 6 weeks Adverse effects: Extrapyramidal symptoms: various scales (SAS, BAS, AIMS), mean change from baseline at 6 weeks Adverse effects: Other (headache, insomnia, psychosis, agitation, abdominal pain, dyspepsia, vomiting, extrapyramidal symptoms, hyperkinesia)
Notes	*This study had > 50% losses to follow-up, only the outcome Leaving the study early could be used

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomized", no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind", no further details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind", no further details reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up greater than 50%.
Selective reporting (reporting bias)	Low risk	All expected outcomes are reported.
Other bias	High risk	Funding sources are pharmaceutical companies, "Dr. Meltzer has received grant support from and is a consultant to Acadia, AstraZeneca, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutica, Lundbeck, Novartis, Pfizer, Sanofi-Synthelabo, and Solvay. He is a consultant to Psychiatric Genomics, Precision Med, Pharmacia, and Roche.

		Drs. Arvanitis and Rein and Ms. Bauer are employees of Sanofi-Synthelabo."

NCT00044044 2002

Methods	Allocation: randomised. Blinding: double-blind. Duration: 6 weeks. Design: parallel. Setting: inpatients. Country: USA. Consent: not stated.
Participants	Diagnosis: schizophrenia. N = 330. Age: mean (SD): 41.2 (10.0) years. Sex: M 262, F 91. History: hospitalised with acute or relapsing schizophrenia within 3 weeks of screening, a duration of illness of at least one year. Exclusions: psychiatric hospitalisations other than current hospitalisations within 1 month prior to screening; treatment resistant; substance abuse; prolactin level of > 200 ng/mL at baseline; pregnancy
Interventions	1. Lurasidone: dose 20mg/day. N = 71. 2. Lurasidone: dose 40mg/day. N = 69. 3. Lurasidone: dose 80mg/day. N = 71. 4. Haloperidol: dose 10mg/day. N = 73. 5. Placebo. N = 72.
Outcomes	Leaving the study early* Unable to use (losses to follow-up > 50%) - Adverse effects: Extrapyramidal symptoms (akathisia, tremor, dystonia, EPS) Adverse effects: Autonomic (sedation) Adverse effects: Cardiovascular and gastric (dizziness, diarrhoea, constipation, abdominal discomfort) Adverse effects: Other (nausea, vomiting, headache, sleepiness, agitation, anxiety, insomnia) Mental state: BPRS total, mean change from baseline at 6 weeks Mental state: PANSS, mean change from baseline at 6 weeks Global state: CGI-S, mean change from baseline at 6 weeks Mental state: MADRS, mean change from baseline at 6 weeks
Notes	ClinicalTrials.gov Identifier: NCT00044044. *This study had > 50% losses to follow-up, only the outcome Leaving the study early could be used

Risk of bias

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

NCT00044044 2002 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"Randomized", no further details reported.
Allocation concealment (selection bias)	Unclear risk	"Randomized", no further details reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The placebo was an "Oral Capsule matching treatment" indicating blinding of participants. Further, the study was described as "Double blind", but there were no further details on blinding of personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double blind", no further details reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	There was a high rate of drop-outs (> 50%) .
Selective reporting (reporting bias)	Low risk	All pre-stated outcomes were reported.
Other bias	High risk	"Sponsored by: Sumitomo Pharmaceuticals America"

Nishikawa 1982

Methods	Allocation: random assignment. Blindness: double-blind. Duration: 3 years*. Location: not stated. Design: cross-over. Setting: outpatients. Country: Japan. Consent: not stated.
Participants	Diagnosis: schizophrenia N = 55. History: outpatients, currently in remission, but have a history of several relapse episodes. Sex: 67% M, 33% F. Age: ~ 25 - 41 years. Exclusions: history of taking medication irregularly.
Interventions	1. Haloperidol: dose 3 mg/day. N = 10. 2. Placebo. N = 10. 3. Chlorpromazine: dose 75 mg/day. N = 10. 4. Diazepam: dose 15 mg/day. N = 13. 5. Imipramine: dose 50 mg/day. N = 12. Nitrazepam or biperiden as required.

Nishikawa 1982 (*Continued*)

Outcomes	Relapse: number remaining in remission < 1 year. Unable to use - Leaving the study early (unclear when losses occurred, no individual group data given)
Notes	*Initial 'cross-over' design of trial was disregarded after participant/clinician reluctance to switch neuroleptics. Data taken from first arm only

Risk of bias

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

Nishikawa 1984

Methods	Allocation: random assignment. Blindness: double-blind. Duration: 1 year. Location: not stated. Design: parallel. Setting: outpatients. Country: Japan. Consent: not stated.
Participants	Diagnosis: (DSM III) schizophrenia. N = 87. History: in recovery stage of remission. Sex: 61% M, 39% F. Age: ~ 28 - 54 years. Exclusions: not stated.
Interventions	1. Haloperidol: dose 1 mg/day. N = 13. 2. Haloperidol: dose 3 mg/day. N = 12. 3. Haloperidol: dose 6 mg/day. N = 12. 4. Placebo. N = 13. 5. Propericiazine: dose 10 mg/day. N = 13. 6. Propericiazine: dose 30 mg/day. N = 13. 6. Propericiazine: dose 60 mg/day. N = 13. Each drug combined with nitrazepam and biperiden.
Outcomes	Relapse: number remaining in remission < 1 year. Leaving the study early.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind", "Drug appearance, with respect to powder colour, taste and volume, was made identical by gastric aid, SMP (Sankyo, Japan)"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" no further details reported.

Nishikawa 1984 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	"Among the entire group of 87 patients, 19 patients continued to receive the assigned drugs since they were in remission during the entire year of the trial, while other patients discontinued use of the assigned drugs due to overdose (N=16), relapse (N= 48) and drop-out (N=4)"
Selective reporting (reporting bias)	High risk	Results not reported for placebo group for number of symptom free days and serum prolactin
Other bias	Unclear risk	Source of funding not reported.

Potkin 2008

Methods	Allocation: randomised. Blinding: double-blind. Duration: 6 weeks. Design: parallel. Setting: not stated. Country: not stated. Consent: written.
Participants	Diagnosis: schizophrenia, DSM-IV. N = 621. Age: 18-65, (range 37-40.1). Sex: M 443, F 178. History: acute or subacute exacerbation of schizophrenia and PANSS total score of at least 60 at screening and at baseline. Exclusions: not stated.
Interventions	1. Iloperidone: dose 4 mg/day. N = 121. 2. Iloperidone: dose 8 mg/day. N = 125. 3. Iloperidone: dose 12 mg/day. N = 124. 4. Haloperidol: dose 15 mg/day. N = 124. 5. Placebo. N = 127.
Outcomes	Leaving the study early* Unable to use (losses to follow-up > 50%, variance not reported) - Mental state: PANSS total, PANSS positive, PANSS negative, PANSS general psychopathology, BPRS, mean change from baseline at 6 weeks Adverse effects
Notes	*This study had > 50% losses to follow-up, only the outcome Leaving the study early could be used

Risk of bias

Potkin 2008 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized", no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind", no further details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind", no further details reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up greater than 50%.
Selective reporting (reporting bias)	High risk	SDs not reported for PANSS or BPRS.
Other bias	High risk	Source of funding from pharmaceutical companies. "Dr Potkin has received grant funding from Astra- Zeneca, Bioline, Bristol-Myers Squibb, Dainippon-Sumitomo, Elan, Forest Laboratories, Fujisawa Healthcare, Janssen Pharmaceutica, Merck, Novartis, Ono, Organon, Otsuka, Pfizer Inc, Solvay Pharmaceuticals, Roche"

Selman 1976

Methods	Allocation: random assignment. Blindness: double-blind. Duration: 12 weeks (preceded by a 2 week medication free period). Location: not stated. Design: parallel. Setting: inpatients. Country: USA. Consent: not stated.
Participants	Diagnosis: schizophrenia. N = 87. History: acute, hospitalised. Sex: 80% M, 20% F. Age: mean ~ 33 years. Exclusions: other significant physical or neurological disorder, < 16 or > 60 years, females of child bearing age, epileptics, substance abuse

Selman 1976 (*Continued*)

Interventions	1. Haloperidol: dose 4-12 mg/day. N = 29. 2. Loxapine: dose 50-150 mg/day. N = 29. 3. Placebo. N = 29. Chloral hydrate or paraldehyde as required.
Outcomes	Adverse effects: various observed effects. Global effect: CGI improved/not improved. Leaving the study early. Unable to use - Mental state: BPRS (no SD). Behaviour: NOSIE (no SD).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"A double-blind process was used in which neither patient nor investigator knew what medication was received until after the study was completed", "All medication was administered in identically appearing capsules"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"A double-blind process was used in which neither patient nor investigator knew what medication was received until after the study was completed"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Eight patients were excluded (1 loxapine, 3 haloperidol and 4 placebo", "All eight were dropped for administrative reasons such as unauthorised departure from the hospital or family objections to patients' participation in the study" Last observation carried forward method used "Patients who continued beyond the fourth week but did not complete the full 12 weeks were included in the analysis through their final rating period, at either 4 or 8 weeks. These included 29 patients"

Selman 1976 (*Continued*)

Selective reporting (reporting bias)	High risk	All pre-stated outcomes were not fully reported (SDs were not reported for the BPRS and NOSIE scales)
Other bias	High risk	Loxitane (Loxapine succinate) supplied by Lederle Laboratories, Division of America Cyanamid Co, Pearle River, New York, who also supported the study

Serafetinides 1972

Methods	Allocation: random assignment. Blindness: double-blind. Duration 3 months. Location: not stated. Design: parallel. Setting: inpatients. Country: not stated. Consent: not stated
Participants	Diagnosis: schizophrenia. N = 57. History: chronic. Sex: 42% M, 48% F . Age: mean ~ 42 years. Exclusions: other physical or neurological disorder.
Interventions	1. Haloperidol: dose up to 15 mg/day. N = 14. 2. Placebo. N = 14. 3. Clopenthixol: dose up to 250 mg/day. N = 15. 4. Chlorpromazine: dose up to 1000 mg/day. N = 14.
Outcomes	Adverse events: various observed effects. Global effect: CGI improved/not improved. Leaving the study early. Unable to use - Mental state: BPRS (no SD). Behaviour: NOSIE, OBRS (no SD). Cognitive response (no data given).
Notes	

Risk of bias

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

Serafetinides 1972 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind", "All medications were prepared in identically appearing capsules"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Four of the 57 subjects, three on CPZ, and one on PL, failed to complete the 12 weeks of study. The PL subject and one CPZ subject were terminated because of behavioural deterioration after 4 and 8 weeks respectively. The other two CPZ subjects developed intestinal obstruction and were terminated in the 7th week of study"
Selective reporting (reporting bias)	High risk	All pre-stated outcomes were not reported (no data reported for cognitive response, no SDs reported for the BPRS, NOSIE and OBRS scales)
Other bias	Low risk	Study supported in part by US Public Health Service Grant MH 11666 and by National Institute of Mental Health Research Scientist Development Award K135278

Simpson 1967

Methods	Allocation: random assignment. Blindness: double-blind. Duration: 14 weeks. Location: not stated. Design: parallel. Setting: inpatients. Country: not stated. Consent: not stated.
Participants	Diagnosis: schizophrenia. N = 24. History: chronic, hospitalised. Sex: male. Age: ~ 37 years. Exclusions: other significant physical or neurological disorder

Simpson 1967 (*Continued*)

Interventions	1. Haloperidol: dose 6 mg/day. N = 8. 2. Haloperidol: dose 30 mg/day. N = 8. 3. Placebo. N = 8. Benztropine mesylate as required.
Outcomes	Adverse events: use of antiparkinson medication. Global effect: improved/not improved. Leaving the study early. Unable to use - Mental state: IMS, PRP (no SD).
Notes	Group numbers not stated in text, reviewers have assumed that they were divided into three sets of 8 (see table 1)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind"; "the staff correctly guessed which patients were on active medication in a high percentage of cases"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The code was broken at the end of the study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details reported.
Selective reporting (reporting bias)	High risk	All pre-stated outcomes were not fully reported (SDs were not reported for IMPS and PRP)
Other bias	Unclear risk	"The haloperidol (HALDOL®) used in this study was supplied by McNeil Laboratories. Inc.,"

Spencer 1992

Methods	Allocation: random assignment. Blindness: double-blind, cross-over. Duration: 10 weeks (preceded by a 2-week single blind placebo washout). Location: not stated. Design: cross-over. Setting: inpatients. Country: USA. Consent: not stated.
Participants	Diagnosis: (DSM-III-R) schizophrenia. N = 12. History: hospitalised. Sex: 75% M, 25% F. Age: ~ 6 - 12 years. Exclusions: other significant physical or neurological disorder, receipt of psychoactive medication within 4 weeks of study
Interventions	1. Haloperidol: dose 4 weeks 0.5-10 mg/day followed by 4 weeks placebo. N = 12. 2. Placebo: 4 weeks followed by 4 weeks 0.5-10 mg/day haloperidol. N = 12
Outcomes	Global effect: improved/not improved. Leaving the study early. Unable to use - Global effect: CGI (no SD). Mental state: CPRS, BPRS-C (no SD). Adverse events: various observed effects (no data for placebo group). Cognitive response: WISC-R, WPPSI, DICA-R (no data).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Random assignment" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" no further details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" For CPRS (one of the outcomes scales), the raters were "all blind to treatment status", no further details reported

Spencer 1992 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no drop-outs.
Selective reporting (reporting bias)	High risk	No SDs reported for CGI, CPRS, BPRS-C. No data reported for adverse events for placebo group. No data reported for cognitive assessments (WISC-R, WPPSI, DICA-R)
Other bias	Unclear risk	Study supported by NIMH Child and Adolescent Mental Health Academic Award MH-00763 and NIMH Institutional Training Grant MH-18915 Haloperidol and placebo tablets provided by McNeil Pharmaceutical

Vichaiya 1971

Methods	Allocation: random assignment. Blindness: double-blind, cross-over. Duration: 12 weeks (preceded by 4 weeks drug free period). Location: hospital. Design: cross-over. Setting: inpatients. Country: Thailand. Consent: unknown.	
Participants	Diagnosis: schizophrenia. N = 30. History: hospitalised, chronic. Sex: female. Age: mean ~ 40 years. Exclusions: unknown.	
Interventions	1. Haloperidol: dose 6 weeks 4.5 mg/day followed by 6 weeks placebo. N = 30. 2. Placebo: 6 weeks placebo followed by 6 weeks 4.5 mg/day haloperidol. N = 30	
Outcomes	Global effect: FFS, improved/not improved. Unable to use - Adverse events: various observed effects (no group data). Leaving the study early (no group data).	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Vichaiya 1971 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"Randomized" no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind"; "The code was worked out by the head of Female In-patient section, which kept it secret until the investigation had ended."; "...it soon became clear that the trial was not, in fact blind. The patients on haloperidol showed extrapyramidal symptoms"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind"; "The code was worked out by the head of Female In-patient section, which kept it secret until the investigation had ended."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only one drop-out reported.
Selective reporting (reporting bias)	Unclear risk	Side-effects in placebo group not mentioned.
Other bias	Unclear risk	Does not report source of funding.

AIMS - Assessment of Involuntary Movement Scale.
BAS - Barnes Akathisa Scale.
BHGRS - Bunney-Hamburg Global Rating Scale.
BPRS - Brief Pyschiatric Rating Scale.
BPRS-C - Brief Psychiatric Rating Scale for Children.

CDS - Calgary Depression Scale.
CGI - Clinical Global Impression.
CGI-I - Clinical Global Impression - Improvement.
CGI-S - Clinical Global Impression - Severity.
CPRS - Childrens Psychiatric Rating Scale.
DICA-R - Diagnostic Interview for Children & Adolescents (Revised).
DSM-III-R - Diagnositic and statistical manual of mental disorders: 3rd edition - revised.
EPS - Extrapyramidal Sypmtoms.
ESRS - Extrapyramidal Symptom Rating Scale.

FFS - Fergus Falls Scale.
GPS - General Psychopathology Subscale.
ICD-9 - 9th International Classification of Diseases.
IMPS - Inpatient Multidimensional Psychiatric Scale.

MADRS - Montgomery Asberg-Depression Scale.

MSC - Mental Status Checklist.
NOSIE - Nurses' Observation Scale for Inpatient Evaluation.
OBRS - Oklahoma Behaviour Rating Scale.
PANSS - Positive And Negative Syndrome Scale.
PGI - Patient Global Impression.
PRP - Psychotic Reaction Profile.

SANS - Scale for the Assessment of Negative Symptoms.
SAS - Simpson Angus Scale.
SD - standard deviation
UKU - side effect rating scale.

WISC-R - Wechsler Intelligence Scale for Children (Revised).
WPPSI - Wechsler Preschool & Primary Scale of Intelligence.

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

Study	Reason for exclusion
Akhondzadeh 2005	Allocation: unclear. Participants: people with schizophrenia. Interventions: haloperidol versus haloperidol plus allopurinol
Allison 2007	Allocation: post-hoc analysis of two RCTs (no references provided, conference abstract)
Alpert 1995	Allocation: unclear.
Alphs 1993	Allocation: unclear. Participants: people with schizophrenia. Interventions: haloperidol versus remoxipride versus placebo. Outcomes: all data unusable - conference proceedings.
Andrezina 2006	Allocation: random. Participants: people with schizophrenia. Interventions: intramuscular injections of haloperidol versus aripiprazole versus placebo
Arvanitis 2002	Allocation: random. Participants: people with schizophrenia. Interventions: SR compound, haloperidol or placebo. Outcomes: all data unusable, conference proceedings.
AstraZeneca 2001	Allocation: random. Participants: people with schizophrenia. Intervention: haloperidol versus quetiapine.
Augustin 1996	Allocation: random. Participants: people with schizophrenia. Interventions: haloperidol versus placebo.

(*Continued*)

	Outcomes: all data unusable - conference proceedings.
Azima 1960	Allocation: unclear. Participants: only 34/84 were people with schizophrenia.
Ban 1969	Allocation: unclear. Participants: people with schizophrenia. Interventions: haloperidol + phenothiazine medication versus trifluperidol + phenothiazine medication versus placebo, not haloperidol alone
Barbee 1992	Allocation: random. Participants: people with schizophrenia. Interventions: haloperidol versus haloperidol plus alprazolam
Bateman 1979	Allocation: random. Participants: unclear if people with schizophrenia. Interventions: supplementation of original neuroleptic with haloperidol or placebo
Baymiller 2002	Allocation: random. Participants: people with schizophrenia. Interventions: clozapine versus haloperidol.
Ben-dor 1998	Allocation: random. Participants: people hospitalised with chronic schizophrenia. Interventions: haloperidol + vitamin E versus haloperidol + placebo, no placebo only group
Bersudsky 2006	Allocation: random. Participants: people with schizophrenia. Intervention: haloperidol plus phenytoin versus haloperidol.
Beuzen 1996	Allocation: random. Participants: healthy elderly, not people with schizophrenia
Blum 1969	Allocation: unclear.
Bogeum 2008	Allocation: random. Participants: people with schizophrenia. Intervention: haloperidol plus aripiprazole versus haloperidol plus placebo
Brandrup 1961	Allocation: random, cross-over study . Participants: people with chronic schizophrenia. Intervention: haloperidol 8 mg/day versus placebo. Outcomes: no usable data from period before first cross-over
Browne 1988	Allocation: random. Participants: people with chronic schizophrenia. Intervention: haloperidol 10-160 mg/day versus placebo. Outcomes: all data unusable, > 50% loss during double-blind phase, people relapsing could re-enter study

(*Continued*)

	under single-blind conditions
Buchsbaum 1992	Allocation: unclear, no recording of random allocation.
Cai 2009	Allocation: random. Participants: people with schizophrenia. Intervention: haloperidol versus haloperidol plus Bezoar xiexin tang (Chinese herbs)
Cao 2006	Allocation: random. Participants: people with schizophrenia. Intervention: ziprasidon versus haloperidol.
Caroli 1975	Allocation: not random, ABA design.
Cho-Boon 1989	Allocation: random. Participants: people with schizophrenia. Interventions: haloperidol 12-18, 30-45, 60-90 mg/day versus placebo. Outcomes: all data unusable - conference proceedings.
Contreas 1988	Allocation: not random, ABA design.
Craft 1965	Allocation: unclear.
Crow 1986	Allocation: random. Participants: 120 people with schizophrenia. Interventions: haloperidol withdrawal versus continuation, not instigation of haloperidol treatment
Czobor 1992	Allocation: not an RCT, only one treatment group.
Deberdt 1971	Allocation: not random, ABA design.
Diamond 1991	Allocation: random. Participants: men with schizophrenia. Interventions: haloperidol 5-75 mg/day versus tiospirone 75-375 mg/day versus placebo. Outcomes: all data unusable - conference proceedings.
Eklund 1990	Allocation: random. Participants: people with schizophrenia. Interventions: intramuscular depot administration of haloperidol versus placebo
Eli Lilly 2005	Allocation: random. Participants: people with schizophrenia. Interventions: intramuscular injections of haloperidol versus olanzapine versus placebo
Gelders 1986	Allocation: random. Participants: people with chronic schizophrenia. Interventions: haloperidol 10 mg/day versus ritanserin 20/mg/day versus placebo. Outcomes: all data unusable, no group numbers given for CGI, no data given for BPRS or adverse effects

(*Continued*)

George 2000	Allocation: random. Participants: people with schizophrenia. Intervention: intramuscular injection of olanzapine versus intramuscular injection of haloperidol versus intramuscular injection of placebo
GlaxoSmithKline 2005	Allocation: random. Participants: people with schizophrenia. Intervention: haloperidol plus placebo versus haloperidol plus alosetron
Glovinsky 1992	Allocation: not random, ABA design.
Herrera 2005	Allocation: random. Participants: people with schizophrenia. Intervention: risperidone plus placebo of haloperidol versus haloperidol plus placebo of risperidone
Huygens 1973	Allocation: random. Participants: 40 women with psychosis. Interventions: dexetimide versus placebo, adjunct to haloperidol
IRCT138809201457N6	Allocation: random. Participants: people with schizophrenia. Intervention: haloperidol verus haloperidol plus celecoxib.
IRCT138809201457N7	Allocation: random. Participants: people with schizophrenia. Intervention: haloperidol versus haloperidol plus ascorbic acid
Itil 1981	Allocation: not random, ABA design.
Jolley 1990	Allocation: random. Participants: people in remission from schizophrenia. Interventions: haloperidol withdrawal versus placebo, no instigation of haloperidol
Jung 2007	Allocation: random. Participants: people with schizophrenia. Intervention: haloperidol versus aripiprazole plus haloperidol
Kapur 2004	Allocation: not an RCT, narrative review.
Kasper 1996	Allocation: random. Participants: people with schizophrenia. Intervention: 4, 8 and 16 mg/day haloperidol versus 12, 20 and 24 mg/day sertindole or placebo. Outcomes: all data unusable, conference proceedings.
Kim 2005	Allocation: random. Participants: people with schizophrenia. Intervention: haloperidol plus placebo versus haloperidol plus donepezil

(*Continued*)

Kinon 2012	Allocation: retrospective study of 3 already excluded or included RCTs
Ko 1989	Allocation: not random, ABA design.
Kostic 2005	Allocation: random. Participants: people with schizophrenia. Intervention: haloperidol versus aripiprazole.
Kramer 1989	Allocation: random. Participants: 56 people with schizophrenia. Interventions: amitriptyline versus desmethylimipramine versus placebo in addition to haloperidol and benztropine, haloperidol not randomised
Kurland 1981	Allocation: random. Participants: 28 people with schizophrenia and scoring >17 on HAM-D. Interventions: adjunctive viloxazine versus placebo, antipsychotics, such as haloperidol, continued as normal
Labarca 1993	Allocation: not random, ABA design.
Lee 1968	Allocation: unclear.
Lee 2007	Allocation: random. Participants: people with schizophrenia. Intervention: haloperidol plus placebo versus haloperidol plus donepezil
Lehmann 1967	Allocation: random. Participants: 30 people with chronic schizophrenia. Interventions: continued on current phenothiazine medication, then randomised to adjunctive haloperidol (1.5 mg/day) versus trifluperidol (0.75 mg/day) versus placebo, not haloperidol alone
Lemmer 1993	Allocation: random. Participants: people with acute schizophrenia. Interventions: pramipexole versus haloperidol or placebo. Outcomes: all data unusable, study stopped early.
Li 2007	Allocation: random. Participants: people with schizophrenia. Intervention: haloperidol plus placebo versus clonazepam plus placebo versus haloperidol plus clonazepam
Liang 1987	Allocation: random. Participants: people with schizophrenia. Interventions: haloperidol versus insulin shock therapy.
Lindborg 2003	Allocation: not random, meta-analysis.

(*Continued*)

Magelund 1979	Allocation: random, cross-over. Participants: 12 people hospitalised with schizophrenia. Interventions: AMPT versus haloperidol, placebo given after each active treatment period, not randomised
Malaspina 1997	Allocation: random. Participants: people with schizophrenia. Interventions: haloperidol decanoate 0.3 mg/kg versus placebo. Outcomes: all data unusable - conference proceedings.
Maoz 2000	Allocation: random. Participants: people with schizophrenia. Intervention: haloperidol versus haloperidol plus propanolol
Meltzer 2008	Allocation: random. Participants: people with schizophrenia. Intervention: risperidone plus placebo versus risperidone plus pimavanserin versus haloperidol plus placebo versus haloperidol plus pimavanserin
Mossaheb 2006	Allocation: random. Participants: people with schizophrenia. Intervention: haloperidol plus clozapine versus clozapine plus placebo
Nagaraja 1977	Allocation: not random.
NCT00018850	Allocation: random. Participants: people with schizophrenia. Intervention: ondasteron versus nicotine versus haloperidol
NCT00156104	Allocation: random. Participants: people with schizophrenia. Intervention: haloperidol versus asenapine, the first phase of the trial includes a placebo group but no results are reported for this phase
NCT00189995	Allocation: random. Participants: people with schizophrenia. Intervention:clozapine versus haloperidol
NCT00947375	Allocation: random. Participants: people with schizophrenia. Intervention: haloperidol plus placebo versus haloperidol plus lamictal
NCT01161277	Allocation: random. Participants: not schizophrenia, psychiatrically healthy participants
Necomer 1992	Allocation: random. Participants: 24 males with schizophrenia. Interventions: haloperidol withdrawal versus placebo, not instigation of haloperidol

(*Continued*)

Nguyen 1984	Allocation: unclear. Participants: people with chronic schizophrenia. Interventions: haloperidol versus placebo. Outcomes: all data unusable - conference proceedings.
North America 1997	Allocation: random. Participants: 523 people with chronic schizophrenia. Interventions: haloperidol 20 mg/day versus placebo versus risperidone 2, 6, 10 or 16 mg/day. Outcomes: combines data from several centres but all unique data from these reports of combined analyses is unusable due to > 50% loss; data from publications of specific centres can be included (Chouinard 1993, Marder 1994).
Octavio 2004	Allocation: random. Participants: people with schizophrenia. Interventions: aripiprazole versus haloperidol.
Okasha 1964	Allocation: random. Participants: 80 people hospitalised with chronic psychosis. Interventions: haloperidol 4.5 mg/day versus placebo. Outcomes: no usable data, leaving study early (no group data), behaviour (no total scale score)
Ortega-Soto 1994	Allocation: random. Participants: drug free people with acute schizophrenia. Interventions: threshold dose of haloperidol + 20 mg haloperidol versus threshold dose of haloperidol + placebo, not haloperidol versus placebo
Ota 1973	Allocation: unclear . Participants: 54 people with chronic schizophrenia. Interventions: haloperidol withdrawal versus placebo, not instigation of haloperidol
Pathiraja 1995	Allocation: random. Participants: men with schizophrenia. Interventions: haloperidol 5-20 mg/day versus risperidone 2-16 mg/day versus MAR 327 50-400 mg/day versus placebo. Outcomes: all data unusable - conference proceedings.
Paykel 2000	Allocation: random. Participants: women with peurperal psychosis .
Pool 1976	Allocation: random but with non-random additions. Participants: 75 people with schizophrenia. Interventions: haloperidol versus loxapine versus placebo. Outcomes: no usable data - those who withdrew during the study were replaced with new patients and data for those randomised not reported separately
Potkin 1984	Allocation: random. Participants: people with schizophrenia. Interventions: haloperidol + IC (insulin coma therapy) versus placebo + IC, not haloperidol alone.

(*Continued*)

	Outcomes: all data unusable - conference proceedings.
Potkin 1995	Allocation: random. Participants: people with schizophrenia. Interventions: haloperidol versus MAR 327 150-300 mg/day versus placebo. Outcomes: all data unusable - conference proceedings.
Potkin 2000	Allocation: random. Participants: people with schizophrenia. Interventions: haloperidol versus clozapine or placebo. Outcomes: PET scan study, outcomes not relevant, data unusable
Price 1985	Allocation: not random, ABA design.
Price 1987	Allocation: random. Participants: people with schizophrenia. Interventions: haloperidol 10-4- mg/day versus verapamil 80 mg/day versus placebo. Outcomes: all data unusable.
Rees 1965	Allocation: random, cross-over. Participants: 14 people with schizophrenia. Interventions: haloperidol versus placebo. Outcomes: all data unusable, none available before cross-over
Reschke 1974	*Please note:* this study was included in the previous versions of this review; as it was clarified that the route of haloperidol administration was not oral, but by intramuscular injection, we decided to exclude this study for this update Allocation: randomised. Participants: patients with psychotic symptoms. Interventions: intramuscular injections of haloperidol versus placebo versus chlorpromazene
Roitman 1989	Allocation: random. Participants: 16 people with schizoaffective disorder. Interventions: adjunctive demeclocycline (DMC) versus placebo, all received haloperidol
Romeo 2009	Allocation: random. Participants: not schizophrenia, participants had intellectual disabilities
Ruskin 1991	Allocation: random. Participants: 35 people with schizophrenia. Interventions: haloperidol withdrawal versus placebo, not instigation of haloperidol
Samuels 1961	Allocation: unclear.
Shim 2007	Allocation: random. Participants: people with schizophrenia. Intervention: haloperidol plus placebo versus haloperidol plus aripiprazole

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Singh 1972	Allocation: not random, ABA design.
Soloff 1986	Allocation: random. Participants: people with "Borderline disorders", not schizophrenia
Stankovska 2002	Allocation: unclear if randomised.
Taverna 1972	Allocation: quasi-randomised.
Teja 1975	Allocation: random. Participants: people with chronic schizophrenia. Interventions: haloperidol 36 mg/week versus chlorpromazine > 1800 mg/week versus trifluoperazine > 90 mg/week versus thiothixene > 90 mg/week versus placebo. Outcomes: all data unusable.
Tran-Johnson 2007	Allocation: random. Participants: people with schizophrenia. Interventions: intramuscular injections of haloperidol versus aripiprazole versus placebo
Van Lommel 1974	Allocation: random. Participants: 19 psychotic males. Interventions: haloperidol withdrawal versus placebo, not instigation of haloperidol
Veser 2006	Allocation: random. Participants: people with psychoses mainly caused by substance abuse, and a minority with bipolar disorder and schizophrenia
Volavka 1992	Allocation: random. Participants: 173 people with acutely exacerbated schizophrenia. Interventions: dosage levels of haloperidol, no placebo group
Wang 2009	Allocation: random. Participants: people with schizophrenia. Intervention: aripiprazole plus haloperidol versus placebo plus haloperidol
Wilson 1994	Allocation: random. Participants: people with schizophrenia. Intervention: haloperidol plus placebo versus haloperidol plus lithium
Wright 2001	Allocation: random. Participants: people with schizophrenia. Interventions: intramuscular injections of haloperidol versus olanzapine versus placebo
Zhan 2000	Allocation: random. Participants: people with schizophrenia. Intervention: haloperidol plus water versus haloperidol plus levamisole ointment versus levamisole ointment plus placebo Outcome: all data unusable (reported measures of immune index and P values of correlation of immune

(*Continued*)

	index and BPRS/SAPS scores)
Zhang 2001	Allocation: random. Participants: people with schizophrenia. Intervention: haloperidol plus extract of Ginkgo biloba versus haloperidol plus placebo
Zhang 2006	Allocation: random. Participants: people with schizophrenia. Intervention: haloperidol plus placebo versus haloperidol plus ondansetron
Zimbroff 1997	Allocation: random. Participants: people with schizophrenia. Interventions: haloperidol 4, 8, 16 mg/day versus sertindole 12, 20, 24 mg/day versus placebo. Outcomes: all data unusable due to > 50% loss, leaving study early (not given as individual group data)

ABA: Before and after trial.
AMPT - alpha-methyl-p-tyrosine.
BPRS - Brief Pyschiatric Rating Scale.
CGI - Clinical Global Impression.
.
HAM-D: Hamilton Depression Scale.
PET - Positron emission tomography.
RCT - randomised controlled trial.
SAPS - Simplified Acute Physiology Score.

DATA AND ANALYSES

Comparison 1. HALOPERIDOL versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global state: 1a. Overall improvement: No marked global improvement	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 up to 6 weeks (clinician rated)	4	472	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.56, 0.80]
1.2 > 6-24 weeks (clinician rated)	8	307	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.58, 0.78]
1.3 > 6-24 weeks (nurse rated)	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.37, 0.92]
2 Global state: 1b. Overall improvement: Average change in CGI-S score (up to 6 weeks; high = poor)	2	353	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.73, -0.25]
3 Global state: 2. Hospital discharge: Not discharged from hospital (> 6-24 weeks)	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.47, 1.52]
4 Global state: 3. Relapse (< 52 weeks)	2	70	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.55, 0.86]
5 Global state: 4. Leaving the study early	24		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 up to 6 weeks	16	1812	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.80, 0.95]
5.2 > 6-24 weeks	8	304	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.29, 1.00]
5.3 < 52 weeks	1	50	Risk Ratio (M-H, Fixed, 95% CI)	2.58 [0.14, 46.83]
6 Mental state: 1. No clinical improvement (< 20% reduction in BPRS score; up to 6 weeks)	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.54, 1.08]
7 Mental state: 2a. General symptoms: Average BPRS total score (up to 6 weeks; high = poor)	3	108	Mean Difference (IV, Fixed, 95% CI)	-9.76 [-14.60, -4.93]
8 Mental state: 2b. General symptoms: Average change in PANSS total score (up to 6 weeks; high = poor)	1	119	Mean Difference (IV, Fixed, 95% CI)	-15.58 [-23.92, -7.24]
9 Mental state: 3. Positive symptoms: Average change in PANSS positive score (up to 6 weeks; high = poor)	2	353	Mean Difference (IV, Fixed, 95% CI)	-3.29 [-4.70, -1.89]
10 Mental state: 4. Negative symptoms: Average change in PANSS negative score (up to 6 weeks; high = poor)	2	353	Mean Difference (IV, Fixed, 95% CI)	-1.18 [-2.32, -0.04]

11 Mental state: 5. Mood: Average change in CDS score (up to 6 weeks; high = poor)	1	234	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.20, 0.60]
12 Adverse effects: 1a. Movement disorders: Extrapyramidal symptoms	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 akathisia	6	695	Risk Ratio (M-H, Fixed, 95% CI)	3.66 [2.24, 5.97]
12.2 dystonia	5	471	Risk Ratio (M-H, Fixed, 95% CI)	11.49 [3.23, 40.85]
12.3 needing antiparkinson medication	4	480	Risk Ratio (M-H, Fixed, 95% CI)	3.23 [2.20, 4.72]
12.4 oculogyric crises	2	83	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.14, 6.57]
12.5 parkinsonism (including EPS)	5	485	Risk Ratio (M-H, Fixed, 95% CI)	5.48 [2.68, 11.22]
12.6 rigidity	5	461	Risk Ratio (M-H, Fixed, 95% CI)	4.98 [2.74, 9.05]
12.7 teeth grinding	1	33	Risk Ratio (M-H, Fixed, 95% CI)	2.53 [0.11, 57.83]
12.8 'thick' speech	1	33	Risk Ratio (M-H, Fixed, 95% CI)	5.89 [0.33, 105.81]
12.9 tremor	5	447	Risk Ratio (M-H, Fixed, 95% CI)	3.93 [1.96, 7.91]
13 Adverse effects: 1b. Movement disorders: Tardive dyskinesia	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 dyskinesia and tardive dyskinesia	2	157	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.14, 7.13]
14 Adverse effects: 1c. Movement disorders: Average changes scores (various scales; up to 6 weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
14.1 AIMS (high = poor)	1	231	Mean Difference (IV, Fixed, 95% CI)	-0.29 [-0.71, 0.13]
14.2 BAS (high = poor)	1	231	Mean Difference (IV, Fixed, 95% CI)	0.31 [0.10, 0.52]
14.3 SAS (high = poor)	1	231	Mean Difference (IV, Fixed, 95% CI)	1.48 [0.76, 2.20]
15 Adverse effects: 2. Other CNS	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 blurred vision	2	240	Risk Ratio (M-H, Fixed, 95% CI)	3.96 [1.21, 12.93]
15.2 confusion	1	33	Risk Ratio (M-H, Fixed, 95% CI)	2.53 [0.11, 57.83]
15.3 dry mouth	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.62, 4.46]
15.4 sedation	1	238	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.24, 3.11]
16 Adverse effects: 3. Cardiovascular effects	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 blood pressure - dizziness/low BP	3	245	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.36, 2.79]
16.2 blood pressure - high BP	1	16	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.14, 64.26]
16.3 bradycardia	1	124	Risk Ratio (M-H, Fixed, 95% CI)	4.27 [0.49, 37.10]
17 Adverse effects: 4. Other adverse effects	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 agitation	2	362	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.54, 2.12]
17.2 anxiety	2	362	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.33, 2.16]
17.3 drooling	3	207	Risk Ratio (M-H, Fixed, 95% CI)	4.00 [0.88, 18.21]
17.4 facial oedema	1	33	Risk Ratio (M-H, Fixed, 95% CI)	2.83 [0.12, 64.89]
17.5 headache	4	593	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.62, 1.39]
17.6 infection	1	24	Risk Ratio (M-H, Fixed, 95% CI)	7.0 [0.40, 122.44]
17.7 insomnia	4	629	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.76, 1.63]
17.8 nausea/vomiting	2	231	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.49, 1.65]
17.9 oral hypoaesthesia	1	238	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 2.92]
17.10 perspiration	2	93	Risk Ratio (M-H, Fixed, 95% CI)	4.74 [0.58, 38.81]
17.11 sleepiness	7	686	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [1.51, 6.31]

17.12 weight gain	2	441	Risk Ratio (M-H, Fixed, 95% CI)	4.89 [1.41, 16.95]
17.13 weight loss	3	385	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.36, 1.64]
18 SUBGROUP ANALYSIS: 1. MEN vs WOMEN: Global state: Overall improvement: No marked global improvement, > 6-24 weeks (clinician rated)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 only men	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.27, 0.82]
18.2 only women	2	88	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.55, 0.87]
19 SUBGROUP ANALYSIS: 2. 18-65 YEARS vs < 18 YEARS: Global state: Overall improvement: No marked global improvement, > 6-24 weeks (clinician rated)	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 18-65 years	7	284	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.61, 0.80]
19.2 < 18 years	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.10, 0.74]
20 SUBGROUP ANALYSIS: 3. ACUTE vs CHRONIC: Global state: Overall improvement: No marked global improvement, > 6-24 weeks (clinician rated)	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 acute phase of illness	1	58	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.30, 1.06]
20.2 chronic phase of illness	7	250	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.59, 0.78]
21 SUBGROUP ANALYSIS: 4. LOW DOSE vs MEDIUM TO HIGH DOSE	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 low dose (≤ 5 mg/day) - Global state: Overall improvement: No marked global improvement, up to 6 weeks (clinician rated)	1	234	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.69, 1.04]
21.2 medium to high dose (> 5 mg/day) - Global state: Overall improvement: No marked global improvement, up to 6 weeks (clinician rated)	3	238	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.35, 0.66]
21.3 low dose (≤ 5 mg/day) - Global state: Overall improvement: No marked global improvement, > 6-24 weeks (clinician rated)	4	149	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.55, 0.81]
21.4 medium to high dose (> 5 mg/day) - Global state: Overall improvement: No marked global improvement, > 6-24 weeks (clinician rated)	5	165	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.54, 0.83]
22 SUBGROUP ANALYSIS: 5. DIAGNOSTIC CRITERIA vs NO DIAGNOSTIC CRITERIA	13		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

22.1 operational criteria used for diagnosis - Global state: Overall improvement: No marked global improvement, up to 6 weeks (clinician rated)	3	414	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.56, 0.81]
22.2 no operational criteria used for diagnosis - Global state: Overall improvement: No marked global improvement, up to 6 weeks (clinician rated)	1	58	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.33, 1.24]
22.3 operational criteria used for diagnosis - Global state: Overall improvement: No marked global improvement, > 6-24 weeks (clinician rated)	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.10, 0.74]
22.4 no operational criteria used for diagnosis - Global state: Overall improvement: No marked global improvement, > 6-24 weeks (clinician rated)	7	284	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.61, 0.80]
22.5 operational criteria used for diagnosis - Global state: Relapse (< 52 weeks)	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.57, 0.91]
22.6 no operational criteria used for diagnosis - Global state: Relapse (< 52 weeks)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.37, 1.03]
23 SENSITIVITY ANALYSIS: 1. ASSUMPTIONS FOR MISSING DATA vs NO ASSUMPTIONS FOR MISSING DATA: Global state: Overall improvement: No marked global improvement, up to 6 weeks (clinician rated)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
23.1 no assumptions for missing data	3	353	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.60, 0.87]

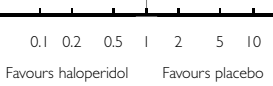
Analysis 1.1. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 1 Global state: 1a. Overall improvement: No marked global improvement.

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

Outcome: 1 Global state: 1a. Overall improvement: No marked global improvement

Study or subgroup	Haloperidol n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 up to 6 weeks (clinician rated)					
Bechelli 1983	9/30	25/31		16.3 %	0.37 [0.21, 0.66]
Garcia 2009 (1)	17/58	36/61		23.2 %	0.50 [0.32, 0.78]
Kane 2010	63/112	81/122		51.3 %	0.85 [0.69, 1.04]
Selman 1976	9/29	14/29		9.3 %	0.64 [0.33, 1.24]
Subtotal (95% CI)	**229**	**243**		**100.0 %**	**0.67 [0.56, 0.80]**
Total events: 98 (Haloperidol), 156 (Placebo)					
Heterogeneity: Chi^2 = 10.73, df = 3 (P = 0.01); I^2 =72%					
Test for overall effect: Z = 4.48 (P < 0.00001)					
2 > 6-24 weeks (clinician rated)					
Durost 1964	14/19	15/15		13.4 %	0.75 [0.56, 0.99]
Garry 1962	19/26	22/26		17.1 %	0.86 [0.65, 1.15]
Howard 1974	9/17	10/13		8.8 %	0.69 [0.40, 1.18]
Selman 1976	9/29	16/29		12.5 %	0.56 [0.30, 1.06]
Serafetinides 1972	10/14	14/14		11.3 %	0.72 [0.51, 1.02]
Simpson 1967	6/16	5/7		5.4 %	0.53 [0.24, 1.15]
Spencer 1992	3/12	11/12		8.6 %	0.27 [0.10, 0.74]
Vichaiya 1971	20/29	29/29		23.0 %	0.69 [0.54, 0.89]
Subtotal (95% CI)	**162**	**145**		**100.0 %**	**0.67 [0.58, 0.78]**
Total events: 90 (Haloperidol), 122 (Placebo)					
Heterogeneity: Chi^2 = 7.63, df = 7 (P = 0.37); I^2 =8%					
Test for overall effect: Z = 5.31 (P < 0.00001)					
3 > 6-24 weeks (nurse rated)					
Serafetinides 1972	8/14	14/14		100.0 %	0.59 [0.37, 0.92]
Subtotal (95% CI)	**14**	**14**		**100.0 %**	**0.59 [0.37, 0.92]**
Total events: 8 (Haloperidol), 14 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.31 (P = 0.021)					
Test for subgroup differences: Chi^2 = 0.32, df = 2 (P = 0.85), I^2 =0.0%					



(1) LOCF approach used to impute missing values.

Analysis 1.2. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 2 Global state: 1b. Overall improvement: Average change in CGI-S score (up to 6 weeks; high = poor).

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

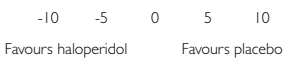
Outcome: 2 Global state: 1b. Overall improvement: Average change in CGI-S score (up to 6 weeks; high = poor)

Study or subgroup	Haloperidol N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Garcia 2009 (1)	58	-1.36 (1.2947)	61	-0.6 (1.3277)		25.7 %	-0.76 [-1.23, -0.29]
Kane 2010 (2)	112	-1.2 (1.0583)	122	-0.8 (1.1045)		74.3 %	-0.40 [-0.68, -0.12]
Total (95% CI)	**170**		**183**			**100.0 %**	**-0.49 [-0.73, -0.25]**

Heterogeneity: Chi^2 = 1.67, df = 1 (P = 0.20); I^2 =40%

Test for overall effect: Z = 4.04 (P = 0.000053)

Test for subgroup differences: Not applicable



(1) LOCF approach used to impute missing values.

(2) Lears squares mean approach used to impute missing values.

Analysis 1.3. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 3 Global state: 2. Hospital discharge: Not discharged from hospital (> 6-24 weeks).

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

Outcome: 3 Global state: 2. Hospital discharge: Not discharged from hospital (> 6-24 weeks)

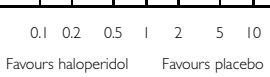
Study or subgroup	Haloperidol n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Howard 1974	9/17	10/16		100.0 %	0.85 [0.47, 1.52]
Total (95% CI)	**17**	**16**		**100.0 %**	**0.85 [0.47, 1.52]**

Total events: 9 (Haloperidol), 10 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.55 (P = 0.58)

Test for subgroup differences: Not applicable



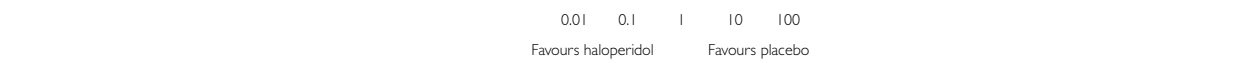
Analysis 1.4. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 4 Global state: 3. Relapse (< 52 weeks).

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

Outcome: 4 Global state: 3. Relapse (< 52 weeks)

Study or subgroup	Haloperidol n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Nishikawa 1982	6/10	10/10		34.7 %	0.62 [0.37, 1.03]
Nishikawa 1984	26/37	13/13		65.3 %	0.72 [0.57, 0.91]
Total (95% CI)	**47**	**23**		**100.0 %**	**0.69 [0.55, 0.86]**
Total events: 32 (Haloperidol), 23 (Placebo)					
Heterogeneity: Chi^2 = 0.35, df = 1 (P = 0.55); I^2 =0.0%					
Test for overall effect: Z = 3.22 (P = 0.0013)					
Test for subgroup differences: Not applicable					

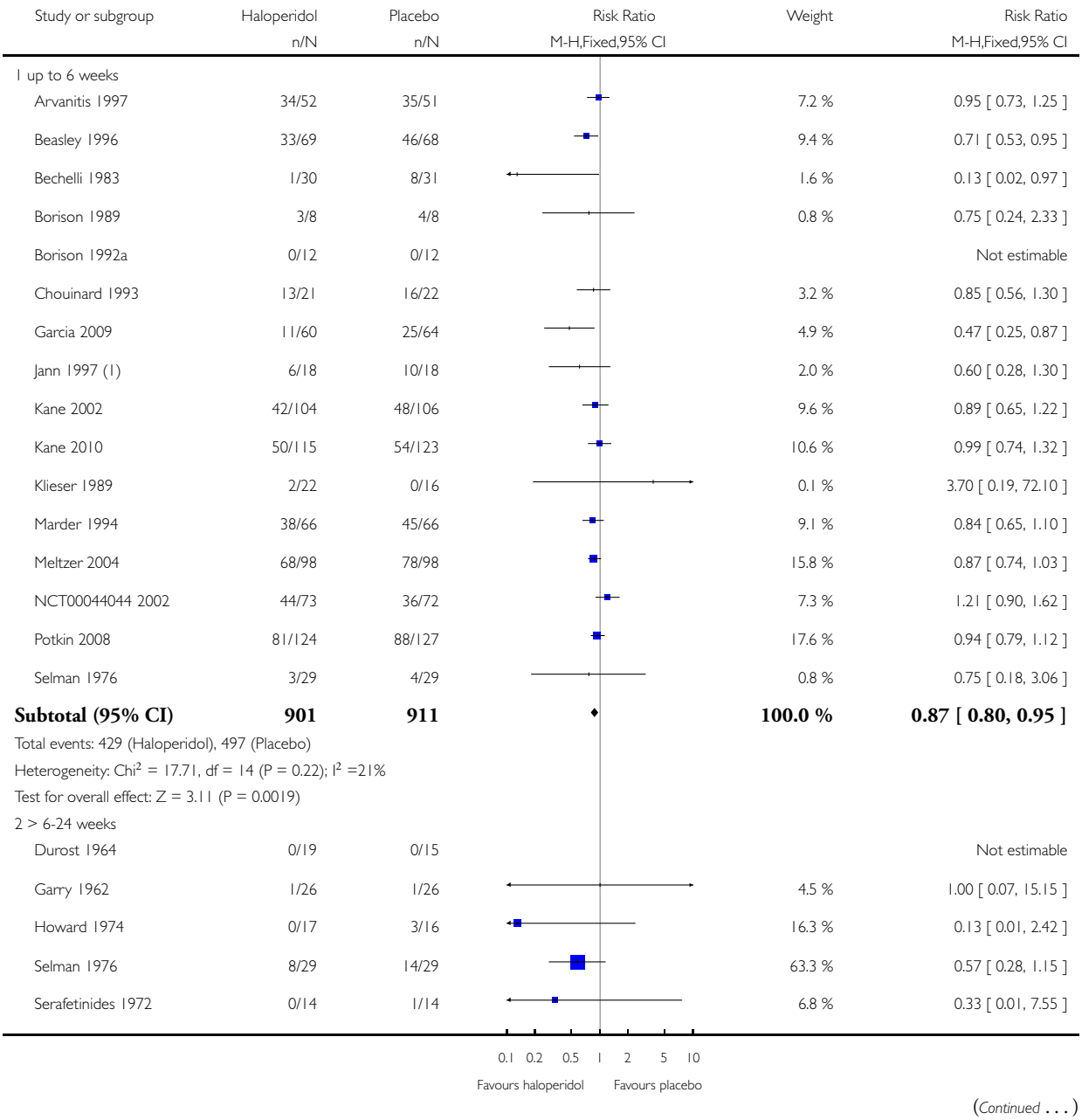


Analysis 1.5. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 5 Global state: 4. Leaving the study early.

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

Outcome: 5 Global state: 4. Leaving the study early



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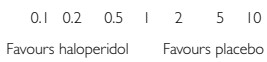
Study or subgroup	Haloperidol n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Simpson 1967	0/8	1/8		6.8 %	0.33 [0.02, 7.14]
Spencer 1992	0/12	0/12			Not estimable
Vichaiya 1971	1/30	0/29		2.3 %	2.90 [0.12, 68.50]
Subtotal (95% CI)	**155**	**149**		**100.0 %**	**0.54 [0.29, 1.00]**
Total events: 10 (Haloperidol), 20 (Placebo)					
Heterogeneity: Chi^2 = 2.38, df = 5 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 1.97 (P = 0.049)					
3 < 52 weeks					
Nishikawa 1984	3/37	0/13		100.0 %	2.58 [0.14, 46.83]
Subtotal (95% CI)	**37**	**13**		**100.0 %**	**2.58 [0.14, 46.83]**
Total events: 3 (Haloperidol), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.64 (P = 0.52)					
Test for subgroup differences: Chi^2 = 2.87, df = 2 (P = 0.24), I^2 =30%					



(1) Loss to follow-up 33% in haloperidol arm and 55% in placebo arm.

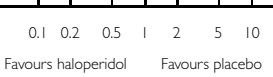
Analysis 1.6. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 6 Mental state: 1. No clinical improvement (< 20% reduction in BPRS score; up to 6 weeks).

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

Outcome: 6 Mental state: 1. No clinical improvement (< 20% reduction in BPRS score; up to 6 weeks)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Borison 1992a	9/12	12/12		100.0 %	0.76 [0.54, 1.08]
Total (95% CI)	**12**	**12**		**100.0 %**	**0.76 [0.54, 1.08]**
Total events: 9 (Treatment), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.55 (P = 0.12)					
Test for subgroup differences: Not applicable					



Analysis 1.7. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 7 Mental state: 2a. General symptoms: Average BPRS total score (up to 6 weeks; high = poor).

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

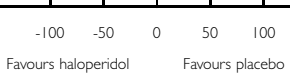
Outcome: 7 Mental state: 2a. General symptoms: Average BPRS total score (up to 6 weeks; high = poor)

Study or subgroup	Haloperidol N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bechelli 1983 (1)	29	24.17 (7.96)	23	36.2 (12.1)		71.2 %	-12.03 [-17.76, -6.30]
Jann 1997 (2)	12	35.6 (10.5)	8	46.9 (14.6)		17.0 %	-11.30 [-23.03, 0.43]
Klieser 1989 (3)	20	2 (22.6)	16	-4.1 (20.4)		11.8 %	6.10 [-7.97, 20.17]
Total (95% CI)	**61**		**47**			**100.0 %**	**-9.76 [-14.60, -4.93]**

Heterogeneity: Chi^2 = 5.55, df = 2 (P = 0.06); I^2 =64%

Test for overall effect: Z = 3.96 (P = 0.000076)

Test for subgroup differences: Not applicable



(1) Average end point data.

(2) Loss to follow-up 33% in haloperidol arm and 55% in placebo arm. Average end point data.

(3) Average change data.

Analysis 1.8. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 8 Mental state: 2b. General symptoms: Average change in PANSS total score (up to 6 weeks; high = poor).

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

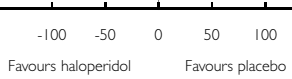
Outcome: 8 Mental state: 2b. General symptoms: Average change in PANSS total score (up to 6 weeks; high = poor)

Study or subgroup	Haloperidol N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Garcia 2009 (1)	58	-28.16 (23.2281)	61	-12.58 (23.1964)		100.0 %	-15.58 [-23.92, -7.24]
Total (95% CI)	**58**		**61**			**100.0 %**	**-15.58 [-23.92, -7.24]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.66 (P = 0.00025)

Test for subgroup differences: Not applicable



(1) LOCF approach used to impute missing values.

Analysis 1.9. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 9 Mental state: 3. Positive symptoms: Average change in PANSS positive score (up to 6 weeks; high = poor).

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

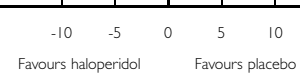
Outcome: 9 Mental state: 3. Positive symptoms: Average change in PANSS positive score (up to 6 weeks; high = poor)

Study or subgroup	Haloperidol N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Garcia 2009 (1)	58	-10.64 (7.3111)	61	-4.61 (7.3416)		28.5 %	-6.03 [-8.66, -3.40]
Kane 2010 (2)	112	-7.3 (6.3498)	122	-5.1 (6.6272)		71.5 %	-2.20 [-3.86, -0.54]
Total (95% CI)	**170**		**183**			**100.0 %**	**-3.29 [-4.70, -1.89]**

Heterogeneity: Chi^2 = 5.81, df = 1 (P = 0.02); I^2 =83%

Test for overall effect: Z = 4.59 (P < 0.00001)

Test for subgroup differences: Not applicable



(1) LOCF approach used to impute missing values.

(2) Least squares mean approach used to impute missing values.

Analysis 1.10. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 10 Mental state: 4. Negative symptoms: Average change in PANSS negative score (up to 6 weeks; high = poor).

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

Outcome: 10 Mental state: 4. Negative symptoms: Average change in PANSS negative score (up to 6 weeks; high = poor)

Study or subgroup	Haloperidol N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Garcia 2009 (1)	58	-4.13 (5.5595)	61	-1.95 (5.5453)		32.5 %	-2.18 [-4.18, -0.18]
Kane 2010 (2)	112	-4 (5.2915)	122	-3.3 (5.5227)		67.5 %	-0.70 [-2.09, 0.69]
Total (95% CI)	**170**		**183**			**100.0 %**	**-1.18 [-2.32, -0.04]**

Heterogeneity: Chi^2 = 1.43, df = 1 (P = 0.23); I^2 =30%

Test for overall effect: Z = 2.03 (P = 0.042)

Test for subgroup differences: Not applicable

(1) LOCF approach used to impute missing values.

(2) Least quares mean approach used to impute missing values.

Analysis 1.11. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 11 Mental state: 5. Mood: Average change in CDS score (up to 6 weeks; high = poor).

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

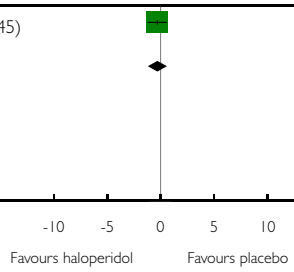
Outcome: 11 Mental state: 5. Mood: Average change in CDS score (up to 6 weeks; high = poor)

Study or subgroup	Haloperidol N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kane 2010 (1)	112	-0.9 (3.3866)	122	-0.6 (3.645)		100.0 %	-0.30 [-1.20, 0.60]
Total (95% CI)	**112**		**122**			**100.0 %**	**-0.30 [-1.20, 0.60]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.65 (P = 0.51)

Test for subgroup differences: Not applicable



(1) Least squares mean approach used to impute missing values.

Analysis 1.12. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 12 Adverse effects: 1a. Movement disorders: Extrapyramidal symptoms.

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

Outcome: 12 Adverse effects: 1a. Movement disorders: Extrapyramidal symptoms

Study or subgroup	Haloperidol n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 akathisia					
Bechelli 1983	1/29	0/31		2.7 %	3.20 [0.14, 75.55]
Borison 1989	3/8	0/8		2.7 %	7.00 [0.42, 116.91]
Garcia 2009	13/60	2/64		10.6 %	6.93 [1.63, 29.45]
Garry 1962	6/25	0/25		2.7 %	13.00 [0.77, 219.11]
Kane 2002	24/103	11/104		60.0 %	2.20 [1.14, 4.26]
Kane 2010	17/115	4/123		21.2 %	4.55 [1.58, 13.11]
Subtotal (95% CI)	**340**	**355**		**100.0 %**	**3.66 [2.24, 5.97]**
Total events: 64 (Haloperidol), 17 (Placebo)					
Heterogeneity: Chi^2 = 4.17, df = 5 (P = 0.53); I^2 =0.0%					
Test for overall effect: Z = 5.18 (P < 0.00001)					
2 dystonia					
Bechelli 1983	4/29	0/31		19.4 %	9.60 [0.54, 170.84]
Borison 1989	3/8	0/8		20.0 %	7.00 [0.42, 116.91]
Garcia 2009	3/60	0/64		19.4 %	7.46 [0.39, 141.45]
Kane 2010	11/115	0/123		19.4 %	24.59 [1.47, 412.51]
Selman 1976	5/18	0/15		21.8 %	9.26 [0.55, 155.04]
Subtotal (95% CI)	**230**	**241**		**100.0 %**	**11.49 [3.23, 40.85]**
Total events: 26 (Haloperidol), 0 (Placebo)					
Heterogeneity: Chi^2 = 0.52, df = 4 (P = 0.97); I^2 =0.0%					
Test for overall effect: Z = 3.77 (P = 0.00016)					
3 needing antiparkinson medication					
Borison 1989	6/8	0/8		1.8 %	13.00 [0.85, 198.14]
Kane 2002	31/103	13/104		45.4 %	2.41 [1.34, 4.33]
Kane 2010	48/112	15/122		50.4 %	3.49 [2.07, 5.86]
Simpson 1967	6/16	0/7		2.4 %	6.12 [0.39, 95.79]
Subtotal (95% CI)	**239**	**241**		**100.0 %**	**3.23 [2.20, 4.72]**
Total events: 91 (Haloperidol), 28 (Placebo)					
Heterogeneity: Chi^2 = 2.25, df = 3 (P = 0.52); I^2 =0.0%					

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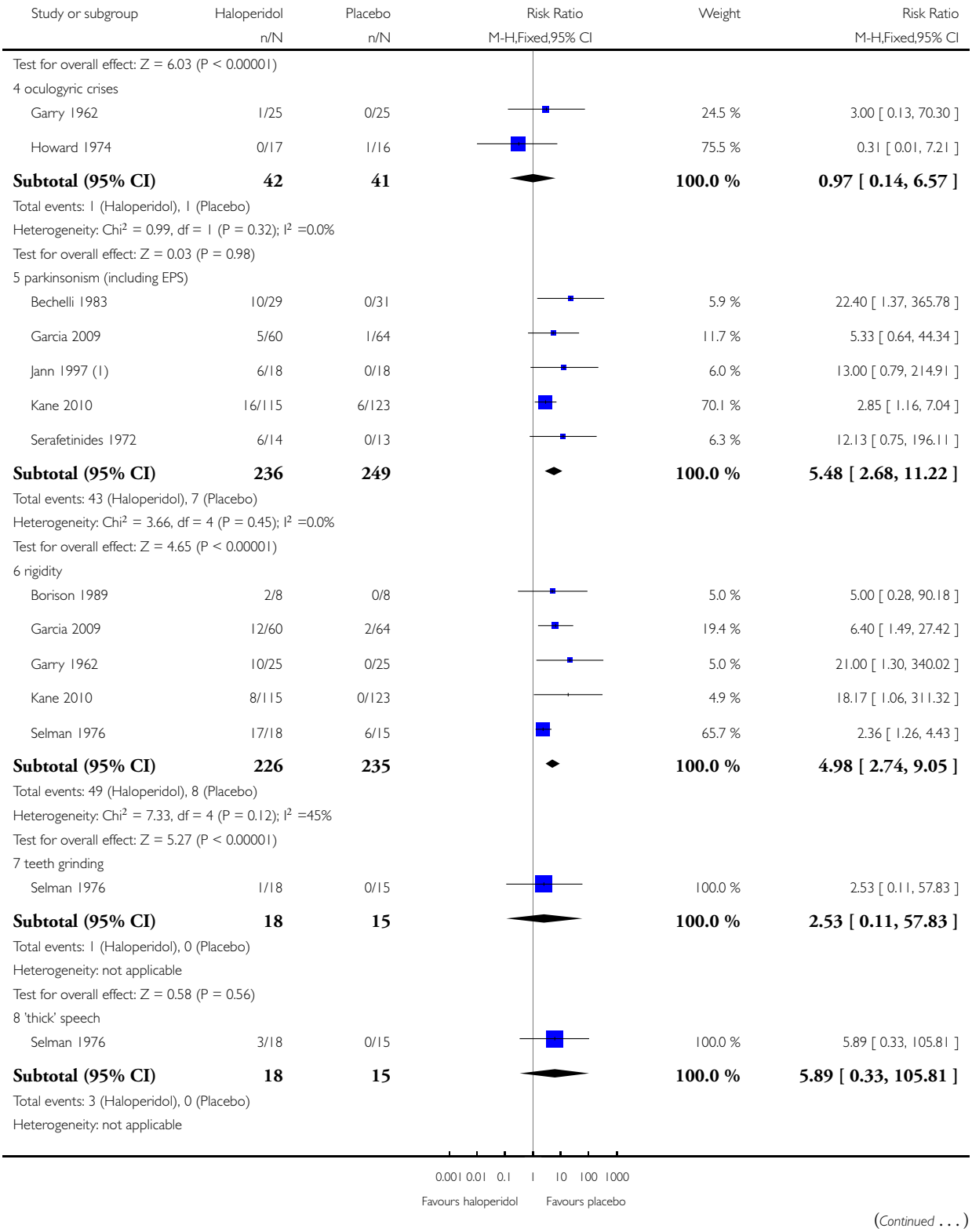

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Study or subgroup	Haloperidol n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 1.20 (P = 0.23)					
9 tremor					
Garcia 2009	14/60	2/64		21.0 %	7.47 [1.77, 31.49]
Garry 1962	10/25	0/25		5.4 %	21.00 [1.30, 340.02]
Howard 1974	2/17	0/16		5.6 %	4.72 [0.24, 91.41]
Kane 2002	7/103	3/104		32.4 %	2.36 [0.63, 8.86]
Selman 1976	2/18	3/15		35.5 %	0.56 [0.11, 2.90]
Subtotal (95% CI)	**223**	**224**		**100.0 %**	**3.93 [1.96, 7.91]**
Total events: 35 (Haloperidol), 8 (Placebo)					
Heterogeneity: Chi^2 = 8.13, df = 4 (P = 0.09); I^2 =51%					
Test for overall effect: Z = 3.84 (P = 0.00012)					
Test for subgroup differences: Chi^2 = 7.51, df = 8 (P = 0.48), I^2 =0.0%					

(1) Loss to follow-up 33% in haloperidol arm and 55% in placebo arm.

Analysis 1.13. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 13 Adverse effects: 1b. Movement disorders: Tardive dyskinesia.

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

Outcome: 13 Adverse effects: 1b. Movement disorders: Tardive dyskinesia

Study or subgroup	Haloperidol n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 dyskinesia and tardive dyskinesia					
Garcia 2009	0/60	1/64		73.8 %	0.36 [0.01, 8.55]
Howard 1974	1/17	0/16		26.2 %	2.83 [0.12, 64.89]
Subtotal (95% CI)	**77**	**80**		**100.0 %**	**1.00 [0.14, 7.13]**
Total events: 1 (Haloperidol), 1 (Placebo)					
Heterogeneity: Chi^2 = 0.83, df = 1 (P = 0.36); I^2 =0.0%					
Test for overall effect: Z = 0.00 (P = 1.0)					
Test for subgroup differences: Not applicable					

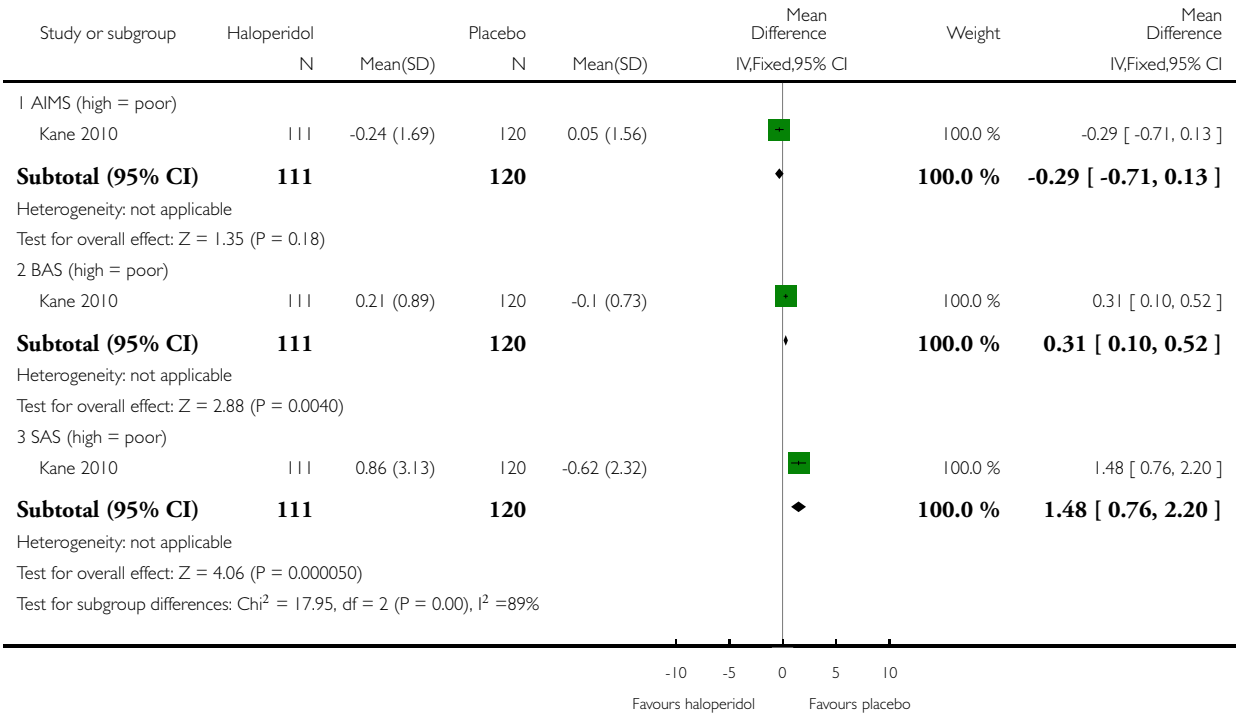
Analysis 1.14. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 14 Adverse effects: 1c. Movement disorders: Average changes scores (various scales; up to 6 weeks).

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

Outcome: 14 Adverse effects: 1c. Movement disorders: Average changes scores (various scales; up to 6 weeks)

Study or subgroup	Haloperidol N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 AIMS (high = poor)							
Kane 2010	111	-0.24 (1.69)	120	0.05 (1.56)		100.0 %	-0.29 [-0.71, 0.13]
Subtotal (95% CI)	**111**		**120**			**100.0 %**	**-0.29 [-0.71, 0.13]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.35 (P = 0.18)							
2 BAS (high = poor)							
Kane 2010	111	0.21 (0.89)	120	-0.1 (0.73)		100.0 %	0.31 [0.10, 0.52]
Subtotal (95% CI)	**111**		**120**			**100.0 %**	**0.31 [0.10, 0.52]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.88 (P = 0.0040)							
3 SAS (high = poor)							
Kane 2010	111	0.86 (3.13)	120	-0.62 (2.32)		100.0 %	1.48 [0.76, 2.20]
Subtotal (95% CI)	**111**		**120**			**100.0 %**	**1.48 [0.76, 2.20]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.06 (P = 0.000050)							
Test for subgroup differences: Chi^2 = 17.95, df = 2 (P = 0.00), I^2 =89%							

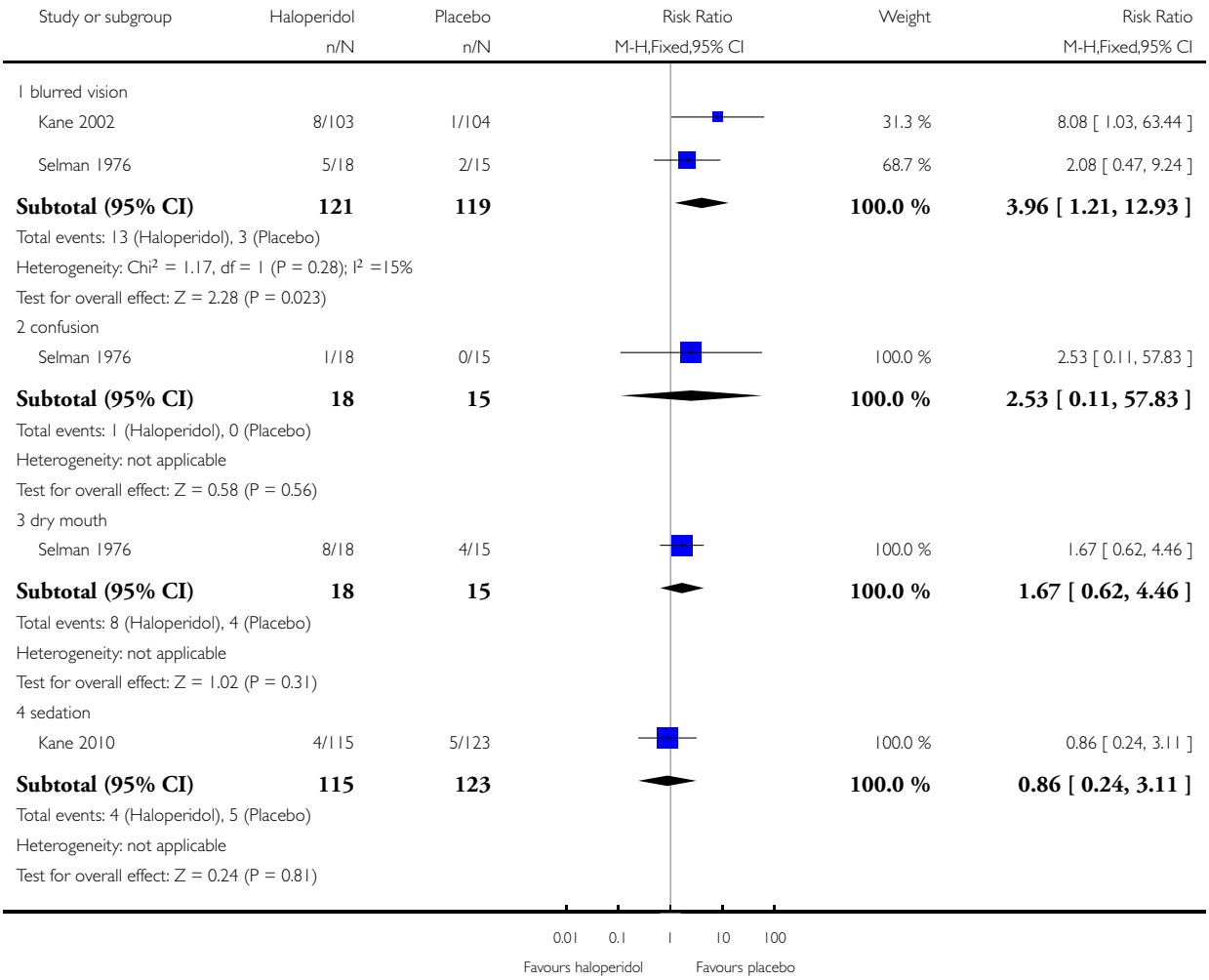


Analysis 1.15. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 15 Adverse effects: 2. Other CNS.

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

Outcome: 15 Adverse effects: 2. Other CNS

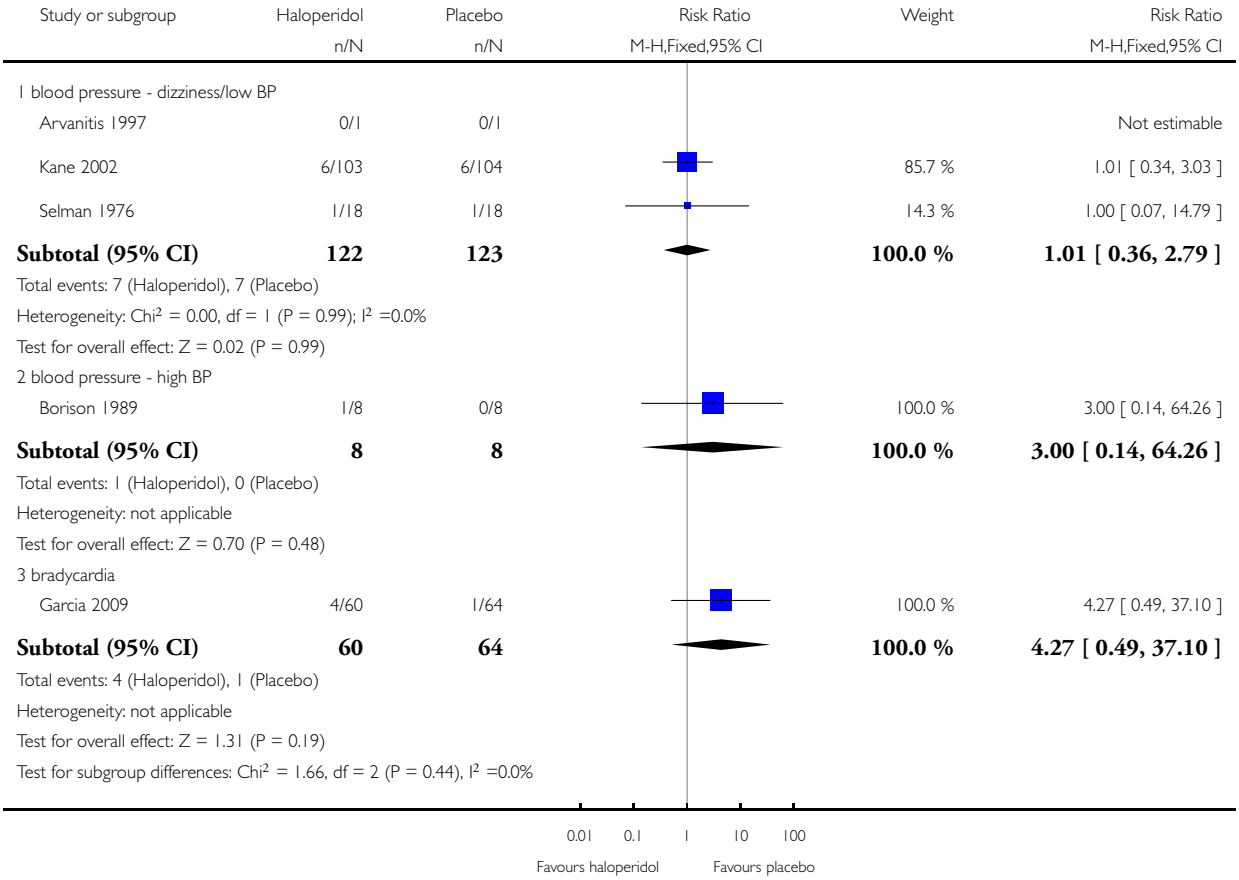


Analysis 1.16. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 16 Adverse effects: 3. Cardiovascular effects.

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

Outcome: 16 Adverse effects: 3. Cardiovascular effects

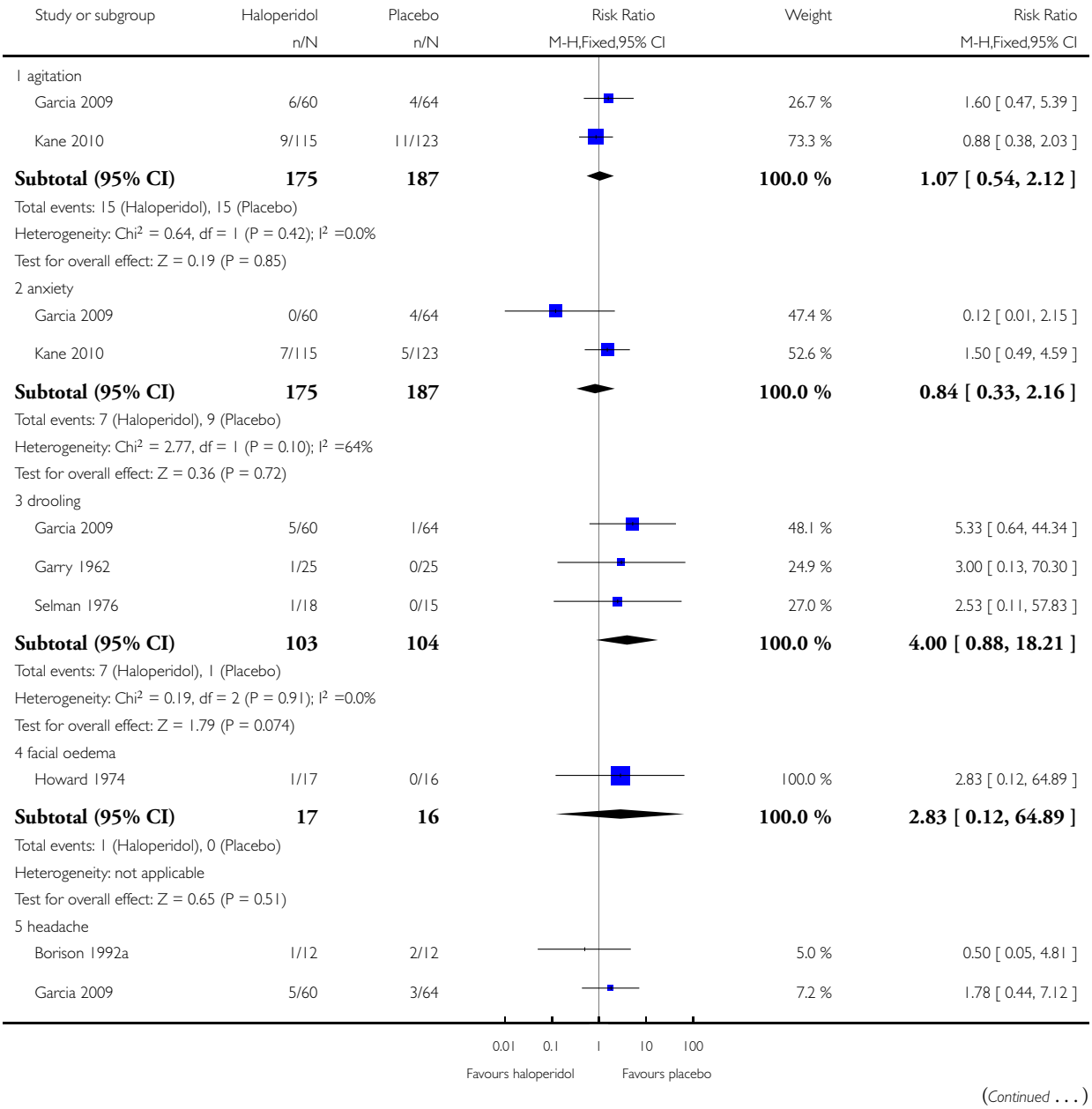


Analysis 1.17. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 17 Adverse effects: 4. Other adverse effects.

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

Outcome: 17 Adverse effects: 4. Other adverse effects



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Study or subgroup	Haloperidol n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kane 2002	26/103	24/104		59.1 %	1.09 [0.67, 1.77]
Kane 2010	5/115	12/123		28.7 %	0.45 [0.16, 1.23]
Subtotal (95% CI)	**290**	**303**		**100.0 %**	**0.93 [0.62, 1.39]**
Total events: 37 (Haloperidol), 41 (Placebo)					
Heterogeneity: Chi^2 = 3.59, df = 3 (P = 0.31); I^2 =17%					
Test for overall effect: Z = 0.37 (P = 0.71)					
6 infection					
Borison 1992a	3/12	0/12		100.0 %	7.00 [0.40, 122.44]
Subtotal (95% CI)	**12**	**12**		**100.0 %**	**7.00 [0.40, 122.44]**
Total events: 3 (Haloperidol), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.33 (P = 0.18)					
7 insomnia					
Bechelli 1983	2/29	1/31		2.3 %	2.14 [0.20, 22.34]
Garcia 2009	3/60	6/64		13.8 %	0.53 [0.14, 2.04]
Kane 2002	25/103	18/104		42.6 %	1.40 [0.82, 2.41]
Kane 2010	16/115	18/123		41.3 %	0.95 [0.51, 1.77]
Subtotal (95% CI)	**307**	**322**		**100.0 %**	**1.11 [0.76, 1.63]**
Total events: 46 (Haloperidol), 43 (Placebo)					
Heterogeneity: Chi^2 = 2.40, df = 3 (P = 0.49); I^2 =0.0%					
Test for overall effect: Z = 0.55 (P = 0.58)					
8 nausea/vomiting					
Borison 1992a	1/12	2/12		10.6 %	0.50 [0.05, 4.81]
Kane 2002	16/103	17/104		89.4 %	0.95 [0.51, 1.78]
Subtotal (95% CI)	**115**	**116**		**100.0 %**	**0.90 [0.49, 1.65]**
Total events: 17 (Haloperidol), 19 (Placebo)					
Heterogeneity: Chi^2 = 0.29, df = 1 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 0.33 (P = 0.74)					
9 oral hypoaesthesia					
Kane 2010	0/115	3/123		100.0 %	0.15 [0.01, 2.92]
Subtotal (95% CI)	**115**	**123**		**100.0 %**	**0.15 [0.01, 2.92]**
Total events: 0 (Haloperidol), 3 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.25 (P = 0.21)					
10 perspiration					
Bechelli 1983	2/29	0/31		47.1 %	5.33 [0.27, 106.61]
Selman 1976	2/18	0/15		52.9 %	4.21 [0.22, 81.47]
Subtotal (95% CI)	**47**	**46**		**100.0 %**	**4.74 [0.58, 38.81]**
Total events: 4 (Haloperidol), 0 (Placebo)					

(*Continued* . . .)

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Study or subgroup	Haloperidol n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² =0.0%					
Test for overall effect: Z = 1.45 (P = 0.15)					
11 sleepiness					
Borison 1992a	3/12	0/12		5.3 %	7.00 [0.40, 122.44]
Garcia 2009	2/60	2/64		20.4 %	1.07 [0.16, 7.33]
Howard 1974	3/17	1/16		10.9 %	2.82 [0.33, 24.43]
Kane 2002	13/103	4/104		42.0 %	3.28 [1.11, 9.73]
Kane 2010	2/115	1/123		10.2 %	2.14 [0.20, 23.27]
Selman 1976	2/18	0/15		5.7 %	4.21 [0.22, 81.47]
Serafetinides 1972	3/14	0/13		5.5 %	6.53 [0.37, 115.49]
Subtotal (95% CI)	**339**	**347**		**100.0 %**	**3.09 [1.51, 6.31]**
Total events: 28 (Haloperidol), 8 (Placebo)					
Heterogeneity: Chi² = 1.90, df = 6 (P = 0.93); I² =0.0%					
Test for overall effect: Z = 3.10 (P = 0.0020)					
12 weight gain					
Kane 2002	10/103	1/104		34.2 %	10.10 [1.32, 77.46]
Kane 2010	4/112	2/122		65.8 %	2.18 [0.41, 11.66]
Subtotal (95% CI)	**215**	**226**		**100.0 %**	**4.89 [1.41, 16.95]**
Total events: 14 (Haloperidol), 3 (Placebo)					
Heterogeneity: Chi² = 1.38, df = 1 (P = 0.24); I² =27%					
Test for overall effect: Z = 2.50 (P = 0.012)					
13 weight loss					
Garcia 2009	1/60	0/64		4.8 %	3.20 [0.13, 76.98]
Kane 2010	0/112	2/122		23.6 %	0.22 [0.01, 4.49]
Serafetinides 1972	6/14	7/13		71.6 %	0.80 [0.36, 1.75]
Subtotal (95% CI)	**186**	**199**		**100.0 %**	**0.77 [0.36, 1.64]**
Total events: 7 (Haloperidol), 9 (Placebo)					
Heterogeneity: Chi² = 1.44, df = 2 (P = 0.49); I² =0.0%					
Test for overall effect: Z = 0.67 (P = 0.50)					
Test for subgroup differences: Chi² = 23.79, df = 12 (P = 0.02), I² =50%					

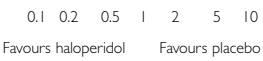
Analysis 1.18. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 18 SUBGROUP ANALYSIS: 1. MEN vs WOMEN: Global state: Overall improvement: No marked global improvement, > 6-24 weeks (clinician rated).

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

Outcome: 18 SUBGROUP ANALYSIS: 1. MEN vs WOMEN: Global state: Overall improvement: No marked global improvement, > 6-24 weeks (clinician rated)

Study or subgroup	Haloperidol n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 only men					
Simpson 1967	7/16	8/8		100.0 %	0.47 [0.27, 0.82]
Subtotal (95% CI)	**16**	**8**		**100.0 %**	**0.47 [0.27, 0.82]**
Total events: 7 (Haloperidol), 8 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.67 (P = 0.0075)					
2 only women					
Howard 1974	9/17	10/13		27.8 %	0.69 [0.40, 1.18]
Vichaiya 1971	20/29	29/29		72.2 %	0.69 [0.54, 0.89]
Subtotal (95% CI)	**46**	**42**		**100.0 %**	**0.69 [0.55, 0.87]**
Total events: 29 (Haloperidol), 39 (Placebo)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.97); I^2 =0.0%					
Test for overall effect: Z = 3.08 (P = 0.0021)					
Test for subgroup differences: Chi^2 = 1.64, df = 1 (P = 0.20), I^2 =39%					



Analysis 1.19. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 19 SUBGROUP ANALYSIS: 2. 18-65 YEARS vs < 18 YEARS: Global state: Overall improvement: No marked global improvement, > 6-24 weeks (clinician rated).

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

Outcome: 19 SUBGROUP ANALYSIS: 2. 18-65 YEARS vs < 18 YEARS: Global state: Overall improvement: No marked global improvement, > 6-24 weeks (clinician rated)

Study or subgroup	Haloperidol n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 18-65 years					
Durost 1964	14/19	15/15		14.2 %	0.75 [0.56, 0.99]
Garry 1962	19/26	22/26		18.1 %	0.86 [0.65, 1.15]
Howard 1974	9/17	10/13		9.3 %	0.69 [0.40, 1.18]
Selman 1976	9/29	16/29		13.2 %	0.56 [0.30, 1.06]
Serafetinides 1972	10/14	14/14		11.9 %	0.72 [0.51, 1.02]
Simpson 1967	7/16	8/8		9.1 %	0.47 [0.27, 0.82]
Vichaiya 1971	20/29	29/29		24.2 %	0.69 [0.54, 0.89]
Subtotal (95% CI)	**150**	**134**		**100.0 %**	**0.70 [0.61, 0.80]**
Total events: 88 (Haloperidol), 114 (Placebo)					
Heterogeneity: Chi^2 = 4.86, df = 6 (P = 0.56); I^2 =0.0%					
Test for overall effect: Z = 4.97 (P < 0.00001)					
2 < 18 years					
Spencer 1992	3/12	11/12		100.0 %	0.27 [0.10, 0.74]
Subtotal (95% CI)	**12**	**12**		**100.0 %**	**0.27 [0.10, 0.74]**
Total events: 3 (Haloperidol), 11 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.56 (P = 0.010)					
Test for subgroup differences: Chi^2 = 3.36, df = 1 (P = 0.07), I^2 =70%					

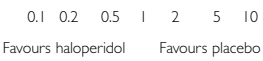
Analysis 1.20. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 20 SUBGROUP ANALYSIS: 3. ACUTE vs CHRONIC: Global state: Overall improvement: No marked global improvement, > 6-24 weeks (clinician rated).

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

Outcome: 20 SUBGROUP ANALYSIS: 3. ACUTE vs CHRONIC: Global state: Overall improvement: No marked global improvement, > 6-24 weeks (clinician rated)

Study or subgroup	Haloperidol n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 acute phase of illness					
Selman 1976	9/29	16/29		100.0 %	0.56 [0.30, 1.06]
Subtotal (95% CI)	**29**	**29**		**100.0 %**	**0.56 [0.30, 1.06]**
Total events: 9 (Haloperidol), 16 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.78 (P = 0.075)					
2 chronic phase of illness					
Durost 1964	14/19	15/15		14.8 %	0.75 [0.56, 0.99]
Garry 1962	19/26	22/26		18.9 %	0.86 [0.65, 1.15]
Howard 1974	9/17	10/13		9.7 %	0.69 [0.40, 1.18]
Serafetinides 1972	10/14	14/14		12.4 %	0.72 [0.51, 1.02]
Simpson 1967	7/16	8/8		9.5 %	0.47 [0.27, 0.82]
Spencer 1992	3/12	11/12		9.4 %	0.27 [0.10, 0.74]
Vichaiya 1971	20/29	29/29		25.3 %	0.69 [0.54, 0.89]
Subtotal (95% CI)	**133**	**117**		**100.0 %**	**0.68 [0.59, 0.78]**
Total events: 82 (Haloperidol), 109 (Placebo)					
Heterogeneity: Chi^2 = 8.41, df = 6 (P = 0.21); I^2 =29%					
Test for overall effect: Z = 5.44 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.31, df = 1 (P = 0.58), I^2 =0.0%					



Analysis 1.21. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 21 SUBGROUP ANALYSIS: 4. LOW DOSE vs MEDIUM TO HIGH DOSE.

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

Outcome: 21 SUBGROUP ANALYSIS: 4. LOW DOSE vs MEDIUM TO HIGH DOSE

Study or subgroup	Haloperidol n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 low dose (≤ 5 mg/day) - Global state: Overall improvement: No marked global improvement, up to 6 weeks (clinician rated)					
Kane 2010	63/112	81/122		100.0 %	0.85 [0.69, 1.04]
Subtotal (95% CI)	**112**	**122**		**100.0 %**	**0.85 [0.69, 1.04]**
Total events: 63 (Haloperidol), 81 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.57 (P = 0.12)					
2 medium to high dose (> 5 mg/day) - Global state: Overall improvement: No marked global improvement, up to 6 weeks (clinician rated)					
Bechelli 1983	9/30	25/31		33.4 %	0.37 [0.21, 0.66]
Garcia 2009 (1)	17/58	36/61		47.6 %	0.50 [0.32, 0.78]
Selman 1976	9/29	14/29		19.0 %	0.64 [0.33, 1.24]
Subtotal (95% CI)	**117**	**121**		**100.0 %**	**0.48 [0.35, 0.66]**
Total events: 35 (Haloperidol), 75 (Placebo)					
Heterogeneity: Chi^2 = 1.53, df = 2 (P = 0.46); I^2 =0.0%					
Test for overall effect: Z = 4.59 (P < 0.00001)					
3 low dose (≤ 5 mg/day) - Global state: Overall improvement: No marked global improvement, > 6-24 weeks (clinician rated)					
Garry 1962	19/26	22/26		32.4 %	0.86 [0.65, 1.15]
Simpson 1967 (2)	3/8	5/7		7.9 %	0.53 [0.19, 1.44]
Spencer 1992	3/12	11/12		16.2 %	0.27 [0.10, 0.74]
Vichaiya 1971	20/29	29/29		43.5 %	0.69 [0.54, 0.89]
Subtotal (95% CI)	**75**	**74**		**100.0 %**	**0.67 [0.55, 0.81]**
Total events: 45 (Haloperidol), 67 (Placebo)					
Heterogeneity: Chi^2 = 6.55, df = 3 (P = 0.09); I^2 =54%					
Test for overall effect: Z = 4.02 (P = 0.000058)					
4 medium to high dose (> 5 mg/day) - Global state: Overall improvement: No marked global improvement, > 6-24 weeks (clinician rated)					
Durost 1964	14/19	15/15		26.7 %	0.75 [0.56, 0.99]
Howard 1974	9/17	10/13		17.6 %	0.69 [0.40, 1.18]
Selman 1976	9/29	16/29		24.8 %	0.56 [0.30, 1.06]
Serafetinides 1972	10/14	14/14		22.5 %	0.72 [0.51, 1.02]
Simpson 1967 (3)	3/8	5/7		8.3 %	0.53 [0.19, 1.44]
Subtotal (95% CI)	**87**	**78**		**100.0 %**	**0.67 [0.54, 0.83]**

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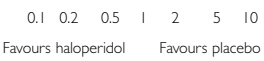
Study or subgroup	Haloperidol n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 45 (Haloperidol), 60 (Placebo)					
Heterogeneity: Chi^2 = 1.35, df = 4 (P = 0.85); I^2 =0.0%					
Test for overall effect: Z = 3.59 (P = 0.00033)					
Test for subgroup differences: Chi^2 = 9.05, df = 3 (P = 0.03), I^2 =67%					



(1) LOCF approach used to impute missing values.

(2) Intervention data from low dose study arm: Haloperidol, 6 mg/day.

(3) Intervention data from high dose study arm: Haloperidol, 30 mg/day.

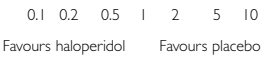
Analysis 1.22. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 22 SUBGROUP ANALYSIS: 5. DIAGNOSTIC CRITERIA vs NO DIAGNOSTIC CRITERIA.

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

Outcome: 22 SUBGROUP ANALYSIS: 5. DIAGNOSTIC CRITERIA vs NO DIAGNOSTIC CRITERIA

Study or subgroup	Haloperidol n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 operational criteria used for diagnosis - Global state: Overall improvement: No marked global improvement, up to 6 weeks (clinician rated)					
Bechelli 1983	9/30	25/31		17.9 %	0.37 [0.21, 0.66]
Garcia 2009 (1)	17/58	36/61		25.6 %	0.50 [0.32, 0.78]
Kane 2010	63/112	81/122		56.5 %	0.85 [0.69, 1.04]
Subtotal (95% CI)	**200**	**214**		**100.0 %**	**0.67 [0.56, 0.81]**
Total events: 89 (Haloperidol), 142 (Placebo)					
Heterogeneity: Chi^2 = 10.65, df = 2 (P = 0.005); I^2 =81%					
Test for overall effect: Z = 4.29 (P = 0.000018)					
2 no operational criteria used for diagnosis - Global state: Overall improvement: No marked global improvement, up to 6 weeks (clinician rated)					
Selman 1976	9/29	14/29		100.0 %	0.64 [0.33, 1.24]
Subtotal (95% CI)	**29**	**29**		**100.0 %**	**0.64 [0.33, 1.24]**
Total events: 9 (Haloperidol), 14 (Placebo)					
Heterogeneity: not applicable					



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Study or subgroup	Haloperidol n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 1.31 (P = 0.19)					
3 operational criteria used for diagnosis - Global state: Overall improvement: No marked global improvement, > 6-24 weeks (clinician rated)					
Spencer 1992	3/12	11/12		100.0 %	0.27 [0.10, 0.74]
Subtotal (95% CI)	**12**	**12**		**100.0 %**	**0.27 [0.10, 0.74]**
Total events: 3 (Haloperidol), 11 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.56 (P = 0.010)					
4 no operational criteria used for diagnosis - Global state: Overall improvement: No marked global improvement, > 6-24 weeks (clinician rated)					
Durost 1964	14/19	15/15		14.2 %	0.75 [0.56, 0.99]
Garry 1962	19/26	22/26		18.1 %	0.86 [0.65, 1.15]
Howard 1974	9/17	10/13		9.3 %	0.69 [0.40, 1.18]
Selman 1976	9/29	16/29		13.2 %	0.56 [0.30, 1.06]
Serafetinides 1972	10/14	14/14		11.9 %	0.72 [0.51, 1.02]
Simpson 1967	7/16	8/8		9.1 %	0.47 [0.27, 0.82]
Vichaiya 1971	20/29	29/29		24.2 %	0.69 [0.54, 0.89]
Subtotal (95% CI)	**150**	**134**		**100.0 %**	**0.70 [0.61, 0.80]**
Total events: 88 (Haloperidol), 114 (Placebo)					
Heterogeneity: Chi^2 = 4.86, df = 6 (P = 0.56); I^2 =0.0%					
Test for overall effect: Z = 4.97 (P < 0.00001)					
5 operational criteria used for diagnosis - Global state: Relapse (< 52 weeks)					
Nishikawa 1984	26/37	13/13		100.0 %	0.72 [0.57, 0.91]
Subtotal (95% CI)	**37**	**13**		**100.0 %**	**0.72 [0.57, 0.91]**
Total events: 26 (Haloperidol), 13 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.73 (P = 0.0063)					
6 no operational criteria used for diagnosis - Global state: Relapse (< 52 weeks)					
Nishikawa 1982	6/10	10/10		100.0 %	0.62 [0.37, 1.03]
Subtotal (95% CI)	**10**	**10**		**100.0 %**	**0.62 [0.37, 1.03]**
Total events: 6 (Haloperidol), 10 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.85 (P = 0.064)					
Test for subgroup differences: Chi^2 = 3.79, df = 5 (P = 0.58), I^2 =0.0%					

(1) LOCF approach used to impute missing values.

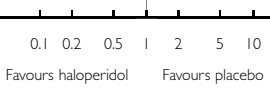
Analysis 1.23. Comparison 1 HALOPERIDOL versus PLACEBO, Outcome 23 SENSITIVITY ANALYSIS: 1. ASSUMPTIONS FOR MISSING DATA vs NO ASSUMPTIONS FOR MISSING DATA: Global state: Overall improvement: No marked global improvement, up to 6 weeks (clinician rated).

Review: Haloperidol versus placebo for schizophrenia

Comparison: 1 HALOPERIDOL versus PLACEBO

Outcome: 23 SENSITIVITY ANALYSIS: 1. ASSUMPTIONS FOR MISSING DATA vs NO ASSUMPTIONS FOR MISSING DATA: Global state: Overall improvement: No marked global improvement, up to 6 weeks (clinician rated)

Study or subgroup	Haloperidol n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 no assumptions for missing data					
Bechelli 1983	9/30	25/31		21.2 %	0.37 [0.21, 0.66]
Kane 2010	63/112	81/122		66.8 %	0.85 [0.69, 1.04]
Selman 1976	9/29	14/29		12.1 %	0.64 [0.33, 1.24]
Subtotal (95% CI)	**171**	**182**		**100.0 %**	**0.72 [0.60, 0.87]**
Total events: 81 (Haloperidol), 120 (Placebo)					
Heterogeneity: Chi^2 = 7.57, df = 2 (P = 0.02); I^2 =74%					
Test for overall effect: Z = 3.39 (P = 0.00071)					
Test for subgroup differences: Not applicable					



APPENDICES

Appendix 1. Previous searches

1. For the original search in 1998, we electronically searched the following databases:
1.1 Biological Abstracts on Silver Platter (1985 to February 1998) using the Cochrane Schizophrenia Group's terms for randomised controlled trials and schizophrenia combined with the phrase:
[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*))]
1.2 CINAHL on Silver Platter (1982 to February 1998) using the Cochrane Schizophrenia Group's terms for randomised controlled trials and schizophrenia combined with the phrase:
[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* or explode "HALOPERIDOL"/ all topical subheadings / all age subheadings))]
1.3 The Cochrane Library (1998, Issue 4) using the Cochrane Schizophrenia Group's terms for schizophrenia combined with the phrase:
[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* or HALOPERIDOL*:ME))]

1.4 The Cochrane Schizophrenia Group's Register (December 1998) using the phrase:
[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* or #42 = 14)]
#42 is the 'Intervention' field and '14' is the code for haloperidol.
1.5 EMBASE (January 1980 to February 1998) using the Cochrane Schizophrenia Group's terms for randomised controlled trials and schizophrenia combined with the phrase:
[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* or explode "HALOPERIDOL / all subheadings))]
1.6 MEDLINE on Silver Platter (January 1966 to February 1998) using the Cochrane Schizophrenia Group's terms for randomised controlled trials and schizophrenia combined with the phrase:
[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* or explode "HALOPERIDOL" / all subheadings))]
1.7 PsycLIT on Silver Platter (January 1974 to February 1998) using the Cochrane Schizophrenia Group's terms for randomised controlled trials and schizophrenia combined with the phrase:
[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* or explode "HALOPERIDOL"))]
2. Cited reference searching
We inspected the references of all identified trials for more studies. We sought each of the included studies as a citation on the SCISEARCH database. We also inspected reports of articles that had cited these studies in order to identify further trials.
3. Personal contact
We contacted primary authors of all studies initially selected for inclusion in order to identify further relevant trials. We also contacted companies producing relevant compounds for copies of published, unpublished and archived trials.
4. Hand Searching
High yield journals identified by electronic searches, if not already hand searched, will be chosen for full page by page inspection.
5. 2005 Search
For the 2005 update we searched The Cochrane Schizophrenia Group's Trials Register (July 2005) using the phrase:
[((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 REFERENCE title, abstract and index fields) OR ((haloperidol* and placebo*) in STUDY intervention field)]

Appendix 2. Previous data collection and analysis

1. Selection of trials
We (CJ and SL) independently inspected all abstracts of studies identified by the above search terms. In addition, to ensure reliability, CEA inspected a random sample of these abstracts, comprising 10% of the total. We ordered full articles of relevant reports and carefully inspected these for a final decision on inclusion (see selection criteria). We were not blinded to the names of the authors, institutions or journal of publication. In turn, we (CJ and SL) inspected all full reports. Again, a random 10% sample of reports were re-inspected by CEA in order to ensure reliable selection. For the 2005 update, CJ inspected all abstracts and subsequent reports from the new 2005 electronic search. CEA carried out the reliability check.
2. Assessment of methodological quality
We assessed the methodological quality of trials included in this review using the criteria described in the *Cochrane Handbook* (Higgins 2005) which is based on evidence of a strong relationship between allocation concealment and the potential for bias in the results. The categories are defined below:
A. Low risk of bias (adequate allocation concealment)
B. Moderate risk of bias (some doubt about the results)
C. High risk of bias (inadequate allocation concealment)
For the purpose of the analysis in this review, we included trials if they met the criteria A or B.
3. Data collection
We (CJ and SL) independently extracted data from selected trials and CEA re-extracted information from a sample of 20%. When disputes arose, resolution was attempted by discussion. If this was not possible and further information was necessary to resolve the dilemma, we did not enter the data. Again, for the 2005 update we (CJ and CEA) followed the same procedures.
4. Data synthesis

4.1 Incomplete data

With the exception of the outcome of leaving the study early, we did not include trial outcomes if more than 50% of people were not reported in the final analysis.

4.2 Dichotomous data

We used an intention-to-treat analysis, on the condition that more than 50% of people completed the study and everyone allocated to the intervention was counted regardless of whether they completed the follow-up. We assumed that those leaving the study early had the negative outcome, with the exception of death. We calculated the Relative risk (RR) and their 95% confidence interval (CI) based on the random-effects model. This takes into account any differences between studies even if there is no statistically significant heterogeneity. We inspected the data to see if analysis using a fixed-effect model made any substantive difference. Where possible we estimated the number needed to treat (NNT).

4.3 Continuous data

4.3.1 Normal data: data on continuous outcomes are frequently skewed, the mean not being the centre of the distribution. The statistics for meta-analysis are thought to be able to cope with some skew, but were formulated for parametric data. To avoid this potential pitfall, we applied the following standards to all data before inclusion: (a) standard deviations and means were reported or obtained from authors, (b) for data with finite limits, such as endpoint scale data, the standard deviation (SD), when multiplied by two, was less than the mean. Otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution (Altman 1996). We reported data that did not meet the first or second standard in 'other data' tables.

For change data (endpoint minus baseline), the situation is even more problematic. In the absence of individual patient data it is impossible to know if data are skewed, though this is likely to be the case. As carried out in other CSG reviews, we presented change data in MetaView in order to summarise available information. In doing this, it was assumed either that data were not skewed or that the analyses could cope with the unknown degree of skewness. Without individual patient data it is impossible to test this assumption. Where both change and endpoint data were available for the same outcome category, we only presented endpoint data. We acknowledge that by doing this much of the published change data were excluded, but argue that endpoint data is more clinically relevant and that if change data were to be presented along with endpoint data it would be given undeserved equal prominence. Authors of studies reporting only change data are being contacted for endpoint figures. We reported non-normally distributed data in the 'Other data types' tables.

4.3.2 Rating scales: a wide range of instruments are available to measure mental health outcomes. These instruments vary in quality and many are not valid, or even ad hoc. For outcome instruments some minimum standards have to be set. These were that: (a) the psychometric properties of the instrument should have been described in a peer-reviewed journal, (b) the instrument should either be: (i) a self-report, or (ii) completed by an independent rater or relative (not the therapist) and (c) the instrument should be a global assessment of an area of functioning (Marshall 2000).

4.3.3 Cluster trials

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

Where clustering was not accounted for in primary studies, we presented the data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. In subsequent versions of this review we will seek to contact first authors of studies to obtain intra-class correlation co-efficients of their clustered data and to adjust for this using accepted methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we will also present these data as if from a non-cluster randomised study, but adjusted for the clustering effect.

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

5. Heterogeneity

Firstly, we undertook consideration of all the included studies within any comparison to estimate clinical heterogeneity. Then we used visual inspection of graphs to investigate the possibility of statistical heterogeneity. This was supplemented employing, primarily, the I-squared statistic. This provides an estimate of the percentage of inconsistency thought to be due to chance. Where the I-squared estimate was greater than or equal to 75% this was interpreted as evidence of high levels of heterogeneity (Higgins 2003). We did not summate data with 75% or greater I-squared statistic, but we presented these separately and investigated reasons for heterogeneity.

6. Addressing publication bias

We entered data from all identified and selected trials into a funnel graph (trial effect versus trial size) in an attempt to investigate the likelihood of overt publication bias.

7. Sensitivity analysis
We anticipated that this review, like chlorpromazine, would be large in comparison to many within the field of mental health and this would allow several sensitivity analyses (see Objectives). We (CJ and SL) selected trials suitable for such analyses at the data extraction stage of the review.

Appendix 3. Previous plain language summary

Schizophrenia is a distressing and long-term mental illness affecting 1% of the population. Medication has been available since the 1950s and haloperidol was one of the first antipsychotics to be offered. Despite the introduction of many other antipsychotics it is still very widely used, and it is the antipsychotic most often used to judge the effectiveness of new medications. This review aims to update the knowledge on the clinical trials comparing placebo and haloperidol.
This review contains 25 studies involving a total of 4651 people who were either inpatients or living in the community. Haloperidol has been found to be better than placebo in improving general functioning and some symptoms in the short term (up to six weeks), and just general functioning in the medium term (greater than six but less than 24 weeks). None of the people in any of these trials have been followed up for longer than 24 weeks. A significant number of people on haloperidol compared to those on placebo suffered from at least one adverse effect, mainly stiffness (dystonia) and movement disorders such as shaking or restlessness (Parkinsonism). In addition seven trials containing 686 people found a significant number of people suffered from sleepiness compared to the control. Overall the data from these trials are not good, with many outcomes being presented in a way that does not allow them to be used in this review. Moreover just less than half of those taking haloperidol and slightly more than half of those receiving placebo left the studies early, suggesting that the design of the trial was possibly not acceptable to these participants. In the light of these results it is therefore somewhat surprising that this medication is used so widely as a comparison for new medication.
(Plain language summary prepared for this review by Janey Antoniou of RETHINK, UK www.rethink.org)

WHAT'S NEW

Last assessed as up-to-date: 15 May 2012.

Date	Event	Description
10 October 2013	New citation required but conclusions have not changed	Update completed, no overall change to conclusions
6 December 2012	New search has been performed	Results from 2012 search added to review,

HISTORY

Protocol first published: Issue 1, 1999

Review first published: Issue 2, 2001

Date	Event	Description
15 May 2012	Amended	Update search of Cochrane Schizophrenia Group's Trial Register (see Search methods for identification of studies), 72 studies added to awaiting assessment.

(*Continued*)

5 October 2011	Amended	Contact details updated.
4 August 2010	Amended	Contact details updated.
14 April 2010	Amended	Contact details updated.
5 August 2009	Amended	Contact details updated.
24 November 2008	Amended	New plain language summary added.
23 April 2008	Amended	Converted to new review format.
23 August 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Claire Irving (nee Joy) - selection of trials, data extraction, writing original review.

Clive Adams - 10% check of trials, writing review and help with update.

Steve Laurie - selection of trials, 10% data extraction check, writing original review.

Hanna Bergman - updated the review to the current version, including applying new methods and adding 'Summary of findings' table.

DECLARATIONS OF INTEREST

Claire Irving (nee Joy) - None.

Clive Adams (CEA) - has attended and presented at functions sponsored by Janssen-Cilag and Eli Lilly. These companies have provided travel, accommodation and speaker expenses but no funds have been paid directly to CEA. Payments related to participation in meetings have been paid to an account to support schizophrenia research. The Cochrane Schizophrenia Group has multiple, and hopefully, balancing, competing interests. Potential conflicts of interest of the Group and individuals are described on http://cebmh.warne.ox.ac.uk/csg/ and sources and quantities of all funding, listed.

Steve Lawrie - has been paid for speaking about critical appraisal by employees of the manufacturers of olanzapine, quetiapine, risperidone, and ziprasidone, and has been paid to speak about the management of schizophrenia by employees of the manufacturers of amisulpiride, olanzapine, risperidone, and clozapine. AM and ZN declare that they have no competing interests.

Hanna Bergman - works for Enhance Reviews. Enhance Reviews Ltd is a private company that performs systematic reviews of the literature.

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Internal sources

- Cochrane Schizophrenia Group General Fund, UK.
- University of Oxford Department of Psychiatry, UK.

External sources

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have updated the methods section to reflect new Cochrane methodology since the last publication of this review, for example addition of a 'Summary of findings' table.

INDEX TERMS

Medical Subject Headings (MeSH)

Akathisia, Drug-Induced [etiology]; Antipsychotic Agents [adverse effects; *therapeutic use]; Dystonia [chemically induced]; Haloperidol [adverse effects; *therapeutic use]; Parkinsonian Disorders [chemically induced]; Placebo Effect; Randomized Controlled Trials as Topic; Schizophrenia [*drug therapy]; Treatment Outcome

MeSH check words

Humans