Sulpiride versus placebo for schizophrenia (Review)

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[Intervention Review]

Sulpiride versus placebo for schizophrenia

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ABSTRACT

Background

Sulpiride is a relatively old antipsychotic drug reputed to have a low incidence of adverse effects and an effect on the negative symptoms of schizophrenia. This relatively inexpensive antipsychotic drug has a similar neuropharmacological profile to several novel atypical drugs.

Objectives

To evaluate the effects of sulpiride for schizophrenia and other similar serious mental illnesses in comparison with placebo.

Search methods

We searched the Cochrane Schizophrenia Group Trials Register (September 2008) and references of all identified studies for further trial citations. We contacted pharmaceutical companies and authors of trials for additional information. We updated this search 7th November 2012.

Selection criteria

We included all randomised controlled trials (RCTs) comparing sulpiride with placebo for people with schizophrenia and other types of schizophrenia-like psychoses. The primary outcome of interest was clinically significant response in global state.

Data collection and analysis

We independently inspected citations and abstracts, ordered papers, re-inspected and quality-assessed these. IMO and JW extracted data. We analysed dichotomous data using a random-effects risk ratio (RR) and estimated the 95% confidence interval (CI) around this. Where continuous data were included, we analysed these data using random-effects mean difference (MD) with a 95% CI.

Main results

No new trials were included from the 2012 search. The review still includes two trials of short duration comparing sulpiride with placebo (total n = 113). No study reported our primary outcome of interest of 'global state: clinically significant response', nor our secondary outcomes of interest of 'quality of life', 'severe adverse effects', and 'safety assessments'. As regards mental state, there were no clear differences between groups for either positive or negative symptoms; measured positive symptoms using the Manchester scale were skewed and therefore not included in meta-analysis (n = 18, 1 RCT, *very low quality evidence*). Measured negative symptoms using the Manchester scale also demonstrated no clear difference (n = 18, 1 RCT, MD -3.0 CI -1.66 to 1.06, *very low quality evidence*). Few

people left these studies by three months (n = 113, 2 RCTs, RR 1.00 CI 0.25 to 4.00). One subscore finding demonstrated a significant improvement in social behaviour using the Current Behaviour Schedule (CBS) when receiving placebo (n = 18, 1 RCT, MD -2.90 CI -5.60 to -0.20). There were no data for many important outcomes such as global outcomes, service use or adverse effects.

Authors' conclusions

Sulpiride may be an effective antipsychotic drug but evidence of its superiority over placebo from randomised trials is very limited. Practice will have to use evidence from sources other than trials until better evidence is generated.

PLAIN LANGUAGE SUMMARY

Sulpiride versus placebo for schizophrenia

Schizophrenia is a severe mental illness with 'positive symptoms' such as hallucinations (hearing voices and seeing things) and delusions (having strange beliefs). People with schizophrenia also suffer from disorganisation and 'negative symptoms' (such as tiredness, apathy and loss of emotion). People with schizophrenia may find it hard to socialise and find employment. Schizophrenia is considered one of the most burdensome illnesses in the world. For some people it can be a lifelong condition.

People with schizophrenia are usually treated with antipsychotic drugs. More recently developed antipsychotic drugs (second generation or atypical) are more expensive and thought to have fewer side effects than the older ones (first generation or typical). These side effects can include distressing movement disorders; as a results, many people find the older drugs difficult to tolerate and prefer the second generation drugs. However, in many developing countries the cost of medication can be a major factor in prescribing, so the first generation drugs are the most widely used.

Sulpiride is a first generation antipsychotic drug, but is said to cause fewer side effects. It has been suggested that sulpiride may be more effective than other older drugs (such as chlorpromazine and haloperidol) for treating the negative symptoms and social withdrawal of schizophrenia.

The aim of this review was to evaluate the effects of sulpiride for schizophrenia compared to placebo ('dummy' treatment). Two short-term (12 weeks) studies with a total of 113 people are included. Information was limited and poorly reported. The inclusion of two small studies with small sample sizes meant that resulting data were not overly robust or meaningful. Overall no clear difference was noted between those receiving sulpiride and those receiving placebo for mental state or for leaving the study early. There was no information on other important outcomes, including: general functioning, service use, hospital admission, employment, family burden, satisfaction with care and side effects. The use of sulpiride seems to be based on clinical experience rather than strong evidence. Its widespread use in developing countries might have more to do with its lower cost than its effectiveness. Longer, well-planned, better conducted and reported randomised control trials would contribute to our knowledge about the effectiveness and potential side effects of this drug.

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

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

SULPIRIDE compared to PLACEBO for schizophrenia

Patient or population: people with schizophrenia
Settings: inpatient (UK hospital)
Intervention: SULPIRIDE
Comparison: 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				
	PLACEBO	SULPIRIDE				
Global state: clinically significant response in global state - by long term - not measured	See comment	See comment	Not estimable	-	See comment	No study measured this outcome.
Mental state: average score for positive symptoms (skewed) - by short term Manchester Scale, positive subset endpoint Follow-up: 12 weeks	See comment	See comment	Not estimable	18 (1 study)	⊕◯◯◯ **very low**[1,2]	Data are skewed and are presented in an additional table (no meta-analysis)
Mental state: average score for negative symptoms - by short term Manchester Scale, negative subset endpoint. Scale from: 0 to 20. Follow-up: 12 weeks	The mean mental state: average score for negative symptoms by medium term in the control groups was **4.1 points**[3]	The mean mental state: average score for negative symptoms by medium term in the intervention groups was **0.3 lower** (-1.66 to 1.06)	Not estimable	18 (1 study)	⊕◯◯◯ **very low**[1,4]	

Mental state: average score for depressive and anxious symptoms - by medium term - not measured	See comment	See comment	Not estimable	-	See comment	No study measured this outcome.
Quality of life: average score - by long term - not measured	See comment	See comment	Not estimable	-	See comment	No study measured this outcome.
Severe adverse effects - medium term - not reported	See comment	See comment	Not estimable	-	See comment	No study reported this outcome.
Safety assessments - medium term - not measured	See comment	See comment	Not estimable	-	See comment	No study measured this outcome.

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

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 Risk of bias: 'serious' - no description of randomisation or blinding techniques.
2 Imprecision: 'very serious' - data are considerably skewed and are presented in a separate table (no forest plot).
3 Assumed risk: presented as the mean score of the control group on the Manchester scale (higher scores indicating greater negative symptoms).
4 Imprecision: 'very serious' - considerably small sample size (n = 18), and 95% confidence intervals for best estimate of effect include both 'no effect' and appreciable benefit/harm.

BACKGROUND

Description of the condition

Schizophrenia is a severe mental illness characterised by a mixture of hallucinations, delusions, disorganisation and negative symptoms. These characteristics are associated with noticeable social or occupational dysfunction or both, and its prevalence in adults is reported to be between 0.5% and 1.5% (APA 1994). Due to its chronic features, one-third of people with schizophrenia suffer from those symptoms continuously for more than ten years (Mason 1996). Schizophrenia is regarded as one of the most burdensome diseases in the world (Rossler 2005).

Description of the intervention

Sulpiride is a relatively old antipsychotic drug that was developed in France in the mid-1960s and has been used for the treatment of schizophrenia since that time in some countries in Europe and Asia (Carrere 1968; Nishiura 1976). In the 1980s a new generation of antipsychotic drugs became available which, in general, had less propensity to cause movement disorders (specifically catalepsy in rats (Kerwin 1994)). These new drugs were collectively classed as 'atypical' compared with what had gone before. Some older drugs, including sulpiride, can also be classed in this way as 'atypical' (Myamoto 2003). It has been suggested that sulpiride may be more effective than drugs such as chlorpromazine and haloperidol, for treating negative symptoms of schizophrenia (poverty of speech, lack of motivation, apathy, emotional impoverishment) (Gerlach 1991; Azorin 1992), and that this effect is best seen when low doses are used (Petit 1987; Mauri 1996). High-dose sulpiride is said to be effective for both negative and positive symptoms (delusions, hallucinations). This higher level of dosing may be safe for elderly people where the cardiovascular effects of other antipsychotics can be problematic (Mauri 1994; Mauri 1996).

How the intervention might work

Sulpiride, a type of benzamide antipsychotic medication, blocks D2 receptors selectively, and does not block D1, adrenergic, cholinergic, histaminergic, or serotonergic receptors to a noticeable extent. Its oral bioavailability is only around 35%. It produces no active metabolites. The drug is excreted in the urine (Caley 1995). Sulpiride can be regarded as an atypical antipsychotic because of these D2-specific properties and a reputed lower tendency for induction of movement disorders such as parkinsonism and tardive dyskinesia (Azorin 1992). Chemically, it is a substituted benzamide derivative related to metoclopramide and trimethobenzamide. It has had other uses including treatment of peptic ulcer, vomiting and vertigo (Bratfos 1979; Edwards 1980).
For sulpiride's structure please see Figure 1 and Figure 2.

Figure 1. Sulpiride - chemical structure

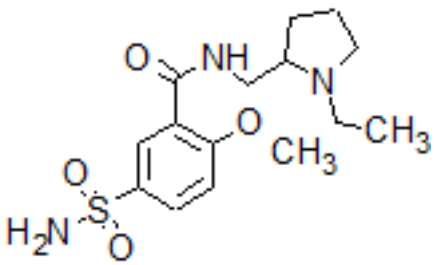
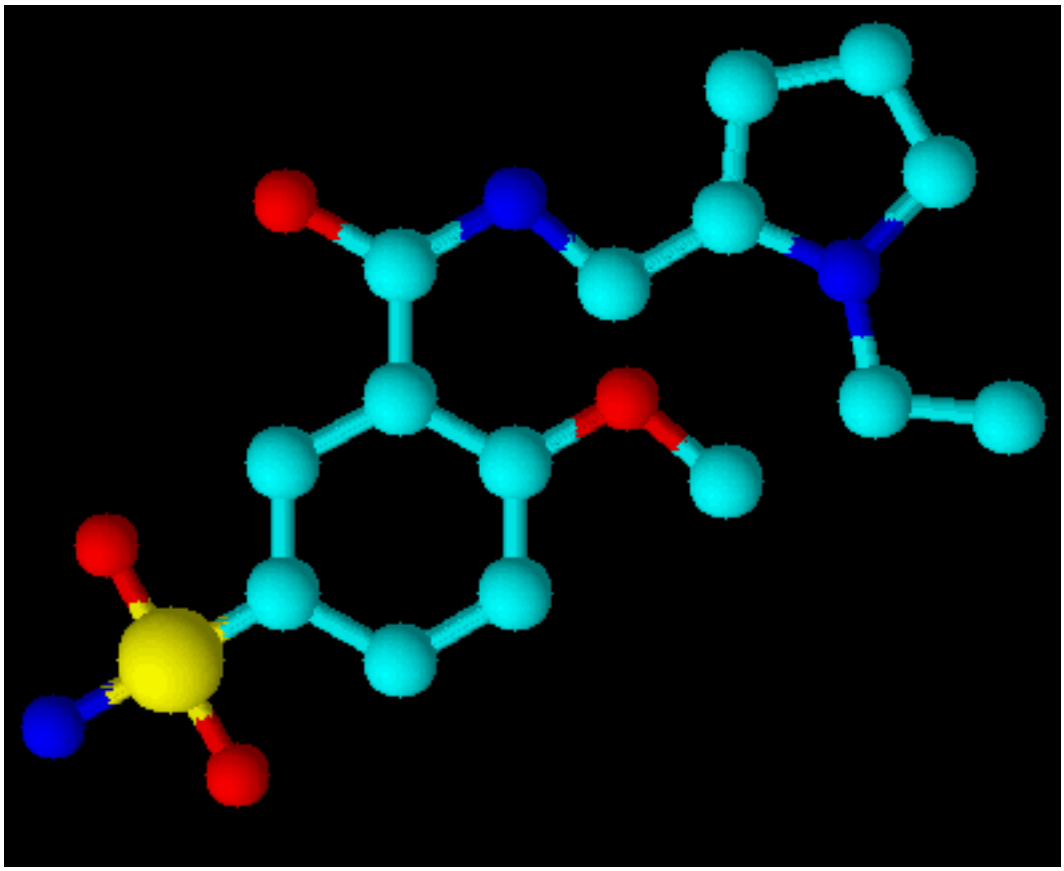


Figure 2. Sulpiride - graphic



Why it is important to do this review

It is reported that in developing countries, basic evidence-based care for people with mental illness is scarce, and many psychiatric patients are suffering from the increased cost of care (Patel 2007). Based on cost-effectiveness analysis, older antipsychotics are more cost-effective than newer drugs in developing countries (Hyman 2006; Chisholm 2008). There are systematic reviews on sulpiride, but they are outdated and suffer from several methodological weaknesses (Caley 1995).
This is one of a series of reviews relevant to the use of sulpiride.

Comparison	Reference	Comment
Sulpiride vs placebo	Omori 2009a	This review represents an update of the 2009 version.
Sulpiride doses	Rezk 2012	Protocol.
Sulpiride vs other antipsychotic drugs	Omori 2009b	Protocol.

(*Continued*)

Sulpiride augmentation of other drugs	Wang 2010	Full review.
Old review		
Sulpiride for schizophrenia*	Soares 1999	This large overview will continue to be published until all comparisons are fully covered by subsidiary reviews

*This out-of-date broad-ranging review will be removed once all comparisons are covered by subsidiary reviews of a size that is easier to maintain.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised control trials (RCTs). We would have included quasi-randomised trials had we identified them in the trial search, such as those where allocation is undertaken based on time of admission to the hospital. Randomised cross-over studies were eligible but only data up to the point of first cross-over, because of the instability of the problem behaviours and the likely carry-over effects of all treatments. However, no cross-over studies were identified.

Types of participants

People with the diagnosis of schizophrenia and other types of schizophrenia-like psychoses (schizophreniform disorder, schizoaffective disorder and acute psychotic disorder), however diagnosed, irrespective of age, sex or severity of illness. Those with 'serious/chronic mental illness' or 'psychotic illness' were also included. If possible, people with psychotic symptoms due to dementia, general medical conditions, depression and primarily problems associated with substance misuse were excluded.

Types of interventions

1. Sulpiride

Any dose and mode or pattern of administration. If a high/low dichotomy was not provided within the trial, high dose was defined as > 800 mg/day and low dose as any lesser dose.

2. Placebo

Active or inactive, or no treatment.

Types of outcome measures

As schizophrenia is often a lifelong illness, and sulpiride is used as an ongoing treatment, outcomes were grouped according to time periods: short-term (less than three months), medium-term (3 to 12 months) and long-term (more than one year).

Primary outcomes

1. Global outcomes

1.1 Clinically significant response in global state, as defined by each of the studies - long-term.

Secondary outcomes

1. Death

1.1 Suicide or natural causes

2. Service utilisation outcomes

2.1 Hospital admission
2.2 Days in hospital

3. Global outcomes

3.1 Clinically significant response in global state, as defined by each of the studies - short/medium-term
3.2 Average score/change in global state

4. Mental state

4.1 Clinically significant response in mental state, as defined by each of the studies
4.2 Average score/change in mental state
4.3 Clinically significant response on negative symptoms, as defined by each of the studies
4.4 Average score/change in negative symptoms
4.5 Relapse as defined in the study

5. Behaviour

5.1 Clinically significant response in behaviour, as defined by each of the studies
5.2 Average score/change in behaviour

6. Leaving the study early

6.1 Any reason
6.2 Due to adverse effects/events
6.3 Loss to follow-up
6.4 Treatment inefficacy

7. Adverse effect

7.1 Extrapyramidal side effects

7.1.1 Incidence of use of antiparkinson drugs

7.1.2 Clinically significant extrapyramidal side effects, as defined by each of the studies

7.1.3 Average score/change in extrapyramidal side effects

7.2 Other adverse effects, general and specific

7.2.1 Cardiac effects

7.2.2 Anticholinergic effects

7.2.3 Antihystamine effects

7.2.4 Prolactin-related symptoms

8. Social functioning

8.1 Clinically significant response in social functioning, as defined by each of the studies
8.2 Average score/change in social functioning

9. Economic outcomes

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

10.1 Significant change in quality of life/satisfaction, as defined by each of the studies
10.2 Average score/change in quality of life/satisfaction
10.3 Employment status

11. Cognitive functioning

12. Safety assessments

12.1 As defined in each study

13. Summary of findings table

We used the GRADE approach to interpret findings (Schünemann 2011) and used the GRADEPRO profiler to import data from Review Manager 5 (Review Manager) to create a '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 participant care and decision-making. We selected the following main outcomes for inclusion in the 'Summary of findings' table.

- Global state - clinically significant response in global state (as defined in each study) - by long term.
- Mental state - average score for positive symptoms - by medium term.
- Mental state - average score for negative symptoms - by medium term.
- Mental state - average score for depressive and anxious symptoms - by medium term.
- Quality of life - average score - by long term.
- Severe adverse events (as defined in each study) - by medium term.

- Safety assessments (as defined in each study) - by medium term

Search methods for identification of studies

Electronic searches

1. For details of previous electronic search - see Appendix 2
2. Cochrane Schizophrenia Group Trials Register
The Trials Search Co-ordinator searched the Cochrane Schizophrenia Group's Trials Register (7th November 2012) using the phrase
[(*ability * or *championyl* or *coolspan* or *col-sulpir* or *digton* or *dixibon* or *dobren* or *do?matil* or *drominetas* or *eglonyl* or *equilid* or *eusulpid* or *guastil* or *isnamid* or *kapirid* or *lavodina* or *leboprid* or *lusedan* or *miradol* or *mirbanil* or *misulvan* or *neuromyfar* or *normum* or *omperan* or *psicocen* or *quiridil* or *sato * or *sernevin* or *sicofrenol* or *sulp?ride* or *sulpisedan* or *suprium* or *sursumid* or *tepavil* or *tonofit* or *ulpir* or *vipral*) AND (*placebo*) in title, abstract and index fields in REFERENCE) OR (sulp?rid* AND *placebo* in interventions field in STUDY)]
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

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

Data collection and analysis

For previous methods and data analysis see Appendix 3.

Selection of studies

Review authors JW and SS independently inspected all study citations identified by the searches, and obtained full reports of the studies of agreed relevance. Where disputes arose, we acquired the full report for more detailed scrutiny. These articles were then inspected independently by two review authors to assess their relevance to this review. Again, where disagreement occurred we attempted to resolve this through discussion; if doubt still remained we added these trials to the list of those awaiting assessment pending acquisition of further information.

Data extraction and management

1. Extraction

For this update, JW and SS extracted data from included studies. We extracted data presented only in graphs and figures whenever possible. When further information was necessary, we contacted authors of studies in order to obtain missing data or for clarification.

2. Management

2.1 Forms

We extracted data onto standard, simple forms.

2.2 Scale-derived data

We included continuous data from rating scales only if:
a. the psychometric properties of the measuring instrument had been described in a peer-reviewed journal (Marshall 2000); and
b. the measuring instrument had not been written or modified by one of the trialists for that particular trial.
Ideally the measuring instrument should either be i. a self report or ii. completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly; we have noted whether or not this is the case in Description of studies.

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 to primarily 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 (MDs) 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:

- standard deviations (SDs) and means are reported in the paper or obtainable from the authors;
- when a scale starts from the finite number zero, the standard deviation, when multiplied by two, is less than the

mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution (Altman 1996));

- if a scale starts from a positive value (such as Positive and Negative Syndrome Scale (PANSS) which can have values from 30 to 210), we would have modified the calculation described above to take the scale starting point into account. In these cases skew is present if 2SD > (S-S min), where S is the mean score and S min is the minimum score.

Endpoint scores on scales often have a finite start and end point and these rules can be applied. We would have enter 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 means if the sample size is large; we would have entered such endpoint data into syntheses had we found them.

When continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not. We would have entered skewed change data into analyses regardless of the size of the study. However, no skewed data were identified throughout the included studies.

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). However, no such data were identified.

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 2005a; Leucht 2005b). If data based on these thresholds were not available, we would have used the primary cut-off presented by the original authors. However, no such data were available.

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 sulpiride. Where keeping to this made it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'not improved') we reported data where the left of the line indicates an unfavourable outcome. This was noted in the relevant graphs.

Assessment of risk of bias in included studies

For this update, JW and SS worked independently using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to assess trial quality. This set of criteria is based on evidence of associations between overestimation of effect and high risk of bias in the report, including sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

Where inadequate details of randomisation and other characteristics of trials were provided, we contacted authors of the studies in order to obtain additional information.

We have noted the level of risk of bias both in 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 the RR is more intuitive (Boissel 1999) than odds ratios and that odds ratios tend to be interpreted as RRs by clinicians (Deeks 2000). The number needed to treat for an additional beneficial or harmful outcome (NNTB or NNTHH) statistic with its confidence interval is intuitively attractive to clinicians but is problematic both in its accurate calculation in meta-analyses and in interpretation (Hutton 2009). For binary data presented in the 'Summary of findings' table/s, where possible, we calculated illustrative comparative risks.

2. Continuous data

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

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 pose problems. Authors often fail to account for intra-class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992), whereby P values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997; Gulliford 1999).

Where clustering is not accounted for in primary studies, we would have presented data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. In subsequent versions of this review we will seek to contact first authors of studies to obtain intra-class correlation coefficients (ICCs) for their clustered data and to adjust for this by using accepted methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we would have presented these data as if from a non-cluster-randomised study, but adjusted for the clustering effect. However, no such studies were identified.

Our statistical support advises that the binary data presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the ICC [Design effect = 1 + (m - 1) * ICC] (Donner 2002). If the ICC is not reported it was assumed to be 0.1 (Ukoumunne 1999). If we had found such studies, they would have been appropriately analysed taking into account ICCs and relevant data documented in the report. Synthesis with other studies would then have been possible using the generic inverse variance technique.

2. Cross-over trials

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

3. Studies with multiple treatment groups

Had we identified studies involving more than two treatment arms, if relevant, we would have presented the additional treatment arms in comparisons. If data were binary we would have added these and combined them within the two-by-two table. If data were continuous we would have combined data following the formula in section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systemic reviews of Interventions (*Higgins 2011) Had we identified such studies, where the additional treatment arms were not relevant, we would not have reproduced these data.

Dealing with missing data

1. Overall loss of credibility

To some degree, loss of follow-up data must compromise study credibility (Xia 2009). We chose that, for any particular outcome, should more than 40% of data be unaccounted for by eight weeks, we would not include these data or use them within analyses. If, however, more than 40% of those in one arm of a study were lost, but the total loss was less than 40%, we would have marked such data with (*) to indicate that such a result may well be prone to bias. However, no such studies were identified.

2. Binary

In the case where attrition for a binary outcome is between 0% and 40% and where these data are not clearly described, we present data on a 'once-randomised-always-analyse' basis (an intention-to-treat analysis). Those leaving the study early are 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 stay in the study in that particular arm of the trial were used for those who did not. We undertook a sensitivity analysis testing how prone the primary outcomes are to change when data only from people who complete the study to that point are 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 is between 0% and 40%, and data only from people who complete the study to that point are reported, we would have presented and used these data.

3.2 Standard deviations

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

would be to exclude a given study's outcome and thus to lose information. In this review, however, we made no imputations of standard deviations.

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 would have included 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 test P value. The I^2 provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 depends on i. magnitude and direction of effects and ii. strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or a confidence interval for I^2). An I^2 estimate greater than or equal to around 50% accompanied by a statistically significant Chi^2 statistic was interpreted as evidence of substantial levels of heterogeneity *Cochrane Handbook for Systemic reviews of Interventions* (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 for Systemic reviews of Interventions (*Higgins 2011). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We chose not to use funnel plots for outcomes where there were 10 or fewer studies, or where all studies were of similar sizes, so no funnel plots have been included in this review.

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 are often the most biased ones. Depending on the direction of effect, these studies can either inflate or deflate the effect size. We chose the random-effects model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses - only primary outcomes

1.1 Clinical state, stage or problem

We proposed to undertake this review and provide an overview of the effects of sulpiride 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 expected that several subgroup analyses could be undertaken within this review. The following hypotheses were tested: when compared with placebo, for the primary outcomes of interest (see: Criteria for considering studies for this review) sulpiride is differentially effective for:

- Men and women
- People who are under 18 years of age (adolescents), between 18 and 64 (adults), or over 65 years of age (the elderly).

- People who became ill recently (i.e. acute episode approximately less than one month's duration) as opposed to people who have been ill for longer.
- People who are given low doses (1 - 800 mg/day) and those given high doses (over 800 mg/day).
- People who have schizophrenia diagnosed according to any operational criterion (i.e. a pre-stated checklist of symptoms, problems, time periods, exclusions) as opposed to those who have entered the trial with loosely-defined illness.
- People treated earlier (pre-1990) and people treated in recent years (1990 to 2012).
- Duration of study: short-term (less than three months), medium-term (3 to 12 months) and long-term (more than one year).

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 studies to see if homogeneity was restored. For this review we decided that, should this occur with data contributing to the 'Summary finding' of no more than around 10% of the total weighting, we would present data. If not, then we did not pool data but discussed the issues. We know of no supporting research for this 10% cut-off, but we use prediction intervals as an alternative to this unsatisfactory state.

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 anticipate undertaking 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 as to imply randomisation. For the primary outcomes we included these studies in the analyses, and if there was no substantive difference when the implied randomised studies were added to those with an unambiguous 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 would have compared the findings of the primary outcomes when we applied our assumption/s and when we used data only from people who completed the study to that point. If there was a substantive difference, we would have reported results and discussed them but continued to employ our assumption. However, no such data were identified. Where assumptions had to be made regarding data for missing standard deviations (see 'Dealing with missing data'), we compared the findings of the primary outcomes when we applied our assumption/s and when we used data only from people who completed the study to that point. A sensitivity analysis was undertaken testing how prone results were to change when completer-only data are compared to the imputed data using the above assumption. If there was a substantive 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 substantively 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

We also planned to undertake a sensitivity analysis to assess the effects of including data from trials where we used imputed values for the ICC in calculating the design effect in cluster-randomised trials, however no such studies were identified.

If we noted substantive differences in the direction or precision of effect estimates in any of the sensitivity analyses listed above, we did not pool data from the trials in question with the other trials contributing to the outcome, but presented them separately.

5. Fixed-effect and random-effects

We undertook a sensitivity analysis to assess the effects of synthesising data using a fixed-effect model.

RESULTS

Description of studies

For detailed descriptions of studies please see: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

1. Overall

For the first version of this review, we inspected 251 electronic reports. One hundred and thirty-six of them were excluded on the basis of their abstracts. We selected 115 references considered to be relevant for our review and obtained full papers for assessment. Of these, one trial remains unfound and 14 references were retrieved for more detailed evaluation. Of these trials, 12 were excluded. Finally, we included two randomised trials meeting the inclusion criteria. The results of the 2012 update search yielded eight new reports, from which no new relevant randomised controlled trials were identified; all of the studies were excluded with reasons, amounting to 20 excluded studies overall (see Figure 3 and Figure 4).

Figure 3. Study flow diagram: original 2008 search

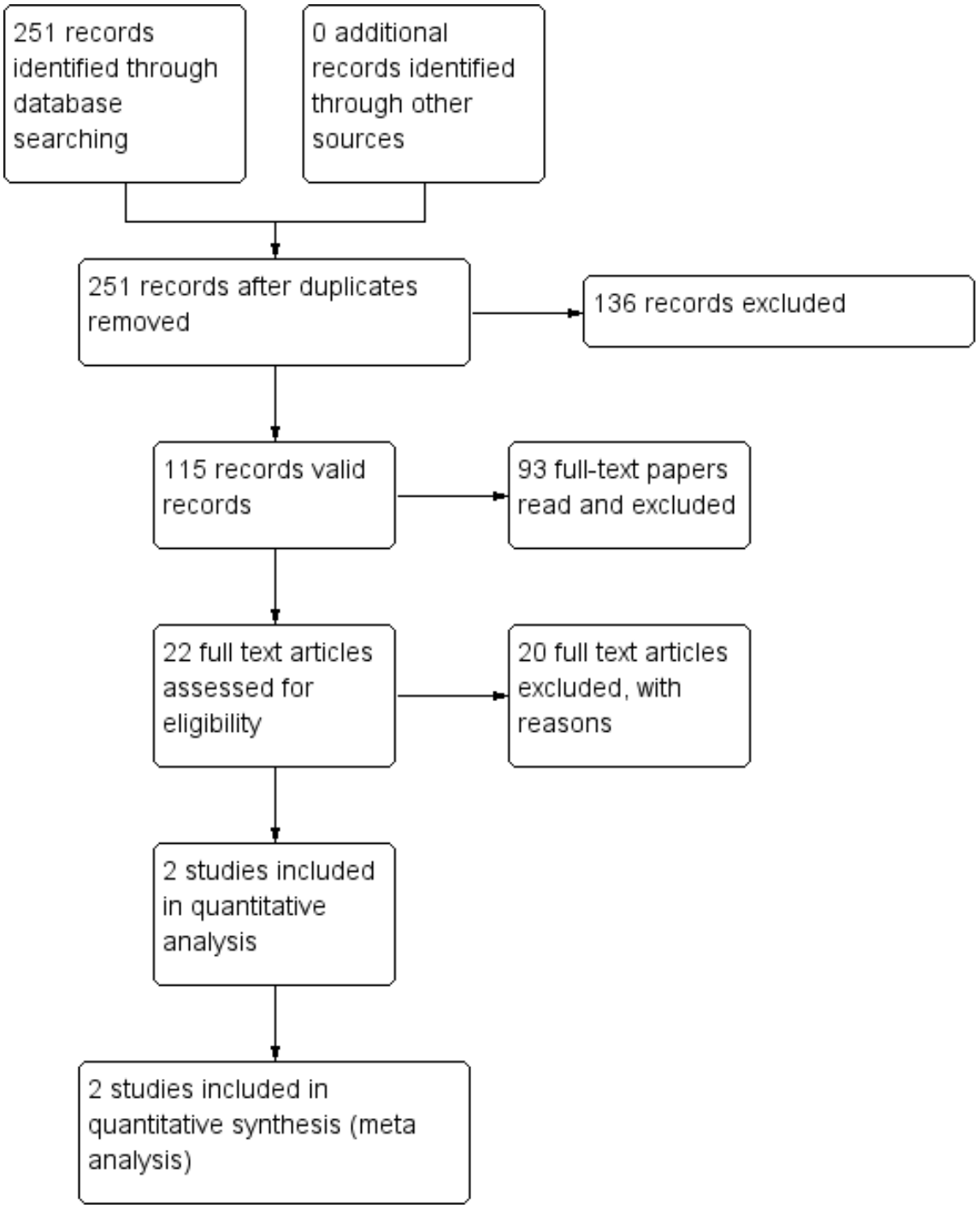
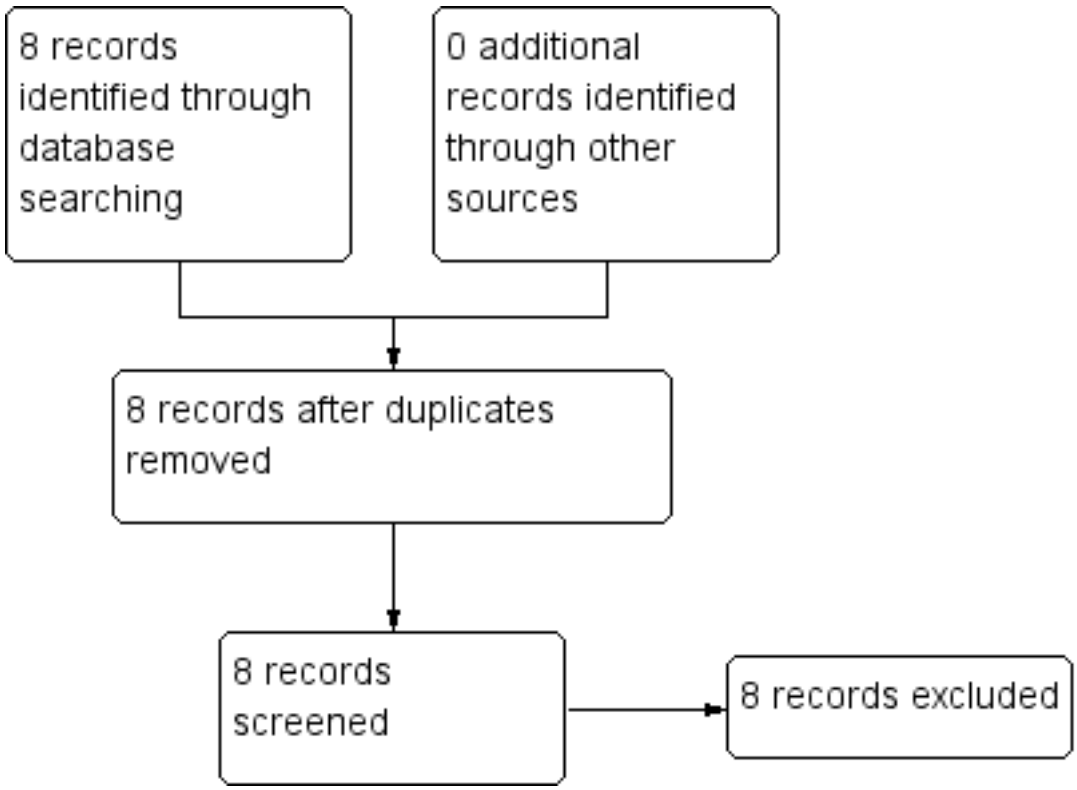


Figure 4. Study flow diagram: 2012 update search



Included studies

We could include two studies (Blanco 1972 and Soni 1990) with a total of 113 participants.

1. Length of studies

Both studies (Blanco 1972; Soni 1990) were of shorter than three months duration (the category 'short-term' as defined above).

2. Setting

Both studies were hospital-based, one in Spain and the other in the United Kingdom (UK).

3. Participants

Participants in both studies were "adult patients" who suffered from chronic schizophrenia. The described diagnostic criteria were WHO-based for Blanco 1972 and DSM-III-based for Soni 1990.

4. Study size

The number of participants was 89 (Blanco 1972) and 24 (Soni 1990).

5. Interventions

5.1 Sulpiride

In Blanco 1972 the dosing schedule of sulpiride was flexible, 800 to 1400 mg/day ("high dose"). Soni 1990 used a fixed schedule, 400 mg/day ("low dose").

5.2 Placebo

Both studies used an inactive placebo.

6. Outcomes

6.1 General remarks

We were unable to extract data on several important outcomes from Blanco 1972 and Soni 1990 because of poor data reporting, but these hospital-based small short studies were nevertheless trying to record outcomes that were meaningful to clinicians as well as to researchers.

6.2 Outcome scales

6.2.1 Mental state

6.2.1.1 Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1984):
This rating instrument is commonly used in studies of schizophrenia. A six-point (0 to 5) scoring system can be used for each global rating of alogia, affective blunting, avolition-apathy, anhedonia-asociality and attention impairment. A low score indicates low levels of psychotic symptoms.
6.2.1.2 Manchester Scale (Krawiecka 1977):
This mental-state scale (also known as the Krawiecka Scale) encompasses both positive and negative symptoms of schizophrenia and consists of eight items covering the positive and negative items of psychosis, rated on a five-point (0 to 4) scoring system, assessing the general psychopathology of schizophrenia. A higher score indicates more severe symptoms. It is used to evaluate the mental state and behaviour of chronically psychotic people.

6.2.2 Behaviour

6.2.2.1 Current Behaviour Schedule (CBS) (Owens 1980):
This observation scale evaluates mainly psychiatric symptoms, and has 24 items to be rated on the basis of descriptors from 0 to 2 or 0 to 4, depending on the item weight. In all instances low scores are pathological. Subscores are: 1) social behaviour, 2) activity, 3) abnormal behaviour, 4) antisocial acts.

6.2.3 Adverse effects

6.2.3.1 Abnormal Involuntary Movement Side Effects Scale (Guy 1976):
This is a 12-item scale designed to record the occurrence of dyskinetic movements. Ten items of this scale have been used to assess tardive dyskinesia, a long-term drug-induced movement disorder. A five-point scoring system, from 0 (none) to 4 (severe), has been used to rate each of the ten items. Using this scale in short-term treatment may be helpful in assessing some short-term abnormal movement disorders. A low score indicates low levels of dyskinetic movements.

6.3 Missing outcomes

Neither of the included studies attempted to quantify death, service use, global outcomes, satisfaction, social function or quality of life and cognitive function. There was no evidence of any direct economic evaluation of sulpiride.

Excluded studies

From the original search, we immediately excluded 136 citations because they were clearly not relevant to this review. However, we had to acquire 15 studies in full text in order to clarify whether they were relevant. Benoit 1969 was not randomised. Ten other studies were eventually excluded because they tested adjunctive use of sulpiride. In these the sulpiride was added to another antipsychotic drug and compared with that other antipsychotic medication alone (Wang 1994; Liu 1996; Yao 1999; Zhu 1999; Yang 2000; Gong 2001; Zhao 2003; Kotler 2004; Wu 2005; Wu 2006). These trials are addressing an important question but not one relevant for this review. Shiloh 1997 also used sulpiride augmentation, but in this case compared with placebo augmentation, for people with schizophrenia already taking clozapine. The update search yielded eight new studies, which were each excluded due to reasons including non-randomisation (Casey 1979); augmentation with other medication (Schwartz 1990; Hong 1995; Wuliji 2003; Ma 2009); use of healthy volunteers (Takeshita 1994; Sahakian 2000) or the inclusion of participants with disorders other than schizophrenia (Quinn 1984).

Awaiting assessment

None.

Ongoing studies

We know of no ongoing studies.

Risk of bias in included studies

Judgement of risks are illustrated in Figure 5 and Figure 6.

Figure 5. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

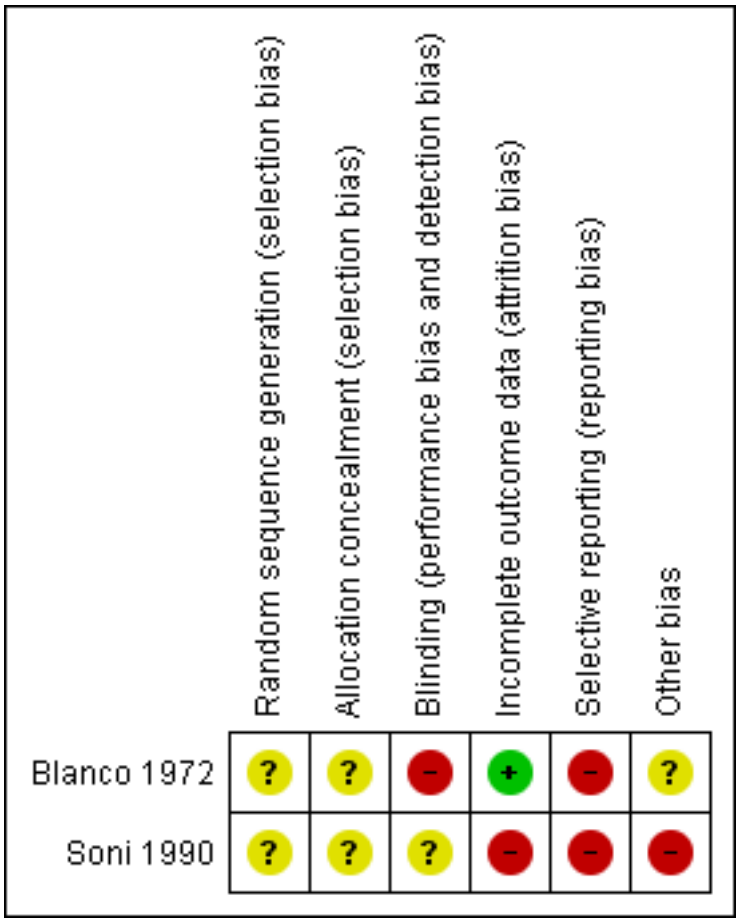
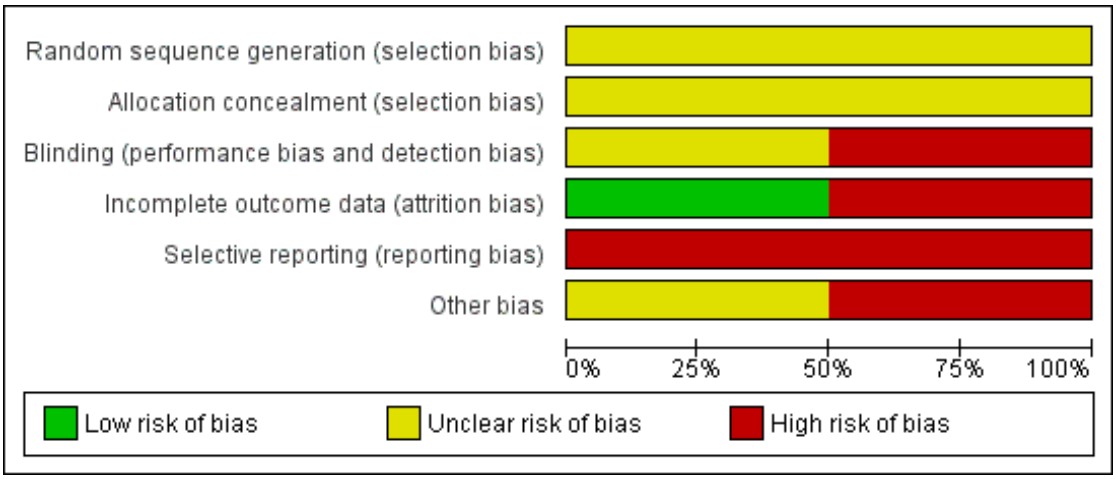


Figure 6. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

In both studies the random sequence generation process and the methods of concealment were not described.

Blinding

In Soni 1990, it was indicated that attempts at double-blinding had been made by using 'matching placebo' but there were no further details. In Blanco 1972, no blinding was carried out as the authors felt blinding would be impractical in their setting.

Incomplete outcome data

In Blanco 1972, there were no missing outcome data. Soni 1990 was explicit about why 25% (confidence interval (CI) 7.7 to 42.3, 6/24) of people left, due to adverse effects or deterioration of psychiatric symptoms. We have reported these data in the relevant section of the outcomes tables. However, the study authors included only those remaining for continuous outcomes. It is possible that estimates of effects are therefore inflated.

Selective reporting

Soni 1990 reported all continuous data at endpoint with standard deviations, but ratings of adverse effects were incomplete and these could not be entered in a meta-analysis. In Blanco 1972, all continuous data are reported without measures of variance, so none could be used within the analyses.

Other potential sources of bias

Both trials had affiliation with the interested drug company. Blanco 1972 stated that the company had "helped" and Soni 1990 had one author who was an employee in the company.

Effects of interventions

See: **Summary of findings for the main comparison** SULPIRIDE compared to PLACEBO for schizophrenia

COMPARISON 1. SULPIRIDE versus PLACEBO

1. Mental state

1.1 Average score for positive symptoms

Soni 1990 reported skewed data on the Manchester scale. There was no clear difference between groups (n = 18, mean score 2.5 (SD 1.4) in sulpiride group, 2.5 (2.3) in placebo group; Analysis 1.1).

1.2 Average score for negative symptoms

Soni 1990 measured negative symptoms in two ways. There were no clear differences between groups for the measures on the Manchester scale (n = 18, mean difference (MD) -0.30, CI -1.66 to 1.06; Analysis 1.2) or on the SANS (n = 18, MD 2.90, CI -0.14 to 5.94; Analysis 1.3).

2. Behaviour

2.1 Social behaviour

Use of sulpiride showed no clear effect on "abnormal behaviour" (n = 18, MD -0.50, CI -2.21 to 1.21) . For the outcome of improving social behaviour (n = 18, MD -2.90, CI -5.60 to -0.20; Analysis 1.4), there was a marginally statistically significant result in favour of placebo.

3. Adverse effects

No numerical data were reported.

4. Leaving the study early

Soni 1990 reported moderate rates of attrition from each group by 12 weeks (25%) with no difference between sulpiride and placebo. Combined data from both studies shows no difference at three months (n = 113, two RCTs, RR 1.00 CI 0.25 to 4.00; Analysis 1.5).

SENSITIVITY ANALYSIS

1. Implication of randomisation

Both studies described use of 'randomisation', but with neither study providing details of methods. Excluding these studies would leave no data to compare, therefore it was not possible to conduct this sensitivity analysis.

2. Assumptions for lost binary data

No data were assumed for people lost to follow-up.

3. Risk of bias

Both studies were rated as being at a high risk of bias across one or more of the domains of randomisation (implied as randomised but with no further details available): sequence generation, allocation concealment, blinding and outcome reporting. Removing both of these studies from analysis would leave us with no data to compare, therefore a sensitivity analysis could not be performed.

4. Imputed values

No values were imputed in data or analyses.

5. Fixed-effect and random-effects

There were no differences in the results when using a random-effects or a fixed-effect model.

DISCUSSION

Trial search

Electronic searching for the original 2008 review produced 251 references, 15 of which were selected for examination in full text. For this 2013 update, eight records were identified in the trial search, however all were subsequently excluded. Although sulpiride has been prescribed for decades by psychiatrists, only two studies met the eligibility criteria for this review. It is possible that (a) we either failed to identify relevant studies but most should have come to light after so many years of use of this drug, or (b) years of established practice may well have mitigated against conducting RCTs using sulpiride versus placebo.

Summary of main results

We found only two small short trials. Blanco 1972 reported no usable clinical outcomes other than leaving the study early.

1. Mental state

The results are all taken from Soni 1990 (n = 24) and there is no indication of an advantage for sulpiride over placebo for positive or negative symptoms. These data were only for the 18 people completing the study. Both skewed and non-skewed data were overall found to be difficult to interpret.

2. Behaviour

2.1 Social behaviour

The Current Behaviour Schedule scores did not show value for use of sulpiride for "abnormal behaviour" subscores but did show some favour for improving social behaviour. We are unclear as to the clinical meaning of a mean difference decline of 2.90 on the Current Behaviour Schedule. In addition, this could be a chance finding and one upon which it would be imprudent to put too much weight.

3. Missing data

There were no data on adverse effects at all. We had hoped to find some data for the global outcome of clinically significant response in global state, but there were none. There were also no data for service utilisation outcomes, other global outcomes, and few on mental state, behaviour and social functioning. There were none on economic outcomes, quality of life or satisfaction with care.

4. Leaving the study early

The only meta-analysis in this review is for the outcome of leaving the study early, and sulpiride seems as acceptable as placebo for this group. Only 6% of people left these studies. This is substantially less than would be expected in many recent studies and may be a function of good study design, although both studies were in the relatively well-defined confines of hospital life.

Overall completeness and applicability of evidence

Participants in both studies were chronic hospitalised patients. Those included in Soni 1990 were maintenance-drug treatment-free over one year because of the policy of prescribing maintenance neuroleptics only for those who clearly required them. Both trials were short-term. Schizophrenia is a lifelong disorder and medications are likely to be used for long periods. These characteristics of the included trials limit the applicability of the findings.

Quality of the evidence

See Figure 5. We included two trials (113 participants). The methodological quality of these included studies was judged to be poor, although it is problematic to judge articles from some time ago by standards of today (Begg 1996; CONSORT). Nevertheless, the reporting in these studies is not good. Such reporting has been associated with an overestimation of the effect measure (Schulz 1995). This should be borne in mind when interpreting the results.

Potential biases in the review process

We attempted to avoid the possibility of publication bias, which should be considered as a potential threat to validity, by undertaking extensive and sensitive searching. However, some publication bias could remain. Selective publication of studies sponsored by pharmaceutical companies is a problematic issue (Melander 2003) and this could lead to an overestimation of effect sizes. It is highly likely that some studies not showing significant results were withheld by pharmaceutical companies. This review found few studies and they are not convincing that sulpiride is of value. This does not mean that sulpiride is not of value, but that these studies do not show this to be so. If other studies do exist they could be expected to drag the finding towards the null. As the finding is essentially at the null already, it would seem unlikely that we are missing important studies.

Agreements and disagreements with other studies or reviews

A previous version of this systematic review (Soares 1999) was divided into subgroups addressing the several comparisons possible using sulpiride. Future reviews will address each of these comparisons. However, for the sulpiride versus placebo comparison within Soares 1999 this version largely agrees with the older review but improves the presentation of the limited data. One study in the original comparison has now been excluded (Shiloh 1997), because in this trial sulpiride was used to supplement treatment for people taking clozapine, and reported a global outcome in favour of sulpiride.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia

For people with schizophrenia, this review would suggest that there is little trial-based evidence for the absolute effectiveness (versus placebo) of sulpiride for treating schizophrenia. Other reviews will address the effectiveness versus other treatments (Omori 2009b). This would seem disappointing after so many years of clinical use of sulpiride. This seems to be the situation, however, and people with schizophrenia should consider other evidence such as data on effectiveness compared with other better-tested drugs and from studies that may not be of such methodological rigour, but may nevertheless provide some level of information.

2. For clinicians

Many clinicians use, and like to use, sulpiride. This review provides no data either to support or to refute that practice. For people for whom there is doubt whether an antipsychotic should or should not be used, it may still be possible to compare sulpiride with placebo within everyday clinical practice. Until such a trial is undertaken clinical practice will be based on evidence other than from trials.

3. For managers or policy makers

Sulpiride is widely available and is an inexpensive atypical antipsychotic. However, currently policy makers have no placebo-controlled trials to support recommendations.

Implications for research

1. General

Trials in this review preceded the CONSORT statement by up to two decades (Begg 1996). Clear reporting of outcomes would certainly have resulted in this review being more informative.

2. Specific

2.1 Reviews

All excluded trials fit into already existing reviews or reviews in preparation - see below.

Study	Comparison	Review		
		Omori 2009b	Wang 2010	Rathbone 2005
Gong 2001	sulpiride vs clozapine vs sulpiride plus clozapine.	√	√	
Hong 1995	sulpiride plus clozapine vs sulpiride		√	
Kotler 2004	sulpiride augmentation vs no add on treatment in people already taking olanzapine		√	
Liu 1996	sulpiride vs clozapine vs sulpiride plus clozapine	√	√	
Ma 2009	sulpiride plus Tianma (gastrodia elata B1) vs sulpiride plus placebo		√	√
Schwartz 1990	sulpiride vs placebo (cross-over) (added to current daily antipsychotic treatment)		√	
Shiloh 1997	sulpiride vs placebo augmentation in people already taking clozapine		√	
Wang 1994	sulpiride vs clozapine vs sulpiride plus clozapine	√	√	
Wu 2005	sulpiride vs olanzapine vs sulpiride plus olanzapine	√	√	

(*Continued*)

Wu 2006	sulpiride vs clozapine vs olanzapine vs risperidone	√		
Wuliji 2003	sulpiride plus placebo vs sulpiride plus Fructus Choerospondiatis/ Semen Ziziphi Spinosae	√		√
Yang 2000	sulpiride injection to acupoint vs no add on treatment in people already taking antipsychotic medication		√	
Yao 1999	sulpiride plus clozapine vs clozapine		√	
Zhao 2003	sulpiride vs chlorpromazine vs sulpiride plus chlorpromazine	√	√	
Zhu 1999	clozapine vs clozapine plus sulpiride vs clozapine plus clomipramine		√	

2.2 Trials

Sulpiride is an inexpensive antipsychotic drug that is under-researched and one that could offer a real alternative to the newer atypical antipsychotics, with the exception of clozapine. The atypical antipsychotics are less accessible to people with schizophrenia from low income countries than drugs such as sulpiride. Even though sulpiride has been used as an antipsychotic drug for decades, there are only a small number of randomised, placebo-controlled trials measuring its efficacy without reporting its potential to cause adverse effects. The use of sulpiride for millions of people is based on clinical experience rather than the two poorly-reported trials that involve only 113 participants.

Undertaking placebo-controlled trials for people with schizophrenia is problematic and many would disagree as to whether such a study was ethical (Fleischhacker 2003). We feel that, despite the evidence that comes of long use, one or more large, well-planned, -conducted and -reported randomised, placebo-controlled trials are indicated. We have suggested a design for such a study (Table 1). Concrete and simple outcomes are of interest, such as clearly reporting improvement, 'hospital admission', 'days in hospital' or even 'healthy days'. In addition, future trials need to report not only those clinically useful data but also information relating to cost effectiveness, employment, family burden, and satisfaction with care which are currently lacking. Any data on adverse effects, including those of medium or long term, would be most welcome. Most of these outcomes do not necessitate the use of scales as outcome measures, but if scales are to be used they should have predefined cut-off points for binary outcomes and be validated.

ACKNOWLEDGEMENTS

The Soares 1999 review thanked Pharmacia and Upjohn Limited for searching the Derwent Drug File (search performed by Jo Borril, 28/04). The Soares 1999 reviewers were also grateful to Dr Som D Soni for sending more details on his trial.

A special thanks to the staff of the Cochrane Schizophrenia Group's Editorial Base and all those who helped by translating papers from Chinese, Spanish and French.

We are sorry that the original lead author of this review is no longer on the byline. Ichiro Omori (IMO) contributed greatly to the original version of this review with protocol writing, searching, trial selection, data extraction and report writing. We were, however, unable to contact him before the update started, while the update was being completed, and during the editorial process. We therefore acknowledge and thank him for his previous substantial contributions and hope we can contact him soon.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Blanco 1972

Methods	Allocation: randomised, method of allocation otherwise not specified or described. Blindness: no. Location and setting: hospital inpatients (45% >15 years), Spain. Duration: 12 weeks.
Participants	Diagnosis: schizophrenia (WHO) - including paranoid, catatonic, hebephrenic and simple. N = 89. Age: range 20 - 60 years (78% >41 years). Sex: no information. History: chronic, hospitalisations >5 years . Excluded: over> 60 years old, those with somatic symptoms.
Interventions	1. Sulpiride: dose 800 - 1400 mg/day. N = 46. 2. Placebo: vitamin C complex. N = 43. Participants in placebo group who decompensated were given chlorpromazine, due to ethical considerations
Outcomes	Leaving the study early. Unable to use: Mental state: Harris, Letemendia and Willems Rating Scale (no SD) Adverse effects: (not presented by group of allocation). General: use of chlorpromazine (not specified by group).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Random"; no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	High risk	Continuous outcome data were reported without SDs, so cannot be entered into analysis

Blanco 1972 (*Continued*)

Other bias	Unclear risk	Authors thank "Delagrange Labs" who manufacture sulpiride for providing the medication for free and for "helping" in the investigation

Soni 1990

Methods	Allocation: randomised. Blindness: double. Location and setting: hospital inpatients, in United Kingdom Duration: 12 weeks.
Participants	Diagnosis: schizophrenia (DSM-III). N = 24. Age: range 51 - 64 years, mean 59 years. Sex: Men 16, women 10. History: chronically ill, mean ~ 30 years, in hospital mean ~ 29 years, poverty of speech and flattening of affect ≥ 3 (Manchester Scale). Neuroleptic-free for about 14 months before the trial
Interventions	1. Sulpiride: dose 400 mg/day. N = 12. 2. Placebo. N = 12.
Outcomes	Leaving the study early. Mental state: negative symptoms (Scale for the Assessment of Negative Symptoms, Manchester Scale), positive symptoms (Manchester Scale). Behaviour (Current Behaviour Schedules) Unable to use: Adverse effects: Extrapyramidal Symptom Checklist (data unclear), AIMS (data unclear)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Allocated randomly"; no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double blind"; no further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	6 of 24 included participants were missing at outcome.

Soni 1990 (*Continued*)

Selective reporting (reporting bias)	High risk	Abnormal involuntary movements and extrapyramidal effects data reported as "virtually zero throughout"; inadequate detail for data to be included
Other bias	High risk	One author was an employee of the drug company.

SD: standard deviation
WHO: World Health Organization

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

Study	Reason for exclusion
Benoit 1969	Allocation: not randomised.
Casey 1979	Allocation: not randomised.
Gong 2001	Allocation: randomised. Participants: people with schizophrenia. Intervention: sulpiride vs clozapine vs sulpiride plus clozapine
Hong 1995	Allocation: randomised. Participants: people with schizophrenia. Intervention: sulpiride plus clozapine vs sulpiride alone.
Kotler 2004	Allocation: randomised. Participants: people with schizophrenia. Interventions: sulpiride augmentation vs no add-on treatment in people already taking olanzapine
Liu 1996	Allocation: randomised. Participants: people with schizophrenia. Interventions: sulpiride vs clozapine vs sulpiride plus clozapine
Ma 2009	Allocation: randomised. Participants: people with schizophrenia. Interventions: sulpiride plus Tianma (gastrodia elata B1 - traditional Chinese medicine) vs sulpiride plus placebo
Quinn 1984	Allocation: randomised. Participants: people with tardive dyskinesia (Huntington's disease or schizophrenia or bipolar affective disorder or depression) Interventions: sulpiride vs placebo.

(*Continued*)

Sahakian 2000	Allocation: randomised. Participants: healthy volunteers. Interventions: sulpiride vs placebo.
Schwartz 1990	Allocation: randomised. Participants: people with tardive dyskinesia (schizophrenia and epilepsy) Interventions: sulpiride vs placebo (cross-over) (added to current daily antipsychotic treatment)
Shiloh 1997	Allocation: randomised. Participants: people with schizophrenia. Interventions: sulpiride vs placebo augmentation in people already taking clozapine
Takeshita 1994	Allocation: randomised. Participants: healthy volunteers (those with psychiatric illness excluded) Interventions: sulpiride vs placebo.
Wang 1994	Allocation: randomised. Participants: people with schizophrenia. Interventions: sulpiride vs clozapine vs sulpiride plus clozapine
Wu 2005	Allocation: randomised. Participants: people with schizophrenia. Interventions: sulpiride vs olanzapine vs sulpiride plus olanzapine
Wu 2006	Allocation: randomised. Participants: people with schizophrenia. Interventions: sulpiride vs clozapine vs olanzapine vs risperidone
Wuliji 2003	Allocation: randomised. Participants: people with schizophrenia. Interventions: sulpiride plus placebo vs sulpiride plus Fructus Choerospondiatis/Semen Ziziphi Spinosae (traditional Chinese medicine)
Yang 2000	Allocation: randomised. Participants: those with schizophrenia. Interventions: sulpiride injection to acupoint vs no add on treatment in people already taking antipsychotic medication
Yao 1999	Allocation: randomised. Participants: people with schizophrenia. Interventions: sulpiride plus clozapine vs clozapine
Zhao 2003	Allocation: randomised. Participants: people with schizophrenia. Interventions: sulpiride vs chlorpromazine vs sulpiride plus chlorpromazine

(*Continued*)

Zhu 1999	Allocation: randomised. Participants: people with schizophrenia. Interventions: clozapine vs clozapine plus sulpiride vs clozapine plus clomipramine

DATA AND ANALYSES

Comparison 1. SULPIRIDE vs PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental state: 1. Average score for positive symptoms (Manchester scale, positive subset, endpoint, high = poor, skewed)			Other data	No numeric data
1.1 short-term			Other data	No numeric data
2 Mental state: 2a. Average score for negative symptoms (Manchester scale, negative subset, endpoint, high = poor)	1	18	Mean Difference (IV, Random, 95% CI)	-0.30 [-1.66, 1.06]
2.1 short-term	1	18	Mean Difference (IV, Random, 95% CI)	-0.30 [-1.66, 1.06]
3 Mental state: 2b. Average score for negative symptoms (SANS endpoint, endpoint, high = poor)	1	18	Mean Difference (IV, Random, 95% CI)	2.90 [-0.14, 5.94]
3.1 short-term	1	18	Mean Difference (IV, Random, 95% CI)	2.90 [-0.14, 5.94]
4 Behaviour: Average social behaviour score (CBS, endpoint, high = good)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 exhibited abnormal behaviour - short-term	1	18	Mean Difference (IV, Random, 95% CI)	-0.5 [-2.21, 1.21]
4.2 social behaviour - short-term	1	18	Mean Difference (IV, Random, 95% CI)	-2.90 [-5.60, -0.20]
5 Leaving the study early	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 any reason - short-term	2	113	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.25, 4.00]
5.2 due to deterioration of psychiatric symptoms - short-term	2	113	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.13, 3.30]
5.3 due to adverse effects - short-term	2	113	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 67.06]

Analysis 1.1. Comparison 1 SULPIRIDE vs PLACEBO, Outcome 1 Mental state: 1. Average score for positive symptoms (Manchester scale, positive subset, endpoint, high = poor, skewed).

Mental state: 1. Average score for positive symptoms (Manchester scale, positive subset, endpoint, high = poor, skewed)

Study	Sulpiride: mean (SD)	n	Placebo: mean (SD)	n
short-term				
Soni 1990	2.5 (1.4)	9	2.5 (2.3)	9

Analysis 1.2. Comparison 1 SULPIRIDE vs PLACEBO, Outcome 2 Mental state: 2a. Average score for negative symptoms (Manchester scale, negative subset, endpoint, high = poor).

Review: Sulpiride versus placebo for schizophrenia

Comparison: 1 SULPIRIDE vs PLACEBO

Outcome: 2 Mental state: 2a. Average score for negative symptoms (Manchester scale, negative subset, endpoint, high = poor)

Study or subgroup	Sulpiride N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 short-term							
Soni 1990	9	3.8 (1.7)	9	4.1 (1.2)		100.0 %	-0.30 [-1.66, 1.06]
Total (95% CI)	**9**		**9**			**100.0 %**	**-0.30 [-1.66, 1.06]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.43 (P = 0.67)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 SULPIRIDE vs PLACEBO, Outcome 3 Mental state: 2b. Average score for negative symptoms (SANS endpoint, endpoint, high = poor).

Review: Sulpiride versus placebo for schizophrenia

Comparison: 1 SULPIRIDE vs PLACEBO

Outcome: 3 Mental state: 2b. Average score for negative symptoms (SANS endpoint, endpoint, high = poor)

Study or subgroup	Sulpiride N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 short-term							
Soni 1990	9	21.6 (4.4)	9	18.7 (1.5)		100.0 %	2.90 [-0.14, 5.94]
Total (95% CI)	**9**		**9**			**100.0 %**	**2.90 [-0.14, 5.94]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.87 (P = 0.061)

Test for subgroup differences: Not applicable

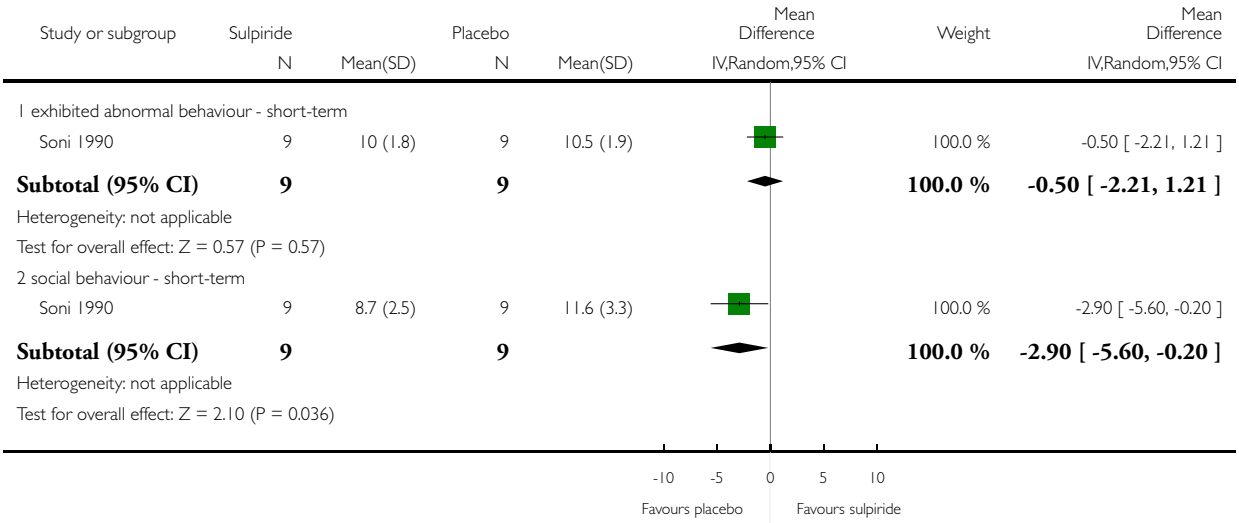
Analysis 1.4. Comparison 1 SULPIRIDE vs PLACEBO, Outcome 4 Behaviour: Average social behaviour score (CBS, endpoint, high = good).

Review: Sulpiride versus placebo for schizophrenia

Comparison: 1 SULPIRIDE vs PLACEBO

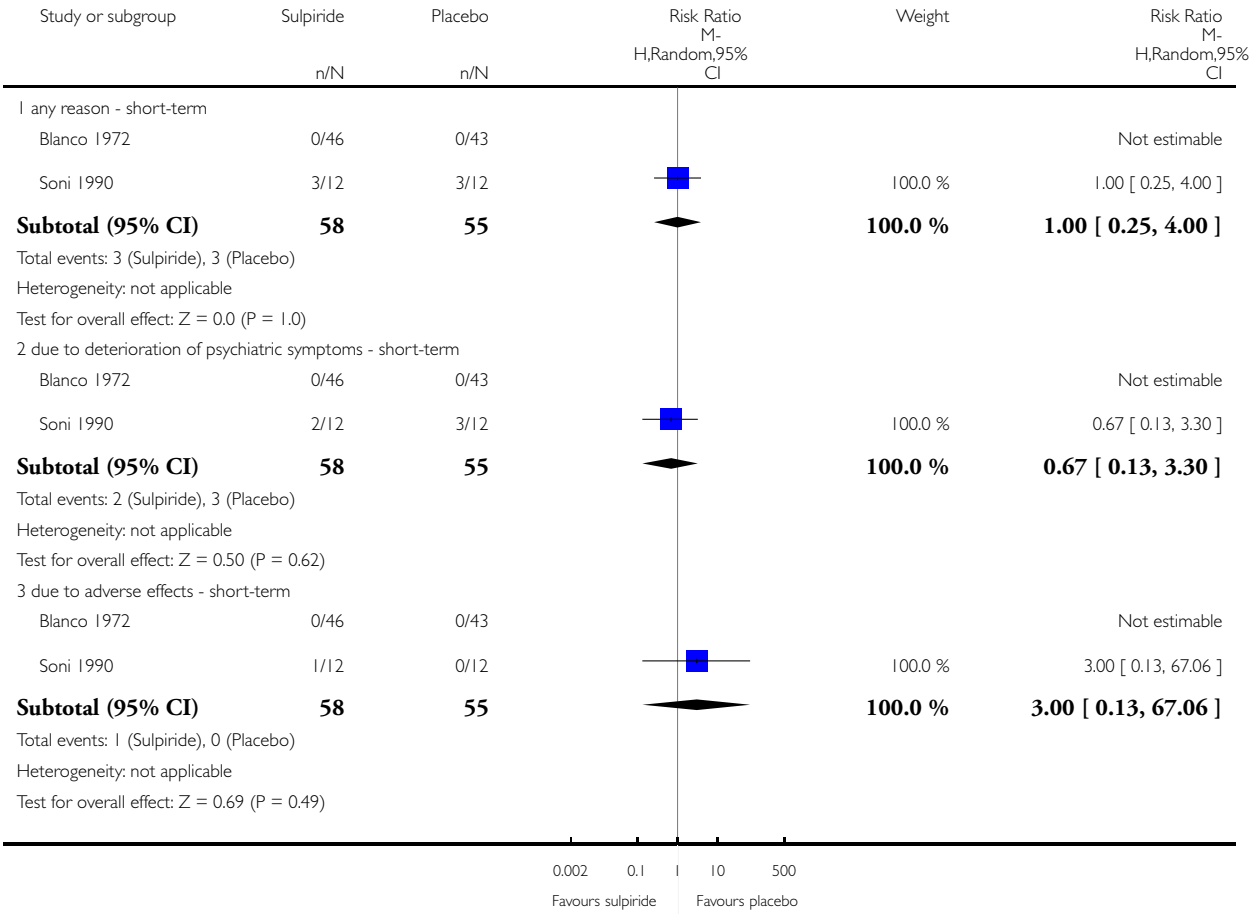
Outcome: 4 Behaviour: Average social behaviour score (CBS, endpoint, high = good)

Study or subgroup	Sulpiride N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 exhibited abnormal behaviour - short-term							
Soni 1990	9	10 (1.8)	9	10.5 (1.9)		100.0 %	-0.50 [-2.21, 1.21]
Subtotal (95% CI)	**9**		**9**			**100.0 %**	**-0.50 [-2.21, 1.21]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.57 (P = 0.57)							
2 social behaviour - short-term							
Soni 1990	9	8.7 (2.5)	9	11.6 (3.3)		100.0 %	-2.90 [-5.60, -0.20]
Subtotal (95% CI)	**9**		**9**			**100.0 %**	**-2.90 [-5.60, -0.20]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.10 (P = 0.036)							



Analysis 1.5. Comparison 1 SULPIRIDE vs PLACEBO, Outcome 5 Leaving the study early.

Review: Sulpiride versus placebo for schizophrenia
Comparison: 1 SULPIRIDE vs PLACEBO
Outcome: 5 Leaving the study early



ADDITIONAL TABLES

Table 1. Suggested design for future study

Methods	Allocation: randomised, clearly described. Blinding: double, tested. Duration: 1 year.
Participants	Diagnosis: schizophrenia. N = 400 - 500.*

Table 1. Suggested design for future study (*Continued*)

	Age: adults. Sex: both. History: not severely ill, those for whom diagnosis is clear but for whom it is unclear if ongoing treatment is indicated
Interventions	1. Sulpiride: dose flexible within recommended limits. N = 200. 2. Placebo. N = 200
Outcomes	Death. Adverse effects: list, including weight change, hypersalivation, blood dyscrasia. Service outcomes: admitted, ready for discharge. Social functioning: working, trouble with family, trouble with police. Satisfaction with treatment: binary outcome, family, clinician and participant. Healthy days. Compliance: attending follow-up, taking medication, blood testing
Notes	* Powered to be able to identify a difference of ~ 20% between groups for primary outcome with adequate degree of certainty

APPENDICES

Appendix 1. Previous plain language summary

Sulpiride versus placebo for schizophrenia

Schizophrenia is a severe mental illness characterised by a mixture of symptoms such as hallucinations, delusions, disorganisation and social withdrawal. For some it can be a life-long condition and people with this diagnosis are usually treated with antipsychotic drugs. There can be quite a large difference in cost between recently developed antipsychotics (second generation) and the older ones (first generation), but the older drugs can have considerably more movement side effects and many people find them difficult to tolerate. In developing countries cost of medication can be a major factor in prescribing, so the first generation drugs are used the most.Sulpiride is a first generation antipsychotic which is said to cause fewer adverse effects. In addition, people whose main symptoms are aspects of social withdrawal may respond better to sulpiride than some of the other older antipsychotics. This review reports trials comparing sulpiride with placebo for people with schizophrenia or similar psychotic illnesses. The two studies contained a total of 113 people with chronic (long term) schizophrenia, were both 12 weeks long and set in hospital. Most of the data from these trials were not reported in a way that would give meaningful statistics. However, in one trial sulpiride was not significantly better than placebo in improving negative symptoms (when measuring all such symptoms). However, the single negative symptom of the social behaviour of the participant, showed a significant improvement in the sulpiride group. The potential side effects of the medication were not measured, but the number of people leaving the trial early was not significantly different between the two groups. Sulpiride is an inexpensive antipsychotic drug that is used all over the world, therefore a well planned, conducted and reported randomised control trial would contribute to our knowledge about this drug.(Plain language summary prepared for this review by Janey Antoniou of RETHINK, UK www.rethink.org).

Appendix 2. Details of past searches for earlier versions of this review

The following search phrase was constructed to assist identification for previous versions of this review (Soares 1999).
(sulpiride-phrase)=(abilit or championyl or coolspan or col-sulpir or digton or dixibon or dobren or dogmatil or dolmatil or drominetas or eglonyl or equilid or eusulpid or guastil or isnamid or kapiride or lavodina or lebopride or lusedan or miradol or mirbanil or misulvan or neuromyfar or normum or omperan or psicocen or quiridil or sato or sernevin or sicofrenol or sulpiride or sulpisedan or suprium or sursumid or tepavil or tonofit or ulpir or vipral)
1. Biological Abstracts (January 1982 to December 1997) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials and for schizophrenia (see Group search strategy) combined with:
[and (sulpiride-phrase)]
2 CINAHL (January 1982 to March 1998) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials and for schizophrenia (see Group search strategy) combined with:
[and (sulpiride-phrase)]
3. Cochrane Schizophrenia Group's Register (March 1998) was searched using:
[(sulpiride-phrase) or #42=110 or #42=563] (#42 is the field in the Register where each intervention is coded. 110 is sulpiride and 563 Dogmatil or Dolmatil).
4. Cochrane Library (Issue 1, 1998) was searched using:
[(sulpiride-phrase) or SULPIRIDE/explode in MeSH] 5. EMBASE (January 1980 to January 1998) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials and for schizophrenia (see Group search strategy) combined with:
[and ((sulpiride-phrase) or explode SULPIRIDE / all)]
6. MEDLINE (January 1966 to April 1998) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials and for schizophrenia (see Group search strategy) combined with:
[and ((sulpiride-phrase) or SULPIRIDE / explode in MeSH)]
7. PsycLIT (January 1974 to September 1997) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials and for schizophrenia (see Group search strategy) combined with:
[and ((sulpiride-phrase) or SULPIRIDE / explode in MeSH)]
8. SIGLE (January 1994 to December 1997) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials and for schizophrenia (see Group search strategy) combined with:
[and (sulpiride-phrase)]
9. Sociofile (January 1974 to December 1997) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials and for schizophrenia (see Group search strategy) combined with:
[and (sulpiride-phrase)]
10. The Cochrane Schizophrenia Group Trials Register was searched (September 2008) using the phrase:
[(ability * or championyl* or coolspan* or col-sulpir* or digton* or dixibon* or dobren* or do?matil* or drominetas* or eglonyl* or equilid* or eusulpid* or guastil* or isnamid* or kapirid* or lavodina* or leboprid* or lusedan* or miradol* or mirbanil* or misulvan* or neuromyfar* or normum* or omperan* or psicocen* or quiridil* or sato * or sernevin* or sicofrenol* or sulp?ride* or sulpisedan* or suprium* or sursumid* or tepavil* or tonofit* or ulpir* or vipral*) in title, abstract and index fields in REFERENCE) OR (sulp?rid* in interventions field in STUDY)]
This register is compiled by systematic searches of major databases, hand searches and conference proceedings (see Group Module). The Cochrane Schizophrenia Group Trials Register is maintained on Meerkat 1.5. This version of Meerkat stores references as studies. When an individual reference is selected through a search, all references which have been identified as the same study are also selected.

Appendix 3. Details of previous methods and data analysis

1. Data Extraction
IMO and JW extracted data from included studies. Again, any disagreement was discussed, decisions documented and, if necessary, authors of studies were contacted for clarification. When this was not possible and further information was necessary to resolve the dilemma, we did not enter data and added the trial to the list of those awaiting assessment.
2. Management
We extracted the data onto standard, simple forms. Where possible, data were entered into RevMan in such a way that the area to the left of the 'line of no effect' indicates a 'favourable' outcome for clozapine. Where this was not possible, for example for scales that calculate higher scores=improvement, graphs in RevMan analyses were labelled accordingly so that the direction of effects were clear.
3. Scale-derived data

3.1 Valid scales

A wide range of instruments are available to measure outcomes in mental health studies. These instruments vary in quality and many are not validated, or are even ad hoc. It is accepted generally that measuring instruments should have the properties of reliability (the extent to which a test effectively measures anything at all) and validity (the extent to which a test measures that which it is supposed to measure) (Rust 1989). Unpublished scales are known to be subject to bias in trials of treatments for schizophrenia (Marshall 2000). Therefore continuous data from rating scales were included only if the measuring instrument had been described in a peer-reviewed journal. In addition, the following minimum standards for instruments were set: the instrument should either be (a) a self-report or (b) completed by an independent rater or relative (not the therapist) and (c) the instrument should be a global assessment of an area of functioning.

3.2 Binary outcomes from scale data

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

Assessment of risk of bias in included studies

IMO and JW worked independently to assess risk of bias by using criteria described in the Cochrane Collaboration Handbook (Higgins 2008) to assess trial quality. This 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.

The categories are defined below:

YES - low risk of bias

NO - high risk of bias

UNCLEAR - uncertain risk of bias

If sequence generation process within the trial was by quasi-random means, such as by odd or hospital record numbers, this was noted and the study was given a "NO - high risk of bias" rating. If data from such studies did not differ from the results of higher grade trials, these were presented. If disputes arose as to which category a trial had to be allocated, again, resolution was made by discussion, after working with the Cochrane Schizophrenia Group's Co-ordinating Editor (CEA).

Measures of treatment effect

1. Binary data

The review uses relative risk (RR) and its 95% confidence interval (CI) based on the random-effects model, as this takes into account any differences between studies even if heterogeneity is not statistically significant, as the preferred statistic for summation. Relative Risk is more intuitive (Boissel 1999) than odds ratios and odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). This misinterpretation then leads to an overestimate of the impression of the effect. Data were inspected to see if analysis using a Mantel-Haenszel odds ratio and fixed-effect model made any substantive difference. For statistically significant results we calculated the number needed to treat/harm statistic (NNT/H), and its 95% confidence interval (CI) using Visual Rx (http://www.nntonline.net/) taking account of the event rate in the control group.

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

2. Continuous data

2.1 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 are even ad hoc. For outcome instruments some minimum standards have to be set. They were that: (i) the psychometric properties of the instrument should have been described in a peer-reviewed journal (Marshall 2000);and (ii) the instrument should either be: (a) a self report, or (b) completed by an independent rater or relative (not the therapist).

2.2 Summary statistic

For continuous outcomes we estimated a random-effects weighted mean difference (WMD) between groups. We did not calculate effect size measures.

2.3 Endpoint versus change data

We preferred to use scale endpoint data, which typically cannot have negative values and is easier to interpret from a clinical point of view. Change data is more problematic and the rule described above does not hold for it. Where both endpoint and change were available for the same outcome the reviewers presented the former in preference.

2.4 Skewed data

Mental health continuous data is often not "normally" distributed. To avoid the pitfall of applying parametric tests to non-parametric data the following standards were applied to all data before inclusion: (i) standard deviations and means were reported in the paper or were obtained from the authors; (ii) if the data were finite number zero, for example 0-100, when the standard deviation was multiplied by two, the result should be less than the mean, otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution (Altman 1996). (III) if a scale starts from a positive value (such as PANSS which can have values from 30 to 210) the calculation described above will be modified to take the scale starting point into account. In these cases skew is present if 2SD>(S-S min), where S is the mean score and S min is the minimum score. Endpoint scores on scales often have a finite start and end point and these rules can be applied.

When continuous data are presented on a scale which includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not. Skewed data from studies of less than 200 participants were entered in additional tables rather than into an analysis. Skewed data pose less of a problem when looking at means if the sample size is large and were entered into syntheses.

Unit of analysis issues

1. Cluster trials

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

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

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

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

2. Cross-over trials

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

3. Studies with multiple treatment groups

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

Dealing with missing data

1. Overall loss of credibility
At some degree of loss to follow-up data must lose credibility (Xia 2007). We are forced to make a judgment where this is for the trials likely to be included in this review. Should more than 40% of data be unaccounted for by 8 weeks we did not reproduce these data or use them within analyses.
2. Binary
Where attrition for a binary outcome is between 0 and 40%, and outcomes of these people are described, we included these data as reported. Where the outcomes of such people were not clearly described, we assumed the worst primary outcome, and rates of adverse effects similar to those who did continue to have their data recorded.
3. Continuous
In the case where attrition for a continuous outcome is between 0 and 40% and completer-only data were reported, we have reproduced these.

Assessment of heterogeneity

1. Clinical heterogeneity
We considered all included studies without any comparison to judge clinical heterogeneity.
2. Statistical
2.1 Visual inspection
We visually inspected graphs to investigate the possibility of statistical heterogeneity.
2.2 Employing the I-squared statistic
This provided an estimate of the percentage of inconsistency thought to be due to chance. I-squared estimate greater than or equal to 50% was interpreted as evidence of high levels of heterogeneity (Higgins 2002).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). 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 ten or fewer studies, or where all studies were of similar sizes. In other cases, where funnel plots were possible, we sought statistical advice in their interpretation.

Data synthesis

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

Subgroup analysis and investigation of heterogeneity

1. Subgroup analysis
It was expected that several subgroup analyses could be undertaken within this review. The following hypotheses were tested: When compared with placebo, for the primary outcomes of interest (see: "Criteria" for considering studies for this review) sulpiride is differentially effective for:
a. Men and women
b. People who are under 18 years of age (adolescent patients), between 18 and 64 (adult patients), or over 65 years of age (elderly patients).
c. People who became ill recently (i.e. acute episode approximately less than one month's duration) as opposed to people who have been ill for longer.
d. People who are given low doses (1-800mg/day) and those given high doses (over 800 mg/day).
e. People who have schizophrenia diagnosed according to any operational criterion (i.e. a pre-stated checklist of symptoms/ problems/ time periods/ exclusions) as opposed to those who have entered the trial with loosely defined illness.
f. People treated earlier (pre-1990) and people treated in recent years (1990 to 2002).

g. Duration of study: short term (less than 3 months), medium term (3-12 months) and long term (more than 1 year).
2. Investigation of heterogeneity
If data are clearly heterogeneous we checked that data are correctly extracted and entered and that we had made no unit of analysis errors. If the high levels of heterogeneity remained we did not undertake a meta-analysis at this point for if there is considerable variation in results, and particularly if there is inconsistency in the direction of effect, it may be misleading to quote an average value for the intervention effect. We would have wanted to explore heterogeneity. We pre-specify no characteristics of studies that may be associated with heterogeneity except quality of trial method. If no clear association could be shown by sorting studies by quality of methods a random-effects meta-analysis was performed. Should another characteristic of the studies be highlighted by the investigation of heterogeneity, perhaps some clinical heterogeneity not hitherto predicted but plausible causes of heterogeneity, these post-hoc reasons will be discussed and the data analysed and presented. However, should the heterogeneity be substantially unaffected by use of random-effects meta-analysis and no other reasons for the heterogeneity be clear, the final data were presented without a meta-analysis.

Sensitivity analysis

If necessary, we analysed the effect of including studies with high attrition rates in a sensitivity analysis. We aimed to include trials in a sensitivity analysis if they were quasi-randomised trials. If we found no substantive differences within primary outcome when these high attrition and 'quasi-randomised' studies were added to the overall results, we included them in the final analysis. However, if there was a substantive difference we only used clearly randomised trials and those with attrition lower than 25%.

WHAT'S NEW

Last assessed as up-to-date: 14 January 2013.

Date	Event	Description
14 January 2014	New citation required but conclusions have not changed	Eight new studies assessed, but none added for inclusion (8 new excluded studies)
14 January 2013	New search has been performed	Results of 2012 search added to review. Summary of findings for the main comparison added.

HISTORY

Review first published: Issue 2, 2009

Date	Event	Description
16 May 2012	Amended	Update search of Cochrane Schizophrenia Group's Trial Register (see Search methods for identification of studies), 8 studies added to awaiting classification.
6 October 2010	Amended	Contact details updated.
15 February 2010	Amended	Contact details updated.

(*Continued*)

11 November 2009	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

Jijun Wang: protocol writing, searching, trial selection, data extraction, completion of original report, completion of update.

Stephanie Sampson: completion of update.

DECLARATIONS OF INTEREST

None known.

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Office of Medical Affairs, Ministry of Health, 2011-873; OMA-MH, 2011-873

- National Institute for Health Research (NIHR), UK.

Cochrane Collaboration Programme Grant 2011; Reference number: 10/4001/15

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review is part of a previous version focusing on the effects of sulpiride for schizophrenia (Soares 1999). The older review was large and we felt it was justified to fragment it for ease of understanding and updating. New methods are incorporated into this version but there are no substantive differences in how data are handled. For the 2013 update, we added a secondary outcome of interest of '12. safety assessments, 12.1 as defined in each study'; we considered the importance of acknowledging safety assessments undertaken in randomised controlled trials, and felt that this is an important outcome to include as part of drug efficacy.

INDEX TERMS

Medical Subject Headings (MeSH)

Antipsychotic Agents [*therapeutic use]; Placebos [therapeutic use]; Randomized Controlled Trials as Topic; Schizophrenia [*drug therapy]; Sulpiride [*therapeutic use]

MeSH check words

Humans