Sulpiride versus placebo for schizophrenia (Review)

Omori IM, Wang J

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[Intervention Review]

Sulpiride versus placebo for schizophrenia

Ichiro M Omori[1], Jijun Wang[2]

[1]Department of Psychiatry, Toyokawa City Hospital, Aichi, Japan. [2]Department of EEG Source Imaging, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Contact address: Ichiro M Omori, Department of Psychiatry, Toyokawa City Hospital, Koumei 1-19, Toyokawa, Aichi, 442-8561, Japan. ichiro.m.omori@gmail.com. mmds@sannet.ne.jp.

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ABSTRACT

Background

Sulpiride is a relatively old antipsychotic drug reputed to have 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 16 May 2012 and added the results to the awaiting classification section of the review.

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 random-effects relative risk (RR) and estimated the 95% confidence interval (CI) around this. Where continuous data were included, we analysed this data using random-effects weighted mean difference (WMD) with a 95% confidence interval.

Main results

Two trials of short duration compare sulpiride with placebo (total n=113). As regards mental state, there were no clear differences between groups for either positive or negative symptoms (n=18, 1 RCT, WMD Manchester scale negative subscore -0.30 CI -1.66 to 1.06; n=18, 1 RCT, WMD SANS 2.90 CI -0.14 to 5.94). Few people left these studies by three months (n=113, 2 RCTs, RR 1.00 CI

0.25 to 4.00). One subscore finding found sulpiride improved social behavior (n=18, 1 RCT, WMD -2.90 CI -5.60 to -0.20). There were no data for many important outcomes such as general functioning, service use or adverse effects.

Update search 2012: the 8 new citations in the awaiting classification section of the review may alter the results and conclusions of the review once assessed.

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 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).

BACKGROUND

Schizophrenia is regarded as one of the most burdensome diseases in the world (Rossler 2005).

Description of the condition

Schizophrenia is a severe mental illness characterized by a mixture of hallucinations, delusions, disorganization and negative symptoms. These characters are associated with noticeable social or occupational dysfunction or both and its prevalence in adults is reported to be between 0.5 to 1.5% (APA 1994). Due to its chronic features, one third of patients with schizophrenia suffered from those symptoms continuously over ten years (Mason 1996).

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, however, also can be classed in this way as 'atypical' with sulpiride being one of this group (Miyamoto 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 (Edwards 1980, Bratfos 1979).

Why it is important to do this review

It is reported that in developing countries, basic, evidence-based care for patients with mental illness are scarce and a good deal of psychiatric patients are suffering from increased cost of care (Patel 2007). Based on cost effective 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).

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. We included quasi-randomised trials such as those where allocation is undertaken based on time of admission to the hospital. Randomised cross-over studies will be 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.

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 life-long illness, and sulpiride is used as an ongoing treatment, outcomes were grouped according to time periods: short term (less than 3 months), medium term (3 to 12 months) and long term (more than 1 year).

Primary outcomes

1. Global outcomes - Clinically significant response in global state - as defined by each of the studies - long term.

Secondary outcomes

1. Death: suicide or natural causes
2. Service utilization 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 Leaving the study early
5.2 Clinically significant response in behaviour - as defined by each of the studies
5.3 Average score/change in behaviour
6. Extrapyramidal side effects
6.1 Incidence of use of antiparkinson drugs
6.2 Clinically significant extrapyramidal side effects - as defined by each of the studies
6.3 Average score/change in extrapyramidal side effects
7. Other adverse effects, general and specific
7.1 Number of people dropping out due to adverse affects
7.2 Cardiac effects
7.3 Anticholinergic effects
7.4 Antihystamine effects
7.5 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 careers
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.

Search methods for identification of studies

Electronic searches

1. 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.
2. Details of previous electronic search - see Appendix 1
3. Cochrane Schizophrenia Group Trials Register (May 2012)
We updated this search. The Trials Search Co-ordinator searched the Cochrane Schizophrenia Group's Trials Register (16 May 2012).

The Cochrane Schizophrenia Group's Trials Register is compiled by systematic searches of major databases, handsearches and conference proceedings (see group module).
Trials identified through the searching activities are each assigned to awaiting classification of relevant review titles.

Searching other resources

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

Data collection and analysis

Selection of studies

Authors IMO and JW independently inspected all study citations identified by the searches, and full reports of the studies of agreed relevance were obtained. Where disputes arose, we acquired the full report for more detailed scrutiny. These articles were then inspected, independently, by two reviewers to assess their relevance to this review. Again, where disagreement occurred attempts were made 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. 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 2005, Leucht 2005a). 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 2005, Leucht 2005a). 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%.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.
For substantive descriptions of studies please see: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

We inspected 251 electronic reports. One hundred and thirty-six of them were excluded on the basis of their abstracts. We selected 15 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 studies were excluded. Finally, we included two randomised trials meeting the inclusion criteria.

Included studies

Blanco 1972 and Soni 1990 involved a total of 113 participants.
1. Length of studies
Both studies 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 UK.
3. Participants
Study participants of both studies were 'adult patients' suffered from chronic schizophrenia. Described diagnostic criteria was WHO for Blanco 1972 and DSM-III for Soni 1990.
4. Study size
The number of participants were 89 (Blanco 1972) and 24 (Soni 1990).
5. Interventions
5.1 Sulpiride
In Blanco 1972, dosing schedule of sulpiride was flexible, 800 to 1400 mg/day ('high dose'). Soni 1990 used fixed schedule, 400 mg/day ('low dose').
5.2 Placebo
Both studies used inactive placebo.
6. Outcomes
6.1 General remarks
Several important outcomes could not be extracted from Blanco 1972 and Soni 1990 because of poor data reporting - but these hospital-based short small studies were, nevertheless trying to record outcomes that were of meaning to clinicians as well as 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 on schizophrenia to assess the severity of negative symptoms. A six-point (0-5) 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 encompasses both positive and negative symptoms of schizophrenia. It is used to evaluate the mental state and behaviour in chronic psychotic people with higher scores indicating greater severity. It is also known as the Krawiecka Scale.
6.2.2 Behaviour
6.2.2.1 Current Behaviour Schedule (CBS) (Owens 1980)
The observation scale rates mainly psychiatric symptoms and has 24 items that are to be rated on basis of descriptors from 0-2 or 0-4 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 twelve-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
None of the included studies attempted to quantify death, service use, global outcomes, satisfaction, social function or quality of life and cognitive function, there is no evidence of any direct economic evaluation of sulpiride.

Excluded studies

We immediately excluded 236 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 were studies of adjunctive use of sulpiride. In these the sulpiride was added to another antipsychotic drug and compared with that other antipsychotic medication alone (Gong 2001, Kotler 2004, Liu 1996, Wang 1994, Wu 2005, Wu 2006, Yang 2000, Yao 1999, Zhao 2003 and Zhu 1999). 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.

Awaiting assessment

Nine studies await assessment. Despite considerable efforts, Hong 1995 remains unfound.

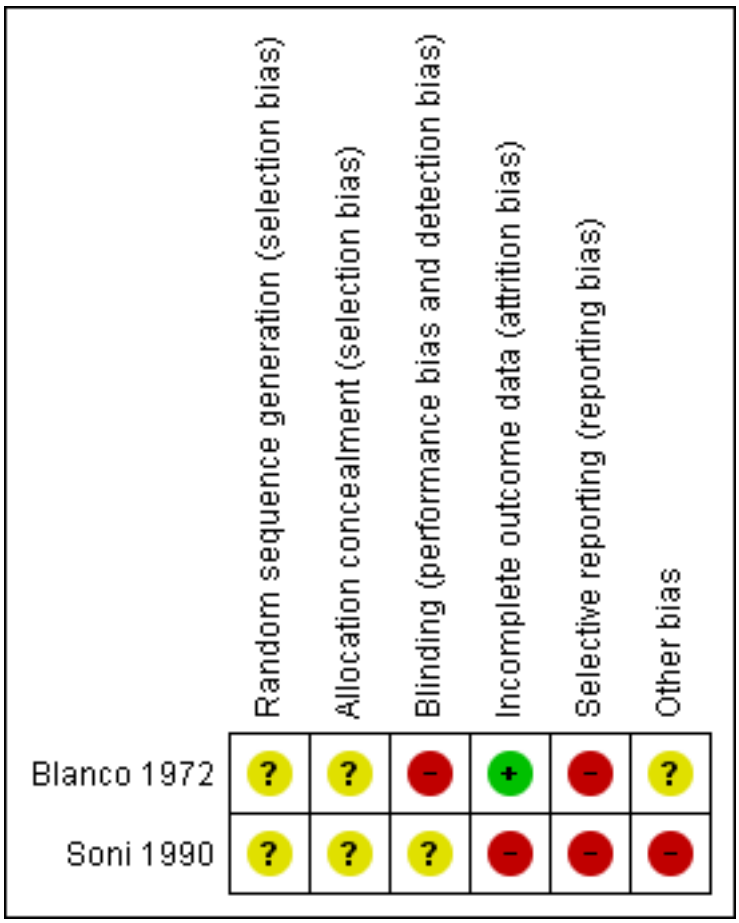
Ongoing studies

We know of no ongoing studies.

Risk of bias in included studies

Judgement of risks are illustrated in Figure 1.

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



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% (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 place in the outcomes tables. However, the study authors included only those remaining for continuous outcomes. It is possible that estimates of effects are prone to exaggeration.

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

COMPARISON 1. SULPIRIDE versus PLACEBO
Two trials compare sulpiride with placebo (Blanco 1972, Soni 1990).
1. Mental state
1.1 Average score for positive symptoms
Soni 1990 reported skewed data on the Manchester scale. There was no clear differences between groups (Analysis 1.1).
1.2 Average score for negative symptoms
Soni 1990 measured negative symptoms in two ways. There was no clear differences between groups for the measures on the Manchester scale (n=18, WMD -0.30 CI -1.66 to 1.06, Analysis 1.2) or the SANS (n=18, WMD 2.90 CI -0.14 to 5.94, Analysis 1.3).
2. Behaviour
2.1 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, 2 RCTs, RR 1.00 CI 0.25 to 4.00, Analysis 1.4).
2.2 Social behaviour
Use of sulpiride showed no clear effect on 'abnormal behaviour (n=18, 1 RCT, WMD -0.50 CI -2.21 to 1.21) . For the outcome of improving social behavior (n=18, 1 RCT, WMD -2.90 CI -5.60 to -0.20, Analysis 1.5), there seemed to be a marginally statistically significant result in favour of placebo.
3. Adverse effects
No numerical data reported.

DISCUSSION

The searches

Electronic searching produced 251 references, 15 of which were selected for examination of the full text. Although sulpiride has been prescribed for decades by psychiatrists, only two studies met the eligibility criteria for this review. It is possible that we failed to identify relevant studies but most should have come to light after so many years of use of this drug.

Summary of main results

We found only two short small trials. Blanco 1972 reported no usable clinical outcomes other than leaving study early.
1. Mental state
The results are all taken from Soni 1990 (n=24) and there is not any indication of 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 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 (n=113, 2 RCTs, RR 1.00 CI 0.25 to 4.00, Analysis 1.4). Only 6% of people did leave these studies. This is a figure 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.
2.2 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 behavior. We are unclear as to the clinical meaning of a WMD 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. There were none. There was also no data for service utilization 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.

Overall completeness and applicability of evidence

Participants included in both studies were chronic hospitalised patients. Patients 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 life-long disorder and medications are likely to be used by people with schizophrenia for long periods. These characters of the included trials limit the applicability of the findings.

Quality of the evidence

See Figure 1. 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 overestimate of the estimate of effect (Schulz 1995) and this should be considered 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 would lead to an overestimate of effect sizes. It is inevitable 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, just that these studies do not show this to be so). If other studies do exist they would 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

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 patients taking clozapine and reported 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 of sulpiride for treating schizophrenia. Other reviews will address the relative effectiveness. This would seem disappointing after so many years of clinical use of sulpiride. This, however, seems to be the situation, 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 nevertheless provide some level of information.

2. For clinicians

Many clinicians use, and like to use, sulpiride. This review provides no data to support - or to refute - that practice. For people for whom there is doubt if 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

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 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 is 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.

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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. Duration: 12 weeks.
Participants	Diagnosis: schizophrenia (WHO) - including paranoid, catatonic, hebephrenic and simple. N=89. Age: range 20-60 (78% >41 years). Sex: no information. Setting: hospital (45% >15 years), Spain History: chronic, hospitalizations >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 Patients 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 - 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. Duration: 12 weeks.
Participants	Diagnosis: schizophrenia (DSM-III). N=24. Age: range 51-64, mean 59 years. Sex: M 16, F 10. Setting: hospital, UK. History: chronically ill, mean ~30 years, in hospital mean ~29 years, poverty of speech & flattening of affect >= 3 (Manchester Scale). Neuroleptic free for about 14 month 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 patients 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 pharmaceutical industry.

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

Study	Reason for exclusion
Benoit 1969	Allocation: not randomised.
Gong 2001	Allocation: randomised. Participants: those with schizophrenia. Intervention: sulpiride vs clozapine vs sulpiride plus clozapine
Kotler 2004	Allocation: randomised. Participants: those with schizophrenia. Interventions: sulpiride augmentation vs no add on treatment in people already taking olanzapine
Liu 1996	Allocation: randomised. Participants: those with schizophrenia. Interventions: sulpiride vs clozapine vs sulpiride plus clozapine
Shiloh 1997	Allocation: randomised. Participants: those with schizophrenia. Interventions: sulpiride vs placebo augmentation in people already taking clozapine
Wang 1994	Allocation: randomised. Participants: those with schizophrenia. Interventions: sulpiride vs clozapine vs sulpiride plus clozapine
Wu 2005	Allocation: randomised. Participants: those with schizophrenia. Interventions: sulpiride vs olanzapine vs sulpiride plus olanzapine
Wu 2006	Allocation: randomised. Participants: those with schizophrenia. Interventions: sulpiride vs clozapine vs olanzapine vs risperidone
Yang 2000	Allocation: randomised. Participants: those with schizophrenia. Interventions: sulpiride injection to acupoint vs no add on treatment in people already taking antipsychotic medication

(*Continued*)

Yao 1999	Allocation: randomised. Participants: those with schizophrenia. Interventions: sulpiride plus clozapine vs clozapine
Zhao 2003	Allocation: randomised. Participants: those with schizophrenia. Interventions: sulpiride vs chlorpromazine vs sulpiride plus chlorpromazine
Zhu 1999	Allocation: randomised. Participants: those with schizophrenia. Interventions: clozapine vs clozapine plus sulpiride vs clozapine plus clomipramine

Characteristics of studies awaiting assessment *[ordered by study ID]*

Casey 1979

Methods	
Participants	
Interventions	
Outcomes	
Notes	To be assessed.

Hong 1995

Methods	
Participants	
Interventions	
Outcomes	
Notes	Paper not available. Ordered.

Ma 2009

Methods	
Participants	
Interventions	

Ma 2009 (*Continued*)

Outcomes	
Notes	To be assessed.

Quinn 1984

Methods	
Participants	
Interventions	
Outcomes	
Notes	To be assessed.

Sahakian 2000

Methods	
Participants	
Interventions	
Outcomes	
Notes	To be assessed.

Schwartz 1990

Methods	
Participants	
Interventions	
Outcomes	
Notes	To be assessed.

Takeshita 1994

Methods	
Participants	
Interventions	

Takeshita 1994 (*Continued*)

Outcomes	
Notes	To be assessed.

Wuliji 2003

Methods	
Participants	
Interventions	
Outcomes	
Notes	To be assessed.

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
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]
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]
4 Behaviour: 1. Leaving the study early	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 any reason	2	113	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.25, 4.00]
4.2 due to deterioration of psychiatric symptoms	2	113	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.13, 3.30]
4.3 due to adverse effects	2	113	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 67.06]
5 Behaviour: 2. Average social behaviour score (CBS, endpoint, high = good)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 exhibited abnormal behaviour	1	18	Mean Difference (IV, Random, 95% CI)	-0.5 [-2.21, 1.21]
5.2 social behaviour	1	18	Mean Difference (IV, Random, 95% CI)	-2.90 [-5.60, -0.20]

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
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
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
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)

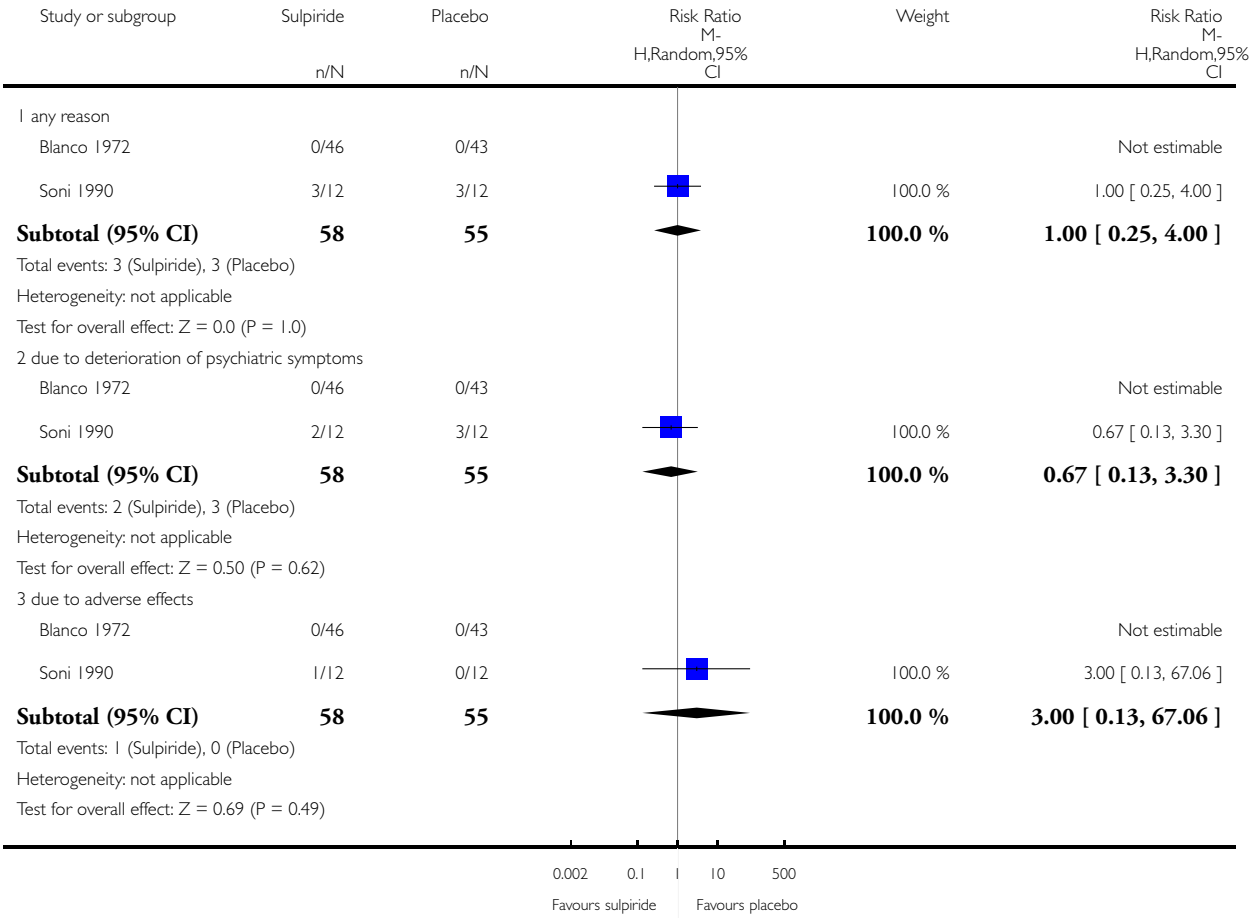
Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 SULPIRIDE vs PLACEBO, Outcome 4 Behaviour: 1. Leaving the study early.

Review: Sulpiride versus placebo for schizophrenia

Comparison: 1 SULPIRIDE vs PLACEBO

Outcome: 4 Behaviour: 1. Leaving the study early

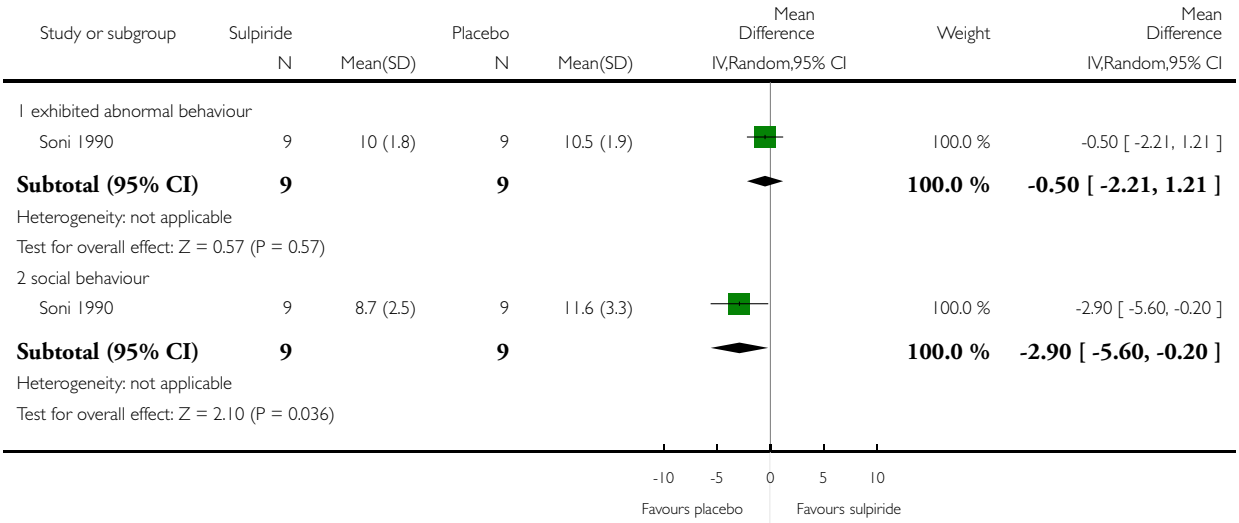


Analysis 1.5. Comparison 1 SULPIRIDE vs PLACEBO, Outcome 5 Behaviour: 2. Average social behaviour score (CBS, endpoint, high = good).

Review: Sulpiride versus placebo for schizophrenia

Comparison: 1 SULPIRIDE vs PLACEBO

Outcome: 5 Behaviour: 2. Average social behaviour score (CBS, endpoint, high = good)



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.* 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.

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

	Satisfaction with treatment: binary outcome, family, clinician and patient. 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. 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)]

WHAT'S NEW

Last assessed as up-to-date: 12 January 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.

HISTORY

Review first published: Issue 2, 2009

Date	Event	Description
6 October 2010	Amended	Contact details updated.
15 February 2010	Amended	Contact details updated.
11 November 2009	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

Ichiro Omori - protocol writing, searching, trial selection, data extraction, completion of report.

Jijun Wang - protocol writing, searching, trial selection, data extraction, completion of report.

DECLARATIONS OF INTEREST

None known.

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Internal sources

- Anonymous grant, Japan.

External sources

- National Natural Science Foundations of China, China.
- National Scientific and Technological 863 Program of China, China.

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 it was felt 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.

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