Sulpiride augmentation for schizophrenia (Review)

Wang J, Omori IM, Fenton M, Soares BGO

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[Intervention Review]

Sulpiride augmentation for schizophrenia

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ABSTRACT

Background

Sulpiride may be used in combination with other antipsychotic drugs in the hope of augmenting effectiveness - especially for those whose schizophrenia has proved resistant to treatment.

Objectives

To evaluate the effects of sulpiride augmentation versus monotherapy for people with schizophrenia.

Search methods

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

Selection criteria

All relevant randomised clinical trials (RCTs).

Data collection and analysis

We extracted data independently. For dichotomous data we calculated relative risks (RR) and their 95% confidence intervals (CI) based on a fixed-effect model. For continuous data, we calculated weighted mean differences (WMD) again based on a fixed-effect model.

Main results

We included three short-term and one long-term trial (total N=221). All participants had schizophrenia that was either treatment-resistant or with prominent negative symptoms. All studies compared sulpiride plus clozapine with clozapine (+/- placebo), were small and at considerable risk of bias.

Short-term data of 'no clinically significant response' in global state tended to favour sulpiride augmentation of clozapine compared with clozapine alone (n=193, 3 RCTs, RR 0.58 CI 0.3 to 1.09).

People allocated to sulpiride plus clozapine had more movement disorders (n=70, 1 RCT, RR 48.24 CI 3.05 to 762.56) and an increase in serum prolactin (skewed data, 1 RCT), but less incidence of hypersalivation (n=162, 3 RCTs, RR 0.49 CI 0.29 to 0.83) and less

weight gain (n=64, 1 RCT, RR 0.30 CI 0.09 to 0.99). The augmentation of clozapine by sulpiride also caused less appetite loss (n= 70, 1 RCT, RR 0.09 CI 0.01 to 0.70, NNT 4 CI 4 to 12, Z=2.31, P=0.02) and less abdominal distension (n=70, 1 RCT, RR 0.10 CI 0.01 to 0.78, NNT 5 CI 4 to 19, Z=2.20, P=0.03).

Long-term data showed no significant difference in global state (n=70, 1 RCT, RR 0.67 CI 0.42 to 1.08) and relapse (n=70, 1 RCT, RR 0.85 CI 0.5 to 1.3).

Authors' conclusions

Sulpiride plus clozapine is probably more effective than clozapine alone in producing clinical improvement in some people whose illness has been resistant to other antipsychotic drugs including clozapine. However, much more robust data are needed.

PLAIN LANGUAGE SUMMARY

The efficacy of sulpiride augmentation for schizophrenia

Schizophrenia is a serious and chronic illness in which psychotic symptoms are prominent. The psychotic symptoms are often managed with drugs. Not all people with schizophrenia respond well to treatment with antipsychotic drugs and sulpiride is often used as an add-on drug for promoting the efficacy of another medication. Several clinical trials reported effects of sulpiride augmentation for management of schizophrenia. We included four small trials which compared sulpiride plus clozapine with clozapine alone for very ill people. Evidence from the present review suggested that short-term sulpiride plus clozapine probably is more effective than clozapine alone in producing clinical improvement in some people. The evidence is, however, weak and prone to considerable bias. This is a good area for more research.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG compared to ANY ANTIPSYCHOTIC DRUG for schizophrenia

Patient or population: patients with schizophrenia
Settings:
Intervention: SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG
Comparison: ANY ANTIPSYCHOTIC DRUG

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	ANY ANTIPSYCHOTIC DRUG	SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG				
Global state: No clinically important response - short term	Study population		RR 0.58 (0.3 to 1.09)	193 (3 studies)	⊕⊕◯◯ low[1,2,3,4,5,6]	
	22 per 100	13 per 100 (7 to 24)				
	Medium risk population					
	25 per 100	14 per 100 (8 to 27)				
Specific adverse effects: 1a. CNS - short term - movement disorder - extrapyramidal effects	Study population		RR 48.24 (3.05 to 762.56)	70 (1 study)	⊕◯◯◯ very low[1,2,3,5,6,7,8]	
	0 per 100	0 per 100 (0 to 0)				
	Medium risk population					
	0 per 100	0 per 100 (0 to 0)				

Specific adverse effects: 3a. Endocrine system - short term - weight gain	**Study population**		**RR 0.3** (0.09 to 0.99)	64 (1 study)	⊕⊕◯◯ **low**[1,2,5,6]
	31 per 100	**9 per 100** (3 to 31)			
	Medium risk population				
	31 per 100	**9 per 100** (3 to 31)			
Specific adverse effects: 4. Gastrointestinal system - short term - salavation - too much	**Study population**		**RR 0.49** (0.29 to 0.83)	162 (3 studies)	⊕⊕◯◯ **low**[1,2,3,5,6,9]
	40 per 100	**19 per 100** (12 to 33)			
	Medium risk population				
	41 per 100	**20 per 100** (12 to 34)			
Mental state: 1a. General - No clinical important improvement - BPRS - short term	**Study population**		**RR 0.55** (0.32 to 0.92)	28 (1 study)	⊕⊕◯◯ **low**[1,5,6]
	917 per 1000	**504 per 1000** (293 to 844)			
	Medium risk population				
	917 per 1000	**504 per 1000** (293 to 844)			
Mental state: 2a. Negative symptoms - No clinical important improvement - negative symptoms (SANS)	**Study population**		**RR 0.76** (0.56 to 1.04)	28 (1 study)	⊕⊕◯◯ **low**[1,5,6]

	1000 per 1000	**760 per 1000** (560 to 1000)			
	Medium risk population				
	1000 per 1000	**760 per 1000** (560 to 1000)			
SENSITIVITY - Global/ mental state: No clinically important response - short term	**Study population**		**RR 0.56** (0.36 to 0.88)	221 (4 studies)	⊕⊕◯◯ **low**[1,2,3,4,5,6,10]
	30 per 100	**17 per 100** (11 to 26)			
	Medium risk population				
	31 per 100	**17 per 100** (11 to 27)			

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

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

[1] Unclear allocation concealment.
[2] Unclear blinding or lack of blinding.
[3] Incomplete outcome data not addressed in one trial.
[4] Selective reporting in 2 trials.
[5] Few patients.
[6] Total number of events less than 300.
[7] Selective reporting.
[8] Large confidence interval.
[9] Selective reporting in one trial.

[10] Unclear blinding or lack of blinding in 3 trials.

BACKGROUND

Description of the condition

Schizophrenia is a serious and chronic illness in which psychotic symptoms are prominent. The psychotic symptoms, including 'positive' symptoms (delusions, hallucinations), 'negative' symptoms (avolition, poverty of thought), emotional symptoms and cognitive deficits, are often managed with antipsychotic drugs. However, not all people with schizophrenia respond well to treatment with drugs. Most continue to suffer some symptoms throughout their lives, resulting in considerable burden (Rossler 2005).

Description of the intervention

It has been estimated that one-fifth to one-third of people with mental illnesses have a condition that is resistant to treatment (Conley 1997). In clinical practice, the lack of a satisfactory response to a single antipsychotic often prompts the addition of another (Pantelis 1996). So called 'polypharmacy' is very common in practice. For example, Farie 2005 reported that about half of people with schizophrenia were receiving more than one antipsychotic drug. The reason for this pharmacological strategy was that a single antipsychotic had not been effective (Pantelis 1996).
Sulpiride, an antipsychotic drug first formulated in the mid-1960s (Carrere 1968), is often used as an add-on drug for promoting the efficacy of another antipsychotic drugs. It has certainly been used to augment the efficacy of first generation antipsychotic drugs, such as chlorpromazine (Zhao 2003). More recently it has been used to augment the efficacy of second generation antipsychotic drugs, including clozapine and olanzapine (Kotler 2004; Raskin 2000; Shiloh 1997).

How the intervention might work

The exact mechanisms underlying sulpiride augmentation strategy have not been systematically documented. Sulpiride may simply increase blood levels of other drugs so the addition of this extra drug may simply increase availability of the companion drug to the central nervous system (Procopio 1998; Shiloh 1997). Sulpiride is a highly selective D_2 antagonist and it may act as another antipsychotic's augmentor by enhancing D_2 blockage (Raskin 2000). An alteration of the interaction between 5-HT and D2 activity might also be relevant (Shiloh 1997). The hypermethylation of GABAergic gene promoters (i.e. reelin and GAD67) is probably associated with the pathogenesis of schizophrenia (Veldic 2004). Animal studies revealed that sulpiride might play a role in activating brain DNA demethylation (Dong 2008).

Why it is important to do this review

There are several reasons why it is important to undertake this review. Firstly, we know that polypharmacy is common and addition of sulpiride to ongoing antipsychotic regimens is one means by which this happens. Secondly, there are already several clinical trials reporting the effects of sulpiride augmentation in the management of schizophrenia and we know of no systematic review of this literature. Polypharmacy is especially common for people whose illness is resistant to treatment and we are aware of work suggesting that sulpiride may be of help to those whose illness has not responded to clozapine. This group of people have illnesses that are especially difficult to treat, and if addition of sulpiride were to benefit this group even a little, that would be an important finding. Clozapine is regarded as the gold standard treatment for refractory schizophrenia (Williams 2002), but little is known about what could be done after its failure. Finally, this is one of a series of reviews on sulpiride (Table 1) updating an older Cochrane review (Soares 1999). This work will be a substantive update with new data and improved use of already identified studies.

OBJECTIVES

To evaluate the effects of sulpiride augmentation versus monotherapy for people with schizophrenia.

METHODS

Criteria for considering studies for this review

Types of studies

We included relevant randomised controlled trials. Where trials are described as 'double-blind' but are only implied as being randomised, we included these trials in a sensitivity analysis. If there were no substantive differences within primary outcomes (see Types of outcome measures) when these 'implied randomisation' studies were added, then we included these in the final analysis. If there were substantive differences, we only used clearly randomised trials and described the results of the sensitivity analysis in the text. We excluded quasi-randomised studies such as those allocating by using alternate days of the week.

Types of participants

People with schizophrenia and other types of schizophrenia-like psychoses (e.g. schizophreniform and schizoaffective disorders),

irrespective of the diagnostic criteria used. There is no clear evidence that the schizophrenia-like psychoses are caused by fundamentally different disease processes or require different treatment approaches (Carpenter 1994).

Types of interventions

1. Sulpiride in combination with any other antipsychotic treatment: any dose of oral administration.
2. Placebo (or no intervention) in combination with any other antipsychotic treatment: any dose of oral administration.

We predefined that 'other antipsychotic treatment' be in two categories. We labelled all studies so that the drug being augmented is clear. We kept the studies using a second-line typical or atypical antipsychotic (such as clozapine) in separate subgroups for the primary outcomes.

Types of outcome measures

We grouped all outcomes by time - short-term (up to 12 weeks), medium-term (13 to 26 weeks) and long-term (over 26 weeks).

Primary outcomes

1. Global state - no clinically significant response in global state - as defined by each of the studies (short-term).
2. Adverse effects - Clinically important specific adverse effects (cardiac effects, death, movement disorders, prolactin increase and associated effects, sedation, seizures, weight gain, effects on white blood cell count), (short-term).

Secondary outcomes

1. Death - suicide and natural causes
2. Global state
2.1 Relapse (defined by deterioration in mental state requiring further treatment or hospitalisation)
2.2 Average endpoint global state score
2.3 Average change in global state scores
3. Service outcomes
3.1 Hospitalisation
3.2 Inability to be discharged from hospital
4. Mental state (with particular reference to the positive and negative symptoms of schizophrenia)
4.1 No clinically important change in general mental state
4.2 Average endpoint general mental state score
4.3 Average change in general mental state scores
4.4 No clinically important change in specific symptoms (positive symptoms of schizophrenia, negative symptoms of schizophrenia, depression, mania)
4.5 Average endpoint specific symptom score
4.6 Average change in specific symptom scores
5. General functioning
5.1 No clinically important change in general functioning including working ability
5.2 Average endpoint general functioning score
5.3 Average change in general functioning scores
5.4 No clinically important change in specific aspects of functioning, such as social or life skills
5.5 Average endpoint specific aspects of functioning, such as social or life skills
5.6 Average change in specific aspects of functioning, such as social or life skills
6. Behaviour
6.1 No clinically important change in general behaviour
6.2 Average endpoint general behaviour score
6.3 Average change in general behaviour scores
6.4 No clinically important change in specific aspects of behaviour
6.5 Average endpoint specific aspects of behaviour
6.6 Average change in specific aspects of behaviour
7. Adverse effects - general
7.1 Clinically important general adverse effects
7.2 Average endpoint general adverse effect score
7.3 Average change in general adverse effect scores
8. Engagement with services
9. Satisfaction with treatment (including subjective well-being and family burden)
9.1 Leaving the studies early
9.2 Recipient of care not satisfied with treatment
9.3 Recipient of care average satisfaction score
9.4 Recipient of care average change in satisfaction scores
9.5 Carer not satisfied with treatment
9.6 Carer average satisfaction score
9.7 Carer average change in satisfaction scores
10. Quality of life
10.1 No clinically important change in quality of life
10.2 Average endpoint quality of life score
10.3 Average change in quality of life scores
10.4 No clinically important change in specific aspects of quality of life
10.5 Average endpoint specific aspects of quality of life
10.6 Average change in specific aspects of quality of life
11. Economic outcomes
11.1 Direct costs
11.2 Indirect costs
12. Cognitive functioning
12.1 No clinically important change in cognitive functioning
12.2 Average endpoint cognitive functioning score
12.3 Average change in cognitive functioning scores
12.4 No clinically important change in specific aspects of cognitive functioning
12.5 Average endpoint specific aspects of cognitive functioning
12.6 Average change in specific aspects of cognitive functioning.

Search methods for identification of studies

We used the following strategies without language restriction.

Electronic searches

1. Cochrane Schizophrenia Group Trials Register (July 2009)
The Cochrane Schizophrenia Group Trials Register was searched 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, registers of ongoing studies 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 searches
For details of the searches used in previous versions please see Appendix 1.

Searching other resources

1. Reference searching
We also searched reference lists of included studies for additional relevant trials.
2. Personal contact
We contacted the first author of each included study and known experts who had published reviews in the field for information regarding unpublished trials and extra data on the published trials.
3. Drug company
We contacted the manufacturers of sulpiride (Lorex Synthelabo Ltd, Bristol-Myers Pharmaceuticals, Pharmacia and Upjohn) to provide relevant published and unpublished data.

Data collection and analysis

Selection of studies

Two review authors (JW and IMO) 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 the two authors to assess their relevance to this review. Again, where disagreement occurred we made attempts 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
We independently extracted data from included studies. Again, any disagreement was discussed, decisions documented and, if necessary, authors of studies 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, we entered data into RevMan in such a way that the area to the left of the 'line of no effect' indicates a 'favourable' outcome for sulpiride augmentation. Where this was not possible (e.g. scales that calculate higher scores = improvement), we labelled the graphs in RevMan analyses 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 we included continuous data from rating scales only if the measuring instrument had been described in a peer reviewed journal. In addition, we set the following minimum standards for instruments: 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, we made efforts 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

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

Measures of treatment effect

1. Binary data

For binary outcomes we calculated a standard estimation of the fixed-effect risk ratio (RR) and its 95% confidence interval (CI). For statistically significant results we were to have 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. However, since the first publication of this protocol use of the Summary of Findings table has become more prevalent and we have used this instead of the NNT/H. It has been shown that RR is more intuitive (Boissel 1999) than odds ratios and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). This misinterpretation then leads to an overestimate of the impression of the effect.

2. Continuous data

2.1 Summary statistic

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

2.3 Endpoint versus change data

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

2.3 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we applied the following standards to all data before inclusion: (a) standard deviations and means are reported in the paper or obtainable from the authors; (b) when a scale starts from the finite number zero, the standard deviation, when multiplied by two, is less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution, (Altman 1996); (c) if a scale starts from a positive value (such as PANSS which can have values from 30 to 210) the calculation described above will be modified to take the scale starting point into account. In these cases skew is present if 2SD>(S-Smin), 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. We entered skewed data from studies of less 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 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. 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 can cause Type I errors (Bland 1997, Gulliford 1999).

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

We have sought statistical advice and have been advised that the binary data as presented in a report should be divided by a design effect. This is calculated using the mean number of participants per cluster (m) and the intraclass correlation 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, we synthesised these with other studies 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 only used data of the first phase of cross-over studies.

3. Studies with multiple treatment groups

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

Dealing with missing data

1. Overall loss of credibility

At some degree of loss 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 eight 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 when accompanied by a p value of <0.05 (Higgins 2003).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. These are described in section 10.1 of the Cochrane Handbook (Higgins 2008). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects (Egger 1997). We did not use funnel plots for outcomes where there were 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 the fixed-effect model.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analysis

If possible, we divided the groups of people with schizophrenia into two - those that were designated by the trialists to have illnesses that were resistant to treatment (any definition) and the studies in which people were not stipulated to have treatment resistant illnesses. We propose to summate all data together but to present these subgroups separately for the primary outcomes.

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, we presented the final data without a meta-analysis.

Sensitivity analysis

Trials comparing sulpiride plus clozapine with clozapine alone would have been taken out to investigate any significant effect of sulpiride augmentation on clozapine monotherapy. As there is concern regarding quality of trials from China (Wu 2006), a sensitivity analysis would have been performed to investigate whether the findings of these trials substantially differed from other trials.

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; Characteristics of studies awaiting classification

Results of the search

We inspected 264 (August 2008 search: 251; July 2009 search: 13) electronic reports. Two hundred and fifty one were excluded on the basis of their abstracts. We selected 13 references considered to be relevant for our review and obtained full papers. Of these trials, four studies were excluded, and five trials were considered to belong to studies awaiting assessment. Finally, we included four randomised trials meeting the inclusion criteria.

Included studies

The review includes six reports describing four studies. All were described as being randomised.
1. Study length
Three studies only reported the short-term data with a maximum length of 12 weeks. No study had reported the medium-term data. One study reported both short and long-term data (Wang 1994).
2. Design
All trials compared sulpiride plus an antipsychotic drug to the antipsychotic drug. One study added sulpiride to an on-going clozapine (Shiloh 1997). The other three studies started with a combination of sulpiride with clozapine after a washout of 1 week to 2 weeks. There were no cross-over trials.
3. Participants
A total of 221 participants are included in these four trials. Three trials were from the People's Republic of China. All studies involved participants with schizophrenia who had been diagnosed using operationalised criteria (DSM-IV,CCMD-2, CCMD-2-R, CCMD-3). The included trials were performed between 1994 and 2006 using several different sets of diagnostic criteria for schizophrenia. Participants were people with schizophrenia who had failed to respond to antipsychotic monotherapy (Shiloh 1997) or whose prominent clinical symptoms were negative (Wang 1994, Xu 2006, Zhu 1999). Shiloh seems to have included people who were partially resistant to clozapine (presumably for positive symptoms) while the other trials randomised people to clozapine and sulpiride simultaneously. People involved in Shiloh 1997 may well have had less chance of responding to clozapine alone, thus favouring the augmentation arm. Although schizophrenia is heterogenous, people with treatment-resistant schizophrenia usually have a relatively large overlap with those with prominent negative symptoms because the negative symptoms are very treatment-resistant. Therefore the heterogeneity of included participants was probably not so high as those from general clinical trials of antipsychotic drugs for schizophrenia.
4. Settings
All trials were set in hospital. The long-term trial was also hospital-based with follow-up of people who had been discharged (Wang 1994).
5. Interventions
The interventions examined in these four trials are all sulpiride augmenting clozapine with the control treatment being clozapine alone (Wang 1994, Xu 2006, Zhu 1999), or placebo plus clozapine (Shiloh 1997). Two trials included an additional arm of sulpiride alone (Wang 1994) or of sulpiride plus chlorimipramine (Zhu 1999).
6. Outcomes
Many trialists used symptom scales to assess treatment effects. They usually used The Brief Psychiatric Rating Scale (BPRS), the Scale for Assessment of Negative Symptoms (SANS) and the Scale for Assessment of Positive Symptoms (SAPS). Average change in the endpoint scores were favoured by some researchers (Shiloh 1997, Wang 1994), but these data were often not normally distributed.
We were able to extract data from some of the included studies on global state, specific adverse effects, mental state and general adverse effects. Outcomes relevant to people's mental state were reported as general mental states or as specific symptom clusters or both. Definitions of improvement differed across studies. This warranted some caution in drawing conclusions, as it was difficult to decide whether the results were comparable. However, as with a pragmatic approach to diagnosis, it seemed unlikely that those judging improvement would have such dramatically differing criteria as to make summation inappropriate.
6.1 Outcome scales: only details of the scales that provided usable data are shown below. Reasons for exclusions of data are given under 'Outcomes' in the 'Characteristics of included studies table.
6.1.1. Global state
Global state evaluation on clinical improvement was determined using a Chinese four grade assessment: recovery, significantly improved, improved and no change. This grading was was defined in the First National Congress on Interventions of Psychiatric Disorders held in China in 1958. Three studies (Wang 1994, Xu 2006, Zhu 1999) reported data from this assessment on overall clinical improvement.
6.1.2 Mental state
6.1.2.1 Brief Psychiatric Rating Scale - BPRS (Overall 1962)
The BPRS is an 18-item scale measuring positive symptoms, general psychopathology and affective symptoms. The original scale has 16 items, but a revised 18-item scale is commonly used. Scores can range from 0-126. Each item is rated on a seven-point scale varying from 'not present' to 'extremely severe', with high scores indicating more severe symptoms. Shiloh 1997 and Zhu 1999 reported data from this scale.

6.1.2.2 Scale for the Assessment of Negative Symptoms - SANS (Andreasen 1984)
This scale allows a global rating of the following negative symptoms: alogia (impoverished thinking), affective blunting, avolition-apathy, anhedonia-asociality, and attention impairment. Assessments are made on a six-point scale from zero (not at all) to five (severe). Higher scores indicate more symptoms. All studies reported data from this scale. In Wang 1994, 5 sub-scales of SANS were assessed in general as five items and reported together with SAPS.
6.1.2.3 Scale for the Assessment of Positive Symptoms - SAPS (Andreasen 1989)
This six-point scale gives a global rating of positive symptoms such as delusions, hallucinations and disordered thinking. Higher scores indicate more symptoms. Shiloh 1997 and Wang 1994 reported data from this scale. In Wang 1994, four sub-scales of SANS were assessed in general as four items and reported together with SAPS.
6.1.3 Adverse effects
Subjective Treatment-Emergent Signs and Symptoms - STESS (Campbell 1985).
This checklist assesses a variety of characteristics for each adverse event, including severity, relationship to the drug, temporal characteristics (timing after a dose, duration and pattern during the day), contributing factors, course, and action taken to counteract the effect. Symptoms can be listed a priori or can be recorded as observed by the investigator. A low score indicates low levels of adverse effects. Zhu 1999 reported data for this outcome.

Excluded studies

We excluded four studies from the review. Two were excluded, because they used an active control treatment (Li 2003, Nakazawa 1985). We had to exclude Yang 2000 because sulpiride was given, not by the oral administration, but by acupuncture point injection. The study by Kotler 2004 was excluded because it is clearly a quasi-randomised trial.
1. Awaiting assessment
Five trials await assessment (Gong 2001, Liu 1996, Wu 2005, Yao 1999, Zhao 2003). It is not entirely clear whether theses studies are really randomised and we are contacting authors for further details. It seems likely that they were all quasi-randomised and will probably not be included in the future update.
2. Ongoing studies
We are not aware of any studies that are currently ongoing.

Risk of bias in included studies

Allocation

All studies were stated to be randomised, but only one provided a description of the methods used to generate the sequence (Shiloh 1997). No study, however, provided any description of the methods used to conceal randomisation from those administering treatment. All studies, therefore, are classified as of 'unclear' quality with a moderate risk of selection bias and of overestimate of positive effect.

Blinding

One trial was stated to have used double- blinding (Shiloh 1997), in which the placebo was made to appear identical to sulpiride tablets by the manufacturer. The study did not involve testing of the success of blinding. One trial used an open-label design. The other two trials did not report whether blinding had been used. Again, this leaves little choice but to rate the risk of observer bias as, at best, 'unclear'. This gathers further potential for overestimate of positive effects and underestimate of negative ones.

Incomplete outcome data

Wang 1994 reported that five people left early, but failed to report the reasons for leaving and their outcomes, and we were unable to report whether attrition was due to protocol violations, adverse effects/events and, therefore, it remains unclear whether this trial was affected by attrition bias. Their final analyses was conducted on those completing the study and possibly introduced some bias. In the other three studies, all participants finished the trail.

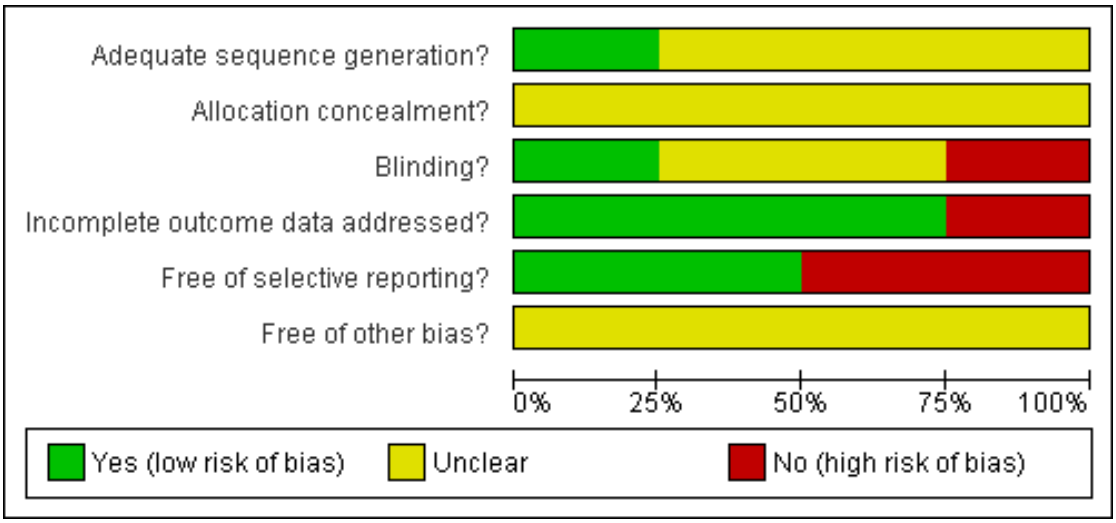
Selective reporting

An overt under reporting of outcomes was identified in the study by Zhu 1999, in which blood cell counting, EKG, EEG and hepatic function data were not reported. The study of Wang 1994 selectively reported a summation of SAPS and SANS general subscale scores for reasons that are not clear.

Other potential sources of bias

None of the trials was stated to be supported by industry - there was, in fact, no description of funding at all. All studies, therefore, are classified as of unclear quality with a moderate risk of other potential sources of bias.
Overall our judgement regarding the overall risk of bias in the individual studies is illustrated in Figure 1. One study had clear descriptions of sequence generation, but none had clear descriptions of allocation concealment. Blinding was only applied in one trial. Reporting biases are common. Whether studies were funded by industry was uncertain. The issues outlined above gave us reason to judge the risk of bias to be high, and therefore our estimates are likely to be exaggerating any true positive effect, and underestimating negative effects.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Effects of interventions

See: **Summary of findings for the main comparison** SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG compared to ANY ANTIPSYCHOTIC DRUG for schizophrenia

1. COMPARISON 1: SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG

As it happens, all trials focused on augmentation of people already treated with clozapine. We had been interested in a broader question of the augmentation of other compounds, but we identified no relevant trials.

1.1 Global state

1.1.1 No clinical important response

We found, in the short-term (up to 12 weeks) that the number of people who had not improved was lower in the sulpiride augmentation group compared with those allocated to clozapine alone (n= 193, 3 RCT, RR 0.58 CI 0.3 to 1.09). Although these three trials are homogeneous (I^2=0%), the differences in the pooled effect fell short of conventional levels of statistical significance (Z=1.69, P= 0.09).

Only Wang 1994 reported data for long-term global state ('clinical and social lack of recovery'). We found no difference between the sulpiride plus clozapine and the clozapine alone group (n=70, RR 0.67 CI 0.42 to 1.08, Z=1.65, P=0.10).

1.1.2 Relapse

Ony Wang 1994 reported the long-term data on relapse. During the 3 years, no group difference was found in the number of relapses between the sulpiride plus clozapine group and the clozapine alone group (n=70, RR 0.85 CI 0.5 to 1.3, Z=0.72, P=0.47).

1.2 Mental state

1.2.1 General mental state

Only one study predefined a criteria of clinically important improvement as more than 20% reduction in mental state scores (Shiloh 1997). The short-term BPRS data indicated that the number of participants showing 'no clinically important improvement' was less in the sulpiride plus clozapine group than in the placebo plus clozapine group (n=28, 1 RCT, RR 0.55 CI 0.32 to 0.92, NNT 3 CI 2 to 14, Z=2.29, P=0.02).

The short term endpoint BPRS scores of Zhu 1999 favoured sulpiride augmentation of clozapine with a three point advantage (n=59, WMD -3.4 CI -6.84 to 0.04, Z=1.94, P=0.05). The short-term data of average endpoint SAPS plus SANS scores in Wang 1994 were skewed, and its WMD was unclear.

The short term average change in endpoint scores of SAPS plus SANS from Wang 1994 showed that the general symptom improvement was greater in the sulpiride plus clozapine group than in the clozapine alone group (n=70, WMD -1.74 CI -3.0 to -0.47, Z=2.69, P=0.007). The skewed data of short-term BPRS change in Shiloh 1997 favoured sulpiride augmentation too (P<0.05) (Analysis 1.12).

Long-term data are available only in one trial (Wang 1994). Data of the 3 year endpoint SAPS plus SANS scores are skewed. Average change in the endpoint SAPS plus SANS scores favoured sulpiride augmentation of clozapine compared with clozapine alone (n=70, WMD -3.47 CI -4.90 to -2.04, Z=4.76, P<0.00001).

1.2.2 Negative symptoms

The binary outcome from short-term SANS scores in Shiloh 1997 tend to favour the sulpiride augmentation (n=28, 1 RCT, RR 0.76 CI 0.56 to 1.04, Z=1.72, P=0.08).

The short-term endpoint data of SANS from another trial Xu 2006 indicated that sulpiride plus clozapine was more effective on negative symptoms than clozapine alone (n=64, WMD -6.9 CI -10.87 to -2.93, Z=3.41, P=0.0007). The short-term endpoint data of SANS are also available in Zhu 1999, but they are skewed.

A greater change in endpoint SANS scores in sulpiride plus clozapine group than in the control group was reported by Shiloh 1997 (P<0.05) (Analysis 1.15).

We did not find any long-term data available about the effect of sulpiride augmentation on negative symptoms.

1.2.3 Positive symptoms

The binary outcome from short term SAPS scores in Shiloh 1997 tend to favour the sulpiride augmentation (n=28, 1 RCT, RR 0.68 CI 0.45 to 1.03, Z=1.80, P=0.07).

The short term average change in endpoint SAPS scores from the same trial (Shiloh 1997) showed a greater improvement on the positive symptoms in the sulpiride augmentation group than in the control group (P<0.05) (Analysis 1.17), but the data are skewed.

No long term data are available about the effect of sulpiride augmentation on positive symptoms.

1.2.4 Affective symptoms

For the effect of sulpiride augmentation on affective symptoms, only short-term data of average change in endpoint HAMD scores are available in Shiloh 1997 (Analysis 1.18). They are skewed and failed to show a group difference (P>0.05).

1.3 Adverse effects

1.3.1 General

General adverse effects were measured using the TESS scale in the trial of Zhu 1999. Data were skewed.

1.3.2 Specific

No death or severe adverse events were reported by any included study. All adverse effects data are for the short-term.

1.3.2.1 CNS

Wang 1994 reported that sulpiride augmentation of clozapine significantly increased the incidence of extrapyramidal movement disorders (n=70, 1 RCT, RR 48.24 CI 3.05 to 762.56, Z=2.75, P=0.006). Shiloh 1997 reported that sulpiride augmentation of clozapine evoked an aggravation of previously existing tardive dyskinesia (n=28, 1 RCT, RR 2.29 CI 0.1 to 51.85), but this effect did not reach conventional levels of statistical significance (Z=0.52, P=0.60). No significant differences were found between sulpiride plus clozapine and clozapine alone for dizziness (n=70, 1RCT RR 0.63 CI 0.19 to 2.04) and sleepiness (n=70, 1 RCT RR 0.77 CI 0.44 to 1.35).

1.3.2.2 Cardiovascular system

Arrhythmia, sinus tachycardia and right bundle branch block in ECG were reported. Sulpiride augmentation did not cause more sinus tachycardia (n=134, 2 RCTs, RR 1.12 CI 0.66 to 1.88, Z=0.41, P=0.68) or sinus arrhythmia (n=70, 1 RCT, RR 1.89 CI 0.18 to 19.89, Z=0.53, P=0.60). No difference was found for incidence of right bundle branch block in ECG (n=70, 1 RCT, RR 0.32 CI 0.01 to 7.48, Z=0.71, P=0.48).

1.3.2.3 Endocrine system

The adverse effects reported were serum prolactin level, galactorrhoea, weight gain and Body Mass Index (i.e. weight Kg/height-square m^2 - this being a common measure of obesity). Only Shiloh 1997 (n=28) reported the serum prolactin level, but data are skewed and we have not presented data graphically. The comparison between groups was not made, but the serum prolactin level was considerably higher in the sulpiride augmentation group compared with the control group (Analysis 1.5). We, however, found no group difference in incidence of galactorrhoea (n=70, 1 RCT, RR 0.47 CI 0.04 to 4.97, Z=0.62, P=0.53). Only Xu 2006 reported weight gain as an outcome. Sulpiride augmentation of clozapine significantly decreased the incidence of weight gain as compared with clozapine alone (n=64, 1 RCT, RR 0.30 CI 0.09 to 0.99, Z=1.98, P=0.05) though the confidence intervals of the relative effect include appreciable as well as non-appreciable benefit.

1.3.2.4 Gastrointestinal system

Trials reported on salivation, nausea, appetite, abdominal distension and constipation. Sulpiride augmentation of clozapine decreased incidence of too much salivation as compared with clozapine alone (n=162, 3 RCTs, RR 0.49 CI 0.29 to 0.83, NNT 5 CI 4 to 15, Z=2.69, P=0.007). The augmentation of clozapine by sulpiride also caused less appetite loss (n=70, 1 RCT, RR 0.09 CI 0.01 to 0.70, NNT 4 CI 4 to 12, Z=2.31, P=0.02) and less abdominal distension (n=70, 1 RCT, RR 0.10 CI 0.01 to 0.78, NNT 5 CI 4 to 19, Z=2.20, P=0.03). Two studies reported the incidence of constipation (n=134, 2 RCTs, 0.22 CI 0.00 to 11.70), but data were heterogeneous (I^2=87%). Random effects analysis made no substantive difference.

1.3.2.5 Haematology

Wang 1994 reported three participants treated with clozapine alone showing an increase of blood white cells, but this effect had no group difference (n=70, 1 RCT, 0.14 CI 0.01 to 2.52, Z=1.34, P=0.18). Shiloh 1997 also reported no significant changes in weekly monitoring blood white cell counts.

1.4 Leaving study early - short-term

There were five people leaving the study early in Wang 1994, but their groups from which they left were unclear. All participants finished the studies in the remaining three trials (Shiloh 1997; Xu 2006; Zhu 1999).

2. Subgroup analysis

2.1 People with treatment-resistant illness

Participants of the included studies are the people with treatment-resistant schizophrenia. Shiloh 1997 selected his participants from those who had showed poor response to several types of antipsychotic drugs including clozapine. The other three trials (Wang 1994, Xu 2006, Zhu 1999) selected their participants from those who were suffering from prominent negative symptoms, also be-

longing to the subgroup of treatment - resistant schizophrenia.

2.2 Augmentation of clozapine

All included studies compared sulpiride plus clozapine with use of clozapine alone or clozapine plus placebo. It is not necessary to perform a separate analysis for trials of sulpiride plus clozapine.

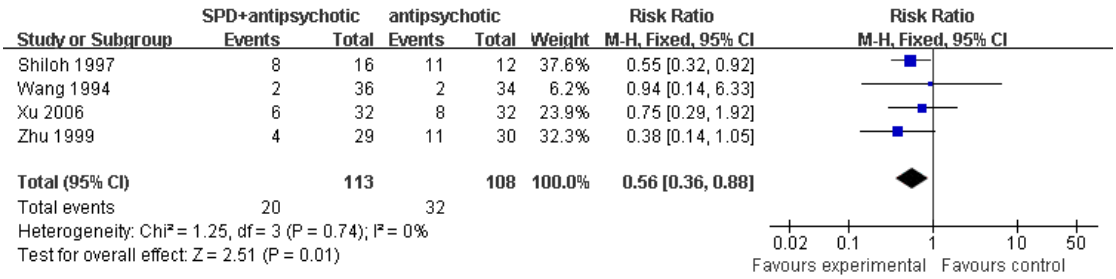
2.3 Chinese studies

Most data extracted are from Chinese studies. If all Chinese studies were removed there would, in many cases, be no data to be analysed. A sensitivity analysis without Chinese studies is not practical.

2.4 Global/mental state: no clinically important response - short-term

Chinese studies often use a four-grade criteria to quantify overall clinical improvement, within which 'no change - no clinical improvement' corresponds to less than 25% improvement. In the only Western study (Shiloh 1997), less than 20% BPRS improvement was regarded as 'no clinically important response'. Using these similar criteria, we performed a post hoc sensitivity analysis to integrate data of Global Impression and general mental state in terms of 'No clinically important response - short-term'. Data from four trials were included in this analysis (Shiloh 1997 Wang 1994, Xu 2006, Zhu 1999). We found that significantly less patients in the sulpiride augmentation of clozapine group showed 'no clinically important response' to the intervention as compared with the clozapine alone (n=221, 4 RCT, RR 0.56 CI 0.36 to 0.88, NNT 8 CI 6 to 29, Z=2.51, P=0.01, I^2=0% P=0.74, see Figure 2).

Figure 2. Forest plot of comparison: 1 SULPIRIDE AUGMENTATION OF CLOZAPINE vs CLOZAPINE, outcome: 1.20 SENSITIVITY - Global/mental state: No clinically important response - short term.



DISCUSSION

Summary of main results

1. COMPARISON 1: SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG

1.1 Global state

The short-term data, extracted from three trials, tend to favour sulpiride augmentation of clozapine. The data are not quite statistically significant but no analysis is based on many participants and therefore confidence intervals are wide. This could be an important finding, and there is a consistency between studies. It is hard to be sure of the findings as there may be publication bias and trials were not of high quality. Only one trial reported the three year long-term outcome of global state in terms of 'lack of clinical and social recovery' with an equivocal outcome. However, only 70 participants were included and more robust data are needed. This is a good area for future research.

Only one trial by Wang 1994 reported an insignificant effect of sulpiride augmentation on the number of people who had a relapse during a period of 3 years. More data are needed to address whether the relapse-preventing effect of sulpiride plus clozapine was superior to that of clozapine alone.

1.2 Mental state

The binary outcome from short term BPRS data of Shiloh 1997 indicated that the number of participants showing 'no clinically important improvement' was less in the sulpiride plus clozapine group than in the placebo plus clozapine group. It is suggestive evidence supporting the sulpiride augmentation strategy, though not strong, since the clinical importance of this difference is unclear. Evidence supporting that sulpiride plus clozapine was more effective in improving general mental state compared with clozapine alone was also found in the short-term endpoint BPRS scores of Zhu 1999, the average change in the short-term endpoint scores of SAPS plus SANS from Wang 1994 and the skewed data of short-term BPRS change in Shiloh 1997.

One set of long-term data of average change in the endpoint scores of SAPS plus SANS also favoured sulpiride augmentation group

with a three point advantage (Wang 1994) though the clinical significance of this difference is unclear. The evidence is not strong. More data are needed.

As regards negative symptoms, the binary outcome from short-term SANS scores in Shiloh 1997 tend to favour the sulpiride augmentation. In addition, the short-term endpoint data of SANS from Xu 2006 also favoured the sulpiride augmentation with a nearly seven point advantage. In addition, the skewed average change in SANS endpoint scores in the trial of Shiloh 1997 was also greater in the sulpiride augmentation group. These findings supported the beneficial effect of sulpiride augmentation on negative symptoms of people with schizophrenia whose illness is really problematic. No long-term data are available. All findings, however, are at considerable risk of bias.

Evidence favouring the sulpiride augmentation for positive symptoms is also not strong. The binary outcome from short-term SAPS scores in Shiloh 1997 tend to favour the sulpiride augmentation. Data of average change in endpoint SAPS scores from the same trial favoured the sulpiride augmentation group, but they are skewed. No long-term data are available.

Data relating to the effect of sulpiride augmentation on affective symptoms are only available in Shiloh 1997 and showed no group difference. More data are needed. Overall, these data are intriguing and do generate some hope that the sulpiride augmentation is of value. These data are weak and of unclear clinical value and some information relevant to real world care should be generated.

1.3 Adverse effects

General adverse effects assessed using the TESS scale were only available in Zhu 1999, but the data are skewed and it is impossible to understand what they mean for people with schizophrenia or their carers.

1.3.1 CNS

One small trial (n=70, Wang 1994) reported an increased incidence of unspecified extrapyramidal movement disorders in the sulpiride augmentation group. As with findings relating to mental state, this is important but in need of replication.

1.3.2 Cardiovascular system

There were no convincing effects of the augmentation on the cardiovascular - but, again, this finding is only based on one or two small trials.

1.3.3 Endocrine system

The serum prolactin level, reported by Shiloh 1997, was increased by sulpiride augmentation. The difference of prolactin associated effects such as galactorrhoea was not, however, significantly increased but with larger studies this may have been more evident. Although the incidence of weight gain in Xu 2006 favoured sulpiride augmentation of clozapine, the sample size is too small to be confident. More robust data are needed

1.3.4 Gastrointestinal system

We found that the incidence of hypersalivation was less for people allocated to sulpiride augmentation of clozapine than for those with clozapine alone. Hypersalivation is a real problem with use of clozapine. Over half of those treated with clozapine experience hypersalivation (Essali 2009), which is both remarkable in its quantity and very social disabling. If sulpiride augmentation could reduce this unpleasant effect this would be an important findings and this deserves further investigation.

1.3.5 Haematology

Problems with acute lowering of white blood cells is a real problem, and a major clinical concern, with clozapine. We found no difference in the number of people showing white cell changes between groups. Again, this important question would be answered with more confidence in a longer, larger trial.

1.4 Leaving study early - short-term

There were five people who left Wang 1994, but their group affiliates were unclear. Because the outcomes of these people were not included in reported data (selective reporting), all subsequent data from Wang 1994 may well be prone to bias.

2. Subgroup analysis

2.1 People with treatment-resistant illness

We had expected to divide the groups of people with schizophrenia into two: treatment-resistant (any definition) subgroup and non-treatment-resistant subgroup. We found that trialists had not recruited people with less problematic schizophrenia to investigate the effects of sulpiride augmentation so we know nothing of the effects of adding sulpiride to another antipsychotic drug for less severely ill people.

2.2 Augmentation of clozapine

All included studies compared sulpiride plus clozapine with use of clozapine alone or clozapine plus placebo.

2.3 Chinese studies

As most data are from Chinese studies a sensitivity analysis without Chinese studies is not practical.

2.4 Global/mental state: no clinically important response - short-term

From the post hoc sensitivity analysis integrating data of 'Global impression' and 'General mental state in terms of 'No clinically important response - short-term', we found that the number of people showing 'no clinically important response' was significantly less for the sulpiride augmentation of clozapine group compared with the control group (n=221, 4 RCT, RR 0.56 CI 0.36 to 0.88, NNT 8 CI 6 to 29). These four trials showed a good homogeneity. The clinical impression is that using sulpiride to augment the treatment of eight people who are already on clozapine would probably bring about an additional important clinical improvement to one person. Although this effect of sulpiride augmentation might be over estimated due to biases, this finding is important. Clozapine itself is the 'gold standard' choice for people whose schizophrenia is resistant to treatments - but, 40-70% of this group fail to benefit from clozapine monotherapy or only partially respond (Kontaxakis 2005). Little is known about what could be done for these people thereafter. Based on evidence from this review, the addition of sulpiride might be an alternative.

Overall completeness and applicability of evidence

1. Completeness

Data are very limited. All randomised trials included in this review are very small with the number of participants in any one group never being more than 36. Both sulpiride and clozapine are relatively old antipsychotic drugs, yet we still do not have any large randomised trials addressing the effects of combining sulpiride with clozapine for schizophrenia. Relevant studies have been published since 1994, but the majority have a duration of only 8 to 12 weeks. Problems of global and social functioning caused by schizophrenia may take much longer to improve, and so any beneficial effect of sulpiride augmentation may be underestimated in short-term studies.

Outcome reporting were mainly symptom and physician-oriented. Participant-oriented global and functional outcomes, such as readiness for discharge and ability to work were seldom reported. Not one study reported participant satisfaction and family burden. There is clearly a need for studies focusing not only on symptoms, but also on general and social functioning, family burden and participant acceptability. Since augmentation strategies involve additional costs, direct and indirect assessment of costs and benefits are also important outcomes to be assessed in future studies.

2. Applicability

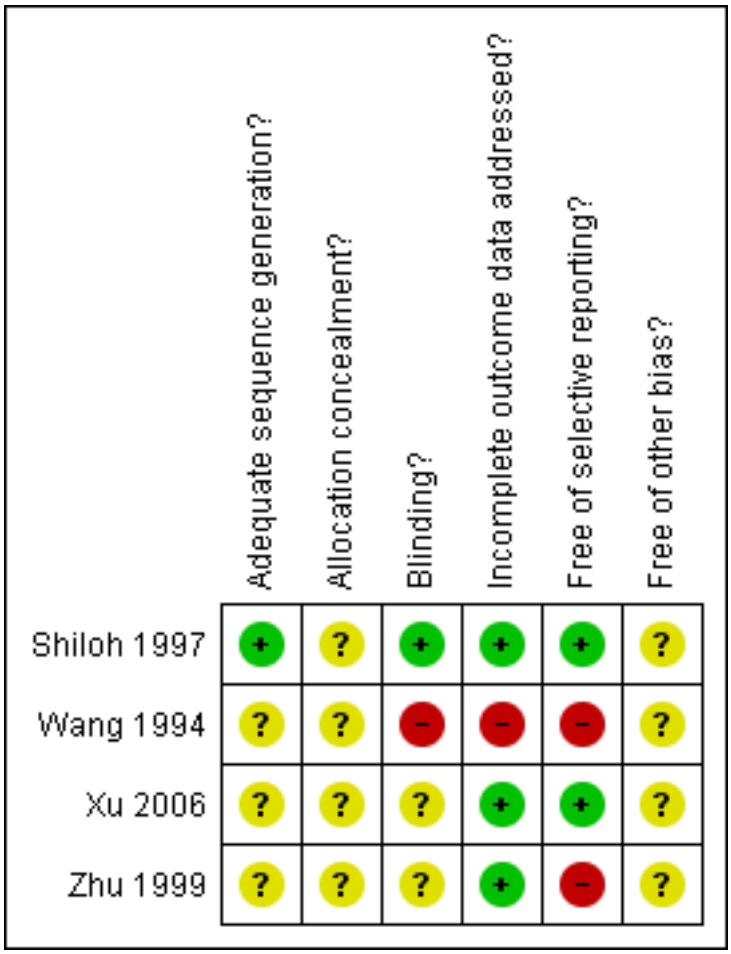
Most included studies were undertaken in hospital, whereas the majority of people with schizophrenia are treated in the community. Perhaps because people were mostly in a controlled environment data on important aspects of functions of normal living are remarkably limited. It is really problematic to apply these data more widely, although hospital care does, of course, remain important.

Most trials were undertaken in China with only the smallest originating from elsewhere. Applying the findings should be undertaken with caution for a large variety of reasons, but also the fact that most data does originate from one system of health care is also important to consider.

Quality of the evidence

The quality of reporting in most studies was poor (Figure 1, Figure 3). Only one trial described adequate sequence generation, and none had stated whether allocation concealment was applied. Two trials had not reported the status of blinding and one trial had not addressed incomplete data. Selective reporting was found with two trials. No study described the source of funding. The studies were all of limited quality and so, with sulpiride plus clozapine being the experimental intervention, there are likely to be significant biases favouring this augmentation. The magnitude of the effects of these biases on, for example, the primary outcome, could be considerable with an overestimate of 30% being entirely credible (Juni 2001). Better, independent, studies are a matter of urgency.

Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Potential biases in the review process

We attempted to avoid the possibility of publication bias but some could still remain. Selective publication of studies sponsored by pharmaceutical companies is a problematic issue (Melander 2003), our search may failed to have identified less positive studies, and this would lead to an overestimate of effect sizes in the review.

Most trials are from the People's Republic of China. These trials have been the focus of specific research and it has been found that many that are stated to be randomised are not (Wu 2006). We have contacted the authors of these trials but have not had any reply to date.

Agreements and disagreements with other studies or reviews

The previous version of this systematic review (Soares 1999) had included the Shiloh 1997 but did not specially include an 'augmentation' comparison. This review utilises these old data but views them from a new perspective.

The findings from the present review are consistent with another review we found addressing a similar issue (Kontaxakis 2005). Kontaxakis 2005 had only included Shiloh 1997 and concluded that the outcome favoured clozapine augmentation with sulpiride.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia

It is not clear if adding sulpiride to any drug other than clozapine is of use. If the response to clozapine is not ideal there are some data to support use of sulpiride as an augmentation treatment. Adding sulpiride may help with mental state and general state but the data suggesting this are not strong, and prone to various biases. The profile of adverse effects after the addition of sulpiride to clozapine is complicated. Augmentation might aggravate movement disorders and increase the serum prolactin level, but reduce the clozapine-induced hypersalivation and weight gain. Long term effects of sulpiride plus clozapine on psychotic symptoms, the social functions and general health and the economic benefits or disadvantages of sulpiride augmentation, are still unknown.

2. For clinicians

It is a really difficult clinical situation when a person has tried clozapine and only had a partial response. This review does suggest that adding sulpiride may be of use but the supporting data are very limited, short term, and very prone to bias. Adding sulpiride may encourage greater compliance with treatment for people complaining about hypersalivation or weight gain. We know of no trials where sulpiride had been combined with other antipsychotic drugs.

3. For managers / policy makers

No special implication for managers/policy makers was found from this review.

Implications for research

1. General

The majority of existing randomised studies on sulpiride augmentation are short term in-hospital trials focusing on clinical outcomes. Short studies may underestimate both adverse effects and global efficacy. The effects of combining sulpiride with clozapine in comparison to clozapine in hospitalised adult patients would have been more clear if studies had been better reported. Compliance with CONSORT (Moher 2001) by both authors and editors would ensure that the methods used were accessible to the readership and would also avoid the loss of valuable data.

The outcomes currently described are largely disease-oriented and may not be very relevant for measuring the global functioning level of a person with schizophrenia. Several important treatment aspects, such as social functioning, family burden and the economic aspects of sulpiride augmentation, have not been assessed in any of the trials. Some highly relevant outcomes, such as the person's own satisfaction with the treatment, their ability to be discharged from hospital, and to work for a living, were not reported, too. Typically reported outcomes were heterogeneous rating scales. The non-reporting of participant-oriented data and reporting of heterogeneous scales of sometimes questionable validity are major obstacles when summating data. There is a compelling need for an internationally agreed set of standardised outcomes for schizophrenia trials.

2. Specific

All included trials are generally small, and most are of poor quality. The finding in this review of the suggestion of a moderate effect on mental state is of importance, but is not strong and prone to considerable bias. A large and high quality randomised trial is required to quantify both the benefits and risks of sulpiride plus clozapine for people whose schizophrenia is resistant to treatment. Such a trial should measure global outcomes such as 'healthy days', 'social functioning', 'satisfaction with treatment', 'ability to live and work in the community', and compliance. One suggested design is presented in Table 2.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Shiloh 1997

Methods	Allocation: randomised. Blindness: double. Duration: 10 weeks. Setting: in-patients, Israel.
Participants	Diagnosis: schizophrenia (DSM-IV). N=28. Sex: 19 M, 9 F. Age: mean 40.3 SD 10.8 years, mean 37.1 SD 12.3 years. History: failed to respond to at least 3 types of typical antipsychotics and partial response to clozapine, illness duration mean 20.5 SD 10.5 years and mean 19.3 SD 7.4 years
Interventions	1. Sulpiride augmentation + clozapine: dose sulpiride 600mg/day, dose clozapine 403.1 SD 137.2 mg/day, N=16. 2. Placebo + clozapine: dose placebo 6 tablets, dose clozapine 445.8 SD 132.2 mg/day, N=12
Outcomes	Global state: Clinical improvement. Mental state: BPRS, SANS, SANS. Adverse effects: various effects, prolactin levels. Leaving the study early. Unable to use - Adverse effects: blood cell count (reported as no significant changes in weekly monitoring)
Notes	Complete non-responders to clozapine were excluded. The control group (placebo+clozapine) has a longer 'previous total duration of hospitalisation' prior to the trial (70.8 vs 32.8 months)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Randomised, 'according to a table of random numbers in a double-blind design to receive'
Allocation concealment?	Unclear risk	No description.
Blinding? All outcomes	Low risk	Placebo-controlled double-blind.
Incomplete outcome data addressed? All outcomes	Low risk	No people leaving the study early.

Shiloh 1997 (*Continued*)

Free of selective reporting?	Low risk	All data reported.
Free of other bias?	Unclear risk	No description.

Wang 1994

Methods	Allocation: randomised. Blindness: open-label. Duration: 3 years. Setting: in-patients, China.
Participants	Diagnosis: schizophrenia (CCMD-III). N=105*. Sex: 105 F. Age: 18-64 years, mean 30.4 SD 11.2 years for 36 participants, mean 31.1 SD 11.8 years for 34 participants, mean 29.4 SD 12.5 years for 35 participants. History: illness duration, range of 0.25-12 years, mean 3.3 SD 3.3 years for 36 participants, 3.5 SD 3.0 years for 34 participants, 3.5 SD 3.3 years for 35 participants
Interventions	1. Sulpiride augmentation + clozapine: dose sulpiride mean 911.03 SD 96.74 mg/day, dose clozapine mean 84.23 SD 47.60 mg/day, N=36 2. Clozapine: dose clozapine mean 265.36 SD 101.25 mg/day, N=34 3. Sulpiride: dose sulpiride mean1076.59 SD 195.92 mg/day, N=35
Outcomes	Global state: relapse, clinical improvement - short-term. Mental state: SANS and SAPS. Global functioning: recovery of social functioning. Leaving the study early. Unable to use - Adverse effects: TESS (total score and item scores - data not reported)
Notes	*Number of reported cases. Clozapine dosage was higher for the clozapine alone group.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	'Randomised into groups' without further detail.
Allocation concealment?	Unclear risk	No description.
Blinding? All outcomes	High risk	Open study.

Wang 1994 (*Continued*)

Incomplete outcome data addressed? All outcomes	High risk	Reasons for leaving early not described.
Free of selective reporting?	High risk	Item scores and total scores of SAPS and SANS, TESS score, not reported
Free of other bias?	Unclear risk	No description.

Xu 2006

Methods	Allocation: randomised. Blindness: unclear. Duration: 8 weeks. Setting: in-patients, China.
Participants	Diagnosis: schizophrenia (CCMD-III). N=64. Sex: 40 M, 24 F. Age: 18-55 years, mean 31.46 SD 8.73 years for 32 participants, mean 32.85 SD 9.53 years for 32 participants. History: illness duration, range of 1-24 years, 8.48 SD 5.42 years for 32 participants, mean 8.79 SD 6.73 years for 32 participants
Interventions	1. Sulpiride augmentation + clozapine: dose sulpiride 200-600 mg/day, dose clozapine (>50mg/day, no description of mean & SD), N=32 2. Clozapine: dose clozapine (>50mg/day, no description of mean & SD), N=32
Outcomes	Global state: clinical improvement-short term. Mental state: SANS. Adverse effects: adverse events.
Notes	No group difference for dosage of clozapine.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	'Randomised into 2 groups' with no further detail.
Allocation concealment?	Unclear risk	No description.
Blinding? All outcomes	Unclear risk	No description.
Incomplete outcome data addressed? All outcomes	Low risk	No attrition.

Free of selective reporting?	Low risk	Report all data.
Free of other bias?	Unclear risk	No description.

Zhu 1999

Methods	Allocation: randomised. Blindness: unclear. Duration: 12 weeks. Setting: in-patients, China.
Participants	Diagnosis: schizophrenia (CCMD-II-R). N=88. Sex: 48 M, 40 F. Age: 18-55 years, mean 34.56 SD 10.23 years for 29 participants, mean 34.67 SD 10. 38 years for 30 participants, mean 35.23 SD 10.44 years for 29 participants. History: illness duration, mean 5.28 SD 2.19 years for 29 participants, mean 5.31 SD 2.34 years for 30 participants, mean 5.34 SD 2.38 years for 29 participants
Interventions	1. Sulpiride augmentation + clozapine: dose sulpiride mean 700 SD 500 mg/day, dose clozapine range 300-500 mg/day, N=29 2. Clozapine: dose clozapine range 300-500 mg/day, N=30. 3. Chlorimipramine+clozapine: dose chlorimipramine mean 108 SD 28 mg/day, dose clozapine range 300-500 mg/day, N=29
Outcomes	Global state: Clinical improvement: clinical improvement (short-term). Mental state: BPRS, SANS. Adverse effects: TESS (skewed data).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Quote: "Randomised into 3 groups' with no detail.
Allocation concealment?	Unclear risk	No description.
Blinding? All outcomes	Unclear risk	No description.
Incomplete outcome data addressed? All outcomes	Low risk	No attrition.
Free of selective reporting?	High risk	Data of blood, EKG, EEG, not reported.

Zhu 1999 (*Continued*)

Free of other bias?	Unclear risk	No description.

BPRS - symptom rating scale (Brief Psychiatric Rating Scale)
CGI - global rating scale (Clinical Global Impressions)
DSM - diagnostic sets of operational criteria (Diagnostic and Statistical Manual of Mental Disorders)
DSM-IV - fourth edition, 1994.
CCMD - Chinese Classification of Mental Disorders
SANS - symptom rating scale (Scale for the Assessment of Negative Symptoms)
SAPS - symptom rating scale (Scale for the Assessment of Positive Symptoms)
SD - a measure of dispersion (standard deviation)
TESS - Treatment Emergent Signs and Symptoms
WBC - white blood cells

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

Study	Reason for exclusion
Kotler 2004	Allocation: quasi-randomised. Participants: people with schizophrenia. Interventions: sulpiride plus olanzapine vs olanzapine.
Li 2003	Allocation: randomised. Participants: people with schizophrenia. Interventions: sulpiride plus clozapine vs venlafaxine plus clozapine
Nakazawa 1985	Allocation: randomised. Participants: people with schizophrenia. Interventions: sulpiride injection plus levomepromazine vs timiperone injection plus levomepromazine
Yang 2000	Allocation: randomised. Participants: people with schizophrenia. Interventions: acupuncture point sulpiride injection plus antipsychotics vs antipsychotics

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

Gong 2001

Methods	Allocation: 'randomisation' - according to admission sequence, no further detail
Participants	Diagnosis: schizophrenia. N=90.

Gong 2001 (*Continued*)

Interventions	1. Sulpiride. 2. Clozapine. 3. Sulpiride plus clozapine.
Outcomes	1. Global state: CGI. 2. Mental state: BPRS. 3. Adverse effects: TESS.
Notes	None.

Liu 1996

Methods	Allocation: 'randomisation' - according to admission sequence, no further detail
Participants	Diagnosis: schizophrenia. N=102.
Interventions	1. Sulpiride. 2. Clozapine. 3. Sulpiride plus clozapine.
Outcomes	1. Global state: CGI. 2. Mental state: BPRS, SANS. 3. Adverse effects: TESS.
Notes	None.

Wu 2005

Methods	Allocation: 'randomisation' - according to a sequence, no further detail
Participants	Diagnosis: schizophrenia. N=97.
Interventions	1. Sulpiride. 2. Olanzapine. 3. Sulpiride plus olanzapine.
Outcomes	1. Global state: CGI. 2. Mental state: BPRS, SANS. 3. QOL: SDSS.
Notes	None.

Yao 1999

Methods	Allocation: 'randomisation' - according to admission sequence, no further detail
Participants	Diagnosis: schizophrenia. N=41.
Interventions	1. Sulpiride plus clozapine. 2. Clozapine.
Outcomes	1. Mental state: BPRS, SANS. 2. Adverse effects: TSSS.
Notes	None.

Zhao 2003

Methods	Allocation: 'randomisation' - according to admission sequence, no further detail
Participants	Diagnosis: schizophrenia. N=60.
Interventions	1. Sulpiride. 2. Chlorpromazine. 3. Sulpiride plus chlorpromazine.
Outcomes	1. Global state: CGI. 2. Mental state: BPRS, SANS. 3. Adverse effects: TESS.
Notes	None.

DATA AND ANALYSES

Comparison 1. SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global state: 1. No clinically important response	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 short term	3	193	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.30, 1.09]
1.2 long term ("clinical and social lack of recovery")	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.42, 1.08]
2 Global state: 2. Relapse	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.54, 1.33]
3 Mental state: 1a. General - No clinical important improvement	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 BPRS - short term	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.32, 0.92]
4 Mental state: 1b. General - Average endpoint scores	1	59	Mean Difference (IV, Fixed, 95% CI)	-3.40 [-6.84, 0.04]
4.1 BPRS - short term	1	59	Mean Difference (IV, Fixed, 95% CI)	-3.40 [-6.84, 0.04]
5 Mental state: 1c. General - Average change in endpoint scores	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 SAPS plus SANS - short term	1	70	Mean Difference (IV, Fixed, 95% CI)	-1.74 [-3.01, -0.47]
5.2 SAPS plus SANS - long term	1	70	Mean Difference (IV, Fixed, 95% CI)	-3.47 [-4.90, -2.04]
6 Mental state: 1d. General - Average endpoint and average change in endpoint scores (skewed data)			Other data	No numeric data
6.1 change in BPRS - short term			Other data	No numeric data
6.2 endpoint SAPS plus SANS - short term			Other data	No numeric data
6.3 endpoint SAPS plus SANS - long term			Other data	No numeric data
7 Mental state: 2a. Negative symptoms - No clinical important improvement	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 negative symptoms (SANS)	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.56, 1.04]
8 Mental state: 2b. Negative symptoms - Average endpoint scores	1	64	Mean Difference (IV, Fixed, 95% CI)	-6.90 [-10.87, -2.93]
8.1 SANS	1	64	Mean Difference (IV, Fixed, 95% CI)	-6.90 [-10.87, -2.93]

9 Mental state: 2c. Negative symptoms - Average endpoint and average change in endpoint scores (skewed data)			Other data	No numeric data
9.1 change in endpoint SANS - short term			Other data	No numeric data
9.2 endpoint SANS - short term			Other data	No numeric data
10 Mental state: 3a. Positive symptoms - No clinical important improvement	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.45, 1.03]
10.1 SAPS	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.45, 1.03]
11 Mental state: 3b. Positive symptoms - Average endpoint and average change in endpoint scores (skewed data)			Other data	No numeric data
11.1 change in endpoint SAPS - short term			Other data	No numeric data
12 Mental state: 4. Emotional symptoms - Average endpoint and average change in endpoint scores (skewed data)			Other data	No numeric data
12.1 depression scores (HAMD) - short term			Other data	No numeric data
13 Adverse effects - general: short term (skewed data)			Other data	No numeric data
13.1 TESS - average endpoint scores (high = poor)			Other data	No numeric data
14 Adverse effects - specific: 1a. CNS - short term	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 dizziness	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.19, 2.04]
14.2 movement disorder - extrapyramidal effects	1	70	Risk Ratio (M-H, Fixed, 95% CI)	48.24 [3.05, 762.56]
14.3 movement disorder - tardive dyskinesia - aggravation	1	28	Risk Ratio (M-H, Fixed, 95% CI)	2.29 [0.10, 51.85]
14.4 Drowsiness	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.44, 1.35]
15 Adverse effects - specific: 2. Cardiovsacular system (short-term)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 arrythmia - sinus arrythmia	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [0.18, 19.89]
15.2 ECG problems - right bundle branch block	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.48]
15.3 tachycardia - sinus tachycardia	2	134	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.66, 1.88]
16 Adverse effects - specific: 3a. Endocrine system (short-term)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 galactorrhea	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.04, 4.97]
16.2 weight gain	1	64	Risk Ratio (M-H, Fixed, 95% CI)	0.3 [0.09, 0.99]

17 Adverse effects - specific: 3b. Endocrine system (short-term, skewed data)			Other data	No numeric data
17.1 prolactin - average endpoint serum level (men)			Other data	No numeric data
17.2 prolactin - average endpoint serum level (women)			Other data	No numeric data
18 Adverse effects - specific: 4. Gastrointestinal system (short-term)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 abdominal distension	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 0.78]
18.2 appetite - loss	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 0.70]
18.3 constipation	2	134	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.24, 0.81]
18.4 salavation - too much	3	162	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.29, 0.83]
18.5 nausea	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.00, 0.93]
19 Adverse effects - specific: 5. Haematology	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 white blood cells - increase	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.52]
20 SENSITIVITY - Global/mental state: No clinically important response (short-term)	4	221	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.36, 0.88]

Analysis 1.1. Comparison 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG, Outcome 1 Global state: 1. No clinically important response.

Review: Sulpiride augmentation for schizophrenia

Comparison: 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG

Outcome: 1 Global state: 1. No clinically important response

Study or subgroup	Sulpiride + clozapine n/N	Clozapine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 short term					
Wang 1994	2/36	2/34		9.9 %	0.94 [0.14, 6.33]
Xu 2006	6/32	8/32		38.3 %	0.75 [0.29, 1.92]
Zhu 1999	4/29	11/30		51.8 %	0.38 [0.14, 1.05]
Subtotal (95% CI)	**97**	**96**		**100.0 %**	**0.58 [0.30, 1.09]**
Total events: 12 (Sulpiride + clozapine), 21 (Clozapine)					
Heterogeneity: Chi^2 = 1.23, df = 2 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 1.69 (P = 0.091)					
2 long term ("clinical and social lack of recovery")					

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Sulpiride + clozapine n/N	Clozapine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wang 1994	15/36	21/34		100.0 %	0.67 [0.42, 1.08]
Subtotal (95% CI)	**36**	**34**		**100.0 %**	**0.67 [0.42, 1.08]**
Total events: 15 (Sulpiride + clozapine), 21 (Clozapine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.65 (P = 0.099)					

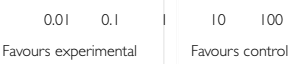
Analysis 1.2. Comparison 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG, Outcome 2 Global state: 2. Relapse.

Review: Sulpiride augmentation for schizophrenia

Comparison: 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG

Outcome: 2 Global state: 2. Relapse

Study or subgroup	Sulpiride + clozapine n/N	Clozapine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wang 1994	17/36	19/34		100.0 %	0.85 [0.54, 1.33]
Total (95% CI)	**36**	**34**		**100.0 %**	**0.85 [0.54, 1.33]**
Total events: 17 (Sulpiride + clozapine), 19 (Clozapine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.72 (P = 0.47)					
Test for subgroup differences: Not applicable					



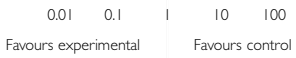
Analysis 1.3. Comparison 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG, Outcome 3 Mental state: 1a. General - No clinical important improvement.

Review: Sulpiride augmentation for schizophrenia

Comparison: 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG

Outcome: 3 Mental state: 1a. General - No clinical important improvement

Study or subgroup	Sulpiride + clozapine n/N	Clozapine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 BPRS - short term					
Shiloh 1997	8/16	11/12		100.0 %	0.55 [0.32, 0.92]
Subtotal (95% CI)	**16**	**12**		**100.0 %**	**0.55 [0.32, 0.92]**
Total events: 8 (Sulpiride + clozapine), 11 (Clozapine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.29 (P = 0.022)					



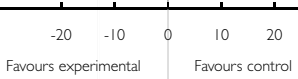
Analysis 1.4. Comparison 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG, Outcome 4 Mental state: 1b. General - Average endpoint scores.

Review: Sulpiride augmentation for schizophrenia

Comparison: 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG

Outcome: 4 Mental state: 1b. General - Average endpoint scores

Study or subgroup	Sulpiride + clozapine N	Mean(SD)	Clozapine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 BPRS - short term							
Zhu 1999	29	23.4 (5.9)	30	26.8 (7.5)		100.0 %	-3.40 [-6.84, 0.04]
Total (95% CI)	**29**		**30**			**100.0 %**	**-3.40 [-6.84, 0.04]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.94 (P = 0.053)							
Test for subgroup differences: Not applicable							

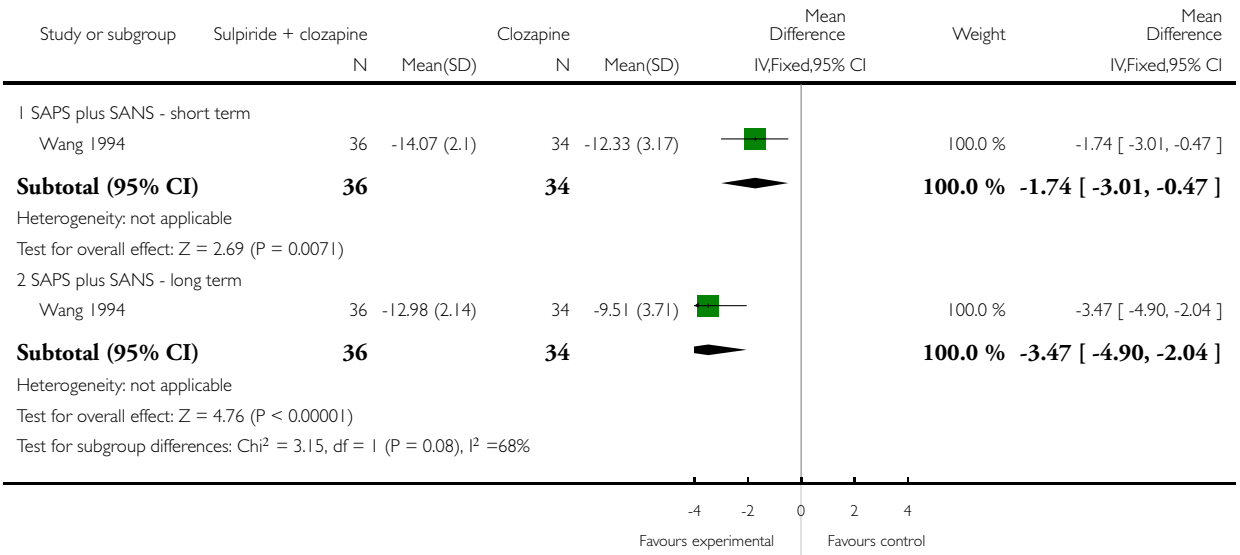


Analysis 1.5. Comparison 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG, Outcome 5 Mental state: 1c. General - Average change in endpoint scores.

Review: Sulpiride augmentation for schizophrenia

Comparison: 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG

Outcome: 5 Mental state: 1c. General - Average change in endpoint scores



Analysis 1.6. Comparison 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG, Outcome 6 Mental state: 1d. General - Average endpoint and average change in endpoint scores (skewed data).

Mental state: 1d. General - Average endpoint and average change in endpoint scores (skewed data)

Study	Intervention	Mean	SD	N	Statistic
change in BPRS - short term					
Shiloh 1997	Sulpiride plus clozapine Clozapine	-8.7 -2.3	8.3 6.2	16 12	P<0.05

Mental state: 1d. General - Average endpoint and average change in endpoint scores (skewed data) (*Continued*)

endpoint SAPS plus SANS - short term					
Wang 1994	Sulpiride plus clozapine Clozapine	3.16 4.91	1.78 2.91	36 34	
endpoint SAPS plus SANS - long term					
Wang 1994	Sulpiride plus clozapine Clozapine	4.02 6.77	2.10 3.15	36 34	

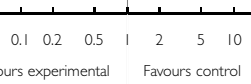
Analysis 1.7. Comparison 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG, Outcome 7 Mental state: 2a. Negative symptoms - No clinical important improvement.

Review: Sulpiride augmentation for schizophrenia

Comparison: 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG

Outcome: 7 Mental state: 2a. Negative symptoms - No clinical important improvement

Study or subgroup	Sulpiride + clozapine n/N	Clozapine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 negative symptoms (SANS)					
Shiloh 1997	12/16	12/12		100.0 %	0.76 [0.56, 1.04]
Subtotal (95% CI)	**16**	**12**		**100.0 %**	**0.76 [0.56, 1.04]**
Total events: 12 (Sulpiride + clozapine), 12 (Clozapine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.72 (P = 0.085)					

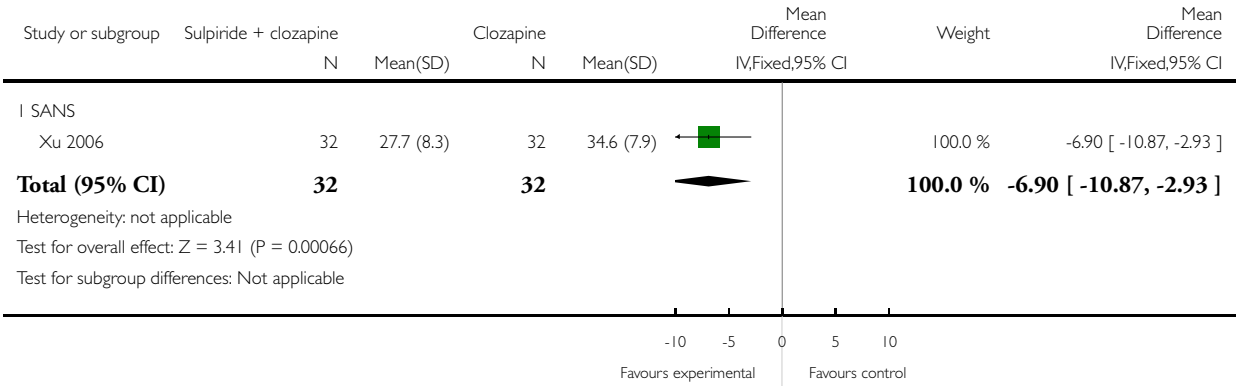


Analysis 1.8. Comparison 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG, Outcome 8 Mental state: 2b. Negative symptoms - Average endpoint scores.

Review: Sulpiride augmentation for schizophrenia

Comparison: 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG

Outcome: 8 Mental state: 2b. Negative symptoms - Average endpoint scores



Analysis 1.9. Comparison 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG, Outcome 9 Mental state: 2c. Negative symptoms - Average endpoint and average change in endpoint scores (skewed data).

Mental state: 2c. Negative symptoms - Average endpoint and average change in endpoint scores (skewed data)

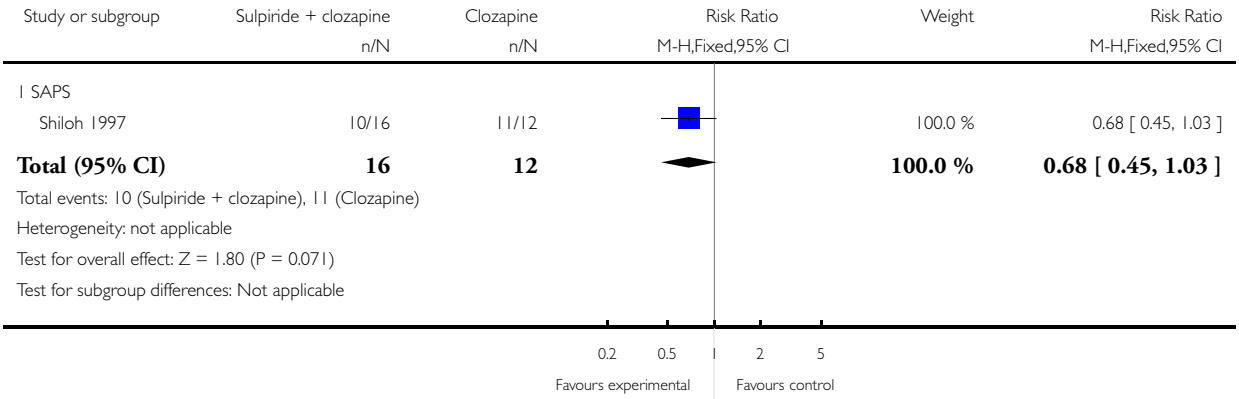
Study	Intervention	Mean	SD	N	Statistic
change in endpoint SANS - short term					
Shiloh 1997	Sulpiride plus clozapine Clozapine	-8.3 -1.5	10.8 4.4	16 12	P<0.05
endpoint SANS - short term					
Zhu 1999	Sulpiride plus clozapine Clozapine	23.6 28.2	14.3 17.5	29 30	

Analysis 1.10. Comparison 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG, Outcome 10 Mental state: 3a. Positive symptoms - No clinical important improvement.

Review: Sulpiride augmentation for schizophrenia

Comparison: 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG

Outcome: 10 Mental state: 3a. Positive symptoms - No clinical important improvement



Analysis 1.11. Comparison 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG, Outcome 11 Mental state: 3b. Positive symptoms - Average endpoint and average change in endpoint scores (skewed data).

Mental state: 3b. Positive symptoms - Average endpoint and average change in endpoint scores (skewed data)

Study	Intervention	Mean	SD	N	Statistic
change in endpoint SAPS - short term					
Shiloh 1997	Sulpiride plus clozapine Clozapine	-6.4 -0.6	7.1 7.6	16 12	P<0.05

Analysis 1.12. Comparison 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG, Outcome 12 Mental state: 4. Emotional symptoms - Average endpoint and average change in endpoint scores (skewed data).

Mental state: 4. Emotional symptoms - Average endpoint and average change in endpoint scores (skewed data)

Study	Intervention	Mean	SD	N	Statistic
depression scores (HAMD) - short term					

Shiloh 1997	Sulpiride plus clozapine Clozapine	-2.7 -0.7	5.8 3.1	16 12	

Analysis 1.13. Comparison 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG, Outcome 13 Adverse effects - general: short term (skewed data).

Adverse effects - general: short term (skewed data)

Study	Intervention	Mean	SD	N	Statistic
TESS - average endpoint scores (high = poor)					
Zhu 1999	Sulpiride plus clozapine Clozapine	3.4 2.9	2.5 2.3	29 30	None reported

Analysis 1.14. Comparison 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG, Outcome 14 Adverse effects - specific: 1a. CNS - short term.

Review: Sulpiride augmentation for schizophrenia

Comparison: 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG

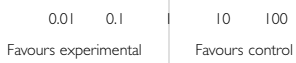
Outcome: 14 Adverse effects - specific: 1a. CNS - short term

Study or subgroup	Sulpiride + clozapine n/N	Clozapine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 dizziness					
Wang 1994	4/36	6/34		100.0 %	0.63 [0.19, 2.04]
Subtotal (95% CI)	**36**	**34**		**100.0 %**	**0.63 [0.19, 2.04]**
Total events: 4 (Sulpiride + clozapine), 6 (Clozapine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.77 (P = 0.44)					
2 movement disorder - extrapyramidal effects					
Wang 1994	25/36	0/34		100.0 %	48.24 [3.05, 762.56]
Subtotal (95% CI)	**36**	**34**		**100.0 %**	**48.24 [3.05, 762.56]**
Total events: 25 (Sulpiride + clozapine), 0 (Clozapine)					
Heterogeneity: not applicable					

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Sulpiride + clozapine n/N	Clozapine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 2.75 (P = 0.0059)					
3 movement disorder - tardive dyskinesia - aggravation					
Shiloh 1997	1/16	0/12		100.0 %	2.29 [0.10, 51.85]
Subtotal (95% CI)	**16**	**12**		**100.0 %**	**2.29 [0.10, 51.85]**
Total events: 1 (Sulpiride + clozapine), 0 (Clozapine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.52 (P = 0.60)					
4 Drowsiness					
Wang 1994	13/36	16/34		100.0 %	0.77 [0.44, 1.35]
Subtotal (95% CI)	**36**	**34**		**100.0 %**	**0.77 [0.44, 1.35]**
Total events: 13 (Sulpiride + clozapine), 16 (Clozapine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.92 (P = 0.36)					

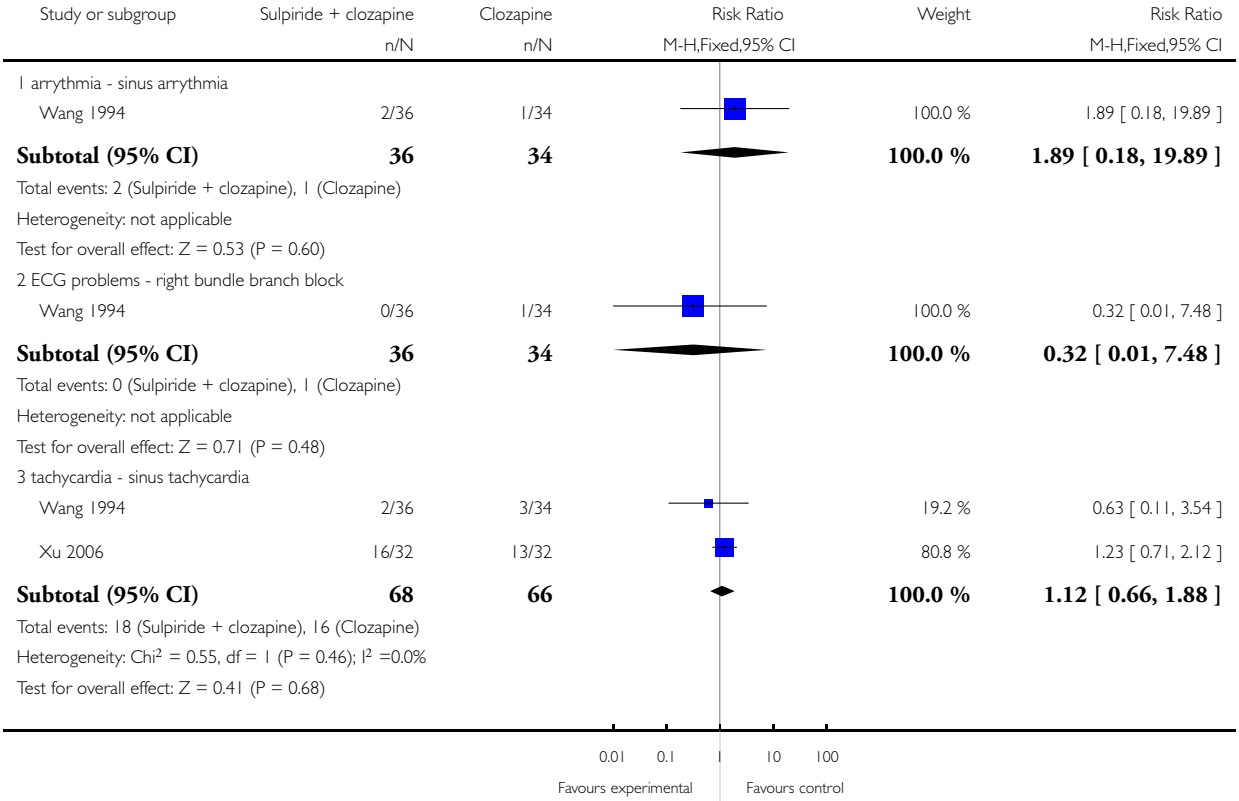


Analysis 1.15. Comparison 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG, Outcome 15 Adverse effects - specific: 2. Cardiovsacular system (short-term).

Review: Sulpiride augmentation for schizophrenia

Comparison: 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG

Outcome: 15 Adverse effects - specific: 2. Cardiovsacular system (short-term)

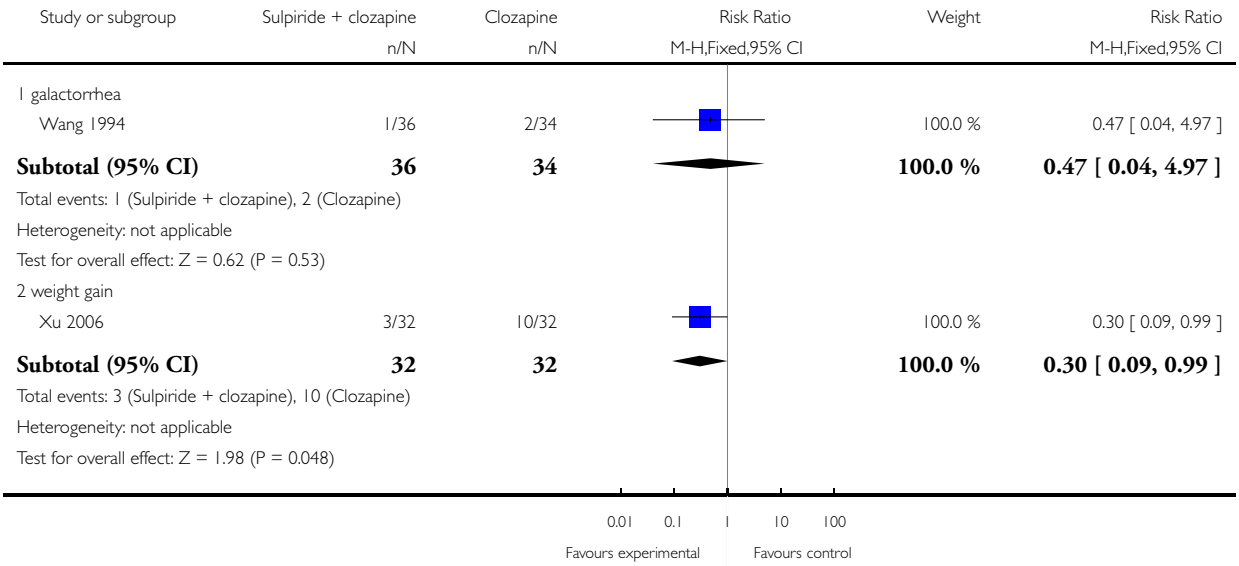


Analysis 1.16. Comparison 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG, Outcome 16 Adverse effects - specific: 3a. Endocrine system (short-term).

Review: Sulpiride augmentation for schizophrenia

Comparison: 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG

Outcome: 16 Adverse effects - specific: 3a. Endocrine system (short-term)



Analysis 1.17. Comparison 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG, Outcome 17 Adverse effects - specific: 3b. Endocrine system (short-term, skewed data).

Adverse effects - specific: 3b. Endocrine system (short-term, skewed data)

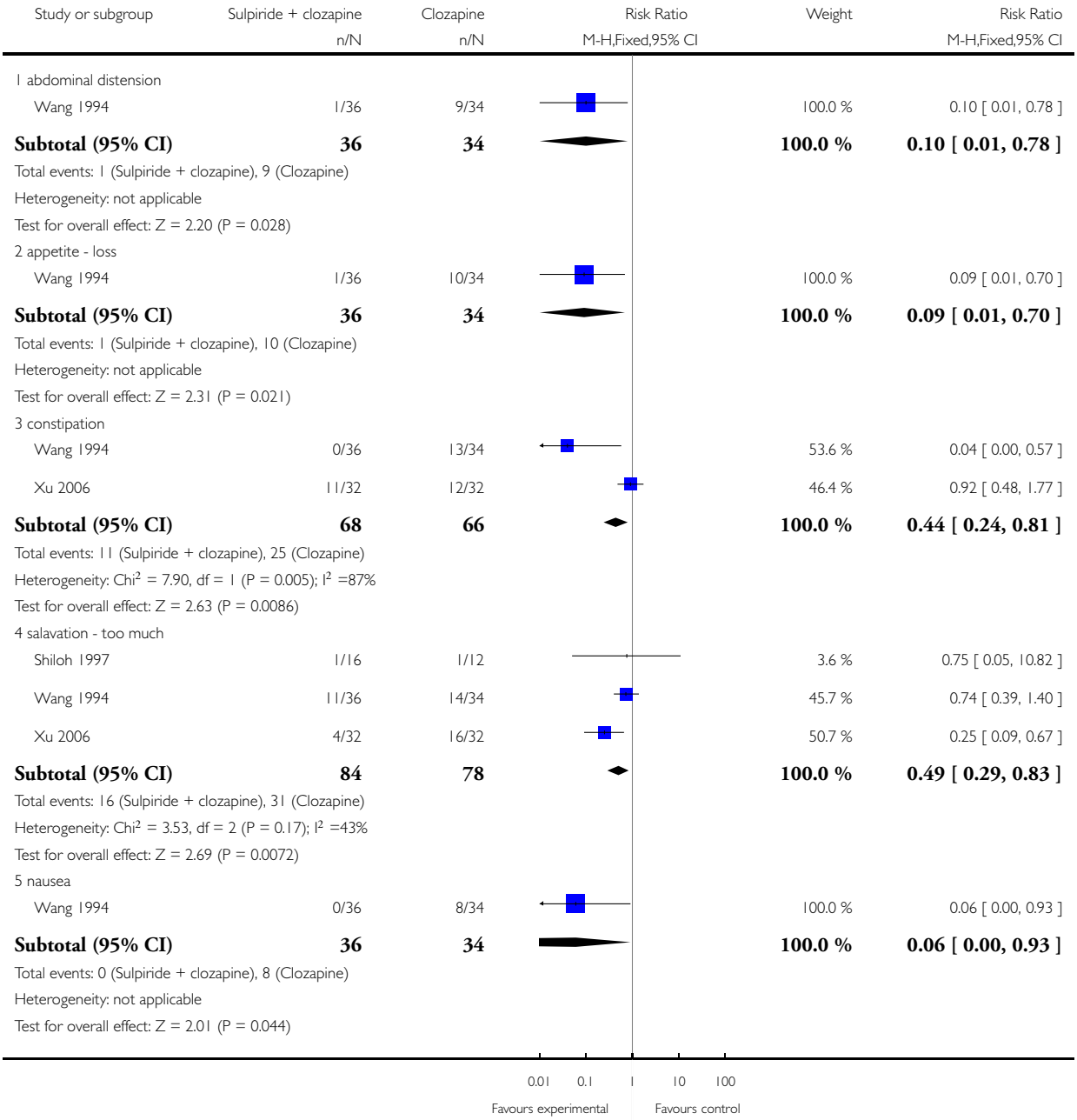
Study	Intervention	Mean	SD	N	Statistic
prolactin - average endpoint serum level (men)					
Shiloh 1997	Sulpiride plus clozapine Clozapine	75.4 18.0	19.8 13.4	11 8	
prolactin - average endpoint serum level (women)					
Shiloh 1997	Sulpiride plus clozapine Clozapine	101.8 16.9	41.0 11.8	5 4	

Analysis 1.18. Comparison 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG, Outcome 18 Adverse effects - specific: 4. Gastrointestinal system (short-term).

Review: Sulpiride augmentation for schizophrenia

Comparison: 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG

Outcome: 18 Adverse effects - specific: 4. Gastrointestinal system (short-term)



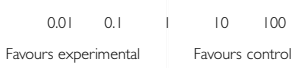
Analysis 1.19. Comparison 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG, Outcome 19 Adverse effects - specific: 5. Haematology.

Review: Sulpiride augmentation for schizophrenia

Comparison: 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG

Outcome: 19 Adverse effects - specific: 5. Haematology

Study or subgroup	Sulpiride + clozapine n/N	Clozapine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 white blood cells - increase					
Wang 1994	0/36	3/34		100.0 %	0.14 [0.01, 2.52]
Subtotal (95% CI)	**36**	**34**		**100.0 %**	**0.14 [0.01, 2.52]**
Total events: 0 (Sulpiride + clozapine), 3 (Clozapine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.34 (P = 0.18)					



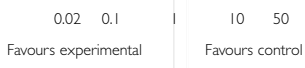
Analysis 1.20. Comparison 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG, Outcome 20 SENSITIVITY - Global/mental state: No clinically important response (short-term).

Review: Sulpiride augmentation for schizophrenia

Comparison: 1 SULPIRIDE AUGMENTATION OF ANY ANTIPSYCHOTIC DRUG vs ANY ANTIPSYCHOTIC DRUG

Outcome: 20 SENSITIVITY - Global/mental state: No clinically important response (short-term)

Study or subgroup	Sulpiride + clozapine n/N	Clozapine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Shiloh 1997	8/16	11/12		37.6 %	0.55 [0.32, 0.92]
Wang 1994	2/36	2/34		6.2 %	0.94 [0.14, 6.33]
Xu 2006	6/32	8/32		23.9 %	0.75 [0.29, 1.92]
Zhu 1999	4/29	11/30		32.3 %	0.38 [0.14, 1.05]
Total (95% CI)	**113**	**108**		**100.0 %**	**0.56 [0.36, 0.88]**
Total events: 20 (Sulpiride + clozapine), 32 (Clozapine)					
Heterogeneity: Chi^2 = 1.25, df = 3 (P = 0.74); I^2 =0.0%					
Test for overall effect: Z = 2.51 (P = 0.012)					



ADDITIONAL TABLES

Table 1. Sulpiride reviews

Focus of review	Stage and Link
Sulpiride	Out of date full review Soares 1999
Sulpiride vs placebo	Full review Omori 2009
Sulpiride vs other antipsychotics	Protocol Omori 2009 b
Sulpiride + antidepressants	Title - in preparation
Sulpiride doses	Title - in preparation

Table 2. Suggested design for future study

Methods	Allocation: randomised, clearly described. Blinding: double, tested. Duration: 1 year.
Participants	Diagnosis: schizophrenia. N=300.* Age: adults. Sex: both. History: severely ill, no clear response to clozapine given continuously in adequate doses for at least 12 weeks
Interventions	1. Sulpiride + clozapine: sulpiride dosage 600-800 mg/day, clozapine dosage previously used dosage. N=150 2. Clozapine: previously used dosage. N=150.
Outcomes	Death. Adverse effects: list, including serum prolactin level, 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. Economic data. 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

1. The Cochrane Schizophrenia Group Trials Register
The 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).
2. The following search phrase was constructed to assist identification for previous versions of this review (New Reference).
(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: 4 November 2009.

Date	Event	Description
18 January 2012	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 4, 2009

Review first published: Issue 1, 2010

Date	Event	Description
8 December 2010	Amended	Contact details updated.
6 October 2010	Amended	Contact details updated.
15 February 2010	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

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

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

Mark Fenton - data extraction, completion of report.

Bernardo Soares - data extraction, completion of report.

DECLARATIONS OF INTEREST

None known.

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to I Omori

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to J Wang

- National Natural Science Foundations of China (30770773), China.

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- National Basic Research Program of China (973 Program, 2007CB512306); Joint Key Project of New Frontier Technology in Shanghai Municipal Hospitals (SHDC12006105), China.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In Measures of treatment effect we have described how we were to use NNT/H to help provide clinically useful data. We did change this at the review stage as, largely the Summary of findings for the main comparison has taken the place of the use of NNT. We undertook one *post hoc* analysis (2.4 Global/mental state: no clinically important response - short-term). This is highlighted in the text.

INDEX TERMS

Medical Subject Headings (MeSH)

Antipsychotic Agents [*administration & dosage]; Clozapine [*administration & dosage]; Drug Synergism; Drug Therapy, Combination [methods]; Randomized Controlled Trials as Topic; Schizophrenia [*drug therapy]; Sulpiride [*administration & dosage]

MeSH check words

Humans