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[Intervention Protocol]

Sulpiride versus other antipsychotics for schizophrenia

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To review the effects of sulpiride for the treatment of schizophrenia and schizophrenia-like psychoses compared with other antipsychotics.

BACKGROUND

Description of the condition

Schizophrenia is a severe and chronic psychiatric illness characterised by a combination of hallucinations, delusions, disorganisation and other 'negative' symptoms. These characteristics are associated with noticeable social and or occupational dysfunction. Schizophrenia affects 0.5 to 1.5% of the population worldwide (APA 1994). One third of people with schizophrenia are likely to suffer symptoms continuously over ten years (Mason 1996) and it is regarded as one of the most burdensome diseases (Rossler 2005). Its economic impact on society is great and medication costs for treating schizophrenia are increasing (McEvoy 2007).

Description of the intervention

Sulpiride is a relatively old antipsychotic drug that was developed in France in the mid-1960s. Although sulpiride is still widely used for treatment of schizophrenia in some European and Asian countries, it is not marketed in the USA (Carrere 1968, Miyamoto 2003, Nishiura 1976). A new generation of antipsychotic drugs became available in the 1980s that generally had less of a propensity to cause movement disorders (specifically catalepsy in rats - Kerwin 1994). Although there is currently no standard definition of the term 'atypical', these new drugs were collectively classed as being atypical compared with previously known antipsychotic drugs. It is possible however, that some older drugs, such as sulpiride and amisulpride, could also be classed in this way (Miyamoto 2003). It has been suggested that sulpiride may be more effective than drugs such as chlorpromazine and haloperidol for treating the negative symptoms of schizophrenia (poverty of speech, lack of motivation, apathy, emotional impoverishment etc.) (Azorin 1992, Gerlach 1991) and that this effect is best seen when low doses are used (Mauri 1996, Petit 1987). High-dose sulpiride is said to be effective for both negative and 'positive' symptoms (delusions, hallu-

cinations etc.). This higher level of dosing may be safe for elderly people, whereas the cardiovascular effects of other antipsychotic drugs can be problematic (Mauri 1994, Mauri 1996).

How the intervention might work

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

Why it is important to do this review

Several guidelines have recommended the use of atypical antipsychotic drugs for patients in the acute phase of schizophrenia (Lehman 2004, NICE 2002). The consumption of expensive atypical antipsychotic medication has increased dramatically and in total worldwide has reached over $12 billion (Snyder 2008). There, however, continues to be debate over the benefits and downsides of these medications. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) advices that these atypical medications may offer few, if any, benefits over some typical antipsychotic drugs (Lieberman 2005). In addition, some meta-analyses have shown that atypical antipsychotic drugs may differ in their efficacy and tolerability and are not homogeneous entities (Davis 2003, Leucht 2009). It has been reported that in developing countries, basic, evidence-based care for patients with mental illness is scarce and a large number of psychiatric patients are suffering because of the increased cost of care (Patel 2007). In these countries inexpensive antipsychotic drugs are believed to be more cost effective than newer, more expensive drugs (Chisholm 2008, Hyman 2006). Sulpiride, which is a relatively inexpensive, older antipsychotic drug, should be re-evaluated as a potentially widely accessible atypical antipsychotic drug.

Several systematic reviews have examined the efficacy and tolerability of sulpiride. For example, Caley 1995 reviewed eight randomised controlled trials of sulpiride in the pharmacotherapy of schizophrenia. This review was limited to published materials and English-language papers, and a validity assessment of the included studies was not reported. Some recent valid systematic reviews of the efficacy of atypical antipsychotic drugs did not include sulpiride (Davis 2003, Leucht 2009). A group of researchers therefore agreed to update the previous Cochrane review (New Reference) and systematically review all available evidence of sulpiride in the treatment of schizophrenia. This is one of a series of reviews (Table 1) with this particular review providing head-to-head comparisons between sulpiride and other antipsychotic drugs for treatment of schizophrenia.

OBJECTIVES

To review the effects of sulpiride for the treatment of schizophrenia and schizophrenia-like psychoses compared with other antipsychotics.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised control trials will be considered. We will include quasi-randomised trials such as those where allocation is undertaken based on time of admission to the hospital. We will also submit these trials to a sensitivity analysis. Where trials are described as 'double-blind', but it is implied that the study is randomised and where the demographic details of each group's participants are similar, trials will be included and sensitivity analysis will be undertaken to the presence or absence of these data. Randomised cross-over studies will be eligible but only data up to the point of first cross-over will be analysed because of the instability of the problem behaviours and the likely carry-over effects of all treatments (Elbourne 2002).

Types of participants

People with the diagnosis of schizophrenia and other types of schizophrenia-like psychoses (schizophreniform disorder, schizoaffective disorder and acute psychotic disorder) however diagnosed, and irrespective of age, sex or severity of illness will be chosen for this study, as well as those with 'serious/chronic mental illness' or 'psychotic illness'. There is no clear evidence that the schizophrenia-like psychoses are caused by fundamentally different disease processes or require different treatment approaches (Carpenter 1994). People with psychotic symptoms due to dementia, general medical conditions, depression and problems associated with substance misuse will be excluded.

Types of interventions

Comparisons will be made between sulpiride and individual comparator drugs. No comparison will be made between sulpiride and comparator drugs as a class, such as typical/atypical antipsychotics.
1. Sulpiride: any dose and mode or pattern of administration. If a high/low dichotomy is not provided within the trial, high dose will be defined as >800 mg/day and low dose as any dose less than that.
2. Other antipsychotic drugs: any dose and mode or pattern of administration.

Types of outcome measures

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

Primary outcomes

1. Global state: Not clinically improved as defined by the individual studies - short term.

Secondary outcomes

1. Leaving the studies early (due to any reason, adverse events, inefficacy of treatment)
2. Global state
2.1 Not clinically improved as defined by the individual studies - medium and long term
2.2 Relapse (as defined by the individual studies)
3. Mental state (with particular reference to the positive and negative symptoms of schizophrenia)
3.1 No clinically important change in general mental state score
3.2 Average endpoint general mental state score
3.3 Average change in general mental state score
3.4 No clinically important change in specific symptoms (positive symptoms of schizophrenia, negative symptoms of schizophrenia)
3.5 Average endpoint specific symptom score
3.6 Average change in specific symptom score
4. General functioning
4.1 No clinically important change in general functioning
4.2 Average endpoint general functioning score
4.3 Average change in general functioning score
5. Quality of life/satisfaction with treatment
5.1 No clinically important change in general quality of life
5.2 Average endpoint general quality of life score
5.3 Average change in general quality of life score
6. Cognitive functioning
6.1 No clinically important change in overall cognitive functioning
6.2 Average endpoint of overall cognitive functioning score
6.3 Average change of overall cognitive functioning score
7. Service use
7.1 Number of participants hospitalised
8. Adverse effects
8.1 Number of participants with at least one adverse effect
8.2 Clinically important specific adverse effects (cardiac effects, death, movement disorders, probating increase and associated effects, sedation, seizures, weight gain, effects on white blood cell count)
8.3 Average endpoint in specific adverse effects
8.4 Average change in specific adverse effects.

Search methods for identification of studies

No language restriction will be applied within the limitations of the search tools.

Electronic searches

1. 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 and conference proceedings (see Group Module). The Cochrane Schizophrenia Group Trials Register is maintained on Meerkat 1.5. This version of Meerkat stores references as studies. When an individual reference is selected through a search, all references which have been identified as the same study are also selected.
2. Details of previous electronic search
See Appendix 1.

Searching other resources

1. Reference searching
In addition to the above searches we will also search reference lists of included studies for additional relevant trials.
2. Personal contact
We will contact 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

The manufacturers of sulpiride (Lorex Synthelabo Ltd, Bristol-Myers Pharmaceuticals, Pharmacia and Upjohn) will be contacted to provide relevant published and unpublished data.

Data collection and analysis

Selection of studies

Authors IMO and JW will independently inspect all study citations identified by the searchers and full reports of the studies of agreed relevance will be obtained. Where disputes arise we will acquire the full report for more detailed scrutiny. These articles will be then inspected, independently, by two reviewers (IMO and JW) to assess their relevance to this review. Again where disagreement occur attempts will be made to resolve this through discussion; if doubts still remain we will add these trials to the list of those awaiting assessment pending acquisition of further information.

Data extraction and management

1. Data Extraction
IMO, JW and BS will independently extract data from the included studies. Again, any disagreement will be discussed, decisions will be documented and, if necessary, authors of studies will be contacted for clarification. When this is not possible and further information is necessary to resolve the dilemma, we will not enter the data and add the trial to the list of those studies awaiting assessment.
2. Management
We will extract the data onto standard, simple forms. Where possible, data will be entered into RevMan in such a way that the area to the left of the 'line of no effect' will indicate a 'favourable' outcome for sulpiride. Where this is not possible, for example for scales that calculate higher scores = improvement, graphs in RevMan analyses will be labelled accordingly so that the direction of effects is clear.
3. Scale-derived data
3.1 Valid scales
A wide range of instruments are available to measure outcomes in mental health studies. These instruments vary in quality and many are not validated, or are even ad hoc. It is accepted generally that measuring instruments should have the properties of reliability (the extent to which a test effectively measures anything at all) and validity (the extent to which a test measures that which it is supposed to measure) (Rust 1989). Unpublished scales are known to be subject to bias in trials of treatments for schizophrenia (Marshall 2000). Therefore continuous data from rating scales will be included only if the measuring instrument was described in a peer-reviewed journal.
3.2 Binary outcomes from scale data
Where possible, efforts will be made to convert outcome measures to binary data. This can be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It will be generally assumed that if there had been a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS, Overall 1962) or the Positive and Negative Syndrome Scale (PANSS, Kay 1986), this could be considered as a clinically significant response (Leucht 2005, Leucht 2005a). If data based on these thresholds are not available, we will use the primary cut-off presented by the original authors.
Regarding categorical measures (e.g. one of seven categories on a global state, such as 'very much improved', 'much improved', 'minimally improved', 'no change', 'minimally worse', 'much worse', 'very much worse' in an overall improvement), we will set the cut-off points between 'much improved' and 'minimally improved', dividing participants into 'clinically improved' or 'not clinically improved'.

Assessment of risk of bias in included studies

IMO, JW and BS will work independently to assess risk of bias by using criteria described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). This set of criteria is based on evidence of associations between overestimation of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting.
The categories are defined below:
YES - low risk of bias
NO - high risk of bias
UNCLEAR - uncertain risk of bias
If sequence generation process within the trial is by quasi-random means, such as by hospital record number, this will be noted and the study will be given a 'NO (high risk of bias)' rating. If disputes will arise as to which category a trial have to be allocated, again resolution will be made by discussion.

Measures of treatment effect

1. Binary data
The review will use relative risk (RR) and its 95% confidence interval (CI) based on the fixed-effect model as this takes into account the true effect of intervention is the same value in every study. RR is more intuitive (Boissel 1999) than odds ratios and odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). This misinterpretation then leads to an overestimate of the impression of the effect. For statistically significant results we will calculate the number needed to treat to provide benefit (NNTB) and the number needed to treat to induce harm (NNTH) as the inverse of the risk difference.
2. Continuous data

2.1 Summary statistic

For continuous outcomes we will estimate a fixed-effect weighted mean difference (WMD) between groups. We will not calculate effect size measures. If SDs are not reported, authors will be asked to supply the data. When standard errors, CIs, *t* values or *P* values are reported, SDs will be calculated according to Higgins 2008. In the absence of these data, the mean standard deviation from other studies will be used (Furukawa 2006).

2.2 Endpoint versus change data

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

2.3 Skewed data

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

Skewed data from studies of less than 200 participants will be entered in additional tables rather than into an analysis. Skewed data pose less of a problem when looking at means if the sample size is large and they will be entered into syntheses.

Unit of analysis issues

1. Cluster trials

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

We have sought statistical advice and have been advised that 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 is not reported it will be assumed to be 0.1 (Ukoumunne 1999).

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

2. Cross-over trials

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

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. Where more than 40% of data is unaccounted for by the end of the trial we will 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 will include these data as reported. Where the outcomes of such people are not clearly described, data will be presented on a 'once-randomised-always-analyse' basis, assuming an intention to treat analysis. Those lost to follow-up are all assumed to have a negative outcome, with the exception of the outcome of death. For example, for the outcome of 'not clinically improved', those who are lost to follow-up are all 'not clinically improved'. A final sensitivity analysis will be undertaken testing how prone the primary outcomes are to change when 'completed' data only are compared to the intention to treat analysis using the negative assumption.

3. Continuous

In the case where attrition for a continuous outcome is between 0 and 40% and completer-only data will be reported, we will use

them within analysis. The method of last observation carried forward (LOCF) will be employed within the study report. As with all methods of imputation to deal with missing data, LOCF introduces uncertainty about the reliability of the results. Therefore, where LOCF data are used in the analysis, it will be indicated in the review.

Assessment of heterogeneity

1. Clinical heterogeneity
We will consider all included studies individually, without any comparison to judge clinical heterogeneity.
2. Statistical
2.1 Visual inspection
We will visually inspect 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. An I-squared estimate greater than or equal to 50% is interpreted as evidence of substantial heterogeneity (Higgins 2008), and reasons for heterogeneity will be explored. If the inconsistency is high and the clear reasons are found, data will be presented separately.

Assessment of reporting biases

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

Data synthesis

Where possible we will employ 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, although, random-effects does put extra weight onto the smaller studies, i.e. those trials that are most vulnerable to bias. For this reason we favour using the fixed-effect model employing random-effects only when investigating heterogeneity.

Subgroup analysis and investigation of heterogeneity

1. Investigation of heterogeneity
If high levels of heterogeneity are found, we will check that data are correctly extracted and entered and that we have made no unit of analysis errors.Then we will re-analyse the data using a random-effects model to see if this will make a substantial difference. If the high levels of heterogeneity remain we will 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 want to explore heterogeneity. Pre-specified subgroup analyses will be undertaken as a means of investigating heterogeneous results.
2. Subgroup analysis
It is expected that several subgroup analyses can be undertaken within this review. The following hypotheses will be tested: when compared with other antipsychotics, for the primary outcomes of interest (Criteria for considering studies for this review), sulpiride is differentially effective for:
2.1 Men and women
2.2 People who are under 18 years of age (adolescent patients), between 18 and 64 (adult patients), or over 65 years of age (elderly patients).
2.3 People who became ill recently (i.e. acute episode approximately less than one month's duration, including first onset of disease or recurrence) as opposed to people who have been ill for longer.
2.4 People who are given low doses (1-800 mg/day) and those given high doses (over 801 mg/day) of sulpiride.
2.5 People who have schizophrenia diagnosed according to any operational criteria (i.e. a pre-stated checklist of symptoms/ problems/ time periods/ exclusions) as opposed to those who have entered the trial with loosely defined illness.
2.6 People treated earlier (pre-1990) and people treated in recent years (1990 to present).
2.7 Duration of study: short term (less than three months), medium term (three to twelve months) and long term (more than one year).

Sensitivity analysis

We plan sensitivity analyses of the primary outcome a priori for examining the change in the robustness of the sensitivity to including studies with quasi-randomisation, with implied randomisation and with high attrition rates (more than 40%). In addition, we will conduct a sensitivity analysis to investigate whether the findings of Chinese trials differ substantially from other trials, as there is concern regarding the quality of trials from China (Wu 2006).

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Sulpiride reviews

Focus of review	Stage and Link
Sulpiride	Out of date full review Soares 2000
Sulpiride vs placebo	Full review Omori 2009
Sulpiride augmentation	Protocol Wang 2009
Sulpiride doses	Title - in preparation
Sulpiride + antidepressants	Title - in preparation

APPENDICES

Appendix 1. Details of past searches for earlier versions of this review

The following search phrase was constructed to assist identification for previous versions of this review (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)]

HISTORY

Protocol first published: Issue 4, 2009

CONTRIBUTIONS OF AUTHORS

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

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

Bernardo Soares - protocol writing, data extraction, completion of review.

Mark Fenton - protocol writing, data extraction, completion of review.

DECLARATIONS OF INTEREST

None known.

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J Wang

External sources

- No sources of support supplied