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Benperidol for schizophrenia (Review)

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[Intervention Review]

Benperidol for schizophrenia

Christian Schwarz¹, Benno Hartung², Stefan Leucht³

¹Psychiatry and Psychotherapy, Technische Universität München, Munich, Germany. ²Institut fuer Rechtsmedizin, Heinrich-Heine-Universitaet Duesseldorf, Dusseldorf, Germany. ³Klinik und Poliklinik für Psychiatrie und Psychotherapie, Technische Universität München Klinikum rechts der Isar, München, Germany

Contact address: Christian Schwarz, Psychiatry and Psychotherapy, Technische Universität München, Möhlstr. 28, Munich, 81675, Germany. schwarz@lrz.tu-muenchen.de.

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ABSTRACT

Background

Benperidol is a relatively old antipsychotic drug that has been marketed since 1966. It has been used in Germany for 30 years but is also available in Belgium, Greece, Italy, the Netherlands and the UK. Benperidol is a butyrophenone antipsychotic, with the highest neuroleptic potency in terms of D2 receptor blockade. Those taking it are therefore reputed to be at high risk of extrapyramidal side-effects, but benperidol's unusual profile may render it valuable to certain subgroups of people with schizophrenia.

Objectives

To examine the clinical effects and safety of benperidol for those with schizophrenia and schizophrenia-like psychoses.

Search methods

We searched the Cochrane Schizophrenia Group's register (March 2009) for this update.

Selection criteria

We included all randomised controlled trials that compared benperidol with other treatments for people with schizophrenia, or schizophrenia-like psychoses.

Data collection and analysis

We reliably selected studies, quality rated them and extracted data. We independently extracted data but excluded data if loss to follow up was greater than 50%. For dichotomous data, we estimated relative risks (RR), with the 95% confidence intervals (CI). Where possible, we calculated the number needed to treat/harm statistic (NNT/H) and used intention-to-treat analysis.

Main results

The update yielded no further studies for inclusion in the review. We identified only one unpublished poorly randomised controlled trial (N=40, duration 30 days, comparison perphenazine). Although benperidol was inferior to perphenazine (1 RCT, N=40, global state no better or worse RR 8.0 CI 2.1 to 30, NNH 1.4 CI 1 to 2) poor reporting suggests that an overestimate of effect is likely. It was not possible to report other outcomes.

Authors' conclusions

Currently, there are insufficient data from randomised trials to assess the clinical effects of benperidol. This compound merits further research interest.

PLAIN LANGUAGE SUMMARY

Benperidol for schizophrenia

Benperidol is a relatively old drug that is used for the treatment of schizophrenia in several European countries. We identified only one small, poorly reported, unpublished, randomised trial comparing benperidol with another antipsychotic. Unfortunately the quality of reporting is so poor that the results cannot be considered reliable. Although benperidol was first marketed in 1966, more trials on this drug are justified as with the advent of new compounds there is a danger that inexpensive drugs such as benperidol remain under-researched and overlooked.

BACKGROUND

Description of the condition

Schizophrenia is usually a chronic and disabling psychiatric disorder which afflicts approximately one per cent of the population worldwide with little gender differences. Its typical manifestations are 'positive' symptoms such as fixed, false beliefs (delusions) and perceptions without cause (hallucinations), 'negative' symptoms such as apathy and lack of drive, disorganisation of behaviour and thought, and catatonic symptoms such as mannerisms and bizarre posturing (Carpenter 1994). The degree of suffering and disability is considerable with 80% to 90% not working (Marvaha 2004) and up to 10% dying (Tsuang 1978).

Description of the intervention

Benperidol is a relatively old antipsychotic drug that was formulated in the 1960s and has been marketed since 1966. It is usually taken orally but can also be given by intramuscular injection for rapid treatment of acutely disturbed psychotic people. Early uncontrolled studies (Fluegel 1967) suggest that benperidol is effective in the treatment of schizophrenia, especially for those with recent onset delusions (fixed, false beliefs out of keeping with the person's education or cultural background) and hallucinations (perceptions with no cause). Benperidol has been associated with a high risk of adverse effects such as rigidity, mask-like appearance, tremor, stooped shuffling gait and other so called extrapyramidal effects such as inner feeling of restlessness (akathisia), acute spinal and ocular rigidity (the acute dystonias) and the slow onset of repetitive movements of the face and body (tardive dyskinesia) (Nedopil 1979).

How the intervention might work

Benperidol is a butyrophenone derivative and a specific dopamine-antagonist, selective for the D2 receptor. It also binds to serotonin receptors but to a lesser extent. In high doses it has antihistaminergic and alpha-adrenergic properties but its anticholinergic effects are small (Fachinformation 1999). Benperidol's potency in terms of dopamine receptor antagonism is assumed to be a hundred times higher than that of chlorpromazine. Haloperidol is only supposed to reach 60% of benperidol's potency (Langer 1983), suggesting a high risk of extrapyramidal adverse effects. Benperidol is absorbed easily and has a high first pass effect. Only one per cent of the original benperidol can be found in the urine, but little is known about the metabolites of this compound (Fachinformation 1999). The recommended initial dose is 2 to 6 mg/day; the maximum dose is 40 mg/day. Due to a short half-life of eight hours, benperidol should be administered three times per day (Fachinformation 1999).

Why it is important to do this review

Although benperidol has been used as an antipsychotic in Germany for 30 years, as far as we can ascertain, its current use is limited to only a few other countries (Belgium, Great Britain, Greece, Italy and the Netherlands) and its market share is unclear. In the UK it is also used as a sexual suppressant. However, its relative effects compared to other antipsychotic drugs based on randomised evidence are largely unknown.

OBJECTIVES

To examine the effects of benperidol for the treatment of schizophrenia or related psychoses, in comparison with placebo, no treatment or other antipsychotic medication.

METHODS

Criteria for considering studies for this review

Types of studies

We included all relevant randomised controlled trials. We excluded studies with inappropriate randomisation methods such as alternate allocation or randomisation by day of the week, date of birth etc (Higgins 2008). Randomised cross-over studies were eligible but only data up to the point of first cross-over because of the instability of the problem behaviours and the likely carryover effects of all treatments (Elbourne 2002, see below).

Types of participants

We included people with schizophrenia, diagnosed by any criteria. We also included those with 'serious/chronic mental illness' or 'psychotic illness'. If possible we excluded those with dementia, depression and problems primarily associated with substance misuse.

Types of interventions

1. Benperidol: any dose, route and pattern of administration against one or more of the following:
2. Placebo or no treatment
3. Other antipsychotic drugs: any dose or pattern of administration.

Types of outcome measures

All outcomes were reported for the short term (up to 12 weeks), medium term (13-26 weeks), and long term (more than 26 weeks).

Primary outcomes

No clinically significant response in global state - as defined by each of the studies

Secondary outcomes

1. Death: suicide or natural causes
2. Leaving the study early
3. Service utilisation outcomes
 - 3.1 Hospital admission
 - 3.2 Days in hospital
 - 3.3 Change in hospital status
4. Clinical response
 - 4.1 Average score/change in global state
 - 4.2 No clinically significant response in mental state - as defined by each of the studies
 - 4.3 Average score/change in mental state
 - 4.4 No clinically significant response on positive symptoms - as defined by each of the studies
 - 4.5 Average score/change in positive symptoms
 - 4.6 No clinically significant response on negative symptoms- as defined by each of the studies

4.7 Average score/change in negative symptoms

5. Behaviour

5.1 No clinically significant response in behaviour (e.g. aggressive behaviour, behaviour on the ward etc.) - as defined by each of the studies

5.2 Average score/change in behaviour

6. Extrapyramidal adverse effects

6.1 Incidence of use of antiparkinson drugs

6.2 No clinically significant extrapyramidal side effects - as defined by each of the studies

6.3 Average score/change in extrapyramidal side effects

7. Other adverse effects, general and specific

7.1 Number of people leaving the studies early due to adverse affects

7.2 Cardiac effects

7.3 Anticholinergic effects

7.4 Antihistamine effects

7.5 Prolactin related symptoms

8. Social functioning

8.1 No clinically significant response in social functioning - as defined by each of the studies

8.2 Average score/change in social functioning

9. Economic outcomes

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

10.1 No significant change in quality of life/ satisfaction - as defined by each of the studies

10.2 Average score/change in quality of life/ satisfaction

10.3 Employment status

11. Cognitive functioning

Search methods for identification of studies

Electronic searches

We searched the Cochrane Schizophrenia Group Register (March 23rd 2009) with the phrase :

[(*benperido* or *benzperidol* or *benzoperidol* or *frenactyl* or *glianimon* or *phenactil* or *frenactil* or *anquil* or *Psychoben* or *CB-8089* or *cb 8089* or *8089 CB* or *McN-JR-4584* or *mcn jr 4584* or *R-4584* or *r 4584 in title, abstract, index terms of REFERENCE) and (benperido* or benzperidol* or benzoperidol* or frenactyl* or glianimon* or phenactil* or frenactil* or anquil* or Psychoben* or CB-8089* or cb 8089* or 8089 CB* or McN-JR-4584* or mcn jr 4584* or R-4584* or r 4584* in interventions of STUDY)].

This register is compiled by systematic searches of major databases, hand searches and conference proceedings (see [group module](#)).

The search strategies of the previous versions of this review are described in [Appendix 1](#).

Searching other resources

1. Reference searching

We inspected references of all identified studies for more studies.

2. Personal contact

We contacted the first author of each included study for further information regarding unpublished trials.

3. Drug companies

We contacted the manufacturers of proprietary benperidol (Bayer AG, Germany) for additional data (relates only to the first version of this review).

Data collection and analysis

Selection of studies

Two review authors independently inspected all citations of studies identified by the search. We resolved any disagreement by discussion, but if there was still doubt, we acquired the full article for further inspection. Once the full articles were obtained author CS decided whether they met review criteria and this was checked by author SL. Once again, we resolved any disagreement by discussion and if doubt remained, the study was put on the list of those awaiting assessment.

Data extraction and management

1. Data Extraction

CS and SL independently extracted data from included studies. Any disagreement was discussed, decisions documented and, if necessary, authors of studies were contacted for clarification. When this was not possible and further information was necessary to resolve the dilemma, we did not enter data and added the trial to the list of those awaiting assessment.

2. Management

We extracted the data onto standard, simple forms. Where possible, data were entered into RevMan in such a way that the area to the left of the 'line of no effect' indicates a 'favourable' outcome for benperidol. Where this was not possible, for example for scales that calculate higher scores = improvement, graphs in RevMan analyses were labelled accordingly so that the direction of effects were clear.

Assessment of risk of bias in included studies

Again working independently, two authors 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 and where allocation was clearly not concealed.

If disputes arise as to which category a trial has to be allocated, again, resolution was made by discussion.

Measures of treatment effect

1. Data types

Outcomes are assessed using continuous (for example, average changes on a behaviour scale), categorical (for example, one of three categories on a behaviour scale, such as 'little change', 'moderate change' or 'much change') or dichotomous measures (for example, either 'no important changes' or 'important changes' in a person's behaviour). Currently RevMan software does not support categorical data so we only presented these in the text of the review.

2. Dichotomous/binary data

2.1 Defining cut-offs

Where the original authors of the studies gave outcomes such as 'clinically improved' or 'not clinically improved', based on their clinical judgement, predetermined criteria, or any scale, we recorded this in RevMan. If data were from a rater not clearly stated to be independent, then we included it provided it did not change the results, otherwise it was presented separately with a label 'prone to bias'. Where possible, we converted relevant categorical or continuous outcome measures to dichotomous data by identifying cut off points on rating scales and dividing subjects into groups accordingly. This was with the cut-off points 'moderate or severe impairment' for end of study data or 'no better or worse' for change data.

For example the Brief Psychiatric Rating Scale (BPRS - Overall 1962) and the Positive and Negative Syndrome Scale (Kay 1986) are frequently used as a measure of change of symptoms in studies. We defined a 50% change on these particular scales as clinically important, although we recognised that for many people, especially those with chronic or severe illnesses, a less rigorous definition of important improvement (for example 25% on the BPRS/PANSS) would be equally valid (Leucht 2005a, Leucht 2005b). Where individual patient data were available, we used the 50% cut-off for the definition in the case of non-chronically ill people, and 25% for those with chronic illness.

2.2 Intention-to-treat analysis

The review presents an intention-to-treat analysis. Provided that more than 50% of people in short and medium-term studies and 40% in long-term studies completed the trial, we counted everyone allocated to the intervention, whether or not they completed follow up. We assumed that those who left the study early had no change in their outcome.

2.3 Effect size

The review uses the relative risk (RR) and 95% confidence interval (CI). It has been shown that RR is more intuitive (Boissel 1999) 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. We did inspect data, however, to see if analysis using a Mantel-Haenszel odds ratio made a substantive difference. Where possible, we estimated the number needed to treat (NNT) using an on-line calculator (<http://www.mango3d.cwc.net/vsx.htm>).

3. Continuous data

3.1 Intention-to-treat versus completer analyses

In the case of continuous data we assumed that in many cases an intention-to-treat analysis would not be available and presented a completer analysis.

3.2 Rating scales

A wide range of instruments is available to measure mental health outcomes. These instruments vary in quality and many are not valid, or even ad hoc. For outcome instruments it is necessary to set minimum standards. We only included continuous data from rating scales if the measuring instrument had been described in a peer-reviewed journal (Marshall 2000), the instrument was either a self report or completed by an independent rater or relative (not the therapist), and the instrument could be considered a global assessment of an area of functioning. However, as it was expected

that therapists would frequently also be the rater, we commented on such data as 'prone to bias'.

3.3 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 were applied to all data before inclusion: (i) standard deviations and means were reported in the paper or were obtained from the authors; (ii) if the data were finite number zero, for example 0-100, when the standard deviation was multiplied by two, the result should be less than the mean, otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution (Altman 1996). (III)

if a scale starts from a positive value (such as PANSS which can have values from 30 to 210) the calculation described above will be modified to take the scale starting point into account. In these cases skew is present if $2SD > (S - S_{min})$, where S is the mean score and S min is the minimum score. Endpoint scores on scales often have a finite start and end point and these rules can be applied. When continuous data are presented on a scale which includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not. Skewed data from studies of less than 200 participants were entered in additional tables rather than into an analysis. Skewed data pose less of a problem when looking at means if the sample size is large and were entered into syntheses.

3.4 Endpoint versus change data

Endpoint scale-derived data are finite, ranging from one score to another. Change data are more problematic and for it the rule described above does not hold. Although most change scores are likely to be skewed, this cannot be proven so they were presented in MetaView. Where possible we presented endpoint data, and if both endpoint and change data were available for the same outcomes, then we reported only the former.

3.5 Summary statistic

For continuous outcomes, we estimated a weighted mean difference (MD) between groups.

Unit of analysis issues

1. Cluster trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice) but analysis and pooling of clustered data poses problems. Firstly, authors often fail to account for intraclass correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby p values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This 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 these 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 = $1 + (m-1) \times \text{ICC}$] (Donner 2002). If the ICC was not reported it was assumed to be 0.1 (Ukoumunne 1999).

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

2. Cross-over trials

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

3. Studies with multiple treatment groups

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

Dealing with missing data

At some degree of loss to follow-up data must lose credibility (Xia 2007). With the exception of the outcome of leaving the study early, we did not include trial outcomes of studies if more than 50% of people in short and medium-term studies, or 60% of people in long-term studies, were not reported in the final analysis. We felt that with such a great degree of attrition, assumptions would have to be made that would threaten the validity of any findings.

Assessment of heterogeneity

1. Clinical heterogeneity

Firstly, we would have considered all the included studies within any comparison to judge clinical heterogeneity.

2. Statistical

2.1 Visual inspection

We would have used visual inspection of graphs to investigate the possibility of statistical heterogeneity.

2.2 Employing the I-squared statistic

The I-squared statistic provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. If the I-squared estimate had been greater than or equal to 50%, we would have interpreted this as indicating the presence of high levels of heterogeneity (Higgins 2003).

Assessment of reporting biases

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

Data synthesis

Where possible we employed a random-effects model for analyses (Der-Simonian 1986). 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 and the random-effects model takes into account differences between studies even if there is no statistically significant heterogeneity. Therefore, the random-effects model is usually more conservative in terms of statistical significance, although as a disadvantage it puts added weight onto smaller studies which can either inflate or deflate the effect size. We examined in a secondary analysis whether using a fixed-model markedly changed the results.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses:

Subgroup analyses were not planned.

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 looked whether differences in the methods of the studies explained the discrepancies. If such differences were found, the studies were not pooled, but rather presented separately. If such differences were not found, we pooled the studies using a random effects model.

Sensitivity analysis

For binary data, results for intention-to-treat analysis were compared with those using completer only data. If analyses using completer data did result in a substantive change in the estimate of effect we discussed this in the 'Discussion' section.

RESULTS

Description of studies

Results of the search

Our initial search in the version of this review yielded 35 citations, but only ten of these were publications about benperidol. We had to exclude nine of these.

The update search in November 2004 yielded 39 citations (in part overlapping with the initial search). Thirty-seven citations were clearly not relevant to our review. The search identified only one study not found by the previous search (Digo 1967 - excluded) and one further reference of the already excluded Seiler 1994 study.

The most recent update search in March 2009 yielded 241 references (from 201 studies, in part overlapping with the initial search). Inspection of the abstracts made it clear that none of them met the inclusion criteria close enough to be reported in this review.

Included studies

We identified only one unpublished manuscript (Eckmann 1984) concerning a small ($n=40$), 30-day, randomised controlled, double-blind study.

1. Participants

People in this study were acutely ill, with paranoid schizophrenia (ICD-9). All participants were in a hospital setting, and most were men in their mid-thirties.

2. Interventions

Oral benperidol (6 to 12 mg/day) was compared with oral perphenazine (12 to 24 mg/day). These doses are seen in routine clinical care.

3. Outcomes

At the end of the trial, raters were asked to judge the 'global effect of treatment' according to the criteria: very much improved, improved, moderately improved, unchanged and worsened. We have made these ratings binary (see below).

A variety of outcome scales were used to monitor mental state (BPRS, AMDP), behaviour (NOSIE) and movement disorders (SAS). As standard deviations were not presented, all data from these scales were impossible to include. We have therefore not shown further details of these scales. The only useable outcomes in this review were leaving the study early and global state which was not

measured by a scale. Results on all other prespecified outcomes for the review were not available.

Excluded studies

There were ten excluded studies. Five excluded studies were not randomised, three did not include people with schizophrenia and two studies compared different doses of benperidol, but did not include a placebo group or a group receiving a comparator antipsychotic (Nedopil 1985, Seiler 1994).

Ongoing studies

We are not aware of any ongoing studies.

Awaiting assessment

There are no studies awaiting assessment.

Risk of bias in included studies

The summary of the risk of bias assessment is shown in Figure 1.

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

Allocation

The only included study (Eckmann 1984) did not describe the method used to generate random allocation. Although no differences in baseline descriptions of the comparator groups were found, the readers were given little assurance that bias was minimised during the allocation procedure.

Blinding

Although Eckmann 1984 did state that the study was double-blind, the report did not describe the precautions taken to minimise observation bias. Both medications were administered in liquid form, but whether colour, taste etc. of the liquids were the same is unclear.

Incomplete outcome data

No data on losses to follow up were given so we had to assume that no participant had left the study early.

Selective reporting

The study is to date only available as an unpublished manuscript. Continuous scale-derived data were very poorly reported. Explicit statements regarding the denominator or standard deviation were not present. Often data were only presented as significance tests or within graphs which made them impossible to include in this review. We therefore do not describe the scales in detail in this review.

Other potential sources of bias

We did not find other clear sources of bias.

Effects of interventions

1. COMPARISON 1. BENPERIDOL versus PLACEBO

No studies were identified comparing benperidol with placebo.

2. COMPARISON 2. BENPERIDOL versus OTHER ANTIPSYCHOTICS

A total of 40 people were randomised to this comparison in the [Eckmann 1984](#) study.

2.1 Global state: No better or deterioration

People allocated to benperidol were more likely to be 'no better or worse' than those given perphenazine (1 RCT, n=40, RR 8.00 CI 2.1 to 30, NNH 1.4 CI 1 to 2).

2.2 Leaving the study early

No person left the study before completion (30 days).

There were no more outcomes that we could use for analysis in this review.

DISCUSSION

Summary of main results

1. The searches

Although benperidol has been used for decades by European psychiatrists, our search only identified one unpublished manuscript that inadequately reported a small randomised controlled trial. The original search of the Cochrane Schizophrenia Group controlled trials register yielded 35 studies, all of which were ordered and inspected. Hand searching of the included trials and contacting the manufacturers of benperidol led to the identification of further publications, but despite this, only one unpublished study met the inclusion criteria. The update search in November 2004 yielded another 39 references, but only one study was relevant which we added to the [Excluded studies](#). The update search in March 2009 yielded 241 additional references, but none of them were relevant.

It is sobering that apparently there are almost no randomised data about this antipsychotic drug which has been frequently used in some countries such as Germany. As the only available trial reported only on leaving the study early and global state, results for all other prespecified outcomes of interest are completely missing.

2. COMPARISON 1. BENPERIDOL versus PLACEBO

The search did not identify any placebo-controlled trials. We excluded two randomised studies that compared different doses of benperidol ([Nedopil 1985](#), [Seiler 1994](#)) as they are not the focus of this review, and are uninformative when the absolute efficacy of the drug is unknown.

3. COMPARISON 2. BENPERIDOL versus OTHER ANTIPSYCHOTICS

The suggestion that benperidol may be significantly inferior to perphenazine in terms of 'global state' must be viewed with great caution. In the one relevant study, the methodology was such that the results are likely to be unreliable. It is therefore impossible to judge the true clinical efficacy and safety of benperidol based on randomised controlled trials.

Overall completeness and applicability of evidence

As there was only one small (n=40) trial comparing benperidol with perphenazine the evidence is clearly incomplete. Many more randomised controlled-trials are needed to investigate the effects of benperidol compared to placebo or other antipsychotic drugs.

Quality of the evidence

The single available study was small and ill reported. Randomisation, allocation and blinding methods have not been reported. It is not entirely clear whether any participants left the study early or whether this has not been reported. The manuscript has to date not been peer-reviewed. Due to all these factors the available evidence is very poor.

Potential biases in the review process

We are not aware of any clear biases in our review process.

Agreements and disagreements with other studies or reviews

We are not aware of other systematic reviews on the effects of benperidol for schizophrenia.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia

People being offered benperidol as a treatment for schizophrenia should also be aware of this lack of data. They may wish to ask if there are other evidence-based treatments, or to engage in treatment in the context of objective evaluation.

2. For clinicians

Clinicians should be aware that there is only one, small, unpublished, uninformative, randomised controlled trial examining the effects of benperidol versus another antipsychotic for schizophrenia. In view of this lack of evidence, possible benefits and harms of prescribing benperidol must be weighed against alternative, better-researched treatments. For clinicians instigating a treatment change, and considering the use or change from benperidol, treatment within a pragmatic randomised controlled trial would be both informative and ethical.

3. For managers or policy makers

Funders should consider supporting trials to assess the effects of benperidol. This drug is used quite frequently and is inexpensive compared to new antipsychotic drugs.

Implications for research

1. General

Had there been superior reporting of the one included study, this review would have been much more informative. Important outcomes such as adverse effects and behaviour were rendered useless by poor reporting. The whole study was devalued by complete lack of description of the means of randomisation ([Jüni 2001](#)). Although this may be seen as judging an old study by today's standards ([Begg 1996](#)), there is some evidence that quality of reporting was better in early mental health studies ([Ahmed 1999](#)) and that the CONSORT statement has made little difference ([Milton 2001](#)).

2. Specific

Given the absence of data from randomised trials, and the limited but widespread use of benperidol, well designed, conducted and reported studies are urgently needed. Benperidol has an interesting receptor binding profile. It is reputed to be the antipsychotic drug with the strongest blockade of central dopamine receptors. It is perfectly feasible that subgroups of people with schizophrenia, for example those with treatment-resistant illness, might benefit from such a profile. This compound, which is likely to be a potent antipsychotic, should not be under-evaluated simply because it is old and inexpensive. There is a danger that truly

valuable compounds are discarded as research becomes dictated by pecuniary interests.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Eckmann 1984

Methods	Allocation: randomised. Blindness: double (raters not stated to be independent of treatment). Duration: 30 days. Design: parallel group.
Participants	Diagnosis: acute paranoid-hallucinatory schizophrenia (ICD 295.3). N=40. Sex: 24 M, 16 F. Age: mean ~ 34 years (range 20-45). Setting: hospital. Exclusion criteria: not specified.
Interventions	1. Benperidol: dose 6 or 12 mg/day (two received 9 mg/day from day 4 to 6, and one also from day 19 to 30). N=20. 2. Perphenazine: dose 12 or 24 mg/day. N=20. Additional medication: anticholinergics and sedating drugs (low-potency antipsychotics, tranquillizers) as needed.
Outcomes	Global state: (clinical judgement). Leaving the study early. Unable to use - Mental state: BPRS, AMDP (no SD). Behaviour: NOSIE (no SD). Adverse effects: SAS (no mean, no SD).
Notes	Unpublished manuscript.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Quote: "randomisiert zugeteilt" (English: randomly allocated). No further details.
Allocation concealment?	Unclear risk	Method not described.
Blinding? All outcomes	Unclear risk	Quote: "double-blind study". Oral liquid medication. No further details.
Incomplete outcome data addressed? All outcomes	Unclear risk	The report does not indicate whether participants left the study early. It only says that there were 40 participants. It could be that these were only the study completers.
Free of selective reporting?	High risk	The study is only available as an unpublished manuscript. Means and standard deviations of rating scale results were often not indicated.
Free of other bias?	Low risk	There was no other clear source of bias.

General abbreviations

EPS - Extrapyramidal side effects.

F - females

Benperidol for schizophrenia (Review)

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M - males
mg = milligram
N = number
SD = standard deviation
Diagnostic tools
ICD-9 - International Classification of Diseases, ninth revision.
Mental state scales
AMDP - Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie
BPRS - Brief Psychiatric Rating Scale
Behaviour scales
NOSIE - Nurses Observational Scale of Inpatients Evaluation
Side effect scales
SAS - Simpson and Angus Scale

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

Study	Reason for exclusion
Bobon 1963	Allocation: randomised. Participants: people with dementia.
Collard 1964	Allocation: randomised. Participants: people with neurosis.
Digo 1967	Allocation: not randomised, CCT using previous treatment with haloperidol as a control.
Flügel 1967	Allocation: not randomised, open study.
Haase 1964	Allocation: not randomised, open study.
Muijen 1992	Allocation: randomised. Participants: people with any psychiatric illness, not schizophrenia.
Nedopil 1981	Allocation: not randomised.
Nedopil 1985	Allocation: randomised. Participants: people with schizophrenia. Interventions: benperidol versus benperidol.
Seiler 1994	Allocation: randomised. Participants: people with schizophrenia. Interventions: benperidol versus benperidol.
Sieberns 1986	Allocation: not randomised.

DATA AND ANALYSES

Comparison 1. BENPERIDOL versus OTHER ANTIPSYCHOTICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global state: No better or deterioration	1	40	Risk Difference (M-H, Fixed, 95% CI)	0.70 [0.48, 0.92]
2 Leaving the study early: Any reason	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 BENPERIDOL versus OTHER ANTIPSYCHOTICS, Outcome 1 Global state: No better or deterioration. **Analysis 1.2. Comparison 1 BENPERIDOL versus OTHER ANTIPSYCHOTICS, Outcome 2 Leaving the study early: Any reason.** **APPENDICES****Appendix 1. Search strategies of previous versions**

In the first version we searched the Cochrane Schizophrenia Group's Register (January 2001) with the phrase:

[benperidol or benperidolo or benperidolum or benzperidol or CB-8089 or "cb 8089" or "8089 CB" or McN-JR-4584 or "mcn jr 4584" or R-4584 or "r 4584" or benperidone or benzoperidol or frenactyl or glianimon or phenactil or frenactil or anquil or Psychoben or "1-[1-[3-(p-Fluorobenzoyl)propyl]-4-piperidyl]-2-benzimidazolinone" or "4'-Fluor-4-[4-(2-oxo-1-benzimidazoliny)l]piperidino]butyrophenon]" or "1 [1 [3 (para fluorobenzoyl)propyl]piperid 4 yl] 2 benzimidazolinone" or "1 [1 [4 (para fluorophenyl) 4 oxobutyl]piperidin 4 yl] 2 benzimidazolinone" or "4' fluoro 4 [4 (2 oxobenzimidazolin 1 yl)]"

In the update search in november 2004 we used a slightly different phrase to search the Cochrane Schizophrenia Group Register:

[benperido* or benzperidol* or benzoperidol* or frenactyl* or glianimon* or phenactil* or frenactil* or anquil* or Psychoben* or CB-8089* or cb 8089* or 8089 CB* or McN-JR-4584* or mcn jr 4584* or R-4584* or r 4584* in title or *benperido* or *benzperidol* or *benzoperidol* or *frenactyl* or *glianimon* or *phenactil* or *frenactil* or *anquil* or *Psychoben* or *CB-8089* or *cb 8089* or *8089 CB* or *McN-JR-4584* or *mcn jr 4584* or *R-4584* or *r 4584* in title, abstract, index terms of REFERENCE] or [benperidol* in interventions of STUDY]}

WHAT'S NEW

Date	Event	Description
15 February 2010	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 2, 2001

Review first published: Issue 1, 2002

Date	Event	Description
17 August 2009	New search has been performed	We updated review. We did not identify any new included studies, but implemented new methodological features of RevMan 5 such as the risk of bias table. This did not change the overall conclusions of the review.
22 October 2008	Amended	Converted to new review format.
23 February 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Christian Schwarz - protocol development, study selection, data extraction, writing of the report (current update).

Benno Hartung - protocol development, study selection, data extraction.

Stefan Leucht - protocol development, study selection, data extraction, writing of the report.

DECLARATIONS OF INTEREST

Christian Schwarz - none known.

Benno Hartung - none known.

Stefan Leucht - received speaker/consultancy/advisory board honoraria from SanofiAventis, BMS, EliLilly, Glaxo SmithKline, Janssen/Johnson and Johnson, Lundbeck and Pfizer. He received financial support for research projects from SanofiAventis and EliLilly.

SOURCES OF SUPPORT

Internal sources

- Freistaat Bayern, Germany.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We implemented the new features of Review Manager 5 in the version and slightly changed the protocol according to current methodological considerations of the Cochrane Schizophrenia Group. As there is still only one included study these modifications did not affect the results of the review.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans