Cochrane
Library

Cochrane Database of Systematic Reviews

Depot perphenazine decanoate and enanthate for schizophrenia (Review)

David A, Quraishi SN, Rathbone J

David A, Quraishi SN, Rathbone J.
Depot perphenazine decanoate and enanthate for schizophrenia.
Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD001717.
DOI: [10.1002/14651858.CD001717.pub2](https://doi.org/10.1002/14651858.CD001717.pub2).

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	3
METHODS	3
RESULTS	6
DISCUSSION	8
AUTHORS' CONCLUSIONS	8
ACKNOWLEDGEMENTS	9
REFERENCES	10
CHARACTERISTICS OF STUDIES	12
DATA AND ANALYSES	15
Analysis 1.1. Comparison 1 PERPHENAZINE ENANTHATE: 1. VERSUS OTHER DEPOT ANTIPSYCHOTICS, Outcome 1 Death (6 months to 1 year).	16
Analysis 1.2. Comparison 1 PERPHENAZINE ENANTHATE: 1. VERSUS OTHER DEPOT ANTIPSYCHOTICS, Outcome 2 Global State: 1. No important improvement (CGI, high score=worse, 6 months to 1 year).	17
Analysis 1.3. Comparison 1 PERPHENAZINE ENANTHATE: 1. VERSUS OTHER DEPOT ANTIPSYCHOTICS, Outcome 3 Global State: 2. Needing additional antipsychotic treatment (6 months to 1 year).	17
Analysis 1.4. Comparison 1 PERPHENAZINE ENANTHATE: 1. VERSUS OTHER DEPOT ANTIPSYCHOTICS, Outcome 4 Global State: 3. Not improved/worse (6 weeks to 5 months).	17
Analysis 1.5. Comparison 1 PERPHENAZINE ENANTHATE: 1. VERSUS OTHER DEPOT ANTIPSYCHOTICS, Outcome 5 Global State: 4. Global judgement of tolerability (medium term 6 weeks to 5 months).	18
Analysis 1.6. Comparison 1 PERPHENAZINE ENANTHATE: 1. VERSUS OTHER DEPOT ANTIPSYCHOTICS, Outcome 6 Mental state: Relapse.	18
Analysis 1.7. Comparison 1 PERPHENAZINE ENANTHATE: 1. VERSUS OTHER DEPOT ANTIPSYCHOTICS, Outcome 7 Leaving the study early.	18
Analysis 1.8. Comparison 1 PERPHENAZINE ENANTHATE: 1. VERSUS OTHER DEPOT ANTIPSYCHOTICS, Outcome 8 Adverse effects: 1. Movement disorders (6 months to 1 year).	19
Analysis 1.9. Comparison 1 PERPHENAZINE ENANTHATE: 1. VERSUS OTHER DEPOT ANTIPSYCHOTICS, Outcome 9 Adverse effects: 2. Additional use of anticholinergics - reason why unclear (6 months - 1 year).	19
Analysis 1.10. Comparison 1 PERPHENAZINE ENANTHATE: 1. VERSUS OTHER DEPOT ANTIPSYCHOTICS, Outcome 10 Adverse effects: 2. Additional use of antiparkinsonian drugs - reason why known (6 weeks to 5 months).	19
Analysis 2.1. Comparison 2 PERPHENAZINE ENANTHATE: 2. VERSUS PERPHENAZINE DECANOATE, Outcome 1 Mental state: Relapse (6 weeks to 5 months).	20
Analysis 2.2. Comparison 2 PERPHENAZINE ENANTHATE: 2. VERSUS PERPHENAZINE DECANOATE, Outcome 2 Leaving the study early (6 weeks to 5 months).	21
Analysis 2.3. Comparison 2 PERPHENAZINE ENANTHATE: 2. VERSUS PERPHENAZINE DECANOATE, Outcome 3 Adverse effects: Movement disorders (6 weeks to 5 months).	21
WHAT'S NEW	21
HISTORY	21
CONTRIBUTIONS OF AUTHORS	22
DECLARATIONS OF INTEREST	22
SOURCES OF SUPPORT	22
NOTES	22
INDEX TERMS	22

[Intervention Review]

Depot perphenazine decanoate and enanthate for schizophrenia

Anthony David¹, Seema N Quraishi¹, John Rathbone²¹Institute of Psychiatry, London, UK. ²Cochrane Schizophrenia Group, Institute of Mental Health, Nottingham, UK**Contact address:** Anthony David, Institute of Psychiatry, De Crespigny Park, BOX PO68, London, SE5 8AF, UK. a.david@iop.kcl.ac.uk.**Editorial group:** Cochrane Schizophrenia Group**Publication status and date:** Edited (no change to conclusions), published in Issue 4, 2009.**Citation:** David A, Quraishi SN, Rathbone J. Depot perphenazine decanoate and enanthate for schizophrenia. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.: CD001717. DOI: [10.1002/14651858.CD001717.pub2](https://doi.org/10.1002/14651858.CD001717.pub2).

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Antipsychotic drugs are usually given orally but compliance with medication given by this route may be difficult to quantify. The development of depot injections in the 1960s gave rise to extensive use of depots as a means of long-term maintenance treatment. Perphenazine decanoate and enanthate are depot antipsychotics that belong to the phenothiazine family and have a piperazine ethanol side chain.

Objectives

To assess the effects of depot perphenazine decanoate and enanthate versus placebo, oral antipsychotics and other depot antipsychotic preparations for people with schizophrenia in terms of clinical, social and economic outcomes.

Search methods

We updated previous searches of the Cochrane Schizophrenia Group Register (June 1998), Biological Abstracts (1982-1998), the Cochrane Library (Issue 2, 1998), EMBASE (1980-1998), MEDLINE (1966-1998), and PsycLIT (1974-1998) by searching the Cochrane Schizophrenia Group Register (March 2004). References of all identified trials were also inspected for more studies and industry contacted.

Selection criteria

We compared randomised clinical trials focusing on people with schizophrenia where depot perphenazine decanoate and enanthate, oral antipsychotics or other depot preparations.

Data collection and analysis

We reliably selected studies, quality rated them and extracted data. For dichotomous data we estimated the Relative Risk (RR) with the 95% confidence intervals (CI). Where possible, we calculated the number needed to treat statistic (NNT). Analysis was by intention-to-treat.

Main results

Only four studies (Ahlfors 1980, Eufe 1979, Knudsen 1985c, Tegeler 1979), randomising a total 313 people could be included in this review and this combined with an overall lack of usable data limits any interpretation of results. Perphenazine enanthate was not significantly any better or worse than other depot antipsychotics in most of the main outcomes such as global state, relapse or leaving the study early. We found some differences favouring the control groups for adverse effects.

One study (Ahlfors 1980) of six months' duration (n=172), compared perphenazine enanthate to clopenthixol decanoate. There were no differences between the two groups for outcomes of global improvement, relapse and leaving the study early. More people in the perphenazine enanthate group, however, required anticholinergic drugs than those allocated to clopenthixol decanoate (RR 1.12 CI 1.0 to 1.2, NNT 10).

A single study (n=64, duration six weeks) compared perphenazine enanthate and its longer acting decanoate ester. Data on relapse and leaving the study early failed to show convincing differences. The enanthate group, however, experienced more movement disorders (RR 1.36, CI 1.1 to 1.8 NNT 5) than those allocated the decanoate ester of the same drug and required more anticholinergic drugs (RR 1.47 CI 1.1 to 2.0, NNT 4).

Authors' conclusions

Depot perphenazine is in clinical use in the Nordic countries, Belgium, Portugal and the Netherlands. At a conservative estimate, a quarter of a million people suffer from schizophrenia in those countries and could be treated with depot perphenazine. The total number of participants in the four trials with useful data is 313. None of the studies observed the effects of oral versus depot antipsychotic drugs. Until well conducted and reported randomised trials are undertaken clinicians will be in doubt as to the effects of perphenazine depots and people with schizophrenia should exercise their own judgement or ask to be randomised.

PLAIN LANGUAGE SUMMARY

Depot perphenazine decanoate and enanthate for schizophrenia

Long acting depot preparations (decanoate and enanthate) of the oral antipsychotics perphenazine are available for people with schizophrenia. Evidence available for their efficacy and safety is limited. This review identifies randomised trials comparing depot perphenazine to other depot antipsychotics and perphenazine decanoate to enanthate.

BACKGROUND

One in every 10,000 people per year are diagnosed with schizophrenia, with a lifetime prevalence of about 1% (Jablensky 1992). It often runs a chronic course with acute exacerbations and often partial remissions. Antipsychotics are the main treatment for this illness (Dencker 1980). These are generally regarded as highly effective, especially in controlling symptoms such as hallucinations and fixed false beliefs (delusions) (Kane 1998). They seem to reduce the risk of acute relapse. A systematic review undertaken over a decade ago suggested that, for those with serious mental illness, stopping antipsychotics resulted in 58% of people relapsing, whereas only 16% of those who were still on the drugs became acutely ill within a one year period (Davis 1986). Evidence also points to the fact that experiencing a relapse of schizophrenia lowers a person's level of social functioning and quality of life (Curson 1995). Relapse prevention also has enormous financial implications. For example, within the UK, a department of health burden of disease analysis in 1996 indicated that schizophrenia accounted for 5.4% of all national health service in-patient expenditure, placing it behind only learning disability and stroke in magnitude (DoH 1996).

Antipsychotic drugs are usually given orally (Aaes-Jorgenson 1985) but compliance with medication given by this route may be difficult to quantify. Problems with treatment adherence are common throughout medicine (Haynes 1979). Those who suffer from long term illnesses such as schizophrenia, where the treatments may have uncomfortable side effects (Kane 1998), the individuals have cognitive impairments (David 1994) and erosion of insight, are especially prone to not take medication on a regular basis. The development of depot injections in the 1960s and initial clinical trials (Hirsch 1973) gave rise to extensive use of depots as a means of long-term maintenance treatment. Depots mainly consist of an ester of the active drug held in an oily suspension. This is injected intramuscularly and is slowly released. Depots may be given every one to six weeks. Individuals may be maintained in the community with regular injections administered by community psychiatric nurses, sometimes in clinics set up for this purpose (Barnes 1994).

This review is one of a series on the effects of depot antipsychotics for those with schizophrenia. The prevalence of depot perphenazine use is unclear, however, the authors are assured that it is widely used in Nordic countries, the Netherlands and Portugal but not licensed in Australia. We would welcome any data on its use.

Technical background

Perphenazine decanoate and enanthate belong to the phenothiazine family and have a piperazine ethanol side chain. The depot preparation (perphenazine enanthate in sesame oil) is known by several trade names (trilafon enanthaat, trilafon enantat, trilafon retard, trilafon enantato, trilafon depot, decentan-depot, and peratsin enantaati). The depot perphenazine decanoate is also in sesame oil and can be known as trilafon decanoate, trilafon decanoat, trilafon dekanoot, and peratsin dekanootti. The decanoate is administered every two to four weeks and enanthate every 10-14 days (Petersson 1971, Kundsén 1985b). Data suggests that the former preparation results in fewer fluctuations in blood plasma concentrations (Kundsén 1985b).

OBJECTIVES

To assess the effects of depot perphenazine decanoate and enanthate versus placebo, oral antipsychotics and other depot antipsychotic preparations for people with schizophrenia in terms of clinical, social and economic outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all relevant randomised controlled trials for inclusion. Where a study was described as 'double-blind' and it was implied that the study was randomised, and where the demographic details of each group's participants were similar, then we included these trials. We excluded quasi-randomised studies, such as those allocating by using alternate days of the week.

Types of participants

People with schizophrenia or other similar psychotic disorders, irrespective of mode of diagnosis, age, ethnicity and sex. Where a study described the participant group as suffering from 'serious/chronic mental illnesses' and did not give a particular diagnostic grouping, we included these trials. The exception to this rule was when the majority of those randomised clearly did not have a functional non-affective psychotic illness.

Types of interventions

1. Perphenazine decanoate: any dose
2. Perphenazine enanthate: any dose
3. Placebo
4. Oral antipsychotic drugs: any dose
5. Other depot antipsychotic drugs: any dose.

Types of outcome measures

Outcomes were grouped into immediate (0 to five weeks), short term (six weeks to five months), medium term (six months to one year) and longer term (over 12 months).

Primary outcomes

1. Clinical response
 - 1.1 Relapse
 - 1.2 Clinically significant response in global state - as defined by each of the studies

2. Service utilisation outcomes

- 2.1 Hospital admission

Secondary outcomes

1. Death, suicide or natural causes.
2. Leaving the study early.
3. Clinical response
 - 3.1 Average score/change in global state
 - 3.2 Clinically significant response on psychotic symptoms - as defined by each of the studies
 - 3.3 Average score/change on psychotic symptoms

3.4 Clinically significant response on positive symptoms - as defined by each of the studies

3.5 Average score/change in positive symptoms

3.6 Clinically significant response on negative symptoms - as defined by each of the studies

3.7 Average score/change in negative symptoms

4. Extrapyramidal adverse effects

4.1 Incidence of use of antiparkinson drugs

4.2 Clinically significant extrapyramidal adverse effects - as defined by each of the studies

4.3 Average score/change in extrapyramidal adverse effects

5. Other adverse effects, general and specific

6. Service utilisation outcomes

6.1 Days in hospital

7. Economic outcomes

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

8.1 Significant change in quality of life/satisfaction - as defined by each of the studies

8.2 Average score/change in quality of life/satisfaction.

Search methods for identification of studies

Electronic searches

1. Electronic searching for update 2004

1.1. We searched the Cochrane Schizophrenia Group's Register (March 2004) with the phrase:

[(((*Perphenazine* AND (*depot* OR *long-act* OR *delayed-act*)) OR (*perphenazine dec* OR *perphenazine ent* OR *trilafon* OR *peratsin* OR *decentan-depot*)) in Reference and [*perphenazine* AND *depot*] in Study.

The Schizophrenia Group's trials register is based on regular searches of BIOSIS Inside; CENTRAL; CINAHL; EMBASE; MEDLINE and PsycINFO; the hand searching of relevant journals and conference proceedings, and searches of several key grey literature sources. A full description is given in the Group's module.

2. Details of previous electronic searches

2.1. We searched Cochrane Schizophrenia Group's Register (June 1998) using the phrase:

(PERPHEN* and DECANOATE) or (PERPHEN* ENANTHATE*) or ((DEPOT* or (LONG and ACTING) or (DELAY* and ACTION)) and (PERPHEN* or TRILAFON* ENANT* or DEKAN* OR DEKAN* or RETARD* or DECENTAN* ENANT* or PERATSIN* ENANT* or DECAN*)) or (#44=56 and #44=581 and #44=580 and #44=551)

#44 is the field of this register that stores intervention codes.

2.2. We searched Biological Abstracts (January 1982 to June 1998) using the Cochrane Schizophrenia Group's phrase for randomised controlled trials and schizophrenia (see Group search strategy) combined with the phrase:

[and (PERPHEN* near1 DECANOATE) or (PERPHEN* ENANTHATE*) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION))

near (PERPHEN* or TRILAFON* ENANT* or DEKAN* OR DEKAN* or RETARD* or DECENTAN* ENANT* or PERATSIN* ENANT* or DECAN*))]

2.3. We searched the Cochrane Library (Issue 2, 1998) using the Cochrane Schizophrenia Group's phrase for schizophrenia (see Group search strategy) combined with the phrase:

[and (PERPHEN* next DECANOATE) or (PERPHEN* ENANTHATE*) or ((DEPOT* or (LONG next ACTING) or (DELAY* next ACTION)) next (PERPHEN* or TRILAFON* ENANT* or DEKAN* or DEKAN* or RETARD* or DECENTAN* ENANT* or PERATSIN* ENANT* or DECAN*)) or (PERPHENAZINE-DECANOATE* ME and DELAYED-ACTION-PREPARATIONS* ME))]

2.4. We searched EMBASE (January 1980 to June 1998) using the Cochrane Schizophrenia Group's phrase for randomised controlled trials and schizophrenia (see Group search strategy) combined with the phrase:

[and (PERPHEN* near1 DECANOATE) or (PERPHEN* ENANTHATE*) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (PERPHEN* or TRILAFON* ENANT* or DEKAN* or DEKAN* or RETARD* or DECENTAN* ENANT* or PERATSIN* ENANT* or DECAN*)) or ("PERPHENAZINE-DECANOATE"/ all subheadings or "PERPHENAZINE-ENANTHATE"/ all subheadings]

2.5. We searched MEDLINE (January 1966 to June 1998) using the Cochrane Schizophrenia Group's phrase for randomised controlled trials and schizophrenia (see Group search strategy) combined with the phrase:

[and (PERPHEN* near1 DECANOATE) or (PERPHEN* ENANTHATE*) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (PERPHEN* or TRILAFON* ENANT* or DEKAN* or DEKAN* or RETARD* or DECENTAN* ENANT* or PERATSIN* ENANT* or DECAN*)) or ("PERPHENAZINE-DECANOATE"/ all subheadings and explode "DELAYED-ACTION-PREPARATIONS"/ all subheadings)) or ("PERPHENAZINE-ENANTHATE"/ all subheadings and explode "DELAYED-ACTION-PREPARATIONS"/ all subheadings))]

2.6. We searched PsycLIT (January 1974 to June 1998) using the Cochrane Schizophrenia Group's phrase for randomised controlled trials and schizophrenia (see Group search strategy) combined with the phrase:

[and (PERPHEN* near1 DECANOATE) or (PERPHEN* ENANTHATE*) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (PERPHEN* or TRILAFON* ENANT* or DEKAN* or DEKAN* or RETARD* or DECENTAN* ENANT* or PERATSIN* ENANT* or DECAN*))]

Searching other resources

1. Reference searching

We also inspected the references of all identified trials for more studies.

2. Personal contact

We contacted the first author of each included study for information regarding unpublished trials. We also contacted those companies producing depots and requested published and unpublished trials.

Data collection and analysis

1. Study selection

The principal reviewer (SQ) inspected all identified citations or studies. A randomly selected sample of 10% of all reports was re-inspected by AD in order to ensure selection was reliable. Where disagreement occurred we (SQ, AD) resolved this by discussion, or where there was still doubt, acquired the full article for further inspection. Once the full articles were obtained, we independently decided whether they met the review criteria. Where disagreement occurred we resolved this by discussion and when this was not possible sought further information. We added these trials to the list of those awaiting assessment pending acquisition of further information. For the 2004 update JR independently inspected citations, identified studies and extracted relevant data.

2. Assessment of methodological quality

Each reviewer allocated trials to three quality categories, as described in the Cochrane Collaboration Handbook (Alderson 2004). When disputes arose as to which category a trial was allocated, again, we attempted resolution by discussion. When this was not possible and further information was necessary to clarify into which category to allocate the trial, we did not enter data and the trial was allocated to the list of those awaiting assessment. We only included trials in Category A or B in the review.

3. Data management

3.1 Data extraction

We (SQ, AD) independently extracted data from selected trials. When disputes arose, we attempted resolution by discussion. When this was not possible and further information was necessary to resolve the dispute, we did not enter data but added this outcome of the trial to the list of those awaiting assessment.

3.2 Incomplete data

Where more than 30% of those randomised were lost to follow-up by six months, or 50% by beyond that time, we felt the data were too prone to bias to use and did not report it. It was our intention to analyse the impact of including studies with high attrition rates (30-50%) in sensitivity analyses. If inclusion of data from this group did result in a substantive change in the estimate of effect of the primary outcomes, we would not have added the data from these studies to trials with less attrition, but would have presented them separately.

4. Data analysis

4.1 Binary data

For binary outcomes, for example 'admitted' or 'not admitted', we estimated the fixed effect Relative Risk (RR) with 95% confidence intervals (CI). Where possible, we calculated the number needed to treat/harm statistic (NNT/H) using Visual Rx (<http://www.nntonline.net/>) which takes account of the event rate in the relevant control group.

4.2 Intention to treat: Data was presented on a 'once-randomised-always-analyse' basis. We assumed that those who were lost to follow up had the negative outcome, with the exception of the outcome of death. For example, for the outcome of relapse, we assumed that those who were lost to follow up all relapsed.

4.3 Continuous data

4.3.1 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 were reported in the paper or were obtainable from the authors; (b) when a scale started from the finite number zero, the standard deviation, when multiplied by two, was 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 started from a positive value (such as PANSS which can have values from 30 to 210) the calculation described above was 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 on a scale), it is difficult to tell whether data are non-normally distributed (skewed) or not. Skewed data from studies of less than 200 participants would have been 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 would have been entered into a synthesis.

4.3.2 Summary statistic: for continuous outcomes we would have estimated a fixed effects weighted mean difference (WMD) between groups.

4.3.3 Valid scales: we included continuous data from rating scales only if the measuring instrument had been described in a peer-reviewed journal (Marshall 2000) and the instrument was either a self-report or completed by an independent rater or relative (not the therapist).

4.3.4 Endpoint versus change data: we find it preferable to use scale end point data, which typically cannot have negative values and we find it somewhat easier to interpret from a clinical point of view. Change data are often not ordinal and are very problematic to interpret. If end point data were not available, we would have used change data.

4.3.5. 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 intra class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby p values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997, Gulliford 1999).

Where clustering 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 intra class correlation co-efficients of their clustered data and to adjust for this by using accepted methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we 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 intra-class correlation co-efficient (ICC) Design

effect = $1 + (m-1) \times ICC$ (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 intra-class correlation co-efficients and relevant data documented in the report, synthesis with other studies would have been possible using the generic inverse variance technique.

5. Investigation for heterogeneity

Firstly, we considered all the included studies within any comparison to judge clinical heterogeneity. Then we visually inspected graphs to investigate the possibility of statistical heterogeneity. This was supplemented, primarily, by employing the I-squared statistic. This provides an estimate of the percentage of inconsistency thought to be due to chance. Where the I-squared estimate was greater than or equal to 75%, this was interpreted as evidence of high levels of heterogeneity (Higgins 2003). If inconsistency was high, we did not summate the data, but presented them separately and investigated reasons for heterogeneity.

6. Addressing small study bias

We entered data from all included studies into a funnel graph (trial effect against trial size) in an attempt to investigate the likelihood of overt publication bias (Egger 1997).

7. Sensitivity analyses

Where a trial was described as 'double-blind' but implied that the study was randomised, these trials were included in a sensitivity analysis. If there were no substantive differences within primary outcomes when these 'implied randomisation' studies were added, then they were included in the final analysis. However, if there was a substantive difference then only clearly randomised trials were used. The effect of including studies with high attrition rates (25-50%) will be analysed in sensitivity analyses. If inclusion of data from this group does result in a substantive change in the estimate of effect of the primary outcomes, data from these studies will be presented separately. A sensitivity analysis on the primary outcomes of this review (see Types of Outcomes) was conducted in order to investigate if this hierarchy of definition made any difference.

8. Tables and figures

Where possible, data were entered into RevMan in such a way that the area to the left of the line of no effect indicated a favourable outcome for the treatment depots.

RESULTS

Description of studies

1. Excluded studies

We excluded eleven trials. Five were not randomised. The remaining six (Angst 1975, Bakke 1973, Dencker 1994, Lindholm 1978, Rapp 1972 and Rapp 1986) were all, potentially, of relevance, but reported no useful data. We contacted these authors requesting raw data but no replies have been received to date.

2. Awaiting assessment

No studies are awaiting assessment

3. Ongoing studies

No studies are thought to be ongoing.

4. Included studies

We identified four studies for inclusion, Ahlfors 1980, Eufe 1979, Knudsen 1985c and Tegeler 1979.

4.1 Length of trial

Three studies Eufe 1979, Knudsen 1985c and Tegeler 1979 were of short term duration (six weeks to five months) and one trial Ahlfors 1980 was of medium term duration (six months to one year).

4.2 Participants

All participants were diagnosed with schizophrenia or some other similar psychotic disorder. Three studies included both men and women and one study Tegeler 1979 included only women. Participants were aged between 18 and 63 years.

4.3 Setting

The majority of those who participated had long histories of illness. Knudsen 1985c included participants from both hospital and community settings. Tegeler 1979 and Eufe 1979 used hospitalised patients. Ahlfors 1980 failed to mention the setting of the study.

4.4 Study size

Ahlfors 1980 was the largest study, randomising 172 people with schizophrenia. Eufe 1979 randomised 32 people, Knudsen 1985c used 64 people and Tegeler 1979 45 people.

4.5 Interventions

Ahlfors 1980 compared perphenazine enanthate, the shorter acting perphenazine depot, to another depot (clopenthixol decanoate). Eufe 1979 perphenazine enanthate to flupentixol decanoate. Knudsen 1985c compared perphenazine enanthate to its own longer acting decanoate ester. Tegeler 1979 compared perphenazine enanthate to fluspirilene.

4.6 Outcomes - reporting

Only dichotomised data from the Clinical Global Impression - CGI (Guy 1976) was possible to use in this review. All other continuous data were poorly reported and impossible to present. Many of the trials presented their findings in graphs or by p-values alone. Graphical presentation made it impossible to acquire raw data for synthesis. Requests for raw data from authors have so far failed. It was also common to use p-values as a measure of association between intervention and outcomes instead of showing the strength of the association. Other data such as relapse, rates of study attrition, use of use of additional medication and some adverse event incidence rates are possible to present.

4.6.1 Outcome scales: details of scales that provided usable data are shown below. We have given reasons for exclusion of data from other instruments under 'Outcomes' in the 'Included studies' section.

4.6.1.1 Clinical Global Impression - CGI (Guy 1976)

The CGI is a three-item scale commonly used in studies on schizophrenia that enables clinicians to quantify severity of illness and overall clinical improvement. The items are: severity of illness; global improvement and efficacy index. A seven-point scoring system is usually used with low scores indicating decreased severity and/or greater recovery.

4.7 Missing outcomes

None of the studies evaluated hospital/service outcomes, satisfaction with care and economic outcomes.

Risk of bias in included studies

1. Randomisation

Ahlfors 1980, Knudsen 1985c and Tegeler 1979 described trials as randomised and double blind. Eufe 1979 described the allocation as 'by chance' and was double blind. None of the trials gave details of the randomisation process. As poor reporting of randomisation has consistently been associated with an overestimate of effect (Schulz 1994) all allocation concealment has been rated as 'unclear' or quality 'B'. The results in these trials are likely to be a 30-40% overestimate of effect (Schulz 1994, Moher 1998).

2. Blindness

All studies were described as 'double blind'. None of the authors who stated a double blind procedure was undertaken reported this being tested. The two questions, one to the participant - "what do you think you have been given?" and one to the rater - "what drug do you think this person was allocated?" would have clarified the situation. It is difficult to say how prone outcomes such as relapse, global improvement, loss to follow up and adverse events are to observation biases. All results, however, must be interpreted with it in mind that such biases have been inadvertently introduced.

3. Follow-up

All studies presented the numbers lost to follow up but not the reasons for the study attrition. This also reflects poorly on study reporting.

4. Data reporting

Often studies reported data in the form of graphs or by p-values alone. Standard deviations around the mean score were often not reported.

Effects of interventions

1. PERPHENAZINE ENANTHATE vs OTHER DEPOT ANTIPSYCHOTIC DRUGS

Three of the four included studies (Ahlfors 1980, Eufe 1979, Tegeler 1979) compared perphenazine enanthate to another depot antipsychotic. The studies randomised a total of 249 people.

1.1 Death

Ahlfors 1980 reported one death occurring in the clopenthixol decanoate group and no difference was found between groups for this outcome (n=172, RR 0.34 CI 0.01 to 8.26).

1.2 Global state

Medium term CGI data reported by Ahlfors 1980 found no significant difference in the number of people being rated as 'not having attained a global improvement by six months' (n=172, RR 1.14 CI 0.9 to 1.5). Ahlfors 1980 also reported findings for the outcome of requiring additional antipsychotic drugs and although it appears as though fewer people required additional antipsychotics in the clopenthixol decanoate group, the difference was not statistically significant (n=172, RR 1.32 CI 0.9 to 1.8). Eufe 1979 and Tegeler 1979 presented data for the number of people reported as not improved/worse. Short-term results just favoured perphenazine enanthate with significantly fewer people being reported as 'not improved/worse' in this group (n=77, 2 RCTs, RR 0.25 CI 0.06 to 1.0, NNT 6 CI 5 to 29). The same studies reported 'global judgement of tolerability' and results were equivocal with no statistical difference between the perphenazine enanthate and other depot antipsychotic groups (n=77, 2 RCTs, RR 0.26 CI 0.05 to 1.5).

1.3 Mental state: Relapse

Two studies (Ahlfors 1980 and Eufe 1979) reported numbers of relapse. Short-term data from Eufe 1979 showed no difference between groups (n=32, RR 0.5 CI 0.05 to 4.98) and while medium-term results from Ahlfors 1980 appear to favour the control group, the result did not reach statistical significance (n=172, RR 1.31 CI 0.8 to 1.9).

1.4 Leaving the study early

All three studies presented data for this outcome. Short-term data from two studies (Eufe 1979 and Tegeler 1979) showed no real differences in numbers leaving a study early (n=77, 2 RCTs, RR 0.5 CI 0.05 to 4.98). Medium-term results from Ahlfors 1980, where 38% of participants had left the study early by six months to one year, initially appears to favour the group allocated clopenthixol decanoate but the difference between groups was not statistically significant (n=172, RR 1.3 CI 0.9 to 1.9).

1.5 Adverse effects

1.5.1 Movement disorders

Ahlfors 1980 presented data for incidence of movement disorders. Although there was a suggestion that the clopenthixol decanoate group's incidence was less, the difference between groups was not statistically significant (n=172, RR 1.31 CI 0.98 to 1.8). Ahlfors 1980 also presented data for use of anticholinergic drugs and found more people in the perphenazine enanthate group required anticholinergic drugs than those allocated to clopenthixol decanoate (n=172, RR 1.12 CI 1.0 to 1.2, NNT 10 CI 8 to 59). It was unclear, however, why these anticholinergic drugs were given. They can be prescribed to prevent or treat cholinergic adverse effects such as dry mouth, blurred vision and constipation or to help manage movement disorders. Specific reasons for why the additional use of antiparkinson drugs was required were given by Eufe 1979. Results showed that there were no significant differences in antiparkinson use between the perphenazine enanthate and flupenthixol decanoate groups for either prophylactic use (n=32, RR 0.5 CI 1.5 to 1.66) or for acute dystonia (n=32, RR 0.5 CI 0.05 to 4.98).

2. PERPHENAZINE ENANTHATE vs LONGER ACTING ESTER-PERPHENAZINE DECANOATE

One study (Knudsen 1985c) randomised 64 people and compared perphenazine enanthate with perphenazine decanoate.

2.1 Mental state: Relapse

No difference was seen in relapse rates between the two perphenazine esters by six weeks (n=64, RR 1.33, CI 0.5 to 3.4).

2.2 Leaving the study early

Although overall loss was fairly high (22% of participants left this short study early), there was no statistically significant difference in attrition between the two groups (n=64, RR 1.33, CI 0.5 to 3.4).

2.3 Adverse effects

At six weeks more people in the perphenazine enanthate group experienced movement disorder (n=63, RR 1.36, CI 1.1 to 1.8, NNT 5 CI 4 to 25) than those allocated the decanoate ester of the same drug. This was supported by finding that significantly more people in the enanthate group required anticholinergic drugs (n=64, RR 1.47, CI 1.1 to 2.0, NNT 4 CI 3 to 22).

DISCUSSION

1. General

We are led to believe that depot perphenazine is in everyday clinical use in the Nordic countries, Belgium, Portugal and the Netherlands. A rough population estimate of these countries totals 54 million, therefore, at a conservative estimate (0.5% lifetime prevalence), a quarter of a million people suffer from schizophrenia in those countries and could be treated with depot perphenazine. The total number of participants in trials with useful data is 313. We were unable to acquire any studies in this review comparing the effect of oral versus depot antipsychotic drugs.

2. Generalisability of results

The diagnoses within these studies were based on Bleuler's criteria (Ahlfors 1980), DSM III (Knudsen 1985c), ICD 9 (Tegeler 1979) and ICD 295 Eufe 1979. The differences in criteria used may mean that diagnoses are heterogeneous. This is hopefully the case as operational criteria, such as DSM III, excludes many people seen in routine practice. The heterogeneity of diagnosis should increase external validity of the findings of this review.

However, the main benefit of depot formulations is that covert non-compliance is eliminated and if relapse does occur under these circumstances, then non-compliance can be ruled out. As always, those entered into clinical trials are usually reasonably compliant people. This must compromise the applicability of the results into the community, where non-compliance or failure to turn up to depot clinics is commonplace. The four studies employed interesting interventions for comparison but reporting was limited to a few outcomes. Extrapolating the results to outcomes such as social functioning and quality of life would be problematic.

3. PERPHENAZINE ENANTHATE vs OTHER DEPOT ANTIPSYCHOTIC DRUGS (clopenthixol decanoate, flupenthixol decanoate, fluspirilene)

3.1 Global state

Ahlfors 1980 (n=172, duration six months) compared perphenazine enanthate with another depot (clopenthixol decanoate) and measured global state using the CGI and need for additional antipsychotics. Data appeared to favour clopenthixol decanoate but did not reach statistical significance. It must be remembered that only one trial is included in this comparison, therefore the results need to be interpreted with caution and confirmed by future research. The other two studies (Eufe 1979 and Tegeler 1979) also presented data for global state using the outcome 'not improved/worse'. Overall results from these two studies suggested that in the short-term, significantly fewer people in the depot perphenazine enanthate group were worse or not improved (NNT=6) than those in the other depot antipsychotic groups. However, Tegeler 1979 (who randomised perphenazine enanthate with fluspirilene) reported that none of those randomised became worse or did not improve and as such the data is not estimable. The same two studies reported global judgement of tolerability and overall results found no difference in tolerability between those receiving perphenazine enanthate or those receiving another type of depot antipsychotic. Again caution in interpreting these results is needed due to the small sizes (overall n=77) of these studies.

3.2 Mental state: Relapse

No significant differences in relapse were seen in the short-term. Ahlfors 1980 looked at relapse by six months to one year and it

seemed as though comparatively more people in the perphenazine enanthate group had, by medium-term, relapsed. However, this difference between the groups was not significant and again results based on one study need to be treated with caution.

3.3 Leaving the study early

Retention rates were good for Eufe 1979 (9%) and Tegeler 1979 (no drop outs) and no differences in loss were found between groups for the short-term follow-up. In contrast Ahlfors 1980 six month study had a much higher rate of attrition (38%) and again it appeared as though more people left early in the perphenazine enanthate group. Why there is such discrepancy in the numbers leaving the study early in these three studies is unclear, although Eufe 1979 (n=32) and Tegeler 1979 (n=55) did randomise smaller numbers of people whilst Ahlfors 1980 randomised 172 people and followed up for six months.

3.4 Adverse effects

Ahlfors 1980 presented data for incidence of movement disorders and use of anticholinergic drugs. No significant differences in movement disorders were found, although it did appear as though those receiving clopenthixol decanoate had fewer movement disorders. Supporting this finding was a significant result for use of anticholinergic medication, with less people in the clopenthixol decanoate group needing medication (NNT=10). No specific reason was given for why this medication was needed, as use of anticholinergic drugs is considered indicative of the incidence of adverse effects produced by medication, the perphenazine depot may have a greater propensity to produce these than clopenthixol decanoate. Eufe 1979 found no difference in antiparkinson use either for prophylactic use or for acute dystonia. Again these are results from single studies only and more research is necessary to confirm such findings.

4. PERPHENAZINE ENANTHATE vs ITS LONGER ACTING ESTER - PERPHENAZINE DECANOATE

Only Knudsen 1985c (n=64, duration six weeks) compared the two preparations of the same drug. The decanoate ester is the newer of the two and considered to have greater efficacy at lower doses.

4.1 Mental state: relapse

Whichever form of the depot was chosen, frequency of relapse was not affected.

4.2 Leaving the study early

Although 22% of participants left this study early, the likelihood of leaving the study early was equivocal between the two groups.

4.3 Adverse effects

Here a significantly greater incidence of movement disorders (NNT=5) and need for anticholinergic drugs (NNT =4) in the enanthate group suggests that this version of perphenazine depot induces more adverse effects, in the short term, than the decanoate ester although more studies would need to replicate this result.

AUTHORS' CONCLUSIONS

Implications for practice

1. For clinicians

Currently no clinically useful trial data has been identified to inform those using depot perphenazine of its advantages or disadvantages over oral medication. Weak data does suggest that the enanthate ester may have more short-term adverse effects than its decanoate

equivalent and than clopenthixol decanoate. Whether any of these depots are more beneficial than placebo, oral antipsychotics or other depots should be demonstrated in 'real world' trials (see implications for research). Those using depot perphenazine may feel that clinical practice that rests on such minimal data should be within the confines of a simple randomised trial.

2. For people with schizophrenia

Although the evidence is not strong, if advised to take depot perphenazine those with schizophrenia may wish to receive the decanoate ester to avoid at least short-term adverse effects. No convincing differences are evident when comparing depot perphenazine with other depot formulations, so those prescribed depot perphenazine may wish to exercise choice, or at least be asked to help evaluate different preparations within well designed trials.

3. For managers or policy makers

No direct data on hospital and services outcomes, satisfaction with care and economics were available. If depot formulations do promote compliance and this leads to a reduction in relapses, this would have important implications for patients and the establishments that care for them. Any suggestion that depot perphenazine reduces relapse and hospital care is not based on trial data.

Implications for research

1. General

If the recommendations of the CONSORT statement (Moher 2001) had been anticipated by trialists, much more data would have been available to inform practice. None of the included studies specified the process by which allocation to the intervention group was undertaken. Allocation concealment is essential for the result

of a trial to be valid and gives the assurance that selection bias is kept to a minimum. Well described and tested blinding could have encouraged confidence in the control of performance and detection bias. It is also important to know how many, and from which groups, people were withdrawn, in order to evaluate exclusion bias. It would have been helpful if authors had presented data in a useful manner which reflects association between intervention and outcome, for example, relative risk, odds-ratio, risk or mean differences, as well as raw numbers. Binary outcomes should be calculated in preference to continuous results, as they are easier to interpret. If p-values are used, the exact value should be reported.

2. Specific

This review highlights the need for good, 'real world' clinical trials (Simon 1995) to investigate the effects of using depot perphenazine enanthate and decanoate for those with schizophrenia. No depot compound has been adequately evaluated by modern standards. Few people have been randomised for all but the perphenazine enanthate versus another depot comparisons. Neither depot was compared with placebo or with an oral antipsychotic. More trials for the depot perphenazine esters are needed to assess clinical outcomes, social and cognitive functioning and adverse effects. Future studies should randomise people for whom giving a depot, or not, is a dilemma, in a 'real world' care setting, and report service utilisation data, as well as satisfaction with care and economic outcomes.

ACKNOWLEDGEMENTS

Clive Adams - acquired funding, helped prepare the protocol, undertake searches, select and acquire studies, extract and summate data, and produce the report.

We would like to thank Leanne Roberts for her help and support.

REFERENCES

References to studies included in this review

Ahlfors 1980 {published data only}

Ahlfors UG, Dencker SJ, Gravem A, Remvig J. Clopenthixol decanoate and perphenazine enanthate in schizophrenic patients. *Acta Psychiatrica Scandinavica* 1980;**61**:77-91.

Eufe 1979 {published data only}

Eufe R, Wegener G. Double blind comparative trial with 2 depot neuroleptics (perphenazine enanthate and flupenthixol decanoate with chronic schizophrenia [Doppelblind vergleich von 2 depotneuroleptika (Perphenazin-onanthat und flupenthixol-decaoat bei chronischer schizophrenie)]. *Nervenarzt* 1979;**50**:534-9.

Knudsen 1985c {published data only}

Knudsen P, Hansen LB, Auken G, Waehrens J, Højholdt K, Larsen NE. Perphenazine decanoate vs perphenazine enanthate efficacy and side effects in a 6 week double-blind, comparative study of 50 drug monitored psychotic patients. *Acta Psychiatrica Scandinavica* 1985;**72**(supp 322):15-28.

Tegeler 1979 {published data only}

Tegeler J, Floru L. A comparative study of the longacting neuroleptics perphenazin enanthate and fluspirilene [Eine Vergleichende Untersuchung Der Depot-Neuroleptika Perphenazin Onanthat Und Fluspirilen]. *Pharmakopsychiatrie Neuropsychopharmakologie* 1979;**12**(5):357-65. [EMBASE 1980018158]

References to studies excluded from this review

Angst 1975 {published data only}

Angst J, Woggon B. Clinical study on five depot neuroleptics. Comparison of effective profiles of fluphenazine decanoate, fluspirilene, penfluridol, perphenazine enanthate and pipothiazine palmitate. *Arzneimittel Forschung* 1975;**25**(2):267-70.

Bakke 1973 {published data only}

Bakke O. Clinical experience with depot neuroleptics. *Acta Psychiatrica Scandinavica* 1973;**246**:32-46.

Dencker 1994 {published data only}

Dencker SJ, Gios I, Martensson E, Norden T, Nyberg G, Persson R, Roman G, Stockman O, Svard KO. A long term cross-over pharmacokinetic study comparing perphenazine decanoate and haloperidol decanoate in schizophrenic patients. *Psychopharmacology* 1994;**114**:24-30.

Giannelli {published data only}

Giannelli A, Rabboni M, Zarattini F. Clinical profiles of action, individual treatment preferences, affects and contraindications of three depot neuroleptics compared in a multicentre trial [Profili clinici di azione, indicazioni preferenziali, effetti terapeutici e controindicazioni di tre neurolettici depot in trial multicentrico di confronto]. *Rivista di Psichiatria* 1990;**25**(1):7-24.

Kistrup 1991 {published data only}

Kistrup K, Gerlacj J, Aaes-Jorgensen T, Larsen N. Perphenazine decanoate and cis(z)-flupenthixol decanoate in maintenance treatment of schizophrenic outpatients. *Psychopharmacology* 1991;**105**:42-8.

Knudsen 1985a {published data only}

Knudsen P, Hansen LB, Højholdt K, Larsen NE. Long-term depot neuroleptic treatment with perphenazine decanoate I. *Acta Psychiatrica Scandinavica* 1985;**76**(supp 322):29-40.

Knudsen P, Hansen LB, Højholdt K, Larsen NE. Long-term depot neuroleptic treatment with perphenazine decanoate II. *Acta Psychiatrica Scandinavica* 1985;**76**(supp 322):40-50.

Kundsen 1985b {published data only}

Knudsen P, Hansen LB, Larsen NE. Perphenazine decanoate in sesame oil vs perphenazine enanthate in sesame oil. *Acta Psychiatrica Scandinavica* 1985;**76**(supp 322):11-14.

Lindholm 1978 {published data only}

Lindholm H, Gullberg BO, Ohman A, Sedvall G. Effects of perphenazine enanthate injections on prolactin levels in plasma from schizophrenic women and men. *Psychopharmacology* 1978;**57**:1-4.

Rapp 1972 {published data only}

Rapp W. Preliminary study of perphenazine enanthate in the treatment of chronic schizophrenia. *Pharmakopsychiatrie Neuro Psychopharmakologie* 1972;**5**:205-14. [EMBASE 1980018158]

Rapp 1986 {published data only}

Rapp W, Hellbom E, Norrman O, Palm U, Rodhe K, Forsman A, Larsson M. A double blind crossover study comparing haloperidol decanoate and perphenazine enanthate. *Current Therapeutic Research* 1986;**39**(5):665-70.

Rysanek 1982 {published data only}

Rysanek R, Svestka J, Nahunek K, Ceskova E. Experience with perphenazine-enanthate in the maintenance therapy of schizophrenic psychoses. *Actas Nervosa Superior (Praha)* 1982;**24**(4):227-8.

Additional references

Aaes-Jorgenson 1985

Aaes-Jorgenson A. Pharmacokinetics of oral and depot neuroleptics-Clinical relevance. Symposium Espo. 1 Feb 1985.

Alderson 2004

Alderson P, Green S, Higgins JPT. Cochrane Reviewers' Handbook 4.2.2 [updated December 2003]. *The Cochrane Library* 2004, Issue Issue 1. [In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd]

Altman 1996

Altman DG, Bland JM. Detecting skewness from summary information. *BMJ* 1996;**313**:1200. [PDE020600]

Barnes 1994

Barnes TRE, Curson DA. Long term depot antipsychotics. A risk benefit assessment. *Drug Safety* 1994;**10**(6):464-79.

Bland 1997

Bland JM. Statistics notes. Trials randomised in clusters. *BMJ* 1997;**315**:600.

Curson 1995

Curson DA, Barnes TRE, Bamber RW, Platt SD, Hirsch SR, Duffy JC. Long-term depot maintenance of chronic schizophrenic out-patients: the seven-year follow-up of the medical research council fluphenazine/ placebo trial. *British Journal of Psychiatry* 1985;**146**:464-80.

David 1994

David AS, Cutting JC (eds). The neuropsychology of schizophrenia. Hove, E.Sussex: Lawrence Erlbaum Associates, 1994.

Davis 1986

Davis JM, Andriukatis S. The natural course of schizophrenia and effective maintenance drug therapy. *Journal of Clinical Psychopharmacology* 1986;**6**(suppl 1):2-10.

Dencker 1980

Dencker SJ, Lepp M, Malm U. Do schizophrenics well adapted in the community need neuroleptics? A depot neuroleptic withdrawal study. *Acta Psychiatrica Scandinavica* 1980;**61**(suppl 279):64-76.

Divine 1992

Divine GW, Brown JT, Frazier LM. The unit of analysis error in studies about physicians' patient care behavior. *Journal of General Internal Medicine* 1992;**7**(6):623-9.

DoH 1996

Department of Health, NHS Executive. Burdens of disease: a discussion document. HMSO 1996.

Donner 2002

Donner A, Klar N. Issues in the meta-analysis of cluster randomized trials. *Statistics in Medicine* 2002;**21**:2971-80.

Egger 1997

Egger M, Davey-Smith G, Schneider M, Minder CSO. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**13**:629-34.

Gulliford 1999

Gulliford MC. Components of variance and intraclass correlations for the design of community-based surveys and intervention studies: data from the Health Survey for England 1994. *American Journal of Epidemiology* 1999;**149**:876-83.

Guy 1976

Guy W. In: National Institute of Mental Health, editor(s). ECDEU Assessment manual for psychopharmacology. Rockville, MD: DHEW publication No (ADM), 1976:124-585.

Haynes 1979

Haynes RB, Taylor WD, Sackett DL (Editors). Compliance in health care. Baltimore: John Hopkins University Press, 1979.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60.

Hirsch 1973

Hirsch SR, Gaidn R, Rohde PD. Outpatient maintenance of chronic schizophrenic patients with long-acting fluphenazine: double-blind placebo controlled trial. *British Medical Journal* 1973;**1**:633-7.

Jablensky 1992

Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, Cooper JE, Day R, Bertelsen ASO. Schizophrenia: manifestations, incidence and course indifferent cultures. A World Health Organization ten-country study. *Psychological Medicine (Monograph Supplement)* 1992;**20**:1-97.

Kane 1998

Kane JM, Aguglia E, Carlo Altamura A, Guitierrez JLA, Brunello N, Fleischhacker WW, et al. Guidelines for depot antipsychotic treatment in schizophrenia. *European Neuropsychopharmacology* 1998;**8**:55-66.

Marshall 2000

Marshall M, Lockwood A, Bradley C, Adams C, Joy C, Fenton M. Unpublished rating scales: a major source of bias in randomised controlled trials of treatments for schizophrenia. *British Journal of Psychiatry* 2000;**176**:249-52.

Moher 1998

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, Tugwell P, Klassen TP. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses?. *Lancet* 1998;**352**:609-13.

Moher 2001

Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001;**285**:1987-91.

Petersson 1971

Petersson H. Chronic schizophrenia treated with depot perphenazine. *Nordic Journal of Psychiatry* 1971;**25**(4):303-8.

Schulz 1994

Schulz KF, Chalmers I, Grimes DA, Altman DG. Assessing the quality of randomization from reports of controlled trials published in obstetrics and gynecology journals. *JAMA* 1994;**272**:125-8.

Simon 1995

Simon G, Wagner E, Vonkorff M. Cost-effectiveness comparisons using "real world" randomized trials: the case of new antidepressant drugs. *Journal of Clinical Epidemiology* 1995;**48**:363-73.

Ukounmunne 1999

Ukounmunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ.
Methods for evaluating area-wide and organisation-based

intervention in health and health care: a systematic review.
Health Technology Assessment 1999;**3**(5):1-75.

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]

Ahlfors 1980

Methods	Allocation: randomised. Blindness: double. Duration: 6 months.
Participants	Diagnosis: schizophrenia (Bleuler criteria). N=172. Age: <20 ->60 years. Sex: 114M, 58F. Setting: not given. History: duration illness < 2 years.
Interventions	1. Perphenazine enanthate: dose mean 141mg/IM, range 20-600 mg/IM, biweekly. N=85. 2. Clopenthixol decanoate: dose mean 280 mg/IM, range 50-800 mg/IM, 2 weeks. N=87.
Outcomes	Death. Global state: CGI improved/not improved, needing additional antipsychotics. Mental state: relapse. Leaving the study early. Adverse effects: movement disorders, use of anticholinergics. Unable to use - Mental state: BPRS (no SD). Serum levels: non-clinical outcome (data not usable). Behaviour: NOSIE-30 (no SD).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Eufe 1979

Methods	Allocation: 'by chance'. Blindness: double. Duration: 12 weeks.
Participants	Diagnosis: schizophrenia (ICD 295). N=32. Age: 28 - 63 years. Sex: 28M, 4F. Setting: hospital. History: chronic, mean duration illness ~ 20 years.
Interventions	1. Perphenazine enanthate: dose 100 mg/IMl, biweekly. N=16.

Depot perphenazine decanoate and enanthate for schizophrenia (Review)

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Eufe 1979 (Continued)

2. Flupenthixol decanoate: dose 20 mg/ml, constant dose. N=16.

Outcomes	Global state: improved/not improved, tolerability. Mental state: relapse. Leaving the study early. Adverse effects: use of antiparkinson medication. Unable to use - Mental state: BPRS (no SD). Behaviour: NOSIE (no SD).
----------	--

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Knudsen 1985c

Methods	Allocation: randomised. Blindness: double. Duration: 6 weeks.
Participants	Diagnosis: psychotic - acute (DSM-III). N=64. Age: 18 - 60 years, mean ~ 29 years. Sex: 21M, 29F. Setting: community/hospital-based. History: duration illness 5 years, not received neuroleptics 2 months prior recruitment.
Interventions	1. Perphenazine decanoate: dose mean 100 mg/IM, biweekly. N=26. 2. Perphenazine enanthate: dose mean 108.5 mg/IM, biweekly. N=24.
Outcomes	Mental state: relapse. Leaving the study early. Adverse effects: movement disorders, needing anticholinergics. Unable to use - Mental state: BPRS (no SD). Blood and plasma sample: non-clinical outcomes (data not usable).

Notes

Authors contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Tegeler 1979

Methods	Allocation: randomised. Blindness: double.
---------	---

Depot perphenazine decanoate and enanthate for schizophrenia (Review)

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Tegeler 1979 (Continued)

Duration: 4 months.

Participants	Diagnosis: schizophrenia (ICD - 9). N=45. Age: 21 - 62 years, mean ~ 42 years. Sex: all female. Setting: hospital. History: average duration illness 9 years.
Interventions	1. Perphenazine enanthate: dose 100/mg/2 weeks. N=24. 2. Fluspirilene: dose 8 mg/week. N=21.
Outcomes	Global state: improved/not improved, tolerability. Leaving the study early. Unable to use - Mental state: AMP scale, PD-S (no SD). Additional medication: (no data). Adverse effects: (no data).

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Diagnostic tools:

DSM - Diagnostic Statistical Manual.

ICD-9 - International Classification of Diseases, version 9.

RDC - Research Diagnostic Criteria.

Rating scales

Behaviour:

NOSIE - Nurses Observational Scale of Inpatients Evaluation

Global impression:

CGI - Clinical Global Impression.

Mental state:

AMP scale - Fuller description being sought.

BPRS - Brief Psychiatric Rating Scale.

CPRS - Comprehensive Psychopathological Rating Scale.

PD-S - Paranoid-Depressivitäts-Skala.

Side effects

AIMS - Abnormal Involuntary Movement Side effects.

DOTES - Dosage Record & Treatment Emergent Symptom Scale.

EPMS - Extrapyrimal Motor Side-effects.

EPSS - Extrapyrimal Side-effects Symptoms.

MARDRS- Montgomery-Asberg Depression Rating Scale.

STESS - Total Score of Side Effects Self Rating.

TESF - Treatment Emergent Symptom Form.

UKU - Side Effects Rating Scale.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Angst 1975	Allocation: not described. Participants: people with schizophrenia.

Depot perphenazine decanoate and enanthate for schizophrenia (Review)

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
	Interventions: fluphenazine decanoate versus fluspirilen versus penfluridol versus perphenazine enanthate versus pipothiazine palmitat. Outcomes: no usable data.
Bakke 1973	Allocation: randomised. Participants: people with psychosis. Interventions: perphenazine enanthate versus fluphenazine enanthate. Outcomes: no data.
Dencker 1994	Allocation: randomised. Participants: people with schizophrenia. Interventions: haloperidol decanoate versus perphanazine decanoate. Outcomes: no usable data, authors contacted.
Giannelli	Allocation: not randomised (quasi-randomised - entered sequentially at three hospitals).
Kistrup 1991	Allocation: not randomised.
Knudsen 1985a	Allocation: not randomised.
Kundsen 1985b	Allocation: not randomised.
Lindholm 1978	Allocation: randomised. Participants: people with schizophrenia. Interventions: perphenazine enanthate of different doses. Outcomes: no usable data.
Rapp 1972	Allocation: not described. Participants: people with schizophrenia. Interventions: perphenazine enanthate versus fluphenazine enanthate. Outcomes: no usable data.
Rapp 1986	Allocation: randomised. Participants: those with schizophrenia. Interventions: haloperidol decanoate versus perphenazine decanoate. Outcomes: no usable data, authors contacted.
Rysanek 1982	Allocation: not randomised.

DATA AND ANALYSES

Comparison 1. PERPHENAZINE ENANTHATE: 1. VERSUS OTHER DEPOT ANTIPSYCHOTICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (6 months to 1 year)	1	172	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.26]
2 Global State: 1. No important improvement (CGI, high score=worse, 6 months to 1 year)	1	172	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.87, 1.49]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Global State: 2. Needing additional antipsychotic treatment (6 months to 1 year)	1	172	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.98, 1.78]
4 Global State: 3. Not improved/worse (6 weeks to 5 months)	2	77	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.06, 1.00]
5 Global State: 4. Global judgement of tolerability (medium term 6 weeks to 5 months)	2	77	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.05, 1.49]
6 Mental state: Relapse	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 short term (6 weeks to 5 months)	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 4.98]
6.2 medium term (6 months to 1 year)	1	172	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.89, 1.92]
7 Leaving the study early	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 short term (6 weeks to 5 months)	2	77	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 4.98]
7.2 medium term (6 months to 1 year)	1	172	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.89, 1.92]
8 Adverse effects: 1. Movement disorders (6 months to 1 year)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 movement disorders	1	172	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.98, 1.76]
9 Adverse effects: 2. Additional use of anticholinergics - reason why unclear (6 months - 1 year)	1	172	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [1.02, 1.23]
10 Adverse effects: 2. Additional use of antiparkinsonian drugs - reason why known (6 weeks to 5 months)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 prophylactic use (6 weeks to 5 months)	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.15, 1.66]
10.2 for acute dystonia (6 weeks to 5 months)	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 4.98]

Analysis 1.1. Comparison 1 PERPHENAZINE ENANTHATE: 1. VERSUS OTHER DEPOT ANTIPSYCHOTICS, Outcome 1 Death (6 months to 1 year).

Analysis 1.2. Comparison 1 PERPHENAZINE ENANTHATE: 1. VERSUS OTHER DEPOT ANTIPSYCHOTICS, Outcome 2 Global State: 1. No important improvement (CGI, high score=worse, 6 months to 1 year).

Analysis 1.3. Comparison 1 PERPHENAZINE ENANTHATE: 1. VERSUS OTHER DEPOT ANTIPSYCHOTICS, Outcome 3 Global State: 2. Needing additional antipsychotic treatment (6 months to 1 year).

Analysis 1.4. Comparison 1 PERPHENAZINE ENANTHATE: 1. VERSUS OTHER DEPOT ANTIPSYCHOTICS, Outcome 4 Global State: 3. Not improved/worse (6 weeks to 5 months).

Analysis 1.5. Comparison 1 PERPHENAZINE ENANTHATE: 1. VERSUS OTHER DEPOT ANTIPSYCHOTICS, Outcome 5 Global State: 4. Global judgement of tolerability (medium term 6 weeks to 5 months).

Analysis 1.6. Comparison 1 PERPHENAZINE ENANTHATE: 1. VERSUS OTHER DEPOT ANTIPSYCHOTICS, Outcome 6 Mental state: Relapse.

Analysis 1.7. Comparison 1 PERPHENAZINE ENANTHATE: 1. VERSUS OTHER DEPOT ANTIPSYCHOTICS, Outcome 7 Leaving the study early.

Analysis 1.8. Comparison 1 PERPHENAZINE ENANTHATE: 1. VERSUS OTHER DEPOT ANTIPSYCHOTICS, Outcome 8 Adverse effects: 1. Movement disorders (6 months to 1 year).

Analysis 1.9. Comparison 1 PERPHENAZINE ENANTHATE: 1. VERSUS OTHER DEPOT ANTIPSYCHOTICS, Outcome 9 Adverse effects: 2. Additional use of anticholinergics - reason why unclear (6 months - 1 year).

Analysis 1.10. Comparison 1 PERPHENAZINE ENANTHATE: 1. VERSUS OTHER DEPOT ANTIPSYCHOTICS, Outcome 10 Adverse effects: 2. Additional use of antiparkinsonian drugs - reason why known (6 weeks to 5 months).

Comparison 2. PERPHENAZINE ENANTHATE: 2. VERSUS PERPHENAZINE DECANOATE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental state: Relapse (6 weeks to 5 months)	1	64	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.52, 3.41]
2 Leaving the study early (6 weeks to 5 months)	1	64	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.52, 3.41]
3 Adverse effects: Movement disorders (6 weeks to 5 months)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 movement disorders	1	64	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.06, 1.75]
3.2 needing anticholinergic drugs	1	64	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.08, 2.02]

Analysis 2.1. Comparison 2 PERPHENAZINE ENANTHATE: 2. VERSUS PERPHENAZINE DECANOATE, Outcome 1 Mental state: Relapse (6 weeks to 5 months).

Analysis 2.2. Comparison 2 PERPHENAZINE ENANTHATE: 2. VERSUS PERPHENAZINE DECANOATE, Outcome 2 Leaving the study early (6 weeks to 5 months).

Analysis 2.3. Comparison 2 PERPHENAZINE ENANTHATE: 2. VERSUS PERPHENAZINE DECANOATE, Outcome 3 Adverse effects: Movement disorders (6 weeks to 5 months).

WHAT'S NEW

Date	Event	Description
5 August 2009	Amended	Contact details updated.

HISTORY

Review first published: Issue 3, 1999

Date	Event	Description
30 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Seema Quraishi - prepared protocol, undertook searches, selected and acquired studies, extracted data, summated data, produced report.

Anthony David - acquired funding, helped prepare protocol, select studies, extract data, and produce the report.

John Rathbone - (update 2004) selected studies, extracted and summated data and produced the report.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NHS-R&D Health Technology Assessment Programme, UK.

NOTES

Cochrane Schizophrenia Group internal peer review complete (see Module).

External peer review scheduled.

INDEX TERMS

Medical Subject Headings (MeSH)

Antipsychotic Agents [*therapeutic use]; Delayed-Action Preparations; Perphenazine [*analogs & derivatives] [therapeutic use]; Randomized Controlled Trials as Topic; Schizophrenia [*drug therapy]

MeSH check words

Humans