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Depot haloperidol decanoate for schizophrenia (Review)

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[Intervention Review]

Depot haloperidol decanoate for schizophrenia

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ABSTRACT

Background

The mainstay of treatment for schizophrenia is the antipsychotic group of drugs. These are usually given orally but compliance with medication given by this route may be difficult to quantify. Problems with treatment adherence are common. The development of depot injections in the 1960s gave rise to their extensive use as a means of long-term maintenance treatment. Haloperidol decanoate is one depot drug available in clinical practice .

Objectives

To assess the effects of haloperidol decanoate versus oral anti-psychotics and other depot antipsychotic preparations for people with schizophrenia in terms of clinical, social and economic outcomes.

Search methods

Relevant trials were identified by searching Biological Abstracts (1982-1998), Cochrane Library (Issue 2, 1998), Cochrane Schizophrenia Group's Register (June 1998), EMBASE (1980-1998), MEDLINE (1966-1998) and PsycLIT (1974-1998). References of all identified trials were also inspected for more studies.

Selection criteria

All relevant randomised trials focusing on people with schizophrenia where haloperidol decanoate, oral anti-psychotics or other depot preparations were compared. Outcomes such as death, clinically significant change in global function, mental state, relapse, hospital admission, adverse effects and acceptability of treatment were sought.

Data collection and analysis

Studies were reliably selected, quality rated and data extracted. For dichotomous data Mantel-Haenszel odds ratios (OR) with the 95% confidence intervals (CI) were estimated. Where possible, the number needed to treat statistic (NNT) was calculated. Analysis was by intention-to-treat. Normal continuous data were summated using the weighted mean difference (WMD). Scale data were presented only for those tools that had attained pre-specified levels of quality.

Main results

In a haloperidol decanoate versus placebo comparison, two small studies reported that significantly fewer people on depot left early (OR 0.09 CI 0.03-0.21, NNT 2 CI 1-3) or experienced no important improvement in mental state (OR 0.04 CI 0.01-0.15). Zississ (1982) suggested that those taking haloperidol decanoate would need less additional antipsychotic medication (OR 0.14 Cl 0.04-0.55, NNT 2 CI 1-5).

Haloperidol decanoate was compared to oral haloperidol in a single trial that showed no differences in global impression, mental state or side effects (Zuardi 1983, n=22). Compliance with medication was not reported in this study. Eight trials compared haloperidol decanoate

to other depot neuroleptics and again no differences were found for the outcomes of death, global impression, mental state, behaviour, or side effects.

Authors' conclusions

Haloperidol decanoate may have a substantial effect in improving the symptoms and behaviour associated with schizophrenia in comparison to placebo, but data are remarkably sparse.

There are no discernible differences between the depot form of haloperidol and its oral equivalent. For those needing and willing to take the drug, the means of administration is then a matter of individual choice and clinical judgement. As there are no clear differences between haloperidol decanoate and other depots, the choice of depot medication could also be individually tailored and patient preference exercised.

Well-conducted and reported randomised trials are needed comparing haloperidol decanoate with other depots but the comparison of haloperidol decanoate to oral antipsychotics is a priority.

PLAIN LANGUAGE SUMMARY

Depot haloperidol decanoate for schizophrenia

Synopsis pending.

BACKGROUND

Schizophrenia affects about one in 10000 people per year, and the lifetime prevalence is approximately one percent (Jablensky 1992). It often runs a chronic course of acute exacerbation and partial remission. The mainstay of treatment for this illness is the antipsychotic group of drugs (Dencker 1980). These are generally regarded as highly effective, especially in controlling such symptoms as hallucinations and fixed false beliefs (delusions) (Kane 1986). They also seem to reduce the risk of acute relapse. For example, over a decade ago a systematic review suggested that stopping antipsychotics caused 58% of people with serious mental illness to relapse. However, only 16% of those who were still on the drugs became acutely ill within a 1 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 1985). 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 Heath Service in-patient expenditure, placing it behind only learning disability and stroke in magnitude (DoH 1996).

Anti-psychotic 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 schizophrenia, where treatments have uncomfortable side effects (Kane 1998) and the illness may cause cognitive impairment (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 (Leff 1971) 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 1 to 6 weeks. Individuals may be maintained in the community with regular injections administered by community psychiatric nurses, and sometimes in clinics set up specifically for this purpose (Barnes 1994).

Haloperidol decanoate (HD) is one depot drug available in clinical practice (Rapp 1986). It has been suggested to be as effective as its oral equivalent in controlling psychotic symptoms (Zissis 1982) and may have slightly less movement disorder (extrapyramidal) side effects when compared with other depot formulations (Reyntijens 1982).

OBJECTIVES

To assess the effects of haloperidol decanoate versus placebo, oral anti-psychotics and other depot neuroleptic preparations for individuals with schizophrenia, in terms of clinical, social and economic outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials were considered. Where a trial 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, trials were included. Quasi-randomised studies, such as those allocating by using alternate days of the week, were excluded.

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 mental illnesses' and did not give a particular diagnostic grouping, these trials were included. 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. Haloperidol decanoate: any dose.
2. Oral anti-psychotic drugs: any dose.
3. Other depot antipsychotic drugs: any dose.

Types of outcome measures

Outcomes were grouped into immediate (0-5 weeks), short term (six weeks-five months), medium term (six months-one year) and longer term (more than 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 clinically significant response in global state - as defined by each of the studies
3.2 average score/change in global state
3.3 clinically significant response on psychotic symptoms - as defined by each of the studies
3.4 average score/change on psychotic symptoms
3.5 clinically significant response on positive symptoms - as defined by each of the studies
3.6 average score/change in positive symptoms
3.7 clinically significant response on negative symptoms - as defined by each of the studies; and
3.8 average score/change in negative symptoms

4. Extrapyramidal side effects
4.1incidence of use of antiparkinson drug
4.2 clinically significant extrapyramidal side effects - as defined by each of the studies
4.3 average score/change in extrapyramidal side 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

Relevant randomised trials were identified by searching several electronic databases (Biological Abstracts, the Cochrane Library, the Cochrane Schizophrenia Group's Register of trials, EMBASE, MEDLINE, PsycLIT and SCISEARCH).

1. Biological Abstracts (January 1982 to June 1998 - current disc issue) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials and schizophrenia (see Group search strategy) combined with the phrase:

[and (HAL* near1 DECANOATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (HALO* or HALDOL or SEREN* or SIGAPERIDOL or BROTOPON or EINALON or LINTON or PELUCES))]

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

and [(HAL* and DECANOATE) or ((DEPOT* or (LONG and ACTING) or (DELAY* and ACTION)) and (HALO* or HALDOL or SEREN* or SIGAPERIDOL or BROTOPON or EINALON or LINTON or PELUCES)) or (HALOPERIDOL* ME and DELAYED-ACTION-PREPARATIONS* ME))]

3 Cochrane Schizophrenia Group's Register (June 1998) was searched using the phrase:

and [(HAL* and DECANOATE) or ((DEPOT* or (LONG and ACTING) or (DELAY* and ACTION)) and (HALO* or HALDOL or SEREN* or SIGAPERIDOL or BROTOPON or EINALON or LINTON or PELUCES) or (#42=14 and #42=230) or #42=549)

4 EMBASE (January 1980 to June 1998 - current disc issue) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials and schizophrenia (see Group search strategy) combined with the phrase:

[and (HAL* near1 DECANOATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (HALO* or HALDOL or SEREN* or SIGAPERIDOL or BROTOPON or EINALON or LINTON or PELUCES)) or "HALOPERIDOL-DECANOATE"/ all subheadings]

5 MEDLINE (January 1966 to June 1998 - current disc issue) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials and schizophrenia (see Group search strategy) combined with the phrase:

and [(HAL* near1 DECANOATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (HALO* or HALDOL or SEREN* or SIGAPERIDOL or BROTOPON or EINALON or LINTON or PELUCES)) or ("HALOPERIDOL"/ all subheadings and explode "DELAYED-ACTION-PREPARATIONS"/ all subheadings))]

6 PsycLIT (January 1974 to June 1998 - current disc issue) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials and schizophrenia (see Group search strategy) combined with the phrase:

[and (HAL* near1 DECANOATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (HALO* or HALDOL or SEREN* or SIGAPERIDOL or BROTOPON or EINALON or LINTON or PELUCES))]

Searching other resources

1. Reference searching
The references of all identified trials were also inspected for more studies. Each of the included studies was sought as a citation on the SCISEARCH database. Reports of articles that had cited these studies were inspected in order to identify further trials.

2. Personal contact
The first author of each included study was contacted for information regarding unpublished trials. Also those companies producing depots were also contacted and requests for published and unpublished trials were made.

Data collection and analysis

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

2. Assessment of methodological quality
Trials were allocated to three quality categories, as described in the Cochrane Collaboration Handbook (Mulrow 1999) by each reviewer. When disputes arose as to which category a trial was allocated to, again, resolution was attempted by discussion. When this was not possible and further information was necessary to clarify into which category to allocate the trial, data were not entered and the trial was allocated to the list of those awaiting assessment. Only trials in Category A or B were included in the review.

3. Data collection
SQ and AD independently extracted data from selected trials. When disputes arose resolution was attempted by discussion. When this was not possible and further information was necessary to resolve the dilemma, data were not entered and this outcome of the trial was added to the list of those awaiting assessment.

4. Data synthesis
4.1 Incomplete data.
Where more than 30% of those randomised were lost to follow-up by 6 months, or 50% by beyond that time, data were felt to be too prone to bias to use and were not reported.

4.2 Dichotomous - yes/no - data.
4.2.1 Statistics: for binary outcomes, for example 'admitted' or 'not admitted', Mantel-Haenszel Odds Ratio with 95% confidence

intervals was estimated. Where possible, the number needed to treat statistic (NNT) was also calculated.

4.2.2 Intention to treat: data were presented on a 'once-randomised-always-analyse' basis. Those lost to follow up were all assumed to have a negative outcome, with the exception of the outcome of death. For example, for the outcome of relapse, those who were lost to follow up all relapsed. A final sensitivity analysis was undertaken testing how prone the primary outcomes were to change when 'completed' data only were compared to the intention to treat analysis using the negative assumption.

4.3 Continuous - scale - data
4.3.1 Normal data: mental health continuous data are 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: (a) standard deviations and means were reported in the paper or were obtainable from the authors; (b) when a continuous outcome starts from a finite number (such as zero), the standard deviation, when multiplied by two, was less than the mean (as otherwise the mean was unlikely to be an appropriate measure of the centre of the distribution - Altman 1996). Data that do not meet the second standard were not entered into the RevMan calculator (which assumes a Normal distribution). However, data not meeting these standards can be reported in the 'Other data types' of the results section if they had been analysed with appropriate non-parametric tests.

If continuous data were recording change, where the finite parameters of measure were unclear then the data were not used.

4.3.2 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 are ad hoc. For outcome instruments some minimum standards have to be set. They could be that: (a) the psychometric properties of the instrument should have been described in a peer-reviewed journal; (b) the instrument was not written or modified by one of the trialists; (c) the instrument should either be: (i) a self-report, or (ii) completed by an independent rater or relative (not the therapist); and (d) the instrument should be a global assessment of an area of functioning).

5. Heterogeneity
As well as inspecting the graphical presentations, differences between the results of each included trial were checked using a test of heterogeneity. This is automatically calculated by RevMan. If heterogeneity is present the reviewers undertake a sensitivity analysis to the presence or absence of these data. All data from studies that have been selected are presented.

6. 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 haloperidol decanoate.

RESULTS

Description of studies

Please see Included and Excluded studies tables.

1. Excluded studies

Studies were most frequently excluded because they were not randomised or, if they were controlled clinical trials, because HD was not used as an intervention. Where relevant trials provided no usable data (Baastrup 1993, Cookson 1991, Dencker 1994, Rapp 1986, Ushakov 1990, Wiles 1990) authors were contacted but no reply has been received. Wiles 1990 was also excluded because, although randomised, it did not measure clinical outcomes but primarily physiological measures such as plasma levels.

2. Included studies
2.1 Duration
This ranged from four months to one year (Cookson 1986).

2.2 Participants
The participant group was reasonably homogeneous with most studies including those with a diagnosis of schizophrenia or similar psychotic disorder, people of both sexes, with ages ranging from 18-71 years old. Although people with recent onset of illness were included in some studies, participants frequently had long histories of illness.

2.3 Setting
The trials were both community and hospital based. In one study the trialists gave participants the first two injections whilst in hospital and continued treatment in the community thereafter (Wistedt 1991). Eklund 1991 included people from both hospital and community. Kissling 1985 failed to mention the setting used.

2.4 Interventions
Two trials compared HD with placebo (Eklund 1991, Zissis 1982), one with its oral equivalent (Zuardi 1983) and the remaining eight with other depot formulations.

2.5 Outcome measures
Apart from leaving the study early and use of additional medication most outcomes, even those later dichotomised, were measured on rating scales which are listed below.

Many trials presented findings in graphs or by p-values alone. Graphical presentation made it impossible to acquire data for synthesis. 'P' values were commonly used as a measure of association between intervention and outcomes instead of showing the strength of the association. With the exception of Drs McKane (McKane 1987) and Zuardi (Zuardi 1983), requests for further information from authors have, so far, failed.

2.5.1 Global functioning
Clinical Global Impression - CGI (Guy 1976)
A rating instrument commonly used in studies on schizophrenia that enables clinicians to quantify severity of illness and overall clinical improvement during therapy. A seven-point scoring system is usually used with low scores indicating decreased severity and/or greater recovery.

2.5.2 Mental state
Brief Psychiatric Rating Scale - BPRS (Overall 1962)
A brief rating scale used to assess the severity of a range of psychiatric symptoms, including psychotic symptoms. The scale has 16 items, and each item can be defined on a seven-point scale varying from 'not present' (zero) to 'extremely severe' (seven). Scoring is from 24-168.

Comprehensive Psychopathological Rating Scale - CPRS (Asberg 1978)

A four-point scale is used by the participant to rate 40 items, and 25 items are rated using the same scale. Global rating of the illness is an additional item also rated using this scale. Assumed reliability of the rating is scored as zero (very poor), one (fair), two (good) or three (very good).

Krawiecka Scale (Krawiecka 1977)
This mental state scale encompasses both positive and negative symptoms of schizophrenia. It is used to evaluate the mental state and behaviour in chronic psychotic people with higher scores indicating greater severity. It is also known as the Manchester Scale.

2.5.3 Behaviour
Nurses Observational Scale of Inpatients Evaluation - NOSIE (Honigfeld 1962).
An 80-item scale in which items are rated from 0-4. Zero means never present and four continually present. Ratings are taken from behaviour over the previous three days. The seven headings are: social competence, social interest, personal neatness, co-operation, irritability, manifest psychosis and psychotic depression. Scoring ranges from 0-320.

2.5.4 Side-Effects
Abnormal Involuntary Movement Side Effects Scale - AIMS (Guy 1976)
This is a twelve-item scale designed to record the occurrence of dyskinetic movements. Ten items of this scale have been used to assess tardive dyskinesia, a long-term drug-induced movement disorder. A five-point scoring system (from zero: none to four: severe) has been used to rate each of the ten items. Using this scale in short-term treatment may be helpful in assessing some short-term abnormal movement disorders. A low score indicates low levels of dyskinetic movements.

Dosage Record and Treatment Emergent Symptoms Scale - DOTES (NIMH 1976)
This side effect tool seems less of a scale, where the degree and severity of a symptom is recorded, and more of a checklist. The DOTES
seems to record the presence or absence of a list of side effects.

Extrapyramidal Symptom Rating Scale - ESRS (Chouinard 1980)
This consists of a questionnaire relating to parkinsonian symptoms (nine items), a physician's examination for parkinsonism and dyskinetic movements (eight items), and a clinical global impression of tardive dyskinesia. High scores indicate severe levels of movement disorder.

Simpson and Angus Scale (Simpson 1970)
A standard physical examination which measures parkinsonism. This scale comprises of a 10-item rating scale, each item rated on a five point scale with zero meaning the complete absence of condition and four meaning the presence of condition in extreme. The total score is obtained by adding the items and dividing by 10.

UKU Side Effects Rating Scale - UKU-SERS (Lingjerde 1987).
The UKU rates four major topics: psychological side effects (10 items), neurological side effects (eight items), autonomic side effects (11 items) and other side effects (19 items). Each item is defined by means of a four-point scale where zero means not or doubtfully present. Scoring range is 0-144.

2.6 Missing outcomes
Not one study evaluated hospital/service outcomes, satisfaction with care and economic outcomes.

Risk of bias in included studies

1. Randomisation
Only Kissling 1985 specified the process by which allocation to the intervention group was undertaken (coin-throwing) but did not specify whether this allocation was impossible for the clinician or participant to influence. 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. Blinding at outcome
All studies described themselves as 'double blind' but there is no report of 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. Failure to test double blinding may cast doubt on the quality of trial data. Scale data, as was often measured in the included studies, may be prone to bias when unblinding has taken place.

3. Follow-up
Overall, losses to follow up were well described.

Effects of interventions

1. The search
Three hundred and seven citations were found using the search strategy. Thirty-two citations were related to haloperidol decanoate but only eleven referred to controlled clinical trials (all published in journals). A small number (four) of non-English papers are still awaiting assessment due to delays in translation.

2. COMPARISON 1. HALOPERIDOL DECANOATE versus PLACEBO

2.1 Not completing the study
Both studies (Eklund 1991, Zissis 1982) reported that significantly fewer people on haloperidol decanoate left the study early (n=74, OR 0.09 CI 0.03-0.21, NNT 2 CI 1-3). Zissis 1982 was a small trial (n=32) lasting only four months and participants were actively withdrawn by the trialists if felt not to be responding. Despite being withdrawn from treatment protocol, data were collected on other outcomes. The Eklund 1991 study was one year long and those not completing represent true attrition. As data were not collected for the considerable proportion that left early this trial does not add further to the review.

2.2 Global Impression
Data from one small trial (Zissis 1982) suggested that those taking haloperidol decanoate would need less of other types of antipsychotic medication (n=32, OR 0.14 CI 0.04-0.55, NNT 2 CI 1-5).

2.3 Mental state
As Zissis 1982 withdrew people from the study if treatment was felt to be ineffective, these data can be used as a proxy for no clinically important improvement in mental state (OR 0.04 CI 0.01-0.15). Zissis 1982 also used a continuous scale for mental state (BPRS) but unfortunately presented total scores for each group without means or standard deviations.

2.4 Side effects
Zissis 1982 reported significantly more people in the placebo group experienced blurred vision as a side effect than in the haloperidol decanoate group (OR 0.17 CI 0.03-0.89). This trial also found no difference between groups for the outcome of tremor (OR 1.0 CI 0.24-4.09).

3. COMPARISON 2. HALOPERIDOL DECANOATE versus ORAL ANTIPSYCHOTICS

Only one small study (Zuardi 1983, n=22) compared haloperidol decanoate an oral antipsychotic, in this case, oral haloperidol.

3.1 Global impression
Zuardi 1983 reported no difference between those allocated to haloperidol decanoate and those taking oral medication (OR 0.61 CI 0.09-4.28) for the outcome of 'no improvement at four months'.

3.2 Mental state
BPRS scores were also not different between groups.

3.3 Side effects
Zuardi 1983 reported no significant differences in numbers needing anticholinergic drugs (OR 3.21 CI 0.39-26.67). This trial also used the Bordeleau Scale to rate extrapyramidal side effects. The skewed data is presented in 'Other data tables' and is not different for those taking haloperidol decanoate and the group allocated to oral drug.

4. COMPARISON 3. HALOPERIDOL DECANOATE versus OTHER DEPOT NEUROLEPTICS

There were eight eligible trials.

4.1 Death
Two deaths occurred in two of the studies, both in control groups (McKane 1987, Wistedt 1991). The result was not statistically significant (n=97, OR 0.15 CI 0.01-2.37).

4.2 Global impression
There was no difference in the numbers of people needing additional antipsychotic medication across groups (n=113, OR 0.63 CI 0.17-2.3). Direct measure of global state at the end of the studies also showed no discernible difference on the Clinical Global Impression (CGI - Guy 1976). The skewed CGI data reported in Wistedt 1991 was also equivocal.

4.3 Mental state
Seven studies reported 'relapse' as an outcome and no difference was found between the haloperidol decanoate group and those allocated to other depots (n=317, OR 1.25 CI 0.65-2.42). The two studies reporting un-skewed BPRS endpoint scores (Bechelli 1985, Chouinard 1984) support this equivocal finding. Skewed data is not formally analysed but is supportive of the overall impression that no difference is apparent in the mental state of those who take haloperidol decanoate and people given other depots.

4.4 Behaviour
Eight trials in which 371 people had been randomised to haloperidol decanoate or other depots had, in total, 18% attrition. There is no significant difference between groups (OR 0.92 CI 0.52-1.6). Skewed endpoint data from the Wing Ward Behaviour Scale seemed to support the finding that there was no clear behavioural differences between those taking haloperidol decanoate and other depots.

4.5 Side effects
The instance of dyskinetic movements was the same across groups in the two small studies reporting this effect (Bechelli 1985, Wistedt 1991). Both reported no significant differences in the number of people who suffered from dyskinesia in either the haloperidol decanoate or the control group (n=105, OR 1.85 CI 0.61-5.63). Bechelli 1985 reported no difference in tremor between the two groups (n=41, OR 0.75 CI 0.2-2.75) and Wistedt 1991, using a questionnaire to identify those with significant adverse effects, also found no difference. Some skewed data generally supports these findings.

Five studies reported there was no difference in the number of people requiring anticholinergic medication, irrespective of the depot treatment they received (n=257, OR 0.8 CI 0.43-1.47).

5. Missing outcomes
No study directly reported hospital and service outcomes or commented on participants' overall satisfaction during or after the trial. Economic outcomes were not assessed by any of the included studies.

DISCUSSION

1. Generalisability
Most trial participants had an operationalised diagnosis of schizophrenia (DSM III, RDC, Feighner's criteria) although Cookson 1986 did not specify if diagnostic criteria were used. The varied criteria suggest that the diagnoses could be heterogeneous, as is the situation in routine practice. On average the duration of illness was long but ranged from 0-31 years.

2. COMPARISON 1. HALOPERIDOL DECANOATE versus PLACEBO

About 40% of the people in the two studies (Eklund 1991, Zissis 1982) left the study early, the maximum duration of either study being one year. However, in the Zissis 1982 study those whose illness had not responded were withdrawn by the trialists so a too rigorous trial protocol cannot be held solely responsible for the loss. In fact, it is this study that provides the limited, but best, trial-based evidence regarding the absolute effectiveness of haloperidol decanoate for the outcome of 'general response' (NNT 1.23 CI 1-2). This trial-base is, however, very limited but it is probable that clinicians' and patients' experience of haloperidol, and its depot, is so great that the reasonable doubt does not exist to allow a good large trial to be undertaken.

The result for 'general response' fits with the finding that people taking haloperidol decanoate need less additional medication than those on placebo group (NNT 2 CI 1-5). It is, however, surprising that significantly more of those allocated placebo experienced blurred vision than those taking haloperidol decanoate and that tremor occurred with equal frequency in both groups.

As is usual for those systematically reviewing trial literature, continuous measures add little to the information provided by simple clinically meaningful outcome such as 'improved' or 'not improved'.

3. COMPARISON 2. HALOPERIDOL DECANOATE versus ORAL ANTIPSYCHOTICS

Zuardi 1983, a single trial with 22 participants, compared haloperidol decanoate with oral haloperidol. The author failed to

report how many people left the study early or relapsed during the trial. This is unfortunate as comparative compliance is currently a major concern in modern-day treatments of schizophrenia. Observing the effect of oral and depot antipsychotic drugs in terms of clinical efficacy, side effects and social implications has a wide role to play in constructing a sound basis for the choice the clinician makes as to what medication to prescribe. The main benefit of depot formulations is that covert non-compliance is eliminated and, if relapse does occur under these circumstances, non-compliance can be ruled out. Of course, generalising any findings of any study to routine care is problematic as those entering trials are usually more compliant than is commonplace in day-to-day practice. This issue becomes academic when there are no results to generalise.

With such a small study it is not surprising that there was little difference between those allocated to the depot and the oral haloperidol. The power of such a study to highlight a real effect is minimal. The non-significant finding for the outcome of 'no improvement at four months' (OR 0.61 CI 0.09-4.28) could mask a real, and important effect in favour of haloperidol decanoate. The same argument applies to the mental state rating and recording of side effects or the need for anticholinergic medication.

For this comparison clinical doubt may be great enough to allow a well designed trial to be instigated.

4. COMPARISON 3. HALOPERIDOL DECANOATE versus OTHER DEPOT NEUROLEPTICS

That two deaths occurred in two small trials (n=97) over a period of about a year serves to highlight the morbidity and mortality associated with schizophrenia. Much larger studies would be needed to find a real difference between haloperidol decanoate and other depot antipsychotics if one really exists.

All other findings relating to the global impression of effect, specific mental state measures, behaviour, and side effects are equivocal. This is not too surprising for small studies where the comparison is perhaps driven by the pharmaceutical industry whose need is to provide data on clinical effectiveness on new agents. Any differences would probably be subtle and such small studies could not highlight these.

That eight randomised trials, with a total of 371 very ill participants, lost only 18% of people over a relatively long period of time shows that such low attrition is possible although generalisation to a wider population must be undertaken with caution.

5. Sensitivity analyses
Undertaking an analysis based solely on study 'completers' as opposed to all those randomised did not make any substantive difference to the results. Intention to treat analyses are presented.

6. Missing outcomes
No study directly reported hospital and service outcomes or commented on participants' overall satisfaction during or after the trial. Economic outcomes were not assessed by any of the included studies.

AUTHORS' CONCLUSIONS

Implications for practice

1. Those with schizophrenia
HD may well have a substantial effect in improving the symptoms and behaviour associated with schizophrenia in comparison to placebo - but data are remarkably sparse.

There are no discernible differences between the depot form of haloperidol and its oral equivalent. For those needing and willing to take the drug, the means of administration is then a matter of individual choice.

As there are no clear differences between HD and other depots, the choice of depot medication could also be individually tailored and patient preference exercised.

2. Managers or policy makers
Data relating to service utilisation, satisfaction with care and economic outcomes were not reported.

3. Clinicians
People with schizophrenia can be assured that depot haloperidol does seem to be more effective than placebo.

The best data in this review relate to the comparison of HD and other depot preparations. There is nothing to choose between depots for outcomes of mental state, behaviour, side effects and compliance/concordance. The choice of which depot to use can therefore be based on clinical judgement and the preferences of the recipients of care and their carers.

Should a person wish to take oral haloperidol and not the depot form, what very limited data there are would suggest that this is a reasonable plan, assuming all other factors are equal.

Implications for research

1. General
If the recommendations of the CONSORT statement (Begg 1996) had been anticipated by trialists much more data would have been available to inform practice. Clear descriptions of randomisation would have reassured the user of the trials that selection bias had been minimised. 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 controlled clinical trials to address the effectiveness and clinical outcome of using haloperidol decanoate for those with schizophrenia. More research is particularly required in the case of haloperidol decanoate compared with oral antipsychotics. Data were poor in this group as only one small trial could be included (Zuardi 1983). This study was based in hospital. As one of the reasons for the use of

haloperidol decanoate is to increase compliance, it would seem important for similar, but larger, trials to be based in the community where supervision may be less rigorous. Future studies should report service utilisation data, as well as satisfaction with care and economic outcomes.

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REFERENCES

References to studies included in this review

Bechelli 1985 *{published data only}*

Bechelli LPC, Lecco MC, Pontes MC. A double-blind trial of haloperidol decanoate and pipothiazine palmitate in the maintenance treatment of schizophrenics in a public out-patient clinic. *Current Therapeutic Research* 1985;**37**:662-71.

Chouinard 1984 *{published data only}*

Chouinard G, Annable L, Campbell W. A randomized clinical trial of haloperidol decanoate and fluphenazine decanoate in the outpatient treatment of schizophrenia. *Journal of Clinical Psychopharmacology* 1989;**9**:247-53.

Chouinard G, Annable L, Campbell W, Boisvert D, Bradwejn J. A double-blind, controlled clinical trial of haloperidol decanoate and fluphenazine decanoate in the maintenance treatment of schizophrenia. *Psychopharmacology Bulletin* 1984;**20**:108-9.

Cookson 1986 *{published data only}*

Cookson JC, Kennedy NM, Gribbon D. Weight gain and prolactin levels in patients on long-term antipsychotic medication: a double-blind comparative trial of haloperidol decanoate and fluphenazine decanoate. *International Clinical Psychopharmacology* 1986;**Suppl 1**:41-51.

Eberhard 1986 *{published data only}*

Eberhard G. Depot antipsychotics in schizophrenic patients: a comparison between haloperidol decanoate and flupenthixol decanaote. *International Clinical Psychopharmacology* 1986;**Suppl 1**:27.

Eberhard G, Hellbom E. Haloperidol decanoate and flupenthixol decanoate in schizophrenia. A long-term double-blind cross-over comparison. *Acta Psychiatrica Scandinavia* 1986;**74**:255-62.

Eklund 1991 *{published data only}*

Eklund K, Forsman A. Minimal effective dose and relapse - double blind trial: haloperidol decanoate versus placebo. *Clinical Neuropharmacology* 1991;**14**(Suppl 2):7-15.

Kissling 1985 *{published data only}*

Kissling W, Moller HJ, Walter K, Wittmann B, Krueger R, Trenk D. Double-blind comparison of haloperidol decanoate and fluphenazine decanoate effectiveness, side-effects, dosage and serum levels during a six months' treatment for relapse prevention. *Pharmacopsychiatry* 1985;**18**:240-5.

McKane 1987 *{published data only}*

McCreadie RG, McKane JP, Robinson ADT, Wiles DH, Stirling GS. Depot neuroleptics as maintenance therapy in chronic schizophrenic in-patients - Abstract. *International Clinical Psychopharmacology* 1986;**Suppl 1**:13-4.

McKane JP, Robinson ADT, Wiles DH, McCreadie RG, Stirling GS. Haloperidol decanoate versus fluphenazine decanoate as maintenance therapy in chronic schizophrenic in-patients. *British Journal of Psychiatry* 1987;**151**:333-6.

Wistedt 1984 *{published data only}*

Wistedt B. A comparison trial of haloperidol decanoate and fluphenazine decanaote in chronic schizophrenic patients. *International Clinical Psychopharmacology* 1986;**Suppl 1**:15-23.

Wistedt B, Persson T, Hellbom E. A clinical double blind comparison between haloperidol decanoate and fluphenazine decanoate. *Current Therapeutic Research* 1984;**35**(5):804-14.

Wistedt 1991 *{published data only}*

Kosiken T, Wistedt B, Thelander S. Zuclopenthixol decanoate vs haloperidol decanoate: A double-blind comparative trial. Proceedings of the 5th World Congress of Biological Psychiatry; Florence, Italy, June 9-14, 1991.

Wistedt B, Koskinen T, Thelander S, Nerdrum T, Pedersen V, Molbjerg C. Zuclopenthixol decanoate and haloperidol decanoate in chronic schizophrenia: a double-blind multicentre study. *Acta Psychiatrica Scandinavica* 1991;**84**:14-6.

Zissis 1982 *{published data only}*

Zissis NP, Psaras M, Lyketsos G. Haloperidol decanoate, a new long acting antipsychotic in chronic schizophrenics: double-blind comparison with placebo. *Current Therapeutic Research* 1982;**31**(4):650-5.

Zuardi 1983 *{published and unpublished data}*

Zuardi AW, Giampietro AC, Grassi ER, Matos Lima AA, Buoncompagno EM, Ribeiro Dos Santos CH, Bredariol MM, Fiestrino A, Oliveria MAS, Moura DSP, Karniol IG. Double-blind comparison between two forms of haloperidol: an oral preparation and a new depot decanoate in the maintenance of schizophrenic inpatients. *Current Therapeutic Research* 1983;**34**(2):253-61.

References to studies excluded from this review

Angus 1997 *{published data only}*

Angus S, Sugars J, Boltezar R, Koskewich S, Scheider N M. A controlled trial of amantadine hydrochloride and neuroleptics in the treatment of tardive dyskinesia. *Journal of Clinical Psychopharmacology* 1997;**17**(2):88-91.

Baastrup 1993 *{published data only}*

Baastrup PC, Alhfors UG, Bjerkenstedt L, Dencker SJ, Fensbo C, Gravem A, Pedersen V, Elgen K, Brekke B, Fredslund-Andersen K, Lindholm H, Lybeck I, Morawski R, Nummi K, Silfverhjelm H, Vartainen H, Wiesel FA, Aarvold A. A controlled Nordic mulitcentre study of zuclopenthixol acetate in oil solution, haloperidol and zuclopenthixol in treatment of acute psychosis. *Acta Psychiatrica Scandinavica* 1993;**87**:48-58.

Bucci 1985 *{published data only}*

Bucci L, Marini S. Haloperidol decanoate in chronic schizophrenic patients. *Current Therapeutic Research* 1985;**37**(6):1091-7.

Cookson 1991 *{published data only}*

Cookson JC. C. Side effects during long term treatment with depot antipsychotic medication. *Clinical Neuropharmacology* 1991;**14**(Suppl 2):24-32.

Curson 1985 *{published data only}*

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.

Deberdt 1980 *{published data only}*

Deberdt R, Elens P, Berghmans W, Heykants J, Woestnborghs R, Dreisens F, Reyntjens A, van Wijngaarden I. Clopenthixol and flupenthixol depot preparations in outpatient schizophrenics. *Acta Psychiatrica Scandinavica* 1980;**62**:356-63.

Dencker 1980 *{published data only}*

Dencker SJ, Lepp M, Malm U. Clopenthixol and flupenthixol depot preparations in outpatient schizophrenics. *Acta Psychiatrica Scandinavica Supplementum* 1980;**279**:10-28.

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 decanaote in schizophrenic patients. *Psychopharmacology* 1994;**114**:24-30.

Fernando 1984 *{published data only}*

Fernando J, Krishna Raju R, Jones GG, Stanley RO. The use of depot neuroleptic haloperidol decanoate. *Acta Psychiatrica Scandanavica* 1984;**69**:175-6.

Gianelli 1990 *{published data only}*

Gianelli A, Rabboni M, Zarattini F. [Profili clinici di azione, indicazinoi preferenziali, effetti terapeutici e controindicazioni di tre neurolettici depot in trial multicentrico di confronto]. *Rivista di Psichiatria* 1990;**25**:8-24.

Jolley 1990 *{published data only}*

Jolley AG, Hirsch SR, Morrison E, McRink A, Wilson L. Trial of brief intermittant neuroleptic prophylaxis for selected schizophrenic outpatients: clinical and social outcome at two years. *British Medical Journal* 1990;**301**:837-42.

Meco 1985 *{published data only}*

Meco G, Falaschi P, Casacchia M, Rocco A, Petrini P, Rosa M, Agnoli A. Neuroendocrine effects of haloperidol decanoate in patients with chronic schizophrenia. *Advanced Biochemical Psychopharmacology* 1985;**40**:89-93.

Meco 1987 *{published data only}*

Meco G, Aniello R, Lestingi L, Petrini P, Castellano A, Casacchia M. Haloperidol decanoate (a new depot neuroleptic drug): double-blind study versus fluphenazine decanoate in schizophreniform disorders and chronic schizophrenia. In: Cazulla CL, Invernizzi G, Bressi C editor(s). Schizophrenia: an integrative view. Milan, Italy, 1987:155-70.

Nair 1986 *{published data only}*

Vasavan Nair NP, Suranyi-Cadotte B, Schwartz G, Thavundayil JX, Achim A, Lizondo E, Nayak R. A clinical trial comparing intramuscular haloperidol decanoate and oral haloperidol in chronic schizophrenic patients: efficacy, safety, and dosage equivalence. *Journal of Clinical Psychopharmacology* 1986;**6**(1):30-7S.

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 perphanazine enanthate. *Current Therapeutic Research* 1986;**39**(5):665-70.

Roose 1982 *{published data only}*

Roose K. Haloperidol decanoate as a replacement for maintenance therapy with intramuscular fluphenazine decanaote in schizophrenia and other chronic psychoses. *Acta Psychiatrica Belgique* 1982;**82**:16-23.

Ushakov 1990 *{published data only}*

Ushakov IV, Kravchenko NE, Kopeiko GI, Kalugina LI, Mirzoian MG. Clinical and economic approach to evaluation of the effectiveness of moditen-depot and haloperidol decanoate in the maintenance therapy of attack-like schizophrenia [Klinicheskii ekonomicheskii podkhod k otsenke sravnitel'noi effektivnosti moditena-depo i galoperidola dekanoata v podderzhi-vaiushchei terapii u bol'nykh pristupoobraznoi shizofreniei]. *Zh Nevropatol-Psikhiatria Im-S-S-Korsakova* 1990;**90**:99-104.

Van Putten 1986 *{published data only}*

Van Putten T, Marder SR. Low-dose treatment strategies. *Journal of Clinical Psychiatry* 1986;**47**(Suppl 5):12-6.

Varma 1989 *{published data only}*

Varma VK, Kulhara P. Open drug trial with haloperidol decanoate injections in schizophrenia. *Indian Journal of Psychiatry* 1989;**31**(2):144-50.

Wei 1996 *{published data only}*

Wei F, Jann MW, Lin H, Piao-Chien C, Chang W. A practical loading dose method converting schizophrenic patients from oral to depot haloperidol therapy. *Journal of Clinical Psychiatry* 1996;**57**(7):298-302.

Weiden 1995 *{published data only}*

Weiden P, Rapkin B, Zygmunt A, Mott T, Goldman D, Frances A. Post-discharge medication compliance of inpatients converted from an oral to a depot neuroleptic regimen. *Psychiatric Services* 1995;**46**(10):1049-54.

Wiles 1990 *{published data only}*

Wiles DM, McCreadie RG, Whitehead A. Pharmacokinetics of haloperidol and fluphenazine decanoates in chronic schizophrenia. *Psychopharmacology* 1990;**101**:274-81.

Youssef 1991 *{published data only}*

Youssef HA. Duration of neuroleptic treatment and relapse rate: a five-year follow-up study with haloperidol decanoate. *Clinical Neuropharmacology* 1991;**4**(Suppl 2):16-23.

Zonda 1992 *{published data only}*

Zonda T, Kovari E. Use of haloperidol decanoate in psychiatric diseases. *Therapia Hungarica* 1992;**40**(2):64-8.

References to studies awaiting assessment

Bernardi 1992 *{published data only}*

Bernardi F, Bocchetta A, del Zompo M, Volonte MV, et al. Efficacy and tolerability to bromperidol decanoate in psychotic patients formerly treated with haloperidol or chlorpromazine [Efficacia terapeutica e tollerabilita del bromperidolo decanoato in pazienti psicotici gia in trattamento con aloperidolo o clorpromazina]. *Rivista di Psichiatria* 1992;**27**:271-5.

Castellani 1988 *{published data only}*

Castellini A, Lorini M. [Flufenazina decanoato e aloperidolo decanoato: due neurolettici a confronto nella patologia psichiatrica non acuta studio crossover a lunga termine]. *Incomplete reference*.

Morasiewicz 1995 *{published data only}*

Morasiewicz J, Baranowski P, Borys J, JanskaSkomorowska M, Kiejna A. Evaluation of clinical usefulness of Decaldol (haloperidol decanoate) produced by WZF Polfa in Warsaw in long-term treatment of schizophrenia [Ocena przydatnosci klinicznej preparatu decaldol (dekanonian haloperidolu) produkcji wzf polfaw warszawie w dlugotrwalym leczeniu schizofrenii]. *Psychiatria Polska* 1995;**29**:405-20.

Rossi 1992 *{published data only}*

Rossi P, Chini C, Casale A, Fusi A, Madonna M, Monaci C, Carta I. Action of bromperidol decanoate in the treatment of negative symptoms of schizophrenia - comparison with haloperidol decanoate [Azione del bromperidolo decanoato nel trattamento dei sintomi negativi della schizofrenia - confronto con l'aloperidolo decanoato]. *Rivista di Psichiatria* 1992;**27**:265-70.

Additional references

Aaes-Jorgenson 1985

Aaes-Jorgensen A. Pharmacokinetics of oral and depot neuoleptics - clinical relevance. Symposium Espo. 1985; Vol. 1.

Agius 1994

Agius AM, Reid AP, Hamilton CAD. Patient compliance with short-term topical aural antibiotic therapy. *Clinical Otolaryngology* 1994;**19**:138-41.

Altamura 1987

Altamura AC, Mauri MC, Guecetti G, Cazzullo CL. Fluphenazine decanoate in acute and maintenance therapy of schizophrenia. *Progress Neuro-Psychopharmacology and Biological Psychiatry* 1987;**11**:613-23.

Altman 1996

Altman DG, Bland JM. Detecting skewness from summary information. *BMJ* 1996;**313**:1200. [HLDC020600]

Asberg 1978

Asberg M, Montgomery SA, Perris C, Schalling D, Sedavll GA. A comprehensive psychopathological rating scale. *Acta Psychiatrica Scandinavica Supplementum* 1978;**271**:5-27.

Barnes 1994

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

Begg 1996

Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, Pitkin R, Rennie D, Schulz KF, Simel D, Stroup DF. Improving the quality of randomized controlled trials. The CONSORT statement. *JAMA* 1996;**276**:637-9.

Chouinard 1980

Chouinard G, Ross-Chouinard A, Annable L. Extrapyramidal symptom rating scale. *Canadian Journal of Neurological Science* 1980;**7**:233.

David 1994

David AS, Cutting JC, editors. 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 Supplementum* 1980;**61**(279):64-76.

DoH 1996

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

Feighner 1972

Feighner JP, Robins E, Guze S, Woodruff RA, Winokur G, Munoz R. Diagnostic criteria for use in psychiatric research. *Archives of General Psychiatry* 1972;**26**:57-62.

Guy 1976

Guy W. Early clinical drug evaluation (ECDEU) assessment manual for psychopharmacology. Washington, DC: US Government Printing Office, 1976. [National Institute of Mental Health Publication No. 76-338]

Haynes 1979

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

Heresco-Levy 1989

Heresco-Levy U, Greenberg D, Wittman L, Dasberg H, Lerer B. Prescribing patterns of neuroactive drugs in 98 schizophrenic patients. *Israel Journal of Psychiatry and Related Sciences* 1989;**26**:157-63.

Honigfeld 1962

Honigfeld G, Gillis RD, Klett CJ. NOSIE-30: A treatment sensitive ward behavior scale. *Psychological Reports* 1962;**10**:799-812.

Jablensky 1992

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

Johnson 1990

Johnson DA, Wright NF. Drug prescribing for schizophrenic out-patients on depot injections. Repeat surveys over 18 years. *British Journal of Psychiatry* 1990;**156**:827-34.

Kane 1986

Kane JM, Woerner M, Sarantakos S. Depot neuroleptics: a comparison review of standard, intermediate and low-dose regimens. *Journal of Clinical Psychiatry* 1986;**47**(Suppl 5):30-3.

Kane 1998

Kane JM, Aguglia E, Carlo Altamura A, Guiterrez JLA, Brunello N, Fleischhacker WW, Gaebel W, Gerlach J, Guelfi JD, Kissling W, Lapierre YD, Lindstrom E, Mendlewicz J, Racagni G, Carulla LS, Schooler NR. Guidelines for depot antipsychotic treatment in schizophrenia. *European Neuropschopharmacology* 1998;**8**:55-66.

Krawiecka 1977

Krawiecka M, Goldberg D, Vaughan M. A standardised psychiatric assessment scale for rating psychotic patients. *Acta Psychiatrica Scandinavica* 1977;**55**:299-308.

Leff 1971

Leff JP, Wing JK. Trial of maintenance therapy in schizophrenia. *British Medical Journal* 1971;**3**:559-604.

Leff 1973

Leff JP, Hirsch SR, Gaind R, Rhhode PD. Outpatient maintenace of chronic schizophrenic patients with long acting fluphenazine: double-blind placebo trial. *British Medical Journal* 1973;**1**:633-7.

Lingjerde 1987

Lingjerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatrica Scandinavica* 1987;**76**(Suppl):334.

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.

Mulrow 1999

Mulrow CD, Oxman A. The Cochrane Handbook [updated 1 March 1999]. *Cochrane Database of Systematic Reviews*.

Overall 1962

Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychological Reports* 1962;**10**:799-812.

Pereira 1997

Pereira S, Pinto R. A survey of the attitudes of chronic psychiatric patients living in the community toward their medication. *Acta Psychiatrica Scandanavica* 1997;**95**:464-8.

Reyntijens 1982

Reyntijens AJM, Heykants JJP, Woestenborghs RJH. Pharmacokinetics of haloperidol decanoate. *Pharmacopsychiatry* 1982;**17**:238-46.

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.

Simpson 1970

Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. *Acta Psychiatria Scandinavia Supplementum* 1970;**212**:11-9.

Spitzer 1977

Spitzer RL, Endicott J, Robins E. Research diagnostic criteria for a selected group of functional disorders. Rockville, MD: National Institute of Mental Health, 1977.

CHARACTERISTICS OF STUDIES

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

Bechelli 1985

Methods	Allocation: randomised, stratified by Schizophrenia subgroups. Blindness: double. Duration: 6 months (preceded by 7 day washout).
Participants	Diagnosis: schizophrenia (RDC). History: >2 episodes, stabilized for 3 months, duration ill - mean 12 yrs (HD) 9 yrs (PP), informed consent given. N = 41.

Bechelli 1985 *(Continued)*

	Age: 19-50 yrs (mean range 30-33 yrs). Sex: all male. Race: caucasian. Setting: out-patient clinic.
Interventions	1. Haloperidol decanoate: dose mean 100mg/injection, monthly, range 50-100mg/injection. N=21. 2. Pipothiazine palmitate: dose mean 75 (**65)mg/ injection, monthly, range 50- 125mg/injection. N=20.
Outcomes	Mental state (BPRS). Leaving the study early. Additional medication. Side effects (Bordeleau Scale/AIMS). Unable to use - Global Impression (CGI - no data). Weight measures (non-clinical outcomes, data not usuable).
Notes	* Spitzer 1997 ** The mean dose of PP is given as 75mg in the abstract and 65mg in the paper.

Risk of bias

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

Chouinard 1984

Methods	Allocation: randomised, stratified by sex & past frequency of depot administration. Blindness: double. Duration: 8 months. Statistics: last observation carried forward.
Participants	Diagnosis: schizophrenia (DSM III). History: on depot >3 months, duration ill - mean 16 yrs, range 3-38, informed consent given. N=72. Age: mean 44 yrs, range 18-66. Sex: 36 M, 36 F. Setting: community.
Interventions	1. Haloperidol decanoate: dose mean 225mg/injection, 2-4 weekly, range 15-900mg/injection. N=36. 2. Fluphenazine decanoate: dose mean 75mg/injection, 2-4 weekly, range 2.5-300mg/injection. N=36.
Outcomes	Global Impression (CGI). Mental state (BPRS). Leaving the study early. Additional medication. Unable to use - Side effects (ESRS - authors own scale*, TESF - no data reported). Physiological measures (prolactin, drug plasma levels - non clinical outcomes, data not usable).
Notes	* Marshall et al, 1998.

Risk of bias

Chouinard 1984 *(Continued)*

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

Cookson 1986

Methods	Allocation: randomised - seperate sequences for males and females. Blindness: double. Duration: 1 year. Statistics: last observation carried forward.
Participants	History: 1 year of treatment with fluphenazine decanoate, overweight BMI 25+, physically fit, stable during prev yr. N= 19. Age: range HD 26-57 yrs/ FD 35-60 yrs. Sex: 9 M, 10 F. Setting: community (depot injection clinic).
Interventions	1. Haloperidol decanoate: dose mean not specified, frequency same as previous depot. N=10. 2. Fluphenazine decanoate: dose mean not specified. N=9. Dose ratio: 4:1 (HD/FD).
Outcomes	Leaving the study early. Unable to use - Mental state (CPRS, Kraweicka -Goldberg Scale - no data). Side effects (Simpson & Angus Scale/ AIMS - no data). Physiological measures (prolactin), weight measures - non clinical outcomes, data not usuable).
Notes	No usuable continuous data. Authors contacted - no reply.

Risk of bias

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

Eberhard 1986

Methods	Allocation: randomised, blocks of 6. Blindness: double. Duration: 24 weeks - no washout period. Crossover X 2.
Participants	Diagnosis: schizophrenia (DSM III). History: previously on antipsychotics (both depot/oral), duration ill - range 1-6 yrs, consent given. N=32. Age: median 38 yrs, range 25-60. Sex: 17 M, 15 F. Setting: 10 inpatients, 28 community, multicentre.
Interventions	1. Haloperidol decanoate: dose mean 131mg/injection (start)- 151mg/injection (24 wks), last 3 injections fixed dose. N=16.

Eberhard 1986 *(Continued)*

	2. Flupenthixol decanoate: dose mean 56mg/injection (start)- 66mg/injection (24 wks), last 3 injections fixed dose. N=16.
Outcomes	Mental state (CPRS). Leaving the study early. Additional medication. Side effects - depression.
Notes	

Risk of bias

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

Eklund 1991

Methods	Allocation: randomised. Blindness: double. Duration: 48 weeks (preceded by 15 week single blind 60mg HD/ month).
Participants	Diagnosis: schizophrenia (RDC). N=56 Age: mean ˜ 52 yrs (SD ˜ 12), range 25-65. Sex: 37 F, 19 M. Setting: 37 community, 19 hospital.
Interventions	1. Haloperidol decanoate: dose mean 60mg/ injection (fixed dose regimen), every 4 weeks. N=18/ N=20* 2. Placebo: N=23
Outcomes	Leaving the study early. Unable to use - Additional medication (>30% attrition) Relapse (>30% attrition). Side effects (EPSS - >30% attrition). Mental state (CPRS - no SD). Physiological measures (plasma levels).
Notes	* N in HD group in abstract differs from N in paper. Authors contacted - no reply.

Risk of bias

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

Kissling 1985

Methods	Allocation: randomised, flip of a coin. Blindness: double.

Kissling 1985 *(Continued)*

	Duration: 6 months. Statistics: last observation carried forward.
Participants	Diagnosis: schizophrenia/ schizoaffective psychosis (DSM III). History: on oral medication, need depot treatment for >6 months, informed consent given. N=54. Age: ˜ 30 years (SD ˜11). Sex: 24 M, 7 F.
Interventions	1. Haloperidol decanoate: dose mean 80mg/ injection (actual dose given 50mg), monthly. N=32. 2. Fluphenazine decanoate: dose mean 21mg/ injection (actual dose given 25mg), every 2 weeks. N=22.
Outcomes	Leaving the study early. Unable to use - Mental state (BPRS).* Additional medication (anticholinergics).* Side effects (EPMS, DOTES, STESS).* Physiological Measures (serum levels - non clinical outcomes, data not usable).*
Notes	*The drop out rate after 6 months for FD=60%, HD=30%.

Risk of bias

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

McKane 1987

Methods	Allocation: randomised. Blindness: double. Duration: 60 weeks (preceded by 12 week 'run in' period where additional medication allowed).
Participants	Diagnosis: schizophrenia (Fiegner criteria*). History: on antipsychotics, duration ill - mean 31 yrs, range 10-50, next of kin gave consent. N=38. Age: mean 56 yrs, range 31- 71. Sex : 22 M, 16 F. Setting: in hospital.
Interventions	1. Haloperidol decanaote: initial dose mean 127 mg/injection, week 12 dose mean 120mg/ injection, monthly. N=17. 2. Fluphenazine decanoate: initial mean dose 106mg/ injection, week 12 dose mean 105/ injection, monthly. N=16.
Outcomes	Mental state (Krawiecka scale). Leaving the study early. Additional medication. Side effects (AIMS). Parkinsonism (Simpson & Angus). Behaviour (Wing Ward Behaviour Scale). Unable to use - Global impresson (Global 5-point scale - no data). Physiological measures (prolactin, drug plasma levels - non clinical outcomes, data not usable).

McKane 1987 *(Continued)*

Notes	* Fiegner 1972

Risk of bias

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

Wistedt 1984

Methods	Allocation: randomisation list, blocks of six. Blindness: double. Duration: 20 weeks.
Participants	Diagnosis: schizophrenia (RDC). History: duration ill - range 0-12 yrs, informed consent given. N=51. Age range: 21-63 yrs. Sex: 33 M, 18 F. Setting: 4 weeks in hospital, community thereafter, multicentre.
Interventions	1. Haloperidol decanoate: dose mean 122mg/injection, monthly. N=25. 2. Fluphenazine decanoate: dose mean 84mg/injection, monthly. N=26.*
Outcomes	Global impression (CGI). Mental state (CPRS). Leaving the study early. Additional medication. Side effects (AIMS, EPS). Unable to use - Physiological measures (drug plasma levels - non-clinical outcomes, data not usable). Weight changes (non-clincal outcomes, data not usable).
Notes	Dose ratio :1:1.4 (FD/HD).

Risk of bias

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

Wistedt 1991

Methods	Allocation: randomised. Blindness: double. Duration: 9 months (preceded by 3 months on either depot).
Participants	Diagnosis: schizophrenia (DSM III). History: BPRS total score 5-26, duration ill - mean >2yrs. N=64. Age: range 25-60 yrs. Sex: 28 M, 33 F.

Wistedt 1991 *(Continued)*

	Setting: community, multicentre.
Interventions	1. Haloperidol decanoate: dose mean 92mg/IM, range 38-200mg/injection, monthly. N=33. 2. Zuclopenthixol decanoate: dose mean 284mg/IM, range 100-600mg/injection, monthly. N=23.
Outcomes	Death. Global Impression (CGI). Mental state (BPRS, MADRS). Side effects (Simpson & Angus, UKU).
Notes	Initial 3 month dose adjustment period + supplementary medication, then 6 months where dose constant.

Risk of bias

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

Zissis 1982

Methods	Allocation: randomised - predetermined code. Blindness: double. Duration: 16 weeks.
Participants	Diagnosis: schizophrenia (Feighner criteria). History: on antipsychotics >2yrs, informed consent given, duration hospitalized ˜ 14 yrs. N=32. Age: mean ˜ 46 yrs (range 28- 60). Sex: 12 F, 4 M. Setting: in hospital.
Interventions	1. Haloperidol decanoate: dose mean 150mg/IM/month, initially, range 0.5-1.5ml/IM, dose adapted to side effects. N=16. 2. Placebo IM. N=16. Haloperidol given orally if individual deteriorated.
Outcomes	Mental state: withdrawn due to lack of effect. Additional medication. Unable to use - Global Impression (CGI - no data reported)*. Mental state (BPRS - no SD)**. Behaviour (NOSIE - no SD)**.
Notes	Abstract & paper differed on numbers withdrawn - used data in body of paper. >30% withdrawn due to lack of effect but all followed up. * reported to be not different between groups. ** reported as statistically different. Authors contacted - no reply.

Risk of bias

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

Zuardi 1983

Methods	Allocation: randomised. Blindiness: double. Duration: 4 months.
Participants	Diagnosis: schizophrenia (ICD-9). History: same drugs for 2 months, stable symptoms 1 month, duration hospitalized 0.3 - 26 yrs. N=22. Age: range 26- 63 yrs. Sex: 13 M, 9 F. Setting: in hospital.
Interventions	1. Haloperidol decanoate: dose schedule individualized. N=11. 2. Haloperidol oral: dose schedule individualized. N=11.
Outcomes	Mental state (BPRS).* Leaving the study early. Additional medication. Side effects (Bordeleau Scale).* Unable to use - Global Impression (CGI - no SD).
Notes	* Authors supplied additional BPRS & Bordeleau scale data.

Risk of bias

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

Diagnostic tools
DSM III - Diagnostic Statistical Manual, version 3.
ICD-9 - International Calssification of Diseases, version 9.
RDC - Research Diagnostic Criteria.
Rating scales
Global impression
CGI - Clinical Global Impression.
Mental state
BPRS - Brief Psychiatric Rating Scale.
CPRS - Comprehensive Psychopathological Rating Scale.
Side effects
AIMS - Abnormal Involuntary Movement Side effects.
DOTES - Dosage Record & Treatment Emergent Symptom Scale.
EPMS - Extrapyramidal Motor Side-effects.
EPSS - Extrapyramidal 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
Angus 1997	Allocation: 'double blind'.

Study	Reason for exclusion
	Participants: those with a psychotic illness. Interventions: amantadine hydrochloride versus neuroleptic, not haloperidol decanoate.
Baastrup 1993	Allocation: randomised. Participants: those with exacerbation of chronic psychosis. Interventions: haloperidol decanoate and oral versus zuclopenthixol acetate versus zuclopenthixol decanoate. Outcomes: no usable data, haloperidol decanoate and oral data pooled.
Bucci 1985	Allocation: not randomised.
Cookson 1991	Allocation: 'double blind'. Participants: those with schizophrenia. Interventions: haloperidol decanoate versus fluphenazine decanoate. Outcomes: no usable data, authors contacted and have replied redirecting the request to a third party who has been contacted.
Curson 1985	Allocation: randomised. Participants: those with schizophrenia. Interventions: fluphenazine decanoate versus placebo, not haloperidol decanoate.
Deberdt 1980	Allocation: not randomised.
Dencker 1980	Allocation: randomised. Participants: those with schizophrenia. Interventions: clopenthixol depot versus flupehthixol depot, not haloperidol decanoate.
Dencker 1994	Allocation: randomised. Participants: those with schizophrenia. Interventions: haloperidol decanoate versus perphanazine decanoate. Outcomes: no usable data, authors contacted.
Fernando 1984	Allocation: not randomised.
Gianelli 1990	Allocation: not randomised.
Jolley 1990	Allocation: randomised. Participants: those with schizophrenia. Interventions: fluphenazine decanoate, not haloperidol decanoate.
Meco 1985	Allocation: not randomised.
Meco 1987	Allocation: not randomised.
Nair 1986	Allocation: not randomised.
Rapp 1986	Allocation: randomised. Participants: those with schizophrenia. Interventions: haloperidol decanoate versus perphenazine decanoate. Outcomes: no usable data, authors contacted.
Roose 1982	Allocation: not randomised.
Ushakov 1990	Allocation: randomised. Participants: those with schizophrenia. Interventions: haloperidol decanoate versus fluphenazine. Outcomes: no usable data.

Study	Reason for exclusion
Van Putten 1986	Allocation: not randomised.
Varma 1989	Allocation: not randomised.
Wei 1996	Allocation: not randomised.
Weiden 1995	Allocation: not randomised.
Wiles 1990	Allocation: 'double blind'. Participants: those with schizophrenia. Interventions: haloperidol decanoate versus fluphenazine decanoate. Outcomes: no usable data, authors contacted.
Youssef 1991	Allocation: not randomised.
Zonda 1992	Allocation: not randomised.

Behaviour scale
NOSIE - Nurses Observation Scale for Inpatient Evaluation.

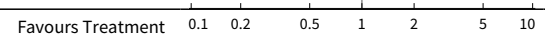
DATA AND ANALYSES

Comparison 1. HALOPERIDOL DECANOATE vs PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Behaviour: Not completing the study	2	74	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.09 [0.03, 0.21]
1.1 short term - withdrawn by trialists due to lack of effect	1	32	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.04 [0.01, 0.15]
1.2 medium term - leaving the study early	1	42	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.16 [0.05, 0.51]
2 Global impression: Needing additional antipsychotic treatment - by 4 months	1	32	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.04, 0.55]
3 Mental state: No discernable effect - by 4 months	1	32	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.04 [0.01, 0.15]
4 Side effects: 1. Anticholinergic problems - blurred vision - by 4 months	1	32	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.17 [0.03, 0.89]
5 Side effects: 2. Movement disorders - tremor - by 4 months	1	32	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.24, 4.09]

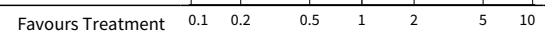
Analysis 1.1. Comparison 1 HALOPERIDOL DECANOATE vs PLACEBO, Outcome 1 Behaviour: Not completing the study.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.1.1 short term - withdrawn by trialists due to lack of effect					
Zissis 1982	0/16	13/16		42.61%	0.04[0.01,0.15]
Subtotal (95% CI)	**16**	**16**		**42.61%**	**0.04[0.01,0.15]**
Total events: 0 (Treatment), 13 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.61(P<0.0001)					
1.1.2 medium term - leaving the study early					
Eklund 1991	5/20	16/22		57.39%	0.16[0.05,0.51]
Subtotal (95% CI)	**20**	**22**		**57.39%**	**0.16[0.05,0.51]**
Total events: 5 (Treatment), 16 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.05(P=0)					
Total (95% CI)	**36**	**38**		**100%**	**0.09[0.03,0.21]**
Total events: 5 (Treatment), 29 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.24, df=1(P=0.13); I^2=55.34%					
Test for overall effect: Z=5.32(P<0.0001)					
Test for subgroup differences: Chi^2=2.24, df=1 (P=0.13), I^2=55.34%					



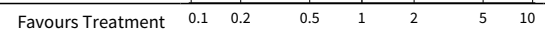
Analysis 1.2. Comparison 1 HALOPERIDOL DECANOATE vs PLACEBO, Outcome 2 Global impression: Needing additional antipsychotic treatment - by 4 months.

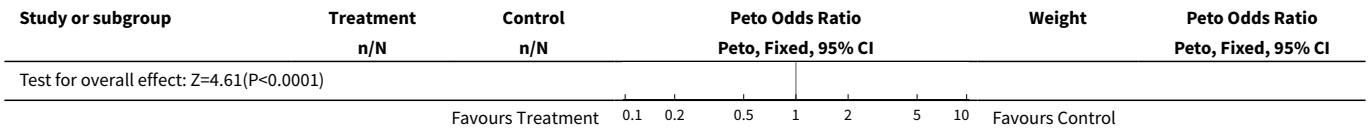
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Zissis 1982	5/16	13/16		100%	0.14[0.04,0.55]
Total (95% CI)	**16**	**16**		**100%**	**0.14[0.04,0.55]**
Total events: 5 (Treatment), 13 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.81(P=0.01)					



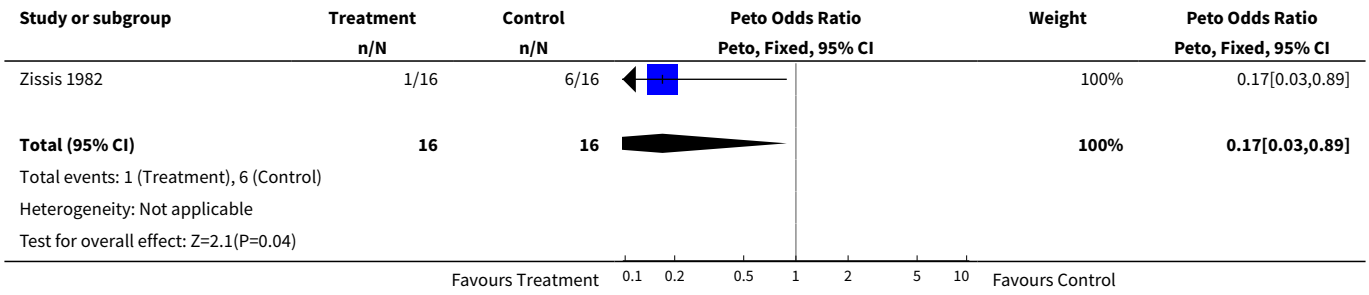
Analysis 1.3. Comparison 1 HALOPERIDOL DECANOATE vs PLACEBO, Outcome 3 Mental state: No discernable effect - by 4 months.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Zissis 1982	0/16	13/16		100%	0.04[0.01,0.15]
Total (95% CI)	**16**	**16**		**100%**	**0.04[0.01,0.15]**
Total events: 0 (Treatment), 13 (Control)					
Heterogeneity: Not applicable					

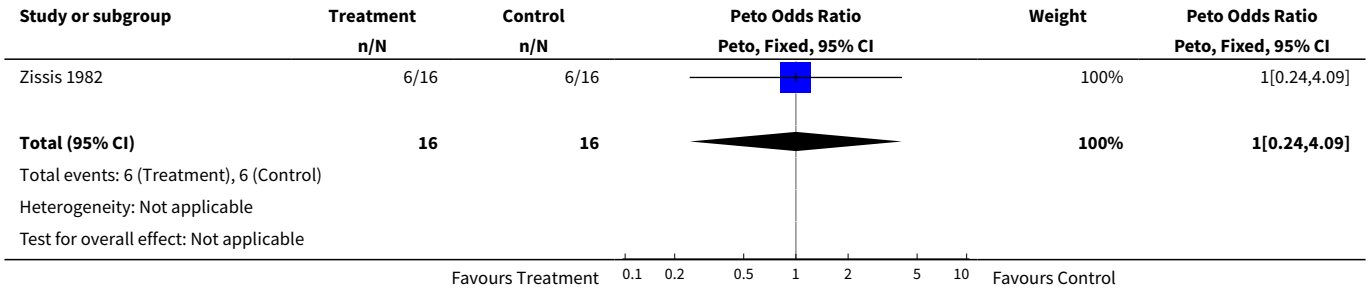




Analysis 1.4. Comparison 1 HALOPERIDOL DECANOATE vs PLACEBO, Outcome 4 Side effects: 1. Anticholinergic problems - blurred vision - by 4 months.



Analysis 1.5. Comparison 1 HALOPERIDOL DECANOATE vs PLACEBO, Outcome 5 Side effects: 2. Movement disorders - tremor - by 4 months.



Comparison 2. HALOPERIDOL DECANOATE vs ORAL HALOPERIDOL

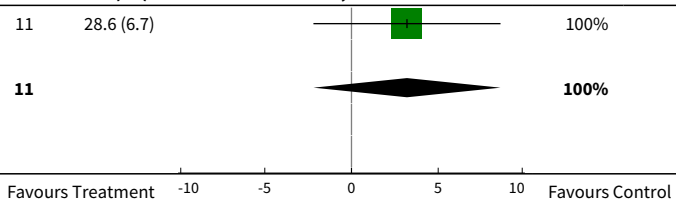
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global impression: Not improved - at 4 months (CGI)	1	22	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.61 [0.09, 4.28]
2 Mental state: BPRS - at 4 months (endpoint score, high=poor)	1	22	Mean Difference (IV, Fixed, 95% CI)	3.20 [-2.19, 8.59]
3 Side effects: 1. Movement disorders - needing anticholinergic drugs.	1	22	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.21 [0.39, 26.67]
4 Side effects: 2. Extrapyramidal symptoms - skewed data (Bordeleau Scale).			Other data	No numeric data

Analysis 2.1. Comparison 2 HALOPERIDOL DECANOATE vs ORAL HALOPERIDOL, Outcome 1 Global impression: Not improved - at 4 months (CGI).

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Zuardi 1983	8/11	9/11		100%	0.61[0.09,4.28]
Total (95% CI)	**11**	**11**		**100%**	**0.61[0.09,4.28]**
Total events: 8 (Treatment), 9 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.5(P=0.62)					

Analysis 2.2. Comparison 2 HALOPERIDOL DECANOATE vs ORAL HALOPERIDOL, Outcome 2 Mental state: BPRS - at 4 months (endpoint score, high=poor).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Zuardi 1983	11	31.8 (6.2)	11	28.6 (6.7)		100%	3.2[-2.19,8.59]
Total ***	**11**		**11**			**100%**	**3.2[-2.19,8.59]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.16(P=0.24)							



Analysis 2.3. Comparison 2 HALOPERIDOL DECANOATE vs ORAL HALOPERIDOL, Outcome 3 Side effects: 1. Movement disorders - needing anticholinergic drugs..

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Zuardi 1983	3/11	1/11		100%	3.21[0.39,26.67]
Total (95% CI)	**11**	**11**		**100%**	**3.21[0.39,26.67]**
Total events: 3 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.08(P=0.28)					

Analysis 2.4. Comparison 2 HALOPERIDOL DECANOATE vs ORAL HALOPERIDOL, Outcome 4 Side effects: 2. Extrapyramidal symptoms - skewed data (Bordeleau Scale)..

Side effects: 2. Extrapyramidal symptoms - skewed data (Bordeleau Scale).

Study	
Zuardi 1983	1. Haloperidol decanoate - mean 1.5 SD 1.7. N=11. 2. Haloperidol tablets - mean 1.2 SD 1.6. N=11.

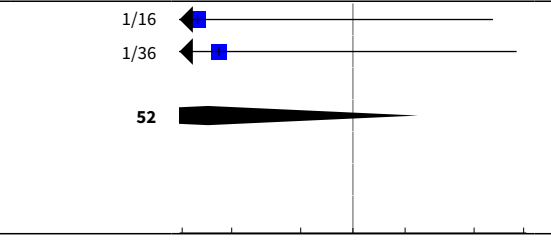
Comparison 3. HALOPERIDOL DECANOATE vs OTHER DEPOT ANTIPSYCHOTICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	2	97	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.15 [0.01, 2.37]
2 Global impression: 1. Needing additional antipsychotic treatment	2	113	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.63 [0.17, 2.30]
3 Global impression: 2. Clinical Global Impression (endpoint score, high=poor)	2	128	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.22, 0.36]
4 Global impression: 3. Clinical Global Impression (skewed data, high=poor).			Other data	No numeric data
5 Mental state: 1. Relapse	7	317	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [0.65, 2.42]
6 Mental state: 2. BPRS (endpoint score, high=poor)	2	113	Mean Difference (IV, Fixed, 95% CI)	0.87 [-0.97, 2.72]
7 Mental state: 3. Various scales (skewed endpoint data)			Other data	No numeric data
7.1 general (BPRS, high = poor)			Other data	No numeric data
7.2 general (CPRS, high = poor)			Other data	No numeric data
7.3 general (Krawiecka scale, high = poor)			Other data	No numeric data
7.4 specific - depression			Other data	No numeric data
8 Behaviour: 1. Leaving the study early	8	371	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.52, 1.60]
9 Behaviour: 2. Wing Ward Behaviour Scale (skewed endpoint data, high=poor).			Other data	No numeric data
10 Side effects: 1. Movement disorders	6		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
10.1 dyskinesia	2	105	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [0.53, 3.06]
10.2 needing anticholinergic drugs	5	257	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.43, 1.47]
10.3 tremor	1	41	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.76 [0.22, 2.59]
11 Side effects: 2. Movement disorders - various scales (skewed endpoint data)			Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
11.1 parkinsonism (Simpson & Angus scale, high = poor)			Other data	No numeric data
11.2 tardive dyskinesia (AIMS, high = poor)			Other data	No numeric data
12 Side effects: 3. Significant side effects reported	1	64	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.26, 1.86]

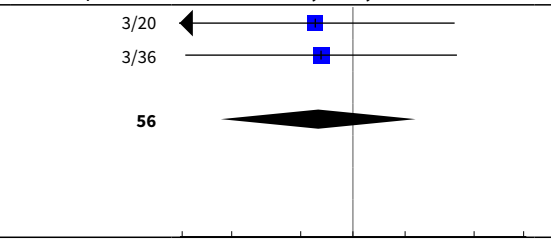
Analysis 3.1. Comparison 3 HALOPERIDOL DECANOATE vs OTHER DEPOT ANTIPSYCHOTICS, Outcome 1 Death.

Study or subgroup	Haldol de-canoate n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
McKane 1987	0/17	1/16		50.37%	0.13[0,6.42]
Wistedt 1991	0/28	1/36		49.63%	0.17[0,8.79]
Total (95% CI)	**45**	**52**		**100%**	**0.15[0.01,2.37]**
Total events: 0 (Haldol decanoate), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.92); I^2=0%					
Test for overall effect: Z=1.35(P=0.18)					



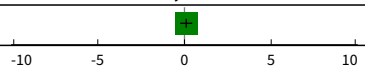
Analysis 3.2. Comparison 3 HALOPERIDOL DECANOATE vs OTHER DEPOT ANTIPSYCHOTICS, Outcome 2 Global impression: 1. Needing additional antipsychotic treatment.

Study or subgroup	Haldol de-canoate n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bechelli 1985	2/21	3/20		48.8%	0.61[0.1,3.86]
Chouinard 1984	2/36	3/36		51.2%	0.65[0.11,3.98]
Total (95% CI)	**57**	**56**		**100%**	**0.63[0.17,2.3]**
Total events: 4 (Haldol decanoate), 6 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.95); I^2=0%					
Test for overall effect: Z=0.7(P=0.48)					



Analysis 3.3. Comparison 3 HALOPERIDOL DECANOATE vs OTHER DEPOT ANTIPSYCHOTICS, Outcome 3 Global impression: 2. Clinical Global Impression (endpoint score, high=poor).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Chouinard 1984	36	2.9 (0.7)	36	2.8 (0.8)		70.15%	0.1[-0.25,0.45]



Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Wistedt 1991	23	3.9 (1)	33	3.9 (1)		29.85%	0[-0.53,0.53]
Total ***	**59**		**69**			**100%**	**0.07[-0.22,0.36]**
Heterogeneity: Tau²=0; Chi²=0.1, df=1(P=0.76); I²=0%							
Test for overall effect: Z=0.47(P=0.64)							

-10 -5 0 5 10

Analysis 3.4. Comparison 3 HALOPERIDOL DECANOATE vs OTHER DEPOT ANTIPSYCHOTICS, Outcome 4 Global impression: 3. Clinical Global Impression (skewed data, high=poor)..

Global impression: 3. Clinical Global Impression (skewed data, high=poor).

Study	
Wistedt 1984	1. Haloperidol decanoate - mean 2.9 SD 1.5. N=25. 2. Fluphenazine decanoate - mean 2.9 SD 2.0. N=26.

t

Analysis 3.5. Comparison 3 HALOPERIDOL DECANOATE vs OTHER DEPOT ANTIPSYCHOTICS, Outcome 5 Mental state: 1. Relapse.

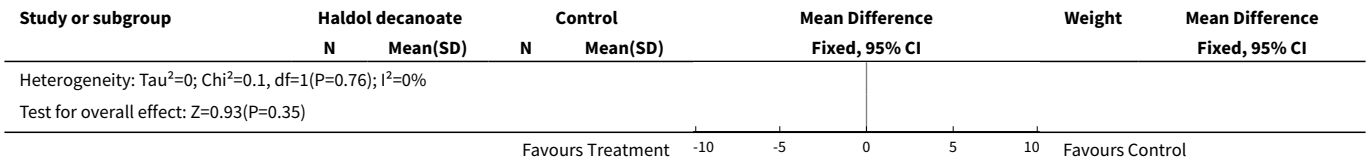
Study or subgroup	Haldol de-canoate n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bechelli 1985	2/21	2/20		10.5%	0.95[0.12,7.28]
Chouinard 1984	0/36	1/36		2.84%	0.14[0,6.82]
Cookson 1986	2/10	0/9		5.35%	7.48[0.43,130.05]
Eberhard 1986	3/16	3/16		14.29%	1[0.17,5.74]
McKane 1987	10/19	10/19		27.62%	1[0.28,3.51]
Wistedt 1984	4/25	4/26		19.53%	1.05[0.23,4.67]
Wistedt 1991	5/28	3/36		19.87%	2.36[0.54,10.37]
Total (95% CI)	**155**	**162**		**100%**	**1.25[0.65,2.42]**
Total events: 26 (Haldol decanoate), 23 (Control)					
Heterogeneity: Tau²=0; Chi²=3.75, df=6(P=0.71); I²=0%					
Test for overall effect: Z=0.67(P=0.51)					

Favours Treatment 0.1 0.2 0.5 1 2 5 10 Favours Control

Analysis 3.6. Comparison 3 HALOPERIDOL DECANOATE vs OTHER DEPOT ANTIPSYCHOTICS, Outcome 6 Mental state: 2. BPRS (endpoint score, high=poor).

Study or subgroup	Haldol decanoate N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bechelli 1985	21	20.4 (5.2)	20	19.3 (1.6)		62.33%	1.1[-1.23,3.43]
Chouinard 1984	36	25 (5.7)	36	24.5 (7.2)		37.67%	0.5[-2.5,3.5]
Total ***	**57**		**56**			**100%**	**0.87[-0.97,2.72]**

Favours Treatment -10 -5 0 5 10 Favours Control

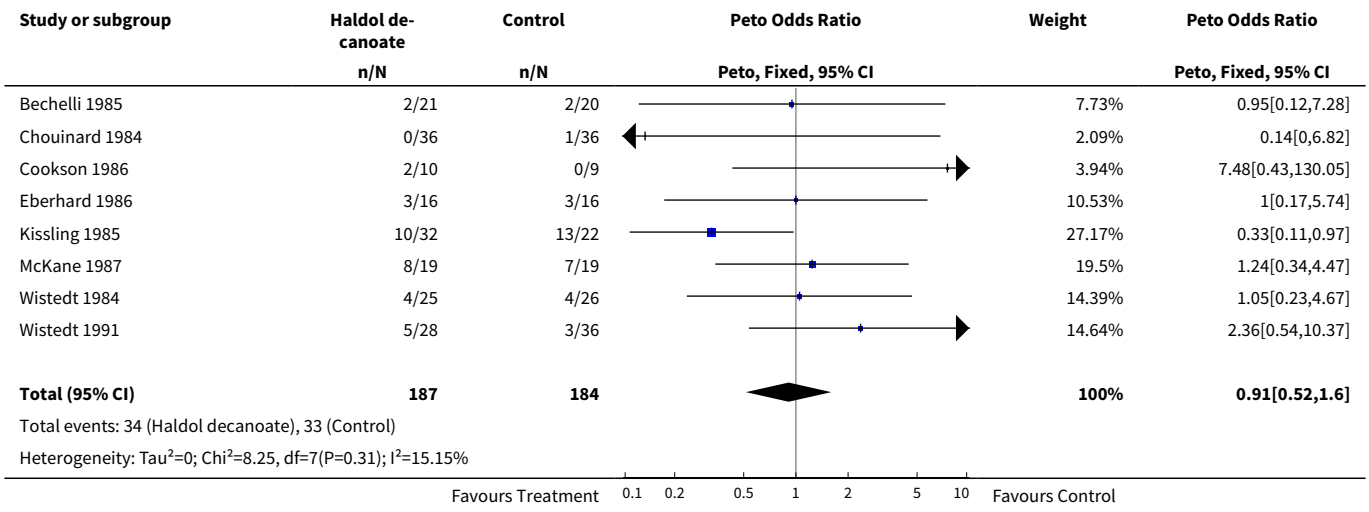


Analysis 3.7. Comparison 3 HALOPERIDOL DECANOATE vs OTHER DEPOT ANTIPSYCHOTICS, Outcome 7 Mental state: 3. Various scales (skewed endpoint data).

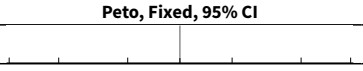
Mental state: 3. Various scales (skewed endpoint data)

Study	
general (BPRS, high = poor)	
Eberhard 1986	1. Haloperidol decanoate - mean 7.3 SD 7.2. N=16. 2. Flupenthixol decanoate - mean 5.7 SD 7.2. N=16.
Wistedt 1991	1. Haloperidol decanoate - mean 8.5 SD 5.5. N=23. 2. Zuclopenthixol decanoate - mean 10.1 SD 7.0. N=33.
general (CPRS, high = poor)	
Eberhard 1986	1. Haloperidol decanoate - mean 7.3 SD 7.2. N=16. 2. Flupenthixol decanoate - mean 5.7 SD 7.2. N=16.
Wistedt 1984	1. Haloperidol decanoate: mean 3, SD 2.5. N=25. 2. Fluphenazine decanoate: mean 4.1 SD 2.0. N=26.
general (Krawiecka scale, high = poor)	
McKane 1987	1. Haloperidol decanoate - mean 8.5 SD 5.0. N=17. 2. Fluphenazine decanoate - mean 8.2 SD 5.4. N=16.
specific - depression	
Eberhard 1986	CPRS - depression subscale, high = poor. 1. Haloperidol decanoate - mean 6.9 SD 6.0. N=16. 2. Flupenthixol decanoate - mean 6.8 SD 6.8. N=16.
Wistedt 1984	CPRS - depression subscale, high = poor. 1. Haloperidol decanoate - mean 0.9 SD 4.5. N=25. 2. Fluphenazine decanoate - mean 2.5 SD 2.6. N=26.
Wistedt 1991	MADRS, high = poor. 1. Haloperidol decanoate - mean 1.5 SD 2.7. N=23. 2. Zuclopenthixol decanoate - mean 1.1 SD 1.5. N=33.

Analysis 3.8. Comparison 3 HALOPERIDOL DECANOATE vs OTHER DEPOT ANTIPSYCHOTICS, Outcome 8 Behaviour: 1. Leaving the study early.



Study or subgroup	Haldol de-canoate n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Test for overall effect: Z=0.33(P=0.74)					



Favours Treatment | Favours Control

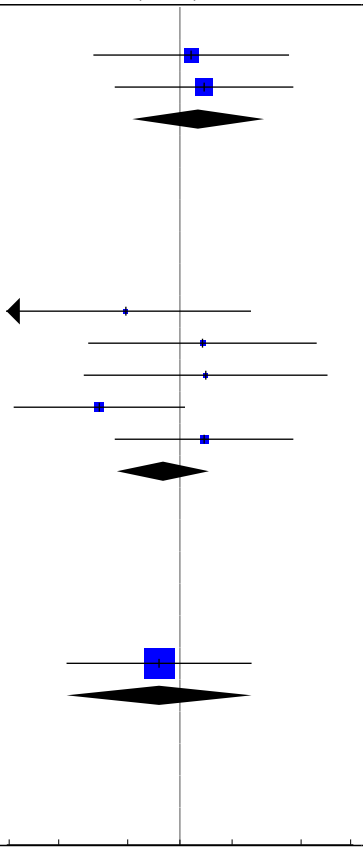
Analysis 3.9. Comparison 3 HALOPERIDOL DECANOATE vs OTHER DEPOT ANTIPSYCHOTICS, Outcome 9 Behaviour: 2. Wing Ward Behaviour Scale (skewed endpoint data, high=poor)..

Behaviour: 2. Wing Ward Behaviour Scale (skewed endpoint data, high=poor).

Study	
McKane 1987	1. Haloperidol decanaote - mean 5.5 SD 4.1. N=17. 2. Fluphenazine decanoate - mean 4.8 SD 4.4. N=16.

Analysis 3.10. Comparison 3 HALOPERIDOL DECANOATE vs OTHER DEPOT ANTIPSYCHOTICS, Outcome 10 Side effects: 1. Movement disorders.

Study or subgroup	Haldol de-canoate n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
3.10.1 dyskinesia					
Bechelli 1985	7/21	6/20		45.4%	1.16[0.32,4.26]
Wistedt 1991	7/28	7/36		54.6%	1.38[0.42,4.51]
Subtotal (95% CI)	**49**	**56**		**100%**	**1.27[0.53,3.06]**
Total events: 14 (Haldol decanoate), 13 (Control)					
Heterogeneity: Tau²=0; Chi²=0.04, df=1(P=0.85); I²=0%					
Test for overall effect: Z=0.54(P=0.59)					
3.10.2 needing anticholinergic drugs					
Chouinard 1984	32/36	34/36		13.63%	0.49[0.09,2.57]
Eberhard 1986	5/16	4/16		16.31%	1.35[0.3,6.15]
McKane 1987	16/19	15/19		14.33%	1.41[0.28,7.1]
Wistedt 1984	13/25	20/26		29.01%	0.34[0.11,1.07]
Wistedt 1991	7/28	7/36		26.72%	1.38[0.42,4.51]
Subtotal (95% CI)	**124**	**133**		**100%**	**0.8[0.43,1.47]**
Total events: 73 (Haldol decanoate), 80 (Control)					
Heterogeneity: Tau²=0; Chi²=4.2, df=4(P=0.38); I²=4.73%					
Test for overall effect: Z=0.72(P=0.47)					
3.10.3 tremor					
Bechelli 1985	8/21	9/20		100%	0.76[0.22,2.59]
Subtotal (95% CI)	**21**	**20**		**100%**	**0.76[0.22,2.59]**
Total events: 8 (Haldol decanoate), 9 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.44(P=0.66)					
Test for subgroup differences: Chi²=0.83, df=1 (P=0.66), I²=0%					



Favours Treatment | Favours Control

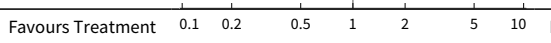
Analysis 3.11. Comparison 3 HALOPERIDOL DECANOATE vs OTHER DEPOT ANTIPSYCHOTICS, Outcome 11 Side effects: 2. Movement disorders - various scales (skewed endpoint data).

Side effects: 2. Movement disorders - various scales (skewed endpoint data)

Study	
parkinsonism (Simpson & Angus scale, high = poor)	
McKane 1987	1. Haloperidol decanoate - mean 3.5 SD 3.2. N=17. 2. Fluphenazine decanoate - mean 4.0 SD 3.0. N=16.
Wistedt 1984	1. Haloperidol decanoate - mean 2.7 SD 6.0. N=25. 2. Fluphenazine decanoate - mean 2.3 SD 8.2. N=26.
tardive dyskinesia (AIMS, high = poor)	
McKane 1987	1. Haloperidol decanoate - mean 4.6 SD 5.1. N=17. 2. Fluphenazine decanoate- mean 2.9 SD 2.9. N=16.

Analysis 3.12. Comparison 3 HALOPERIDOL DECANOATE vs OTHER DEPOT ANTIPSYCHOTICS, Outcome 12 Side effects: 3. Significant side effects reported.

Study or subgroup	Haldol de-canoate n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Wistedt 1991	13/28	20/36		100%	0.7[0.26,1.86]
Total (95% CI)	**28**	**36**		**100%**	**0.7[0.26,1.86]**
Total events: 13 (Haldol decanoate), 20 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.72(P=0.47)					



F E E D B A C K

General comment

Summary

The review is hard to read and assimilate. One problem is that the typographical distinctions between different levels of heading and subheading are insufficient. The editorial team rather than the reviewers need to address this.

1. Category: Abstract
The abstract does not state the number of included trials.

2. Category: Objectives
This could be improved by adding the comparisons examined in the review.

3. Category: Results
The number of trials and number of participants contributing to each comparison is missing.

4. Category: Included studies table
The standard alphabetical arrangement of trials by author's name makes it laborious to separate the various comparisons. It would be better to group them according to comparisons they make.

5. Category: Acknowledgements
It is a surprise to see the authors acknowledging their own contributions!
Presumably this is just a problem of syntax - conflating a statement of what each author contributed to the review with an acknowledgement to others who were not authors.

Reply

The Cochrane Library is evolving and such comments help to improve the readability of the reviews and as such will be addressed by the editorial body.

1. Category: Abstract
This information is now included.

2. Category: Objectives
This omission will be rectified in the next update.

3. Category: Results
The data will be included in the next update.

4. Category: Included studies table
The included studies table will be amended in the update.

5. Category: Acknowledgements
Reviews in the Cochrane Library, formatted in RevMan 4.0.4 are now using contributorship, making explicit the input of each author. The Cochrane Schizophrenia Group instigated this policy when RevMan 3.1 was being used and as there was no obvious place to cite the contributions of each author it was put into the area dedicated to acknowledgements.

Contributors

Comment received from Andrew Herxheimer, London, March 1999.
Reply from Seema Quraishi, London, December 1999.

WHAT'S NEW

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.

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; Haloperidol [*analogs & derivatives] [therapeutic use]; Schizophrenia [*drug therapy]

MeSH check words

Humans