Bromperidol decanoate (depot) for schizophrenia (Review)

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TABLE OF CONTENTS

[Intervention Review]

Bromperidol decanoate (depot) for schizophrenia

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ABSTRACT

Background

Antipsychotic drugs are the mainstay treatment for schizophrenia. Long-acting depot injections of drugs such as bromperidol decanoate are extensively used as a means of long-term maintenance treatment.

Objectives

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

Search methods

For this 2011 update we searched the Cochrane Schizophrenia Group's Register (February 2011).

Selection criteria

We sought all randomised trials focusing on people with schizophrenia where depot bromperidol, oral antipsychotics or other depot preparations. Primary outcomes were clinically significant change in global function, service utilisation outcomes (hospital admission, days in hospital), relapse.

Data collection and analysis

For this 2011 update MP independently extracted data, CEA carried out the reliability check. We calculated fixed-effect risk ratios (RR) and 95% confidence intervals (CI) for dichotomous data, and calculated weighted or standardised means for continuous data. Where possible, we calculated the number needed to treat statistic (NNT). Analysis was by intention-to-treat.

Main results

We have included no new trials in this 2011 update (4 RCTs, total n = 117). A single, small study of six months' duration compared bromperidol decanoate with placebo injection. Similar numbers left the study before completion (n = 20, 1 RCT, RR 0.4 CI 0.1 to 1.6) and there were no clear differences between bromperidol decanoate and placebo for a list of adverse effects (n = 20, 1 RCT, RR akathisia 2.0 CI 0.21 to 18.69, RR increased weight 3.0 CI 0.14 to 65.9, RR tremor 0.33 CI 0.04 to 2.69). When bromperidol decanoate was compared with fluphenazine depot, we found no important change on global outcome (n = 30, RR no clinical important improvement 1.50 CI 0.29 to 7.73). People allocated to fluphenazine decanoate and haloperidol decanoate had fewer relapses than those given bromperidol decanoate (n = 77, RR 3.92 Cl 1.05 to 14.60, NNH 6 CI 2 to 341). People allocated bromperidol decanoate

required additional antipsychotic medication somewhat more frequently than those taking fluphenazine decanoate and haloperidol decanoate, but the results did not reach conventional levels of statistical significance (n = 77, 2 RCTs, RR 1.72 CI 0.7 to 4.2). The use of benzodiazepine drugs was very similar in both groups (n = 77, 2 RCTs, RR 1.08 CI 0.68 to 1.70). People left the bromperidol decanoate group more frequent than those taking other depot preparation due to any cause (n = 97, 3 RCTs, RR 2.17 CI 1.00 to 4.73). Anticholinergic adverse effects were equally common between bromperidol and other depots (n = 47, RR 3.13 CI 0.7 to 14.0) and additional anticholinergic medication was needed with equal frequency in both depot groups, although results did tend to favour the bromperidol decanoate group (n = 97, 3 RCTs, RR 0.80 CI 0.64 to 1.01). The incidence of movement disorders was similar in both depot groups (n = 77, 2 RCTs, RR 0.74 CI 0.47 to 1.17).

Authors' conclusions

Minimal poorly reported trial data suggests that bromperidol decanoate may be better than placebo injection but less valuable than fluphenazine or haloperidol decanoate. If bromperidol decanoate is available it may be a viable choice, especially when there are reasons not to use fluphenazine or haloperidol decanoate. Well-conducted and reported randomised trials are needed to inform practice.

PLAIN LANGUAGE SUMMARY

Depot bromperidol decanoate for schizophrenia

Bromperidol decanoate is used as a long-acting antipsychotic medication in at least Belgium, Germany, Italy and the Netherlands. The preparation seems to be less potent than other depot antipsychotics (such as fluphenazine and haloperidol decanoate) and better than placebo injection. However, this older antipsychotic preparation has very few data from good quality studies and new trials are needed to fully understand the effects of this preparation.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Bromperidol decanoate compared to placebo for schizophrenia

Patient or population: patients with schizophrenia
Settings: outpatient department
Intervention: bromperidol decanoate
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Bromperidol decanoate				
Global state: Relapse	See comment	See comment	Not estimable	0 (0)	See comment	No trial reported this outcome
Global state: Hospital admission	See comment	See comment	Not estimable	0 (0)	See comment	No trial reported this outcome
Global state: Response - proxy outcome - mental state: 1. General - average score (Brief Psychiatric Rating Scale) Follow-up: 6 months		The mean global state: Response - proxy outcome - mental state: 1. General - average score in the intervention groups was **11.2 lower** (20.25 to 2.15 lower)		20 (1 study)	⊕◯◯◯ **very low**[1,2,3]	No trial reported global response - we used one general mental state measure as a proxy
Quality of life	See comment	See comment	Not estimable	0 (0)	See comment	No trial reported this outcome
Adverse effects - increased weight	**Low risk population**[4]		**RR 3** (0.14 to 65.9)	20 (1 study)	⊕⊕◯◯ **low**[1,3]	No people in the control group had increased weight.

	0 per 1000	**0 per 1000** (0 to 0)			
	Medium risk population[4]				
	20 per 1000	**60 per 1000** (3 to 1000)			
	High risk population[4]				
	40 per 1000	**120 per 1000** (6 to 1000)			
Adverse effects - stiffness	**Low risk population**[5]		**RR 0.25** (0.03 to 1.86)	20 (1 study)	⊕⊕◯◯ **low**[1,3]
	200 per 1000	**50 per 1000** (6 to 372)			
	Medium risk population[5]				
	400 per 1000	**100 per 1000** (12 to 744)			
	High risk population[5]				
	600 per 1000	**150 per 1000** (18 to 1000)			

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

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

[1] Limitations in design - rated 'serious': randomisation stated but not described, blinding stated but not tested.
[2] Indirectness - rated 'serious': used proxy measure as no trial reported on response.
[3] Publication bias - rated as 'likely': small trial.
[4] Low risk is approximately that of the control group.
[5] Medium level risk is approximately that of trial control group.

BACKGROUND

Description of the condition

Schizophrenia is a disabling mental disorder characterised by psychosis, apathy and social withdrawal, and cognitive impairment, which results in impaired functioning in work, school, parenting, self-care, independent living, interpersonal relationships and leisure time (Mueser 2004). The annual incidence of schizophrenia is 0.2-0.4 per 1000, with a lifetime prevalence (risk) about 1% (Jablensky 1997). It often runs a chronic course with acute exacerbations and often partial remissions. Antipsychotics are the primary medication for schizophrenia, with major effects on reduction of psychotic symptoms and prevention of relapses (Kane 1993).

Description of the intervention

Antipsychotic drugs are usually given orally (Aaes-Jorgensen 1985) but non-adherence is highly prevalent among schizophrenia patients, with at least one-third estimated to be non-adherent with their medication regimens (West 2005). Those who suffer from long-term illnesses such as schizophrenia, where the treatments may have uncomfortable adverse effects (Kane 1998) and where individuals have cognitive impairments (David 1994) and erosion of insight, are especially prone to avoid taking medication on a regular basis. Depots mainly consist of an ester of the active drug held in an oily suspension. This is injected intramuscularly and is slowly released. Depots may be given every one to six weeks. Individuals may be maintained in the community with regular injections administered by community psychiatric nurses, sometimes in clinics set up for this purpose (Barnes 1994). Evidence suggests that depot may improve outcomes compared with oral antipsychotics (Fleischhacker 2009), because medication intake is assured and because the doctor immediately knows when a patients stops treatment (Leucht 2011). Nevertheless in some countries, due to various reasons such as refusal by patients or reservations by psychiatrists, depot formulations are rarely prescribed (Hamann 2010; Heres 2006; Heres 2007).

This review is one in a series focusing on the effects of depot preparations for those with schizophrenia (Abhijnhan 2007; David 2005). Bromperidol (R 11.333, azuren, 4-[4-(p-bromophenyl)-4-hydroxypiperidino]-4'-fluorobutyro phenone, impromen, tesoprel, bromidol, bromperidol) belongs to the butyrophenone class of drugs (Figure 1).

Figure 1. Chemical structure of bromperidol

How the intervention might work

Bromperidol's depot preparation is a decanoate in sesame oil (bromidol depot, impromen decanoas). The pharmacokinetic composition of the drug is similar to that of haloperidol decanoate, a more frequently used depot (Someya 1991). It is a strong D2 and very weak D1 antagonist. It has incisive activity and no active metabolites. The slow release of the decanoate ester from the oily depot has an elimination half-life of about 28 days.

Bromperidol decanoate is available as 'Impromen' in Belgium, Germany and the Netherlands and as 'Tesoprel' in Italy. How prevalent its use is has not been possible to ascertain. Janssen Cilag has already been helpful in supplying data and is attempting to identify data on prevalence of use. The reviewers would welcome information relating to use of this preparation.

Why it is important to do this review

Although most psychiatrists acknowledge a greater efficacy of depot with regard to relapse prevention (Patel 2010), the depot formulations are seldom prescribed in the treatment of schizophrenia (Heres 2006) and evidence about depot preparations is unclear. While an early meta-analysis suggested a superiority of depot compared with oral administration (Davis 1994), the Cochrane reviews of the various depots did not find any convincing difference (Adams 2001). The information on efficacy and tolerability of specific depot preparations, such as depot bromperidol decanoate, is now out of date and needs to be updated.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials (RCTs). If a trial is described as 'double blind' but implies randomisation, we included such trials in a sensitivity analysis (see Sensitivity analysis). If their inclusion did not result in a substantive difference, they remained in the analyses. If their inclusion did result in statistically significant differences, we did not add the data from these lower-quality studies to the results of the better trials, but presented such data within a subcategory. We excluded quasi-randomised studies, such as those allocating by alternate days of the week. Where people were given additional treatments within the depot bromperidol or control group, we only included data if the adjunct treatment was evenly distributed between groups and it was only the depot bromperidol that was randomised.

Types of participants

Anyone with a diagnosis of schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder and delusional disorder, again, by any means of diagnosis.

We are interested in making sure that information is as relevant to the current care of people with schizophrenia as possible, so propose to clearly highlight the current clinical state (acute, early post-acute, partial remission, remission) as well as the stage (prodromal, first episode, early illness, persistent) and as to whether the studies primarily focused on people with particular problems (for example, negative symptoms, treatment-resistant illnesses).

Types of interventions

1. Bromperidol decanoate: any dose
2. Placebo
3. Oral anti-psychotic drugs: any dose
4. Other depot antipsychotic drugs: any dose

Types of outcome measures

We grouped outcomes into immediate (zero to five weeks), short term (six weeks to five months), medium term (six months to 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

2.2 Days in hospital

Secondary outcomes

1. Leaving the study early

2. Clinical response

2.1 Average score/change in global state
2.2 Clinically significant response on psychotic symptoms - as defined by each of the studies
2.3 Average score/change on psychotic symptoms
2.4 Clinically significant response on positive symptoms - as defined by each of the studies
2.5 Average score/change in positive symptoms
2.6 Clinically significant response on negative symptoms - as defined by each of the studies
2.7 Average score/change in negative symptoms
2.8 Other general or specific effects on mental state
2.9 Clinically significant general or specific effects on mental state - as defined by each of the studies
2.10 Average score/change in general or specific effects on mental state
2.11 Additional medication

3. Adverse events/effects, general and specific

3.1 Death, suicide or natural causes
3.2 Incidence of use of antiparkinson drugs
3.3 Clinically significant extrapyramidal adverse effects - as defined by each of the studies
3.4 Average score/change in extrapyramidal adverse effects
3.5 Other general or specific adverse effects
3.6 Clinically significant general or specific adverse effects - as defined by each of the studies
3.7 Average score/change in general or specific adverse effects

4. Economic outcomes

4.1 Cost benefit
4.2 Cost utility

5. Quality of life/satisfaction with care

5.1 Significant change in quality of life/satisfaction - as defined by each of the studies
5.2 Average score/change in quality of life/satisfaction

6. General functioning

6.1 Clinically significant change in general functioning
6.2 Average score/change in general functioning score

7. Cognitive functioning

7.1 Clinically significant change in general functioning
7.2 Average score/change in general functioning score

Search methods for identification of studies

For previous searches please see Appendix 1 and Appendix 2.

Electronic searches

Cochrane Schizophrenia Group Trials Register (February 2011)

We searched the register using the phrase:
[(*r 11.333* or *r 46541* or *r46541*or *azuren* or *bromperidol* or *bromop* or *bridel* or *bromidol* or *erodium* or *impromen* or *lunapron* or *prindil* or *ropel* or *tesoprel* in title, abstract or index terms of REFERENCE) or (bromperidol in interventions of STUDY)]
This register is compiled by systematic searches of major databases, handsearches and conference proceedings (see group module).

Searching other resources

1. Reference searching

We inspected references of all identified studies for further relevant studies.

2. Personal contact

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

Data collection and analysis

Methods used in data collection and analysis for this 2011 update are below; for previous methods please see Appendix 1.

Selection of studies

For this 2011 update MP independently inspected citations from the new electronic search and identified relevant abstracts. MP also inspected full articles of the abstracts meeting inclusion criteria. CEA carried out the reliability check of all citations from the new electronic search.

Data extraction and management

1. Extraction

For this 2011 update, MP extracted data from included studies. We extracted data presented only in graphs and figures whenever possible. When further information was necessary, we contacted authors of studies in order to obtain missing data or for clarification. If studies were multi-centre, where possible, we extracted data relevant to each component centre separately.

2. Management

2.1 Forms

We extracted data onto standard, simple forms.

2.2 Scale-derived data

We included continuous data from rating scales only if:
a. the psychometric properties of the measuring instrument have been described in a peer-reviewed journal (Marshall 2000); and
b. the measuring instrument has not been written or modified by one of the trialists for that particular trial.
Ideally the measuring instrument should either be i. a self-report or ii. completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly; we have noted whether or not this is the case in Description of studies.

2.3 Endpoint versus change data

There are advantages of both endpoint and change data. Change data can remove a component of between-person variability from the analysis. On the other hand, calculation of change needs two assessments (baseline and endpoint), which can be difficult in unstable and difficult to measure conditions such as schizophrenia. We decided to primarily use endpoint data, and only use change data if the former were not available. We combined endpoint and change data in the analysis as we used mean differences (MD) rather than standardised mean differences throughout (Higgins 2011, Chapter 9.4.5.2).

2.4 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we aimed to apply the following standards to all data before inclusion: a) standard deviations and means are reported in the paper or obtainable from the authors; b) when a scale starts from the finite number zero, the standard deviation, when multiplied by two, is less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution (Altman 1996)); c) if a scale started from a positive value (such as PANSS which can have values from 30 to 210), we modified the calculation described above to take the scale starting point into account. In these cases skew is present if 2SD>(S-S min), where S is the mean score and S min is the minimum score. Endpoint scores on scales often have a finite start and end point and these rules can be applied. When continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not. We entered skewed data from studies of fewer than 200 participants in additional tables rather than into an analysis. Skewed data pose less of a problem when looking at mean if the sample size is large; we entered such data into syntheses.

2.5 Common measure

To facilitate comparison between trials, we intended to convert variables that can be reported in different metrics, such as days in hospital (mean days per year, per week or per month) to a common metric (e.g. mean days per month).

2.6 Conversion of continuous to binary

Where possible, we made efforts to convert outcome measures to dichotomous data. This can be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It is generally assumed that if there is a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS, Overall 1962) or the Positive and Negative Syndrome Scale (PANSS, Kay 1986), this could be considered as a clinically significant response (Leucht 2005; Leucht 2005a). If data based on these thresholds were not available, we used the primary cut-off presented by the original authors.

2.7 Direction of graphs

Where possible, we entered data in such a way that the area to the left of the line of no effect indicated a favourable outcome for depot bromperidol decanoate. Where keeping to this made it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'Not improved') we reported data where the left of the line indicates an unfavourable outcome. This was noted in the relevant graphs.

2.8 Summary of findings table

We used the GRADE approach to interpret findings (Schünemann 2008) and used the GRADE profiler to import data from Review Manager (RevMan) to create 'Summary of findings' tables. These tables provide outcome-specific information concerning the overall quality of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and

the sum of available data on all outcomes we rated as important to patient-care and decision making. We selected the following main outcomes for inclusion in the summary of findings table.

1. Relapse
2. Hospital admission
3. Clinically significant response in global state - as defined by each of the studies
4. Quality of life
5. Adverse effects

Assessment of risk of bias in included studies

For this 2011 update, MP worked independently by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to assess trial quality. This new set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

Where inadequate details of randomisation and other characteristics of trials were provided, we contacted authors of the studies in order to obtain additional information.

We have noted the level of risk of bias in both the text of the review and in the Summary of findings for the main comparison.

Measures of treatment effect

1. Binary data

For binary outcomes we calculated a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI). It has been shown that RR is more intuitive (Boissel 1999) than odds ratios and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). For statistically significant results, we had planned to calculate the number needed to treat to provide benefit/to induce harm statistic (NNTB/H), and its 95% CI using Visual Rx (http://www.nntonline.net/), taking account of the event rate in the control group. This, however, has been superseded by the Summary of findings for the main comparison and calculations therein.

2. Continuous data

For continuous outcomes we estimated mean difference (MD) between groups. We would prefer not to calculate effect size measures (standardised mean difference (SMD)). However, if scales of very considerable similarity were used, we presumed there was a small difference in measurement, and we would have calculated effect size and transformed the effect back to the units of one or more of the specific instruments.

Unit of analysis issues

1. Cluster trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice), but analysis and pooling of clustered data poses problems. Authors often fail to account for intra-class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby P values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997; Gulliford 1999).

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

We have sought statistical advice and have been advised that the binary data as presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the intra-class correlation coefficient (ICC) [Design effect = 1+(m-1)*ICC] (Donner 2002). If the ICC is not reported it was assumed to be 0.1 (Ukoumunne 1999).

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

2. Cross-over trials

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

3. Studies with multiple treatment groups

Where a study involves more than two treatment arms, if relevant, we presented the additional treatment arms in comparisons. If data are binary we simply added these and combined within the two-by-two table. If data were continuous we combined data following the formula in section 7.7.3.8 (Combining groups) of the *Handbook* (Higgins 2011). Where the additional treatment arms were not relevant, we did not reproduce these data.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up data must lose credibility (Xia 2009). We chose that, for any particular outcome, should more than 50% of data be unaccounted for, we did not reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a study were lost, but the total loss was less than 50%, we marked such data with (*) to indicate that such a result may well be prone to bias.

2. Binary

In the case where attrition for a binary outcome was between 0% and 50% and where these data were not clearly described, we presented data on a 'once-randomised-always-analyse' basis (an intention-to-treat analysis). Those leaving the study early were all assumed to have the same rates of negative outcome as those who completed, with the exception of the outcome of death and adverse effects. For these outcomes the rate of those who stayed in the study - in that particular arm of the trial - were used for those who did not. We undertook a sensitivity analysis testing how prone the primary outcomes were to change when 'completer' data only were compared to the intention-to-treat analysis using the above assumptions.

3. Continuous

3.1 Attrition

In the case where attrition for a continuous outcome is between 0% and 50% and completer-only data are reported, we reproduced these.

3.2 Standard deviations

If standard deviations were not reported, we first tried to obtain the missing values from the authors. If not available, where there are missing measures of variance for continuous data, but an exact standard error and confidence intervals available for group means, and either P value or T value available for differences in mean, we can calculate them according to the rules described in the *Handbook* (Higgins 2011): When only the standard error (SE) is reported, standard deviations (SDs) are calculated by the formula SD = SE * square root (n). Chapters 7.7.3 and 16.1.3 of the *Handbook* (Higgins 2011) present detailed formula for estimating SDs from P values, T or F values, confidence intervals, ranges or other statistics. If these formula do not apply, we would calculate the SDs according to a validated imputation method which is based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome and thus to lose information. We nevertheless examined the validity of the imputations in a sensitivity analysis excluding imputed values.

3.3 Last observation carried forward

We anticipated that in some studies the method of last observation carried forward (LOCF) would be employed within the study report. As with all methods of imputation to deal with missing data, LOCF introduces uncertainty about the reliability of the results (Leucht 2007). Therefore, where LOCF data have been used in the trial, if less than 50% of the data have been assumed, we reproduced these data and indicated that they are the product of LOCF assumptions.

Assessment of heterogeneity

1. Clinical heterogeneity

We considered all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We simply inspected all studies for clearly outlying people or situations which we had not predicted would arise. When such situations or participant groups arose, we fully discussed these.

2. Methodological heterogeneity

We considered all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We simply inspected all studies for clearly outlying methods which we had not predicted would arise. When such methodological outliers arose, we fully discussed these.

3. Statistical heterogeneity

3.1 Visual inspection

We visually inspected graphs to investigate the possibility of statistical heterogeneity.

3.2 Employing the I^2 statistic

We investigated heterogeneity between studies by considering the I^2 method alongside the Chi^2 P value. The I^2 provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 depends on i. magnitude and direction of effects and ii. strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or a confidence interval for I^2). I^2 estimate greater than or equal to

around 50% accompanied by a statistically significant Chi^2 statistic was interpreted as evidence of substantial levels of heterogeneity (Higgins 2011). When substantial levels of heterogeneity were found in the primary outcome, we explored reasons for heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in Section 10 of the *Handbook* (Higgins 2011). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We did not use funnel plots for outcomes where there were 10 or fewer studies, or where all studies were of similar sizes. In other cases, where funnel plots are possible, we sought statistical advice in their interpretation.

Data synthesis

We understand that there is no closed argument for preference for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us and the random-effects model takes into account differences between studies even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the random-effects model: it puts added weight onto small studies which often are the most biased ones. Depending on the direction of effect, these studies can either inflate or deflate the effect size. We chose the fixed-effect model for all analyses. The reader is, however, able to choose to inspect the data using the random-effects model.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses - only primary outcomes

1.1 Clinical state, stage or problem

We proposed to undertake this review and provide an overview of the effects of depot bromperidol decanoate for people with schizophrenia in general. In addition, however, we tried to report data on subgroups of people in the same clinical state, stage and with similar problems.

2. Investigation of heterogeneity

If inconsistency was high, we have reported this. First, we investigated whether data had been entered correctly. Second, if data were correct, we visually inspected the graph and successively removed studies outside of the company of the rest to see if homogeneity was restored. For this review we decided that should this occur with data contributing to the summary finding of no more than around 10% of the total weighting, we would present data. If not, then we did not pool data and discussed issues. We know of no supporting research for this 10% cut-off, but we use prediction intervals as an alternative to this unsatisfactory state.

When unanticipated clinical or methodological heterogeneity is obvious simply stated hypotheses regarding these for future reviews or versions of this review. We do not anticipate undertaking analyses relating to these.

Sensitivity analysis

We applied all sensitivity analyses to the primary outcomes of this review.

1. Implication of randomisation

We aimed to include trials in a sensitivity analysis if they were described in some way so as to imply randomisation. For the primary outcomes we included these studies and if there was no substantive difference when the implied randomised studies were added to those with better description of randomisation, then we entered all data from these studies.

2. Assumptions for lost binary data

Where assumptions had to be made regarding people lost to follow-up and missing SDs data (see Dealing with missing data), we compared the findings on primary outcomes when we used our assumption compared with complete data only. We undertook a sensitivity analysis testing how prone results were to change when 'completer' data only were compared to the imputed data using the above assumption. If there was a substantial difference, we reported results and discussed them but continued to employ our assumption.

3. Risk of bias

We analysed the effects of excluding trials that were judged to be at high risk of bias across one or more of the domains of randomisation (implied as randomised with no further details available): allocation concealment, blinding and outcome reporting for the meta-analysis of the primary outcome. If the exclusion of trials at high risk of bias did not substantially alter the direction of effect or the precision of the effect estimates, then we included data from these trials in the analysis.

4. Imputed values

We also undertook a sensitivity analysis to assess the effects of including data from trials where we used imputed values for ICC in calculating the design effect in cluster randomised trials.
If we noted substantial differences in the direction or precision of effect estimates in any of the sensitivity analyses listed above, we did not pool data from the excluded trials with the other trials contributing to the outcome, but presented them separately.

5. Fixed-effect and random-effects

We synthesised data using a fixed-effect model.

6. Setting

We performed a sensitivity analysis to investigate whether the setting where participants were recruited can influence outcome results. As recently argued in a review of depot antipsychotic drugs for schizophrenia, the setting where people receive treatment might influence adherence; the inpatient setting, where medication is usually administered by a nurse, might help improve compliance (Leucht 2011). Therefore authors suggest that outpatient setting is more appropriate to investigate the value of depot antipsychotics.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
Please also see Characteristics of included studies, Characteristics of excluded studies.

Results of the search

The 2011 update search identified six new studies. We have not added any of these to the included studies table.

Included studies

Overall the review includes four studies published between 1990 and 1992. That only 117 people, on current estimate, have been randomised to bromperidol decanoate or a control intervention probably reflects that this preparation was licensed some time before requirements of drug regulatory authorities tightened.

1. Methods

All studies were stated to be randomised and double blind. For further details please see sections below on Allocation and Blinding.

2. Duration

Two studies had a follow-up of six months, two studies of 12 months.

3. Participants

All participants (total n = 117) were diagnosed with schizophrenia. People of both sexes were included. Ages ranged between 20 and 68 years, the average age being about 35 years. People were described as either having illnesses that were chronic (McLaren 1992; Rossi 1992) or in a 'residual' stage (Smeraldi 1990). Rossi 1990 reported that the modal duration of the current episode was between one and six months.

4. Setting

Three trials were conducted in a community setting and one was set in a hospital (Rossi 1992).

5. Comparison group

Only Smeraldi 1990 compared bromperidol decanoate with placebo intramuscular injection. The other three studies compared bromperidol decanoate with another depot antipsychotic (McLaren 1992, Rossi 1990 - fluphenazine decanoate; Rossi 1992 - haloperidol decanoate). The McLaren 1992 study used both depots in higher than usual doses (bromperidol decanoate mean = 242 mg/IM/month; fluphenazine decanoate = 103 mg/IM/month).

6. Outcomes

6.1 Possible to use

We identified some data for mental state, leaving the study early and adverse effects on each of two comparisons (bromperidol decanoate versus placebo/bromperidol decanoate versus other depot antipsychotic drugs). We also found some data for global effects for the second comparison.

6.2 Reporting

We could not extract some outcomes due to missing means, standard deviations or standard errors. Apart from a few dichotomous outcomes for relapse, leaving the study early and adverse effects, it was not possible to use most data. Scale data were poorly reported and either lacked explicit statements regarding denominator (Rossi 1990; Smeraldi 1990), variance (Rossi 1992) or any data at all (McLaren 1992). In this 2011 update we reported scale data assuming as denominator the number of randomised patients.

6.3 Measures that were possible to include

6.3.1 Global functioning

a. 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.
b. Brief Psychiatric Rating Scale - BPRS (Overall 1962)
A rating scale to measure psychiatric symptoms such as depression, anxiety, hallucinations and unusual behaviour. Each symptom is rated 1-7 and, depending on the version, between a total of 18-24 symptoms are scored.
c. Dosage Record and Treatment Emergent Symptoms Scale - DOTES (Guy 1976)
This adverse 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 adverse effects.
d. Hamilton Depression Rating Scale - HDRS (Hamilton 1960)
A clinician-administered depression assessment scale that rates the severity of symptoms observed in depression such as low mood, insomnia, agitation, anxiety and weight loss.
e. Scale for the Assessment of Negative Symptoms - SANS (Andreasen 1982)
This scale assesses five symptom complexes to obtain clinical ratings of negative symptoms in patients with schizophrenia. They are: affective blunting; alogia; avolition/apathy; anhedonia/asociality; and disturbance of attention.
f. Scale for the Assessment of Positive Symptoms - SAPS (Andreasen 1984)
A scale designed to assess positive symptoms, principally those that occur in schizophrenia. It is intended to serve as a complementary instrument to the SANS. Positive symptoms include hallucinations, delusions, bizarre behavior and positive formal thought disorder.

6.4 Missing outcomes

Some important outcomes such as days in hospital and quality of life were not reported in any trial. Also secondary outcomes (economic outcomes, satisfaction with care, general and cognitive functioning) were not reported.

Excluded studies

For this 2011 update we excluded six studies: four compared oral bromperidol versus other drugs, one compared non-pharmacological interventions and one compared other antipsychotic agents than bromperidol. There are now 37 excluded studies.

Risk of bias in included studies

Please also refer to Risk of bias tables in the Characteristics of included studies and Figure 2; Figure 3 for overview and graphical representations of the risk of bias in the included studies.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

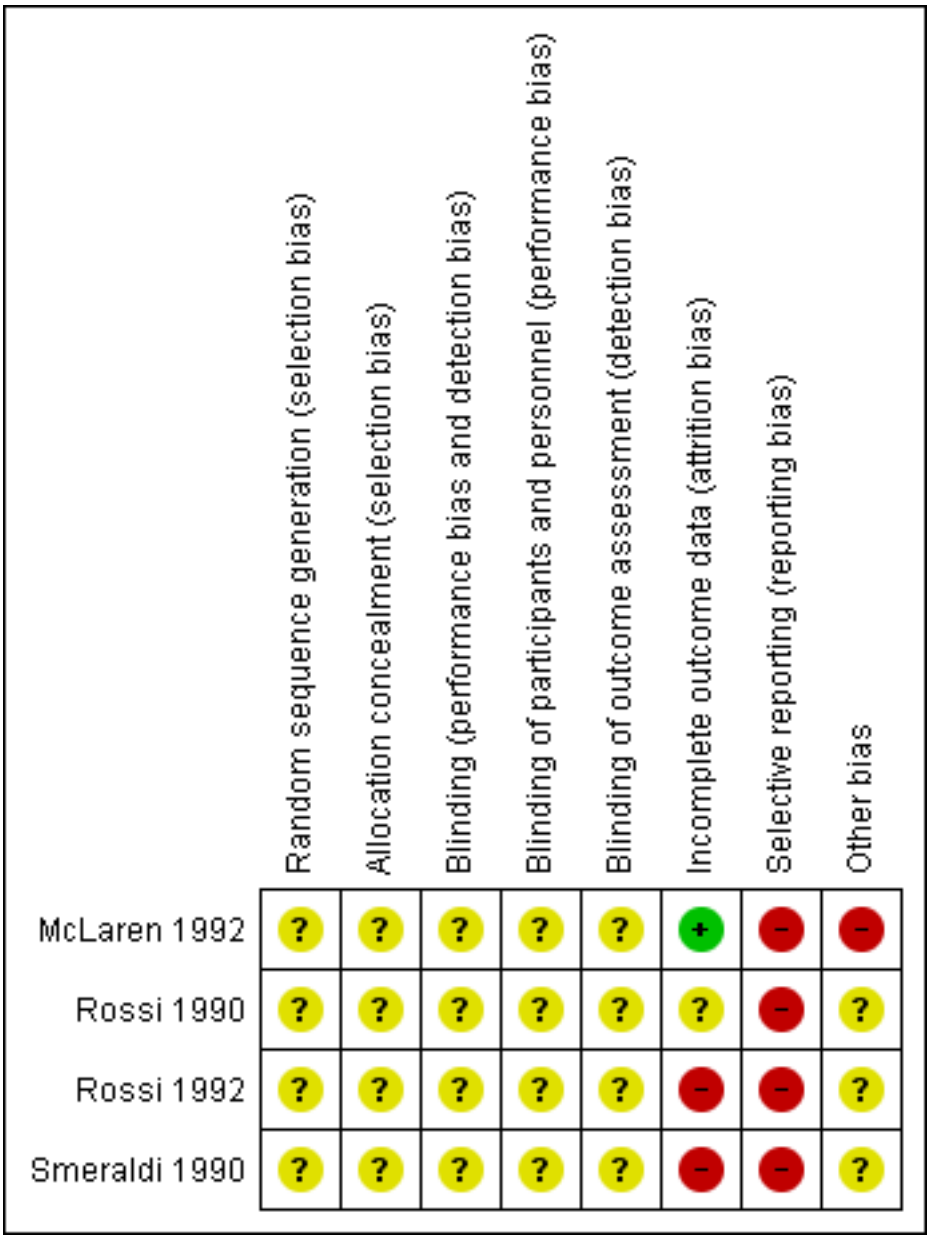
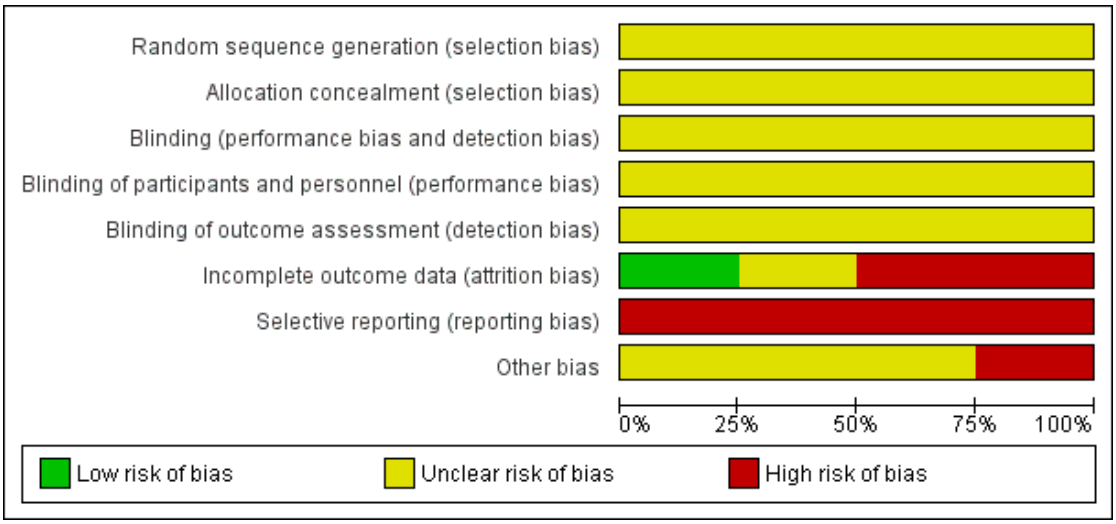


Figure 3. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

All studies failed to specify the process by which allocation to the intervention group was undertaken. As poor reporting of randomisation has consistently been associated with an overestimate of effect (Schulz 1994), we have rated all allocation concealment as 'unclear'. The results in these trials are likely to be a 30% to 40% overestimate of effect (Moher 1998; Schulz 1994).

Blinding

Studies were all described as "double blind" but this does not seem to have been 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. As data are prone to observation bias, failure to test double blinding does not reassure the reader that every effort was made to minimise this problem.

Incomplete outcome data

All studies described loss to follow-up and gave the reasons why this occurred. This is better than has been seen in other trials of depot antipsychotics.

Selective reporting

All data in this review originates from published reports. We have had no opportunity to see trials protocols to compare the outcomes reported in the full publications with what was measured during the conduct of the trial.

Other potential sources of bias

All studies had small or very small sample sizes. One of the studies had the drugs used in the trials provided by pharmaceutical companies (McLaren 1992), and the remaining studies gave no details of funding (Rossi 1990; Rossi 1992; Smeraldi 1990).

Effects of interventions

See: **Summary of findings for the main comparison** Bromperidol decanoate compared to placebo for schizophrenia; **Summary of findings 2** Bromperidol decanoate compared to other depot antipsychotic drugs

1. Comparison 1: bromperidol decanoate versus placebo depot injection

We identified a single small (n = 20) study of six months' duration (Smeraldi 1990). The results as presented in the published account

show no statistically significant differences between bromperidol decanoate and placebo injection, although all ratings did favour the active drug.

1.1 Mental state

Skewed data on rating scales (BPRS, SANS, SAPS) were derived from only 20 people and then reported in an additional table.

1.2 Leaving the study early

Half of those allocated placebo left the study early but this was not significantly greater than the active depot group (n = 20, 1 RCT, RR 0.4 CI 0.1 to 1.6).

1.3 Adverse effects

There were no clear differences between bromperidol decanoate and placebo for a list of adverse effects (n = 20, 1 RCT, RR akathisia 2.0 CI 0.21 to 18.69, RR increased weight 3.0 CI 0.14 to 65.9, RR tremor 0.33 CI 0.04 to 2.69), but the numbers upon which findings were based were very small and confidence intervals wide.

2. Comparison 2: bromperidol decanoate versus another depot antipsychotic

2.1 Global impression

Rossi 1990 reported no important change on the categorical Clinical Global Impression scale. No difference was found between bromperidol and fluphenazine depots at six months (n = 30, RR 1.50 CI 0.29 to 7.73).

2.2 Mental state

2.2.1 Relapse

People allocated to bromperidol decanoate experienced relapse more frequently than those taking fluphenazine decanoate and haloperidol decanoate (n = 67, 2 RCTs, RR 3.92 CI 1.05 to 14.60).

2.2.2 Needing additional medication

People allocated bromperidol decanoate required additional antipsychotic medication more frequently than those taking fluphenazine decanoate and haloperidol decanoate (n = 77, 2 RCTs, RR 1.72 CI 0.7 to 4.2) although this did not reach conventional levels of statistical significance. The use of benzodiazepine drugs was similar in both groups (n = 77, 2 RCTs, RR 1.08 CI 0.68 to 1.70).

2.2.3 Average score (BPRS, high = bad)

Rossi 1990 reported continuous data on the BPRS scale. Again, they found no difference between bromperidol and fluphenazine depots at six months (n = 30, MD 0.80 CI -7.25 to 8.85).

2.3 Leaving the study early

People left the bromperidol decanoate group more frequently than those allocated other depots due to any cause (n = 97, 3 RCTs, RR 2.17 CI 1 to 4.73). On specific reasons, participants left bromperidol decanoate less frequently than other antipsychotics due to side effects (n = 47, 1 RCT, RR 0.35 CI 0.01 to 8.11); and more frequently than other antipsychotic due to inefficacy (n = 77, 2 RCTs, RR 1.35 CI 0.33 to 5.48) and relapse (n = 47, 1 RCT, RR 11.46 CI 0.67 to 196.19). Again, data did not reach conventional levels of statistical significance.

2.4 Adverse effects

McLaren 1992 found no significant difference between the groups in the frequency of anticholinergic adverse effects (n = 47, RR blurred vision, constipation, dry mouth and low blood pressure 3.13 CI 0.7 to 14.0). Additional anticholinergic medication was needed with equal frequency in both groups, although results did tend to favour the bromperidol decanoate group (n = 97, 3 RCTs, RR 0.80 CI 0.64 to 1.01). The incidence of movement disorders was similar in both groups (n = 77, 2 RCTs, RR 0.74 CI 0.47 to 1.17).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Bromperidol decanoate compared to other depot antipsychotics for schizophrenia

Patient or population: patients with schizophrenia
Settings: in and out-patients
Intervention: bromperidol decanoate
Comparison: other depot antipsychotics

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Other depot antipsychotics	Bromperidol decanoate				
Global state: Relapse Follow-up: 12 months	**Low risk population**		**RR 3.92** (1.05 to 14.6)	67 (2 studies)	⊕⊕◯◯ **low**[1,2]	
	50 per 1000	**196 per 1000** (52 to 730)				
	Medium risk population					
	100 per 1000	**392 per 1000** (105 to 1000)				
	High risk population					
	200 per 1000	**784 per 1000** (210 to 1000)				
Global state: Hospital admission Follow-up: 12 months	**Low risk population**		**RR 1.72** (0.7 to 4.24)	67 (2 studies)	⊕⊕◯◯ **low**[1,2]	
	100 per 1000	**172 per 1000** (70 to 424)				

	Medium risk population					
	200 per 1000	**344 per 1000** (140 to 848)				
	High risk population					
	300 per 1000	**516 per 1000** (210 to 1000)				
Global state: Response - proxy outcome - mental state: 1. General - average score (Brief Psychiatric Rating Scale by over 24 weeks		The mean global state: Response - proxy outcome - mental state: 1. General - average score (Brief Psychiatric Rating Scale by over 24 weeks in the intervention groups was **0.8 higher** (7.25 lower to 8.85 higher)		30 (1 study)	⊕○○○ **very low**[1,2,3]	
Quality of life	See comment	See comment	Not estimable	0 (0)	See comment	No trial reported this outcome
Adverse effects - needing anticholinergic drugs	**Low risk population**		**RR 0.8** (0.63 to 1.02)	97 (3 studies)	⊕○○○ **very low**[1,2,4]	
	400 per 1000	**320 per 1000** (252 to 408)				
	Medium risk population					
	600 per 1000	**480 per 1000** (378 to 612)				
	High risk population					

	800 per 1000	**640 per 1000** (504 to 816)			
Adverse effects - anticholinergic effects Follow-up: 12 months	**Low risk population**		**RR 3.13** (0.7 to 13.95)	47 (1 study)	⊕○○○ **very low**[1,2,5]
	10 per 1000	**31 per 1000** (7 to 139)			
	Medium risk population				
	100 per 1000	**313 per 1000** (70 to 1000)			
	High risk population				
	200 per 1000	**626 per 1000** (140 to 1000)			
Adverse effects - movement disorders	**Low risk population**		**RR 0.74** (0.47 to 1.17)	77 (2 studies)	⊕○○○ **very low**[1,2,4]
	400 per 1000	**296 per 1000** (188 to 468)			
	Medium risk population				
	600 per 1000	**444 per 1000** (282 to 702)			
	High risk population				
	800 per 1000	**592 per 1000** (376 to 936)			

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

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

[1] Limitations in designs - rated 'serious': randomisation stated but not described, blinding stated but not tested.
[2] Publication bias - rated as 'likely': small trials
[3] Indirectness - rated 'serious': used proxy measure as no trial reported on response.
[4] Inconsistency - rated as 'serious': insufficient information.
[5] Inconsistency - rated as 'serious': $I^2 = > 50\%$, $P = 0.12$, but removal of one small study ($n = 20$) reduces I^2 to zero.

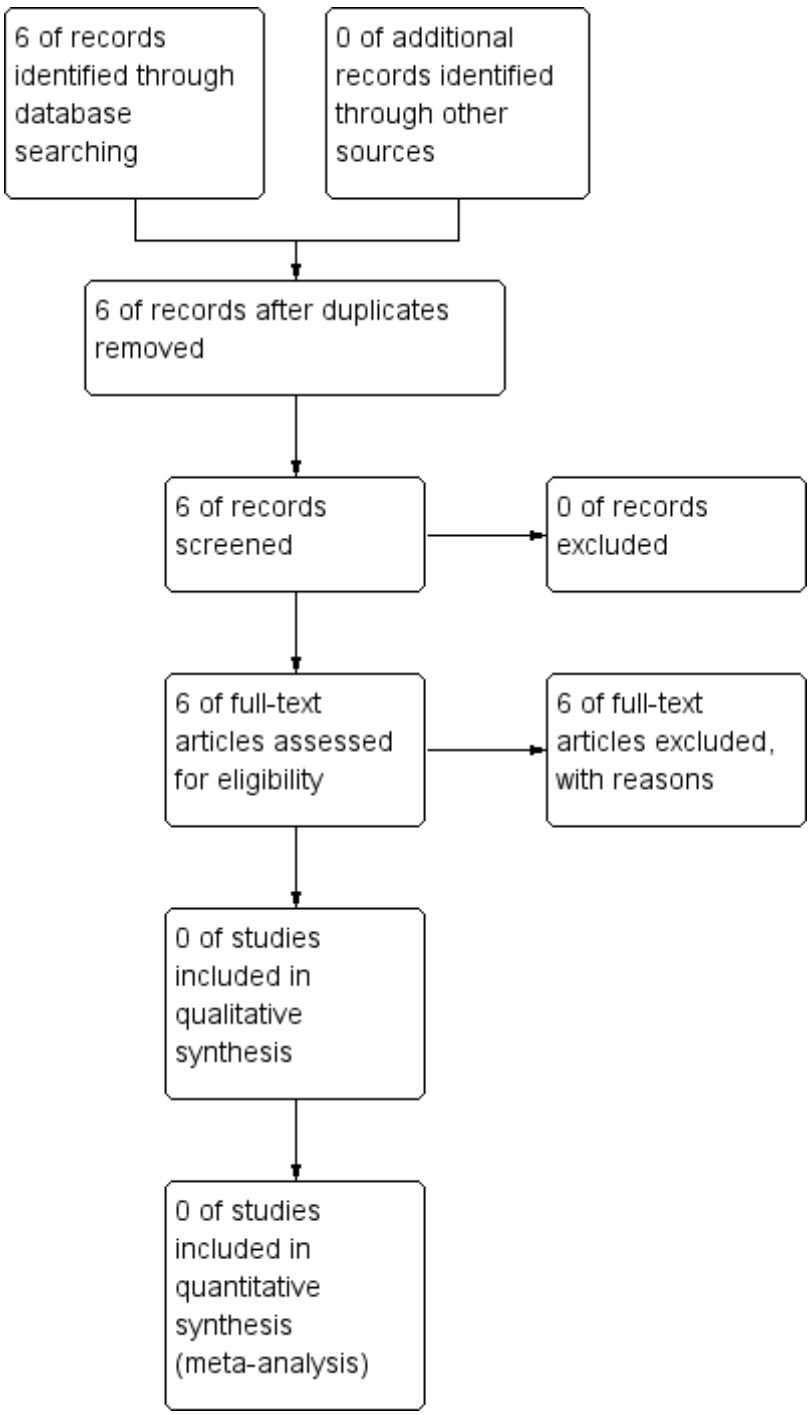
DISCUSSION

Summary of main results

1. Search

This 2011 update did not find new relevant trials to be included (see Figure 4). Currently, research on bromperidol decanoate does not seem to be active. Four trials are included in this Systematic Review: two of six months' duration and two of one year's duration.

Figure 4. Study flow diagram - 2011 version



2. Strengths and weaknesses

Although there is a danger of judging the past by standards of today, it does hold true that this review would be more comprehensive if reporting of the existing trials had been to a higher standard (Begg 1996; CONSORT; Moher 2001). It is clear that researchers invested considerable effort recording scale-derived outcomes, but poor reporting leaves much of these data impossible to include. The weakness of the review may be the paucity of data, but the strength is that it is, to our knowledge, the first systematic review of this topic.

3. Comparison 1: bromperidol decanoate versus placebo depot injection

Any study of 20 people would not have much power to highlight even dramatic differences between two groups. The trial included was not of high quality, thus opening the possibility of inclusion of considerable bias and over estimate of effects. It is difficult to comment on the bromperidol decanoate versus placebo comparison.

3.1 Mental state

Skewed data present a problem to the systematic reviewer. Data in this review are based only on 20 participants and are inappropriate to present in graphs (Data extraction and management). There is some suggestion that the 'active' depot does effect 'positive' symptoms.

3.2 Leaving the study early

Assuming that leaving the study early is not a sign of a positive effect, it would seem that bromperidol decanoate may have some effects on mental state/behaviour. Again, numbers are very small and nothing is conclusive.

3.3 Adverse effects

Adverse effect data tells us little, although there is the impression that bromperidol decanoate may cause some akathisia and weight gain.

4. Comparison 2: bromperidol decanoate versus another depot antipsychotic

4.1 Global impression and mental state

Rossi 1990 found no clear difference between bromperidol and fluphenazine depots at six months for global outcomes (CGI, BPRS). For preventing relapse, bromperidol decanoate seemed less valuable than other depots, even when small numbers were randomised. This is consistent with findings that people given bromperidol decanoate seem to require additional antipsychotic medication somewhat more frequently than those taking fluphenazine decanoate and haloperidol decanoate, and leave studies (due to any cause) more frequently than those allocated other depots. These findings consistently cast doubt on the comparative efficacy of bromperidol decanoate, which may explain its limited clinical use. No differences were found in BPRS score between depot bromperidol and other agents.

4.2 Adverse effects

We found no clear differences between people taking bromperidol decanoate and other depot antipsychotic drugs. This does not mean that true differences do not exist, but from the few studies we have identified there is no impression that bromperidol decanoate is any more prone to cause adverse effects than fluphenazine decanoate or haloperidol decanoate.

Overall completeness and applicability of evidence

1. Completeness

No outcomes in this review involve large numbers of people. Some are general measures and more subtle findings are not recorded. Moreover, there were no data on hospital and service utilisation outcomes, economic outcomes, quality of life/satisfaction with care, behaviour or cognitive response.

2. Applicability

It is unlikely that the results from the included trials can be applied to a wider population of people with schizophrenia eligible for treatment with depot bromperidol without careful consideration. Participants in the included studies seemed relatively compliant and this is not the type of person who would normally be offered treatment with a depot antipsychotic. Often that would be a person who found it difficult to adhere to a regimen of oral medication.

Quality of the evidence

Overall the quality of reporting of these trials was poor (see Summary of findings for the main comparison, Summary of findings 2). Allocation concealment was not described, generation of the sequence was not explicit, studies were not clearly blinded,

and we are unsure if other biases were operating (see Figure 2, Figure 3). The small trial size, along with the poor reporting of trials, would be associated with an exaggeration of effect of the experimental treatment if an effect had been detected.

Potential biases in the review process

We are not aware of biases in the review process. We have made every effort to identify all relevant trials, but we may have failed to identify small studies because of a degree of publishing bias operating in this review (Egger 1997). We do not think it likely that we have failed to identify large relevant studies.

Agreements and disagreements with other studies or reviews

The only other relevant quantitative review we know of is the previous version of this Cochrane review (Adams 2004). This 2011 update expands and improves this review.

AUTHORS' CONCLUSIONS

Implications for practice

1. For those with schizophrenia

No convincing differences are evident when adverse effects of depot bromperidol and fluphenazine or haloperidol decanoate are compared. This, of course, does not mean that real differences do not exist, as all data are derived from poorly reported small studies. When it comes to choosing between bromperidol decanoate and another depot, people with schizophrenia may wish to exercise their own judgement. They could ask to be randomised in order to help produce better evidence for the effects of bromperidol decanoate for schizophrenia.

2. For clinicians

Currently, remarkably few and weak data exist on the effects of bromperidol decanoate. It may be better than a placebo injection but less valuable than fluphenazine or haloperidol decanoate. These findings should be replicated and do not justify routine use of depot bromperidol. If, however, there are reasons not to use other depots, bromperidol decanoate might be a viable choice.

3. For managers, policy makers and funders

No data have emerged about economic outcomes and there are minimal trial-based data to inform those with power to make wide-ranging decisions on clinical policy, funding of medication or research. If bromperidol decanoate is a treatment option it would seem important to encourage appropriate research into the effects of this preparation.

Implications for research

1. General

If the recommendations of the CONSORT statement (Schulz 2010) had been anticipated by trialists, much more data would have been available from the trials already identified to inform practice. Both authors and editors would help to clarify methodology and ensure outcome data were more transparent and usable. Failure to comply produces loss of data and confusion in the results, neither of which help clinicians, patients or policy makers. The included trials failed to specify the process by which allocation to the intervention group was undertaken. Allocation concealment is essential for the result of a trial to be considered valid, and importantly gives the assurance that selection bias is minimised. Well-described and tested blinding could have encouraged confidence in the control of performance and detection bias. Moreover, it would have been helpful if authors had presented data in a useful manner which reflects association between intervention and outcome: for example, risk ratio, 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

2.1 Reviews

We have identified some trials that were not relevant for this review, but could be included in other new and related meta-analyses (Table 1).

2.2 Trials

This review highlights the need for good, 'real world' clinical trials (Simon 1995) to investigate the effects of using depot bromperidol for people with schizophrenia. This particular depot is far from adequately evaluated by modern standards. Few people have been randomised (n = 117), and the depot has not been compared with an oral antipsychotic. More trials are needed to assess clinical outcomes, social and cognitive functioning and adverse effects. Future studies should randomise people for whom prescribing a depot or not is a dilemma in a 'real world' care setting, and report

outcomes such as hospitalisation as well as satisfaction with care and cost. We do realise that design of a full randomised trial takes great care and thought but, because we have considered the past studies in some detail, have some suggestions on how such a trial may be designed (Table 2).

ACKNOWLEDGEMENTS

The Cochrane Schizophrenia Group Editorial Base in Nottingham produces and maintains standard text for use in the Methods section of their reviews. We have used this text as the basis of what appears here and adapted it as required.

For the 2004 version of this review (Adams 2004) David Wong selected studies, extracted data, contacted authors, and helped produced the report and Seema Quraishi helped prepare the protocol, undertook searches, selected and acquired studies, extracted data, summated data and assisted in the production of the report.

For the 2011 version of this review we would like to acknowledge Anthony David and Seema Quraishi for their valued involvement in previous versions of this review but they were not involved in this update.

In previous versions Anthony David acquired funding for the first version of this review and for the subsequent version helped prepare protocol, select studies, extract data, and produce the report.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

McLaren 1992

Methods	Allocation: randomised. Blindness: double. Duration: 1 year.
Participants	Diagnosis: schizophrenia (ICD-9). History: good physical health, received antipsychotics > 1 year before episode, ill ~ 18 years SD 18 yrs, informed consent. N = 47. Age: 20-65 years. Sex: 27M, 20F. Setting: outpatients.
Interventions	1. Bromperidol decanoate: mean dose 242 mg/IM/month, range 67-400 mg. N=23 2. Fluphenazine decanoate: mean dose 103 mg/IM/month, range 16.7-300 mg/IM. N= 24
Outcomes	Leaving the study early. Additional medication. Adverse effects. Unable to use - Mental state: Krawiecka-Goldberg scale, NSRS (no usable data). Depression: MARDRS (no usable data). Parkinsonism: Simpson & Angus scale (no usable data). Social disability: MRSS (no usable data). Tardive dyskinesia: AIMS (no usable SD). Weight measures & blood samples (no usable data).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated ....." - no further information
Allocation concealment (selection bias)	Unclear risk	No information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Bromperidol decanoate or fluphenazine decanoate in identical ampoules". Unclear if raters independent and unclear if blinding was successful

McLaren 1992 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if raters were independent and unclear if blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number randomised, and number lost during follow-up reported
Selective reporting (reporting bias)	High risk	No endpoint scores at Krawiecka-Goldberg scale, NSRS, MARDRS, Simpson & Angus scale, MRSS, AIMS, weight measures and blood samples
Other bias	High risk	Funded by Jannsen Pharmaceuticals - who make bromperidol decanoate

Rossi 1990

Methods	Allocation: randomised - no further details. Blindness: double. Duration: 6 months.
Participants	Diagnosis: schizophrenia (DSM-III-R). History: mode duration of episode 1-6 months. N = 30. Sex: 18M, 12F. Age: mean ~ 29 years. Setting: outpatients.
Interventions	1. Bromperidol decanoate: dose 85 mg/IM/month, range 50-100 mg/IM/month. N = 15 2. Fluphenazine decanoate: dose 30 mg/IM/month, range 25-50 mg/IM/month. N = 15
Outcomes	General impression: not improved (CGI). Adverse effects: number with adverse effect (DOTES). Unable to use - General impression: CGI score (not reported). Adverse effects: DOTES scores (not reported).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Rossi 1990 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Randomised - no further information.
Allocation concealment (selection bias)	Unclear risk	No information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Investigator involved in selection and outcome evaluation, did not access randomisation list and drug administration
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if raters were independent and unclear if blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Rating scale scores reported without denominator.
Selective reporting (reporting bias)	High risk	No endpoint scores (CGI, DOTES, TESS Write), scores reported without denominator (CBS, BPRS), vital signs measures - not reported
Other bias	Unclear risk	Insufficient information.

Rossi 1992

Methods	Allocation: randomised - no further details. Blindness: double. Duration: 1 year.
Participants	Diagnosis: schizophrenia (DSM-III-R). History: chronic. N = 20. Age: mean ~ 48 years, range 34-68. Setting: inpatients.
Interventions	1. Bromperidol decanoate: dose mean 164 mg/month. N = 10. 2. Haloperidol decanoate: dose mean 119 mg/month. N = 10.
Outcomes	Leaving the study early. Additional medication. Adverse effects. Unable to use - Mental state: BPRS, HAM-D, SANS, SAPS (no SD). Adverse effects: DOTES and TWIS scores (not reported). Vital signs measures (not

Rossi 1992 (*Continued*)

	reported)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised - no further information.
Allocation concealment (selection bias)	Unclear risk	No information.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Drugs were provided in identical packages in order to maintain double-blindness"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if blinding was successful.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias) All outcomes	High risk	Rating scale scores reported without denominator.
Selective reporting (reporting bias)	High risk	No endpoint scores (DOTES and TWIS scales), scores without SD (BPRS, HAM-D, SANS, SAPS), no vital signs measures
Other bias	Unclear risk	Insufficient information.

Smeraldi 1990

Methods	Allocation: randomised - no further details. Blindness: double. Setting: multicentre. Duration: 6 months.
Participants	Diagnosis: schizophrenia (DSM-III). History: 'residual' stage, outpatients. N = 20. Sex: 10 M, 10 F. Age: mean ~ 40 years. Setting:outpatients.
Interventions	1. Bromperidol decanoate: dose 150 mg/month. N = 10. 2. Placebo. N = 10.

Smeraldi 1990 (*Continued*)

Outcomes	Leaving the study early. Adverse effects. Mental state: BPRS, HRS-D, SAPS, SANS. Unable to use - Adverse effects: DOTES, SAFTEE-SI scores (not reported). Vital sign measures (not reported).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised (no information about randomisation procedure).
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "The placebo and bromperidol phials were perfectly identical"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if raters were independent and unclear if blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias) All outcomes	High risk	Rating scale scores reported without denominator.
Selective reporting (reporting bias)	High risk	No endpoint scores (DOTES, SAFTEE-SI), vital signs measures.
Other bias	Unclear risk	Insufficient information.

Diagnostic tools
DSM - Diagnostic Statistical Manual
ICD-9 - International Classification of Diseases, version 9.
Rating scales
AIMS - Abnormal Involuntary Movement Side effects.
BPRS - Brief Psychiatric Rating Scale
CBS - Current Behavioural Schedule
CGI - Clinical Global Impression
DOTES - Dosage and Treatment Emergent Symptoms Scale
HRS-D - Hamilton Rating Scale - Depression
MARDRS- Montgomery-Asberg Depression Rating Scale.

MRSS - Morningside Rehabilitation Rating Scale. NSRS - Negative Symptom Rating Scale. SAFTEE-SI -Systematic Assessment For Treatment Emergent Effects Self- Report Inventory.
SAPS - Scale for Assessment of Positive Symptoms.
SANS - Scale for Assessment of Negative Symptoms. TESS - Treatment Emergent Symptom Scale.

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

Study	Reason for exclusion
Bernardi 1992	Allocation: not randomised, case series.
Boeykens 1984	Allocation: not randomised, case series.
Brannen 1981	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral bromperidol versus oral haloperidol, no depots
Bures 1978	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral bromperidol versus oral haloperidol, no depots
Denijs 1980	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral bromperidol versus oral haloperidol, no depots
Fukahori 1995	Allocation: not randomised, case series.
Germana 1990	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral bromperidol versus oral haloperidol, no depots
Gould 1981	Allocation: not randomised, case series.
Gould 1982	Allocation: 'double-blind study' - randomisation implied. Participants: 54 people with 'chronic' schizophrenia. Interventions: bromperidol decanoate versus fluphenazine decanoate for 6 months. Outcomes: plasma drug concentrations, overall clinical response (BPRS), social behaviour (NOSIE); no figures reported
Hucker 1978	Allocation: not randomised, case series.
Hyugano 1986	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral bromperidol versus oral haloperidol, no depots
Itoh 1985	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral bromperidol versus oral haloperidol, no depots

(*Continued*)

Kaumeier 1978	Allocation: not randomised, case series.
Kodama 1984	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral bromperidol versus oral clocapramine, no depots
Kokasa 1984	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral bromperidol versus oral clocapramine, no depots
Kudo 1984	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral bromperidol versus oral clocapramine, no depots
Levi Minzi 1992	Allocation: not randomised, case series.
Malfroid 1978	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral bromperidol versus oral haloperidol, no depots
Mauri 1994	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral bromperidol versus oral haloperidol, no depots
Mihara 2000	Allocation: randomised, method of blinding unclear. Participants: people with schizophrenia. Interventions: relationship between Taq1 a polymorphism of D2 receptor gene and extrapyramidal adverse effects of bromperidol and nemonapride
Mihara 2001	Allocation: randomised. Participants: people with schizophrenia (DSM-III-R). Interventions: relationship between 141C Ins/Del a polymorphism of D2 receptor and extrapyramidal adverse effects of oral bromperidol and oral nemonapride. No depot
NCT00237913	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral aripiprazole, oral olanzapine, oral risperidone, oral quetiapine. No bromperidol decanoate depot
Nishizono 1984	Allocation: not randomised, case series.
Onodera 1984	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral bromperidol versus oral haloperidol.
Otani 1997	Allocation: randomised. Participants: people with schizophrenia. Interventions: trihexyphenidyl or biperiden as adjuncts to bromperidol

(*Continued*)

Parent 1983	Allocation: not randomised, case series.
Poldinger 1977	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral bromperidol versus oral haloperidol, no depots
Psaras 1984	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral bromperidol versus oral chlorpromazine, no depots
Saito 2008	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral bromperidol versus oral nemonapride versus oral risperidone, no depots
Scapicchio 1993	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral bromperidol (morning dose) versus oral bromperidol (evening dose), no depots
Smeraldi 1996	Allocation: not randomised, case series.
Spina 1992	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral bromperidol versus oral haloperidol, no depots
Suarez 1984	Allocation: not randomised, case series.
Suzuki 1997	Allocation: randomised. Participants: people with schizophrenia. Interventions: levomepromazine or thioridazine as adjuncts to bromperidol
Woggon 1978	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral bromperidol versus oral perphenazine, no depots
Yamagami 1993	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral bromperidol versus oral sulpiride, no depots
Zhao 2008	Allocation: randomised. Participants: families of schizophrenic people. Interventions: health education versus standard treatment, no depots

DATA AND ANALYSES

Comparison 1. Bromperidol decanoate vs placebo (all data 24 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental state: specific - average scores (various scales, data skewed)			Other data	No numeric data
1.1 depression (HDRS, high = bad)			Other data	No numeric data
1.2 negative (SANS, high = bad)			Other data	No numeric data
1.3 positive (SAPS, high = bad)			Other data	No numeric data
2 Leaving the study early (reasons unclear)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.10, 1.60]
3 Adverse effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 akathisia	1	20	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.21, 18.69]
3.2 dry mouth	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.45]
3.3 fatigue	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 7.32]
3.4 increased weight	1	20	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.14, 65.90]
3.5 tremor	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 2.69]
3.6 stiffness	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 1.86]

Comparison 2. Bromperidol decanoate vs other depot antipsychotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global impression: no important improvement (CGI)	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.29, 7.73]
2 Mental state: 1. Relapse	2	67	Risk Ratio (M-H, Fixed, 95% CI)	3.92 [1.05, 14.60]
3 Mental state: 2. Needing additional medication	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 antipsychotics	2	67	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [0.70, 4.24]
3.2 benzodiazepines	3	97	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.68, 1.70]
4 Mental state: 3. Average score (BPRS, high = bad)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 immediate (less than 5 weeks)	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 between 5 and 24 weeks	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 by over 24 weeks	1	30	Mean Difference (IV, Fixed, 95% CI)	0.80 [-7.25, 8.85]
5 Leaving the study early (specified reasons)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 any reason	3	97	Risk Ratio (M-H, Fixed, 95% CI)	2.17 [1.00, 4.73]

5.2 adverse effects	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.11]
5.3 inefficacy	2	77	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.33, 5.48]
5.4 relapse	1	47	Risk Ratio (M-H, Fixed, 95% CI)	11.46 [0.67, 196.19]
5.5 unclear	1	20	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.68, 5.85]
6 Adverse effects: general	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 anticholinergic effects	1	47	Risk Ratio (M-H, Fixed, 95% CI)	3.13 [0.70, 13.95]
6.2 needing anticholinergic drugs	3	97	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.63, 1.02]
6.3 movement disorders	2	77	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.47, 1.17]

ADDITIONAL TABLES

Table 1. Suggested reviews

Review title
Oral bromperidol for people with schizophrenia
Clocapramine for people with schizophrenia
Nemonapride for people with schizophrenia

Table 2. Suggested design of new trial

Methods	Allocation: randomised - clearly described generation of sequence and concealment of allocation. Blindness: double, described and tested. Setting: community. Duration: 12 months.
Participants	Diagnosis: schizophrenia (operational criteria). N = 300.* Age: any. Sex: both. History: any.
Interventions	1. Bromperidol decanoate: dose acceptable to patient and clinician. N = 150. 2. Haloperidol decanoate: dose acceptable to patient and clinician. N = 150
Outcomes	Service outcomes: hospitalised, days in hospital, attending outpatient clinics. Global outcomes: CGI, overall improvement, use of additional medication. Mental state: PANSS. Adverse events: UKU. Leaving the study early (any reason, adverse events, inefficacy). Economic outcomes (cost benefit, cost utility). Quality of life (QOL scale)
Notes	* For adequate power 80% 5% for 20% difference is binary outcome (e.g. not improved) 150 people are needed per group

WHAT'S NEW

Last assessed as up-to-date: 28 February 2011.

Date	Event	Description
5 July 2011	New citation required but conclusions have not changed	Change of lead author, 2011 update search carried out, no new studies found
2 March 2011	New search has been performed	New search undertaken. Formatted for RevMan 5.1

HISTORY

Review first published: Issue 3, 1999

Date	Event	Description
11 November 2009	Amended	Contact details updated.
24 April 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Marianna Purgato - for the 2011 updated the protocol, selected studies, extracted data and produced the report.

Clive Adams - acquired funding for the first version of this review, helped prepare protocol, undertake searches, select and acquire studies, extract and summate data, and produced the report.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University of Verona, Italy.
- University of Nottingham, UK.
- Institute of Psychiatry, UK.

External sources

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The text of the protocol from the 1999 and 2003 versions of this review has been extensively revised. The original text is available in Appendix 1 and Appendix 2. We do not feel the improved text is a threat to validity.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans