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Flupenthixol versus placebo for schizophrenia (Review)

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TABLE OF CONTENTS

[Intervention Review]

Flupenthixol versus placebo for schizophrenia

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ABSTRACT

Background

Flupenthixol, first made available in the UK in 1965, has been used as a treatment for schizophrenia for decades.

Objectives

To evaluate the absolute clinical effects of flupenthixol for schizophrenia in comparison with placebo.

Search methods

We searched the Cochrane Schizophrenia Group Trials Register (August 2011), inspected references of all included or excluded studies for further trials, and contacted authors of trials for additional information.

Selection criteria

All randomised controlled trials (RCTs) that compared flupenthixol with placebo for adults with schizophrenia or related disorders by any means of diagnosis. Primary outcomes of interest were clinically important change in global state, mental state and behaviour, and adverse effects.

Data collection and analysis

We extracted data from the one included study, discussed any disagreement, documented decisions and contacted the authors of the included study for further information. We analysed binary outcomes using a standard estimation of the risk ratio (RR) and its 95% confidence intervals (CI). For homogenous data we used a fixed-effect model. For rare events we analysed dichotomous data using Peto Odds ratio (OR), again with 95% CIs.

Main results

We could include only one small (n = 45) study of moderate quality. When the active α-flupenthixol was compared with the inactive placebo or β-flupenthixol groups combined, fewer people in the active treatment group needed additional antipsychotic medication by around four weeks for deterioration in their general state (n = 45, OR 0.19 CI 0.05 to 0.71). There was no clear difference in social functioning at one year (n = 45, RR 1.33 CI 0.91 to 1.96). We found no clear data on mental state and behaviour, adverse effects, service use, satisfaction with treatment or costs.

Authors' conclusions

We were surprised that this well-established drug had so few data from trials investigating its absolute effects. We think this is unlikely to be rectified some 50 years after its launch and know that this would not happen today. However, even though data are very limited, flupenthixol may well be worthy of careful investigation - partly to ensure that this inexpensive active drug is not forgotten.

PLAIN LANGUAGE SUMMARY

Flupenthixol versus placebo for schizophrenia

Flupenthixol is an antipsychotic drug, first made available in the UK in 1965. Available both as a tablet and long-acting injection, it has been used to treat schizophrenia for nearly 50 years and has been found to be effective and well tolerated by people with schizophrenia. The main side-effects are shaking, restlessness, a dry mouth and some weight gain.

Although this drug has been available for many years, few systematic reviews of its effectiveness are available and the effects of this drug in helping people cope with the symptoms of schizophrenia are not currently well measured, quantified and known. This systematic review could include only one small study which was small and 30 years old. Flupenthixol was compared with a placebo (dummy drug). Fewer people taking flupenthixol required additional antipsychotic medication but there was no clear difference in people's ability to cope and function socially. There was no clear information on: improving people's mental state; helping their behaviour; increasing their use of services; people's satisfaction with treatment; or costs and cost effectiveness. Flupenthixol is widely available and inexpensive so it is perhaps understandable that it remains a popular drug used for treating people with serious mental illnesses. However, the use of flupenthixol is based more on clinical experience and the decisions of psychiatrists rather than results from large-scale research studies and evidence-based information. The effectiveness and benefits of flupenthixol remain largely unknown and incomplete. Large randomised and placebo-controlled trials could be helpful in increasing knowledge about this drug.

This summary has been written by Ben Gray from RETHINK.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

α-FLUPENTHIXOL versus PLACEBO or β-FLUPENTHIXOL for schizophrenia

Patient or population: patients with schizophrenia
Settings: hospital
Intervention: α-FLUPENTHIXOL versus PLACEBO or β-FLUPENTHIXOL

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/β-FLUPENTHIXOL	α-FLUPENTHIXOL				
Global state: clinically important change in global state needing additional medication - chlorpromazine Follow-up: 4 weeks	**Low**[1]		**OR 0.19** (0.05 to 0.71)	45 (1 study)	⊕○○○ **very low**[2,3,4]	
	200 per 1000	**45 per 1000** (12 to 151)				
	Moderate[1]					
	400 per 1000	**112 per 1000** (32 to 321)				
	High[1]					
	600 per 1000	**222 per 1000** (70 to 516)				
Mental state and behaviour: clinically important change in general mental state and behaviour	See comment	See comment	Not estimable	45 (1 study)	See comment	Incomplete data are skewed and not pooled into α-flupenthixol versus placebo or β-flupenthixol comparison No indication of differences between groups.

Adverse effects/events: incidence of adverse effects/events	See comment	See comment	Not estimable	0 (0)	See comment	No trial reported this outcome.
Service outcomes: hospital admission	See comment	See comment	Not estimable	0 (0)	See comment	No trial reported this outcome.
General functioning: Poor social functioning - modified Cooper's ratings[5,6] Follow-up: 12 months	**Low**[1]		**RR 1.33** (0.91 to 1.96)	45 (1 study)	⊕○○○ **very low**[3,4,7]	
	300 per 1000	**399 per 1000** (273 to 588)				
	Moderate[1]					
	600 per 1000	**798 per 1000** (546 to 1000)				
	High[1]					
	900 per 1000	**1000 per 1000** (819 to 1000)				
Satisfaction with treatment: satisfaction with care for recipients of care or careers	See comment	See comment	Not estimable	0 (0)	See comment	No trial reported this outcome.
Economic outcomes: direct costs	See comment	See comment	Not estimable	0 (0)	See comment	No trial reported this outcome.

*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; **OR:** Odds 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] Moderate risk approximately that of the control group in the trial.
[2] Indirectness: rated 'serious' - need of additional medication only global state outcome.
[3] Imprecision: rated 'very serious' - Only one small study with 45 participants and a few events.
[4] Publication bias: rated 'undetected' - but small positive trial and publication bias remains a possibility.
[5] Modified scale - no published data on reliability or validity of modified version.
[6] Analysis includes assumptions on the functioning of those who left early.
[7] Indirectness: rated 'serious' - unclear of how direct the modified Cooper scale rating is.

BACKGROUND

Description of the condition

Schizophrenia is a mental disorder characterised by a disintegration of thought processes and of emotional responsiveness. The main signs and symptoms are hallucinations, delusions and disorganised thinking and speech. Throughout the world, the global lifetime prevalence of schizophrenia is about 0.3% to 0.7% (Van Os 2009). Forty per cent of affected men and 23% of affected women are diagnosed with schizophrenia before the age of 19 years (Cullen 2008). Schizophrenia seems to occur 1.4 times more frequently in men than women and typically appears earlier in men (Picchioni 2007). People with schizophrenia have a significantly reduced life expectancy compared with the general population (Tiihonen 2009). As estimated by the World Health Organization, "though the incidence is low (3/10,000), the prevalence is high due to chronicity"; schizophrenia affects 24 million people worldwide, more than 50% of people with schizophrenia are not receiving appropriate care, and 90% of people with untreated schizophrenia are in developing countries (WHO 2011).

After a century of studying schizophrenia, the cause of the disorder remains unclear. Continuous maintenance treatment is often important and therapy focuses on treating symptoms of the disease.

Description of the intervention

Antipsychotic medication (also called neuroleptics) remains the mainstay treatment for schizophrenia. These drugs help to normalise biochemical imbalances which seem to cause the symptoms of schizophrenia, and these drugs also reduce the likelihood of relapse. Overall, there is a good response in 40% to 50% of people, a partial response in 30% to 40%, and treatment resistance (failure of symptoms to respond satisfactorily after at least six weeks with two to three different antipsychotics) in about 20% of the total population of people with schizophrenia (Smith 2010).

Flupenthixol was first made available in the UK in 1965, and it is a traditional antipsychotic belonging to the thioxanthene drug category. It has been used as an antipsychotic for nearly five decades. It has been considered as a "partially atypical" antipsychotic (Kuhn 2000; Gattaz 2004). Flupenthixol is available both as tablet and long-acting depot injection. Having been investigated in numerous studies, flupenthixol was found to be effective and well tolerated (Wistedt 1983; Martyns-Yellowe 1993; Pach 1998; Philipp 2003; Kuhn 2004; Ruhrmann 2007). The main adverse effects are similar to most other typical antipsychotics, namely extrapyramidal symptoms, dry mouth and some weight gain (Gerlach 1975; Parent 1982).

How the intervention might work

Flupenthixol is an antipsychotic drug that is prescribed to treat schizophrenia and similar illnesses, and also used as an antidepressant for mild to moderate depression (Hamilton 1989). It is not thought suitable for people with mania as it may worsen symptoms. Flupenthixol is a dopamine D_1/D_2 and 5-HT_2 receptor antagonist without affecting the muscarinic acetylcholine receptors (Golds 1980; Hyttel 1985; Wetzel 1998; Weiner 2001). It therefore, increases the amount of serotonin and noradrenaline that control mood and thinking, and, by this mechanism, may improve mood. Oral dosage in the management of schizophrenic disorders usually is 2 mg to 20 mg daily. If treating severely psychotic patients, the dosage will be higher. The mood elevating and anxiolytic properties are reported at low dosage (1 mg to 3 mg per day) (Lundbeck 2011). Flupenthixol decanoate is usually given intramuscularly every two to four weeks. In pharmacokinetic studies measuring flupenthixol blood levels, peak concentrations of the drug are found between days four and seven following intramuscular injections of 40 mg of flupenthixol 2% or 10%. It can still be detected in the blood three weeks after injection (Internet Mental Health 2011).

Why it is important to do this review

Although flupenthixol has been available for schizophrenia for decades, few systematic reviews exist on its efficacy for schizophrenia. This is one of a series of Cochrane reviews relevant to this drug (Table 1). The absolute effects of this widely accessible drug are not currently quantified. We wish to update past work, undertake a review that is systematic and quantify the absolute effects of this inexpensive "partially atypical" drug.

OBJECTIVES

To review the effects of flupenthixol compared with placebo for people with schizophrenia.

METHODS

Criteria for considering studies for this review

Types of studies

We sought all relevant randomised controlled trials. Had a trial been described as 'double blind' but implied randomisation, we would have included such trials in a sensitivity analysis (see

Sensitivity analysis). If their inclusion did not result in a substantive difference, they would have remained in the analyses. If their inclusion did result in important clinically significant but not necessarily statistically significant differences, we would not have added 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 groups, we only included data if the adjunct treatment was evenly distributed between groups and it was only the flupenthixol that was randomised.

Types of participants

Adults, however defined, with schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder and delusional disorder, again, by any means of diagnosis.

Types of interventions

1. Flupenthixol: tablets or injections, any dose.
2. Placebo.

Types of outcome measures

We categorised all outcomes as immediate (zero to six weeks), short-term (seven weeks to six months), medium-term (seven months to 12 months), and long-term (over 12 months).

Primary outcomes

1. Global state

1.1 Clinically important change in global state (for example, a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS, Overall 1962)) - as defined by each of the studies.

2. Mental state and behaviour

2.1 Clinically important change in general mental state and behaviour.

3. Adverse effects/events

3.1 Incidence of adverse effects/events.

Secondary outcomes

1. Global state

1.1 Any change in global state.
1.2 Average change in global state score.
1.3 Average endpoint in global state scores.
1.4 Relapse.
1.5 Needing additional medication.

2. Mental state and behaviour

2.1 Psychotic symptoms.
2.2 Positive symptoms.
2.3 Negative symptoms.
2.4 Clinically important change in other specific aspects.

3. Adverse effects/events

3.1 Incidence of general adverse effects/events.
3.2 Description of general adverse effects/events and therapy.
3.3 Incidence of specific adverse effects/events.
3.4 Description of specific adverse effects/events and therapy.
3.5 Incidence of extrapyramidal side effects.
3.6 Clinically significant extrapyramidal side effects.
3.7 Incidence of use of antiparkinson drugs.
3.8 Incidence of severe adverse effects/events.
3.9 Description of severe adverse effects/events and therapy.
3.10 Death (all causes except suicide)
3.11 Suicide

4. Service outcomes

4.1 Hospital admission.
4.2 Days in hospital.

5. General functioning

5.1 Clinically important change in general functioning.
5.2 Average change in general functioning score.
5.3 Average endpoint in general functioning scores.
5.4 Clinically important change in specific aspects of functioning, such as social or life skills.
5.5 Average change in specific aspects of functioning, such as social or life skills.
5.6 Average endpoint in specific aspects of functioning, such as social or life skills.

6. Satisfaction with treatment

6.1 Leaving the study early - for specific reasons.
6.2 Leaving the study early - for general reasons.
6.3 Satisfaction with care for recipients of care or careers.
6.4 Average satisfaction score.
6.5 Average change in satisfaction scores.
6.6 Compliance with medication.

7. Economic outcomes

7.1 Direct costs.
7.2 Indirect costs.

8. Summary of findings table

We used the GRADE approach to interpret findings (Schünemann 2008) and used the GRADE profiler (GRADEPRO) to import data from RevMan 5.1 (Review Manager) to create 'Summary of findings' tables. These tables provided 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 aimed to select the following main outcomes for inclusion in the 'Summary of findings' table.

1. Global state: clinically important change in global state.
2. Mental state and behaviour: clinically important change in general mental state and behaviour.
3. Adverse effects/events: incidence of adverse effects/events.
4. Service outcomes: hospital admission.
5. General functioning: clinically important change in general functioning.
6. Satisfaction with treatment: satisfaction with care for recipients of care or careers.
7. Economic outcomes: direct costs.

Search methods for identification of studies

Electronic searches

Cochrane Schizophrenia Group Trials Register
We searched the register (last searched August 2011) using the phrase:
(*Flupenthixol* AND *placebo* 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 included or excluded 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

Selection of studies

One review author (XS) inspected citations from the searches and identified relevant abstracts. A second review author (JX) independently re-inspected a random 20% sample to ensure reliability. Where disputes arose, the full report was acquired for more detailed scrutiny. Full reports of the abstracts meeting the review criteria were obtained and inspected by XS. Again, JX re-inspected a random 20% of reports in order to ensure reliable selection. Where difficulties or disputes arose, we asked the third review author (CEA) for assistance. Where it was not possible to resolve disagreement by discussion, we attempted to contact the authors of the study for clarification.

Data extraction and management

1. Extraction

To ensure reliability, review authors XS and JX independently extracted data from the one included study. Any disagreements were discussed, decisions documented and, where necessary, we contacted the authors of this study for clarification. With any remaining problems, CEA helped clarify issues and these final decisions were documented. We extracted data presented only in graphs and figures whenever possible, but we only included the data if two review authors independently extracted the same results. We attempted to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. If multicentre studies had been included, we planned, where possible, to extract 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 planned to include continuous data from rating scales only if:
a. the psychometric properties of the measuring instrument had been described in a peer-reviewed journal (Marshall 2000); and
b. the measuring instrument had 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, therefore, we have noted if this is the case or not 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 primarily to use endpoint data, and only use change data if the former were not available. If necessary, we would have combined endpoint and change data in the analysis as we planned to use mean differences (MD) rather than standardised mean differences (SMD) throughout (Higgins 2011).

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:

- standard deviations (SDs) and means were reported in the paper or obtainable from the authors;
- when a scale started from the finite number zero, the SD, when multiplied by two, should be less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution) (Altman 1996);
- if a scale started from a positive value (such as the Positive and Negative Syndrome Scale (PANSS) which can have values from 30 to 210), the calculation described above should be modified to take the scale starting point into account. In these cases, skew is present if 2SD> (S-S min), where S is the mean score and S min is the minimum score.

Endpoint scores on scales often have a finite start and endpoint 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 less than 200 participants as 'other data' (Analysis 1.3; Analysis 2.2). Skewed data pose less of a problem when looking at means if the sample size is large and skewed data from trials with over 200 participants would have been entered into the 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 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 flupenthixol. 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.

Assessment of risk of bias in included studies

Review authors XS and JX assessed the risk of bias by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to assess trial quality. This 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.

Any disagreements between raters were resolved through discussion with CEA. Where inadequate details of randomisation and other characteristics of the trial were provided, we contacted the authors of the study in order to obtain further information. All disagreements in quality assessment were recorded and reported. If disputes arose as to which quality category the trial was rated, again, we resolved through discussion.

We have noted the level of risk of bias in both the text of the review and in the 'Summary of findings' table.

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). However, for rare events, we analysed dichotomous data using Peto Odds ratio (OR), again with 95% CIs. For statistically significant results, we used 'Summary of findings' tables to calculate the number needed to treat to provide benefit /to induce harm statistic and its 95% CI.

2. Continuous data

For continuous outcomes, we planned to estimate MD between groups. We would prefer not to calculate effect size measures

(SMD). However, if we had included studies that used scales of very considerable similarity, we would have 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. Firstly, authors often fail to account for intra-class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby P values are spuriously low, CIs unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997; Gulliford 1999).

If we had included cluster trials, we planned that where clustering was not accounted for in primary studies, we would present data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. We would have contacted the first authors of studies to obtain intra-class correlation coefficients (ICC) for their clustered data and adjusted for this by using accepted methods (Gulliford 1999). If clustering had been incorporated into the analysis of primary studies, we would have 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 ICC [Design effect = 1+ (m-1)*ICC] (Donner 2002). If the ICC is not reported it will be assumed to be 0.1 (Ukoumunne 1999).

If cluster studies have been appropriately analysed taking into account ICC and relevant data documented in the report, synthesis with other studies would be 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, if we had identified any cross-over trials, we planned only to use the data of the first phase of cross-over studies.

3. Studies with multiple treatment groups

We had planned that where a study involves more than two treatment arms, if relevant, we would present the additional treatment arms in the comparisons. If data were binary we would simply add these and combine within the two-by-two table. If data were continuous, we would have combined data following the formula in section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Where the additional treatment arms were not relevant, these data were not be used.

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 present these data or use them within analyses, (except for the outcome 'leaving the study early'). 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 to test how prone the primary outcomes were to change when data only from people who completed the study to that point were compared with the intention-to-treat analysis using the above assumptions.

3. Continuous

3.1 Attrition

We planned that if attrition for a continuous outcome had been between 0% and 50%, and data only from people who completed the study to that point were reported, we would have reproduced these.

3.2 Standard deviations

If SDs 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 (SE) and confidence intervals (CIs) are available for group means, and either 'P' value or 't' value are available for differences in mean, we could calculate them according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011): When only the SE is reported, SDs are calculated by the formula SD = SE * square root (n). Chapters 7.7.3 and 16.1.3 (Higgins 2011) present detailed formula for estimating SDs from P values, t or F values, CIs, ranges or other statistics. If these formulae did not apply, we would have calculated 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 presented these data and indicated that they are the product of LOCF assumptions.

Assessment of heterogeneity

1. Clinical heterogeneity

In future updates of this review, if we identify additional studies, we will consider all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We will simply inspect all studies for clearly outlying people or situations which we had not predicted would arise. When such situations or participant groups arise, we will discuss these fully.

2. Methodological heterogeneity

In future updates of this review, if we identify additional studies, we will consider all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We will simply inspect all studies for clearly outlying methods which we had not predicted would arise. When such methodological outliers arise, we will dicuss these fully.

3. Statistical heterogeneity

3.1 Visual inspection

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

3.2 Employing the I^2 statistic

In future updates of this review, if we identify additional studies, we will investigate heterogeneity between studies by considering the I^2 statistic 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). An I^2 estimate greater than or equal to around 50% accompanied by a statistically significant Chi^2 statistic, will be interpreted as evidence of substantial levels of heterogeneity (Section 9.5.2 - Higgins 2011). If substantial levels of heterogeneity are found in the primary outcome, we will explore reasons for heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

1. Protocol versus full study

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 10.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We tried to locate the protocol of the included trial. Had the protocol been available, we planned to compare outcomes in the protocol and in the published report. As the protocol was not available, we compared outcomes listed in the methods section of the trial report with actually reported results.

2. Funnel plot

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are again described in Section 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (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. As only one study was included, we did not prepare a funnel plot.

Data synthesis

We understand that there is no closed argument for preference for the 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 used the fixed-effect model for all analyses as we had only planned to use the random-effects model when heterogeneity was present.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary outcomes

In order to reduce clinical and methodological reasons for heterogeneity, we planned to subgroup trials that compare flupenthixol versus placebo and by duration of six weeks or less, between seven weeks and six months, between seven and 12 months, and longer than 12 months.

1.2 Clinical state, stage or problem

We carried out this review to provide an overview of the effects of flupenthixol for people with schizophrenia in general. In addition, however, we planned to report data on subgroups of people in the same clinical state, stage and with similar problems.

2. Investigation of heterogeneity

If more than one trial had been included and inconsistency between trials high, we would have reported this. First, we would have investigated whether data had been entered correctly. Second, if data were correct, we would have visually inspected the graph and removed outlying studies to see if homogeneity was restored. For this review, we decided that should this occur with data contributing to the summary findings of no more than around 10% of the total weighting, we would present the data. If not, we would not pool the data but discuss the issues. We know of no supporting research for this 10% cut-off but are investigating use of prediction intervals as an alternative to this unsatisfactory state.
When unanticipated clinical or methodological heterogeneity were obvious, we would have simply stated hypotheses regarding these for future reviews or versions of this review. We do not anticipate undertaking analyses relating to these.

Sensitivity analysis

1. Implication of randomisation

In future updates of this review, if we identify additional studies, we will include trials in a sensitivity analysis if they are described in some way as to imply randomisation. For the primary outcomes, we will include these studies and if there is no substantive difference when the implied randomised studies are added to those with better description of randomisation, then we will use all data from these studies.

2. Assumptions for lost binary data

Where assumptions had to be made regarding people lost to follow-up (see Dealing with missing data), we compared the findings of the primary outcomes when we used our assumption/s and when we used data only from people who completed the study to that point. If there was a substantial difference, we reported results and discussed them but continued to employ our assumption.
Where assumptions had to be made regarding missing SDs data (see Dealing with missing data), we compared the findings of the primary outcomes when we used our assumption/s and when we used data only from people who completed the study to that point. We undertook a sensitivity analysis to test how prone results were to change when completer-only data only were compared with 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

In future updates of this review, if we identify additional studies, we plan to analyse the effects of excluding trials that are 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 does not substantially alter the direction of effect or the precision of the effect estimates, then we will include data from these trials in the analysis.

4. Imputed values

In future updates, we also plan to undertake 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 any identified cluster randomised trials.
If we note substantial differences in the direction or precision of effect estimates in any of the sensitivity analyses listed above, we will not pool data from the excluded trials with the other trials contributing to the outcome, but present them separately.

RESULTS

Description of studies

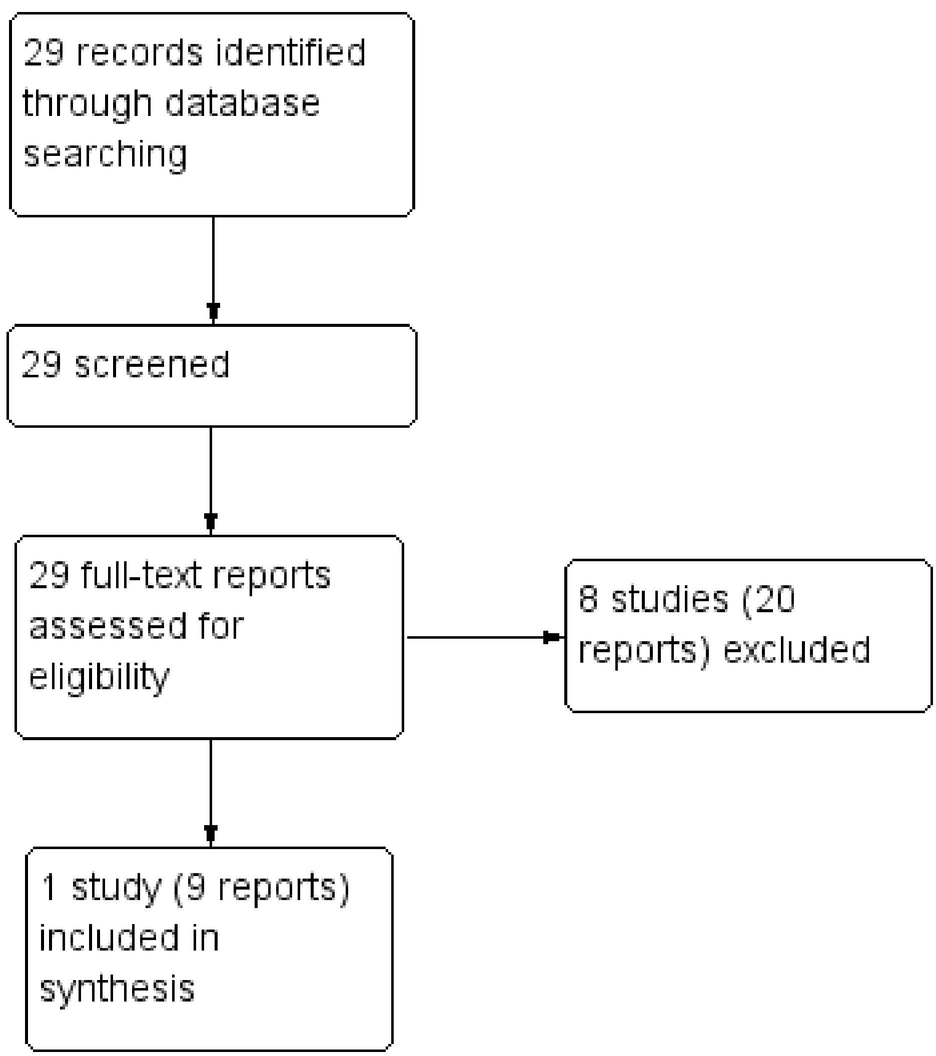
See: Characteristics of included studies; Characteristics of excluded studies.

For substantive descriptions of studies please see Characteristics of included studies and Characteristics of excluded studies.

Results of the search

The original searches in 2011 yielded references to 29 reports (Figure 1), and after initial appraisal we selected nine studies for further inspection of full papers. We were able to include only one relevant study.

Figure 1. Study Flow Diagram.



Included studies

Only one study with 45 participants met the inclusion criteria (Johnstone 1978).

1. Length of studies

The duration of treatment was four weeks with a follow-up of 12 months.

2. Setting

The study was hospital-based. During the treatment period all participants were cared for in a research ward (three weeks). Only two people improved enough to be treated as day-patients for the final week.

3. Participants

All participants suffered from acute schizophrenia; 44 were in the NS (+) (nuclear schizophrenia) category and one in the CS (+) (catatonic syndrome) category when the Present State Examination was used for rating (Wing 1974). According to Brockington and Kendell's (unpublished) criteria for schizoaffective psychosis, there were 18 people with schizoaffective disorder and 27 without schizoaffective disorder. According to Feighner's criteria for 'definite schizophrenia' (Feighner 1972), there were 24 who were Feighner-positive. All the participants had developed new symptoms in the previous month and gave informed consent. People taking 200 mg chlorpromazine per day or an equivalent dose of another neuroleptic for at least seven days during the previous month were excluded. The study included both men (26) and women (19) and were aged 16 or over. Twenty-one participants had a definite history of previous psychotic illness, two participants had a suggestive history of a previous psychotic illness.

4. Study size

The total number of participants was 45. All completed the study but seven people were lost to follow-up at 12 months.

5. Interventions

There were two isomers of flupenthixol - α (cis) and β (trans) forms and participants were randomly and blindly allocated to three groups.

5.1 α-flupenthixol

The dose used was 6 mg daily for six days, and 9 mg daily for 22 days.

5.2 β-flupenthixol

The dose used was 6 mg daily for six days, and 9 mg daily for 22 days.

5.3 Placebo

The dose mirrored that of the two isomers of flupenthixol, was 6 mg daily for six days, and 9 mg daily for 22 days.
Because, as the trialists had presupposed, placebo and β-flupenthixol did behave as non-active controls we have combined both in Comparison Three.
All participants received combination therapy with orphenadrine 50 mg three times daily and nitrazepam 10 mg orally at night.

6. Outcomes

6.1 General remarks

Data were poorly presented and we could only use data for two outcomes, global state and general functioning. The data for mental state and behaviour were skewed and reported as other data.

6.2 Outcome scales from which data were possible to use

6.2.1 Cooper Ratings

This scale rates social functioning in terms of a. economic status, b. social liability, and c. self-care, each being assessed on a three-point scale. The ratings obtained are combined to give a total 'Social Adjustment' score. This varies from a possible maximum of six points to a possible minimum of zero. Patients with five or six points are classed as having a 'good' level; people with three or four points are classed as having a 'fair' level; and those with one, two, or no points as having a 'poor' level (Cooper 1961). In Johnstone 1978, the only included trial, the trialists added a forth area to rate - return to work - also assessed on a three-point scale. If all ratings were summed the minimum possible score was four. Those who scored only four were classed as having a good outcome in social terms; those who failed to achieve this only because they were not economically independent and who lived in circumstances where economic independence would not be expected were also classed as having a good outcome (Johnstone 1978). We are not clear of how adding the additional parameter of return to work effects the reliability or validity of ratings. (See Differences between protocol and review).

6.2.2 Krawiecka Rating Scale

This metal state scale consists of both positive and negative symptoms of schizophrenia. It has been relatively popular in the United Kingdom and continental Europe. With this scale eight variables (depression, anxiety, flattening or incongruity of affect, psychomotor retardation, hallucinations, delusions, incoherence of thought, and poverty of speech or muteness) are assessed on a zero to four scale. It is used to assess the mental state and behaviour in chronically psychotic people with higher scores indicating greater severity. It is also know as the Manchester Scale (Krawiecka 1977). In the only included trial, flattening of affect and incongruity of affect were rated separately to yield nine variables (Johnstone 1978). We are not clear of how this modification effects the reliability or validity of overall ratings.

7. Missing outcomes

The included study did not attempt to quantify adverse effects/ events, service outcomes, satisfaction with treatment, economic outcomes of flupenthixol.

Excluded studies

We excluded eight studies. Twenty-nine records were originally seen in electronic form but studies listed in the Characteristics of excluded studies had to be inspected in hard copy in order to make the final decision. Two studies, Blanc 1968 and Vinar 1968, were not randomised. The remaining six trials did not compare flupenthixol with placebo (Nahunek 1970; Agrup-Andersson 1974; Wistedt 1981; MacMillan 1984; SSRG 1987; Gattaz 2004).

Awaiting assessment

No studies await assessment.

Ongoing

We know of no ongoing studies.

Risk of bias in included studies

We judged the risk of bias for the included study and, overall, we felt the risk of bias to be moderate (Figure 2; Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about eachrisk of bias item presented as percentages across all included studies.

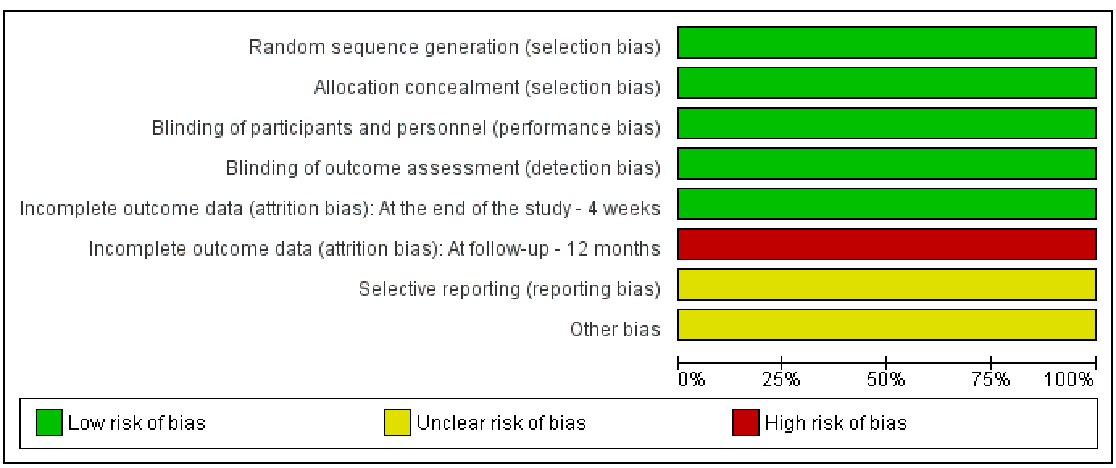
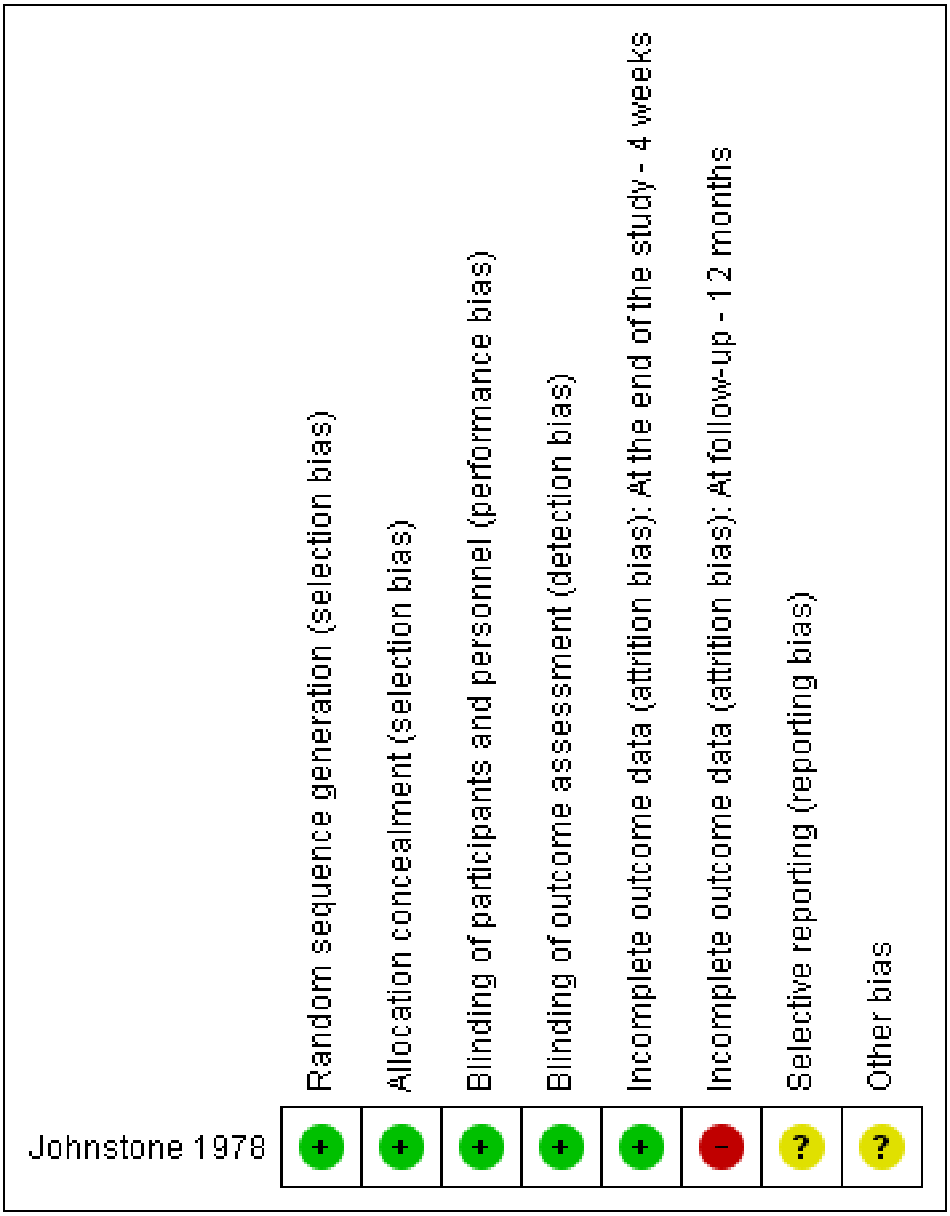


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Participants were randomly allocated to one of three groups. We contacted Professor Eve Johnstone (the original investigator) and she replied that randomisation was undertaken using a randomised number code controlled by the hospital pharmacy.

Blinding

Reports described that the study was double-blind. Also, all participants were given orphenadrine to prevent the allocation of medication being revealed by parkinsonian side-effects. We are unsure if this device was successful. In addition, the rating was performed by one of two investigators. Professor Johnstone informed us that she carried out the assessment and was blind to drug allocation as were the ward staff and patients. Participants were not asked to guess what treatment they had been allocated.

Incomplete outcome data

All participants completed the four-week phase and seven participants were lost to follow-up. Only 36 participants' follow-up data were used. The author reported the reasons (Table 2).

Selective reporting

The study's protocol is not available so we could not compare outcomes in the protocol and in the published reports. Outcomes were published in nine reports and some of them only reported statistical measures of probability (P values) or using figures. This often made it impossible to acquire raw data for synthesis. P values depend on the sample size of the groups. It is sometimes possible to extract raw data from P values, but in the reviewed study this was not possible, because they were reported as 'P < 0.05', 'P < 0.02' or 'P < 0.10'. As a result, a lot of potentially informative data were lost.

Other potential sources of bias

The pharmaceutical company with a pecuniary interest in the result (Lundbeck) made preparations of the isomers of flupenthixol available and the trial author thanked them for their interest and encouragement. We do not think this represents a major threat to validity.

Effects of interventions

See: **Summary of findings for the main comparison** α-FLUPENTHIXOL versus PLACEBO or β-FLUPENTHIXOL for schizophrenia

1. COMPARISON 1: α-FLUPENTHIXOL versus PLACEBO

1.1 Global state: Needing additional medication - four weeks

All participants received combination therapy with 50 mg orphenadrine three times daily and 10 mg nitrazepam orally at night. Where acute behavioural disturbance or severe distress made it necessary, chlorpromazine was administered in single doses of 100 mg orally. We found no significant difference in adding chlorpromazine comparing α-flupenthixol group with placebo group (n = 30, odds ratio (OR) 0.25 95% confidence interval (CI) 0.04 to 1.64, Analysis 1.1).

1.2 General functioning: Poor social functioning (modified Cooper's ratings) -12 months

We considered the reasons why participants' data had not been available for the analysis (Table 2). Some reasons implied that participants' social functioning was poor with the exceptions of two people for whom we were unclear. Based on this, we assumed these people also had poor social outcomes at one-year follow-up (n = 30, RR 1.71 CI 0.94 to 3.12). Using only data as reported made little difference (n = 23, risk ratio (RR) 2.18 95% CI 0.91 to 5.25, Analysis 1.2).

1.3 Mental state and behaviour: Average score (modified Krawiecka rating scale, high score = worse, data skewed) - four weeks

The few and incomplete data are skewed and difficult to interpret (Analysis 1.3).

2. COMPARISON 2: α-FLUPENTHIXOL versus β-FLUPENTHIXOL

2.1 Global state: Needing additional medication - four weeks

Participants allocated α-flupenthixol needed additional chlorpromazine significantly less than those allocated to β-flupenthixol (n = 30, OR 0.10 CI 0.02 to 0.44, Analysis 2.1).

2.2 General functioning: Poor social functioning (modified Cooper's ratings) -12 months

As with finding 1.2 above, we considered the reasons why participants' data had not been available for the analysis (Table 2). Based on this, we assumed these people also had poor social outcomes at one-year follow-up and found no differences between groups at 12 months follow-up (n = 30, RR 1.09 95% CI 0.73 to 1.62). This is a similar result to that of analysing the data as reported (n = 24, RR 1.05 CI 0.63 to 1.75, Analysis 2.2).

2.3 Mental state and behaviour: Average score (modified Krawiecka rating scale, high score = worse, data skewed) - four weeks

The few and incomplete data are skewed and difficult to interpret (Analysis 2.3).

3. COMPARISON 3: α-FLUPENTHIXOL versus PLACEBO or β-FLUPENTHIXOL

3.1 Global state: Needing additional medication - four weeks

We found adding chlorpromazine's ratio in α-flupenthixol group was lower than in the placebo and β-flupenthixol groups (n = 45, OR 0.19 95% CI 0.05 to 0.71, Analysis 3.1).

3.2 General functioning: Poor social functioning (modified Cooper's ratings) - 12 months

When assuming those missing data were 'poor' outcomes we found no significant difference in social functioning between α-flupenthixol group and people allocated to the placebo or β-flupenthixol group (n = 45, RR 1.33 CI 0.91 to 1.96). If we analysed only data as reported we found similar results (n = 36, RR 1.40 CI 0.83 to 2.36, Analysis 3.2).

D I S C U S S I O N

Because mental state data were presented in a way that was impossible to combine, it left us little choice but to present Comparison 1. and Comparison 2. It is, however, really Comparison 3. that contains most data relevant to the review question.

Summary of main results

An overall summary is presented in Summary of findings for the main comparison. The one trial is small and findings are at moderate risk of bias. Many outcome data were not reported in this trial and the data of mental state and behaviour are skewed.

1. Global state: Needing additional medication - four weeks

We found fewer participants allocated α-flupenthixol needed additional chlorpromazine compared with those in the inactive control group (OR 0.19 CI 0.05 to 0.71). If, currently, about four out of 10 need the additional top-up medication when on inactive placebo this reduces to a little over one out of 10 by use of the active compound. If we take this proxy measure as an indication of disturbance or distress, this finding is important. It is, however, weak, being of very low quality and based on very few un-replicated data.

2. General functioning: Poor social functioning (modified Cooper's ratings) - 12 months

Whether we used our assumptions or not made little difference. We found no difference in social functioning between groups at about 12 months. This could have been for a variety of reasons. Perhaps the study did not have the power to illustrate moderate effects, perhaps these effects genuinely did not occur or events in the months following the four-week intensive trial modified the situation to such an extent that any initial effect was lost.

3. Missing outcomes

Flupenthixol has been available for nearly five decades. We found no really useful data on mental state. We found no data at all on adverse effects, service outcomes, satisfaction with treatment or economics. As a result we have to rely on comparative data - where flupenthixol is compared with another drug (Tardy 2011). Flupenthixol may be as good as other drugs for mental state outcomes but if both medications had no effect compared with placebo then it may cause reconsideration of whether to use either drug. If both flupenthixol and, for example, amisulpride had considerable adverse effects but in equal proportions then data could be presented as being no different (Silveira 2002). Placebo comparisons are useful for estimates of absolute effects. Indirect comparisons are problematic. It is remarkable, and embarrassing that many, many people will have been given this potent drug without the clear support of data from high-grade trials.

Overall completeness and applicability of evidence

1. Completeness

Many outcomes of interest are missing. We do not have clinically useful data derived from trials on the absolute effects of this old drug on mental state, adverse effects, service use or a series of other valuable outcomes. This situation is unlikely to change and it will remain likely that we have to rely on data from trials comparing flupenthixol with other drugs, indirect comparisons or non-randomised sources.

2. Applicability

It is important to consider that the one included study was published several decades ago and the circumstances of conduct will be different to the situations that many find themselves in today. Also, the trial design could hardly be called 'real-world' by today's standards (Thorpe 2009), however, participants were carefully diagnosed and very likely to suffer from schizophrenia and be similar to people treated now in everyday care and the dose of flupenthixol is similar to that used today. The simple outcome of 'needing additional medication' is of universal interest as is poor social functioning even if the latter is problematic to interpret three decades down the line and when derived from a scale of unproven value. What data we have may well be applicable, but schizophrenia is often a chronic illness and more long-term data are needed.

Quality of the evidence

The one study is pioneering but small, with rare events and of a quality that suggests results are at moderate risk of bias (Figure 3). The author reported some graphs with only P values and figures, but we could not collect useful data (Johnstone 1978).

Potential biases in the review process

Thorough search strategies were used and we strictly followed review protocol in the process of study selection, data extraction and analysis. We did work with published reports and could not exclude the possibility that studies with negative results or small sample size may not have been identified. One small negative study could overturn any of the findings we have reported above. Publishing bias is a real risk.

Agreements and disagreements with other studies or reviews

None known.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia

There are few clinically meaningful high-grade data on the absolute effects of flupenthixol. Some evidence from the one, small, dated but pioneering trial was positive but many important outcomes were not recorded. The impression of the effects of this drug come more from studies comparing it with other drugs and long experience of its use. This less robust evidence may not be good enough for some people with schizophrenia.

2. For clinicians

It is surprising how few studies have investigated the absolute effect of flupenthixol. The relevant study was performed over 30 years ago and suggests that, when combining with orphenadrine and nitrazepam, after four weeks treatment, α-flupenthixol could really reduce the numbers needing additional chlorpromazine when compared with inactive control treatments. This is important - albeit limited. We are not sure how to interpret the social functioning at 12 months data. Long experience with this drug (Gross 1965) would support its antipsychotic properties and the findings of this review. We are, however, disappointed that clinicians are still left somewhat stranded should they be asked regarding the quantitative effects of this drug.

3. For managers or policy makers

Flupenthixol is widely available and inexpensive. It is understandable that it remains one of many drugs used for treating people with serious mental illnesses. In situations where flupenthixol is still used it could be justified to undertake a well-designed study to quantify the absolute effects of this drug. Such a study need not be expensive and could be highly informative.

Implications for research

1. Reviews

Most excluded studies have already found their way into reviews related to flupenthixol (Table 1) or other antipsychotics. However one study compared any one of a range of antipsychotics - flupenthixol being one - with placebo (MacMillan 1984) and it is possible that such a comparison would be of interest to future reviewers.

2. Trials

Even though flupenthixol has been used as an antipsychotic drug for decades, there is still only one placebo-controlled trial. The use of flupenthixol is more based on clinical experience than high-grade trial-derived data. The story of flupenthixol remains incomplete and large, randomised, placebo-controlled trials could be helpful. With the development of new drugs, however, the day for studies comparing flupenthixol with placebo may not come.

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.

Many thanks for Samantha Roberts for the trials 2011 search. We are most grateful for the ongoing support of Claire Irving at the Cochrane Schizophrenia Group editorial base.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Johnstone 1978

Methods	Allocation: randomised. Blindness: double blind. Duration: 4 weeks. Follow up: 12 months post-trial.
Participants	Diagnosis: schizophrenia schizoaffective (Present State Examination, Brockington and Kendell criteria, Feighner). History: "acute", 21 had definite, and 2 a suggestive, history of previous psychotic illness. N = 45. Age: 16 or over. Sex: 19 women, 26 men. Setting: all participants cared for in research ward for first 3 weeks, 2 people improved enough to be treated as day-patients for last week Inclusion criteria: people who developed new symptoms in past month and gave informed consent Exclusion criteria: participants taking 200 mg chlorpromazine per day or an equivalent for at least 7 days during previous month
Interventions	1. α-flupenthixol: 6 mg daily for 6 days, and 9 mg daily for 22 days. N = 15. 2. β-flupenthixol: 6 mg daily for 6 days, and 9 mg daily for 22 days. N = 15 3. Placebo: 6 mg daily for 6 days, and 9 mg daily for 22 days. N = 15 Combination therapy: all participants also received orphenadrine 50 mg three times daily. Nitrazepam 10 mg was given orally at night as a hypnotic
Outcomes	Global state: needing additional medication[1], 4 weeks. General functioning: social functioning (modified Cooper's ratings), 12 months Mental state and behaviour[2]: average scores (modified Krawiecka rating scale), 4 weeks. Unable to use (4 weeks) 1. Lab test: HPRL, HGH, FSH, LH, testosterone, urinary MHPG, platelet MAO activity (not clinical outcomes). 2. Physiological test: skin conductance responsivity (not clinical outcomes)
Notes	1. Where acute behavioural disturbance or severe distress made it necessary, chlorpromazine was administered in single doses of 100 mg orally, and the number of doses given counted 2. All the participants completed the 4 weeks study. Author assessed the endpoint and scores change of mental state and reported that there were significant differences in endpoint between α-flupenthixol and β-flupenthixol, between α-flupenthixol and placebo; α-flupenthixol was superior to the other two treatments in each case of the scores change but there was no significant difference between α-flupenthixol and placebo. We could

	not extract the useful analysed data of mental state	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Reports state - "randomly allocated" to one of three groups. Author replied that randomisation undertaken by a randomised number code
Allocation concealment (selection bias)	Low risk	Author informed us that number code was controlled by hospital pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reports state - "double blind". All given orphenadrine to minimise parkinsonian adverse-effects. Author assured us that ward staff and patients were blind to drug allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Author undertook assessments blind to the drug allocation.
Incomplete outcome data (attrition bias) At the end of the study - 4 weeks	Low risk	All participants completed the study and were included in the final analysis
Incomplete outcome data (attrition bias) At follow-up - 12 months	High risk	Seven participants lost to follow-up at 12 months: numbers by original group of allocation reported but reasons for loss not reported by group Two additional people who scored 4 on social functioning assessment had been readmitted with recurrence of psychosis at least once since discharge from hospital - author omitted them from calculation of results: unclear original group of allocation
Selective reporting (reporting bias)	Unclear risk	No protocol is available. We could not compare outcomes in protocol and final reports
Other bias	Unclear risk	Author thanked Lundbeck for making preparations of flupenthixol isomers and for their interest and encouragement

FSH: follicle stimulating hormone
HGH: human growth hormone

HPRL: prolactin
LH: luteinizing hormone
MAO: platelet monoamine oxidase
MHPG: 3-Methoxy-4-hydroxyphenylglycol

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

Study	Reason for exclusion
Agrup-Andersson 1974	Allocation: randomised. Participants: 4 participants with paranoic syndromes, the other 53 participants with schizophrenia. Interventions: flupenthixol decanoate vs fluphenazine decanoate + placebo, not flupenthixol vs placebo
Blanc 1968	Allocation: not randomised.
Gattaz 2004	Allocation: randomised. Participants: people with schizophrenia. Interventions: olanzapine + placebo vs flupenthixol + placebo, 5-day placebo run-in and a 4-week double-blind treatment period, not flupenthixol vs placebo
MacMillan 1984	Allocation: participants not randomised into three groups; only participants in the clinical trial entrants group were randomised into two subgroups. Participants: people with first episodes of schizophrenia. Interventions: clinical trial entrants (active drug [flupenthixol, chlorpromazine, haloperidol, pimozide, trifluoperazine] vs placebo) vs trial eligible patients vs non-discharged patients, not flupenthixol vs placebo
Nahunek 1970	Allocation: not mentioned. Participants: people with schizophrenia. Interventions: both flupenthixol and perphenazine were applied alternately for 3 weeks, inserting placebo intervals individually for each participant, not flupenthixol vs placebo
SSRG 1987	Allocation: randomised. Participants: people with first episodes of schizophrenia. Interventions: firstly randomised to pimozide vs oral flupenthixol; after 5 weeks, those who responded received first year maintenance therapy (once-weekly pimozide vs intramuscular flupenthixol decanoate); during second year, those who had not relapsed, entered an active medication (once-weekly pimozide or intramuscular flupenthixol decanoate) vs placebo trial; at the end of the second year all were treated with neuroleptics of the clinician's choice, not flupenthixol vs placebo
Vinar 1968	Allocation: not randomised.
Wistedt 1981	Allocation: randomised. Participants: people with chronic schizophrenia. Interventions: firstly randomised to long-acting neuroleptics (flupenthixol decanoate or fluphenazine decanoate) vs placebo (6 months); then those who did not relapse were followed up for another 24 months, not flupenthixol vs placebo

vs: versus

DATA AND ANALYSES

Comparison 1. α-FLUPENTHIXOL versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global state: Needing additional medication (chlorpromazine) - 4 weeks	1	30	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.25 [0.04, 1.64]
2 General functioning: Poor social functioning (modified Cooper's ratings) - 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 data including our assumptions	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.94, 3.12]
2.2 data as reported	1	23	Risk Ratio (M-H, Fixed, 95% CI)	2.18 [0.91, 5.25]
3 Mental state and behaviour: Average score (modified Krawiecka rating scale, high score= worse, data skewed) - 4 weeks			Other data	No numeric data

Comparison 2. α-FLUPENTHIXOL versus β-FLUPENTHIXOL

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global state: Needing additional medication (chlorpromazine) - 4 weeks	1	30	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.10 [0.02, 0.44]
2 General functioning: Poor social functioning (modified Cooper's ratings) - 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 data including our assumptions	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.73, 1.62]
2.2 data as reported	1	24	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.63, 1.75]
3 Mental state and behaviour: Average score (modified Krawiecka rating scale, high score= worse, data skewed) - 4 weeks			Other data	No numeric data

Comparison 3. α-FLUPENTHIXOL versus PLACEBO or β-FLUPENTHIXOL

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global state: Needing additional medication (chlorpromazine) - 4 weeks	1	45	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.19 [0.05, 0.71]
2 General functioning: Poor social functioning (modified Cooper's ratings) - 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 data including our assumptions	1	45	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.91, 1.96]
2.2 data as reported	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.83, 2.36]

ADDITIONAL TABLES

Table 1. Other relevant reviews

Title	Stage	Link
Depot flupenthixol decanoate for schizophrenia or other similar psychotic disorders	Review	David 1999
Flupenthixol versus low-potency first generation antipsychotic drugs for schizophrenia	Protocol	Tardy 2011

Table 2. Information on participants who were not included in social functioning analyses

No.	Reason
1	Unsettled existence: No co-operation with drug treatment or follow-up. Repeated self-terminated admissions to various hospitals
2	Defaulted from clinic attendance and drug treatment. At time of follow-up receiving in-patient care for severe self-inflicted burns
3	Not traced.
4	Died following burning accident.
5	In judicial custody having been arrested for fraud.
6	Not traced.
7	Did not recover from acute episode: transferred to long-term care

Table 2. Information on participants who were not included in social functioning analyses *(Continued)*

8	Scored only 4 on the social functioning assessment but had been readmitted to in-patient care with a recurrence of psychosis at least once since their discharge from hospital
9	Scored only 4 on the social functioning assessment but had been readmitted to in-patient care with a recurrence of psychosis at least once since their discharge from hospital

HISTORY

Protocol first published: Issue 4, 2012

Review first published: Issue 11, 2012

CONTRIBUTIONS OF AUTHORS

Xiaohong Shen - protocol writing, trial selection, data extraction and assimilation, and review writing.

Jun Xia - protocol writing, trial selection, data extraction and assimilation, and review writing .

Clive E Adams - protocol writing, trial selection, and assimilation, and review writing.

DECLARATIONS OF INTEREST

Xiaohong Shen - None known.

Jun Xia - None known.

Clive E Adams - None known.

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Internal sources

- Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, China.
- The University of Nottingham, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. α isomer and β form

β-flupenthixol did indeed show very low pharmacological activity (Nielsen 1973) and the therapeutic potency of flupenthixol was confined to the α-isomer (Crow 1977). This had been the original premise of the trial and we therefore felt justified to add data from the β-flupenthixol group to the placebo to make a larger 'inactive control' group.

2. OR vs RR

When events were very few indeed we used Peto's method to compute Odds Ratios (OR) rather than relative risk (RR) as is recommended (Higgins 2011).

3. Use of modified scales

We stated in our protocol that we would not use modified scales unless their properties had been published (Data extraction and management - 2.2) but we have because data were so few. We remain unsure of the properties of the scales in their modified form.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Adult; Humans