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Fluphenazine (oral) versus placebo for schizophrenia

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Abstract

Background—Fluphenazine is one of the first drugs to be classed as an ‘antipsychotic’ and has been widely available for five decades.

Objectives—To compare the effects of oral fluphenazine with placebo for the treatment of schizophrenia.

Search methods—We updated searches of the Cochrane Schizophrenia Group's trials register, which includes relevant randomised controlled trials from the bibliographic databases Biological Abstracts, CINAHL, The Central Register of Controlled Trials in *The Cochrane Library*, EMBASE, MEDLINE, PsycLIT, LILACS, PSYNDEX, Sociological Abstracts and Sociofile, 15 May, 2012. References of all identified studies were searched for further trial citations.

Selection criteria—We sought all randomised controlled trials comparing oral fluphenazine with placebo relevant to people with schizophrenia. Primary outcomes of interest were global state and adverse effects.

Data collection and analysis—We inspected citations and abstracts independently, ordered papers and re-inspected and quality assessed trials. We extracted data independently. Dichotomous

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CONTRIBUTIONS OF AUTHORS

Hosam E Matar screened the search results, organised the retrieval of papers, appraised the papers and extracted data, analysed and interpreted the data, managed the data and entered data in RevMan, and wrote the final report.

Muhammad Qutayba Almerie screened the search results, organised the retrieval of papers, appraised the papers and extracted data, managed the data and entered data in RevMan, analysed and interpreted the data and wrote the final report.

Stephanie Sampson updated the abstract, search and results section, constructed PRISMA diagram and Summary of findings table.

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DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Antipsychotic Agents [*therapeutic use]; Fluphenazine [*therapeutic use]; Placebos [therapeutic use]; Randomized Controlled Trials as Topic; Schizophrenia [*drug therapy]

MeSH check words

Humans

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data were analysed using fixed-effect risk ratio (RR) and the 95% confidence interval (CI). Continuous data were excluded if more than 50% of people were lost to follow-up, but, where possible, mean differences (MD) were calculated.

Main results—From over 1200 electronic records of 415 studies identified by our initial search and this updated search, we excluded 48 potentially relevant studies and included seven trials published between 1964 and 1999 that randomised 439 (mostly adult participants). No new included trials were identified for this review update. Compared with placebo, global state outcomes of 'not improved or worsened' were not significantly different in the medium term in one small study (n = 50, 1 RCT, RR 1.12 CI 0.79 to 1.58, *very low quality of evidence*). The risk of relapse in the long term was greater in two small studies in people receiving placebo (n = 86, 2 RCTs, RR 0.39 CI 0.05 to 3.31, *very low quality of evidence*), however with high degree of heterogeneity in the results. Only one person allocated fluphenazine was reported in the same small study to have died on long-term follow-up (n = 50, 1 RCT, RR 2.38 CI 0.10 to 55.72, *low quality of evidence*). Short-term extrapyramidal adverse effects were significantly more frequent with fluphenazine compared to placebo in two other studies for the outcomes of akathisia (n = 227, 2 RCTs, RR 3.43 CI 1.23 to 9.56, *moderate quality of evidence*) and rigidity (n = 227, 2 RCTs, RR 3.54 CI 1.76 to 7.14, *moderate quality of evidence*).

Authors' conclusions—The findings in this review confirm much that clinicians and recipients of care already know, but they provide quantification to support clinical impression. Fluphenazine's global position as an effective treatment for psychoses is not threatened by the outcome of this review. However, fluphenazine is an imperfect treatment and if accessible, other inexpensive drugs less associated with adverse effects may be an equally effective choice for people with schizophrenia.

BACKGROUND

Description of the condition

One in every 10,000 people per year is diagnosed with schizophrenia, with a lifetime prevalence of about 1% (Jablensky 1992). It often runs a chronic course with acute exacerbations and often partial remissions. Over the past few decades, a large body of evidence has accumulated linking excessive dopamine transmission to psychosis and more direct evidence emerges from neuro-imaging studies which showed an increased dopamine synthesis (Hietala 1995; Lindstrom 1999; Meyer 2002), an exaggerated release of dopamine and a higher than normal levels of dopamine at baseline (Abi-Dargham 2000; Gjedde 2001). The antipsychotic group of drugs with its anti-dopaminergic effects is the mainstay treatment for this illness (Dencker 1980). These are generally regarded as highly effective, especially in controlling such symptoms as hallucinations and fixed false beliefs (delusions) (Kane 1986). Moreover, they seem to reduce the risk of acute relapse. A systematic review undertaken two decades ago also suggested that, for those with serious mental illness, stopping antipsychotics resulted in 58% of people relapsing, whereas only 16% of those who were still on the drugs became acutely ill within a one-year period (Davis 1986). Schizophrenia usually begins in young adulthood and has a lifetime prevalence of about 1% irrespective of culture, social class and race. Schizophrenia is a chronic relapsing mental illness, characterised by symptoms such as hallucinations, delusions, disordered thinking,

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and emotional withdrawal. Antipsychotic drugs are effective for controlling florid symptoms such as hallucinations and delusions but are less effective for treating emotional withdrawal. Antipsychotics are associated with adverse effects such as movement disorders, and the overall cost of the illness to the individual, their carers and the community is considerable.

Description of the intervention

Fluphenazine, a phenothiazine derivative, was one of the first drugs to be classed as an 'antipsychotic' and was approved by the FDA in 1959. In Britain it was first used for the relief of anxiety. The American reports, however, were the first to indicate its value in psychotic illness (Darling 1959; Holt 1960). Fluphenazine has trifluoromethyl and piperazine groups which bring about increase in potency that in many pharmacodynamic properties may be about 40 times as potent as chlorpromazine. This is associated with a rapid and prolonged action, relatively little sedative activity and little or no increase in autonomic and haemodynamic effects. Fluphenazine is an inexpensive and widely accessible antipsychotic drug that has been available to treat people with schizophrenia for five decades. In this review, for perhaps the first time, we objectively quantify the effects of oral administration of fluphenazine in comparison with placebo. It is indeed a potent antipsychotic but with considerable adverse effects. Other drugs may well be preferable.

How the intervention might work

Fluphenazine is thought to elicit its antipsychotic effects via interference with central dopaminergic pathways and blocking receptors, particularly D2, in the mesolimbic zone of the brain. Extrapyramidal side effects are a result of interaction with dopaminergic pathways in the basal ganglia. As fluphenazine is not specific to one action within the body, it is known to cause adverse effects ranging from orthostatic hypotension as a result of its alpha adrenergic blocking activity to anticholinergic and extrapyramidal symptoms (tardive dyskinesia, pseudo-parkinsonism, dystonia, dyskinesia, akathisia). In addition, the use of fluphenazine has been associated with a potentially fatal disturbance of blood pressure, temperature and muscle control (neuroleptic malignant syndrome). As with all antipsychotic medications, fluphenazine is characterised by inter-individual variability in pharmacokinetics, most marked with the oral preparation. It is extensively metabolised, undergoing 'first pass' metabolism by the liver and is excreted in both the urine and faeces. Fluphenazine is highly protein-bound (greater than 90%) in plasma. With oral fluphenazine, peak plasma/serum levels are attained within a few hours. The serum half-life of it is approximately 15 hours. Fluphenazine crosses the blood-brain barrier, crosses the placenta easily and cannot be removed by dialysis (Wikipedia 2006).

Why it is important to do this review

Fluphenazine is still one of the drugs commonly used for people with schizophrenia and is given by mouth or short-acting injection. Although we have not found precise data on how much fluphenazine is used worldwide, it is one of the World Health Organization's Essential Drugs (WHO 2005) and in the developing world, where non-proprietary preparations of fluphenazine are inexpensive, it may be one of the only drug treatments available. However, although it is still available in most of Europe and North America, the arrival of a newer generation of antipsychotic drugs has reduced its market share in the respective countries.

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This version of the review updates our past work (Matar 2007a; Matar 2007b). This is an update of a Cochrane Review first published in 2007 (Issue 1) of *The Cochrane Database of Systematic Reviews*.

OBJECTIVES

To compare the effects of oral fluphenazine with placebo for the treatment of schizophrenia.

METHODS

Criteria for considering studies for this review

Types of studies—We included all relevant randomised controlled trials. We included trials described as ‘double-blind’ if it was implied that the study was randomised and we included these in a 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 these within a subcategory. We excluded quasi-randomised studies, such as those allocating by alternate days of the week.

Types of participants—We included people diagnosed with schizophrenia or schizophrenia-like illnesses using any criteria, irrespective of age, sex or severity of illness.

Types of interventions—1. Fluphenazine: any dose of only oral administration

2. Placebo: (active or inactive) or no treatment

Types of outcome measures—Where possible, outcomes were made binary by dividing them into two categories - ‘clinically significant change’ and ‘no clinically significant change’.

We categorised outcomes as short term (0-8 weeks), medium term (9 to 26 weeks) and long term (27 weeks to 104 weeks).

Primary outcomes—1. Global state

1.1 Not improved or worsened

2. Adverse effects

2.1 General

2.2 Specific

2.2.1 Extrapyramidal symptoms (parkinsonian symptoms, dystonia, akathisia, and tardive dyskinesia)

2.2.2 Anticholinergic symptoms

2.2.3 Others

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Secondary outcomes—1. Global state

1.1 Relapse

1.2 Time in exacerbated state

1.3 Leaving the study early

1.4 Length of stay in hospital

1.5 Satisfaction with treatment - participant/carer

1.6 Death

2. Mental state

2.1 General symptoms

2.2 Specific symptoms

2.2.1 Positive symptoms (delusions, hallucinations, disordered thinking)

2.2.2 Negative symptoms (avolition, poor self-care, blunted affect)

2.2.3 Mood - depression

3. Behaviour

3.1 General behaviour

3.2 Specific behaviours (e.g. aggressive or violent behaviour)

3.2.1 Social functioning

3.2.2 Employment status during trial (employed/unemployed)

3.2.3 Occurrence of violent incidents (to self, others or property)

4. Economic

4.1 Cost of care

5. ‘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’ table/s. 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.

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1. Global state - not improved or worsened - medium term.
2. Relapse - long term.
3. Adverse effects: death - long term.
4. Adverse effects: extrapyramidal effects (akathisia) - short term.
5. Adverse effects: extrapyramidal effects (rigidity) - short term.

Search methods for identification of studies

Electronic searches—1. Cochrane Schizophrenia Group's trials register (May 2012)

The Trial Search Co-ordinator searched the Cochrane Schizophrenia Group's Trials Register 15th May 2012 using the same search criteria as our initial 2006 review.

For details of previous search please see Appendix 1. [((fluphen* or flufen* or modec* or moditen* or eutimax* or prolixin* or siqualon* or anaten* or dapotum* or decazate* or decafen* or decentan* or fludecate* or lyogen* or lyoridin* or mirenil*) in title, abstract and index fields in REFERENCE) OR (fluphenazin* in interventions field in STUDY)]

The Cochrane Schizophrenia Group's Trials 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 update are below; for previous methods please see Appendix 2.

Selection of studies—For this 2012 update, review authors HEM and MQA inspected citations from the new electronic search and identified relevant abstracts. HEM and MQA also inspected full articles of the abstracts meeting inclusion criteria and carried out the reliability check of all citations from the new electronic search.

Data extraction and management—1. Extraction

For this update, HEM and MQA 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. We encountered multi-centre trials, however, we were unable to extract data

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relevant to each component centre separately; this was because the study was published many years ago, and such data were unavailable (Goldberg 1964).

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 primarily to use endpoint data, and only use change data if the former were not available. Had enough studies reported continuous data, we would have combined endpoint and change data in the analysis and used mean differences (MD) rather than standardised mean differences (SMD) 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 (SDs) and means are reported in the paper or obtainable from the authors;

b) when a scale starts from the finite number zero, the SD, 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 the Positive and Negative Syndrome Scale (PANSS), (Kay 1986)), 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 2 SD > (S-S min), where S is the mean score and S min is the minimum score.

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Endpoint scores on scales often have a finite start and end point and these rules can be applied. We entered skewed endpoint data from studies of fewer than 200 participants as 'other data' within the Data and analyses rather than into a statistical analysis. Skewed data pose less of a problem when looking at mean if the sample size is large; we would have entered such endpoint data into syntheses had we encountered such data.

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; therefore, we entered skewed change data into analyses regardless of size of study.

2.5 Common measure

Had we encountered such measures, in order to facilitate comparison between trials, we would have converted 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

Had such data been available, we would have 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 would have used the primary cut-off presented by the original authors.

2.7 Direction of graphs

We entered data in such a way that the area to the left of the line of no effect indicated a favourable outcome for oral fluphenazine. 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 the case with outcome 1.10 Leaving the study early: 3. marked improvement/ hospital discharge (Analysis 1.8), which reflected a positive outcome.

Assessment of risk of bias in included studies

For this update, HEM and MQA 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.

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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 used 'Summary of findings' tables to calculate the number needed to treat to provide benefit (NNTB)/to induce harm (NNTH) statistic and its 95% CI.

2. Continuous data

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

Unit of analysis issues

1. Cluster trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice), but analysis and pooling of clustered data poses problems. 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).

Had we encountered such studies, we would have 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 (ICCs) or their clustered data and to adjust for this by using accepted methods (Gulliford 1999). 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). No cluster trials were identified in this review; however, if in future updates of this review cluster-randomised studies are identified, where the ICC is not reported it will be assumed to be 0.1 (Ukoumunne 1999).

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. This was the case in Millar 1963.

3. Studies with multiple treatment groups

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Had we found studies that involved more than two relevant treatment arms, we would have presented the additional treatment arms in comparisons. However, we found no such studies; if, in future updates of this review, if such studies are identified, binary data will be simply added and combined within the two-by-two table. If data are continuous, we will combine data following the formula in section 7.7.3.8 (Combining groups) of the Cochrane Handbook for Systemic reviews of Interventions (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 60% of data be unaccounted for, we would not reproduce these data or use them within analyses. If, however, more than 60% of those in one arm of a study were lost, but the total loss was less than 40%, we would have 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 is between 0% and 60% and where these data are not clearly described, had we found such studies, we would have presented data on a ‘once-randomised-always-analyse’ basis (an intention-to-treat analysis). Those leaving the study early would be 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 stay in the study - in that particular arm of the trial - would be 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 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 60%, and data only from people who complete the study to that point are reported, we presented and used these data.

3.2 Standard deviations

Had standard deviations not been reported, we first would have tried to obtain the missing values from the authors. If not available, where there were 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 would have calculated them according to the rules described in the Cochrane Handbook for Systemic reviews of Interventions (Higgins 2011). Had only the standard error (SE) been reported, standard deviations (SDs) can be calculated by the formula SD = SE * square root (n). Chapters 7.7.3 and 16.1.3 of the Cochrane Handbook for Systemic reviews of Interventions

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(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 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. Had we imputed data, and if future updates of this review employ use of imputed data, we will examine the validity of the imputations in a sensitivity analysis excluding the imputed values. Had we needed to, we would have imputed standard deviations using this model for Clark 1971.

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 CI for I^2). An I^2 estimate greater than or equal to around 50% accompanied by a statistically significant Chi^2 statistic was interpreted as evidence of

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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 C*ochrane 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.

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, but used of the random-effects model where heterogeneity was present.

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 oral fluphenazine 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 outlying studies 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 used prediction intervals as an alternative to this unsatisfactory state.

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

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Sensitivity analysis

1. Hypotheses

It was expected that several sensitivity analyses could be undertaken within this review. The following hypotheses were to be tested: When compared with placebo, for the primary outcomes of interest (see: Criteria for considering studies for this review), fluphenazine is differentially effective for:

1.1 Men and women.

1.2 People who are under 18 years of age, between 18 and 64, or over 65 years of age.

1.3 People who became ill recently (i.e. acute episode approximately less than one month's duration) as opposed to people who have been ill for a longer duration.

1.4 People who are given low doses (1- 5 mg/day), and those given high doses (over 5 mg/day).

1.5 People who have schizophrenia diagnosed according to any operational criterion i.e. a pre-stated checklist of symptoms/problems/time periods/exclusions) as opposed to those who have entered the trial with loosely defined illness.

1.6 People treated earlier (pre-1990) and people treated in recent years (1990 to 2006).

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

2. 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.

3. 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 use 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. A sensitivity analysis was undertaken to test how prone results are to change when completer-only data only are compared to the imputed data using the above assumption. If there was a substantial difference, we reported results and discussed them.

4. Risk of bias

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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 analyses.

5. Imputed values

We also sought 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 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.

6. Fixed-effect and random-effects

We synthesised data using a fixed-effect model; however, we also synthesised data for the primary outcome using a random-effects model to evaluate whether this altered the significance of the results.

RESULTS

Description of studies

For substantive descriptions of studies please see the Included studies and Excluded studies tables.

Results of the search

The initial 2006 search yielded 1274 electronic records for 422 studies, of which we rejected 834 during the first inspection. We inspected the remaining 433 papers. Three hundred and forty-three were rejected, as they were clearly not relevant. The remaining 82 papers (55 studies) were considered to match the inclusion criteria closely enough to be mentioned in either the ‘Included studies’; ‘excluded studies’ and ‘awaiting classification’ tables. The 2012 update search yielded seven studies, each of which was excluded. The seven studies previously awaiting ‘classification’ were moved to ‘excluded studies’ for this review. Therefore, the current review cites 48 studies as ‘excluded studies’ and 16 reports of the seven ‘included studies’. There was over 90% agreement for trial selection and once we had investigated any disagreement and acquired and reassessed the papers, concordance was 100%. Initially, there was also over 90% agreement in the extracted data. We easily resolved any disagreement by discussion (see Figure 1 and Figure 2).

Included studies

We included seven studies (total n = 439 participants).

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1.1 Methods

In all included studies, randomisation was either reported or implied. The mean duration of treatment was about 170 days (~six months), but this was highly skewed (standard deviation (SD) 253). The most common study length was six weeks (Carpenter 1999; Clark 1971; Millar 1963) but the range was considerable with the longest lasting two years (Marder 1994).

1.2 Setting

Four studies were hospital-based (Clark 1971; Goldberg 1964; Hordern 1964; Millar 1963), while three were undertaken in the community (Carpenter 1999; Marder 1994; Rifkin 1976). Five studies were conducted in the United States of America (Carpenter 1999; Clark 1971; Goldberg 1964; Marder 1994; Rifkin 1976), one in Australia (Hordern 1964) and one in the United Kingdom (Millar 1963).

1.3 Participants

All trials included participants diagnosed with schizophrenia and two of the seven trials described the diagnostic criteria used (Diagnostic and Statistical Manual version III (DSM-III) or Research Diagnostic Criteria (RDC)). The other studies used a clinical diagnosis of schizophrenia. The mean age of the participants was about 38 years, range 16 to 75, and they were mostly chronic patients with a mean hospitalisation period of about 20 years. In Marder 1994, all participants were men, whilst in Hordern 1964 and Millar 1963 the participants were all women. In the remaining studies participants were of mixed sex.

1.4 Study size

The mean number of participants was about n = 60, ranging from 36 to 190.

1.5 Interventions

All trials compared oral fluphenazine with inactive placebo. The doses of oral fluphenazine in these studies ranged from 2.5 mg/day (Millar 1963) up to a potential of 20 mg/day (Rifkin 1976). The mean dose was 8.2 mg per day (SD 3.9). The standard oral dosage in minor disturbances 2 mg to 5 mg/day, or in the treatment of psychotic disorders up to 20 mg to 40 mg daily (www.psychotropics.dk).

1.6 Outcomes

1.6.1 General remarks

Most outcomes were dichotomous, and presented as such, or were continuous data. In many studies, outcomes were few and where data were reported they were rendered unusable. None of the included studies attempted to quantify levels of satisfaction or quality of life and there is no evidence of any direct economic evaluation of fluphenazine. However, we were able to measure some aspects of the global and mental state and adverse effects.

1.7 Outcome scales

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The following scales were used and provided data for the analysis.

1.7.1 Global state

1.7.1.1 Clinical Global Impression (CGI) Guy 1976

A rating instrument commonly used in studies in schizophrenia that enables clinicians to quantify severity of illness and overall clinical improvement. A seven-point scoring system is usually used with low scores indicating decreased severity and/or greater recovery. Carpenter 1999 and Clark 1971 reported dichotomised data from this scale, measuring improvement scores. Continuous data from Clark 1971 were also used in our results, however SDs were imputed using the method described in Dealing with missing data.

1.7.1.2 The Multidimensional Scale for Rating Psychiatric Patients (MDRSP) Lorr 1953

The Multidimensional Rating Scale or Hamilton's schizophrenia scale is a modification of the Inpatient Multidimensional Psychiatric Scale. The MDRSP is completed after a psychiatric interview. It consists of 18 items, in the form of simple questions, to be rated along a four-point scale. The severity scores are defined by short behavioural descriptions on the form, thus avoiding interpretation problems. The scale is mainly designed for the evaluation of chronically hospitalised schizophrenic patients. Hordern 1964 reported dichotomised data from this scale for levels of improvement.

1.7.1.3 Brief Psychiatric Rating Scale (BPRS)

Overall 1962 The scale measures positive symptoms and quantifies factors such as thought disorder, activation, hostility. somatic, hallucinatory, and depressive states. The original scale had 16 items, but a revised 18-item scale is more commonly used, with scores ranging from 0 to 126. Each item is defined on a seven-point scale from 0 = not present to seven = extremely severe. Higher scores equate to severity of illness.

Excluded studies

We excluded 48 studies. Seven were not randomised, did not imply randomisation or did not describe the allocation procedure at all. In one study, participants were not suffering from schizophrenia. Another sizeable proportion of the trials did not compare oral fluphenazine with placebo, but with other treatments. A few were fluphenazine-withdrawal studies which are not relevant to this review. These withdrawal studies will be included in a future review. Three studies had no usable outcomes. Either data did not have clear clinical implications or genuinely relevant clinical data were not adequately reported. Frequently the numbers of participants in each group were not specified, means or SDs were not given or data were not reported from individual arms of cross-over studies. The seven studies identified in the 2012 search were all excluded, owing either to no randomisation (Kinross-Wright 1963; Matheu 1961), no diagnosis of schizophrenia (Hanlon 1970; Howell 1961), not the appropriate intervention (Marder 1993; Shafti 2009) or no usable data were presented (Zahn 1993).

Awaiting assessment

No studies are awaiting assessment.

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Ongoing studies

We are not aware of any ongoing studies.

Risk of bias in included studies

Please see the relevant ‘Risk of bias’ tables in the Characteristics of included studies section and Figure 3; Figure 4.

Allocation

None of the seven included studies described the methods used to generate random allocation, yet six of them were reported to be “randomly assigned” and readers are given little assurance that bias was minimised during the allocation procedure. Hordern 1964, did not mention “random assignment”, and reported that assignment of participants to fluphenazine or placebo groups was matched on age, length of illness, and severity of illness and the number of participants in each group was identical. Millar 1963 also obtained the same numbers in each group in a randomly assigned procedure with no further description.

Blinding

Only two studies (25%) gave a description of their attempts to make the investigation double-blind. Clark 1971 reported that identically appearing medication was administrated from a bottle labelled only with the participant's name and Millar 1963 reported that only the hospital pharmacist knew the composition of the groups. However neither of them actually tested how successful these attempts were. In the other six trials, it was indicated that attempts at blinding had been made, but without any further description.

Incomplete outcome data

Five studies reported that participants left the study early. Only two, Goldberg 1964 and Clark 1971, reported specifically the reasons for withdrawal.

Selective reporting

Studies frequently presented both dichotomous and continuous data in graphs, or just reported statistical measures of probability (P values). This often made it impossible to acquire raw data for synthesis. Continuous data were frequently poorly described; often no standard deviations/standard errors were presented or no data were presented at all. In this way a lot of potentially informative data were lost. In some studies it seemed that attempts had been made to use the original trials as vehicles for answering a host of other questions about schizophrenia. As a consequence, data from the randomised parts of the studies became buried beneath copious subgroup analyses.

Other potential sources of bias

The quality of trials has been assessed in individual ‘Risk of bias’ tables under the Characteristics of included studies section, using the guidance from the Cochrane Handbook for Systematic Reviews of Interventions categories (Higgins 2011). Due to poor reporting standards from particularly old studies, the majority of the risk of bias domains have been rated ‘unclear’ for the risk of bias.

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Effects of interventions

See: **Summary of findings for the main comparison** ORAL FLUPHENAZINE versus PLACEBO for Schizophrenia

1. COMPARISON: ORAL FLUPHENAZINE versus PLACEBO

1.1 Global state

1.1.1 Not improved or worsened

We found no significant difference between oral fluphenazine and placebo for 'not improved or worse' (CGI) over short-term assessment (n = 125, 3 RCTs). Dichotomised multidimensional rating scale scores at 12 weeks 'not improved or worse' were also nonsignificant (n = 50, 1 RCT, Analysis 1.1).

1.1.2 Relapse

Only Millar 1963 reported on relapse up to six weeks (short term) with results indicating a trend favouring fluphenazine (n = 38, 1 RCT, risk ratio (RR) 0.25 95% confidence interval (CI) 0.06 to 1.03, P = 0.05). Two studies, Marder 1994 and Rifkin 1976, reported data for long-term relapse, which significantly favoured fluphenazine but data are heterogeneous (I^2 92%). Using a random-effects model rendered data equivocal (n = 86, 2 RCTs, Analysis 1.2).

1.1.3 Percentage of time in prodrome state

Marder 1994 reported data at one- and two-year time points, but data are skewed (high SDs) and are best inspected outside of a forest plot, using an additional table (Analysis 1.3). The data suggest that a greater amount of time was spent in a prodromal state amongst placebo participants, at both one and two years.

1.1.4 Percentage of time in exacerbated state

Again, Marder 1994 reported data at one- and two-year time points, but data are skewed and are best inspected outside of a forest plot, using an additional table (Analysis 1.4). Data suggest that, by one year, participants receiving oral fluphenazine spent more time in an exacerbated state that those on placebo. However, by two years, people receiving placebo spent longer in an exacerbated state.

1.1.5 CGI severity of illness - average score

Data for global state using the CGI were reported in one study (Clark 1971), which demonstrated greater improvement in global state (n = 36, 1 RCT, mean difference (MD) -0.77 95% CI -1.39 to -0.15), this was a statistically significant result (P = 0.02); however, these data were imputed using the adjusted final mean and the P value between studies, and the significance of the results should be treated with caution (Analysis 1.5).

1.2 Leaving study early

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1.2.1 Non-specific reasons

Although people allocated to oral fluphenazine left the study less often than participants who were given placebo in the short term, the data did not reach statistical significance (n = 227, 2 RCTs). For -medium-term assessment, we found only one study reporting on attrition (n = 50) and data were not significantly different. Long-term follow-up from two studies (n = 86) were also equivocal, and as a proxy measure for treatment acceptability the oral fluphenazine group did not find treatment any more acceptable than the placebo group when assessed over short-, medium- and long-term evaluation. Overall, across all time periods, only about 15% of people left these studies early (n = 363, 5 RCTs, Analysis 1.6).

1.2.2 Specific reasons

Leaving the study early due to court case transfers was significantly higher (P = 0.02) in the fluphenazine group (n = 190, 1 RCT, RR 10.65 95% CI 1.39 to 81.58). Other reasons for leaving the study early: ‘incorrect diagnosis’ (n = 190, 1 RCT), ‘marked early remission’ (n = 190, 1 RCT) and ‘serious complication of treatment’ (n = 190, 1 RCT) were not significantly different. We found the number of participants leaving the study early due to treatment failure favoured oral fluphenazine with significantly more people dropping out from the placebo group (n = 190, 1 RCT, RR 0.11 95% CI 0.03 to 0.35, Analysis 1.7).

1.2.3 Marked improvement/ hospital discharge

Data were equivocal for this positive outcome (forest plots are presented to display results right to the line of no effect, indicating a favourable outcome for oral fluphenazine). Only one participant receiving oral fluphenazine in one small study was discharged due to marked improvement (n = 36, 1 RCT, Analysis 1.8).

1.3 Adverse effects

1.3.1 Anticholinergic effects

There is some suggestion that fluphenazine increases a person's chance of experiencing anticholinergic effects such as constipation (n = 190, 1 RCT, RR 2.22 95% CI 1.19 to 4.15), dry mouth (n = 227, 2 RCTs, RR 3.62 95% CI 1.39 to 9.42) and increased salivation (n = 190, 1 RCT, RR 18.10 95% CI 1.06 to 309.15). Data for blurred vision, drooling, gastrointestinal distress, nasal congestion, urinary disturbance, and vomiting were not significantly different (Analysis 1.9).

1.3.2 Cardiovascular effects

No significant differences were found between fluphenazine and placebo for dizziness/ faintness/weakness (n = 190, 1 RCT), hypotension (n = 37, 1 RCT), syncope (n = 37, 1 RCT), or tachycardia (n = 37, 1 RCT, Analysis 1.10).

1.3.3 Central nervous system

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There is also some suggestion that fluphenazine increases a person's chance of experiencing some neurological symptoms such as drowsiness (n = 190, 1 RCT, RR 3.91 95% CI 1.98 to 7.71). Reports of headache did not reveal any significant differences between fluphenazine and placebo groups (n = 190, 1 RCT). Other outcomes, anxiety, convulsion/seizures, depression, sedation/lethargy were equivocal (Analysis 1.11).

1.3.4 Death

Only one study (Rifkin 1976) reported on the outcome of death, with one death occurring in the fluphenazine group during long-term follow-up (n = 50, 1 RCT, Analysis 1.12).

1.3.5 Endocrine

We found no statistically significant difference between fluphenazine and placebo for the outcomes of amenorrhoea (n = 190, 1 RCT), lactation (n = 190, 1 RCT) or swelling of the breasts (n = 190, 1 RCT) at short term (Analysis 1.13).

1.3.6 Extrapyramidal effects

In the short term, there is evidence that fluphenazine increases a person's chances of experiencing akathisia (n = 227, 2 RCTs, RR 3.43 95% CI 1.23 to 9.56), facial rigidity (n = 190, 1 RCT, RR 2.77 95% CI 1.03 to 7.46), ‘loss of associated movements’ (n = 190, 1 RCT, RR 6.39 95% CI 1.95 to 20.98), rigidity (n = 227, 2 RCTs, RR 3.54 95% CI 1.76 to 7.14) and tremor (n = 227, 2 RCTs, RR 3.19 95% CI 1.25 to 8.11). We found measures of akinesia, associated movements, dystonia and restlessness/insomnia were not significantly different from those allocated to placebo. Evidence in the medium term indicates that fluphenazine increases the likelihood of having parkinsonism (n = 50, 1 RCT, RR 5.50 95% CI 1.36 to 22.32), but akathisia, akinesia and dystonia were equivocal (Analysis 1.14).

1.3.7 Other

We did not find any statistically significant data for the outcomes of convulsion/seizures (n = 190, 1 RCT), diarrhoea (n = 190, 1 RCT), infection (n = 190, 1 RCT), or rash (n = 227, 2 RCTs, Analysis 1.16).

2. SENSITIVITY ANALYSES

2.1 Men and women

Three studies included either all male (Marder 1994) or all female (Hordern 1964; Millar 1963) participants. However, only Marder 1994 reported data for any of our primary outcomes; therefore, a sensitivity analysis was not possible for this comparison. Note HM: this section is repeated below.

2.2 People who are under 18 years of age, between 18 and 64, or over 65 years of age

The age ranges of all participants across the included studies were all similar (between 16 and 58 years old). Where participants younger than 18 were included in the relevant studies (the youngest being 16 years old in Goldberg 1964, and 17 years old in Rifkin 1976), it was

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not possible to extract their data from the individual reports. Therefore, a sensitivity analysis has not been undertaken.

2.3 Chronic versus acutely ill people (< one month in duration)

Limited data were available from only one study. Participants who were chronically ill did not leave the study early in greater numbers than acutely ill patients. We found relapse did occur more often in the placebo arm of those chronically ill compared with those acutely ill, but the sample sizes were small and uneven and more data are required to draw any inferences (Analysis 1.17).

2.4 Low doses (1-5 mg/day) and high doses (over 5 mg/day)

Again, limited data were available, but it is suggested that there is little difference between levels of improvement between participants in studies that used either a high dose (15 mg/day used in Carpenter 1999; n = 38, 1 RCT) or a flexible dose regimen in the short term (2-10 mg/day in Clark 1971; or up to 14 mg/day in Hordern 1964; n = 87, 2 RCTs, Analysis 1.18).

2.5 Diagnosed according to any operational criterion versus those with loosely defined illness

It is indicated that there is again little difference in results for no improvement when participants have been diagnosed according to operational criteria (DSM-III-R, n = 38, 1 RCT) or with loose diagnostic criteria or definitions (n = 87, 2 RCTs, Analysis 1.19).

2.6 Studies published before 1990 versus studies published between 1990 and the present

Data were available for the outcomes of ‘no global improvement’ in the short term. There were no clear differences between the results of earlier studies and those published in the last 16 years (Analysis 1.20).

2.7 Implication of randomisation

Only one study was rated as a low risk of bias for adequate randomisation (Clark 1971); results for the primary outcome of global state (not improved or worse) remain the same when all other studies that implied randomisation were removed from the meta-analysis (n = 37, 1 RCT, RR 0.59, 95% CI 0.24 to 1.42). For the other secondary outcomes of adverse effects; the effect of removing the other studies that were meta-analysed with Clark 1971 and implied as being randomised is that data are no longer statistically significant for short-term extrapyramidal akathisia (from P = 0.02 to P = 0.18), or tremor (P = 0.01 to P = 0.09).

2.8 Assumptions for lost binary data

There were no clear differences between the results when completer-only data were used compared to data assumed for those lost to follow-up.

2.9 Risk of bias

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Each included study was rated as a '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. The result of excluding each study on this basis leaves us with no data to compare, therefore a sensitivity analysis was not possible.

2.10 Imputed values

We also sought 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 cluster-randomised trials. However, we encountered no such studies.

2.11 Fixed-effect and random-effects

We found that there was no difference in the results when synthesising data for the primary outcome of global state (not improved or worse) using a random-effects model. However, for short-term extrapyramidal effects (tremor), when using a random-effects model, results were no longer statistically significant (from P = 0.01 to P = 0.07).

DISCUSSION

Summary of main results

1. COMPARISON ONE: ORAL FLUPHENAZINE versus PLACEBO

1.1 Global State

1.1.1 No improvement

There were few data available for global improvement. Data were only obtained from three studies, and both short-term and medium-term assessment did not reveal any significant differences between fluphenazine and placebo, although a trend may be evident from the graphical representations of the data, suggesting that oral fluphenazine is superior to placebo, and perhaps this would have clearly emerged if larger and longer studies were used.

1.1.2 Relapse

There are surprisingly little data regarding relapse but the strongest results come from a small study with a duration of one year (Rifkin 1976), however, there was substantial heterogeneity present, perhaps due to the difference between the participant population and stages (remitted, non-psychotic participants in Rifkin 1976, and participants with at least two episodes of acute schizophrenia or continuing psychotic symptoms in previous two years in Marder 1994). A larger sample size would have probably ensured more unequivocal data in favour of fluphenazine.

1.2 Leaving study early

The finding that using fluphenazine resulted in more people staying in the study could be seen as heartening. Perhaps a genuine decrease in the distressing symptoms of schizophrenia

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leads to an increased concordance with medication, despite the unpleasant adverse effects of this drug.

1.3 Mental state

In spite of more than five decades of research on this benchmark antipsychotic treatment, very little can be said from trials regarding its direct effect on mental state regarding general or specific symptoms of schizophrenia.

1.4 Adverse effects

Although we were able to include a few studies in this review, clinicians will not be surprised that fluphenazine produces acute extrapyramidal disorders; dystonia, parkinsonism, akathisia, tremor, rigidity, weakness and anticholinergic effects. This Cochrane review, however, is a rare report of the best available and quantitative data on a compound over half a century old. Estimates of the incidence of extrapyramidal disorders, however, are not available from this review, as these necessitate a long follow-up period that was only attempted in a few trials. It may be surprising that there was only one death incident reported among over 439 people with schizophrenia who were randomised to oral fluphenazine or placebo. The lifetime incidence of suicide for people suffering from schizophrenia is 10% to 13% (Caldwell 1992). The occur-rence of only one death indicates that either trial-care is more vigilant than routine care or that death is an under-reported outcome.

2. SENSITIVITY ANALYSES

As we knew would be likely from the start, the power to detect a real difference between studies in any one of the sensitivity analyses was very low. Only subsets of already limited lists of trials were available. The wide confidence intervals could be hiding true differences in effect between the acutely and chronically ill people, and early trials versus current studies.

Overall completeness and applicability of evidence

1. Generalisability

This work includes studies that span nearly four decades of evaluative studies within psychiatry. It is possible that the rigour of these experiments has changed over time, as have the participants. There is some empirical evidence that the quality of schizophrenia trial reporting has not changed much over time (Thornley 1998) or, if it has changed, it may even have deteriorated (Ahmed 1998). We have found no time-related differences in reporting of studies within this review and no suggestion of a change of the effect size over time. We identified trials by meticulous searching; nevertheless, for a compound formulated so long ago, publication biases may be difficult to avoid. The strength of this review is that it presents up-to-date quantitative data for a benchmark treatment for schizophrenia which is used throughout the world.

2. Applicability

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The seven included studies involve many people who would be recognisable in everyday practice. There are those with strictly diagnosed illnesses, very likely to suffer from schizophrenia, and people whose illness was diagnosed using less rigorous criteria. The dose of fluphenazine in the studies included in this review could be considered standard (mean 8.2 mg/day SD 3.9). Although the outcomes that have been used in this review are accessible to both clinicians and recipients of care, generalising to treatment in community settings, could be problematic. Four studies were undertaken in hospital and three in the community, which is where most people with schizophrenia now reside.

3. Heterogeneity

Two outcomes were heterogeneous, but all other outcomes were homogeneous. However, no more than five studies were pooled so the chances of data being heterogeneous were always small. In addition, several methods were used to observe different adverse effects e.g. tremor and blurred vision. This made analyses and interpretation for the results even more difficult.

4. Limited data

Data were often inadequately reported and rendered many outcomes unusable. Most trials report only six- to 12-week outcomes for a mostly lifelong illness. No studies reported on service utilisation, economic outcomes, or on satisfaction with care.

Quality of the evidence

Generally, the quality of the available evidence was rated as either *very low*, *low* to *moderate* (See Summary of findings for the main comparison). This was largely due to the age of the included studies and poor reporting standards, some of which were published up to 50 years ago, pre-dating the CONSORT statement (Moher 2001; Schulz 2010). Missing or unreported outcomes were common, which restricted the amount of evidence available for use in this systematic review and data that may have been relevant in meta-analysis. Any future studies in this area must adhere to CONSORT principles, ensuring that all trials are transparently reported, that all tables and figures express what data they are presenting, so that no trials can reach publication without revelation of methodological inadequacies. A flow diagram should also be used in order to document the process in which participants are recruited to those that are ultimately followed-up, promoting completeness, clarity and transparency of reporting.

Potential biases in the review process

The review authors sought to adhere to the protocol, through the independent inspection of citations and full articles of potentially relevant studies. Furthermore, the review authors independently extracted data onto standard simple forms; however, we met for discussion where inconsistencies or disagreements arose regarding the available data.

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Agreements and disagreements with other studies or reviews

We are not aware of other systematic reviews evaluating the effects of oral fluphenazine versus placebo in the treatment of schizophrenia.

AUTHORS 'CONCLUSIONS

Implications for practice

1. For people with schizophrenia

Many people with schizophrenia and their non-professional carers recognise psychotic symptoms as phenomena generated by a damaging and pernicious illness and may see the effect of fluphenazine, as demonstrated within this review, as positive. Others may consider these data as supporting well-publicised objections to the use of drugs; drugs potent in their ability to cause unpleasant adverse effects, and to potentially erode a person's ability to make informed decisions.

2. For clinicians

This review will confirm much that clinicians already know, but it does provide some quantification to support clinical impression. Fluphenazine is an antipsychotic, prone to cause a variety of extrapyramidal and anticholinergic effects. Evidence about its short-term antipsychotic effect is weak. However, fluphenazine is a low-cost and widely available choice for the clinician. Despite its many adverse effects, fluphenazine is likely to remain one of the most widely used treatments for schizophrenia worldwide.

3. For managers or policy makers

Fluphenazine is widely available and inexpensive. It is understandable that it remains one of the many drugs used for treating people with serious mental illnesses. However, some of fluphenazine's adverse effects could be expensive in terms of human suffering and cost of treatment. It could, therefore, be more beneficial to use another drug if the latter was equally potent, but had a more favourable adverse-effect profile.

Implications for research

1. General

So much more could have been learnt about the effects of oral fluphenazine if the studies in this review had clearly described the method of allocation and the integrity of blinding; especially for the more subjective outcomes. Most included studies, however, predated the CONSORT statement (Moher 2001). Concrete and simple outcomes are of interest. For example, clearly reporting improvement, 'number of violent incidents', 'relapse' (giving some description of criteria), 'hospital discharge or admission', and 'presence of delusions or hallucinations' would have been helpful, and simple reporting of levels of satisfaction and quality of life would have been very informative.

2. Specific

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Even though fluphenazine has been used as an antipsychotic drug for decades, there are still a surprisingly small number of well-conducted randomised, placebo-controlled trials measuring its efficacy and potential to cause adverse effects. The use of oral fluphenazine for millions of people is based on clinical experience rather than the poorly reported trials that involve, in total, only a few hundred participants. Clinicians and researchers are mainly satisfied with the current levels of understanding, and, therefore new studies evaluating oral fluphenazine versus placebo will be very rare. The fluphenazine story is, however, incomplete. Questions remain regarding the effect of this drug on mental state and long-term extrapyramidal effects. One or more large, methodologically sound, randomised, placebo-controlled trials could help answer these questions. With the advent of universally available effective, even moderately effective, antipsychotic drugs, the day for studies comparing oral fluphenazine with placebo has passed.

Date	Event	Description
9 July 2013	New citation required but conclusions have not changed	No new conclusions made to the review after results of 2012 update search added
18 March 2013	New search has been performed	Review update completed: seven new studies identified in update search, each of which was excluded with reasons. ‘Summary of findings’ table added to grade the quality of the evidence. New format ‘Risk of bias’ tables have been constructed, with new ratings applied

Date	Event	Description
15 May 2012	Amended	Update search of Cochrane Schizophrenia Group's Trial Register (see Search methods for identification of studies). 7 studies added to awaiting assessment
5 October 2011	Amended	Contact details updated.
4 August 2010	Amended	Contact details updated.
15 February 2010	Amended	Contact details updated.
13 August 2008	Amended	Contact Author details updated
25 April 2008	Amended	Converted to new review format.
14 November 2006	New citation required and conclusions have changed	Substantive amendment

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The Cochrane Schizophrenia Group produce and maintain a template for the methods section of their reviews. We have used this template and adapted it for our requirements.

SOURCES OF SUPPORT

Internal sources

• No internal sources of support provided, Not specified.

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External sources

• National Institute for Health Research (NIHR), UK.

UK Cochrane Collaboration Programme Grant 2011; Reference number: 10/4001/15

APPENDICES

Appendix 1. Previous search strategy

1. Cochrane Schizophrenia Group's trials register (September 2006)

We searched the Cochrane Schizophrenia Group's trials register (September 2006) using the phrase: [((fluphen* or flufen* or modec* or moditen* or eutimax* or prolixin* or siqualon* or anaten* or dapotum* or decazate* or decafen* or decentan* or fludecate* or lyogen* or lyoridin* or mirenil*) in title, abstract and index fields in REFERENCE) OR (fluphenazin* in interventions field in STUDY)]

The Cochrane Schizophrenia Group's Trials Register is compiled by systematic searches of major databases, handsearches and conference proceedings (see group module).

Appendix 2. Previous data collection and analysis section

1. Selection of trials

We (HEM, MQA) independently inspected the citations identified from the search. We identified potentially relevant abstracts and ordered full papers to reassess these for inclusion and methodological quality. We discussed and reported any disagreements. **2. Assessment of methodological quality**

We assessed the methodological quality of included trials in this review using the criteria described in the Cochrane Handbook (Higgins 2005). These criteria are based on the evidence of a strong relationship between allocation concealment and direction of effect (Schulz 1995), and define the following categories: A. Low risk of bias (adequate allocation concealment) B. Moderate risk of bias (some doubt about the results) C. High risk of bias (inadequate allocation concealment). For the purpose of the analysis in this review, trials were included if they met the Cochrane Handbook criteria A or B.

Only trials falling in category A or category B were included in this review. **3. Data collection**

3.1 Data extraction

We (HEM and MQA) independently extracted data and, where further clarification was needed, the authors' of trials were contacted to provide missing data. Any disagreements were discussed and the decisions documented. 3.2 Intention to treat analysis

Where people were lost to follow-up at the end of the study, it was assumed that they had a poor outcome and once they were randomised they were included in the analysis (intention-to-treat (ITT) analysis).

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4. Data synthesis

4.1 Data types: We assessed outcomes using continuous (e.g. average changes on a behaviour scale), categorical (e.g. one of three categories on a behaviour scale, such as ‘little change’, ‘moderate change’ or ‘much change’) or dichotomous measures, e.g. either ‘no important changes’ or ‘important changes’ in a person's behaviour. RevMan software does not currently support categorical data, so we only presented these in the text of the review.

4.2 Dichotomous - yes/no - data

Where the original authors of the studies gave outcomes such as ‘clinically improved’ or ‘not clinically improved’ we recorded this. If possible, we attempted to convert relevant outcome measures to dichotomous data by identifying cut off points on rating scales and dividing people accordingly into ‘clinically improved’ or ‘not clinically improved’. For example, the Brief Psychiatric Rating Scale (BPRS) (Overall 1962) is used frequently as a measure of change of symptoms in studies. We defined a 50% change on this particular scale as clinically important although it was recognised that for many people, especially those with chronic or severe illness, a less rigorous definition of important improvement (e.g. 25% on the BPRS) would be equally valid. If individual patient data were available, we used the 50% cut-off for the definition in the case of non-chronically ill people and 25% for those with chronic illness. For dichotomous data we estimated fixed-effect (FE) relative risk (RR) with a 95% confidence interval (CI), and calculated the number needed to treat/ harm (NNT/H) statistic. If heterogeneity was found (see section 5) we used a random-effects model.

4.3 Continuous data: We excluded continuous data if more than 50% of people were lost to follow-up. Continuous data were reported as presented in the original studies, without making any assumptions about those lost to follow-up.

4.3.1. Skewed data: Continuous data on mental health outcomes are often not ‘normally’ distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we applied the following standards to all data before inclusion: (a) standard deviations (SD) and means were reported in the paper or were obtainable from the authors, (b) when a scale started from a finite number (such as zero), the SD, when multiplied by two, was less than the mean (as otherwise the mean was unlikely to be an appropriate measure of the centre of the distribution - (Altman 1996). Endpoint scores on scales often have a finite start and end point and this rule can be applied to them. However, we reported data not meeting these standards in the text of the results section if they had been analysed with appropriate nonparametric tests. Scale-derived change data were reported if no endpoint data were available. Their normality cannot be tested as above, despite the distinct possibility of skew.

4.3.2. Rating scales: a wide range of instruments are available to measure outcomes in mental health studies. These instruments vary in quality and many are not validated, or are even ad hoc. It is accepted generally that measuring instruments should have the properties of reliability (the extent to which a test effectively measures anything at all) and validity (the extent to which a test measures that which it is supposed to measure) (Rust 1989). Unpublished scales are known to be subject to bias in trials of treatments for schizophrenia

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(Marshall 2000). Therefore, we only included continuous data from rating scales if the measuring instrument had been described in a peer-reviewed journal. In addition, we set the following minimum standards for instruments: The instrument should either be (a) a self-report or (b) completed by an independent rater or relative (not the therapist) and (c) the instrument should be a global assessment of an area of functioning.

4.3.3 Summary statistic: For continuous outcomes we estimated the weighted mean difference (WMD) between groups. Again, if heterogeneity was found (see section 5) we used a random-effects model.

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

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

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

5. Investigation for heterogeneity

We judged clinical heterogeneity within all comparisons between included studies, and visually inspected graphs in order to investigate the possibility of statistical heterogeneity. This was supplemented by the I^2 statistic which provides an estimate of the percentage of variability due to heterogeneity rather than to chance alone. An I^2 estimate equal to or greater than or equal to 75% indicates the presence of high levels of heterogeneity (Higgins 2003). In such cases, we sought to remove outlying trial(s) and perform a sensitivity analyses both with and without these outlying trials. Where no obvious outlying trial(s) could be identified, we analysed and reported the result using a random-effects model, which takes into account that the effects being estimated are not identical.

6. Sensitivity analyses

We undertook several sensitivity analyses (see: Objectives).

7. General

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If possible, we presented data in the graphs so that a result to the left of the line of no effect favoured oral fluphenazine.

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* *Indicates the major publication for the study*

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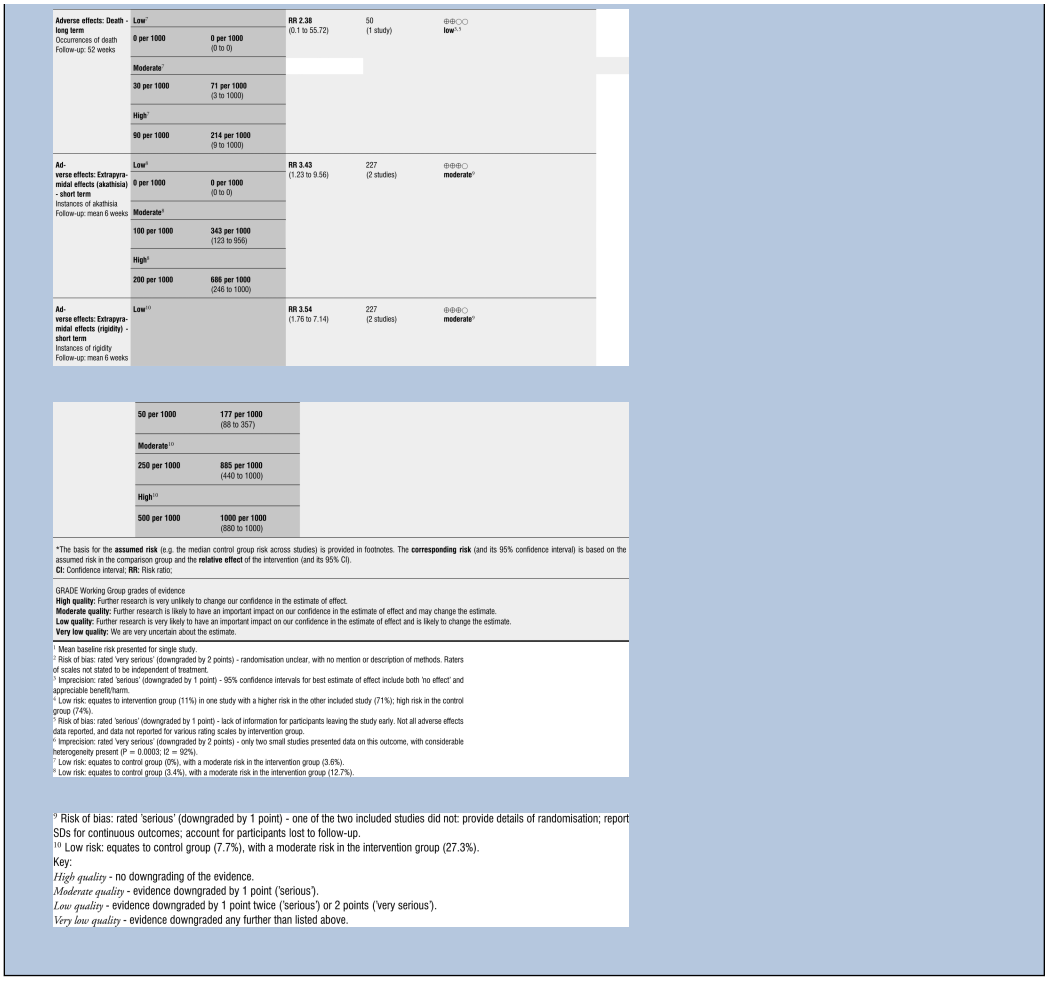
PLAIN LANGUAGE SUMMARY

Oral fluphenazine versus placebo for schizophrenia

Antipsychotic drugs are the first line and mainstay of treatment for schizophrenia. They help to effectively treat psychotic symptoms such as hearing voices and seeing things (hallucinations) and having strange beliefs (delusions). Fluphenazine was one of the first antipsychotics and has been available for around 50 years. Fluphenazine is inexpensive and in developing countries, may be one of the only drug treatments available. In most of Europe and North America, despite still being available, the arrival of newer antipsychotic drugs has reduced the use of fluphenazine and its market share. Fluphenazine has debilitating side effects, including: dizziness; movement disorders such as involuntary movements or spasms; shaking and tremors; inner restlessness and the inability to sit still; and problems with blood pressure, fever and muscle stiffness.

This review included seven studies and compared the effects of fluphenazine taken by mouth with placebo (‘dummy’ treatment). In the main, the findings of the review support the widespread view that fluphenazine is a potent and effective antipsychotic but has considerable side effects, other antipsychotic drugs may well be preferable. Fluphenazine is an imperfect treatment with serious side effects, so other inexpensive antipsychotic drugs with fewer side effects may be better for people with schizophrenia. Despite this, fluphenazine has a low cost and is widely available, so is likely to remain one of the most widely used treatments for schizophrenia worldwide. However, some of fluphenazine's side effects could be expensive in terms of human suffering and personal cost of treatment. Even though fluphenazine has been used as an antipsychotic drug for decades, there are still a surprisingly small number of well-conducted studies measuring its effectiveness and potential to cause side effects. Future large-scale research should report on important outcomes such as improvement in mental health, relapse, hospital discharge and admission, levels of satisfaction with treatment and quality of life.

This plain language summary has been written by a consumer Ben Gray from RETHINK.



Adverse effects: Death - long term Occurrences of death Follow-up: 52 weeks	**Low**[7]		**RR 2.38** (0.1 to 55.72)	50 (1 study)	⊕⊕◯◯ **low**[4,5]
	0 per 1000	**0 per 1000** (0 to 0)			
	Moderate[7]				
	30 per 1000	**71 per 1000** (3 to 1000)			
	High[7]				
	90 per 1000	**214 per 1000** (9 to 1000)			
Adverse effects: Extrapyramidal effects (akathisia) - short term Instances of akathisia Follow-up: mean 6 weeks	**Low**[8]		**RR 3.43** (1.23 to 9.56)	227 (2 studies)	⊕⊕⊕◯ **moderate**[9]
	0 per 1000	**0 per 1000** (0 to 0)			
	Moderate[1]				
	100 per 1000	**343 per 1000** (123 to 956)			
	High[8]				
	200 per 1000	**686 per 1000** (246 to 1000)			
Adverse effects: Extrapyramidal effects (rigidity) - short term Instances of rigidity Follow-up: mean 6 weeks	**Low**[10]		**RR 3.54** (1.76 to 7.14)	227 (2 studies)	⊕⊕⊕◯ **moderate**[9]
	50 per 1000	**177 per 1000** (88 to 357)			
	Moderate[10]				
	250 per 1000	**885 per 1000** (440 to 1000)			
	High[10]				
	500 per 1000	**1000 per 1000** (880 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] Mean baseline risk presented for single study.
[2] Risk of bias: rated 'very serious' (downgraded by 2 points) - randomisation unclear, with no mention or description of methods. Raters of scales not stated to be independent of treatment.
[3] Imprecision: rated 'serious' (downgraded by 1 point) - 95% confidence intervals for best estimate of effect include both 'no effect' and appreciable benefit/harm.
[4] Low risk: equates to intervention group (11%) in one study with a higher risk in the other included study (71%); high risk in the control group (74%).
[5] Risk of bias: rated 'serious' (downgraded by 1 point) - lack of information for participants leaving the study early. Not all adverse effects data reported, and data not reported for various rating scales by intervention group.
[6] Imprecision: rated 'very serious' (downgraded by 2 points) - only two small studies presented data on this outcome, with considerable heterogeneity present ($P = 0.003$; $I^2 = 92\%$).
[7] Low risk: equates to control group (0%), with a moderate risk in the intervention group (3.6%).
[8] Low risk: equates to control group (3.4%), with a moderate risk in the intervention group (12.7%).

[9] Risk of bias: rated 'serious' (downgraded by 1 point) - one of the two included studies did not: provide details of randomisation; report SDs for continuous outcomes; account for participants lost to follow-up.
[10] Low risk: equates to control group (7.7%), with a moderate risk in the intervention group (27.3%).
Key:
High quality - no downgrading of the evidence.
Moderate quality - evidence downgraded by 1 point ('serious').
Low quality - evidence downgraded by 1 point twice ('serious') or 2 points ('very serious').
Very low quality - evidence downgraded any further than listed above.

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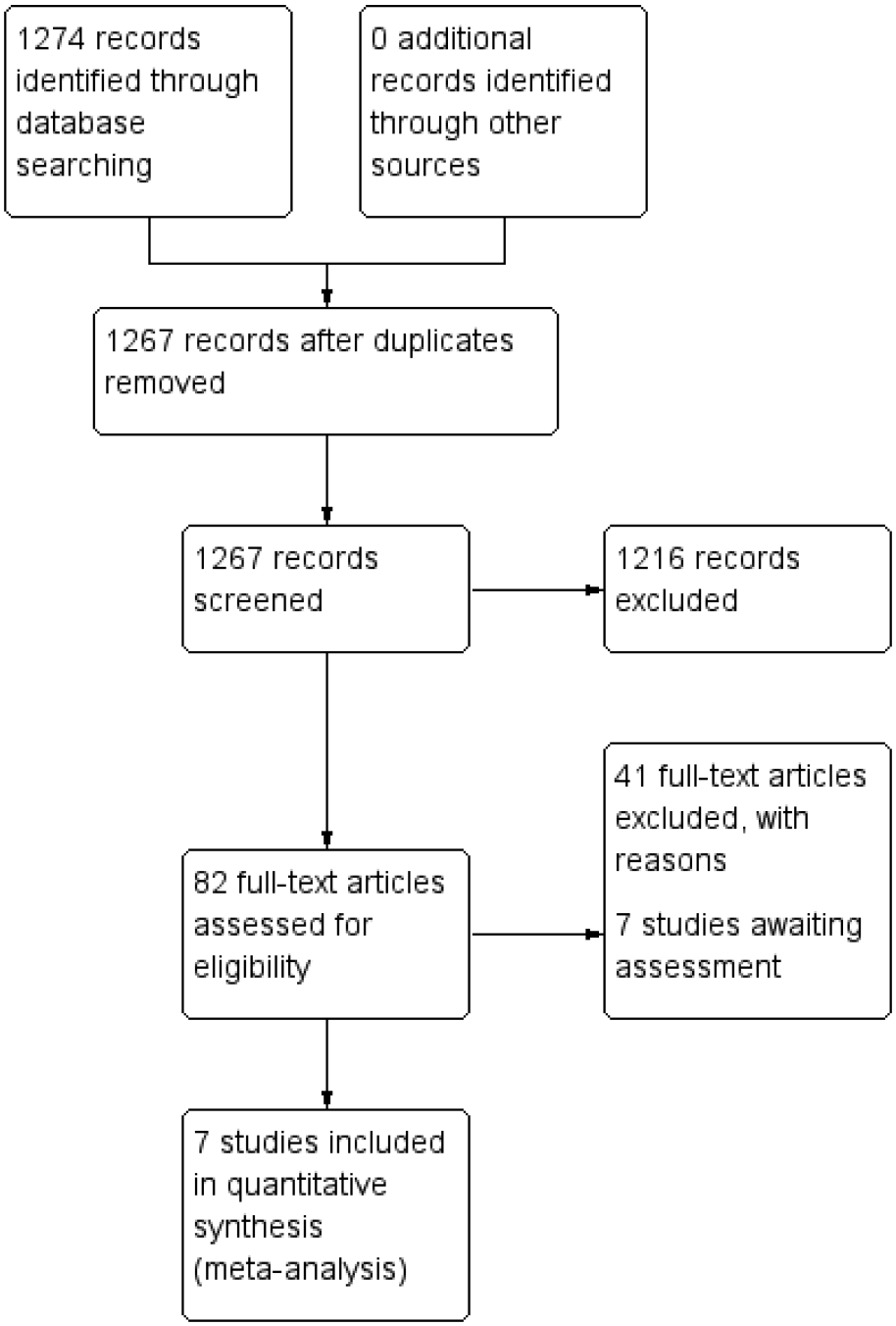

Figure 1.
Study flow diagram: 2006 search.

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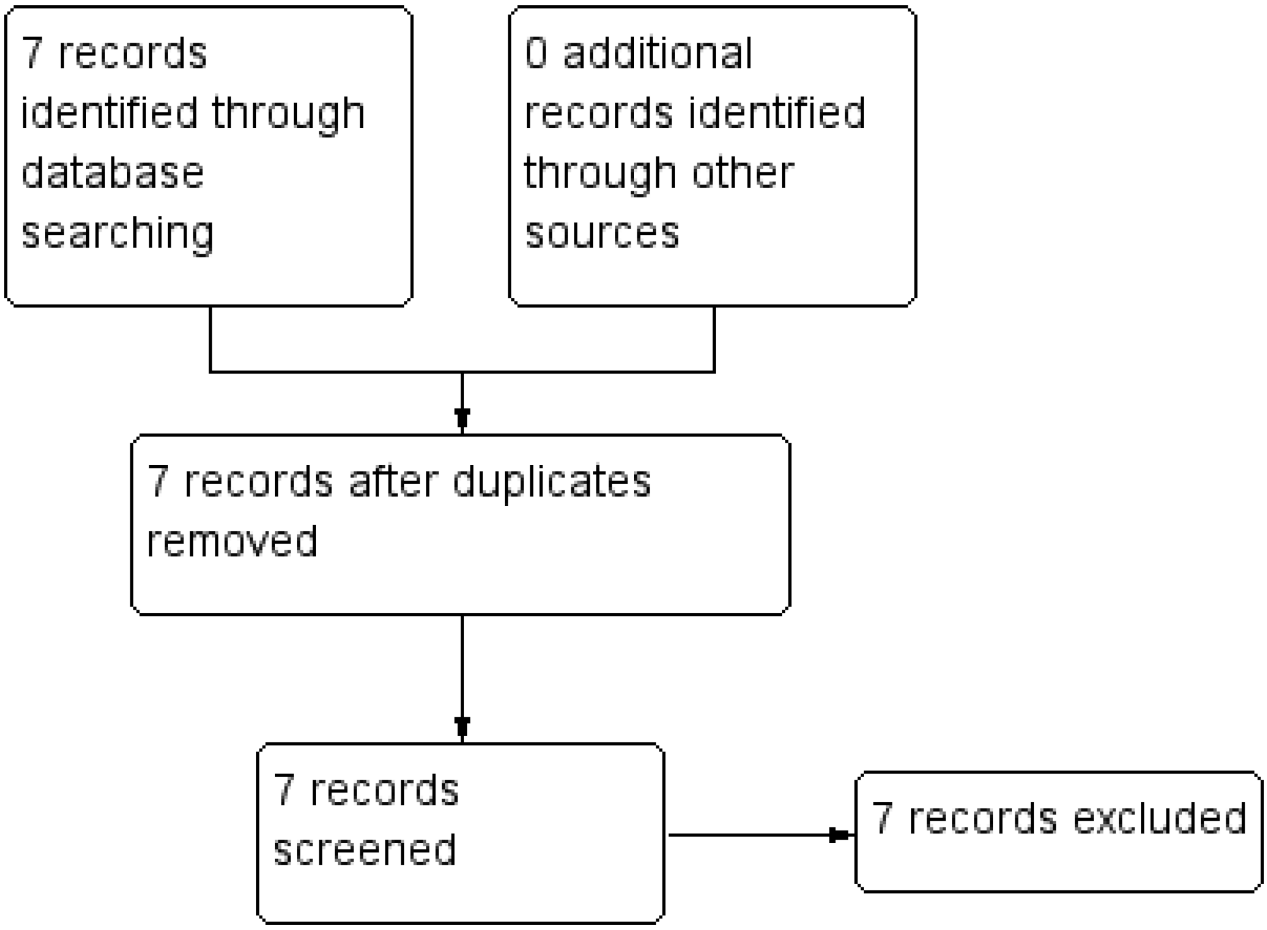

Figure 2.
Study flow diagram: 2012 update search (no additional studies).

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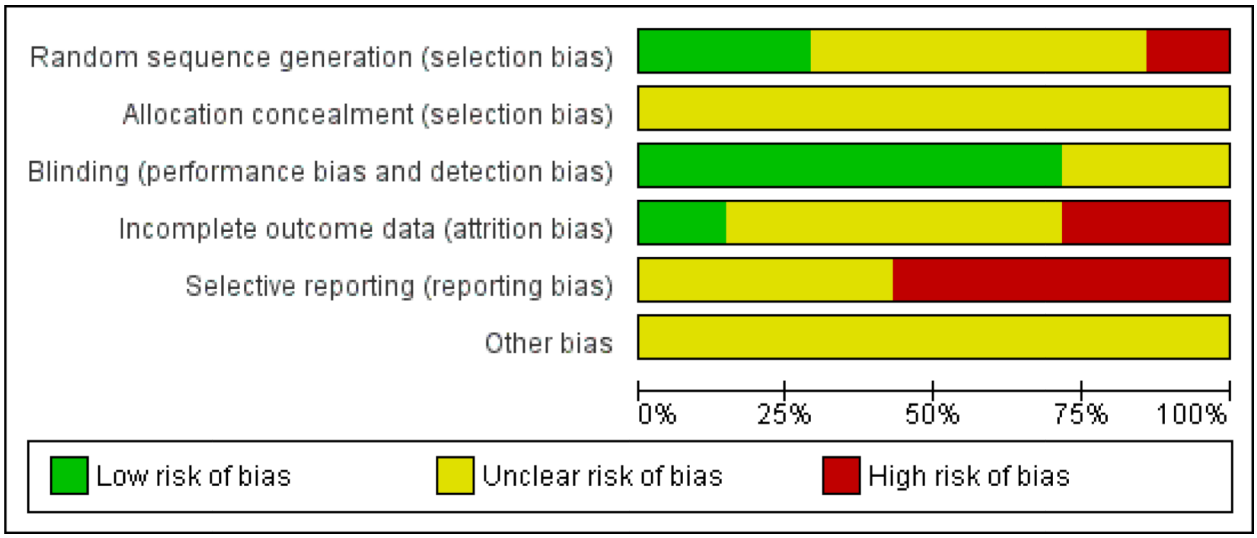

Figure 3.

'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

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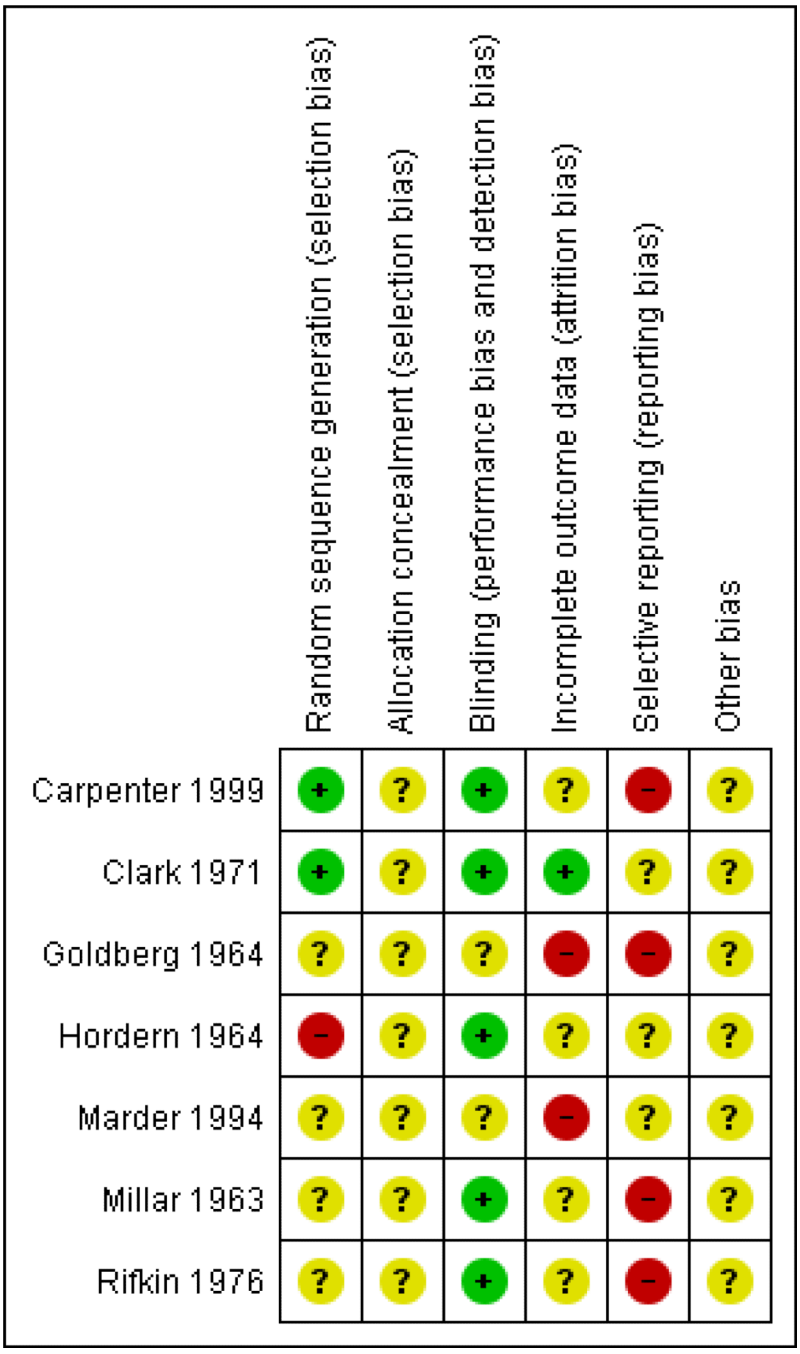

Figure 4.

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

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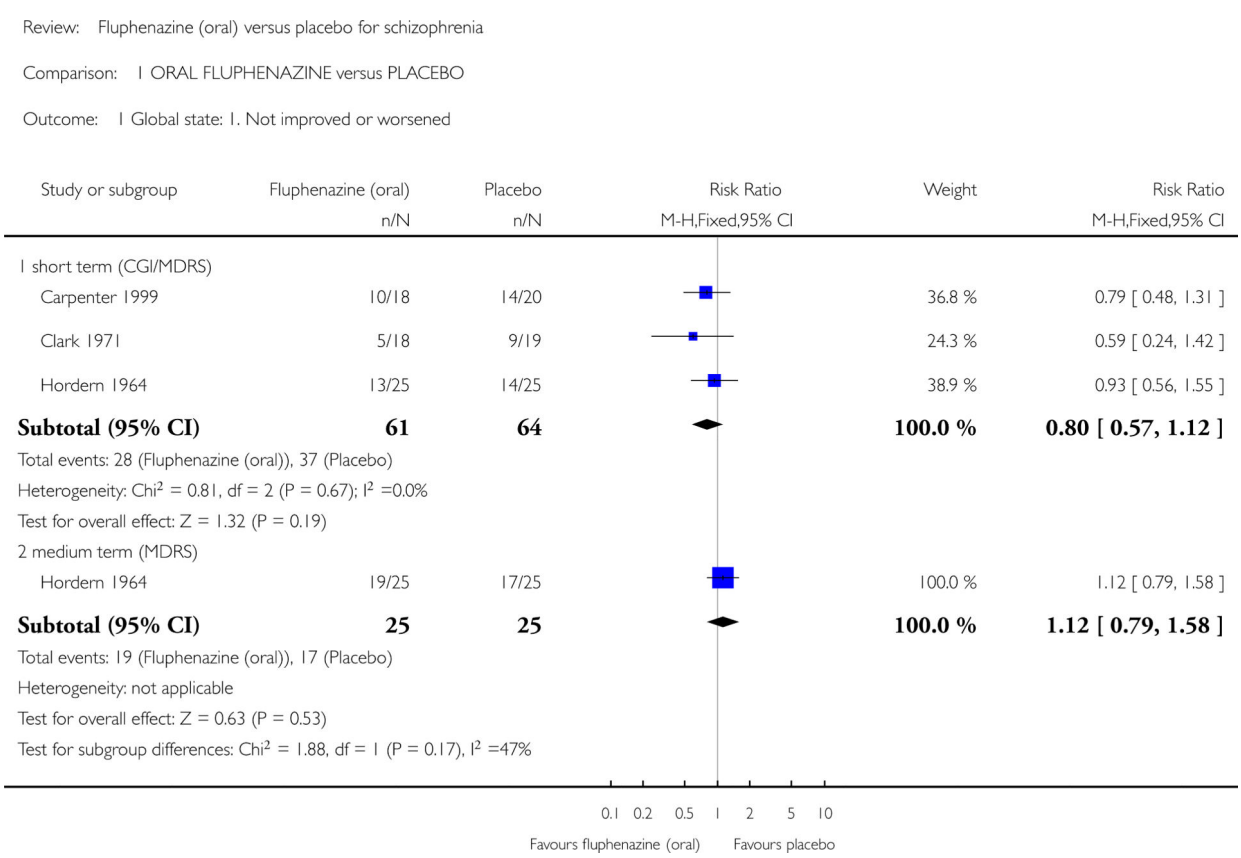

Analysis 1.1.

Comparison 1 ORAL FLUPHENAZINE versus PLACEBO, Outcome 1 Global state: 1. Not improved or worsened.

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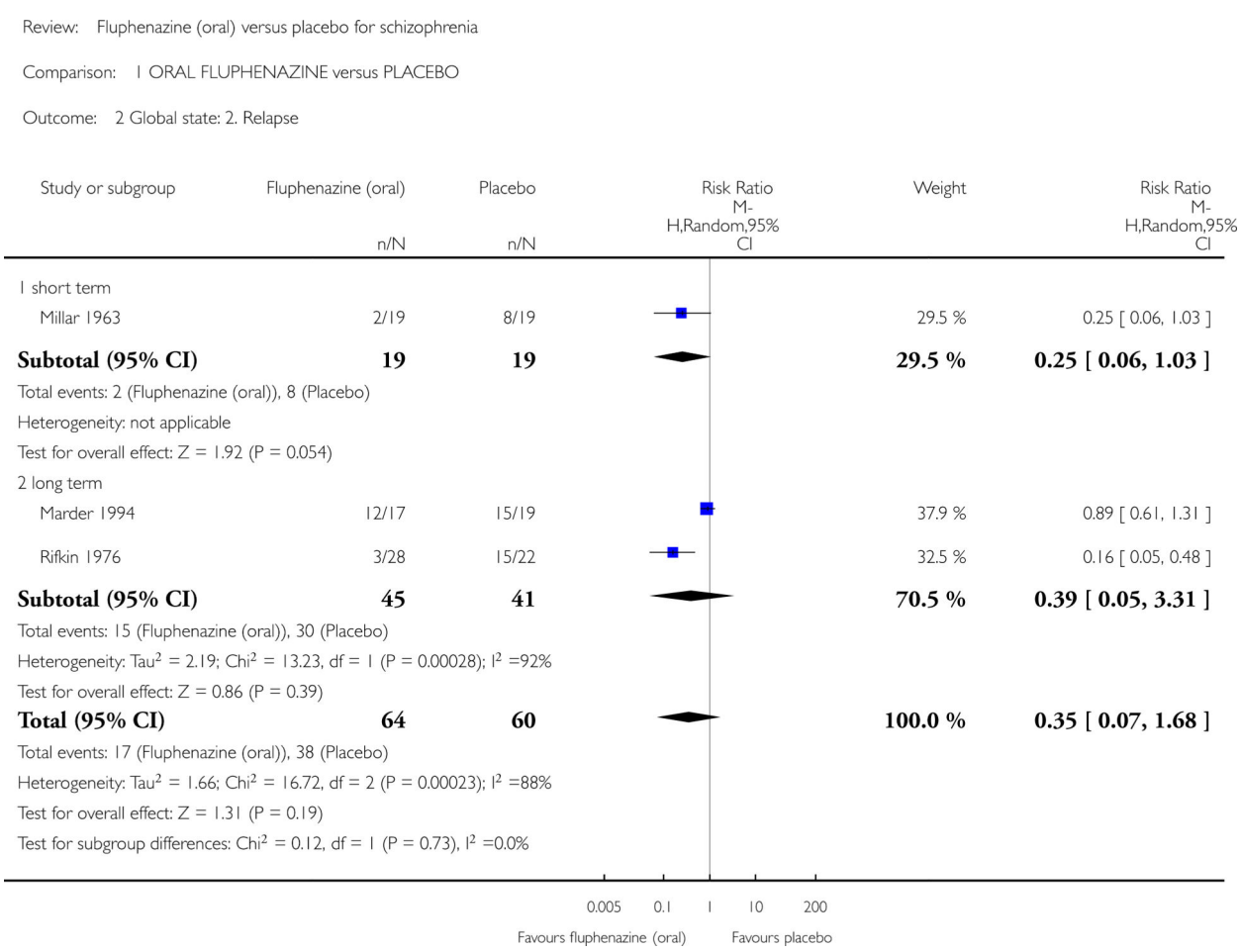
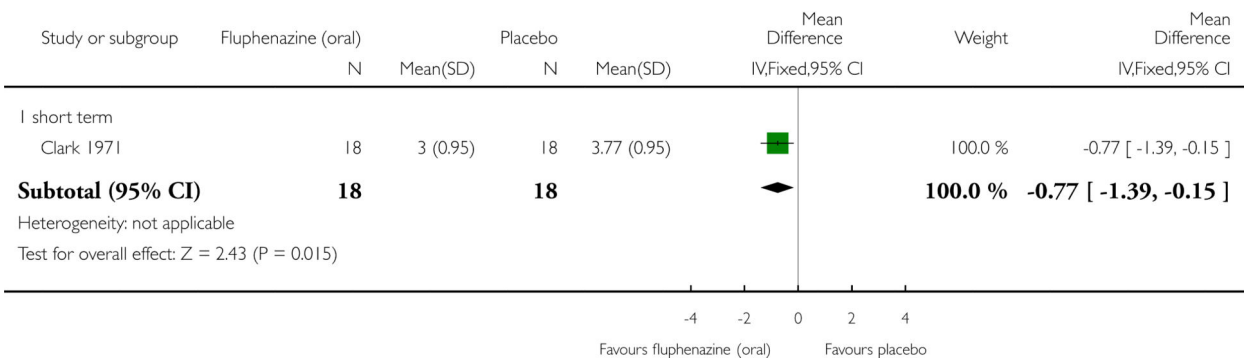


Analysis 1.2.
Comparison 1 ORAL FLUPHENAZINE versus PLACEBO, Outcome 2 Global state: 2. Relapse.



Analysis 1.5.

Comparison 1 ORAL FLUPHENAZINE versus PLACEBO, Outcome 5 Global state: 5. average score: CGI - severity of illness score (high = poor).

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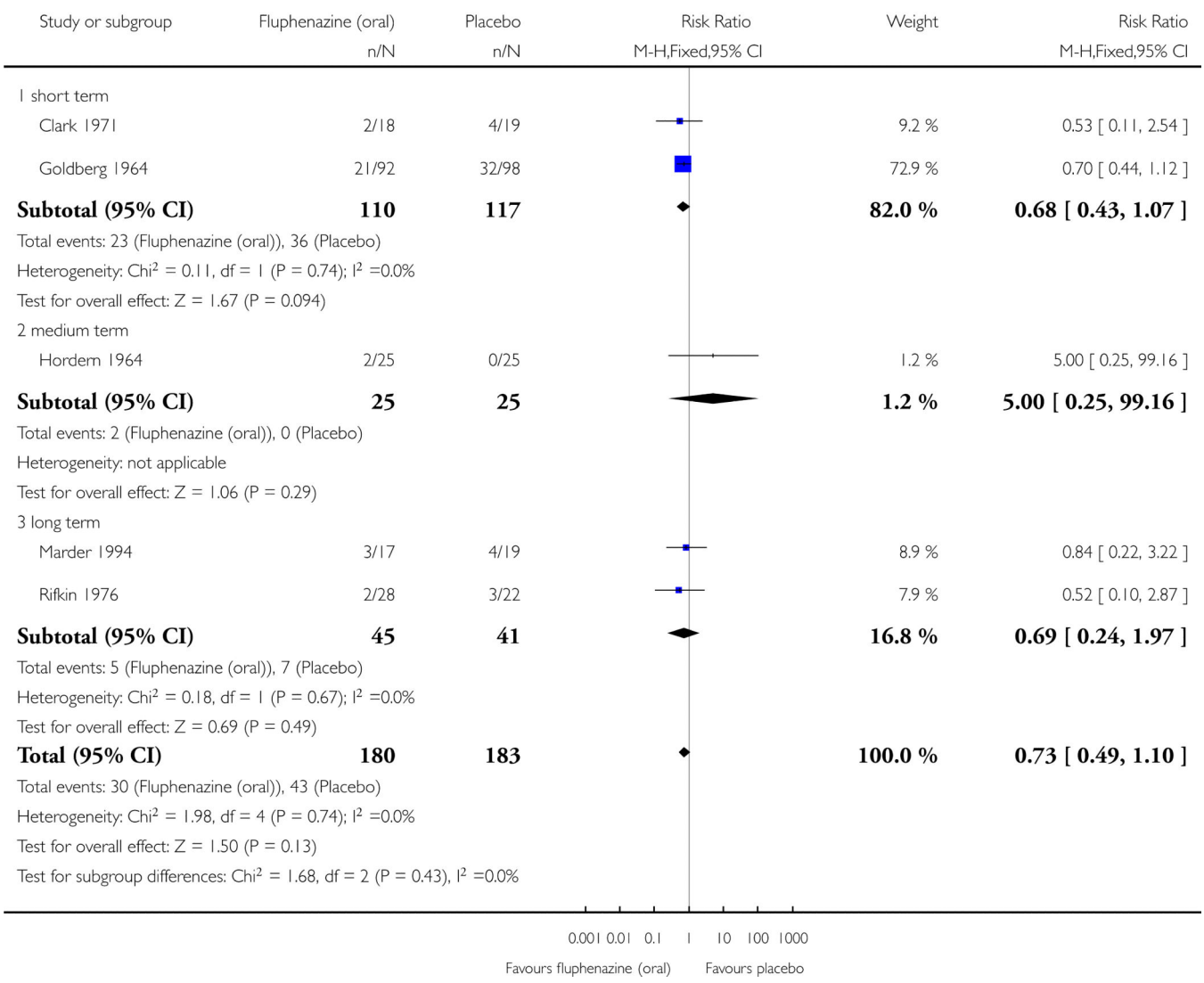
Review: Fluphenazine (oral) versus placebo for schizophrenia
Comparison: 1 ORAL FLUPHENAZINE versus PLACEBO
Outcome: 6 Leaving the study early: 1. Non-specific reasons



Analysis 1.6.

Comparison 1 ORAL FLUPHENAZINE versus PLACEBO, Outcome 6 Leaving the study early: 1. Non-specific reasons.

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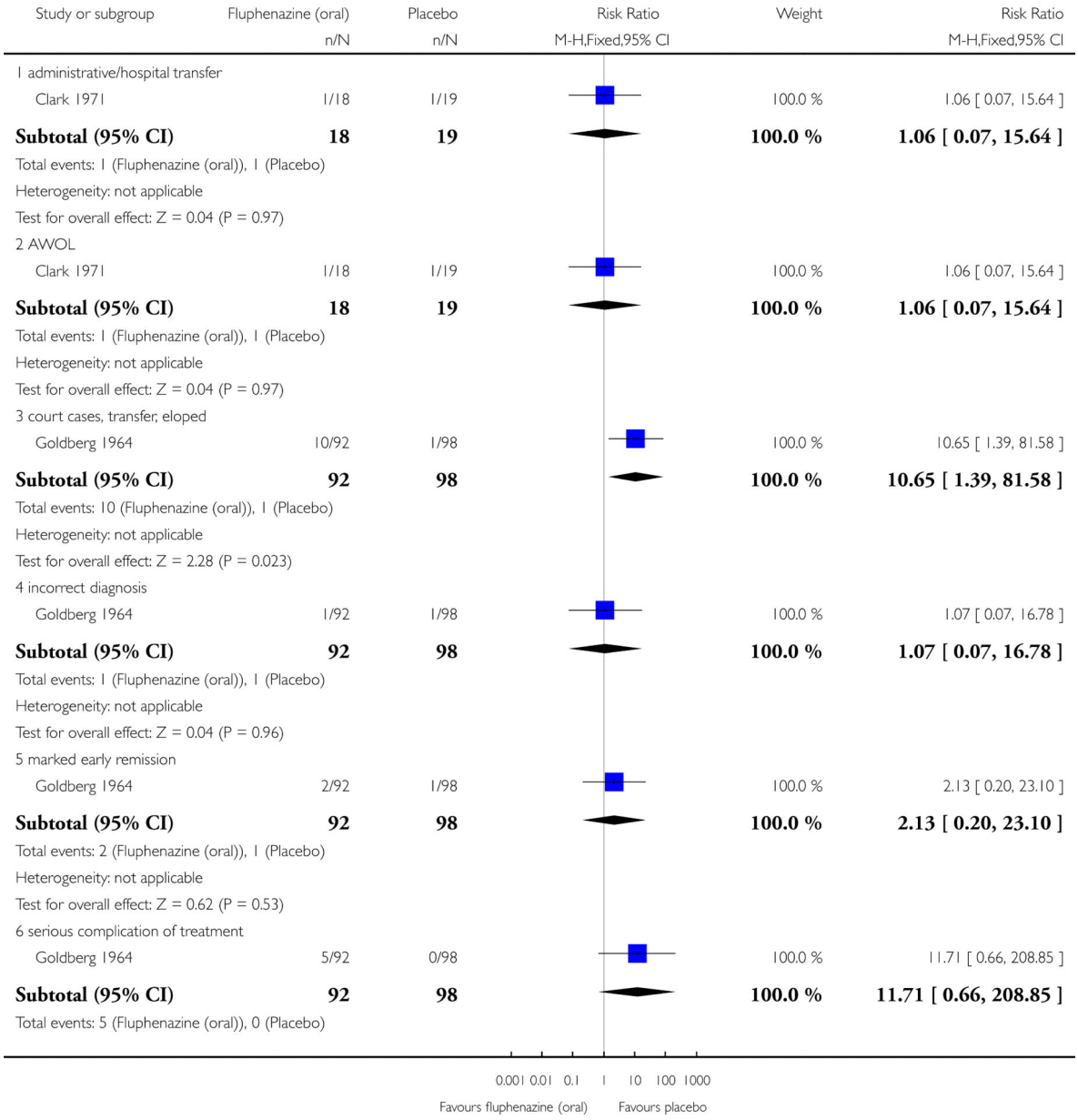
Review: Fluphenazine (oral) versus placebo for schizophrenia
Comparison: 1 ORAL FLUPHENAZINE versus PLACEBO
Outcome: 7 Leaving the study early: 2. Specific reason - short term



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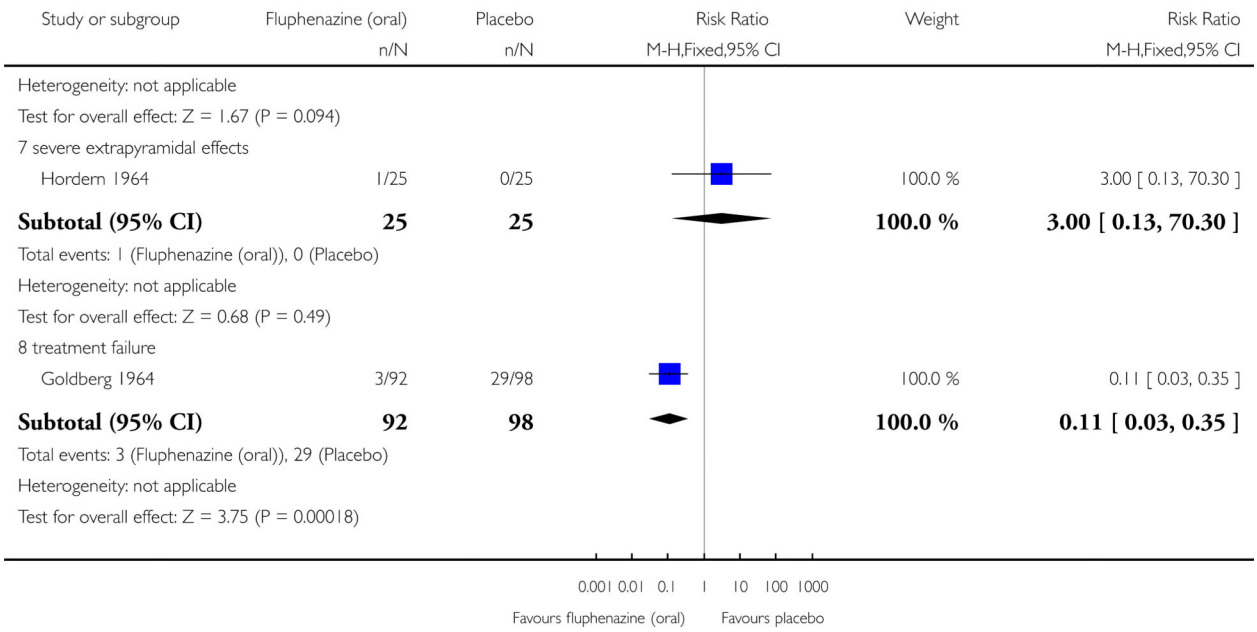

Analysis 1.7.

Comparison 1 ORAL FLUPHENAZINE versus PLACEBO, Outcome 7 Leaving the study early: 2. Specific reason - short term.

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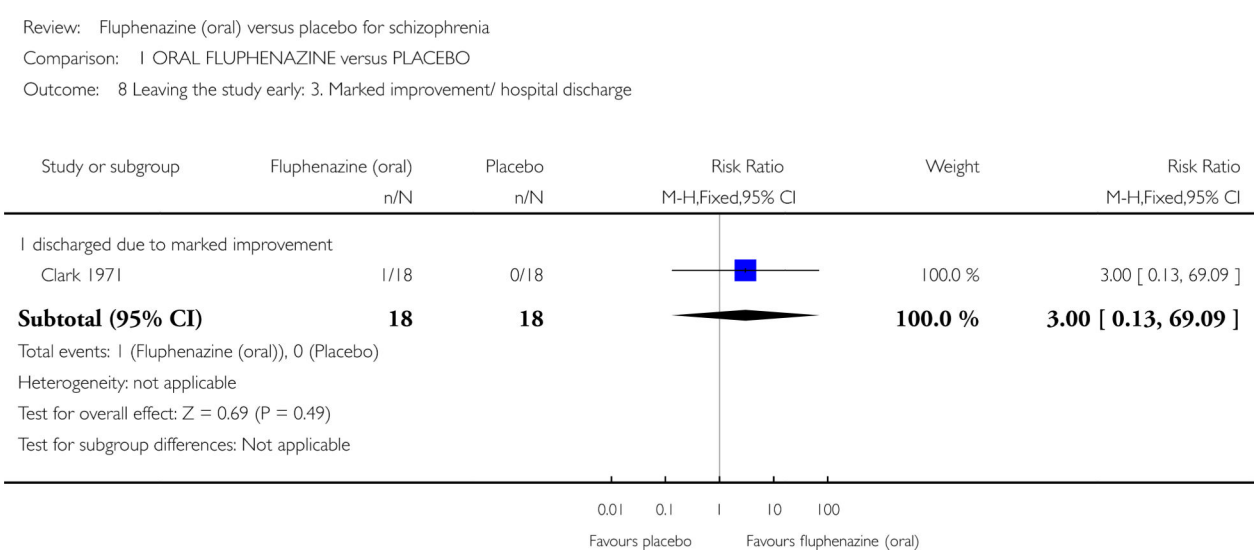

Analysis 1.8.

Comparison 1 ORAL FLUPHENAZINE versus PLACEBO, Outcome 8 Leaving the study early: 3. Marked improvement/ hospital discharge.

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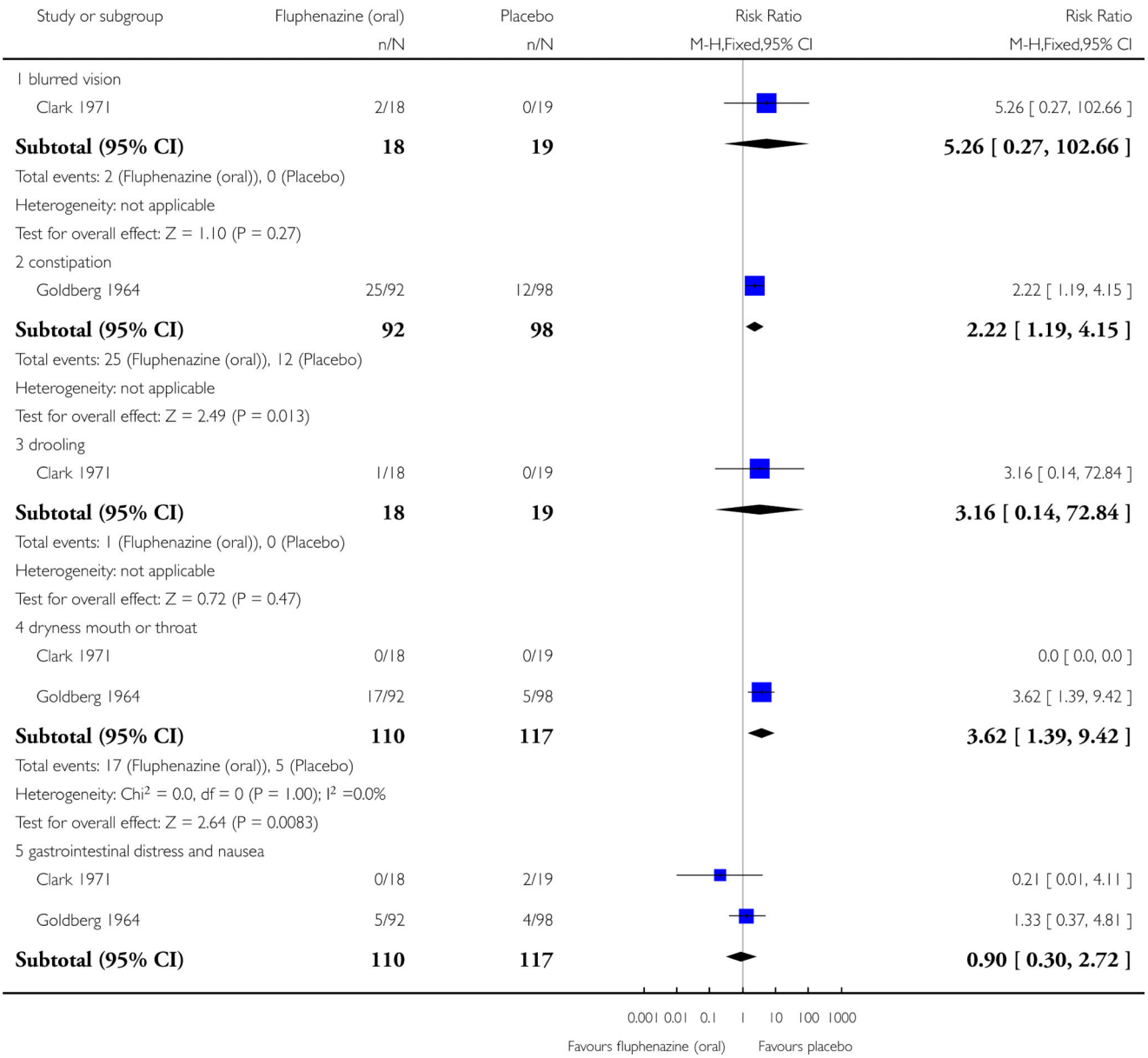
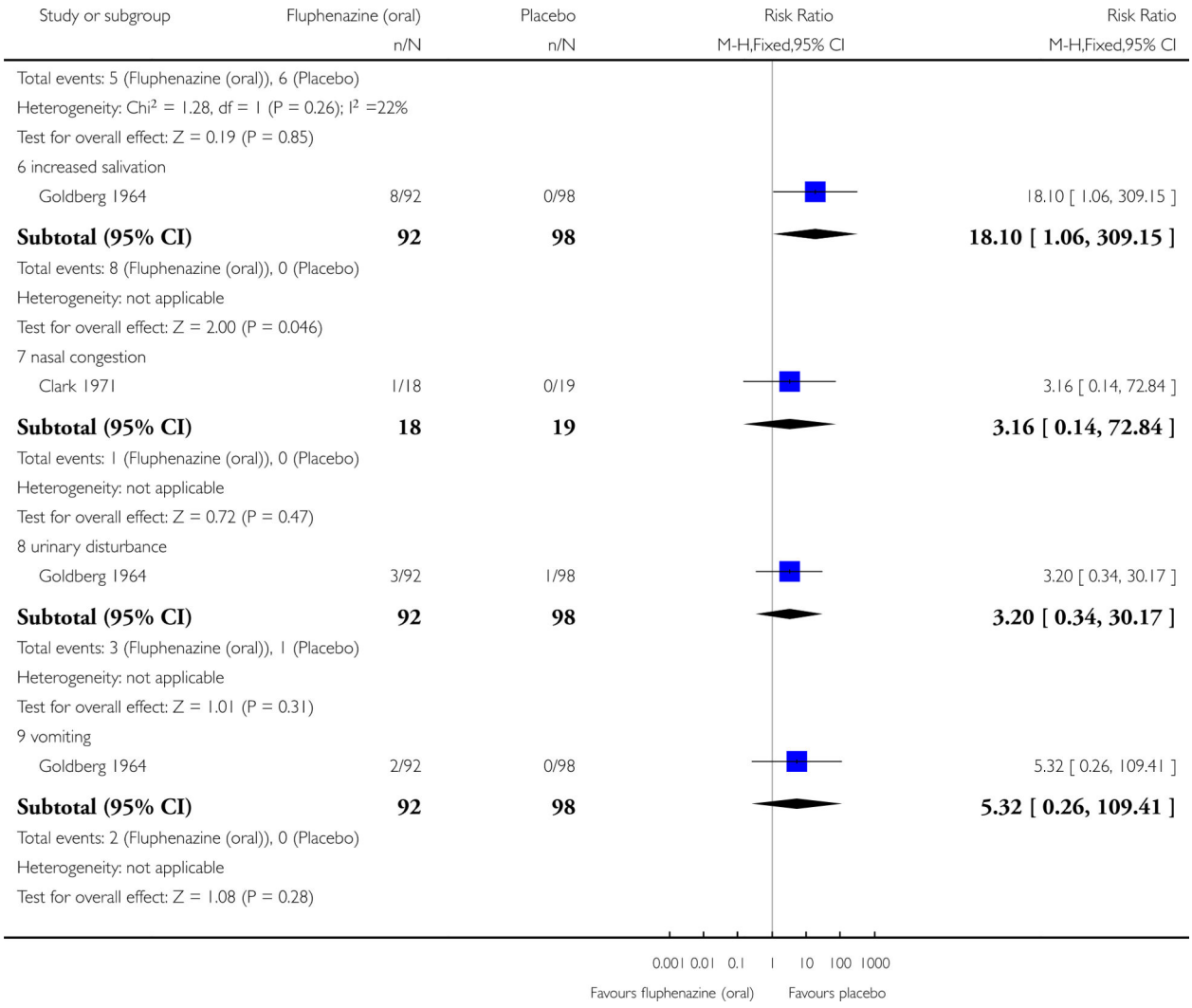
Review: Fluphenazine (oral) versus placebo for schizophrenia
Comparison: 1 ORAL FLUPHENAZINE versus PLACEBO
Outcome: 9 Adverse effects: 1. Anticholinergic effects - short term





Analysis 1.9.

Comparison 1 ORAL FLUPHENAZINE versus PLACEBO, Outcome 9 Adverse effects: 1. Anticholinergic effects - short term.

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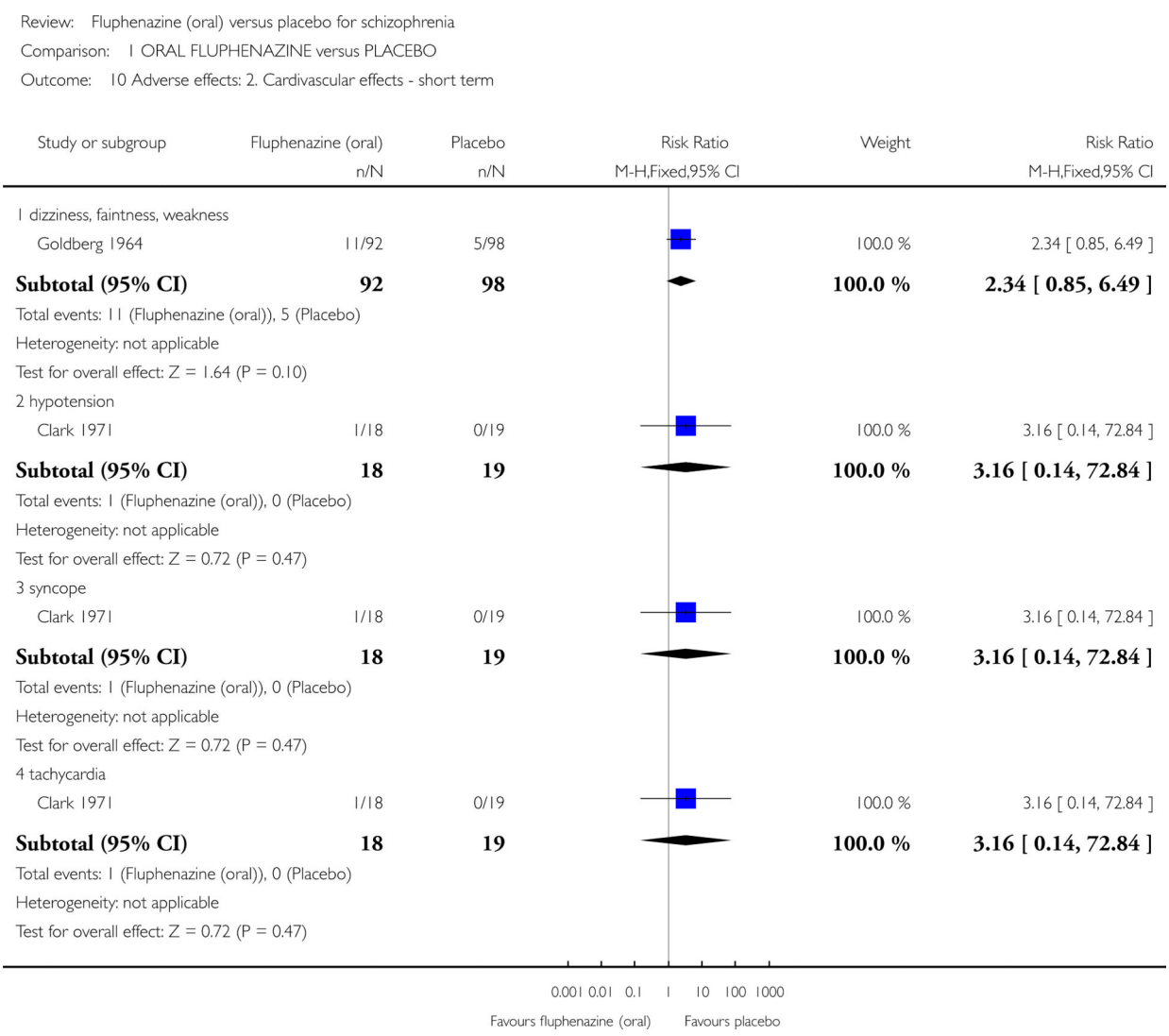

Analysis 1.10.

Comparison 1 ORAL FLUPHENAZINE versus PLACEBO, Outcome 10 Adverse effects: 2. Cardivascular effects - short term.

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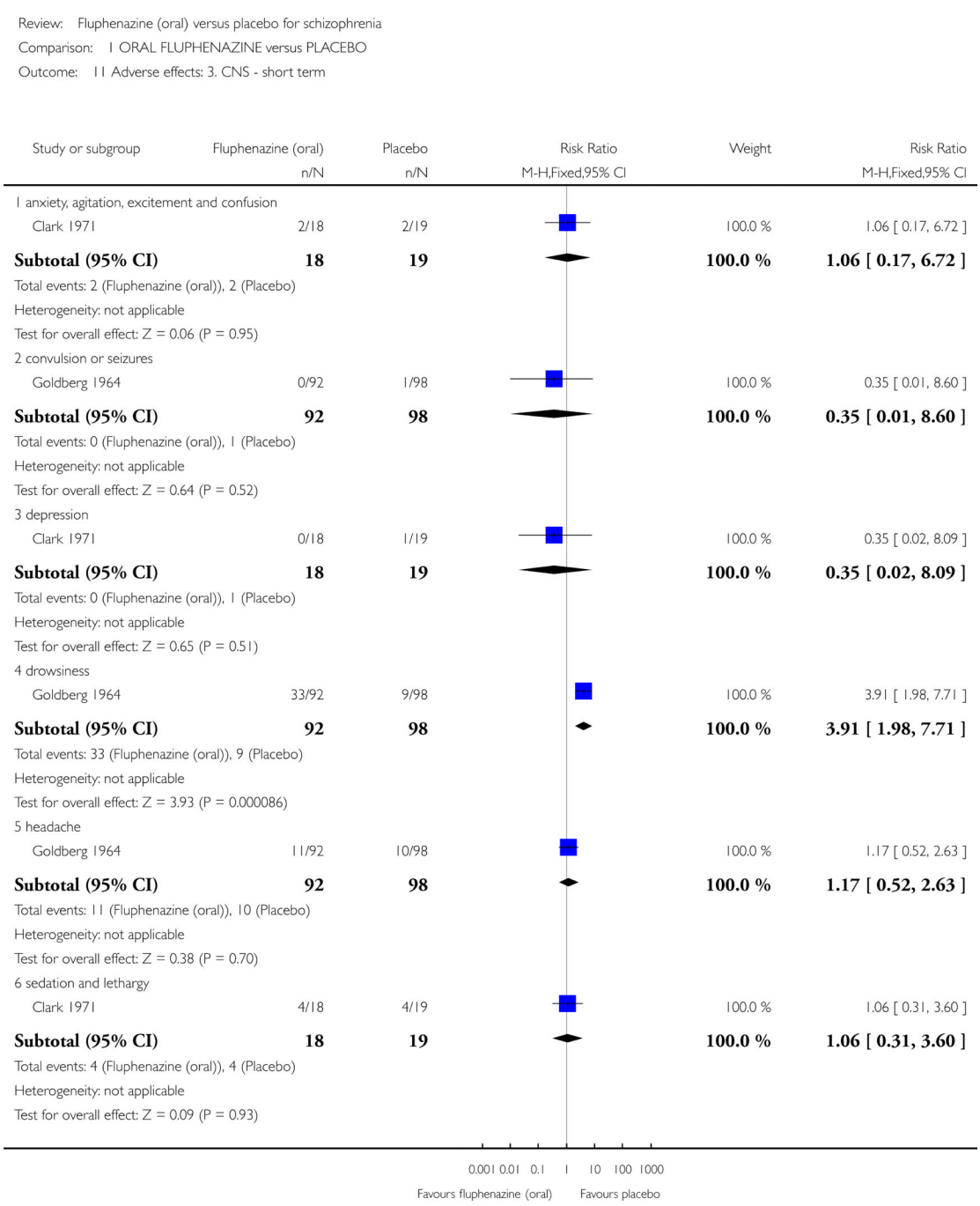
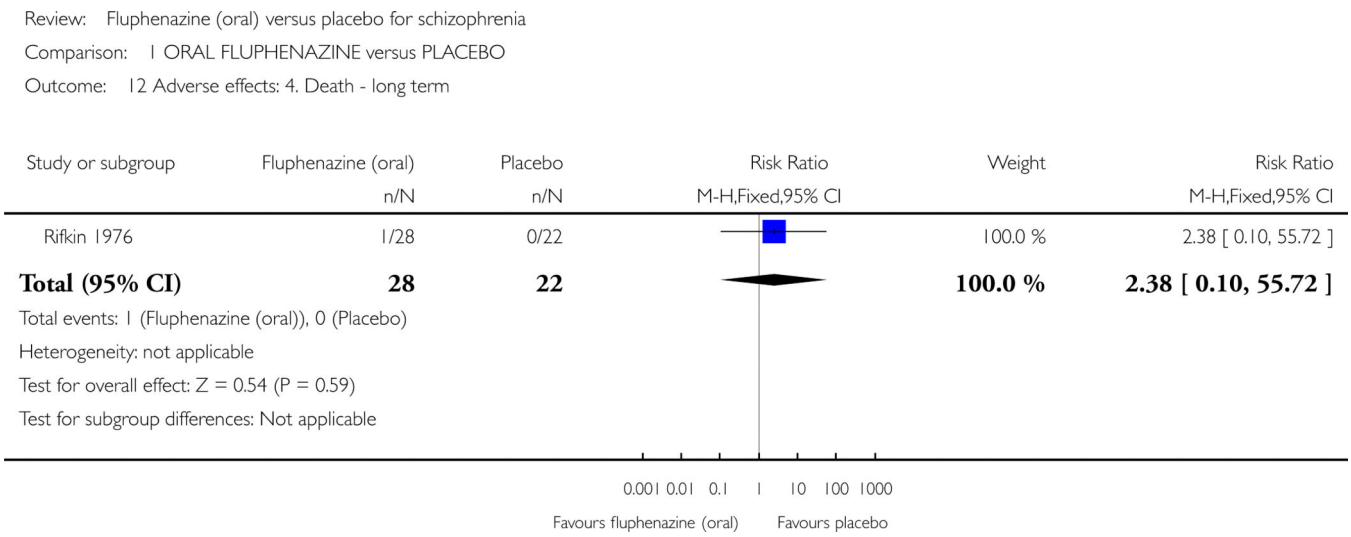


Analysis 1.11.

Comparison 1 ORAL FLUPHENAZINE versus PLACEBO, Outcome 11 Adverse effects: 3. CNS - short term.



Analysis 1.12.

Comparison 1 ORAL FLUPHENAZINE versus PLACEBO, Outcome 12 Adverse effects: 4. Death - long term.

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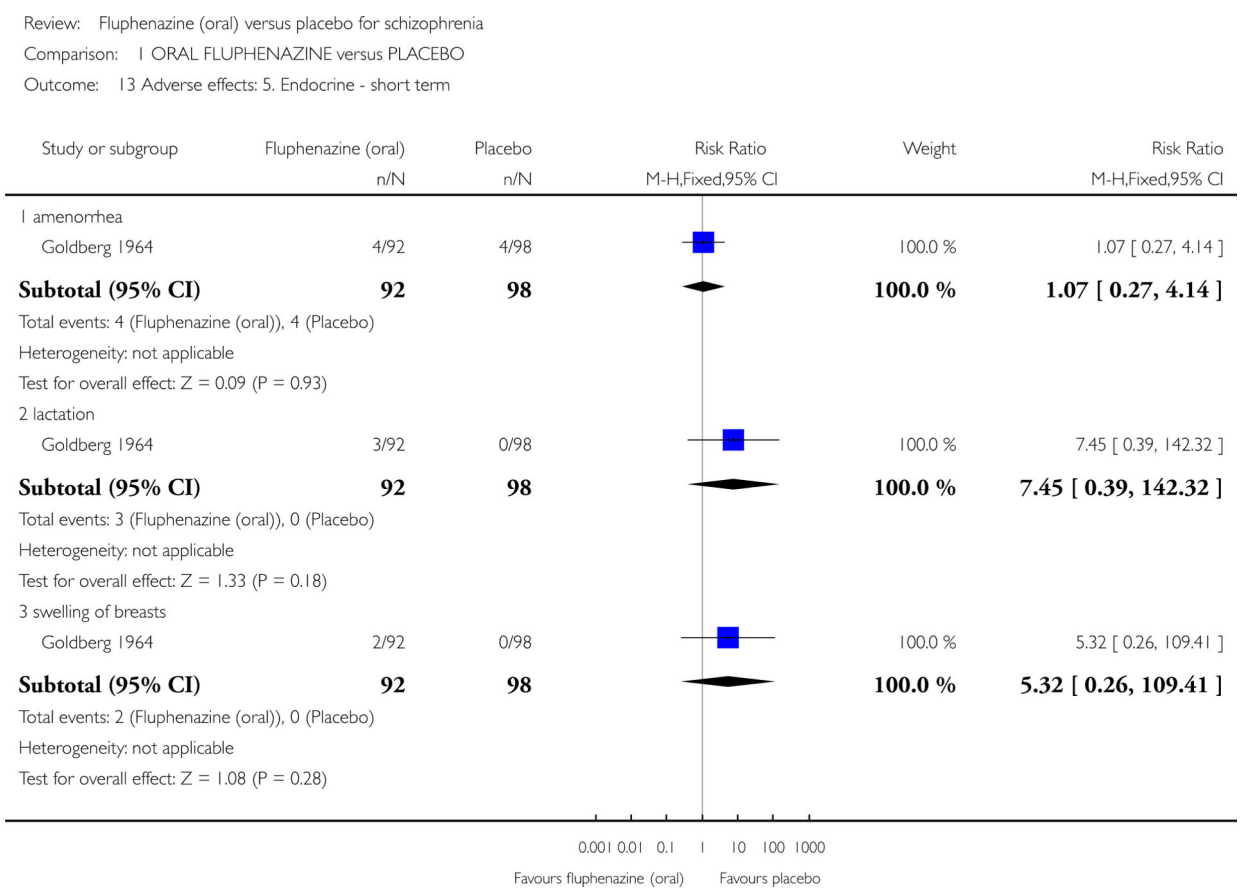

Analysis 1.13.

Comparison 1 ORAL FLUPHENAZINE versus PLACEBO, Outcome 13 Adverse effects: 5. Endocrine - short term.

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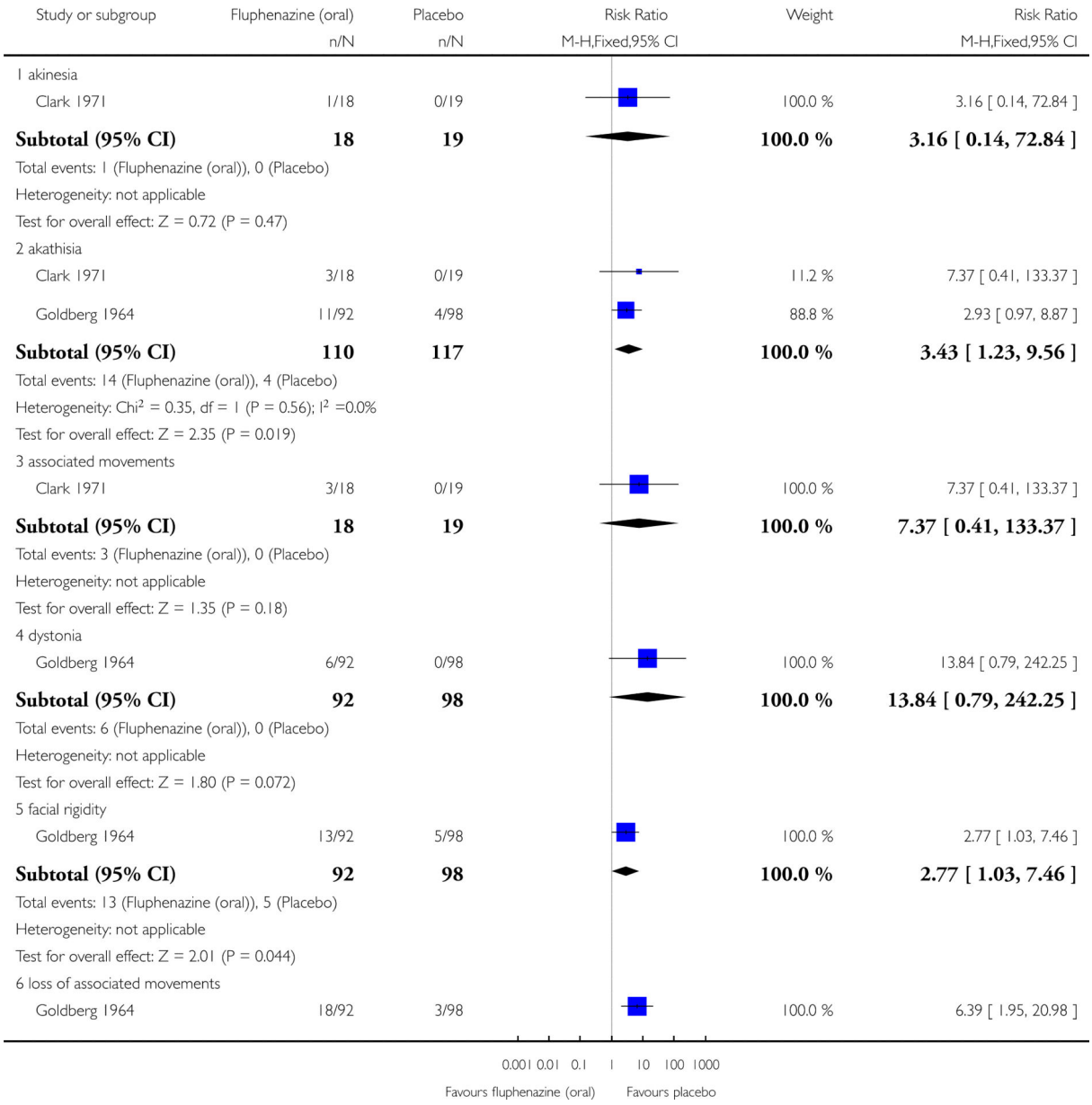
Review: Fluphenazine (oral) versus placebo for schizophrenia

Comparison: 1 ORAL FLUPHENAZINE versus PLACEBO

Outcome: 14 Adverse effects: 6a. Extrapyramidal effects - short term



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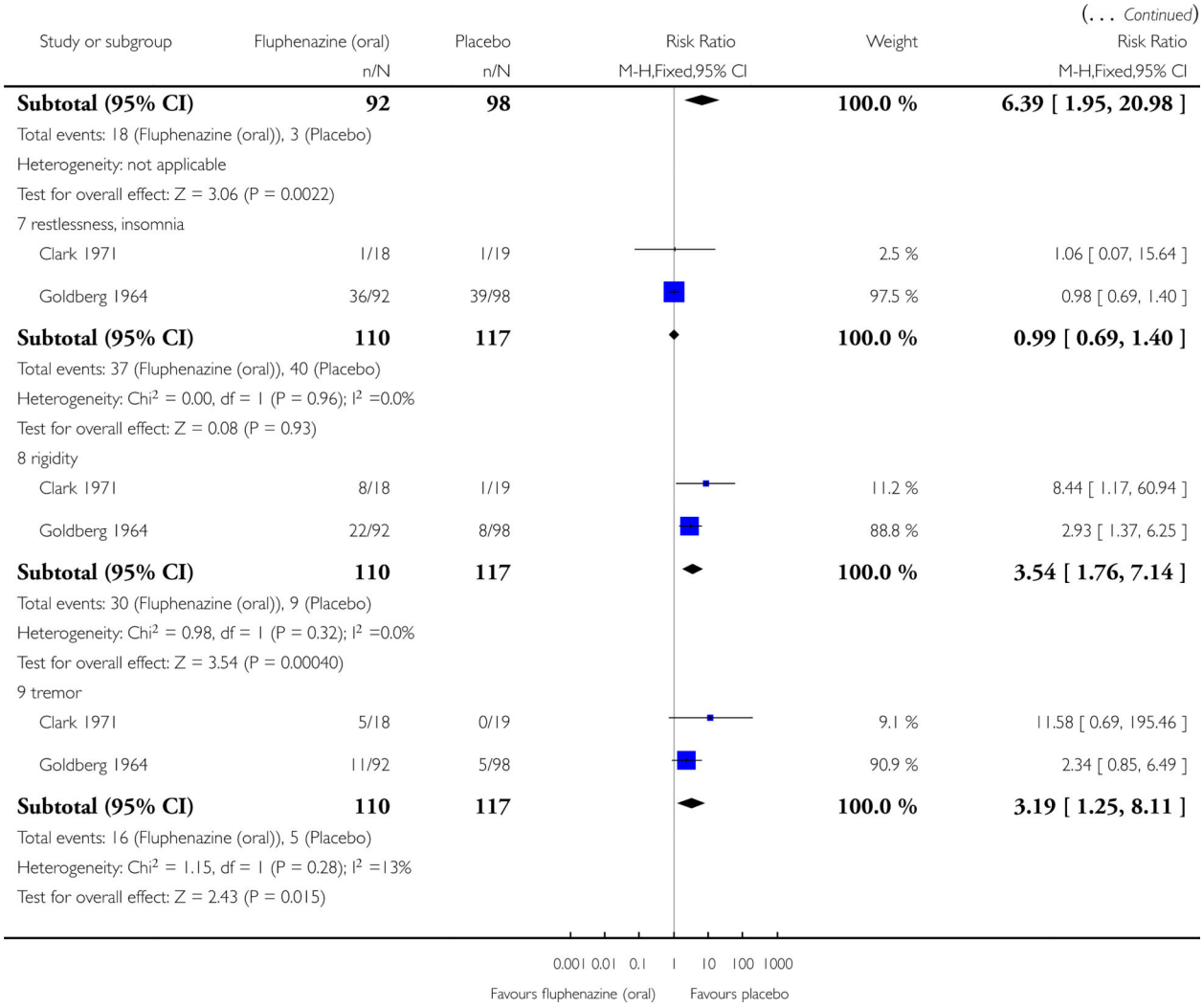

Analysis 1.14.

Comparison 1 ORAL FLUPHENAZINE versus PLACEBO, Outcome 14 Adverse effects: 6a. Extrapyramidal effects - short term.

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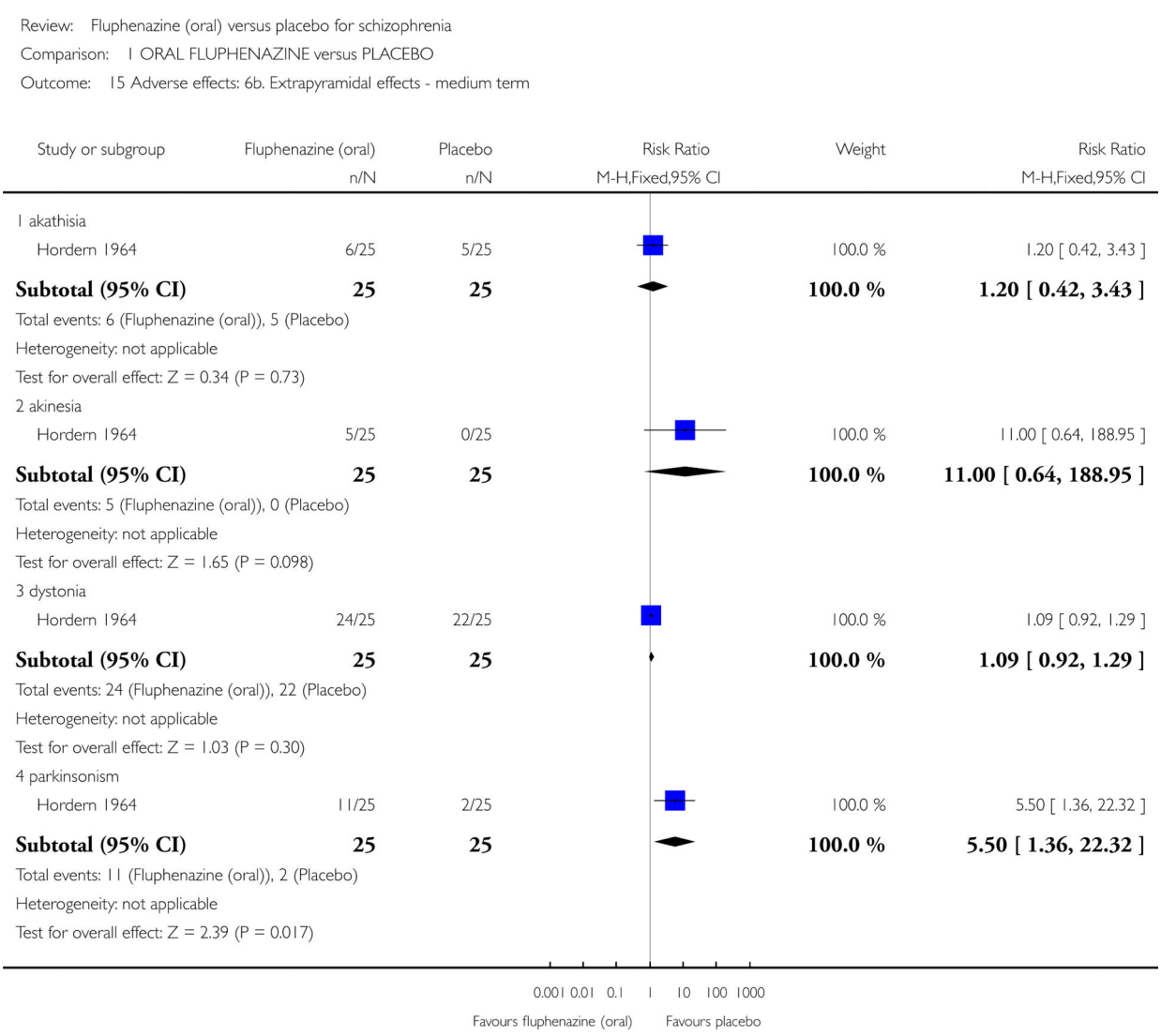

Analysis 1.15.

Comparison 1 ORAL FLUPHENAZINE versus PLACEBO, Outcome 15 Adverse effects: 6b. Extrapyramidal effects - medium term.

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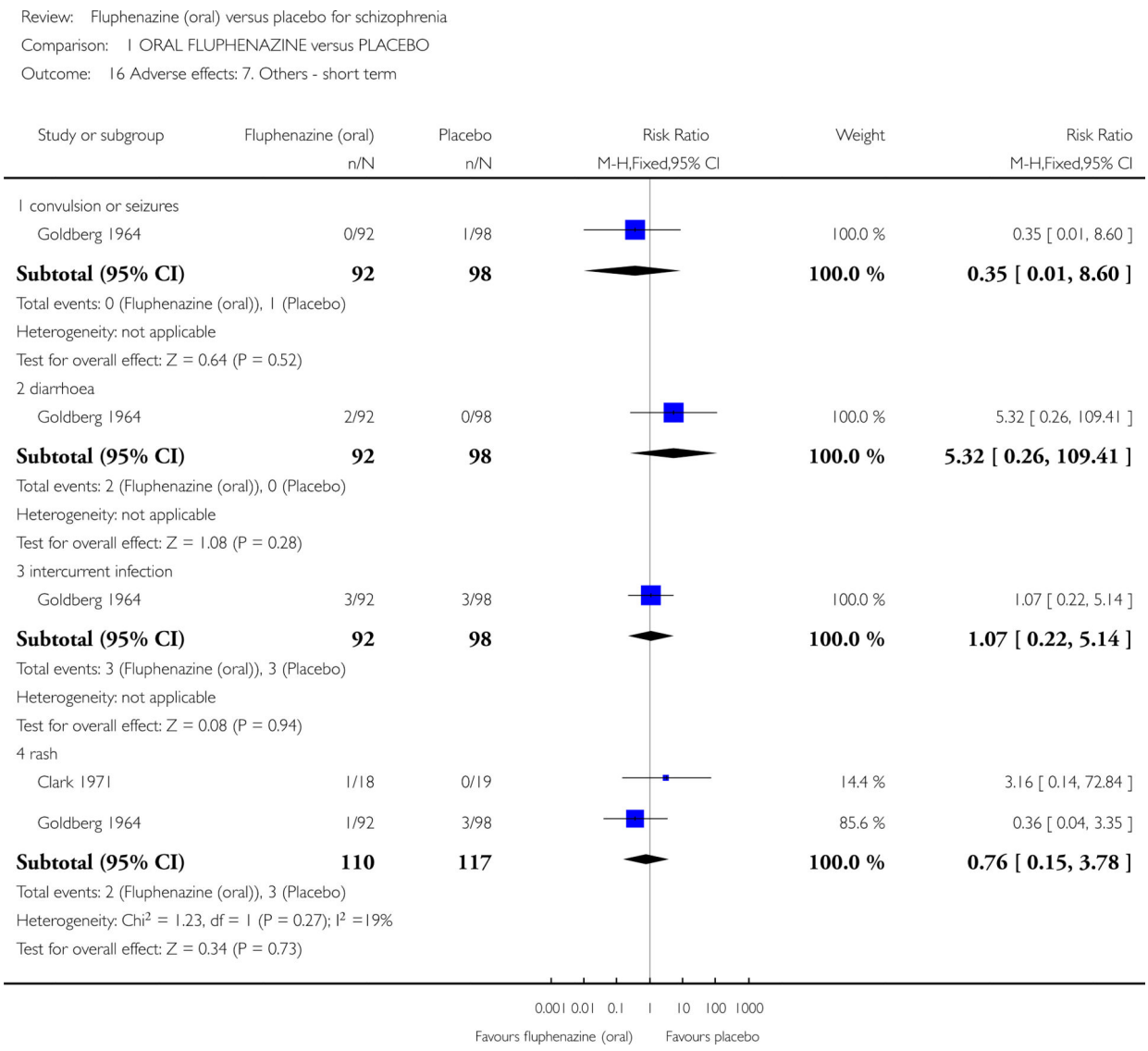

Analysis 1.16.

Comparison 1 ORAL FLUPHENAZINE versus PLACEBO, Outcome 16 Adverse effects: 7. Others - short term.

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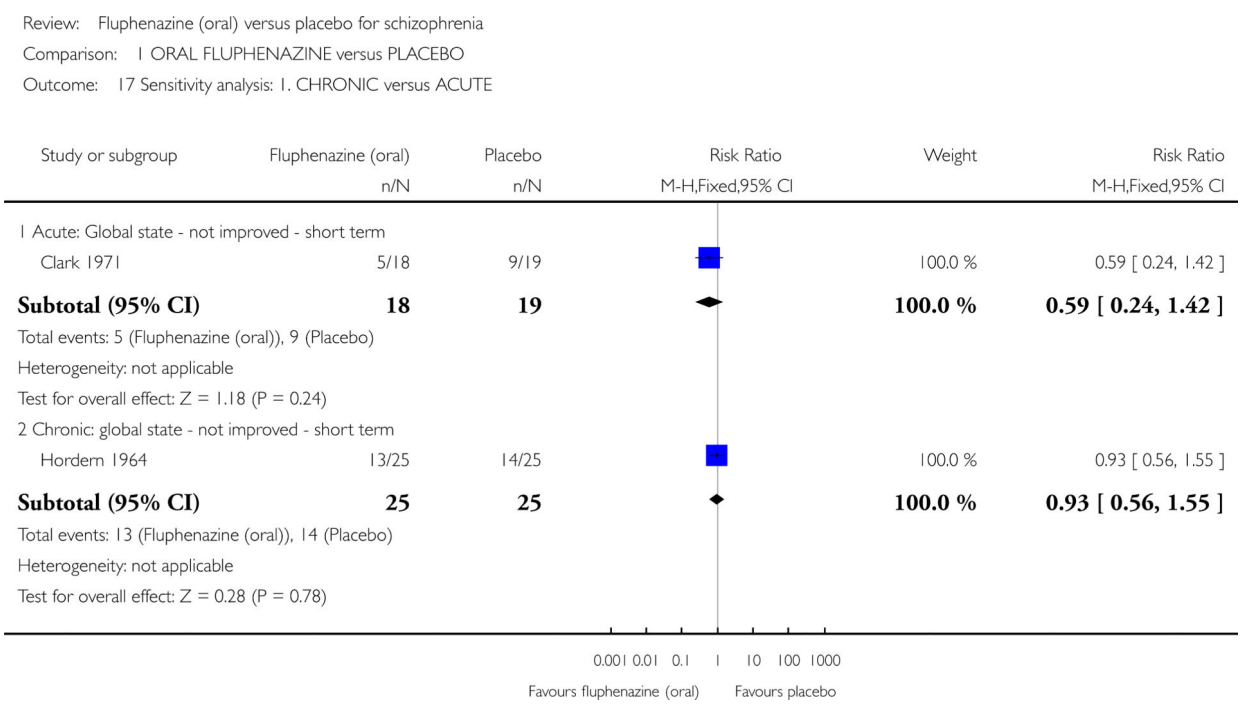

Analysis 1.17.

Comparison 1 ORAL FLUPHENAZINE versus PLACEBO, Outcome 17 Sensitivity analysis: 1. CHRONIC versus ACUTE.

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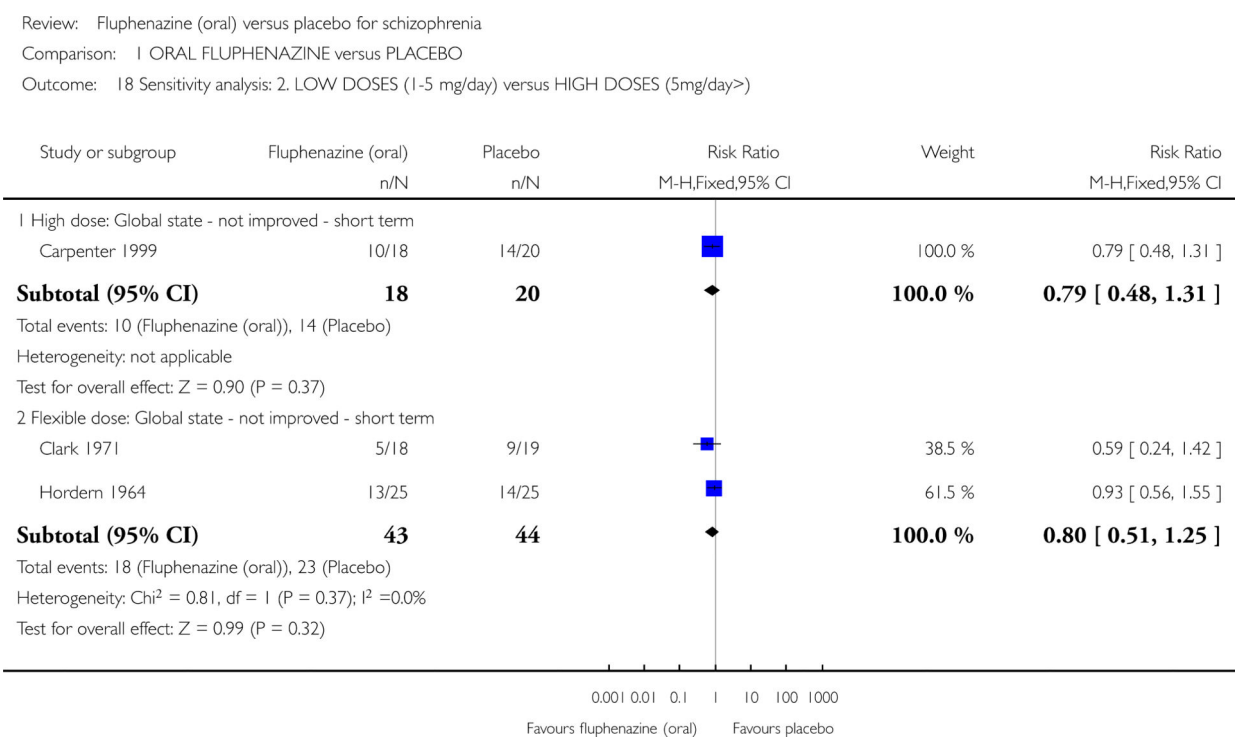

Analysis 1.18.

Comparison 1 ORAL FLUPHENAZINE versus PLACEBO, Outcome 18 Sensitivity analysis: 2. LOWDOSES (1-5 mg/day) versus HIGH DOSES (5mg/day>).

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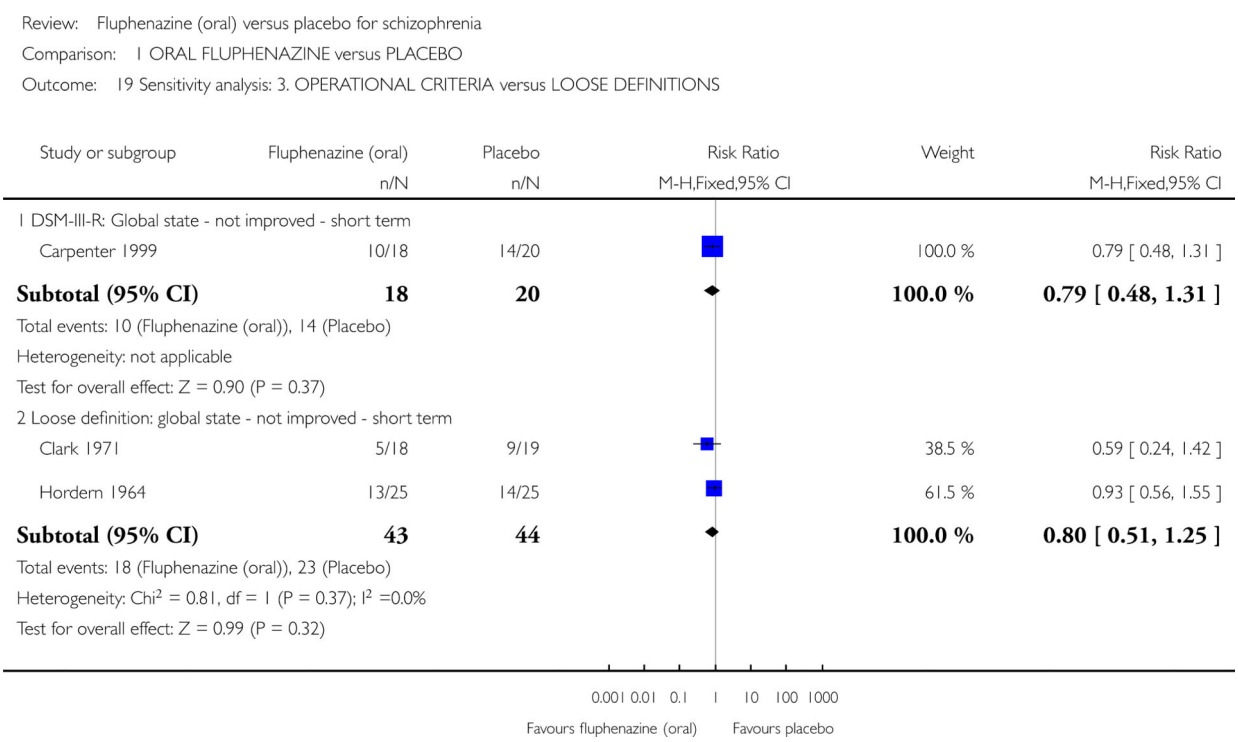
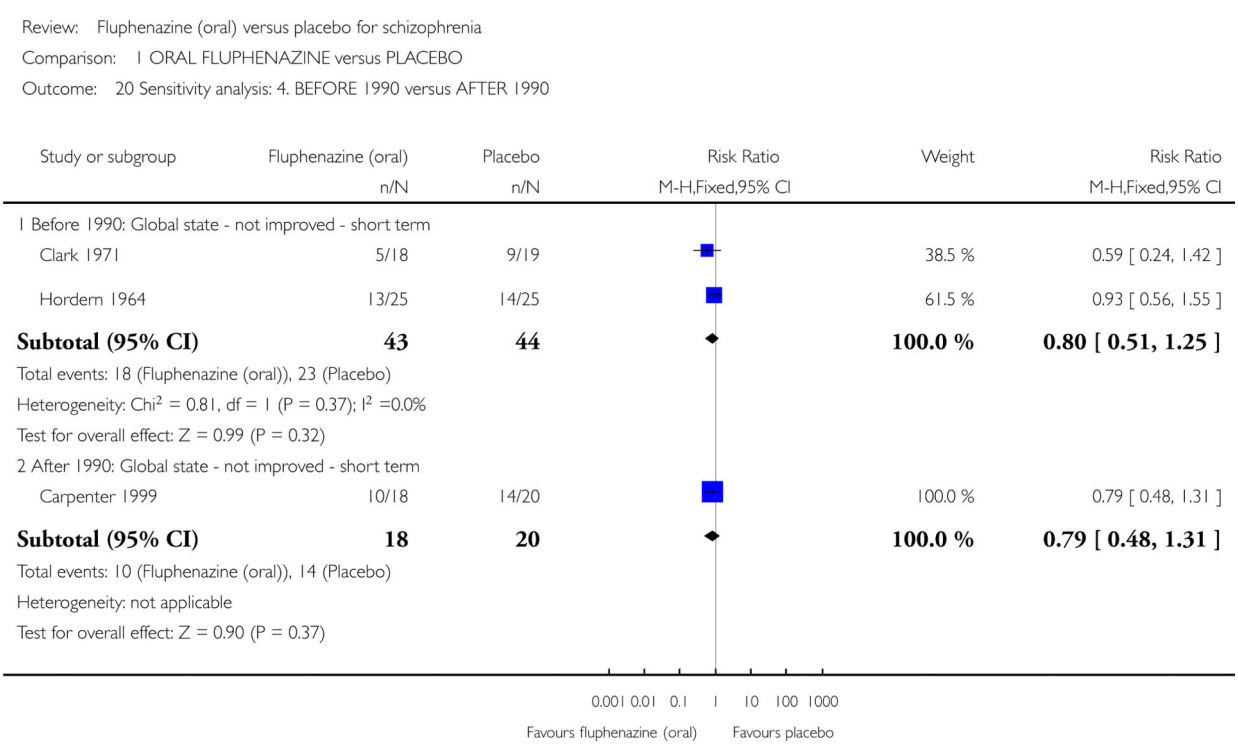


Analysis 1.19.

Comparison 1 ORAL FLUPHENAZINE versus PLACEBO, Outcome 19 Sensitivity analysis: 3. OPERATIONAL CRITERIA versus LOOSE DEFINITIONS.



Analysis 1.20.

Comparison 1 ORAL FLUPHENAZINE versus PLACEBO, Outcome 20 Sensitivity analysis: 4. BEFORE 1990 versus AFTER 1990.

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

Carpenter 1999	
Methods	Allocation: random. Blinding: double. Duration: 6 weeks (4 weeks presented usable data).* Design: parallel.
Participants	Diagnosis: schizophrenia (DSM-III-R or RDC). N = 53 (38 to relevant interventions).** Age: mean 37 yrs. Sex: M 38 (26 relevant), F 15 (12 relevant). History: illness for ~13 yrs, clinically stable patients. Excluded: patients with concurrent drug abuse, alcoholism, organic brain disorders and mental retardation. Setting: community, Maryland Psychiatric Research Center Outpatient Program (US) Consent: written informed consent required.
Interventions	1.Oral fluphenazine: dose 15 mg/day, N = 18. 2.Placebo, N = 20. [3. Diazepam: dose 30 mg/day, N = 15].
Outcomes	Global state (CGI) - not improved or worsened. Unable to use - Mental state: BPRS (no usable data). Relapse (not given by each group). Sleep change ratings (no data).
Notes	* Data were given only for the first 4 weeks of the study. ** Demographic data relate to the total of 38 people.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random - "a stratified randomization procedure...was used to assign drug treatment to balance study groups on gender, prior social function, and past duration of hospital care" (p300). No details as to randomisation methods
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind - no further details. If participants experienced worsening or exacerbation of symptoms, they were removed from the study and treated on an open basis with fluphenazine Rating scales: raters not stated to be independent of treatment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of participants lost to follow-up or leaving the study early
Selective reporting (reporting bias)	High risk	No scale data reported for BPRS or CGI.
Other bias	Unclear risk	Funding: supported in part by NIMH grants (MH-35996 and MH-40279)

Clark 1971	
Methods	Allocation: random. Blinding: double "identically appearing medication administrated from a bottle labelled only with the patient's name". Duration: 6 weeks. Design: parallel.
Participants	Diagnosis: chronic schizophrenia. N = 76 (37 to relevant interventions). Age: mean 33 yrs (range 18 to 45). Sex: M 23, F 53. History: 6 months preadmission period free of hospitalisation or shock treatment. Excluded: childhood schizophrenia or autism, brain syndrome, IQ < 70, alcoholism, recent hepatitis, chronic physical illness, epilepsy, drug addiction. Setting: inpatient, Central State Griffin Memorial Hospital (Oklahoma, US) Consent: not stated.

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Clark 1971	
Interventions	1.Oral fluphenazine: dose 2-10 mg/day. N = 18. 2.Placebo. N = 19. [3. Chlorpromazine: dose 100-1000 mg/day. N = 20]. [4. Thioridazine: dose 100-1000 mg/day. N = 19].
Outcomes	Global state (using CGI): not improved or worsened; average score (CGI severity of illness*) Mental state: average score (BPRS*). Leaving the study early: any reason; administrative/hospital transfer; AWOL; marked improvement allowing discharge. Adverse effects: anticholinergic (dry mouth; blurred vision; nasal congestion; tachycardia; gastrointestinal distress); EPS (tremor; rigidity; associated movements; akinesia; akithisia; drooling; restlessness/ insomnia); CNS (anxiety/agitation/ excitement/ confusion; sedation and lethargy; depression); cardiovascular (hypotension; syncope); others (rash) Unable to use - Global state: NOSIE (no SD). Toxicity (no usable data).
Notes	Unscheduled dose adjustments were permitted for toxicity or intolerance *SDs imputed 'between groups' using RevMan calculator.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random: "patients were assigned to treatment randomly in blocks of four" (p404) - no further details
Allocation concealment (selection bias)	Unclear risk	Participants were "assigned to treatment randomly in blocks of four" (p404) - no further details
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind: "double blind design was maintained throughout the study" (p404) - no further details. Identically-appearing capsules were dispensed from a bottle labelled only with the participant name Rating scales: raters not stated to be independent of treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up: 85% - n = 2 participants left the study early, but their final measures were obtained and used in the analysis (n = 1 receiving placebo due to behavioural deterioration and n = 1 receiving fluphenazine was discharged from the hospital as markedly improved after two weeks). Afurther n = 11 participants, however, were dropped without final measures being obtained (placebo: n = 1 went AWOL; n = 1 on convalescent leave; n = 1 transferred to another hospital. Thioridazine group: n = 2 AWOL; n = 1 medication intolerance. Chlorpromazine: n = 1 AWOL; n = 2 refused oral medication. Fluphenazine: n = 1 administrative transfer, n = 1 AWOL). Dichotomised data presented as ITT (only n = 1 missing from placebo). LOCF for CGI and BPRS
Selective reporting (reporting bias)	Unclear risk	No SDs reported for all scale data.
Other bias	Unclear risk	Funding: supported in part by Public Health Service Grant MH 11666 and Research Scientist Development award No. K135278 from NIMH. Medication supplied by Smith Kline and French Laboratories (chlorpromazine and placebo); Sandoz Inc (thioridazine) and ER Squibb & Sons (fluphenazine)

Goldberg 1964	
Methods	Allocation: random. Blinding: double. Duration: 6 weeks. Design: multi-centre, parallel.
Participants	Diagnosis: schizophrenia. N = 463 (190 to relevant interventions). Age: 16-45 yrs. Sex: male and female (equal distribution stated, however no number given). History: newly admitted patients. Excluded: childhood autism, brain syndrome, IQ < 70, epilepsy, drug addiction. Setting: inpatient, Boston State Hospital (Massachusettes); District of Columbia General Hospital (Washington DC); Kentucky State Hospital (Kentucky); Malcolm Bliss Mental Health Center (Missouri); Mercy-Dougleaa Hosptial (Pennsylvania); Payne-Whitney CLinic (New York); Rochester State Hosptial (Rochester, New York); Springfield State Hospital (Maryland); Institute of Living (Conneticut, US) Consent: not stated.
Interventions	1.Oral fluphenazine: dose 1-16 mg/day. N = 92. 2.Oral placebo. N = 98. [3. Paraenteral fluphenazine. N = 23].

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Goldberg 1964	
	[4. Chlorpromazine: dose 200 mg/day. N = 112]. [5. Thioridazine: dose 200 mg/day. N = 111]. [6. Paraenteral placebo. N = 27]. Additional medication: Anti-parkinsonian medications.*
Outcomes	Leaving the study early (any reason; treatment failure; serious complication of treatment; marked early remission; incorrect diagnosis; court cases, transfer, eloped). Adverse effects: CNS (headache; drowsiness; convulsions or seizures) cardiovascular effects (dizziness, faintness, weakness) anticholinergic effects (increased salivation; dry mouth/throat; gastrointestinal distress and nausea; urinary disturbance; constipation; vomiting) endocrine (lactation; amenorrhoea; swelling of breasts) extrapyramidal effects (loss of associated movements; facial rigidity; rigidity; restlessness/insomnia; tremor; akithisia; dystonia) others (convulsion or seizures; diarrhoea; intercurrent infection; rash) Unable to use - Global state (no SD).** Mental state: IMPS, WBRS (no SD).***
Notes	*44% of fluphenazine group and 5% of placebo received anti-parkinsonian drugs. **Global rating of severity of metal illness, Global rating of improvement. ***Results were not broken down by each drug group.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Random: participants were "randomly assigned to one of four treatments on a double-blind basis" (p247)
Allocation concealment (selection bias)	Unclear risk	Stratified by sex with "randomized assignment to drug treatment within each sex group" (p247). In the three out of nine hospitals participating in the study that admitted approximately equal number of White and Black participants, this was taken into account and groups were further stratified by race
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double blind described, no further details. Participants received individually numbered containers of medication. A flexile dosage schedule permitted the treating physician to adjust dosage according to individuals' needs Rating scales: raters not stated to be independent of treatment
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up: 74%. Reasons for removal of study included administrative removals (incorrect diagnoses; intercurrent medical illness; court cases, transfer, elopement, etc) , treatment-related removals (marked early remission; serious complication of treatment; treatment failure). Those lost were not included in the study report analysis
Selective reporting (reporting bias)	High risk	No SDs reported for continuous data.
Other bias	Unclear risk	Funding: supported by NIMH grants (MH 04661, 04663, 04667, 04673, 04674, 04675, 04679, 04803). Medications provided free of charge from Sandoz Pharmaceuticals (Hanover); Squibb Institute for Medical Research (New Brunswick); Smith Kline and French Laboratories (Philiadelphia) Rating scales: raters not stated to be independent of treatment

Hordern 1964	
Methods	Allocation: unclear. Blinding: double. Duration: 12 weeks. Design: parallel.
Participants	Diagnosis: chronic schizophrenia. N = 75 (50 to relevant interventions). Age: mean 49 yrs. Sex: all female. History: hospitalisation > 2 yrs (mean ~20 yrs, ~SD 9), all have had previous unsuccessful phenothiazines treatment, and none leucotomised. Excluded: physical illness, epilepsy. Setting: inpatient, Mont Park Hospital, Victoria (Australia) Consent: not stated.
Interventions	1.Oral fluphenazine: dose < 14 mg/day. N = 25. 2.Placebo. N = 25. [3. Thioproperazine (max dose of 140 mg/day). N = 25].
Outcomes	Global state: MADRS* - not improved or worsened. Adverse effects - extrapyramidal effects: dystonia; akinesia; parkinsonism; akathisia.

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Hordern 1964	
	Leaving study early.**
Notes	*Rated as either 'no change', 'clear worsening' and 'marked worsening' using the Multidimensional Rating Scale of the Veterans' Administration (Lorr 1953). **Two participants from fluphenazine group left the study early and they were considered to have the worst outcomes. The ward sister's blind ratings of change of behaviour at the end of the trial: 9 placebo participants deteriorated in contrast to 6 participants on fluphenazine. One placebo participant required additional nursing care because of severe negativism

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Randomisation unclear - participants were "divided into three groups of 25 matched on age, chronicity and severity of illness" (p532)
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind (implied) - members of the ward staff were told that powerful phenothiazine drugs were to be administered, but were unaware of which participants were receiving the active medication. All medications were identical-looking tablets, dispensed by a medical officer who "took no part in the rating procedure" (p533). Maximum blindness preserved in evaluations claimed, as neither physicians entered the closed wards between ratings and did not observe side effects during period of treatment. A blind assessment of overall change was made at the end of the trial by the ward sister Rating scales: raters not stated to be independent of treatment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Follow-up: 95% - n = 4 participants were lost to follow-up by 12 weeks of treatment, only n = 2 were accounted for as having discontinued from active drugs (n = 1 from fluphenazine; n = 1 from thioproperazine). ITT used for medium-term data
Selective reporting (reporting bias)	Unclear risk	None detected.
Other bias	Unclear risk	Funding: all drugs and placebos were provided free of charge by May and Baker (Australia) Limited ('Majeptil') and ER Squibb and Sons (Australia) Limited ('Anatensol')

Marder 1994	
Methods	Allocation: randomly assigned. Blindness: double. Duration: 2 years (preceded by 2 months stabilisation phase with low dose of fluphenazine decanoate 5-10 mg) Design: parallel.
Participants	Diagnosis: schizophrenia (DSM-III-R). N = 36. Age: mean 40 yrs. Sex: all male. History: at least two documented episodes of acute schizophrenic illness or at least 2 years of continuing psychotic symptoms, randomly assigned when getting prodromal symptoms using Idiosyncratic Prodromal Scale. Excluded: patients who could not be stabilised for 2 or more months with 10 mg or less of fluphenazine decanoate every 2 weeks. Setting: community, outpatients at Brentwood Division of West Los Angeles Verterans Affairs Medical Center (US) Consent: not stated.
Interventions	1.Oral fluphenazine hydrochloride: dose 10 mg/day. N = 17. 2.Placebo. N = 19. Additional medication - Fluphenazine decanoate: dose 5-10 mg/2weeks for all patients. N = 36 Factored to: A.Behavioural skills training. B.Supportive group therapy.**
Outcomes	Relapse: defined as number of psychotic exacerbations.* Percentage of time in exacerbated state (skew). Percentage of time in prodrome (skew). Leaving the study early: non-specific reasons. Unable to use - Adverse effects (no data).
Notes	*Defined as worsening of four points or more on the sum of the BPRS clusters for thought disturbance and paranoia or increase of three or more points on either cluster

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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random - possible participants were stabilised on low dose fluphenazine decanoate (5 to 10 mg every 14 days) for two months and monitored every week using an idiosyncratic prodromal rating scale. Participants were randomised to either oral fluphenazine or placebo when they met criteria for a prodromal episode
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double blind (implied), as participants who never experienced prodromal episodes nor were assigned to either treatment were treated with 5 mg oral fluphenazine on an open label basis during exacerbations Rating scales: raters not stated to be independent of treatment
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up: 81% - n = 6 participants lost to follow-up by two years of treatment. Only two participants accounted for as being omitted from analysis (n = 1 who dropped-out during a prodromal episode, and n = 1 who reached the two-year end point during a prodrome)
Selective reporting (reporting bias)	Unclear risk	None detected.
Other bias	Unclear risk	Funding: study supported by the Medical Research Service of the Department of Veterans Affairs, Washington DC (grant MH-41573) from National Institute of Mental Health, Bethesda, Md; UCLA Mental Health Clinical Research Center for Schizophrenia (grant MH-30911) from the National Institute of Mental Health

Millar 1963

Methods	Allocation: random. Blindness: double. Duration: 6 weeks. Design: cross-over (after 3 weeks).
Participants	Diagnosis: chronic schizophrenia. N = 38. Age: 28-58 yrs (mean 46 yrs). Sex: all female. Excluded: advanced age, doubtful diagnostic classification, epilepsy, severe sub-normality. History: in hospital 2-35 yrs (mean 18 yrs). Setting: inpatient, UK. Consent: not stated.
Interventions	1.Oral fluphenazine: dose 2.5 mg/day. N = 19. 2.Placebo. N = 19.
Outcomes	Relapse. Unable to use - Improvement: no better or worse (data not reported by group). Adverse effects (no data). Lorr psychiatric rating scale (no SD, mean only). Baker and Thorpe behaviour rating scale (no SD, mean only).
Notes	Participants had been receiving chlorpromazine three times a day and were "mostly stabilised" on a certain dose. They were then given doses of fluphenazine, with this drug substituted for the chlorpromazine at approx. one fortieth of the dose. A single daily dose was given of 2.5 mg (with the exception of two cases who received 20 mg) with dose increase of 2.5 mg/day (one tablet). After participants received fluphenazine for 2 months, they were rated and randomised into intervention groups, receiving dosages established in the stabilisation phase

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random - participants were divided into two random groups; no further details
Allocation concealment (selection bias)	Unclear risk	Only hospital pharmacist knew the composition of the groups.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind - only hospital pharmacist knew the composition of the groups; medication was administered with matching placebo Rating scales: raters not stated to be independent of treatment
Incomplete outcome data (attrition bias)	Unclear risk	No mention of participants lost to follow-up or leaving the study early

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Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
All outcomes		
Selective reporting (reporting bias)	High risk	Data not clearly described as to the stage of trial and relevant groups (i.e. pre-cross-over or post-cross-over). Full data not reported for continuous outcomes (missing means and SDs)
Other bias	Unclear risk	Funding: fluphenazine tablets were provided by ER Squibb & Sons

Rifkin 1976	
Methods	Allocation: random. Blindness: double. Duration: 1 year (preceded by several months transitional period during which all patients were treated exclusively with fluphenazine decanoate and oral fluphenazine) Design: parallel.
Participants	Diagnosis: schizophrenia (remitted). N = 73 (50 to relevant interventions). Sex: M 50, F 23. Age: 17-40 yrs. History: reached a stable remission while receiving FD and FPZ and showed no adverse effects. Excluded: history of severe drug abuse or chronic schizophrenics.* Setting: psychiatric aftercare clinic, Long Island Jewish-Hillside Medican Center (US) Consent: informed consent obtained.
Interventions	1.Oral fluphenazine: dose 5-20 mg/day. N = 28. 2.Placebo. N = 22. [3. Fluphenazine decanoate: dose 0.5-2.0 mL/2weeks. N = 23]. Additional medication: Prophylactic procyclidine (5-15 mg/day).** Placebo procyclidine. Psychotherapy biweekly during the first 6 months and monthly thereafter
Outcomes	Death. Relapse (clinical judgement). Leaving the study early. Unable to use - Social and vocational functioning (results not broken down by individual drugs). Mental state: BPRS (no data). Global state: CGI, PER-C (no data). KAS (no usable data).
Notes	*Chronic patients > 3 previous hospitalisations. **Prophylactic procyclidine for patients receiving active treatment and in the first 2 months for patients receiving placebo to prevent the emergence of extrapyramidal side effects during the fluphenazine decanoate washout period

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Random: "randomly assigned" (p44). 15% of patients referred schizophrenics were re-diagnosed using Kraepelinian Criteria as non schizophrenic and randomised separately but treated in the same manner
Allocation concealment (selection bias)	Unclear risk	"Randomly assigned" (p44) - no further details.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind: drugs were given in a "double blind fashion" (p44) Rating scales: raters not stated to be independent of treatment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Follow-up: 89%. Drop-outs mainly due to moving from the geographical area or refusing further care. None of these patient's conditions had deteriorated clinically
Selective reporting (reporting bias)	High risk	Not all adverse effects reported by group. No data reported for individual groups using the BPRS, CGI, PER-C, KAS scales
Other bias	Unclear risk	Funding: supported by NIMH grant MH 21337-03.

RDC - Research Diagnostic Criteria for schizophrenia or schizoaffective disorders

DSM - Diagnostic and Statistical Manual

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FD - Fluphenazine Decanoate

FPZ - Oral fluphenazine

Rating Scales:

KAS- Katz Adjustment Scale

Global state:

CGI - Clinical Global Impression

NOSIE - Nurse's Observation Scale for Inpatient Evaluation

Mental state:

BPRS - Brief Psychiatric Rating Scale

IMPS - Inpatient Multidimensional Psychiatric Scale

MADRS - modified Montgomery-Asberg Depression Rating Scale

PER-C - Periodic Evaluation Record-Community

WBRS - Burdock Ward Behaviour Rating Scale

Other:

CNS - central nervous system

EPS - extrapyramidal symptoms

ITT - intention-to-treat

LOCF - last observation carried forward

SD - standard deviation

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

Study	Reason for exclusion
Adler 1994	Allocation: randomised. Participants: people with non-organic psychosis (schizophrenia, schizoaffective disorder, unipolar disorder, bipolar disorder or a delusional disorder). Interventions: vitamin E versus placebo.
Baladini 1970	Allocation: randomised. Participants: people with schizophrenia. Interventions: amitriptyline and fluphenazine (combination tablets) versus placebo
Boyer 1995	Allocation: randomised. Participants: people with schizophrenia. Interventions: amisulpride versus fluphenazine versus placebo
Breier 1987	Allocation: unclear. Participants: people with schizophrenia. Interventions: fluphenazine versus placebo (withdrawal study)
Carpenter 1992	Allocation: randomised. Participants: people with schizophrenia. Interventions: diazepam versus depot fluphenazine versus placebo
Chacon 1972	Allocation: randomised. Participants: people with schizophrenia. Interventions: depot fluphenazine versus chlorpromazine versus placebo
Chacon 1973	Allocation: randomised. Participants: people with schizophrenia. Interventions: depot fluphenazine versus chlorpromazine versus placebo
Coffman 1987	Allocation: unclear. Participants: people with schizophrenia. Interventions: depot fluphenazine versus placebo (oral fluphenazine as a background)
Del Giudice 1975	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral phenothiazine versus phenothiazine enanthate
Doran 1990	Allocation: not randomised.
Dowing 1963	Allocation: randomised. Participants: people with schizophrenia. Interventions: fluphenazine versus chlorpromazine versus thioridazine versus placebo. Outcomes: mental state (no SD).
Elman 1999	Allocation: not randomised.
Haider 1968	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral fluphenazine versus fluphenazine enanthate
Hanlon 1970	Allocation: unclear. Participants: newly admitted patients to psychiatric wards, alcoholics, drug addicts, psychosis
Held 1970	Allocation: randomised. Participants: people with schizophrenia. Interventions: phenothiazines versus placebo.
Hogarty 1979	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral fluphenazine versus fluphenazine decanoate
Holden 1970	Allocation: unclear. Participants: people with schizophrenia. Interventions: oral fluphenazine versus haloperidol.
Howell 1961	Allocation: unclear. Participants: people with functional psychosis.
Itil 1971	Allocation: unclear. Participants: people with schizophrenia. Interventions: oral fluphenazine low dose versus high dose.

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Study	Reason for exclusion
Itil 1975	Allocation: randomised. Participants: people with schizophrenia. Interventions: fluphenazine versus haloperidol versus thiothixene
Kane 1982	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral fluphenazine, fluphenazine decanoate versus placebo. Outcomes: results are not broken down by individual drug.
Kinross-Wright 1963	Allocation: not randomised.
Kinross-Wright 1964	Allocation: randomised. Participants: people with schizophrenia. Interventions: first stage - oral fluphenazine versus fluphenazine enanthate, second stage - fluphenazine enanthate versus placebo
Leff 1971	Allocation: randomised. Participants: people with schizophrenia. Interventions: trifluoperazine versus chlorpromazine versus placebo
Litman 1994	Allocation: randomised. Participants: people with schizophrenia. Interventions: fluphenazine versus clozapine.
Marder 1989	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral fluphenazine versus fluphenazine decanoate
Marder 1993	Allocation: randomised. Participants: people with schizophrenia. Interventions: intensive behavioural skills training versus supportive group psychotherapy
Martin 1975	Allocation: randomised. Participants: people with schizophrenia. Interventions: benzhexol versus placebo.
Matheu 1961	Allocation: not randomised.
Mattes 1984	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral fluphenazine versus fluphenazine decanoate versus lithium
Pichot 1988	Allocation: randomised. Participants: people with schizophrenia. Interventions: fluphenazine versus amisulpride and haloperidol versus amisulpride
Pickar 1986	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral fluphenazine versus placebo (withdrawal study)
Pickar 1992	Allocation: not randomised.
Quitkin 1978	Allocation: randomised. Participants: people with schizophrenia. Interventions: fluphenazine decanoate versus penfluridol.
Sampath 1992	Allocation: randomised. Participants: people with schizophrenia. Interventions: fluphenazine decanoate versus placebo (withdrawal study)
Schlosberg 1978	Allocation: randomised. Participants: people with schizophrenia. Interventions: pipotiazine palmitate versus fluphenazine decanoate versus placebo
Schooler 1976	Allocation: randomised. Participants: people with schizophrenia. Interventions: fluphenazine decanoate versus oral fluphenazine, oral fluphenazine versus placebo (withdrawal study), fluphenazine decanoate versus placebo (withdrawal study)
Shafti 2009	Allocation: randomised. Participants: people with schizophrenia. Interventions: fluphenazine decanoate (IM) versus placebo.
Shenoy 1981	Allocation: randomised. Participants: people with schizophrenia. Interventions: fluphenazine decanoate versus placebo (withdrawal study)

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Study	Reason for exclusion
Steingard 1994	Allocation: randomised. Participants: people with schizophrenia. Interventions: fluphenazine versus placebo. Outcomes: no usable data.
Stevens 1976	Allocation: randomised. Participants: people with schizophrenia. Interventions: fluphenazine decanoate versus placebo.
Turner 1966	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus fluphenazine versus placebo. Outcomes: critical flicker fusion frequency (no usable data)
Van Praag 1970	Allocation: randomised. Participants: people with schizophrenia. Interventions: oral fluphenazine versus fluphenazine decanoate
Vestre 1962	Allocation: randomised. Participants: people with schizophrenia. Interventions: fluphenazine versus triflupromazine versus phenobarbital
Watt 1978	Allocation: randomised. Participants: people with schizophrenia. Interventions: fluphenazine versus oral pimozide.
Wistedt 1981	Allocation: randomised. Participants: people with schizophrenia. Interventions: fluphenazine decanoate or flupentixol decanoate versus placebo (withdrawal study)
Wistedt 1983	Allocation: randomised. Participants: people with schizophrenia. Interventions: fluphenazine decanoate, flupenthixol decanoate versus placebo
Zahn 1993	Allocation: randomised. Participants: people with schizophrenia. Interventions: clozapine versus conventional neuroleptics including oral fluphenazine and placebo Outcomes: no useable data - results not presented for individual groups

IM - intramuscular

SD - standard deviation

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Comparison 1

ORAL FLUPHENAZINE versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global state: 1. Not improved or worsened	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 short term (CGI/MDRS)	3	125	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.57, 1.12]
1.2 medium term (MDRS)	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.79, 1.58]
2 Global state: 2. Relapse	3	124	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.07, 1.68]
2.1 short term	1	38	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.06, 1.03]
2.2 long term	2	86	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.05, 3.31]
3 Global state: 3. Percentage of time in prodrome state (skewed data)			Other data	No numeric data
3.1 one-year data			Other data	No numeric data
3.2 two-year data			Other data	No numeric data
4 Global state: 4. Percentage of time in exacerbated state (skewed data)			Other data	No numeric data
4.1 one-year data			Other data	No numeric data
4.2 two-year data			Other data	No numeric data
5 Global state: 5. average score: CGI - severity of illness score (high = poor)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 short term	1	36	Mean Difference (IV, Fixed, 95% CI)	−0.77 [−1.39, −0.15]
6 Leaving the study early: 1. Non-specific reasons	5	363	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.49, 1.10]
6.1 short term	2	227	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.43, 1.07]
6.2 medium term	1	50	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.25, 99.16]
6.3 long term	2	86	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.24, 1.97]
7 Leaving the study early: 2. Specific reason - short term	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 administrative/hospital transfer	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.07, 15.64]
7.2 AWOL	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.07, 15.64]
7.3 court cases, transfer, eloped	1	190	Risk Ratio (M-H, Fixed, 95% CI)	10.65 [1.39, 81.58]
7.4 incorrect diagnosis	1	190	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.07, 16.78]
7.5 marked early remission	1	190	Risk Ratio (M-H, Fixed, 95% CI)	2.13 [0.20, 23.10]
7.6 serious complication of treatment	1	190	Risk Ratio (M-H, Fixed, 95% CI)	11.71 [0.66, 208.85]
7.7 severe extrapyramidal effects	1	50	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 70.30]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.8 treatment failure	1	190	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.03, 0.35]
8 Leaving the study early: 3. Marked improvement/ hospital discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 discharged due to marked improvement	1	36	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 69.09]
9 Adverse effects: 1. Anticholinergic effects - short term	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 blurred vision	1	37	Risk Ratio (M-H, Fixed, 95% CI)	5.26 [0.27, 102.66]
9.2 constipation	1	190	Risk Ratio (M-H, Fixed, 95% CI)	2.22 [1.19, 4.15]
9.3 drooling	1	37	Risk Ratio (M-H, Fixed, 95% CI)	3.16 [0.14, 72.84]
9.4 dryness mouth or throat	2	227	Risk Ratio (M-H, Fixed, 95% CI)	3.62 [1.39, 9.42]
9.5 gastrointestinal distress and nausea	2	227	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.30, 2.72]
9.6 increased salivation	1	190	Risk Ratio (M-H, Fixed, 95% CI)	18.10 [1.06, 309.15]
9.7 nasal congestion	1	37	Risk Ratio (M-H, Fixed, 95% CI)	3.16 [0.14, 72.84]
9.8 urinary disturbance	1	190	Risk Ratio (M-H, Fixed, 95% CI)	3.20 [0.34, 30.17]
9.9 vomiting	1	190	Risk Ratio (M-H, Fixed, 95% CI)	5.32 [0.26, 109.41]
10 Adverse effects: 2. Cardivascular effects - short term	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 dizziness, faintness, weakness	1	190	Risk Ratio (M-H, Fixed, 95% CI)	2.34 [0.85, 6.49]
10.2 hypotension	1	37	Risk Ratio (M-H, Fixed, 95% CI)	3.16 [0.14, 72.84]
10.3 syncope	1	37	Risk Ratio (M-H, Fixed, 95% CI)	3.16 [0.14, 72.84]
10.4 tachycardia	1	37	Risk Ratio (M-H, Fixed, 95% CI)	3.16 [0.14, 72.84]
11 Adverse effects: 3. CNS - short term	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 anxiety, agitation, excitement and confusion	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.17, 6.72]
11.2 convulsion or seizures	1	190	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.60]
11.3 depression	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.02, 8.09]
11.4 drowsiness	1	190	Risk Ratio (M-H, Fixed, 95% CI)	3.91 [1.98, 7.71]
11.5 headache	1	190	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.52, 2.63]
11.6 sedation and lethargy	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.31, 3.60]
12 Adverse effects: 4. Death - long term	1	50	Risk Ratio (M-H, Fixed, 95% CI)	2.38 [0.10, 55.72]
13 Adverse effects: 5. Endocrine - short term	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 amenorrhea	1	190	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.27, 4.14]
13.2 lactation	1	190	Risk Ratio (M-H, Fixed, 95% CI)	7.45 [0.39, 142.32]
13.3 swelling of breasts	1	190	Risk Ratio (M-H, Fixed, 95% CI)	5.32 [0.26, 109.41]
14 Adverse effects: 6a. Extrapyramidal effects - short term	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 akinesia	1	37	Risk Ratio (M-H, Fixed, 95% CI)	3.16 [0.14, 72.84]
14.2 akathisia	2	227	Risk Ratio (M-H, Fixed, 95% CI)	3.43 [1.23, 9.56]
14.3 associated movements	1	37	Risk Ratio (M-H, Fixed, 95% CI)	7.37 [0.41, 133.37]
14.4 dystonia	1	190	Risk Ratio (M-H, Fixed, 95% CI)	13.84 [0.79, 242.25]
14.5 facial rigidity	1	190	Risk Ratio (M-H, Fixed, 95% CI)	2.77 [1.03, 7.46]
14.6 loss of associated movements	1	190	Risk Ratio (M-H, Fixed, 95% CI)	6.39 [1.95, 20.98]
14.7 restlessness, insomnia	2	227	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.69, 1.40]
14.8 rigidity	2	227	Risk Ratio (M-H, Fixed, 95% CI)	3.54 [1.76, 7.14]
14.9 tremor	2	227	Risk Ratio (M-H, Fixed, 95% CI)	3.19 [1.25, 8.11]
15 Adverse effects: 6b. Extrapyramidal effects - medium term	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 akathisia	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.2 [0.42, 3.43]
15.2 akinesia	1	50	Risk Ratio (M-H, Fixed, 95% CI)	11.0 [0.64, 188.95]
15.3 dystonia	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.92, 1.29]
15.4 parkinsonism	1	50	Risk Ratio (M-H, Fixed, 95% CI)	5.5 [1.36, 22.32]
16 Adverse effects: 7. Others - short term	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 convulsion or seizures	1	190	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.60]
16.2 diarrhoea	1	190	Risk Ratio (M-H, Fixed, 95% CI)	5.32 [0.26, 109.41]
16.3 intercurrent infection	1	190	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.22, 5.14]
16.4 rash	2	227	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.15, 3.78]
17 Sensitivity analysis: 1. CHRONIC versus ACUTE	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 Acute: Global state - not improved - short term	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.24, 1.42]
17.2 Chronic: global state - not improved - short term	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.56, 1.55]
18 Sensitivity analysis: 2. LOW DOSES (1-5 mg/day) versus HIGH DOSES (5mg/day>)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 High dose: Global state - not improved - short term	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.48, 1.31]
18.2 Flexible dose: Global state - not improved - short term	2	87	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.51, 1.25]
19 Sensitivity analysis: 3. OPERATIONAL CRITERIA versus LOOSE DEFINITIONS	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 DSM-III-R: Global state - not improved - short term	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.48, 1.31]
19.2 Loose definition: global state - not improved - short term	2	87	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.51, 1.25]
20 Sensitivity analysis: 4. BEFORE 1990 versus AFTER 1990	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 Before 1990: Global state - not improved - short term	2	87	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.51, 1.25]
20.2 After 1990: Global state - not improved - short term	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.48, 1.31]

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Analysis 1.3

Comparison 1 ORAL FLUPHENAZINE versus PLACEBO, Outcome 3 Global state: 3. Percentage of time in prodrome state (skewed data).

Global state: 3. Percentage of time in prodrome state (skewed data)				
Study	**Intervention**	**Mean**	**SD**	**N**
one-year data				
Marder 1994	Oral fluphenazine	10.5	15.90	17
Marder 1994	Placebo	19.4	22.30	19
two-year data				
Marder 1994	Oral fluphenazine	2.80	3.80	14
Marder 1994	Placebo	4.90	5.70	15

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Analysis 1.4

Comparison 1 ORAL FLUPHENAZINE versus PLACEBO, Outcome 4 Global state: 4. Percentage of time in exacerbated state (skewed data).

Global state: 4. Percentage of time in exacerbated state (skewed data)				
Study	**Intervention**	**Mean**	**SD**	**N**
one-year data				
Marder 1994	Oral fluphenazine	11.8	15.00	17
Marder 1994	Placebo	7.20	10.70	19
two-year data				
Marder 1994	Oral fluphenazine	5.50	10.40	14
Marder 1994	Placebo	12.9	13.6	15