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Amisulpride for schizophrenia (Review)

Silveira da Mota Neto JI, Soares BGO, Silva de Lima M

Silveira da Mota Neto JI, Soares BGO, Silva de Lima M.
Amisulpride for schizophrenia.
Cochrane Database of Systematic Reviews 2002, Issue 2. Art. No.: CD001357.
DOI: [10.1002/14651858.CD001357](https://doi.org/10.1002/14651858.CD001357).

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Amisulpride for schizophrenia (Review)

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	3
METHODS	3
RESULTS	6
DISCUSSION	12
AUTHORS' CONCLUSIONS	14
ACKNOWLEDGEMENTS	15
REFERENCES	16
CHARACTERISTICS OF STUDIES	22
DATA AND ANALYSES	38
Analysis 1.1. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 1 Leaving the study early - overall.	40
Analysis 1.2. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 2 Leaving the study early - specific reasons.	40
Analysis 1.3. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 3 Global state: CGI 'less than much improved'.	42
Analysis 1.4. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 4 Mental State: 1. General - BPRS total score at endpoint (high = poor).	42
Analysis 1.5. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 5 Mental State: 2. Specific - Positive symptoms (unable to use- skewed data)..	42
Analysis 1.6. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 6 Mental State: 3. Specific - Negative symptoms - SANS total score at endpoint (high = poor).	42
Analysis 1.7. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 7 Mental State: 4. Specific - Depressive symptoms (unable to use - skewed data)..	43
Analysis 1.8. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 8 Mental state: 5. Need for additional medication.	43
Analysis 1.9. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 9 Adverse events: 1. Presence of at least one adverse event.	43
Analysis 1.10. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 10 Adverse events: 2. Movement disorders.	44
Analysis 1.11. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 11 Adverse events: 3. Movement disorder - unable to use (skewed data)..	44
Analysis 1.12. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 12 Adverse events: 4. Anticholinergic symptoms.	45
Analysis 1.13. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 13 Adverse events: 5. Sleep disorders.	45
Analysis 1.14. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 14 Adverse events: 6. Other.	45
Analysis 2.1. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 1 Death.	49
Analysis 2.2. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 2 Leaving the study early - overall.	50
Analysis 2.3. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 3 Leaving the study early - specific reasons.	51
Analysis 2.4. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 4 Global state: 1. CGI less than 'much' improved.	52
Analysis 2.5. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 5 Global state: 2. CGI at endpoint.	52
Analysis 2.6. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 6 Mental State: 1.1 General - BPRS - less than 40% reduction of the total score.	53
Analysis 2.7. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 7 Mental State: 1.2 General - BPRS total score at endpoint.	53
Analysis 2.8. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 8 Mental State: 2. Specific - Negative symptoms - less than 1 point reduction of the MS negative subscale.	53
Analysis 2.9. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 9 Mental State: 3. Specific - Negative symptoms - continuous data.	54
Analysis 2.10. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 10 Mental State: 4. Specific - Positive symptoms - PANSS positive subscale at endpoint.	54
Analysis 2.11. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 11 Mental State: 5. Need of anxiolytic/hypnotic medication.	55

Analysis 2.12. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 12 Adverse events: 1. Presence of at least one adverse event.	55
Analysis 2.13. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 13 Adverse events: 2. Movement disorders.	55
Analysis 2.14. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 14 Adverse events: 3. Movement disorders - skewed data..	57
Analysis 2.15. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 15 Adverse events: 4. Anticholinergic symptoms.	58
Analysis 2.16. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 16 Adverse events: 5. Cardiovascular symptoms (tachycardia/palpitations).	59
Analysis 2.17. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 17 Adverse events: 6. Endocrine and sexual events.	59
Analysis 2.18. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 18 Adverse events: 7. Other.	60
Analysis 3.1. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 1 Leaving the study early.	63
Analysis 3.2. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 2 Global state: CGI 'less than much improved'.	64
Analysis 3.3. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 3 Mental State: 1. General - BPRS total score (dichotomised data).	64
Analysis 3.4. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 4 Mental state: 2. General - BPRS total score at endpoint.	64
Analysis 3.5. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 5 Mental State: 3. Specific - negative symptoms - PANSS negative scale at endpoint.	65
Analysis 3.6. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 6 Mental state: 4. Specific - positive symptoms - PANSS positive subscale at endpoint.	65
Analysis 3.7. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 7 Mental State: 5. Use of additional anxiolytic medication (diazepam).	65
Analysis 3.8. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 8 Adverse events: 1. At least one adverse event.	65
Analysis 3.9. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 9 Adverse events: 2. Movement disorders.	66
Analysis 3.10. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 10 Adverse events: 3. Endocrine and sexual adverse events.	67
Analysis 3.11. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 11 Adverse events: 4. 'Psychiatric' adverse events.	67
Analysis 3.12. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 12 Adverse events: 5. Other.	68
Analysis 4.1. Comparison 4 SUBGROUP ANALYSIS: AMISULPRIDE versus PLACEBO - SHORT DURATION OF ILLNESS versus CHRONIC ILLNESS, Outcome 1 Leaving the study early - overall.	70
Analysis 4.2. Comparison 4 SUBGROUP ANALYSIS: AMISULPRIDE versus PLACEBO - SHORT DURATION OF ILLNESS versus CHRONIC ILLNESS, Outcome 2 Mental State: Specific - negative symptoms - SANS total score at endpoint.	70
Analysis 4.3. Comparison 4 SUBGROUP ANALYSIS: AMISULPRIDE versus PLACEBO - SHORT DURATION OF ILLNESS versus CHRONIC ILLNESS, Outcome 3 Adverse events: 1. At least one adverse event.	70
Analysis 4.4. Comparison 4 SUBGROUP ANALYSIS: AMISULPRIDE versus PLACEBO - SHORT DURATION OF ILLNESS versus CHRONIC ILLNESS, Outcome 4 Adverse events: 2. Extrapyramidal symptoms.	71
Analysis 4.5. Comparison 4 SUBGROUP ANALYSIS: AMISULPRIDE versus PLACEBO - SHORT DURATION OF ILLNESS versus CHRONIC ILLNESS, Outcome 5 Adverse events: 3. Sleep disorders.	71
Analysis 5.1. Comparison 5 POST-HOC ANALYSIS: EFFICACY - AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 1 Global state: CGI less 'than much improved'.	72
Analysis 5.2. Comparison 5 POST-HOC ANALYSIS: EFFICACY - AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 2 Mental State: 1. General - BPRS total score at endpoint.	72
Analysis 5.3. Comparison 5 POST-HOC ANALYSIS: EFFICACY - AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 3 Mental State: 2. Specific - negative symptoms - PANSS negative subscale at endpoint.	73
Analysis 5.4. Comparison 5 POST-HOC ANALYSIS: EFFICACY - AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 4 Mental State: 3. Specific - positive symptoms - PANSS positive subscale at endpoint.	73
WHAT'S NEW	73
HISTORY	74
CONTRIBUTIONS OF AUTHORS	74

DECLARATIONS OF INTEREST	74
SOURCES OF SUPPORT	74
NOTES	74
INDEX TERMS	75

[Intervention Review]

Amisulpride for schizophrenia

Joaquim I Silveira da Mota Neto¹, Bernardo GO Soares², Mauricio Silva de Lima³

¹Evidence Based Medicine Centre, Universidade Federal de Pelotas, Pelotas, Brazil. ²Brazilian Cochrane Centre, Universidade Federal de São Paulo, São Paulo, Brazil. ³Medical, Eli Lilly & Co, Basingstoke, UK

Contact address: Joaquim I Silveira da Mota Neto, Evidence Based Medicine Centre, Universidade Federal de Pelotas, Avenida Duque de Caxias, 250, Pelotas, 96100, Brazil. motaneto@ufpel.tche.br.

Editorial group: Cochrane Schizophrenia Group

Publication status and date: Edited (no change to conclusions), published in Issue 1, 2013.

Citation: Silveira da Mota Neto JI, Soares BGO, Silva de Lima M. Amisulpride for schizophrenia. *Cochrane Database of Systematic Reviews* 2002, Issue 2. Art. No.: CD001357. DOI: [10.1002/14651858.CD001357](https://doi.org/10.1002/14651858.CD001357).

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ABSTRACT

Background

The treatment of schizophrenia with old, 'typical' antipsychotic drugs such as haloperidol can be problematic, because many people treated with these drugs will suffer from movement disorders. Amisulpride is said to be an "atypical" antipsychotic which induces less movement disorder and which is effective for the negative symptoms of schizophrenia.

Objectives

To evaluate the effects of amisulpride as compared with placebo, typical and atypical antipsychotic drugs for schizophrenia.

Search methods

The authors carried out electronic searches of Biological Abstracts (1982-1999), CINAHL (1982-1999), Cochrane Library (Issue 4, 1999), Cochrane Schizophrenia Group's Register (November 2000), EMBASE (1980-1999), LILACS(1982-1999), MEDLINE (1966-1999) and PsycLIT (1974-1999). They checked all identified studies for further trial citations, and sought these studies in the Science Citation Index. They also contacted authors of trials and the manufacturer of amisulpride.

Selection criteria

All randomised controlled trials comparing amisulpride to placebo, typical or atypical antipsychotic drugs for schizophrenia or other non-affective serious mental illnesses.

Data collection and analysis

Data were independently extracted and analysed on an intention-to-treat basis. The relative risk (RR) and 95% confidence intervals (CI) of dichotomous data were calculated using a random effects model, and, where possible, the number needed to treat was calculated. Weighted mean differences (WMD) were calculated for continuous data.

Main results

This review currently includes 19 randomised studies with a total of 2443 participants. Most trials were of short duration. Data from 4 trials with 514 participants with predominantly negative symptoms suggest that low-dose (up to 300mg/day) amisulpride was a more acceptable treatment than placebo (n=514, RR 0.6 CI 0.5 to 0.8, NNT 3 CI 3 to 7), it was superior in the improvement of the participants' global state (n=242, RR 0.6 CI 0.5 to 0.8, NNT 3 CI 2 to 6) and in the treatment of negative symptoms (n=167, WMD -10.00 CI -17.16 to -2.84).

Compared to typical antipsychotics, the pooled results of a total of fourteen trials suggest that amisulpride was more effective in improving global state (n=651, RR 0.7 CI 0.5 to 0.9, NNT 6 CI 4 to 11), the general mental state (n=695, WMD -4.2 CI -6.5 to -1.9) and the negative symptoms of schizophrenia (n=506, WMD -2.8 CI -4.3 to -1.3). Regarding positive symptoms, amisulpride was as effective as typical

antipsychotics. Amisulpride was less prone to cause at least one general adverse event ($n=751$, RR 0.9 CI 0.8 to 0.97, NNH 9 CI 6 to 18), one extrapyramidal symptom ($n=771$, RR 0.7 CI 0.6 to 0.9, NNH 5 CI 4 to 9) or to require the use of antiparkinson medication ($n=851$, RR 0.6 CI 0.5 to 0.8, NNH 4 CI 3 to 6). No clear differences in other adverse events compared to typical drugs were found. Amisulpride also seemed to be more acceptable than conventional drugs as measured by the outcome 'leaving the studies early' ($n=1512$, RR 0.8 CI 0.7 to 0.9, NNT 16 CI 9 to 69) than conventional drugs, but this result might have been overestimated due to a publication bias which could not be excluded with certainty.

A single trial compared amisulpride to another 'atypical' antipsychotic, risperidone. With the exception of agitation, which was more frequent in the amisulpride group ($n=228$, RR 3.4 CI 1.2 to 10.1, NNH 11 CI 6 to 50) no significant differences were recorded on efficacy or acceptability.

Authors' conclusions

This systematic review confirms that amisulpride is an effective 'atypical' antipsychotic drug for those with schizophrenia. Amisulpride may offer a good general profile, at least compared to high-potency 'typical' antipsychotics. It may also yield better results in some specific outcomes related to efficacy, such as improvement of global state and general negative symptoms. It might be more acceptable and more tolerable than high-potency conventional antipsychotics, especially regarding extrapyramidal side-effects.

Longer term randomised trials are needed to evaluate the comparative value of amisulpride, particularly compared to other expensive atypical antipsychotics. These should focus on important outcomes which have not been sufficiently monitored such as service use, family burden and quality of life.

PLAIN LANGUAGE SUMMARY

Amisulpride for schizophrenia

Amisulpride is a new antipsychotic compound. This review suggests that it is more effective than a placebo for the treatment of schizophrenia. Amisulpride also has some advantages for the treatment of the general and negative symptoms of schizophrenia, and it is associated with less movement disorder than high-potency conventional drugs. In terms of other side-effects, no relevant differences were found.

BACKGROUND

Amisulpride is an atypical antipsychotic drug that has been used to treat schizophrenia in some European countries since the 1980's. Treatment of the 'positive' symptoms of schizophrenia (delusions, hallucinations) with typical antipsychotics has been well established (Thornley 1998), but treatment of 'negative' symptoms (poverty of speech, apathy, anhedonia, affective flattening) still remains a challenge in spite of the discovery of 'atypical' antipsychotics with distinct chemical profiles. It has been suggested that amisulpride, especially at low doses, may be effective for negative symptoms through an 'energising' effect (Boyer 1995). Amisulpride is also said to be at least as effective as haloperidol in improving 'positive' symptoms whilst provoking significantly fewer movement disorders (parkinsonism, tardive dyskinesia) (Puech 1998).

Clozapine has been shown to be effective for those with 'treatment-resistant' illnesses (Wahlbeck 1998) and, with the exception of agranulocytosis, has a moderate side-effect profile. It is, however, an expensive choice in comparison to 'typical' drugs. Amisulpride could be a good, cost-effective alternative in these situations (Souetre 1992).

Technical background

Amisulpride, a substituted benzamide, has a selective and high affinity for dopamine (D3/D2) receptors and presents an interesting pharmacological profile. The profile is said to enable a dose-dependent modulation of dopamine activity. Amisulpride increases dopaminergic transmission at low doses via presynaptic receptor blockade and decreases dopaminergic transmission at high doses via postsynaptic receptor blockade, preferentially in limbic structures, as opposed to the striatum (Freeman 1997, Rein 1997). It has no affinity for other receptor or transporter systems. This unusual property could theoretically make amisulpride different from conventional antipsychotic drugs in its ability to treat 'positive' and 'negative' symptoms, and in its side-effect profile.

OBJECTIVES

To assess the clinical and adverse effects of amisulpride compared to placebo, typical and atypical antipsychotic drugs for those with schizophrenia.

We also tried to evaluate, for the primary outcomes of interest (see 'Types of outcome measures') whether:

1. low dose amisulpride (up to 300mg/day) was more effective than standard or high dose (>300mg/day) for negative symptoms when compared to other drugs;
2. those whose illnesses were described as 'treatment resistant' differed in their response from those whose illnesses were not designated as such; and
3. those experiencing their first episode of schizophrenia differed in their response from those who had been ill for a longer time.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials.

Types of participants

People with schizophrenia and non-affective serious/chronic mental illness irrespective of mode of diagnosis, age, sex, and chronicity of illness.

Types of interventions

1. Amisulpride: any dose and mode or pattern of administration.
2. Placebo.
3. Typical antipsychotic drugs: any dose and mode or pattern of administration. Examples of such drugs are chlorpromazine and haloperidol.
4. Atypical antipsychotic drugs: any dose and mode or pattern of administration. Examples of such drugs are clozapine, olanzapine, quetiapine and risperidone.

Types of outcome measures

1. Death*:
 - 1.1 suicide;
 - 1.2 natural causes.
2. Service utilisation outcomes:
 - 2.1 hospital admission*;
 - 2.2 days in hospital.
3. Leaving the study early*.
4. Global outcomes:
 - 4.1 clinically significant response in global state - as defined by each of the studies*;
 - 4.2 average score/change in global state.
5. Mental state:
 - 5.1 clinically significant response in mental state - as defined by each of the studies*;
 - 5.2 average score/change in mental state;
 - 5.3 clinically significant response on positive symptoms - as defined by each of the studies;
 - 5.4 average score/change in positive symptoms;
 - 5.5 clinically significant response on negative symptoms - as defined by each of the studies;
 - 5.6 average score/change in negative symptoms;
 - 5.7 clinically significant response on depressive symptoms - as defined by each of the studies;
 - 5.8 average score/change in depressive symptoms;
 - 5.9 relapse as defined in the study.
6. Behaviour:
 - 6.1 clinically significant response in behaviour - as defined by each of the studies;
 - 6.2 average score/change in behaviour.
7. Extrapyramidal side-effects:
 - 7.1 incidence of use of antiparkinson drugs;
 - 7.2 clinically significant extrapyramidal side-effects- as defined by each of the studies;
 - 7.3 average score/change in extrapyramidal side-effects.
8. Other adverse effects, general and specific:
 - 8.1 number of people dropping out due to adverse effects;
 - 8.2 cardiac effects;
 - 8.3 anticholinergic effects;
 - 8.4 antihistamine effects;

8.5 prolactin related symptoms.

9. Social functioning:

9.1 clinically significant response in social functioning - as defined by each of the studies;

9.2 average score/change in social functioning.

10. Economic outcomes.

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

11.1 significant change in quality of life/satisfaction - as defined by each of the studies;

11.2 average score/change in quality of life/satisfaction;

11.3 employment status.

12. Cognitive functioning.

As schizophrenia is often a lifelong illness, and amisulpride is used as an ongoing treatment, outcomes and trials were grouped according to time periods: short term (less than 3 months), medium term (3-12 months) and long term (more than 1 year).

* primary outcomes.

Positive and depressive symptoms had been overlooked in the protocol and have been added. Compared to the protocol, 'leaving the study early' was considered as an outcome of its own and not as a behaviour outcome.

Search methods for identification of studies

1. Electronic searching

Relevant randomised trials were identified by searching the follow electronic databases:

1.1 Biological Abstracts (January 1982 to September 1999) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials and its phrase for schizophrenia (see Group search strategy) combined with:

[and (amisulpride* or amitrex or "dan 2163" or deniban* or socian* or solian* or sulamid* or 71675-85-9)]

1.2 CINAHL (January 1982 to September 1999) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials and its phrase for schizophrenia (see Group search strategy) combined with:

[and (amisulpride* or amitrex or "dan 2163" or deniban* or socian* or solian* or sulamid* or 71675-85-9)]

1.3 Cochrane Library (Issue 4, 1999) was searched using the Cochrane Schizophrenia Group's phrase for schizophrenia (see Group search strategy) combined with:

[and (amisulpride* or amitrex or (dan next 2163) or deniban* or socian* or solian* or sulamid* or 71675-85-9)]

1.4 Cochrane Schizophrenia Group's Register (November 2000) was searched using:

[(#42 = amisulpride*) or (#42 = amitrex) or (#42 = dan AND 2163) or (#42 = deniban) or (#42 = socian*) or (#42 = solian*) or (#42 = sulamid*) or (#42 = sulamid*)]

#42 is the field within this register that contains codes for every intervention relevant to the care of those with schizophrenia.

1.5 EMBASE (January 1980 to September 1999) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials and its phrase for schizophrenia (see Group search strategy) combined with:

[and (("amisulpride"/ all subheadings) or amisulpride* or amitrex or "dan 2163" or deniban* or socian* or solian* or sulamid* or 71675-85-9)]

1.6 LILACS (January 1982 to January 1998) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials and its phrase for schizophrenia (see Group search strategy) combined with:

[and (amisulpride-phrase)]

1.7 MEDLINE (January 1966 to November 1999) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials and its phrase for schizophrenia (see Group search strategy) combined with:

[and (amisulpride* or amitrex or "dan 2163" or deniban* or socian* or solian* or sulamid* or 71675-85-9)]

1.8 PsycLIT (January 1974 to September 1999) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials and its phrase for schizophrenia (see Group search strategy) combined with:

[and (amisulpride* or amitrex or "dan 2163" or deniban* or socian* or solian* or sulamid* or 71675-85-9)]

2. Reference searching

The references of all identified studies were also inspected for more trials. SCISEARCH (Science Citation Index (1974 to 1999)) was used to trace papers that had cited included trials. These reports were inspected in order to identify further studies.

3. Personal contact

The first author of each included study was contacted for information regarding unpublished trials and, when necessary, to clarify data.

4. Drug company

The manufacturer of amisulpride (Sanofi-Synthélabo Ltd, Brasil) was contacted for additional data.

Data collection and analysis

1. Selection of trials

Material downloaded from electronic sources included details of author, institution or journal of publication. The principal reviewer (JMN) inspected all reports. These were then re-inspected by BGOS and MSL in order to ensure reliable selection. Any disagreement was resolved by discussion, and where there was still doubt, the full article was acquired for further inspection. Once the full articles were obtained, JMN and BGOS decided whether the studies met the review criteria. MSL was sent 10% of all acquired articles to help promote reliability at this stage. Whenever any disagreement could not be resolved by discussion, further information was sought; these trials were meanwhile added to the list of those awaiting assessment.

2. Assessment of methodological quality

The methodological quality of the trials included in this review was assessed using the criteria described in the Cochrane Handbook (Mulrow 1997) and the Jadad Scale (Jadad 1996). The former is based on the evidence of a strong relationship between allocation concealment and direction of effect. The categories are defined below:

- 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)

The Jadad Scale measures a wider range of factors that impact on the quality of a trial. It includes three items:

- 1. Was the study described as randomised?
- 2. Was the study described as double-blind?
- 3. Was there a description of withdrawals and dropouts?

Each item receives one point if the answer is positive. In addition, a point can be deducted if either the randomisation or the blinding/masking procedures described were inadequate.

For the purpose of the analysis in this review, trials were included if they met the Cochrane Handbook criteria A or B. Additionally, if the study did not gain at least 2 points on the Jadad Scale it was not included.

3. Data collection

JMN independently extracted data from selected trials, while BGOS and MSL separately re-extracted information from two different samples (10%). When disputes arose resolution was attempted by discussion. When this was not possible and further information was necessary to resolve the dilemma, data were not entered and this outcome of the trial was added to the list of those awaiting assessment.

4. Data synthesis

4.1 Incomplete data

With the exception of the outcome of leaving the study early, trial outcomes were not included if more than 40% of people were not reported in the final analysis.

4.2 Dichotomous - yes/no - data

An intention to treat analysis was done. On the condition that more than 60% of people completed the study, everyone allocated to the intervention was counted, whether they completed the follow up or not. It was assumed that those who dropped out had the negative outcome, with the exception of death.

The relative risk (RR) and their respective 95% confidence interval (CI) were calculated based on the random effects model, as it takes into account any differences between studies even if there is no statistically significant heterogeneity. Data were inspected to see if an analysis using a fixed effects model made any substantive difference. Where possible the number needed to treat (NNT) was estimated.

4.3 Continuous data

4.3.1 Normal data: data on continuous outcomes are frequently skewed, the mean not being the centre of the distribution. The statistics for meta-analysis are thought to be able to cope with some skew, but were formulated for parametric data. To avoid this potential pitfall the following standards were applied to all data

before inclusion: (a) standard deviations and means were reported or obtained from authors and (b) for data with finite limits, such as endpoint scale data, the standard deviation (SD), when multiplied by two, was less than the mean. Otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution (Altman 1996). The reviewers reported data that did not meet the first or second standard in the 'other data' tables.

For change data (endpoint minus baseline), the situation is even more problematic. In the absence of individual patient data it is impossible to know if data are skewed, though this is likely. After consulting the ALLSTAT electronic statistics mailing list, the reviewers presented change data in MetaView in order to summarise available information. In doing this, it is assumed either that data were not skewed or that the analyses could cope with the unknown degree of skewness. Without individual patient data it is impossible to test this assumption. Where both change and endpoint data were available for the same outcome category only endpoint data are presented. The reviewers acknowledge that by doing this much of the published change data were excluded, but argue that endpoint data is more clinically relevant and that if change data were to be presented along with endpoint data it would be given undeserved equal prominence. Authors of studies reporting only change data are being contacted for endpoint figures. Non-normally distributed data were reported in the 'Other data types' tables.

4.3.2 Rating scales: a wide range of instruments is available to measure mental health outcomes. These instruments vary in quality and many are not valid, or even ad hoc. For outcome instruments some minimum standards have to be set. They were that: (a) the psychometric properties of the instrument should have been described in a peer-reviewed journal, (b) the instrument should either be: (i) a self-report, or (ii) completed by an independent rater or relative (not the therapist) and (c) the instrument should be a global assessment of an area of functioning.

Frequently it is unclear in the papers if scale based data were rated independently of treatment..

4.3.3 Summary statistic

For continuous outcomes a weighted mean difference (WMD) between groups was estimated, again based on the random effects model, as it takes into account any differences between studies even if there is no statistically significant heterogeneity. Data were inspected to see if analysis using a fixed effects model made any substantive difference.

5. Heterogeneity

Heterogeneity in the results of the trials was assessed both by inspection of graphical presentations and by calculating a Chi-square test. A significance level less than 0.10 was interpreted as evidence of heterogeneity. If heterogeneity was present only homogeneous trials were pooled, i.e. the outlying data were excluded.

6. Addressing publication bias

Data from all identified and selected trials were entered into a funnel graph (trial effect versus trial size) in an attempt to investigate the likelihood of overt publication bias.

7. Sensitivity analyses

7.1 Dose: results for high doses (however 'high' was defined in the study), or >300mg/day if not defined, were compared to those for lower doses for the treatment of negative symptoms.

7.2 Treatment resistance: results from those whose illnesses were described as 'treatment resistant' were compared to those whose illnesses were not designated as such.

7.3 First episode: results from those experiencing their first episode of schizophrenia were compared to those with illness of longer duration.

8. General

Where possible, reviewers entered data in such a way that the area to the left of the line of no effect indicated a favourable outcome for amisulpride.

RESULTS

Description of studies

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

1. Excluded studies

Most of the excluded studies were non-randomised open trials (17 studies) or reviews (17 studies). Another three were prospective studies described as randomised (Bogetto 1995, Dollfus 1992 and Lecrubier 1988), but these did not fulfil the inclusion criteria due to inappropriate intervention or patient group. One retrospective medico-economic assessment study (Souetre 1992) described random allocation, but the data were obtained only from patients' dossiers. Clerc 1989 did not use an adequate comparison group and Duval 1993 may have been randomised but it did not report any data on clinically relevant outcomes.

2. Studies awaiting assessment

One study was ordered but it is still awaiting assessment, because it has not yet been possible to obtain the reference, either in the form of an abstract or the full article, despite considerable effort (Gray 1998).

3. Ongoing studies

No ongoing studies were identified.

4. Included studies

Nineteen randomised controlled studies fulfilled the inclusion criteria and presented data that could be used for at least one of the main comparisons. The trial centres were mainly in Europe.

It is important to point out that there were several clinical trials on those with predominant negative symptoms of schizophrenia (see 'participants' below), since amisulpride is probably the only atypical antipsychotic for which such studies have been done.

4.1 Length of trials

The duration of the included trials covered a considerable range, from 21 days to 12 months, with the most common duration being six weeks. Fourteen of the studies were of 'short duration' and only five trials (Carrière 2000, Colonna 2000, Danion 1999, Loo 1997, Speller 1997) fell into the 'medium-term' category. None of the included trials lasted more than one year.

4.2 Design

All included trials were conducted in a 'parallel groups' design.

4.3 Participants

This review currently includes 2443 people randomised in trials comparing amisulpride for schizophrenia or chronic/serious psychotic illness. The mean age of participants was about 36 years and the majority were men (about 64%). One small study (Paillère-Martinot 95) considered only young and untreated individuals, whose mean age was 20 years.

In three studies (Boyer 1995, Pichot 1988a and Puech 1998) the American DSM-III criteria were used to diagnose schizophrenia, another seven studies used the revised edition DSM-III-R (Colonna 2000, Danion 1999, Loo 1997, Möller 1997, Paillère-Martinot 95, Speller 1997 and Wetzel 1998). The most recent version (DSM-IV) was used in two trials (Carrière 2000, Peuskens 1999). Six trialists (Costa e Silva 1989, Delcker 1990, Klein 1985, Rütther 1988, Saletu 1994 and Ziegler 1989) used the ninth edition of the international classification of diseases (ICD-9). In one trial (Pichot 1988b) participants corresponded to a 'strict diagnostic criteria' and also included those with 'acute functional delusional psychosis'.

Seven trials included only participants presenting with predominantly negative schizophrenic symptoms. One of them, (Paillère-Martinot 95) considered only a short disease course and also included six people with schizotypal personality disorder, whereas another six studies included sub-chronic or chronic participants (Boyer 1995, Danion 1999, Loo 1997, Pichot 1988a; Saletu 1994, Speller 1997). The remaining twelve trials required acute exacerbation of chronic or sub-chronic schizophrenia for inclusion (Carrière 2000, Colonna 2000, Costa e Silva 1989, Delcker 1990, Klein 1985, Möller 1997, Peuskens 1999, Pichot 1988b, Puech 1998, Rütther 1988, Wetzel 1998, Ziegler 1989). In two of these trials, psychotic disorders other than schizophrenia, such as acute paranoid states or transient organic psychosis, were also included (Costa e Silva 1989, Pichot 1988b). No trial focused exclusively on individuals with 'treatment-resistant' schizophrenia.

4.4 Setting

Thirteen studies randomised only participants who were in hospitals, at least at the beginning of the trial. Four studies took place in a mixture of inpatient and outpatient settings (Colonna 2000, Danion 1999, Paillère-Martinot 95, Peuskens 1999). Only two trials did not clearly describe the setting (Loo 1997, Rütther 1988).

4.5 Study size

Colonna 2000 was the largest study with 488 randomised participants on a 3:1 basis (3 amisulpride:1 haloperidol), and Klein 1985 was the smallest one (n=19). Eight trials included more than one hundred people, and four of them enrolled more than two hundred.

4.6 Interventions

4.6.1 Amisulpride: overall, a total number of 1498 people were given amisulpride in the trials. Doses varied from a minimum of 50mg to a maximum of 1200mg/day and were fixed or flexible. Generally, in all studies on participants with predominantly negative symptoms (see above) low doses of amisulpride between 50 and 300mg/day were used. Three of these trials used fixed low doses (Boyer 1995, Danion 1999, Loo 1997) and four of them used flexible low doses (Paillère-Martinot 95, Pichot 1988a, Saletu 1994, Speller 1997).

Of the trials on participants with acute exacerbations, three studies used fixed high doses between 300 and 1200mg/day (Klein 1985, Möller 1997, Peuskens 1999) and a flexible high dose scheme was used in another four (Carrière 2000, Costa e Silva 1989, Pichot

1988b, Wetzel 1998). Three studies used both low and high doses of amisulpride in a flexible regimen (Colonna 2000, Rther 1988, Speller 1997). In one trial (Ziegler 1989) amisulpride at high doses was used in both a fixed and a flexible regimen.

Puech 1998 (n=319) is special because its participants were randomised to five groups: amisulpride 100mg, 400mg, 800mg, 1200mg and haloperidol 16mg daily. For the purpose of this review only, data from the third experimental group were considered. The trialists considered 100mg/day a potentially sub-therapeutic dose for acutely psychotic participants and 800mg/day a median dose between the other two amisulpride groups. Due to this decision, only 129 participants from this study were summarised in the meta-analysis.

4.6.2 Control interventions: four trials compared amisulpride with a placebo control group (n=202) in the treatment of those with predominantly negative symptoms (Boyer 1995, Danion 1999, Loo 1997, Paillre-Martinot 95). Considering comparisons with typical antipsychotic drugs, most trials used haloperidol (n=504) as the control intervention. Fluphenazine (n=49) was used in two trials, flupenthixol (n=62) in one trial and perazine (n=15) in another one. Only one trial (Peuskens 1999) compared amisulpride with another atypical antipsychotic, risperidone (n=113).

4.7 Outcomes

4.7.1 General remarks

There was a relatively high degree of conformity in terms of the outcome measures used in the included trials. However, a general problem was that many trials presented results in graphics which made it impossible to extract data. The use of continuous data was impossible on several occasions due to a lack of standard deviations, and in other cases because the data seemed to be skewed, especially in the adverse effect rating scales.

4.7.2 Acceptability (leaving the study early)

The number of patients 'leaving the studies early', which can be used as a measure of acceptability of treatment, could be extracted from all trials.

4.7.3 Efficacy

The number of patients who were less than much improved according to the Clinical Global Impression (CGI) was used in eight trials. The Brief Psychiatric Rating Scale (BPRS) is probably the most widely used rating scale to monitor the general mental state of those with schizophrenia and fourteen studies described mostly continuous data derived from this scale. Specific aspects of mental state, negative and positive symptoms, were measured with the Scale for the Assessment of Negative Symptoms (SANS) in six studies and by the Scale for the Assessment of Positive Symptoms (SAPS) in five included trials, respectively. A number of more recent studies (N=4) used the Positive and Negative Symptom Scale (PANSS) to evaluate both kinds of symptoms. Behavioural changes were measured with the Nurse's Observation Scale for Inpatient Evaluation (NOSIE) in some trials, but no data could be extracted.

4.7.4 Adverse events

As global measures of side-effects, the number of participants with at least one adverse event and those who left the studies early due to adverse events could be extracted from many trials. Extrapyramidal adverse events (EPS) were most intensively

monitored in the studies and for this open interviews, the number of participants who needed antiparkinson medication at least once and specific scales such as the Simpson Angus Scale (SAS), the Acquired Involuntary Movement Scale (AIMS), and the Barnes Akathisia Scale (BAS) were used. The occurrence of other adverse events than EPS was much less consistently indicated.

4.7.5 Outcome scales

Details of scales that provided usable data are shown below. Reasons for the exclusion of data from other instruments are given under 'Outcomes' in the 'Included studies' section.

4.7.5.1 Global state

Clinical Global Impression - CGI (Guy 1976)

A rating instrument that enables clinicians to quantify severity of illness and overall clinical improvement during therapy. A seven-point scoring system is usually used with low scores indicating decreased severity and/or greater recovery.

Global Assessment Scale - GAS (Endicott 1976)

Used to evaluate the overall functioning of a person during a specified time period in terms of psychological well-being or sickness. Time period assessed is generally one week prior to evaluation. Scale covers entire range of severity and can be used in any situation or study where an overall evaluation of the severity of the illness or degree of health is needed.

4.7.5.2 Mental state

Brief Psychiatric Rating Scale - BPRS (Overall 1962)

This scale is used to assess the severity of abnormal mental state. The original scale has 16 items, but a revised 18-item scale is commonly used. Each item is defined on a seven-point scale varying from 'not present' to 'extremely severe', scoring from 0-6 or 1-7. Scores can range from 0-126, with high scores indicating more severe symptoms. The BPRS-positive cluster comprises four items, which are conceptual disorganisation, suspiciousness, hallucinatory behaviour and unusual thought content. The BPRS-negative cluster comprises only three items, which are emotional withdrawal, motor retardation, and blunted affect.

Positive and Negative Symptom Scale - PANSS (Kay 1987)

The Positive and Negative Symptom Scale was originated as a method for evaluating positive, negative and other symptom dimensions in schizophrenia. The scale has 30 items, and each item can be defined on a seven-point scoring system varying from one (absent) to seven (extreme). This scale can be divided into three sub-scales for measuring the severity of general psychopathology, positive symptoms (PANSS-P) and negative symptoms (PANSS-N). A low score indicates low levels of symptoms.

Montgomery Asberg Depression Rating Scale - MADRS (Montgomery 1979)

A 65-item comprehensive psychopathology scale was used to identify the 17 most commonly occurring symptoms in primary depressive illness. Ratings are based on 10 items, with higher scores indicating more symptoms.

Manchester Scale (Krawiecka 1977)

This scale is used to assess the general psychopathology of schizophrenia, including negative and positive symptoms. The negative symptom subscore consists of the items flattening of affect and poverty of speech and the positive symptom subscore includes

the items delusions, hallucinations, incoherence of speech and incongruity of affect. High scores mean more symptoms.

Scale for the Assessment of Negative Symptoms - SANS ([Andreasen 1983](#))

This six-point scale allows a global rating of the following negative symptoms: alogia, affective blunting, avolition-apathy, anhedonia-asociality and attention impairment. Higher scores indicate more symptoms.

Scale for the Assessment of Positive Symptoms - SAPS ([Andreasen 1984](#))

This six-point scale gives a global rating of positive symptoms such as delusions, hallucinations and disordered thinking. Higher scores indicate more symptoms.

4.7.5.3 Behaviour

Nurses Observational Scale of Inpatients Evaluation - NOSIE ([Honigfeld 1965](#))

An 80-item scale with items rated on a five-point scale from zero (not present) to four (always present). Ratings are based on behaviour over the previous three days. The seven headings are social competence, social interest, personal neatness, cooperation, irritability, manifest psychosis and psychotic depression. The total score ranges from 0-320 with high scores indicating a poor outcome.

4.7.5.4 Adverse events

Abnormal Involuntary Movement Scale - AIMS ([NIMH 1975](#))

The Abnormal Involuntary Movement Scale has been used to assess tardive dyskinesia, a long-term, drug-induced movement disorder. However, using this scale in short-term trials may also be helpful to assess some rapidly occurring abnormal movement disorders such as tremor.

Simpson Angus Scale ([Simpson 1970](#))

This 10-item scale, with a scoring system of 0-4 for each item, measures drug-induced parkinsonism, a short-term drug-induced movement disorder. A low score indicates low levels of parkinsonism.

Barnes Akathisia Scale ([Barnes 1989](#))

Akathisia is also drug-induced movement disorder. The scale comprises items rating the observable, restless movements that characterise akathisia, the subjective awareness of restlessness and any distress associated with the condition. These items are rated from zero (normal) to three (severe). In addition, there is an item for rating the global severity which starts from zero (absent) to five (severe). A low score indicates low levels of akathisia.

4.7.6 Missing outcomes

Many very important outcomes such as costs, issues of hospital admission and satisfaction with care were not addressed in the included studies. Quality of life was only assessed in two trials ([Carrière 2000](#), [Colonna 2000](#)), but no data could be extracted. Social and occupational functioning was evaluated in five studies ([Carrière 2000](#), [Colonna 2000](#), [Loo 1997](#), [Peuskens 1999](#), [Speller 1997](#)). Again no data could be used for this review.

Risk of bias in included studies

1. Randomisation

Although all trials were described as 'randomised', no publication presented adequate information about allocation concealment.

Thanks to further information provided by some authors, seven studies were classified as 'A' according to the quality assessment criteria: [Carrière 2000](#), [Loo 1997](#), [Möller 1997](#), [Peuskens 1999](#) and [Puech 1998](#) used a 'randomisation list', whereas in [Paillère-Martinot 95](#) and [Saletu 1994](#) the assignment schedule was carried out by the sponsor/pharmaceutical company. Numbered bottles, sealed and opaque envelopes were also used to guarantee adequate concealment.

All twelve remaining included trials fell into the quality category 'B' (unclear allocation concealment), because it was unknown how exactly the randomisation had been carried out.

2. Blindness

Although eighteen studies were conducted in a double-blind fashion, many of them did not explicitly describe how blindness was assured and whether the blindness of raters, clinicians and trial participants was verified. One study ([Klein 1985](#)) stated that 'patients, personnel and investigators stayed blind', and another one ([Costa e Silva 1989](#)) reported that 'the appearance of the tablets was identical'. More information was provided by the authors of seven studies: [Carrière 2000](#), [Loo 1997](#), [Möller 1997](#), [Peuskens 1999](#) and [Puech 1998](#) used 'identical packaging'; [Paillère-Martinot 95](#) stated that the blinding procedure was done by the manufacturer of amisulpride and that 'neither recruiters nor patients could know whether the prescribed treatment was placebo or amisulpride'; [Saletu 1994](#) used a 'dummy technique'. This double-dummy design was indicated also by two other studies ([Speller 1997](#), [Wetzel 1998](#)). Only one open randomised trial was included in this review ([Colonna 2000](#)).

3. Loss to follow up

All included randomised trials described those who were unable to complete the trial protocol. The dropout rates were 20% or less in six trials ([Boyer 1995](#), [Costa e Silva 1989](#), [Delcker 1990](#), [Saletu 1994](#), [Speller 1997](#), [Ziegler 1989](#)), but among them only [Boyer 1995](#) had more than 100 participants. Three studies had an attrition rate of more than 40% ([Colonna 2000](#), [Loo 1997](#), [Rüther 1988](#)), and as stated in the methods section of this review, only data for the outcome of 'leaving the study early' were used.

Nine studies ([Boyer 1995](#), [Carrière 2000](#), [Colonna 2000](#), [Danion 1999](#), [Loo 1997](#), [Möller 1997](#), [Peuskens 1999](#), [Puech 1998](#), [Wetzel 1998](#)) used an intention-to-treat analysis, but in this only participants who had had at least one available post-baseline treatment evaluation were included. Five studies ([Carrière 2000](#), [Colonna 2000](#), [Möller 1997](#), [Paillère-Martinot 95](#), [Wetzel 1998](#)) said that they analysed continuous data on an intention-to-treat basis using the last observation carried forward (LOCF). When a participant leaves a study before its end, his last evaluation is used ("carried-forward") in the endpoint analysis.

4. Overall quality according to the Jadad scale

The quality of included trials presented different values as measured by the Jadad scale. The most common score was '3' (n=8), seven were high and achieved a score of '5' ([Carrière 2000](#), [Loo 1997](#), [Möller 1997](#), [Paillère-Martinot 95](#), [Peuskens 1999](#), [Puech 1998](#), [Saletu 1994](#)). No study received less than '2' according to Jadad's criteria.

Effects of interventions

1. The search:

The original searches yielded 131 electronic records and the abstract of each identified reference was analysed. Sixty-eight possibly relevant reports were selected, ordered and inspected. During this inspection process, the papers' reference lists were examined and a further 46 references were identified as being relevant. Personal mail contact with the first authors of each included trial, experts and the manufacturers provided additional five reports.

Twenty of all these 119 papers were rejected while 99 were considered to match the review's inclusion criteria closely enough to be mentioned in either the 'Included studies' (51 references of the 19 RCTs) or 'Excluded studies' (47 references) section. One remaining report is still 'awaiting assessment' because it has not yet been obtained, as mentioned above.

2. COMPARISON 1. AMISULPRIDE versus PLACEBO

Four studies compared amisulpride (n=312) with placebo (n=202). [Loo 1997](#) and [Paillère-Martinot 95](#) only contributed to the outcome of 'leaving the study early' because these studies had greater than 40% loss to follow up. All studies used amisulpride at low doses (up to 300mg/day) in a fixed or flexible regimen and the primary aim was to evaluate the treatment of the negative symptoms of schizophrenia. Therefore, all participants had to suffer predominantly from negative symptoms when they were included in the studies.

2.1 Death

This event was not reported in the relevant RCTs.

2.2 Leaving the study early

Homogeneous data, pooling three short-term studies ([Boyer 1995](#), [Danion 1999](#), [Paillère-Martinot 95](#)) and one medium-term ([Loo 1997](#)) study showed that those randomised to amisulpride were less likely to leave the study early for any reason (n=514, RR 0.6 CI 0.5 to 0.8, NNT 4 CI 3 to 7). Considering attrition due to lack of efficacy, the results also favour the drug compared to placebo (n=514, RR 0.5 CI 0.3 to 0.8, NNT 6 CI 4 to 10). This is also true for those who dropped out due to adverse events (n=383, RR 0.5 CI 0.3 to 0.97, NNT 17 CI 9 to 100). No significant differences between amisulpride and placebo were found in other reasons for leaving the studies early.

2.3 Global state: not improved or worse

Only [Danion 1999](#) reported this outcome and the result was in favour of amisulpride when a cut-off of 'less than much improved' according to the CGI was used (n=242, RR 0.6 CI 0.5 to 0.8, NNT 3 CI 2 to 6).

2.4 Mental State

2.4.1 General: BPRS total score at endpoint

One study, [Danion 1999](#), found a significant difference favouring amisulpride 100 mg/day compared to placebo (n=157, WMD -7.5 CI -11.9 to -3.0). This result also holds for amisulpride at 50 mg/day (n=167, WMD -5.0 CI -9.5 to -0.5).

2.4.2 Specific: Negative Symptoms - SANS total score at endpoint

This outcome was evaluated by one short-term study, [Danion 1999](#) (n=242). Amisulpride showed significantly better results than placebo, irrespective of whether the amisulpride 50mg/day (n=167, WMD -10.00 CI -17.16 to -2.84) or the amisulpride 100mg/day group was used for the comparison (n=157, WMD -8.80 CI -15.96 to -1.64). No standard deviation for endpoint or change data was presented

in one trial ([Boyer 1995](#)), but the trialist stated the mean total SANS score decreased significantly more in the amisulpride groups.

2.4.3 Specific: Positive Symptoms - SAPS total score at endpoint

Only skewed data were available in one study ([Danion 1999](#)) and a second one ([Boyer 1995](#)) did not report the standard deviations. In the first trial ([Danion 1999](#)) there was a significant difference between drug groups and placebo, but this effect was not found in the other two trials.

2.4.4 Specific: Depressive Symptoms - MADRS and DRRS scores at endpoint

One study assessed this outcome. [Danion 1999](#) presented skewed data with a significant difference in favour of amisulpride.

2.4.5 Mental state - need of additional medication

There was no significant difference between amisulpride and placebo when the use of additional drugs (anxiolytic/sleep medication) during the trials was evaluated (n=104, RR 0.97 CI 0.51 to 1.84).

2.5 Adverse events

2.5.1 General

Two studies ([Boyer 1995](#), [Danion 1999](#)) reported the outcome of 'at least one adverse event'. No differences were seen between placebo and amisulpride at any dose up to 300mg/day (n=346, RR 1.00 CI 0.51 to 1.97).

2.5.2 Movement disorder

Those taking amisulpride were not more prone to have extrapyramidal symptoms (n=242, RR 2.09 CI 0.45 to 9.61), as observed in one trial ([Danion 1999](#)). Considering people who required antiparkinson medication at least once, there was no difference between amisulpride and placebo (n=346, RR 0.7 CI 0.2 to 2.1) according to two studies ([Boyer 1995](#), [Danion 1999](#)). Skewed data derived from rating scales also showed no clear differences between groups.

2.5.3 Other adverse events

For other adverse events such as anxiety or agitation, anticholinergic symptoms, endocrine disturbances and sleep disorders, no differences were observed but only few data were available, because each study recorded these outcomes in different ways.

3. COMPARISON 2. AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS

Fourteen studies compared amisulpride (n=1071) with typical antipsychotics (n=630) and most of them included participants with acute forms of schizophrenia (n=11), using amisulpride at high doses. Three small studies considered only subchronic or chronic participants with predominantly negative symptoms and employed low doses up to 300mg/day. One short-term trial ([Rüther 1988](#)) and one medium-term study ([Colonna 2000](#)) had drop-out rates of more than 40% and therefore contributed only to the outcome 'leaving the study early'.

3.1 Death

In two studies ([Colonna 2000](#), [Möller 1997](#)) a suicide was recorded in the haloperidol group, but this fact did not constitute a significant difference.

3.2 Leaving the study early

According to data from all fourteen included studies, fewer people taking amisulpride discontinued treatment for any reason when compared to typical antipsychotics and this difference reached statistical significance ($n=1512$, RR 0.8 CI 0.7 to 0.9, NNT 16 CI 9 to 69).

When 'leaving the study early' due to adverse events was analysed, amisulpride also showed a significant superiority compared to conventional drugs ($n=1402$, RR 0.4 CI 0.3 to 0.6, NNT 12 CI 9 to 20). Similarly, significantly fewer patients treated with amisulpride left the studies earlier due to 'lack of efficacy' in eleven trials ($n=1401$, RR 0.6 CI 0.5 to 0.9, NNT 24 CI 13 to 115). No differences were observed when other reasons for leaving the studies early such as uncooperativeness or recovery were analysed.

However, a 'funnel plot' showed a gap at the right bottom which means that there might be a publication bias in the sense that small trials with no beneficial effects for amisulpride might not have been published. Therefore, the interpretation of the results about acceptability must be done with caution.

3.3 Global state: CGI less than much improved and mean CGI at endpoint

Four studies (Carrière 2000, Möller 1997, Puech 1998, Wetzel 1998) used the 'Clinical Global Impression Scale' and indicated the number of patients who were less than much improved according to this measure. There was a significant difference in favour of amisulpride ($n=651$, RR 0.7 CI 0.5 to 0.9, NNT 6 CI 4 to 11). One small trial (Saletu 1994) reported endpoint scores of the CGI and no difference was observed between amisulpride and fluphenazine. Both drugs were used at low doses for participants with predominantly negative symptoms.

3.4 Mental State - general

3.4.1 Less than 40% reduction of the BPRS global score

Only one trial (Wetzel 1998) presented dichotomous data on the basis of the BPRS and considered a reduction of at least 40% of BPRS total score to be a reasonable cut-off to distinguish between responders and non-responders. No clear difference between amisulpride and flupenthixol was observed ($n=132$, RR 0.9 CI 0.7 to 1.1).

3.4.2 BPRS global score at endpoint

Five trials (Carrière 2000, Möller 1997, Pichot 1988a, Puech 1998, Wetzel 1998) compared amisulpride with different typical antipsychotic drugs and reported BPRS endpoint total scores. When summated, the results of the single studies were homogeneous and showed a significant superiority of amisulpride ($n=695$, WMD -4.2 CI -6.5 to -1.9).

3.4.2.1 Negative Symptoms

Less than 2 points reduction on the negative symptoms subscore of the Manchester scale

Only a single study (Speller 1997) reported this kind of dichotomous data on negative symptoms but no differences between amisulpride and haloperidol were found.

3.4.2.2 Endpoint scores of scales measuring negative symptoms (PANSS-negative symptom subscore, SANS and DSAS)

Three studies (Carrière 2000, Möller 1997 and Puech 1998) reported ratings of negative symptoms derived from the PANSS and found a statistically significant result favouring amisulpride over haloperidol ($n=506$, WMD -2.8 CI -4.3 to -1.3). Pooling the results

from three different scales to measure negative symptoms (PANSS, SANS, DSAS) using a standardised mean difference amisulpride was again significantly superior ($n=589$, SMD -0.3, CI -0.6 to -0.1), although the results of the single studies were heterogeneous (Chi square 8.4, $df=4$, $p=0.08$).

3.4.2.3 Positive Symptoms: PANSS-positive subscore at endpoint

No significant differences were recorded in two short-term trials (Möller 1997, Puech 1998) regarding PANSS derived data on positive symptoms ($n=312$, WMD -1.4 CI -3.0 to 0.3).

3.4.3 Need of additional anxiolytic/hypnotic medication

According to heterogeneous data no significant difference in numbers of participants who needed additional anxiolytic or hypnotic medication was recorded in three trials ($n=372$, RR 0.8 CI 0.6 to 1.1).

3.5 Adverse events

3.5.1 At least one adverse event

According to the pooled results of six studies (Carrière 2000, Costa e Silva 1989, Möller 1997, Puech 1998, Speller 1997, Wetzel 1998) which reported on the outcome 'at least one adverse event' fewer participants treated with amisulpride than with typical antipsychotics had this negative outcome ($n=751$, RR 0.9 CI 0.8 to 0.97, NNH 9 CI 6 to 18).

3.5.2 Movement disorders

In seven studies (Carrière 2000, Costa e Silva 1989, Möller 1997, Puech 1998, Saletu 1994, Wetzel 1998) the occurrence of 'at least one extrapyramidal symptom' was less frequent in those who were treated with amisulpride ($n=771$, RR 0.7 CI 0.6 to 0.9, NNH 5 CI 4 to 9). The suggestion that amisulpride causes fewer movement disorders is also supported by the number of patients who needed antiparkinson medication at least once in nine trials ($n=851$, RR 0.6 CI 0.5 to 0.8, NNH 4 CI 3 to 6). Only three studies presented dichotomous data on akathisia (Klein 1985, Möller 1997, Speller 1997) and again amisulpride was superior in this regard ($n=270$, RR 0.7 CI 0.5 to 0.9, NNH 7 CI 4 to 33). Participants who took amisulpride had significantly less rigidity ($n=239$, RR 0.5 CI 0.3 to 0.8, NNH 8 CI 5 to 25) and tremor ($n=239$, RR 0.4 CI 0.3 to 0.7, NNH 8 CI 5 to 31) than those treated with conventional antipsychotics in two trials (Carrière 2000, Costa e Silva 1989).

Continuous data from rating scales on EPS such as the Simpson-Angus Scale, the Barnes akathisia scale and the AIMS were skewed and could only be presented in the 'other data tables'.

3.5.3 Anticholinergic adverse events

Regarding anticholinergic adverse events such as blurred vision, constipation or dry mouth, no significant differences between groups were found and this category of adverse events was only reported by some trials.

3.5.4 Cardiovascular adverse events

In the small trials by Costa e Silva 1989 and Speller 1997 a similar number of participants in both groups had tachycardia or palpitations ($n=100$, RR 0.9 CI 0.3 to 2.6)

3.5.5 Endocrine/sexual adverse events

The outcome 'at least one endocrine adverse event' was reported by four trialists (Carrière 2000, Möller 1997, Puech 1998, Speller 1997) and there was no significant difference between amisulpride and conventional antipsychotics ($n=579$, RR 0.9 CI 0.4 to 2.0). Carrière 2000 and Wetzel 1998 reported that a similar number of

female participants in both groups presented with amenorrhea, galactorrhea and gynecomastia. Among the male population of three studies (Carrière 2000, Möller 1997, Wetzel 1998), there was no significant difference between amisulpride and typical antipsychotics concerning ejaculatory/erectile dysfunction (n=329, RR 0.5 CI 0.1 to 2.2).

3.5.6 Other adverse events

Other important adverse events such as anxiety/agitation, headache, insomnia, sedation, increased sleep duration, sweating, suicide attempts and weight gain occurred with similar frequency in the amisulpride and the typical antipsychotics groups. However, these adverse events were only reported by a small number of trials. In the study by Wetzel 1998, flupenthixol was less prone to cause headache than amisulpride, but this difference reached only a borderline level of statistical significance (n=132, RR 2.5 CI 0.95 to 6.5). On the other hand, those taking amisulpride presented somewhat less insomnia or increased sleep duration than those on typical drugs, but again the differences reached only a borderline level of statistical significance.

4. COMPARISON 3. AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS

One single short-term trial (Peuskens 1999) compared amisulpride (800 mg/day) with another atypical antipsychotic, risperidone (8mg/day) and included 228 participants with an acute exacerbation of schizophrenia.

4.1 Death

Death was not explicitly reported by the authors.

4.2 Leaving the study early

There were no significant differences in terms of leaving the study early between amisulpride and risperidone (n=228, RR 1.1 CI 0.8 to 1.7). It was reported that the main reasons for premature withdrawals, for both amisulpride and risperidone, were extrapyramidal adverse events and agitation.

4.3 Global state: not improved or worse

Peuskens 1999 reported the number of participants who were 'not improved or worse' according to the Clinical Global Impression Scale. No clear difference between both drugs was found (n=228, RR 0.8 CI 0.6 to 1.1).

4.4 Mental State

4.4.1 General - less than 20% or 40% BPRS reduction

When responders were defined as those who experienced 'at least a 20% reduction in BPRS total score', the results were broadly similar (n=228, RR 0.9 CI 0.6 to 1.4). Using the criterion of 'less than 40% reduction', again no significant difference was found (n=228, RR 0.8 CI 0.6 to 1.1).

4.4.2 General - BPRS total score at endpoint

Again, there was no significant difference between both groups (n=228, WMD -1.5 CI -5.4 to 2.4).

4.4.3 Specific - negative symptoms (PANSS-negative subscore at endpoint)

No significant difference between amisulpride and risperidone was found (n=228, WMD -1.8 CI -3.8 to 0.2).

4.4.4 Positive Symptoms: PANSS-P endpoint scores

The trialists stated that great improvements were recorded on the PANSS-positive symptoms subscale: 52% for amisulpride and 48% for risperidone, but there was no significant difference between both treatment groups (n=228, WMD 0.0 CI -1.9 to 1.9).

4.4.5 Use of additional anxiolytic medication

A similar number of patients in both groups received diazepam at least once during the trial.

4.5 Adverse events

4.5.1 At least one adverse event

When the outcome 'at least one adverse event' was analysed, there was no statistical difference between the two compounds (n=228, RR 1.1 CI 0.97 to 1.3).

4.5.2 Movement disorder

There were no significant differences between amisulpride and risperidone in the numbers of participants who reported 'at least one extrapyramidal symptom' (n=228, RR 1.2 CI 0.8 to 1.7) or who had a full 'extrapyramidal syndrome' (n=228, RR 1.3 CI 0.7 to 2.5) or who 'received antiparkinsonian medication' at least once (n=228, RR 1.3 CI 0.9 to 2.1). When specific extrapyramidal symptoms such as akathisia, hyperkinesia, hypertonia or tremor were analysed separately, there were no differences between both drugs.

4.5.3 Endocrine and sexual adverse events

Considering 'at least one endocrine event', no differences were observed. The incidence of galactorrhea and impotence, among women and men respectively, were not different between groups.

4.5.4 'Psychiatric' adverse events

Concerning so called 'psychiatric' adverse events, those taking amisulpride had a greater tendency to experience agitation (n=228, RR 3.4 CI 1.2 to 10.1, NNH 11 CI 6 to 50) than those on risperidone. Results on anxiety and insomnia were similar for both interventions.

4.5.5 Other adverse events

Headache, increased salivation and other adverse events occurred with similar frequency in both groups. Only constipation seemed to be more common among those taking amisulpride (n=228, RR 7.9 CI 1.0 to 61.8), but the confidence interval was very wide. The trialists reported that those taking risperidone experienced a significant increase in weight during the study (1.4 kg), which was not found in those receiving amisulpride (mean increase of 0.4 kg). However, no significant difference in numbers of participants with weight gain in each group was detected (n=228, RR 0.7 CI 0.2 to 2.3).

4.6 Social Functioning

The SOFAS scale was used to assess patients' social functioning and coping abilities, but the scores were presented without the standard deviation. The trialists stated that both groups showed a marked improvement at endpoint.

5. SUBGROUP ANALYSIS 1. HIGH VERSUS LOW DOSE - AMISULPRIDE COMPARED TO TYPICAL ANTIPSYCHOTICS FOR NEGATIVE SYMPTOMS

Concerning this comparison, it must be noted that the three trials (Pichot 1988a, Saletu 1994, Speller 1997) which compared low-dose amisulpride with low-dose typical antipsychotics all involved participants suffering predominantly from negative symptoms, whereas the studies with high-dose amisulpride only included patients with acute exacerbations. To compare the results of these

different trial designs would be like comparing apples and oranges. Therefore, only the dose finding trial by [Puech 1998](#) provides data on whether low doses of amisulpride are more effective for the treatment of negative symptoms compared to typical antipsychotics. The authors reported that the negative symptoms which were measured by the PANSS negative subscale, decreased in every treatment group. There was no statistically significant difference between amisulpride 100mg, 400mg, 800mg or 1200mg, compared to haloperidol 16mg/day.

6. SUBGROUP ANALYSIS 2. TREATMENT RESISTANT PARTICIPANTS

No trial included only individuals with treatment-resistant schizophrenia. It was therefore not possible to assess whether individuals designated as treatment resistant differ in their response to amisulpride and conventional antipsychotics.

7. SUBGROUP ANALYSIS 3. SHORT DURATION OF ILLNESS VERSUS CHRONIC ILLNESS (placebo-controlled studies)

One small trial ([Paillère-Martinot 95](#), n=27) included only young and neuroleptic-naïve participants who had a short duration of schizophrenia with predominantly negative symptoms, but this study had an attrition rate higher than 40% and could therefore only be used for the outcome leaving the study early. Therefore, this outcome is the only one that differs from the primary analysis. The other three placebo-controlled studies ([Boyer 1995](#), [Danion 1999](#), [Loo 1997](#)) randomised participants with a longer duration of illness. All trialists used low doses of amisulpride of up to 300 mg daily.

7.1 Leaving the study early

No differences were reported between the drug and placebo in the small study with young people (n=27, RR 1.1 CI 0.5 to 2.8). The pooled result of the larger results which included more chronic participants showed that fewer people who received amisulpride left the studies early than those who received placebo (n=487, RR 0.6 CI 0.5 to 0.7, NNT 5 CI 4 to 9).

POST-HOC ANALYSIS - AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS

Two randomised trials ([Colonna 2000](#), [Rüther 1988](#)), one of them with nearly five hundred patients ([Colonna 2000](#)), were excluded from the efficacy analysis because of their dropout rates. A post-hoc analysis was done with the aim to assess the impact of such exclusion criteria on the current results. The inclusion of these studies led to one main consequence concerning efficacy. The PANSS positive subscale at endpoint was significantly lower in the amisulpride group (n=794, WMD -1.7 CI -2.9 to -0.4).

DISCUSSION

1. General remarks

1.1 Generalisability

All studies were set in Europe and several of them were multi-centre trials. Most studies randomised those with operationally diagnosed schizophrenia and the participants seem broadly similar to those in clinical practice in terms of duration and characteristics of illness. The vast majority of studies were undertaken in hospitals and this fact could make it difficult to generalise the findings, because a high number of people with schizophrenia are treated in the community. Since many studies evaluated the treatment of participants with acute symptoms it is, however, reasonable that these participants were hospitalised at the time. It was frequently likely that the scale assessments were carried out by the patients' therapists, although

clear statements were frequently not made. Much of the data must therefore be considered as prone to bias.

The included studies mainly fell into the 'short term' category. The lack of longer-term studies is unfortunate, because schizophrenia is typically a chronic illness. Only two trials had a duration of more than six months and their results could not be used in this review due to high attrition rates (>40%). Little can therefore be concluded regarding the long-term effects of amisulpride. More long-term trials are needed.

Regarding interventions and doses, the studies in this review presented strategies that are similar to those used in daily clinical practice. Amisulpride was mainly compared to haloperidol, a high potency typical antipsychotic, and it is not possible to generalise all findings to other typical antipsychotics such as chlorpromazine. Superiority in causing less movement disorder may be less when compared to lower potency typical antipsychotics.

About 35% of all participants left the studies early. This probably reflects the rigidity of study protocols, which may potentially reduce both the internal and external validity / generalisability of the results. Future randomised trials should be more pragmatic and more closely imitate routine care.

1.2 Quality of reporting

The quality of reporting was deficient in some studies. The procedure by which random allocation took place was never described in the papers, and 12 out of 19 included studies have been classified as category B (unclear allocation concealment). This may be a source of bias.

1.3 Heterogeneity

The principal outcomes under consideration did not demonstrate a significant heterogeneity between studies.

1.4 Publication bias

Unfortunately, detecting publication bias with the funnel plot method requires a minimum number of trials so this it could only be done using the outcome 'leaving the study early', comparing amisulpride to typical antipsychotics. The finding that studies reporting this outcome were not evenly distributed in the 'funnel plot' is not very impressive and therefore there is no strong suggestion of a bias in favour of amisulpride. This should be taken into account when interpreting the results.

2. COMPARISON 1. AMISULPRIDE versus PLACEBO

It should be noted that only low doses of amisulpride (up to 300mg/day) have been compared with placebo. These low doses are said to be especially effective for negative symptoms. However, the use of low-doses only does, of course, limit the generalisability of the occurrence of adverse events.

2.1 Acceptability of treatment (leaving the studies early)

When the acceptability of treatment is indirectly assessed by considering the numbers of people leaving the studies early, amisulpride does appear to be more acceptable to those with schizophrenia than placebo. These results are as much valid for drop-outs due to any reason as for drop outs due to lack of efficacy or adverse events. Four individuals with schizophrenia need to be treated with amisulpride in order to prevent one person dropping out of the treatment provided during a randomised controlled trial.

2.2 Global improvement

The data on global improvement is limited. Participants taking amisulpride showed greater improvement than those on placebo (NNT 3) when reported as a dichotomous measure on the CGI, although these data were provided by only one trial (Danion 1999, n=242). Concerning the other placebo-controlled trials, Boyer 1995 and Paillère-Martinot 95 (attrition higher than 40%) did not use this efficacy outcome, whereas Loo 1997 recorded it but had an attrition rate of >40%, limiting the reviewers to include data only for the outcome of 'leaving the study early'.

2.3 Mental state

Findings on mental state are compatible with amisulpride being more effective than placebo in improving some aspects of mental state. Continuous data from the BPRS total score, a measure of general symptoms of schizophrenia, showed a greater improvement favouring amisulpride in the study by Danion 1999. Regarding results on the improvement of negative symptoms, available data on the SANS total score at endpoint also suggest that amisulpride is more effective than placebo, according to one trial. It is especially noteworthy that all these trials examined participants with predominant negative symptoms. Amisulpride therefore seems to be effective for primary negative symptoms.

2.4 Tolerability

Considering general symptoms or the specific outcome of 'at least one adverse event', amisulpride used at low doses (<300mg/ day) seemed to be as well tolerated as placebo, because no significant differences were recorded in the three included short-term trials.

As regards movement disorders, pooled dichotomous data from one study showed that amisulpride did not cause more extrapyramidal symptoms than placebo. Furthermore, when the use of antiparkinson drugs was assessed, no differences between amisulpride and placebo were recorded.

3. COMPARISON 2. AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS

3.1 Leaving the study early

Overall, amisulpride seems to be somewhat more acceptable to those with schizophrenia than typical antipsychotics such as haloperidol as estimated by the number of people leaving the study early due to any reason, lack of efficacy or adverse events. However, the fact that studies reporting this outcome were not absolutely evenly distributed in the 'funnel plot analysis' suggests a publication bias in favour of amisulpride, so this result must be considered with provisos.

3.2 Global state

It is disappointing that only five trials reported on the improvement of the global state as measured by the CGI. The Clinical Global Impression is less focused on specific symptoms than other scales and it takes into account behavioural and social aspects of the person's improvement. It can therefore be more intuitively understood than many of the more sophisticated rating scales. However, when evaluated as a dichotomous outcome (CGI 'less than 'much improved') in four included trials (n=651), amisulpride had a better performance than typical antipsychotics and according to the NNT analysis only 6 participants need to be treated in order to achieve one positive outcome.

3.3 Mental State

3.3.1 General

Continuous data from five studies reporting on the BPRS, a scale which attempts to assess all clinical symptoms of schizophrenia, showed that people taking amisulpride achieved better scores at endpoint than those on typical antipsychotics. Thus, those with schizophrenia might get somewhat better when treated with amisulpride compared to typical drugs.

3.3.2 Negative symptoms

Scores from the PANSS negative subscale and different other scales used to measure negative symptoms favoured amisulpride over conventional antipsychotics. Given that most participants of these studies had a high degree of positive symptoms, the improvement of negative symptoms may have been to a large extent secondary to the improvement of positive symptoms. More data from studies where low doses of amisulpride are compared with low doses of typical antipsychotics in patients suffering from predominant ('primary') negative symptoms are needed.

3.3.3 Positive symptoms

Amisulpride appeared to be as effective as the reference antipsychotics for the treatment of 'positive' symptoms, but this finding is limited by the fact that only two studies reported usable data.

3.4 Tolerability

3.4.1 Movement disorder

People treated with amisulpride experienced fewer adverse events. This advantage might be mainly the expression of fewer movement disorders (extrapyramidal symptoms) compared to conventional drugs. Five people need to be treated with amisulpride in order to prevent one from experiencing one of these uncomfortable and distressing side-effects. This finding is robust, because it was found for several outcomes relating to movement disorder - at least one extrapyramidal symptom, use of antiparkinson medication, akathisia, rigidity and tremor. This indicates that amisulpride is an "atypical" antipsychotic.

3.4.2 Other adverse events

Overall, people receiving amisulpride did not have significantly different rates of most other adverse events than those receiving conventional antipsychotics. No difference between amisulpride and control groups were found in terms of anticholinergic, cardiovascular, endocrine or general side-effects, but the data on these outcomes are limited because few studies reported them.

3.5 Missing data

It is disappointing that despite considerable investment in clinical trials, no data are available on social functioning, employment status, cognitive functioning, satisfaction with care, hospital admission, family burden and costs.

4. COMPARISON 3. AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS

One study was available and the two compounds seemed to be broadly similar in most aspects. More studies comparing new antipsychotics are urgently needed.

4.1 Leaving the study early

Leaving the study early may be viewed as a measure of how acceptable a treatment is. Amisulpride was found to be similar compared to risperidone in this regard.

4.2 Global state

No difference was observed between amisulpride and another atypical antipsychotic, risperidone, regarding improvement as measured by the Clinical Global Impression Scale.

4.3 Mental state

4.3.1 General

The evaluation of the general mental state as assessed by the BPRS did not identify any differences between the ratings which were achieved by those taking amisulpride or risperidone.

4.3.2 Specific - negative and positive symptoms

Continuous data derived from the PANSS also did not show a significant difference between the drugs concerning negative and positive symptoms, although there is a trend that amisulpride may be superior in alleviating negative symptoms. More research will be needed to confirm or refute this finding.

4.4 Tolerability

4.4.1 Movement disorder

About 30% of participants in each group presented at least one extrapyramidal symptom and then the two compounds seem to be equivalent in their propensity to cause these side-effects at the doses studied. However, newer data on risperidone suggest that generally not more than 6mg/day should be used and this fact might have biased the results in favour of amisulpride.

4.4.2 Endocrine and sexual adverse events

Amisulpride and risperidone were similar in this regard. It is noteworthy that both drugs are known to lead to an increase of prolactin levels.

4.4.3 Psychiatric adverse events

Among psychiatric symptoms, those receiving amisulpride were clearly more prone to experience agitation. This might be related to the fact that in the amisulpride group there was a tendency to need more anxiolytic medication at least once during the trial.

4.5 Missing data

Again, unfortunately, no data for service utilisation, quality of life, family burden and economic assessment were found.

5. SUBGROUP ANALYSES

5.1 Treatment resistant schizophrenia

Due to a lack of data no analyses about those with treatment resistant forms of schizophrenia could be done. Such studies would be very important, because the treatment of this group is especially problematic.

5.2 Low versus high doses of amisulpride for negative symptoms

More trials are necessary to examine this issue. This would be of economical as well as scientific interest. If low doses of amisulpride were as effective as higher doses, this could lead to substantial cost savings.

5.3 Short duration of illness versus chronic illness

The results described in the results section must be considered with great caution, because one very small study with participants with a short duration of illness ($n=27$, [Paillère-Martinot 95](#)) was compared with a relatively large study with chronically ill participants ($n=242$, [Danion 1999](#)). Larger trials with first-episode participants might show different results. Such trials would be important, because it is often said that 'atypical' antipsychotics should be especially used

for these individuals with schizophrenia, but it is unclear whether this strategy is evidence-based.

6. POST-HOC ANALYSIS

The inclusion of two randomised trials with high attrition in the efficacy analysis confirmed the original results and revealed only one different result - a significant superiority of amisulpride concerning the treatment of positive symptoms. This change was probably due to an increase of statistical power when these studies were included.

AUTHORS' CONCLUSIONS

Implications for practice

1. For those with schizophrenia

Most data concerning amisulpride relate to a short treatment period. Amisulpride seems to be more effective and more acceptable than placebo. It appears to have a greater effect than typical neuroleptics on general symptoms and on the negative symptoms of this condition. It might be more acceptable than some typical antipsychotics and it is less likely to cause movement disorders than the latter. Data from only one study comparing it to another atypical drug, risperidone, are currently too sparse to make any conclusions about the differences between amisulpride and other new antipsychotics.

2. For clinicians

Amisulpride results are quite similar to those found for some atypical antipsychotics such as olanzapine, quetiapine and risperidone. It is at least as effective as typical antipsychotics but it is associated with fewer extrapyramidal side-effects than high-potency antipsychotics. For this reason, amisulpride can be considered as an 'atypical' antipsychotic, although it is a selective dopamine receptor antagonist. Its profile makes this compound a useful drug for the treatment of those with schizophrenia. However, clinicians should also know that the results of the kind of studies presented are not necessarily generalisable to the daily routine and that this gap might be filled by future, more pragmatic, trials.

3. For managers or policy makers

No data relating to service utilisation, functioning in the community or cost features were reported in the included studies. Such data are needed by managers and policy makers for their decision-making. Amisulpride is more expensive than typical antipsychotics and this can be troublesome for many countries. Cost-effectiveness studies are needed to show whether the advantages of amisulpride outweigh its higher acquisition costs.

Implications for research

1. General

Clear and strict adherence to the CONSORT statement ([Begg 1996](#)) for all outcomes would have resulted in this review being more informative. Allocation concealment gives the assurance that selection bias is kept to a minimum and it should be properly described. Well reported and verified blinding could have enhanced the confidence in the findings. Authors should present raw data in order to facilitate meta-analytic calculations. When data are presented in a graph, the exact numbers and standard deviations should also be reported. The use of binary outcomes should be preferred to continuous results, because they are easier to interpret. Similar to the results of Cochrane reviews about other

'atypical' antipsychotics, the tight protocols used in most of the included trials might prevent the generalisability of the findings to routine practice. For this reason more pragmatic trials should be undertaken.

2. Specific

Longer and better reported randomised trials are needed which do not address pure efficacy, but also clinically relevant outcomes such as relapse, hospital admission, satisfaction with care, social functioning, family burden and employment. Some data relating to global functioning, mental state and behaviour which are already reported in the trials need replication and expansion. For example, the superior efficacy of low doses of amisulpride on primary as well as secondary negative symptoms of schizophrenia still needs to be shown. More trials comparing amisulpride with other atypical drugs are needed. Finally, it is unclear whether amisulpride is more effective for those with treatment resistant schizophrenia

and for those with a first episode of schizophrenia than 'typical' antipsychotics.

ACKNOWLEDGEMENTS

The reviewers would like to thank Clive Adams, Leanne Roberts and Nancy Owens (Cochrane Schizophrenia Group, UK) for their administrative help and support and Dr. Stefan Leucht for his invaluable comments and corrections.

Many letters were sent by the reviewers to authors, asking for extra information about their trials. Prof Pierre Pichot, Dr Odile Fleurot, Dr Marie-Laure Paillre-Martinot, Prof P Berner, Prof Bernd Saletu, Dr Bernd Kufferle, Prof HJ Mller, Prof Henri Loo, Dr Philippe Carrire and Dr Ziegler were kind enough to respond, for which we are very grateful.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Boyer 1995

Methods	Allocation: random - no further details. Blindness: double - no further details. Duration: 6 weeks (preceded by 6 weeks washout phase for those treated with neuroleptics or antidepressants before the beginning of the trial, or by 12 weeks if they had received depot neuroleptics). Design: parallel, multi-centre (20 centres).
Participants	Diagnosis: schizophrenia (DSM-III), Andreasen's criteria for 'negative schizophrenia', SANS score at least 75 and SAPS score less than 60. N=104. Age: mean 32.5 years, range 19-49 years. Sex: female 39, male 65. History: long-standing (mean duration 10 years) schizophrenia with negative symptoms of early onset (duration 8 years). Setting: inpatients.
Interventions	1. Amisulpride: dose 100mg/day. N=34. 2. Amisulpride: dose 300mg/day. N=36. 3. Placebo. N=34.
Outcomes	Leaving the study early. Adverse events. Use of other drugs. Unable to use - Negative symptoms: SANS (no SD). Positive symptoms: SAPS (no SD). Extrapyramidal symptoms: 13-item scale (no SD).
Notes	Dropouts:18%. The following drugs were allowed during the study: antiparkinsonian drugs (for one day), benzodiazepines and promethazine. Intention-to-treat analysis was undertaken but only data for completers are presented. Jadad =3.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Carrière 2000

Methods	Allocation: random - randomisation was equally balanced by blocks of 4. Blindness: double - identical capsules. Duration: 4 months. Design: parallel, multi-centre.
Participants	Diagnosis: paranoid schizophrenia and schizophreniform disorder (DSM-IV). N=199. Age: mean 31 years. Sex: female 63, male 136.

Amisulpride for schizophrenia (Review)

Carrière 2000 (Continued)

	History: chronic. Setting: initially inpatients.
Interventions	1. Amisulpride: dose range 400-1200 mg/day. N=94. 2. Haloperidol: dose range 10-30 mg/day. N= 105.
Outcomes	Leaving the study early. Global state (CGI - those rated 'very much' or 'much improved' were considered as responders). Mental state (BPRS, PANSS). Use of additional drugs. Adverse events. use of other drugs. Unable to use - Quality of life: QLS (no mean). Social adjustment: FSQ (no mean).
Notes	Dropouts: 35%. An ITT analysis was performed and included only those with at least one available evaluation post baseline. Drugs allowed during the study: anxiolytics, hypnotics, drugs to control extrapyramidal symptoms and drugs for somatic disorders. Jadad=5.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Colonna 2000

Methods	Allocation: random - no further details. Blindness: open. Duration: 12 months. Design: parallel, multicentre, international study.
Participants	Diagnosis: schizophrenia (DSM-III-R), with a minimum score of 4 on at least two of the four BPRS positive items. N=489. Age: mean ~37 years. Sex: females 161, males 327. History: chronic or subchronic disease (mean duration 12 years) with acute exacerbation. Setting: patients followed as outpatients but 76% were hospitalised at baseline.
Interventions	1. Amisulpride: dose 200-800mg/day (max.1200mg/d). N=370. 2. Haloperidol: 5-20mg/day (max.30mg/d). N=118.
Outcomes	Leaving the study early. All following outcomes could not be used because the global drop-out was >40%: Mental state: BPRS, PANSS. EPS: AIMS, Barnes, Simpson-Angus. Other adverse events. Quality of life: QLS. Global functioning: GAF.

Amisulpride for schizophrenia (Review)

Colonna 2000 (Continued)

Notes Dropouts: 47%.
An ITT analysis was performed and included those with at least one dose of study treatment (one patient on haloperidol excluded).
Jadad = 2.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Costa e Silva 1989

Methods Allocation: random - no further details.
Blindness: double - the tablets' appearance was identical.
Duration: 21 days.
Design: parallel.

Participants Diagnosis: ICD-9 criteria for acute or subacute delusional schizophrenic episode (295.0 to 295.9), acute or subacute confusion of transient organic psychotic states (293.0 and 293.1), acute hallucinatory episode (298.31) and psychogenic paranoid psychosis (298.4). Global score on the BPRS of at least 50. N=40.
Age: mean ~ 35 years.
Sex: female 12, male 28.
History: acute psychotic states.
Setting: inpatients.

Interventions 1. Amisulpride: dose range 800-1200mg/ day. N=20.
2. Haloperidol: dose range 20-30 mg/ day. N=20.

Outcomes Leaving the study early.
Adverse events.

Unable to use-
Mental state: BPRS (no SD).
Behaviour: NOSIE (no SD).

Notes Dropouts: 10%.
The following drugs were allowed during the study: biperiden for extrapyramidal symptoms, promethazine for dyskinesia and flunitrazepam for insomnia.
Jadad=4.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Danion 1999

Methods Allocation: random - no further details.
Blindness: double - no further details.

Amisulpride for schizophrenia (Review)

Danion 1999 (Continued)

Duration: 12 weeks (preceded by a 4 week, single-blind placebo washout phase).
Design: parallel, multicentre (35 centres), multinational (4 countries).

Participants	Diagnosis: schizophrenia, residual type (DSM-III-R), SANS total score >59, SAPS total score <51. N=242. Age: mean age 34.7 years. Sex: female 88, male 154. History: predominant negative symptoms; illness of no more than 20 years' duration.
Interventions	1. Amisulpride: dose 50 mg/day. N=84. 2. Amisulpride: dose 100 mg/day. N=75. 3. Placebo. N=83.
Outcomes	Leaving the study early. Global state: CGI (those rated 'very much' or 'much improved' were considered to be responders). Mental state: BPRS, SANS, SAPS, MADRS. Extrapyramidal symptoms. Other adverse events.
Notes	Dropouts: 26%. The following drugs were allowed during the study: lorazepam <6mg/day for no more than two periods of up to 7days, separated by at least 7days. The ITT analysis included those who had at least one available treatment evaluation. Jadad =3.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Delcker 1990

Methods	Allocation: 'random basis' - no further details. Blindness: double - no further details. Duration: 6 weeks (preceded by a washout phase of 1-90 days (mean ~3 days) in the haloperidol group and of 4-28 days (mean ~9 days) in the amisulpride group). Design: parallel, single-centre.
Participants	Diagnosis: schizophrenia (ICD-9). N=41. Age: mean 43.3 years in the amisulpride group and 40.1 in the haloperidol group. Sex: female 8, male 33. History: mean duration ill 17.3 years in the amisulpride group and 14.3 years in the haloperidol group. Setting: inpatients.
Interventions	1. Amisulpride: dose range 490-1000mg/day (mostly 500-700mg/day). N=21. 2. Haloperidol: dose range 5-40mg/day (mostly 20-25mg/day). N=20.
Outcomes	Leaving the study early. Use of other drugs. Unable to use - Mental state: BPRS, AMDP (no means). Global state: CGI (no mean). Extrapyramidal adverse events: Simpson scale, Webster scale (no endpoint data).

Amisulpride for schizophrenia (Review)

Delcker 1990 (Continued)

Laboratory changes: (no mean).

Notes Dropouts: 10%.
The following drugs were allowed during the study: biperiden, diazepam and flunitrazepam. Jadad =3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Klein 1985

Methods	Allocation: random - no further details. Blindness: double - patients, personnel and investigators were blind. Duration: 4 weeks. Design: parallel.
Participants	Diagnosis: schizophrenia (ICD-9). N=19. Age: mean 41 years, range 22-64. Sex: female 9, male 10. History: acute schizophrenia, with a median of 2.5 times admitted to psychiatric hospital prior to present symptoms. Setting: inpatients.
Interventions	1. Amisulpride: 10mg/kg/day for 8 days, and thereafter 5mg/kg/day until the end of the trial. N=9. 2. Haloperidol: 0.5mg/kg/day for 8 days, and then 0.25mg/kg/day until the end of the trial. N=10.
Outcomes	Leaving the study early. Adverse events. Unable to use - Mental state: AMP, BPRS (no data). Extrapyramidal effects: Webster and Simpson scale (no data).
Notes	Dropouts: 26%. The following drugs were allowed during the study: chloralhydrate, diazepam and biperiden. Jadad=4.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Loo 1997

Methods	Allocation: random - no further details. Blindness: double - no further details. Duration: 6 months. Design: parallel, multi-centre.
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Amisulpride for schizophrenia (Review)

Loo 1997 (Continued)

Participants	<p>Diagnosis: Schizophrenia (DSM-III-R), disorganised or residual types, SANS score >59 and SAPS score < 51.</p> <p>N=141.</p> <p>Age: mean 34 years.</p> <p>Sex: female 41, male 100.</p> <p>History: chronic or subchronic schizophrenia and predominantly negative symptoms, with a mean duration of illness of 11 years.</p>
Interventions	<p>1. Amisulpride: dose 100mg/day. N=69.</p> <p>2. Placebo. N=72.</p>
Outcomes	<p>Leaving the study early.</p> <p>Unable to use -</p> <p>Global improvement: CGI (attrition >40%).</p> <p>Mental state: SANS, SAPS (attrition >40%).</p> <p>Global functioning: GAF (attrition >40%).</p> <p>EPS: AIMS, Barnes, Webster (attrition >40%).</p> <p>Other adverse events (attrition >40%).</p>
Notes	<p>Dropouts: 57%.</p> <p>The following drugs were allowed during the study: Oxazepam (up to 150mg/day), lorazepam (up to 7.5mg/day) and levomepromazine (up to 50mg/day) could be prescribed for hypnotic or anxiolysis effect only.</p> <p>The intention-to-treat analysis included those with at least one treatment evaluation.</p> <p>Jadad=3.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Möller 1997

Methods	<p>Allocation: 'randomisation list, labelled bottles and sealed envelopes.'</p> <p>Blindness: double - identical packaging.</p> <p>Duration: 6 weeks (preceded by a 7 days single-blind placebo washout phase).</p> <p>Design: parallel, multi-centre (31 centres).</p>
Participants	<p>Diagnosis: schizophrenia (DSM-III-R), BPRS a minimum score of 4 on at least two of the four core positive symptoms.</p> <p>N=191.</p> <p>Age: mean 36 years.</p> <p>Sex: female 72, male 119.</p> <p>History: Chronic or subchronic schizophrenia, mean duration ill 9.5 years, with an acute exacerbation.</p> <p>Setting: inpatients.</p>
Interventions	<p>1. Amisulpride: dose 800mg/day. N=95.</p> <p>2. Haloperidol: dose 20mg/day. N=96.</p>
Outcomes	<p>Leaving the study early.</p> <p>Global state: CGI (those rated 'very much' or 'much improved' at endpoint were considered to be responders).</p> <p>Mental state: BPRS, PANSS.</p> <p>Extrapyramidal adverse events: AIMS, BARS, EPRS.</p>

Amisulpride for schizophrenia (Review)

Möller 1997 (Continued)

Other adverse events.

Notes

Dropouts: 34%.

The following drugs were allowed during the study: biperiden, chloral hydrate and oxazepam.

The ITT analysis included those who had at least one end-point assessment.

Jadad =5.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Paillère-Martinot 95

Methods

Allocation: random - randomisation procedure was done by the pharmaceutical company, using numbered bottles, with serially numbered, sealed and opaque envelopes.

Blindness: double - blindness procedure performed by industry, "neither recruiters nor patients could know whether the prescribed treatment was placebo or amisulpride".

Duration: 6 weeks.

Design: parallel.

Participants

Diagnosis: schizophrenia (DSM-III-R), SANS mean items rating of 3 on at least two subscales.

N=27.

Age: mean 20 years.

Sex: female 7, male 20.

History: short disease course with important negative symptoms and neuroleptic-naïve condition or lifetime treatment shorter than 1month.

Setting: in and outpatients.

Interventions

1. Amisulpride: dose 50mg/day (if no improvement at week 3, dose was increased to 100mg/day). N=14.

2. Placebo. N=13.

Outcomes

Leaving the study early.

Unable to use:

Mental state: DRRS, MADRS, SANS, SAPS (>40% attrition).

Extrapyramidal adverse events: AMDP system (>40% attrition).

Other adverse effects (>40% attrition).

Notes

Dropouts: 41%.

Six participants met the criteria for schizotypal personality disorder, which was considered to be simple schizophrenia with negative symptoms.

Jadad=5.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Peuskens 1999

Methods	Allocation: random - randomisation list and sealed envelopes. Blindness: double - identical opaque capsules Duration: 8 weeks, after a single-blind placebo washout period of 3 to 6 days. Design: parallel, multicentre, multinational.
Participants	Diagnosis: schizophrenia (DSM-IV), paranoid, disorganised or undifferentiated type. BPRS total score >36. N=228. Age: mean 36.5 years. Sex: female 91, male 137. History: Acutely ill patients with a mean duration of illness of 9 years. Setting: in- and outpatients.
Interventions	1. Amisulpride: dose 800mg/day. N=115. 2. Risperidone: dose 8mg/day. N=113.
Outcomes	Leaving the study early. Global state: CGI. Mental state: BPRS, PANSS. General adverse events. Unable to use - Behaviour: SOFAS (no SD). EPS: AIMS, Simpson-Angus scale (no SD).
Notes	Dropouts: 30%. The following drugs were allowed during the study: procyclidine or biperiden to control incapacitating EPS, and diazepam for agitation and/or insomnia (up to 30mg/day).The ITT analysis included those with at least one available evaluation. Jadad=5.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Pichot 1988a

Methods	Allocation: random - no further details. Blindness: double - no further details. Duration: 6 weeks (preceded by 1 week washout if participants had received any anti-depressant or neuroleptic treatment during previous week). Design: parallel, multi-centre (9 centres).
Participants	Diagnosis: schizophrenia (DSM-III), disorganised, undifferentiated or residual form, minimal score of 7 on the DSAS. N=60. Age: mean age in amisulpride group 42 years (22-53) and in fluphenazine group 35 years (21-49). Sex: female 19, male 43 History: chronic schizophrenia (present for at least 20 years) with a negative syndrome. Setting: inpatients.
Interventions	1. Amisulpride: dose range 50-300mg/day. N=34. 2. Fluphenazine: dose range 2-12mg/day. N=28.

Amisulpride for schizophrenia (Review)

Pichot 1988a (Continued)

Outcomes	Leaving the study early. Mental state: BPRS, DSAS. Unable to use - Global clinical assessment (no data). Behaviour: NOSIE (no data). Adverse events: CHES (no data). General tolerance: somatic and neurological examinations, ECG,EEG and lab tests (no data).
Notes	Dropouts: 32%. Jadad=3.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Pichot 1988b

Methods	Allocation: random - no further details. Blindness: double - no further details. Duration: 21 days (preceded by a 2 days washout phase for those that required a neuroleptic during the 48 hours preceding the trial). Design: parallel, multi-centre (8 centres).
Participants	Diagnosis: acute paranoid states, acute schizophrenia and acute episode of chronic schizophrenia corresponding to INSERM categories 04 and 02, BPRS total score at least 50. N=40. Age: mean age in amisulpride group 27 years (18-44) and in haloperidol group 29 years (18-60). Sex: female 17, male 22. History: acute psychotic state.
Interventions	1. Amisulpride: IM mean daily dose 860mg/day and PO mean daily dose 900mg/day. N=20. 2. Haloperidol: IM mean daily dose 19.5mg/day, PO mean daily doses 22.5mg/day (5th-10th day) and 21.5mg/day (10th-21st day). N=20. Everyone was treated IM for 4 days and PO for 17 days.
Outcomes	Leaving the study early. Unable to use - Mental state: BPRS (no endpoint). Behaviour: NOSIE (no data). Global assessment: (no data). Tolerance: CHES, neurological examination (no data). Physiological monitoring: ECG,EEG, lab tests (no data).
Notes	Dropouts: 40%. Conventional agents for EPS, blood pressure changes, insomnia or agitation were allowed. Jadad=3.

Risk of bias

Bias	Authors' judgement	Support for judgement
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Amisulpride for schizophrenia (Review)

Pichot 1988b (Continued)

Allocation concealment (selection bias)	Unclear risk	B - Unclear
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Puech 1998

Methods	Allocation: random - randomisation list, labelled bottles and sealed envelopes. Blindness: double - identical packaging. Duration: 28 days (preceded by a 3-7 days single-blind placebo washout phase). Design: parallel, multi-centre (56 centres).
Participants	Diagnosis: schizophrenia (DSM-III-R), a minimum score of 4 on at least two of four core positive symptoms of the BPRS. N=319. Age: mean 36 years. Sex: female 122, male 197. History: chronic or subchronic schizophrenia, duration ill mean 10.1 years, with acute exacerbation.
Interventions	1. Amisulpride: dose 100mg/day. N=61. 2. Amisulpride: dose 400mg/day. N=64. 3. Amisulpride: dose 800mg/day. N=65. 4. Amisulpride: dose 1200 mg/day. N=65. 5. Haloperidol: dose 16mg/day. N=64.
Outcomes	Leaving the study early. Global state: CGI (those rated 'very much' or much improved' at endpoint were considered as responders). Mental state: BPRS, PANSS. Extrapyramidal adverse events: EPRS. Other adverse events: UKU scale. Unable to use - EPS: AIMS, BAS (no data).
Notes	Dropouts: 26%. The following drugs were allowed during the study: biperiden or procyclidine, chloral hydrate, benzodiazepines. The ITT analysis included those who had at least one post-baseline evaluation. For the purpose of this work, the reviewers elected the amisulpride 800mg/day group for the comparison with haloperidol. Jadad=5.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Rüther 1988

Methods	Allocation: random - no further details. Blindness: double - no further details. Duration: 4 weeks. Design: parallel.
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Amisulpride for schizophrenia (Review)

Rüther 1988 (Continued)

Participants	Diagnosis: schizophrenia (ICD-9). N=30. Age: mean 36,6 years (SD 10.9 years). History: acutely ill. Sex: female 16, male 14.
Interventions	1. Amisulpride: dose range 200-1000 mg/day. N=15. 2. Perazine: dose range 200-1000 mg/day. N=15.
Outcomes	Leaving the study early. Unable to use - Global impression (attrition >40%). Mental state: BPRS (attrition >40%). Extrapyramidal symptoms: Webster scale (attrition >40%). Use of additional medication: (attrition >40%).
Notes	Dropouts: 53%. Jadad=2.
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment (selection bias)	Unclear risk B - Unclear

Saletu 1994

Methods	Allocation: random - randomisation was done by the sponsor, using coded numbers, coded bottles and serially numbered, sealed and opaque envelopes Blindness: double - a dummy technique was used. Duration: 6 weeks (preceded by a wash-out period of 3 days). Design: parallel, single-centre.
Participants	Diagnosis: schizophrenia (ICD 9), simple, hebephrenic or residual type. N=40. Age: mean 31 years. Sex: females 8, males 32. History: minimal length of illness of one year and a minimal age of 18 years. Setting: inpatients.
Interventions	1. Amisulpride: 50mg/day (week 1- 2), increased to 100mg/day (week 3-6). N=19. 2. Fluphenazine: 2mg/day (week 1-2), increased to 4mg/day (week 3-6). N=21.
Outcomes	Leaving the study early. Global state: CGI. Negative symptoms: AMDP system - under special consideration of the apathy syndrome, SANS). Extrapyramidal adverse events. Unable to use - EPS: Webster scale (no endpoint data). 'Noopsyche and thymopsyche symptoms' (no mean). Psychophysiological tests (no means). EEG Mapping (no mean).
Notes	Dropouts: 20%.

Amisulpride for schizophrenia (Review)

Saletu 1994 (Continued)

Jadad=5.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Speller 1997

Methods	Allocation: random - no further details. Blindness: double using a double-dummy technique. Duration: 1 year (for those receiving depot medication there was a 3-month washout phase, during which they received an equivalent oral dose of haloperidol). Design: parallel.
Participants	Diagnosis: schizophrenia (DSM-III-R), MS combined score of 4 or more on negative subscale. N=60. Age: median 63 years, range 35-76 years. Sex: female 14, male 46. History: chronic schizophrenia (median duration ill 36.7 years) with persistent and moderate to severe negative symptoms. Setting: inpatients.
Interventions	1. Amisulpride: dose range 100-800mg/day. N=29. 2. Haloperidol: dose range 3-20mg/day. N=31.
Outcomes	Leaving the study early. Mental state: MS - binary outcome. Extrapyramidal adverse events (use of antiparkinsonian medication). Other adverse events. Unable to use - Mental state: BPRS, CPRS, MS, SANS (no means). Social behaviour: SBS (no data). Extrapyramidal adverse events: BARS, EPRS, TDS (no data).
Notes	Dropouts: 20%. Jadad=4.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Wetzel 1998

Methods	Allocation: random - no further details. Blindness: double using a double-dummy technique. Duration: 6 weeks (preceded by 1-9 days single-blind placebo washout phase, mean duration 3.2 days in amisulpride group and 3.2 in flupenthixol group).
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Amisulpride for schizophrenia (Review)

Wetzel 1998 (Continued)

Design: parallel, multi-centre (11 centres).

Participants	Diagnosis: schizophrenia (DSM-III-R), BPRS total score at least 36. N=132. Age: mean ~ 34 years. Sex: female 58, male 74. History: acute schizophrenia with predominant positive symptoms. Setting: inpatients.
Interventions	1. Amisulpride: dose 1000mg/day, mean daily dosage was 956mg/day. N=70. 2. Flupentixol: dose 25mg/day, mean daily dosage was 22.6mg/day. N=62.
Outcomes	Leaving the study early. Global state: CGI. Mental state: BPRS, GAS, SAPS. Extrapyramidal symptoms. Adverse events: UKU. Unable to use - EPS scales: AIMS, BARS, EPRS (no endpoint data). Physiological monitoring: ECG, EEG, lab tests (no data). Prolactin levels.
Notes	Dropouts: 33%. The following drugs were allowed during the study: biperiden and diazepam. Jadad=4.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Ziegler 1989

Methods	Allocation: random - no further details. Blindness: double - no further details. Duration: 4 weeks days (preceded by a 3 days neuroleptic washout). Design: parallel.
Participants	Diagnosis: schizophrenia with paranoid and/or delusional symptoms (295.3). N=40. Age: mean 35.5 years, range 21-63. Sex: female 28, male 12. History: productive schizophrenia, illness mean duration of 5 years in AMI group and 7.5 years in HAL group.
Interventions	1. Amisulpride: a fixed-dose of 600mg/day for the first ten included patients. The following 10 patients received a flexible dose between 300-750mg/day. N=20. 2. Haloperidol: a fixed-dose of 12mg/ day for the first ten included patients . The following 10 patients received a flexible dose between 2.5-22.5mg/day. N=20.
Outcomes	Leaving the study early. Adverse events. Unable to use -

Amisulpride for schizophrenia (Review)

Ziegler 1989 (Continued)

Mental state: BPRS (no data).

Notes	Dropouts: 2.5%. The following drugs were allowed during the study: oxazepam as a sedative, chloral hydrate as sleep-medication and biperiden for extrapyramidal disorders. Jadad=3.
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Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

General abbreviations:

AMI - amisulpride.

HAL - haloperidol.

FPX - flupentixol.

ECG - Electrocardiograph.

EEG - Electroencephalograph.

EPS - Extrapyramidal side effects.

IM - intramuscular.

PO - per os (orally).

lab - laboratory.

SD - standard deviation.

Diagnostic tools:

DSM-III-R - Diagnostic and Statistical Manual of Mental disorders, third edition.

DSM-III-R - Diagnostic and Statistical Manual of Mental disorders, third edition, revised.

DSM-IV - Diagnostic and Statistical Manual of Mental disorders, fourth edition.

ICD-9 - International Classification of Diseases, ninth revision.

Global effect scales:

CGI - Clinical Global Impression.

GAS - Global Assessment Scale.

GCI - Global Clinical Impression.

Behaviour scale:

NOSIE - Nursing Observation Rating Scale for Inpatient Evaluation.

SBS - Social Behaviour Schedule.

SOFAS - Social and Occupational Functioning Assessment Scale.

Mental state scales:

AMDP system - Association for Methodology and Documentation in Psychiatry.

BPRS - Brief Psychiatric Rating Scale.

CPRS - Comprehensive Psychopathological Rating Scale.

DRRS - Depressive Retardation Rating Scale.

DSAS - Abridged scale of inhibition and deficiency.

MADRS - Montgomery and Asberg Depression Rating Scale.

MS - Manchester Scale

PANSS - Positive and Negative Symptom Scale.

PAS - Psychotic Anxiety Scale.

SADS-C - Schedule for Affective Disorders and Schizophrenia.

SANS - Scale for Assessment of Negative Symptoms.

SAPS - Scale for Assessment of Positive Symptoms.

Side effect scales:

AIMS - Abnormal Involuntary Movement Scale.

BARS - Barnes Akathisia Rating Scale.

CGI - Clinical Global Impression, side effects.

CHES - specific scale of unwanted effects.

DVP - scale for drug tolerance.

EPRS - Extrapyramidal Rating Scale by Simpson and Angus

ESRS - Extrapyramidal Symptom Rating Scale.

Amisulpride for schizophrenia (Review)

TDS - Tardive Dyskinesia Scale
 UKU - UKU Side Effects Rating Scale.
 Webster scale - for Parkinson's disease.
 Additional scales
 FSQ - Functional Status Questionnaire.
 QLS - Quality of Life Scale.

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

Study	Reason for exclusion
Baldauf 1988	Allocation: not randomised, review.
Bogetto 1995	Allocation: randomised. Participants: chronic schizophrenic outpatients with negative symptoms and treated with a stable dose of haloperidol for over 6 months. Interventions: addition of amisulpride or of fluoxetine, i.e. no relevant control group.
Brunner 1987	Allocation: not randomised, open trial.
Casey 1997	Allocation: not randomised, review.
Cassan 1985	Allocation: not randomised, review.
Chabannes 1998	Allocation: not randomised, open trial.
Clerc 1989	Allocation: randomised. Participants: those with schizophrenia. Interventions: amisulpride at different doses, no placebo or other antipsychotic as a comparator.
Colonna 1997	Allocation: not randomised, review.
Coukell 1996	Allocation: not randomised, review.
Coulouvrat 1999	Allocation: not randomised, review.
Darondel 1983	Allocation: not randomised, open trial.
Dollfus 1992	Allocation: randomised. Participants: children with autism and severe mental retardation, none with schizophrenia.
Duval 1993	Allocation: unclear, furthermore no clinical outcomes were indicated.
Gayral 1981	Allocation: not randomised, open trial.
Josserand 1988	Allocation: not randomised, review.
Jäger-Becker 1996	Allocation: not randomised, letter (review).
Lecrubier 1981	Allocation: not randomised, open trial.
Lecrubier 1988	Allocation: possibly randomised. Participants: non-psychotic participants with a "negative syndrome", those with schizophrenia were excluded.
Linde 1982	Allocation: not randomised, open trial.

Study	Reason for exclusion
Mann 1984	Allocation: not randomised, open trial.
Martinot 1996	Allocation: not randomised, open trial.
Maubray a 1988	Allocation: not randomised, review.
Maubray b 1988	Allocation: not randomised, review.
Mecheri 1993	Allocation: not randomised, open trial.
Pichot 1986	Allocation: not randomised, review.
Rein 1995	Allocation: not randomised, review.
Rein a 1996	Allocation: not randomised, review.
Rein b 1996	Allocation: not randomised, review.
Rein c 1996	Allocation: not randomised, review.
Singer 1983	Allocation: not randomised, open trial.
Singer 1990	Allocation: not randomised, open trial.
Souetre 1992	Allocation: random, but the data were extracted retrospectively from charts.
Sutter 1983	Allocation: not randomised, open trial.
Terra 1990	Allocation: not randomised, open trial.
Toren 1998	Allocation: not randomised, review.
Trichard 1998	Allocation: not randomised, PET study.
Tridon 1989	Allocation: not randomised, open trial.
Trieloff 1996	Allocation: not randomised, review.
Turjanski 1998	Allocation: not randomised, review.
Vaiva 1994	Allocation: not randomised, open trial.
Widlocher 1990	Allocation: not randomised, review.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Gray 1998

Methods
Participants
Interventions

Amisulpride for schizophrenia (Review)

Gray 1998 (Continued)

Outcomes

Notes

Probably a review - reference not obtained yet

DATA AND ANALYSES
Comparison 1. AMISULPRIDE versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early - overall	4	514	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.45, 0.80]
1.1 short term	3	373	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.36, 0.92]
1.2 medium/long term	1	141	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.49, 0.90]
2 Leaving the study early - specific reasons	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 lack of efficacy	4	514	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.29, 0.80]
2.2 adverse events	2	383	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.27, 0.97]
2.3 uncooperativeness	2	269	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.23, 2.34]
2.4 other reasons	3	487	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.53, 1.79]
2.5 worsening of negative symptoms	2	131	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.11, 2.07]
2.6 exacerbation of positive symptoms	2	131	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.07, 8.13]
2.7 mixed symptoms	2	131	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.02, 2.10]
3 Global state: CGI 'less than much improved'	1	242	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.52, 0.76]
4 Mental State: 1. General - BPRS total score at endpoint (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 Amisulpride 50mg/day	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Amisulpride 100mg/day	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Mental State: 2. Specific - Positive symptoms (unable to use- skewed data).			Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Mental State: 3. Specific - Negative symptoms - SANS total score at endpoint (high = poor)	1	324	Mean Difference (IV, Random, 95% CI)	-9.40 [-14.47, -4.34]
6.1 Amisulpride 50mg/day	1	167	Mean Difference (IV, Random, 95% CI)	-10.0 [-17.16, -2.84]
6.2 Amisulpride 100mg/day	1	157	Mean Difference (IV, Random, 95% CI)	-8.80 [-15.96, -1.64]
7 Mental State: 4. Specific - Depressive symptoms (unable to use - skewed data).			Other data	No numeric data
8 Mental state: 5. Need for additional medication	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 anxiolytics/sleep medications	1	104	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.51, 1.84]
9 Adverse events: 1. Presence of at least one adverse event	2	346	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.51, 1.97]
10 Adverse events: 2. Movement disorders	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 use of antiparkinsonian drug	2	346	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.23, 2.14]
10.2 extrapyramidal symptoms	1	242	Risk Ratio (M-H, Random, 95% CI)	2.09 [0.45, 9.61]
10.4 dyskinesia	1	242	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.17, 14.82]
10.5 tremor	1	242	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.02, 2.84]
11 Adverse events: 3. Movement disorder - unable to use (skewed data).			Other data	No numeric data
12 Adverse events: 4. Anticholinergic symptoms	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 overall	1	104	Risk Ratio (M-H, Random, 95% CI)	1.94 [0.44, 8.66]
13 Adverse events: 5. Sleep disorders	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 overall	2	346	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.67, 4.02]
14 Adverse events: 6. Other	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 somatic complaints	1	104	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.41, 3.59]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.2 at least one endocrine symptom	1	242	Risk Ratio (M-H, Random, 95% CI)	2.63 [0.13, 54.05]
14.3 anxiety/agitation	1	242	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.29, 1.89]
14.4 increase of 5% or more on body weight	1	242	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.47, 2.34]

Analysis 1.1. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 1 Leaving the study early - overall.

Analysis 1.2. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 2 Leaving the study early - specific reasons.

Analysis 1.3. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 3 Global state: CGI 'less than much improved'.

Analysis 1.4. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 4 Mental State: 1. General - BPRS total score at endpoint (high = poor).

Analysis 1.5. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 5 Mental State: 2. Specific - Positive symptoms (unable to use- skewed data)..

Mental State: 2. Specific - Positive symptoms (unable to use- skewed data).	
Study	
Danion 1999	<p>SAPS endpoint score - high = poor.</p> <p>1. Amisulpride 50mg/day: N=84, mean 20.5 , SD 18.2.</p> <p>2. Amisulpride 100mg/day: N=74, mean 17.5, SD 19.0.</p> <p>3. Placebo: N=83, mean 24.1, SD 20.8.</p>

Analysis 1.6. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 6 Mental State: 3. Specific - Negative symptoms - SANS total score at endpoint (high = poor).

Analysis 1.7. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 7 Mental State: 4. Specific - Depressive symptoms (unable to use - skewed data)..

Mental State: 4. Specific - Depressive symptoms (unable to use - skewed data).

Study

Danion 1999	MADRS endpoint scores - high=poor. 1. Amisulpride 50mg/day: N=84, mean 9.4, SD 8.5. 2. Amisulpride 100mg/day: N=74, mean 10.0, SD 7.5. 3. Placebo: N=83, mean 14.0, SD 9.9.
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Analysis 1.8. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 8 Mental state: 5. Need for additional medication.

Analysis 1.9. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 9 Adverse events: 1. Presence of at least one adverse event.

Analysis 1.10. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 10 Adverse events: 2. Movement disorders.

Analysis 1.11. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 11 Adverse events: 3. Movement disorder - unable to use (skewed data)..

Adverse events: 3. Movement disorder - unable to use (skewed data).

Study	
Danion 1999	Simpson-Angus Scale endpoint score - high=poor. 1. Amisulpride 50mg/day: N=84, mean 0.11, SD 1.26. 2. Amisulpride 100mg/day: N=74, mean 0.17, SD 0.33. 3. Placebo: N=83, mean 0.15, SD 0.34.
Danion 1999	AIMS endpoint score - high=poor. 1. Amisulpride 50mg/day: N=82, mean 0.9, SD 2.3. 2. Amisulpride 100mg/day: N=68, mean 1.6, SD 3.5. 3. Placebo: N=73, mean 1.0, SD 2.5.

Analysis 1.12. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 12 Adverse events: 4. Anticholinergic symptoms.

Analysis 1.13. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 13 Adverse events: 5. Sleep disorders.

Analysis 1.14. Comparison 1 AMISULPRIDE versus PLACEBO, Outcome 14 Adverse events: 6. Other.

Comparison 2. AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	3	519	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.09, 3.05]
1.1 suicide	2	390	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.04, 3.37]
1.2 suicide attempts	1	129	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.06, 15.41]
2 Leaving the study early - overall	14	1512	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.66, 0.87]
2.1 short term	11	764	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.55, 0.87]
2.2 medium/long term	3	748	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.57, 1.01]
3 Leaving the study early - specific reasons	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 lack of efficacy	11	1401	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.46, 0.87]
3.2 adverse events	11	1392	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.26, 0.59]
3.3 uncooperativeness	5	1140	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.81, 1.62]
3.4 recovery	5	901	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.27, 3.71]
3.5 other reasons	10	1383	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.60, 1.43]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Global state: 1. CGI less than 'much' improved	4	651	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.52, 0.87]
5 Global state: 2. CGI at endpoint	1	36	Mean Difference (IV, Random, 95% CI)	0.34 [-0.22, 0.90]
6 Mental State: 1.1 General - BPRS - less than 40% reduction of the total score	1	132	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.69, 1.14]
7 Mental State: 1.2 General - BPRS total score at endpoint	5	695	Mean Difference (IV, Random, 95% CI)	-4.21 [-6.53, -1.89]
8 Mental State: 2. Specific - Negative symptoms - less than 1 point reduction of the MS negative subscale	1	60	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.81, 1.54]
9 Mental State: 3. Specific - Negative symptoms - continuous data	5	589	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.58, -0.07]
9.1 SANS score (endpoint)	1	36	Std. Mean Difference (IV, Random, 95% CI)	0.35 [-0.31, 1.01]
9.2 PANSS negative sub-scale (endpoint)	3	506	Std. Mean Difference (IV, Random, 95% CI)	-0.33 [-0.50, -0.15]
9.3 DSAS score (endpoint)	1	47	Std. Mean Difference (IV, Random, 95% CI)	1.00 [-1.64, -0.35]
10 Mental State: 4. Specific - Positive symptoms - PANSS positive subscale at endpoint	2	312	Mean Difference (IV, Random, 95% CI)	-1.36 [-3.02, 0.29]
11 Mental State: 5. Need of anxiolytic/hypnotic medication	3	372	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.54, 1.11]
12 Adverse events: 1. Presence of at least one adverse event	6	751	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.78, 0.97]
13 Adverse events: 2. Movement disorders	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 at least one extrapyramidal symptom	7	771	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.56, 0.85]
13.2 use of antiparkinsonian drugs	9	851	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.49, 0.76]
13.3 akathisia	3	270	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.45, 0.94]
13.4 akinesia	2	59	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.33, 1.13]
13.5 dystonia	2	59	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.21, 3.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.6 parkinsonian side effects at endpoint	1	60	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.49, 1.04]
13.7 rigidity	2	239	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.28, 0.80]
13.8 tardive dyskinesia	2	259	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.00, 33.80]
13.9 tremor	2	239	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.25, 0.71]
14 Adverse events: 3. Movement disorders - skewed data.			Other data	No numeric data
15 Adverse events: 4. Anticholinergic symptoms	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 blurred vision	3	232	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.41, 1.16]
15.2 dry mouth	3	299	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.20, 2.38]
15.3 constipation	3	232	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.58, 2.80]
15.4 urinary retention	1	60	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.16, 7.10]
15.5 nasal stuffiness	1	60	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.13, 1.61]
16 Adverse events: 5. Cardiovascular symptoms (tachycardia/palpitations)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
17 Adverse events: 6. Endocrine and sexual events	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
17.1 galactorrhea	2	331	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.23, 3.21]
17.2 gynecomastia	1	132	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.13, 6.10]
17.3 menstrual disturbance	2	257	Risk Ratio (M-H, Random, 95% CI)	1.94 [0.36, 10.60]
17.4 ejaculatory/erectile dysfunction	3	329	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.18, 1.67]
17.5 at least one endocrine event	4	579	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.44, 1.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18 Adverse events: 7. Other	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
18.1 anxiety/agitation	3	363	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.68, 1.54]
18.2 insomnia	3	291	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.23, 1.08]
18.3 drowsiness/sedation	5	622	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.45, 1.73]
18.4 increased duration of sleep	1	132	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.35, 1.01]
18.5 headache	1	132	Risk Ratio (M-H, Random, 95% CI)	2.48 [0.95, 6.49]
18.6 suicide attempts	1	129	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.06, 15.41]
18.7 sweating	2	192	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.57, 2.54]
18.8 weight gain	2	331	Risk Ratio (M-H, Random, 95% CI)	2.98 [0.15, 60.76]

Analysis 2.1. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 1 Death.

Study or subgroup	Amisulpride n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: $Z=0.71$ ($P=0.48$)					
Test for subgroup differences: $\chi^2=0.32$, $df=1$ ($P=0.57$), $I^2=0\%$					
<div>amisulpride 0.1 0.2 0.5 1 2 5 10 typical</div>					

Analysis 2.2. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 2 Leaving the study early - overall.

Study or subgroup	Amisulpride n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 short term					
Costa e Silva 1989	2/20	2/20		0.58%	1[0.16,6.42]
Delcker 1990	1/21	3/20		0.42%	0.32[0.04,2.8]
Klein 1985	0/9	5/10		0.26%	0.1[0.01,1.59]
Möller 1997	25/95	39/96		11.66%	0.65[0.43,0.98]
Pichot 1988a	10/34	10/28		3.86%	0.82[0.4,1.69]
Pichot 1988b	7/20	9/20		3.38%	0.78[0.36,1.68]
Puech 1998	10/65	21/64		4.47%	0.47[0.24,0.92]
Rüther 1988	9/15	7/15		4.32%	1.29[0.65,2.54]
Saletu 1994	3/19	5/21		1.2%	0.66[0.18,2.41]
Wetzel 1998	19/70	25/62		8.38%	0.67[0.41,1.1]
Ziegler 1989	0/20	1/20		0.2%	0.33[0.01,7.72]
Subtotal (95% CI)	388	376		38.74%	0.7[0.55,0.87]
Total events: 86 (Amisulpride), 127 (Control)					
Heterogeneity: $\tau^2=0$; $\chi^2=7.91$, $df=10$ ($P=0.64$); $I^2=0\%$					
Test for overall effect: $Z=3.13$ ($P=0$)					
2.2.2 medium/long term					
Carrière 2000	24/94	46/105		12.05%	0.58[0.39,0.88]
Colonna 2000	167/370	62/119		47.32%	0.87[0.71,1.06]
Speller 1997	5/29	7/31		1.89%	0.76[0.27,2.14]
Subtotal (95% CI)	493	255		61.26%	0.76[0.57,1.01]
Total events: 196 (Amisulpride), 115 (Control)					
Heterogeneity: $\tau^2=0.02$; $\chi^2=3$, $df=2$ ($P=0.22$); $I^2=33.28\%$					
Test for overall effect: $Z=1.91$ ($P=0.06$)					
Total (95% CI)	881	631		100%	0.76[0.66,0.87]
Total events: 282 (Amisulpride), 242 (Control)					
Heterogeneity: $\tau^2=0$; $\chi^2=11.93$, $df=13$ ($P=0.53$); $I^2=0\%$					
Test for overall effect: $Z=3.86$ ($P=0$)					
Test for subgroup differences: $\chi^2=0.21$, $df=1$ ($P=0.64$), $I^2=0\%$					
<div>Favours amisulpride 0.1 0.2 0.5 1 2 5 10 Favours typical</div>					

Analysis 2.3. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 3 Leaving the study early - specific reasons.

Analysis 2.4. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 4 Global state: 1. CGI less than 'much' improved.

Analysis 2.5. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 5 Global state: 2. CGI at endpoint.

Analysis 2.6. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 6 Mental State: 1.1 General - BPRS - less than 40% reduction of the total score.

Analysis 2.7. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 7 Mental State: 1.2 General - BPRS total score at endpoint.

Analysis 2.8. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 8 Mental State: 2. Specific - Negative symptoms - less than 1 point reduction of the MS negative subscale.

Analysis 2.9. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 9 Mental State: 3. Specific - Negative symptoms - continuous data.

Analysis 2.10. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 10 Mental State: 4. Specific - Positive symptoms - PANSS positive subscale at endpoint.

**Analysis 2.11. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS,
Outcome 11 Mental State: 5. Need of anxiolytic/hypnotic medication.** **Analysis 2.12. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS,
Outcome 12 Adverse events: 1. Presence of at least one adverse event.** **Analysis 2.13. Comparison 2 AMISULPRIDE versus TYPICAL
ANTIPSYCHOTICS, Outcome 13 Adverse events: 2. Movement disorders.**

Analysis 2.14. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 14 Adverse events: 3. Movement disorders - skewed data..

Adverse events: 3. Movement disorders - skewed data.			
Study	General EPS	Dyskinesia	Akathisia
Möller 1997	Simpson-Angus Scale endpoint score - high=poor. 1. Amisulpride: N=93, mean 0.40, SD 0.51. 2. Haloperidol: N=93, mean 0.63, SD 0.59.	AIMS endpoint scores - high=poor. 1. Amisulpride: N=87, mean 2.6, SD 4.6. 2. Haloperidol: N=85, mean 3.8, SD 5.3.	
Puech 1998	Simpson-Angus Scale endpoint score - high=poor. 1. Amisulpride 100mg/day: N=61, mean 0.18, SD 0.33. 2. Amisulpride 400mg/day: N=64, mean 0.20, SD 0.33. 3. Amisulpride 800mg/day: N=65, mean 0.26, SD 0.45. 4. Amisulpride 1200mg/day: N=65, mean 0.23, SD 0.40. 5. Haloperidol 16mg/day: N=64, mean 0.40, SD 0.49, N=64.		
Wetzel 1998	Simpson-Angus Scale change - low=poor. 1. Amisulpride: N=70, mean 1.1, SD 3.7. 2. Flupentixol: N=62, mean 3.8, SD 5.9.	AIMS change - low=poor. 1. Amisulpride: N=70, mean 0.0, SD 2.8. 2. Flupentixol: N=62, mean 1.8, SD 4.4.	BAS total score change - low=poor: 1. Amisulpride: N=70, mean 0.2, SD 1.9. 2. Flupentixol: N=62, mean 1.6, SD 2.4.

Analysis 2.15. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 15 Adverse events: 4. Anticholinergic symptoms.

**Analysis 2.16. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS,
Outcome 16 Adverse events: 5. Cardiovascular symptoms (tachycardia/palpitations).**

Study or subgroup	Amisulpride n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Costa e Silva 1989	7/20	5/20		0%	1.4[0.53,3.68]
Speller 1997	3/29	7/31		0%	0.46[0.13,1.61]

**Analysis 2.17. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS,
Outcome 17 Adverse events: 6. Endocrine and sexual events.**

Study or subgroup	Amisulpride n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.17.1 galactorrhea					
Carrière 2000	0/94	2/105		18.85%	0.22[0.01,4.59]
Wetzel 1998	4/70	3/62		81.15%	1.18[0.27,5.07]
Subtotal (95% CI)	164	167		100%	0.86[0.23,3.21]
Total events: 4 (Amisulpride), 5 (Control) Heterogeneity: Tau ² =0; Chi ² =0.97, df=1(P=0.32); I ² =0% Test for overall effect: Z=0.22(P=0.83)					
2.17.2 gynecomastia					
Wetzel 1998	2/70	2/62		100%	0.89[0.13,6.1]
Subtotal (95% CI)	70	62		100%	0.89[0.13,6.1]
Total events: 2 (Amisulpride), 2 (Control) Heterogeneity: Not applicable Test for overall effect: Z=0.12(P=0.9)					
2.17.3 menstrual disturbance					
Carrière 2000	3/94	0/105		26.53%	7.81[0.41,149.26]
Wetzel 1998	5/34	3/24		73.47%	1.18[0.31,4.46]
Subtotal (95% CI)	128	129		100%	1.94[0.36,10.6]
Total events: 8 (Amisulpride), 3 (Control) Heterogeneity: Tau ² =0.56; Chi ² =1.41, df=1(P=0.24); I ² =29% Test for overall effect: Z=0.77(P=0.44)					
2.17.4 ejaculatory/erectile dysfunction					
Carrière 2000	1/64	0/72		12.12%	3.37[0.14,81.27]
Möller 1997	0/61	1/58		12.14%	0.32[0.01,7.63]
Wetzel 1998	3/36	7/38		75.74%	0.45[0.13,1.62]
Subtotal (95% CI)	161	168		100%	0.55[0.18,1.67]
Total events: 4 (Amisulpride), 8 (Control) Heterogeneity: Tau ² =0; Chi ² =1.46, df=2(P=0.48); I ² =0% Test for overall effect: Z=1.05(P=0.29)					
2.17.5 at least one endocrine event					
Carrière 2000	5/94	2/105		21.89%	2.79[0.55,14.06]
Möller 1997	0/95	1/96		5.63%	0.34[0.01,8.17]
Puech 1998	7/65	9/64		66.76%	0.77[0.3,1.93]
Speller 1997	0/29	1/31		5.72%	0.36[0.02,8.39]
Subtotal (95% CI)	283	296		100%	0.93[0.44,1.98]

Analysis 2.18. Comparison 2 AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 18 Adverse events: 7. Other.

Comparison 3. AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 overall	1	228	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.76, 1.69]
1.2 lack of efficacy	1	228	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.32, 1.92]
1.3 adverse events	1	228	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.53, 2.08]
1.4 other reasons	1	228	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.75, 3.94]
2 Global state: CGI 'less than much improved'	1	228	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.56, 1.09]
3 Mental State: 1. General - BPRS total score (dichotomised data)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 20% reduction in total score	1	228	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.55, 1.41]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 40% reduction in total score	1	228	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.56, 1.09]
4 Mental state: 2. General - BPRS total score at endpoint	1	228	Mean Difference (IV, Random, 95% CI)	-1.5 [-5.39, 2.39]
5 Mental State: 3. Specific - negative symptoms - PANSS negative scale at endpoint	1	228	Mean Difference (IV, Random, 95% CI)	-1.80 [-3.82, 0.22]
6 Mental state: 4. Specific - positive symptoms - PANSS positive subscale at endpoint	1	228	Mean Difference (IV, Random, 95% CI)	0.0 [-1.87, 1.87]
7 Mental State: 5. Use of additional anxiolytic medication (diazepam)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8 Adverse events: 1. At least one adverse event	1	228	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.97, 1.34]
9 Adverse events: 2. Movement disorders	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 at least one extrapyramidal symptom	1	228	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.79, 1.71]
9.2 'extrapyramidal syndrome'	1	228	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.65, 2.52]
9.3 akathisia at endpoint according to the Barnes akathisia scale	1	228	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.91, 1.09]
9.4 hyperkinesia	1	228	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.64, 2.79]
9.5 hypertonia	1	228	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.54, 4.01]
9.6 use of antiparkinsonian drugs	1	228	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.86, 2.05]
9.7 tremor	1	228	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.21, 1.82]
10 Adverse events: 3. Endocrine and sexual adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 at least one endocrine event	1	228	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.36, 2.71]
10.2 galactorrhea (females)	1	91	Risk Ratio (M-H, Random, 95% CI)	2.67 [0.55, 13.06]
10.3 impotence (males)	1	137	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.03, 2.91]
11 Adverse events: 4. 'Psychiatric' adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 agitation	1	228	Risk Ratio (M-H, Random, 95% CI)	3.44 [1.17, 10.13]
11.2 anxiety	1	228	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.55, 3.56]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.3 insomnia	1	228	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.50, 3.00]
12 Adverse events: 5. Other	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 constipation	1	228	Risk Ratio (M-H, Random, 95% CI)	7.86 [1.00, 61.84]
12.2 headache	1	228	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.59, 2.64]
12.3 increased salivation	1	228	Risk Ratio (M-H, Random, 95% CI)	1.77 [0.61, 5.12]
12.4 rhinitis	1	228	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.29, 1.98]
12.5 vomiting	1	228	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.52, 5.71]
12.6 weight increase	1	228	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.19, 2.26]

Analysis 3.1. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 1 Leaving the study early.

Analysis 3.2. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 2 Global state: CGI 'less than much improved'.

Analysis 3.3. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 3 Mental State: 1. General - BPRS total score (dichotomised data).

Analysis 3.4. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 4 Mental state: 2. General - BPRS total score at endpoint.

Analysis 3.5. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 5 Mental State: 3. Specific - negative symptoms - PANSS negative scale at endpoint.

Analysis 3.6. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 6 Mental state: 4. Specific - positive symptoms - PANSS positive subscale at endpoint.

Analysis 3.7. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 7 Mental State: 5. Use of additional anxiolytic medication (diazepam).

Analysis 3.8. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 8 Adverse events: 1. At least one adverse event.

Analysis 3.9. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 9 Adverse events: 2. Movement disorders.

Analysis 3.10. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 10 Adverse events: 3. Endocrine and sexual adverse events.

Analysis 3.11. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 11 Adverse events: 4. 'Psychiatric' adverse events.

Study or subgroup	Amisulpride n/N	Risperidone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Not applicable Test for overall effect: $Z=0.45(P=0.65)$					
			amisulpride 0.1 0.2 0.5 1 2 5 10 control		

Analysis 3.12. Comparison 3 AMISULPRIDE versus ATYPICAL ANTIPSYCHOTICS, Outcome 12 Adverse events: 5. Other.

Study or subgroup	Amisulpride n/N	Risperidone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.12.1 constipation					
Peuskens 1999	8/115	1/113		100%	7.86[1.61,84]
Subtotal (95% CI)	115	113		100%	7.86[1.61,84]
Total events: 8 (Amisulpride), 1 (Risperidone) Heterogeneity: Not applicable Test for overall effect: $Z=1.96(P=0.05)$					
3.12.2 headache					
Peuskens 1999	14/115	11/113		100%	1.25[0.59,2.64]
Subtotal (95% CI)	115	113		100%	1.25[0.59,2.64]
Total events: 14 (Amisulpride), 11 (Risperidone) Heterogeneity: Not applicable Test for overall effect: $Z=0.59(P=0.56)$					
3.12.3 increased salivation					
Peuskens 1999	9/115	5/113		100%	1.77[0.61,5.12]
Subtotal (95% CI)	115	113		100%	1.77[0.61,5.12]
Total events: 9 (Amisulpride), 5 (Risperidone) Heterogeneity: $\text{Tau}^2=0$; $\text{Chi}^2=0$, $\text{df}=0(P<0.0001)$; $I^2=100\%$ Test for overall effect: $Z=1.05(P=0.29)$					
3.12.4 rhinitis					
Peuskens 1999	7/115	9/113		100%	0.76[0.29,1.98]
Subtotal (95% CI)	115	113		100%	0.76[0.29,1.98]
Total events: 7 (Amisulpride), 9 (Risperidone) Heterogeneity: Not applicable Test for overall effect: $Z=0.55(P=0.58)$					
3.12.5 vomiting					
Peuskens 1999	7/115	4/113		100%	1.72[0.52,5.71]
Subtotal (95% CI)	115	113		100%	1.72[0.52,5.71]
Total events: 7 (Amisulpride), 4 (Risperidone) Heterogeneity: Not applicable Test for overall effect: $Z=0.88(P=0.38)$					
3.12.6 weight increase					
Peuskens 1999	4/115	6/113		100%	0.66[0.19,2.26]
Subtotal (95% CI)	115	113		100%	0.66[0.19,2.26]
Total events: 4 (Amisulpride), 6 (Risperidone) Heterogeneity: Not applicable					
			amisulpride 0.1 0.2 0.5 1 2 5 10 amisulpride

Comparison 4. SUBGROUP ANALYSIS: AMISULPRIDE versus PLACEBO - SHORT DURATION OF ILLNESS versus CHRONIC ILLNESS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early - overall	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 short course	1	27	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.45, 2.78]
1.2 chronic	3	487	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.46, 0.73]
2 Mental State: Specific - negative symptoms - SANS total score at endpoint	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 short course	1	20	Mean Difference (IV, Random, 95% CI)	-16.6 [-33.00, -0.20]
2.2 chronic	1	157	Mean Difference (IV, Random, 95% CI)	-8.80 [-15.96, -1.64]
3 Adverse events: 1. At least one adverse event	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 short course	1	27	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.74, 1.39]
3.2 chronic	2	346	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.51, 1.97]
4 Adverse events: 2. Extrapyramidal symptoms	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 short course	1	27	Risk Ratio (M-H, Random, 95% CI)	2.23 [1.08, 4.58]
4.2 chronic	1	242	Risk Ratio (M-H, Random, 95% CI)	2.09 [0.45, 9.61]
5 Adverse events: 3. Sleep disorders	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 short course	1	27	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.65, 3.39]
5.2 chronic	2	346	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.67, 4.02]

Analysis 4.1. Comparison 4 SUBGROUP ANALYSIS: AMISULPRIDE versus PLACEBO - SHORT DURATION OF ILLNESS versus CHRONIC ILLNESS, Outcome 1 Leaving the study early - overall.

Analysis 4.2. Comparison 4 SUBGROUP ANALYSIS: AMISULPRIDE versus PLACEBO - SHORT DURATION OF ILLNESS versus CHRONIC ILLNESS, Outcome 2 Mental State: Specific - negative symptoms - SANS total score at endpoint.

Analysis 4.3. Comparison 4 SUBGROUP ANALYSIS: AMISULPRIDE versus PLACEBO - SHORT DURATION OF ILLNESS versus CHRONIC ILLNESS, Outcome 3 Adverse events: 1. At least one adverse event.

Analysis 4.4. Comparison 4 SUBGROUP ANALYSIS: AMISULPRIDE versus PLACEBO - SHORT DURATION OF ILLNESS versus CHRONIC ILLNESS, Outcome 4 Adverse events: 2. Extrapyramidal symptoms.

Analysis 4.5. Comparison 4 SUBGROUP ANALYSIS: AMISULPRIDE versus PLACEBO - SHORT DURATION OF ILLNESS versus CHRONIC ILLNESS, Outcome 5 Adverse events: 3. Sleep disorders.

Comparison 5. POST-HOC ANALYSIS: EFFICACY - AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global state: CGI less 'than much improved'	4	940	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.61, 0.93]
2 Mental State: 1. General - BPRS total score at endpoint	5	983	Mean Difference (IV, Random, 95% CI)	-4.26 [-6.42, -2.10]
3 Mental State: 2. Specific - negative symptoms - PANSS negative subscale at endpoint	3	794	Mean Difference (IV, Random, 95% CI)	-2.89 [-4.12, -1.65]
4 Mental State: 3. Specific - positive symptoms - PANSS positive subscale at endpoint	3	794	Mean Difference (IV, Random, 95% CI)	-1.66 [-2.87, -0.44]

Analysis 5.1. Comparison 5 POST-HOC ANALYSIS: EFFICACY - AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 1 Global state: CGI less 'than much improved'.

Analysis 5.2. Comparison 5 POST-HOC ANALYSIS: EFFICACY - AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 2 Mental State: 1. General - BPRS total score at endpoint.

Analysis 5.3. Comparison 5 POST-HOC ANALYSIS: EFFICACY - AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 3 Mental State: 2. Specific - negative symptoms - PANSS negative subscale at endpoint.

Analysis 5.4. Comparison 5 POST-HOC ANALYSIS: EFFICACY - AMISULPRIDE versus TYPICAL ANTIPSYCHOTICS, Outcome 4 Mental State: 3. Specific - positive symptoms - PANSS positive subscale at endpoint.

WHAT'S NEW

Date	Event	Description
12 December 2012	Amended	In response to comments, we have realised that in one study (Paillère-Martinot 95) the attrition rate was higher than 40%. According to our protocol this study had to be removed from all outcomes except for leaving the study early. This only changed

Date	Event	Description
		<p>results for one outcome, amisulpride no longer caused more EPS than placebo. However, this is an outcome we had critically commented on in the original version because it was not consistent using the risk difference and because a similar measure, use of antiparkinson medication, was also not significant.</p> <p>Overall conclusions of the review are not altered.</p> <p>See also Published notes.</p>

HISTORY

Protocol first published: Issue 1, 1999

Review first published: Issue 2, 2002

Date	Event	Description
26 April 2012	Amended	Additional table: removed and text moved to Studies awaiting classification
14 January 2009	Amended	Author correction
24 April 2008	Amended	Converted to new review format.
22 January 2002	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Joaquim Ignacio Silveira da Mota Neto - prepared protocol, selected studies, extracted data, summated data, produced report.

Mauricio Silva de Lima - checked selection of abstracts and studies, checked data extraction, helped to write the report.

Bernardo Garcia de Oliveira Soares - checked selection of abstracts and studies, checked data extraction.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Universidade Federal de Pelotas, Brazil.

External sources

- No sources of support supplied

NOTES

It has been drawn to our attention that parts of the data of this review needed correction (1). All comments relate to the placebo comparison. We have amended the review by removing from the analyses data from the study [Paillère-Martinot 95](#) for all outcomes, except for leaving the study early, due to high attrition. However we have found no substantive issue that changes conclusions.

1. Hutton P, Morrison AP, Yung AR, Taylor PJ, French P, Dunn G. Effects of drop-out on efficacy estimates in five Cochrane reviews of popular antipsychotics for schizophrenia. *Acta Psychiatr Scand*. 2012 Jul;126(1):1–11.

INDEX TERMS

Medical Subject Headings (MeSH)

Amisulpride; Antipsychotic Agents [*therapeutic use]; Randomized Controlled Trials as Topic; Schizophrenia [*drug therapy]; Sulpiride [*analogs & derivatives] [*therapeutic use]

MeSH check words

Humans