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Risperidone versus placebo for schizophrenia (Review)

Rattehalli RD, Zhao S, Li BG, Jayaram MB, Xia J, Sampson S

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[Intervention Review]

Risperidone versus placebo for schizophrenia

Ranganath D Rattehalli[1], Sai Zhao[2], Bao Guo Li[3], Mahesh B Jayaram[4], Jun Xia[5], Stephanie Sampson[6]

[1]General Psychiatry, Logan Hospital, Brisbane, Australia. [2]Systematic Review Solutions Ltd, Tianjin, China. [3]Interventional therapy department, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China. [4]Department of Psychiatry, Melbourne Neuropsychiatry Centre, Melbourne, Australia. [5]Cochrane Schizophrenia Group, The University of Nottingham, Nottingham, UK. [6]The University of Nottingham, Nottingham, UK

Contact address: Ranganath D Rattehalli, General Psychiatry, Logan Hospital, Meadowbrook, Brisbane, QLD 4131, Australia. rdrattehalli@hotmail.com.

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ABSTRACT

Background

Risperidone is the first new-generation antipsychotic drug made available in the market in its generic form.

Objectives

To determine the clinical effects, safety and cost-effectiveness of risperidone compared with placebo for treating schizophrenia.

Search methods

On 19th October 2015, we searched the Cochrane Schizophrenia Group Trials Register, which is based on regular searches of CINAHL, BIOSIS, AMED, EMBASE, PubMed, MEDLINE, PsycINFO, and registries of clinical trials. We checked the references of all included studies and contacted industry and authors of included studies for relevant studies and data.

Selection criteria

Randomised clinical trials (RCTs) comparing oral risperidone with placebo treatments for people with schizophrenia and/or schizophrenia-like psychoses.

Data collection and analysis

Two review authors independently screened studies, assessed the risk of bias of included studies and extracted data. For dichotomous data, we calculated the risk ratio (RR), and the 95% confidence interval (CI) on an intention-to-treat basis. For continuous data, we calculated mean differences (MD) and the 95% CI. We created a 'Summary of findings table' using GRADE (Grading of Recommendations Assessment, Development and Evaluation).

Main results

The review includes 15 studies (N = 2428). Risk of selection bias is unclear in most of the studies, especially concerning allocation concealment. Other areas of risk such as missing data and selective reporting also caused some concern, although not affected on the direction of effect of our primary outcome, as demonstrated by sensitivity analysis. Many of the included trials have industry sponsorship of involvement. Nonetheless, generally people in the risperidone group are more likely to achieve a significant clinical improvement in mental state (6 RCTs, N = 864, RR 0.64, CI 0.52 to 0.78, *very low-quality evidence*). The effect withstood, even when three studies with >50% attrition rate were removed from the analysis (3 RCTs, N = 589, RR 0.77, CI 0.67 to 0.88). Participants receiving placebo were less likely to have a clinically significant improvement on Clinical Global Impression scale (CGI) than those receiving risperidone (4 RCTs, N = 594, RR

0.69, CI 0.57 to 0.83, *very low-quality evidence*). Overall, the risperidone group was 31% less likely to leave early compared to placebo group (12 RCTs, N = 2261, RR 0.69, 95% CI 0.62 to 0.78, *low-quality evidence*), but Incidence of significant extrapyramidal side effect was more likely to occur in the risperidone group (7 RCTs, N = 1511, RR 1.56, 95% CI 1.13 to 2.15, *very low-quality evidence*).

When risperidone and placebo were augmented with clozapine, there is no significant differences between groups for clinical response as defined by a less than 20% reduction in PANSS/BPRS scores (2 RCTs, N = 98, RR 1.15, 95% CI 0.93 to 1.42, *low-quality evidence)* and attrition (leaving the study early for any reason) (3 RCTs, N = 167, RR 1.13, 95% CI 0.53 to 2.42, *low quality evidence)*. One study measured clinically significant responses using the CGI, no effect was evident (1 RCT, N = 68, RR 1.12 95% CI 0.87 to 1.44, *low quality evidence*). No data were available for extrapyramidal adverse effects.

Authors' conclusions

Based on low quality evidence, risperidone appears to be benefitial in improving mental state compared with placebo, but it also causes more adverse events. Eight out of the 15 included trials were funded by pharmaceutical companies. The currently available evidence is*very low* to *low quality*.

PLAIN LANGUAGE SUMMARY

Risperidone versus placebo for schizophrenia

Review question

Is risperidone (tablet form) more effective than placebo in treating the symptoms of schizophrenia or schizophrenia-like illnesses?

Background

People with schizophrenia often hear voices and see things (hallucinations) and have strange beliefs (delusions). These are called ‘positive symptoms’. Mental illness also causes tiredness, apathy, emotional numbness, and withdrawal. These are called ‘negative symptoms’. The main treatment for the symptoms of schizophrenia are antipsychotic drugs. Antipsychotic drugs can be classified into typical (older) and atypical (newer) drugs. Typical antipsychotics such as chlorpromazine and haloperidol have been the mainstay of treatment for decades, and have been effective in reducing the positive symptoms of schizophrenia. Negative symptoms, however, have been fairly resistant to treatment. In addition, drug treatments are associated with unpleasant side effects that cause people to stop taking medication, which may lead to relapse. It is thought that newer atypical antipsychotics, such as risperidone, are more effective than the older antipsychotics as they reduce the positive symptoms but cause fewer side effects.

Study characteristics

Searches for high-quality randomised trials were carried out in 2008, 2013 and 2015. The review now includes 15 studies with 2428 participants. The studies randomised participants (in- and outpatients) with schizophrenia or schizophrenia-like illnesses into treatment groups that received oral risperidone or placebo.

Key results

Results from limited data suggest that risperidone is more effective than placebo for reducing the overall symptoms of schizophrenia, and participants receiving risperidone were more likely to comply with treatment. However, like the older typical antipsychotics, risperidone was also associated with serious side effects, such as parkinsonism.

Quality of the evidence

The evidence available was very low quality. Information and data were limited, poorly reported, and probably biased in favour of risperidone . Nearly half of the included trials were funded by drug companies. Firm conclusions are difficult to make based on the results of this review. Better conduct and reporting of trials could increase confidence in the results.

Ben Gray, Senior Peer Researcher, McPin Foundation. http://mcpin.org/

Summary of findings for the main comparison. RISPERIDONE compared to PLACEBO for schizophrenia

RISPERIDONE compared to PLACEBO for schizophrenia

Patient or population: patients with schizophrenia
Settings: inpatient and outpatient
Intervention: RISPERIDONE
Comparison: PLACEBO

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	PLACEBO	RISPERIDONE				
Mental state: no clinically significant response in psychotic symptoms (defined by various scale total score change) - short term (up to 12 weeks) - defined by PANSS/BPRS <20% decline Follow-up: 12 weeks	**Study population**		**RR 0.64** (0.52 to 0.78)	864 (6 studies)	⊕⊝⊝⊝ **Very Low** [1,2,3]	
	692 per 1000	**443 per 1000** (360 to 540)				
	Moderate					
	733 per 1000	**469 per 1000** (381 to 572)				
Leaving the study early - short term (up to 12 weeks) - any reason Follow-up: 12 weeks	**Study population**		**RR 0.69** (0.62 to 0.78)	2261 (12 studies)	⊕⊕⊝⊝ **Low** [1,3]	
	495 per 1000	**342 per 1000** (307 to 386)				
	Moderate					
	486 per 1000	**335 per 1000** (301 to 379)				
Global state: 2. no significant clinical improvement - CGI, short term (up to 12 weeks) Follow-up: 12 weeks	**Study population**		**RR 0.69** (0.57 to 0.83)	594 (4 studies)	⊕⊝⊝⊝ **very low** [1,2,3]	
	744 per 1000	**513 per 1000** (424 to 618)				
	Moderate					

	732 per 1000	**505 per 1000** (417 to 608)			
Adverse effects: 1a. extrapyramidal - various effects - short term (up to 12 weeks) - general - any significant EPS Follow-up: 12 weeks	**Study population**		**RR 1.56** (1.13 to 2.15)	1511 (7 studies)	⊕⊕⊝⊝ **Low** [1,3]
	73 per 1000	**113 per 1000** (82 to 156)			
	Moderate				
	106 per 1000	**165 per 1000** (120 to 228)			

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

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

[1] Downgraded one level due to risk of bias: studies contributing data to this body of evidence have unclear or high risk of bias in one or more domains, some were also sponsored by pharmaceutical companies.
[2] Downgraded one level due to inconsistency: some concerns of heterogeneity were identified.
[3] Downgraded one level due to publication bias: 'strongly suspected' - most studies were sponsored by pharmaceutical companies.

Summary of findings 2. RISPERIDONE + CLOZAPINE compared to PLACEBO + CLOZAPINE for schizophrenia

RISPERIDONE + CLOZAPINE compared to PLACEBO + CLOZAPINE for schizophrenia

Patient or population: people with schizophrenia
Settings: inpatient and outpatient
Intervention: RISPERIDONE + CLOZAPINE
Comparison: PLACEBO + CLOZAPINE

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				

	PLACEBO + CLOZAPINE	RISPERIDONE + CLOZAPINE				
Mental state: no clinically significant response in psychotic symptoms - short term PANSS/BPRS < 20% decline Follow-up: 6-8 weeks	**Moderate**[1] **725 per 1000**	**834 per 1000** (674 to 1000)	**RR 1.15** (0.93 to 1.42)	98 (2 studies)	⊕⊕⊖⊖ **low** [1,2]	
Leaving the study early due to any reason - short term Follow-up: 12 weeks	**119 per 1000**	**135 per 1000** (63 to 288)	**RR1.13** (0.53 to 2.42)	167 (3 studies)	⊕⊖⊖⊖ **very low** [1,2,3]	
Global state: no significant clinical improvement - CGI short term Follow-up: 8 weeks	**735 per 1000** [3]	**824 per 1000** (640 to 1000)	**RR 1.12** (0.87 to 1.44)	68 (1 study)	⊕⊕⊖⊖ **low** [1,2]	
Adverse effects: extrapyramidal - short term Follow-up: 12 weeks	See comment	See comment	Not estimable	-	See comment	No study reported this outcome

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

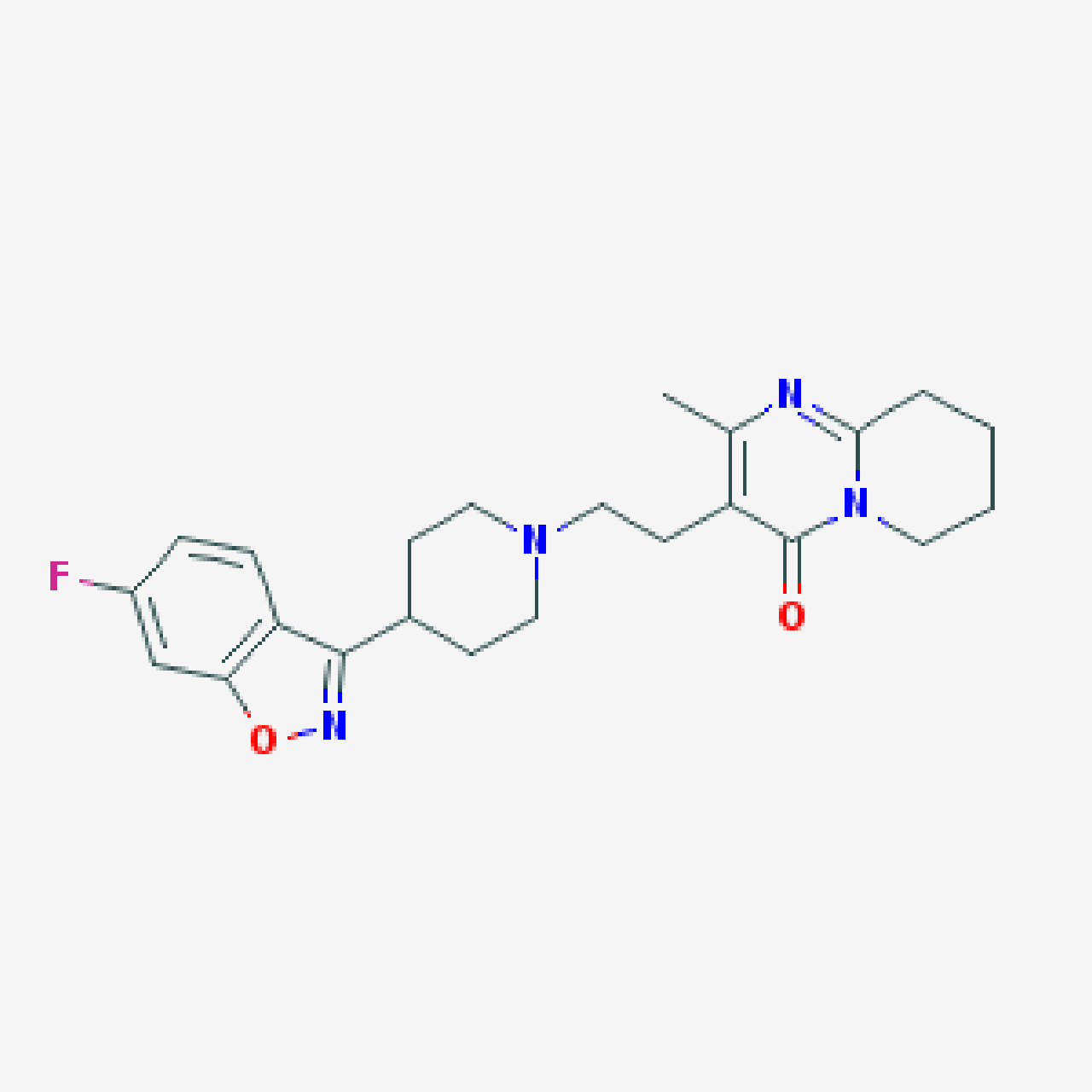
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further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

[1] Downgraded one level due to risk of bias: studies contributing data to this body of evidence have unclear risk of bias in one or more domains.
[2] Downgraded one level due to imprecision: wide confidence interval including no effect and appreciable harm, and less than optimal information size.
[3] Downgraded one level due to publication bias: 'strongly suspected' - most studies were sponsored by pharmaceutical companies.

BACKGROUND

Risperidone (Figure 1) is the first new-generation antipsychotic drug made available in the market in its generic form. It has been used in the treatment of schizophrenia and related psychotic disorders for over a decade.

Figure 1. Risperidone



Description of the condition

Schizophrenia is a serious, chronic, and relapsing mental illness with a worldwide lifetime prevalence of about 1%. It is characterised by positive symptoms such as hallucinations and delusions, and negative symptoms such as emotional numbness and withdrawal. One-third of those who experience an episode of schizophrenia recover and the illness does not recur. Another 30% experience an unremitting illness. The remainder have a recurrent illness but with long episodes of considerable recovery from the positive symptoms. The overall cost of the illness to the individuals, their families, and the community is considerable.

Description of the intervention

Conventional antipsychotic drugs were introduced into widespread use in the 1950s, and have since formed the mainstay of drug treatment for schizophrenia. Although these drugs were indeed a revolution, their early promise of complete recovery was unfulfilled. Continued interests in further developments led to the

formulation of clozapine in the early 1960s, which, in turn, paved the way for a series of new atypical antipsychotic drugs. This disparate grouping was said to be 'atypical' because they did not seem to cause movement disorders to the same extent as the older generation of drugs.

This series of newer drugs appeared on the market in the early 1990s, risperidone being one of the first. Initially, risperidone was compared with placebo and then with the older-generation antipsychotic drugs, especially haloperidol (Hunter 2003). More recently, risperidone has been used as the control compound when other new antipsychotic drugs are compared with a 'standard atypical'. In 2007 risperidone became off-licence, and it seems likely that this drug will emerge as the new standard care comparator, replacing the older and more problematic haloperidol (Joy 2006).

The absolute effects of a drug are often less well investigated when a standard treatment is widely used, and it is seen as unethical not to treat with drug therapy. With almost everyone having access to older drug treatments for schizophrenia, placebo-controlled trials in this area are now difficult to justify (Carpenter 2003; Laughren 2001). Yet in many physical diseases, such as angina pectoris, bronchial asthma, herpes simplex, and duodenal ulcers, placebo effects can account for up to 33% of clinical improvement (Benson 1996). When it comes to new drugs such as risperidone, clinicians and the public are often provided the evidence for the comparative effects, but the newer drug has been compared with a less-than-ideal drug (Hunter 2003). We argue that knowledge of the effects of a drug compared with placebo assists development of a rational therapeutic approach (Vallance 2006).

How the intervention might work

Risperidone (4-[2-[4-(6-fluorobenzo[d]isoxazol-3-yl)-1-piperidyl]ethyl]-3-methyl-2,6-diazabicyclo[4.4.0]deca-1,3-dien-5-one) is a strong postsynaptic dopamine receptor antagonist, but also acts as a 5-HT2A antagonist and is called a serotonin/dopamine antagonist (Leysen 1994). Risperidone is rapidly and very well absorbed after administration orally, and less than 1% is excreted unchanged in the faeces (Heykants 1994). It reaches peak plasma levels quickly regardless of whether it is administered as a liquid or pill. It is 90% plasma protein bound (Darby 1997). Risperidone binds to D2 and D3 receptors with 50 and 20 times greater affinity than clozapine and is only 2 to 3 times less potent than haloperidol. Also, its affinity for D1 receptors is 100 times lower than for D4 receptors (Leysen 1994).

Why it is important to do this review

Comparing any drug with a placebo has always been an intriguing aspect of drug trials, and some authors, such as Vallance 2006, feel that outcome measures are best measured when compared with a placebo as it partly accounts for the philosophical obstacles such as the mind/body dichotomy, which are inherent in conceptualising these effects. In 60% to 90% of diseases, including angina pectoris, bronchial asthma, herpes simples, and duodenal ulcers, placebo effects can account for up to 33% of clinical improvement and yield clinical results (Benson 1996). The placebo effect ultimately allows a rationalised therapeutic approach to be developed to maximise the clinical benefit of the therapeutic encounter and evaluate various outcome measures (Vallance 2006).

Cochrane reviews to date have evaluated the efficacy of risperidone for schizophrenia by comparing it with typical and other atypical antipsychotics. This comparison of risperidone versus placebo is one of a set of reviews on risperidone (Table 1).

OBJECTIVES

To determine the clinical effects, safety, and cost-effectiveness of risperidone compared with placebo for treating schizophrenia.

METHODS

Criteria for considering studies for this review

Types of studies

We included all relevant RCTs. If a trial was described as 'double-blind', but only implied that the study is randomised, then we included it in a sensitivity analysis. If in such a trial there was no implied randomisation, we contacted the authors to clarify the randomisation. We excluded trials where randomisation did not occur. If there was no substantive difference within primary outcomes (see Types of outcome measures) when these 'implied randomisation' studies were added, then we included these in the final analysis. If there was a substantive difference, we only used clearly randomised trials and described the results of the sensitivity analysis in the text. We excluded quasi-randomised studies, such as those allocated by using alternate days of the week.

Types of participants

We included people (above 17 years of age) with schizophrenia and other types of schizophrenia-like psychoses (schizophreniform and schizoaffective disorders), as evidence suggests that they are fundamentally not too dissimilar (Carpenter 1994).

Types of interventions

1. Oral risperidone: any dose or form

2. Placebo

Types of outcome measures

We grouped outcomes into short term (up to 12 weeks), medium term (13 to 26 weeks), and long term (over 26 weeks).

Primary outcomes

1. Mental state

1.1 Clinical response: no clinically significant response in psychotic symptoms, as defined by each of the studies (short term)

2. Service utilisation

2.1 Hospital admission and/or re-admission

Secondary outcomes

1. Leaving the study early

2. Global state

2.1 Average score/change in global state
2.2 No clinically significant response on global state, as defined by each of the studies

3. Mental state

3.1 Average score/change on psychotic symptoms

3.2 No clinically significant response on positive symptoms, as defined by each of the studies
3.3 Average score/change in positive symptoms
3.4 No clinically significant response on negative symptoms, as defined by each of the studies
3.5 Average score/change in negative symptoms
3.6 Use of additional medication (other than anticholinergics) for psychiatric symptoms

4. Extrapyramidal adverse effects

4.1 Use of antiparkinson drugs
4.2 No clinically significant extrapyramidal adverse effects, as defined by each of the studies
4.3 Average score/change in extrapyramidal adverse effects

5. Other adverse effects

5.1 General and specific (including deaths by suicide or natural causes)

6. Service utilisation outcomes

6.1 Days in hospital

7. Economic outcomes

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

8.1 Significant change in quality of life/satisfaction, as defined by each of the studies
8.2 Average score/change in quality of life/satisfaction

9. 'Summary of findings' table

We used the GRADE approach to interpret findings and used GRADEpro to import data from RevMan 5.1 to create 'Summary of findings' tables (Schünemann 2008). These tables provide outcome-specific information concerning the overall quality of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rated as important to patient-care and decision making. We selected the following main outcomes for inclusion in the 'Summary of findings' table:

1. Mental state - no clinically significant response
2. Leaving the study early - for any reason
3. Global state - no significant clinical improvement
4. Adverse events - extrapyramidal effects

Search methods for identification of studies

Electronic searches

1. Cochrane Schizophrenia Group Trials Register

On 19th October 2015, the Trials Search Co-ordinator searched the Cochrane Schizophrenia Group Trials Register using the following search strategy:

((risperidone* or Risperdal*) AND placebo*):ti,ab of REFERENCES or ((risperidone* or Risperdal*) AND placebo*):sin of STUDIES

The Cochrane Schizophrenia Group Trials Register is compiled by systematic searches of major resources (including AMED, BIOSIS, CINAHL, EMBASE, MEDLINE, PsycINFO, PubMed, and registries of clinical trials) and their monthly updates, handsearches, grey literature, and conference proceedings (see Group Module). There are no language, date, document type, or publication status limitations for inclusion of records into the register.

For details of the previous search, please see Appendix 1.

Searching other resources

1. Reference lists

We searched all references of the reports of included trials for further relevant studies.

2. Authors of studies

When necessary, we contacted authors of studies to clarify data and request additional studies, but received no response. We also contacted authors for information on any published or unpublished additional studies that they were aware of, but again, received no response.

3. Pharmaceutical companies

We contacted relevant pharmaceutical companies for additional studies and to clarify study data. However, we did not receive any further information.

Data collection and analysis

We have updated some text of the methods to reflect changes and updates in Cochrane methodology; please see Appendix 2 for details of methods used in original version.

Selection of studies

Two review authors (RR, MJ) independently inspected all reports of studies identified for the original search. Any disagreements were resolved by consensus; where doubt remained, we acquired the full article. Review authors (RR, BL and JX) independently decided whether these studies met the review criteria. We did not intend to blind the names of authors, institutions, and journal of publication. Again, any disagreements were resolved by consensus. When this was not possible, we sought further information and, in the interim, added these trials to the Studies awaiting classification list.

SS screended results from 2013 search and review authors SZ and BL independently inspected citations from the subsequent updated search (19th October 2015) to identify relevant abstracts. We obtained and inspected full reports of the abstracts meeting the review criteria.

Data extraction and management

1. Extraction

Review authors RR, MJ (original search), SS (2013 search), SZ, BL (2015 search) independently extracted data from all included studies. In addition, to ensure reliability, JX independently extracted data from a random sample of these studies comprising 10% of the total. Again, we discussed any disagreements and documented decisions. The need did not arise, but we had planned to extract data presented only in graphs and figures whenever possible, while only including the data if two review authors independently reached the same result. We also attempted to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary.

2. Management

2.1 Forms

We extracted data on to standard, simple forms.

2.2 Scale-derived data

We included continuous data from rating scales only if:
a. the psychometric properties of the measuring instrument have been described in a peer-reviewed journal (Marshall 2000); and
b. the measuring instrument was not written or modified by one of the trialists for that particular trial.

2.3 Endpoint versus change data

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

2.4 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we aimed to apply the following standards to all data before inclusion: a) standard deviations and means are reported in the paper or obtainable from the authors; b) when a scale starts from the finite number 0, the standard deviation, when multiplied by 2, is less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution (Altman 1996)); c) if a scale started from a positive value (such as the Positive and Negative Syndrome Scale (PANSS), which can have values from 30 to 210), we modified the calculation described above to take the scale starting point into account. In these cases, skew is present if 2 SD > (S - S min), where S is the mean score and S min is the minimum score. Endpoint scores on scales often have a finite start and endpoint, and these rules can be applied. We entered skewed endpoint data from studies of fewer than 200 participants in 'other tables' within the Data and analyses section rather than into a statistical analysis. Skewed data pose less of a problem when looking at mean if the sample size is large; we entered such data from studies with over 200 participants into syntheses. When continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not, we entered skewed change data into analyses.

2.5 Common measure

Had we identified such data, we intended to convert variables that can be reported in different metrics, such as days in hospital (mean days per year, per week, or per month) to a common metric (for example mean days per month) to facilitate comparison between trials. However, we did not identify such data.

2.6 Conversion of continuous to binary

Where possible, we made efforts to convert outcome measures to dichotomous data. This can be done by identifying cutoff points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It is generally assumed that if there is a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale, Overall 1962, or the PANSS, Kay 1986, this could be considered as a clinically significant response (Leucht 2005a; Leucht 2005b). If data based on these thresholds were not available, we used the primary cutoff the original authors presented. Some included studies provided a definition of response as a reduction in PANSS or Clinical Global Impression scores, in which case we employed the dichotomous data provided from the primary study report.

2.7 Direction of graphs

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

Assessment of risk of bias in included studies

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

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

We have noted the level of risk of bias in both the text of the review and in Summary of findings table 1 and Summary of findings 2.

Measures of treatment effect

1. Binary data

For binary outcomes, we calculated a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI). It has been shown that RR is more intuitive than odds ratios and that clinicians tend to interpret odds ratios as RR (Boissel 1999; Deeks 2000). The number needed to treat to harm statistic with its CIs is intuitively attractive to clinicians but is problematic both in its accurate calculation in meta-analyses and in its interpretation (Hutton 2009). For binary data presented in the 'Summary of findings' table/s, where possible, we calculated illustrative comparative risks.

2. Continuous data

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

Unit of analysis issues

To facilitate comparison between trials, we intended to convert variables (such as days in hospital) that can be reported in different metrics (mean days per year, per week, or per month) to a common metric (for example mean days per month), but no studies reported data for these types of outcomes.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up, data loses credibility (Xia 2009). For outcomes where more than 50% of data were unaccounted for, we intended to not reproduce these data or use them within analyses. If more than 50% of data in one arm of a study were lost, but the total loss was less than 50%, we intended to mark data with (*) to indicate that such a result may well be prone to bias.

2. Binary

In cases where attrition for a binary outcome was between 0% and 50% and where these data were not clearly described, we presented data on a 'once-randomised-always-analyse' basis wherever possible (an intention-to-treat (ITT) analysis). For every outcome with the exception of the outcome of death, we had planned to assume those participants leaving the study early to have the same rates of negative outcome as those who completed. However, doing this drastically changed the significance of many outcomes and sometimes the direction of significant results, so we only presented data that was already available from the studies to reduce the risk of making incorrect assumptions.

3. Continuous

3.1 Attrition

In cases where attrition for a continuous outcome was between 0% and 50% and completer-only data were reported, we reproduced these.

3.2 Standard deviations

We didn't need to calculate any standard deviations (SD) in this review, but our protocol stated that we would first try to obtain missing values from the authors. If not available, where measures of variance for continuous data were missing but an exact standard error (SE) and CI were available for group means, and either the P value or t value was available for differences in means, we calculated SDs according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). When only the SE was reported, we would calculate SDs using the formula SD = SE * square root (n). Sections 7.7.3 and 16.1.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* Higgins 2011present detailed formulae for estimating SDs from P values, t or F values, CIs, or other statistics (Higgins 2011). If these formulae did not apply, we would calculate the SDs according to a validated imputation method that is based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome and thus to lose information. We would nevertheless examine the validity of the imputations in a sensitivity analysis excluding imputed values.

3.3 Last observation carried forward

We anticipated that some studies would employ the method of last observation carried forward (LOCF). As with all methods of imputation to deal with missing data, LOCF introduces uncertainty about the reliability of the results. Therefore, where a trial used LOCF data, if less than 50% of the data were assumed, we reproduced these data and indicated that they were the product of LOCF assumptions.

Assessment of heterogeneity

Firstly, we considered all the included studies within any comparison to judge clinical heterogeneity. We then visually inspected the graphs in order to investigate the possibility of statistical heterogeneity; to supplement this we used, primarily, the I^2 statistic, which provides an estimate of the percentage of variability due to heterogeneity rather than due to chance alone. Where the I^2 estimate was greater than or equal to 75%, we interpreted this as indicating the presence of high levels of heterogeneity (Higgins 2003). If inconsistency became high, we did not summate data, but presented it separately, and we investigated the reasons for heterogeneity.

Assessment of reporting biases

In order to investigate the likelihood of overt publication bias, we entered all data from all identified and selected trials into a funnel graph (trial effect against trial size) (Egger 1997).

Data synthesis

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

Subgroup analysis and investigation of heterogeneity

If data were clearly heterogeneous, we checked that they had been extracted and entered correctly, and that we had made no unit of analysis errors. If the high levels of heterogeneity remained, we did not undertake a meta-analysis at this point, because if there is considerable variation in results, and particularly if there is inconsistency in the direction of effect, it may be misleading to quote an average value for the intervention effect. We prespecified no characteristics of studies that may be associated with heterogeneity except quality of trial method.

Sensitivity analysis

If studies had high attrition rates, we analysed the effect of including these studies in a sensitivity analysis, but we did not include any figures with more than 50% attrition in the analysis of efficacy. Where a trial was described as 'double-blind', but it was implied that the study was randomised, we had intended to include such studies in the sensitivity analysis, but we did not come across any such studies.

RESULTS

Description of studies

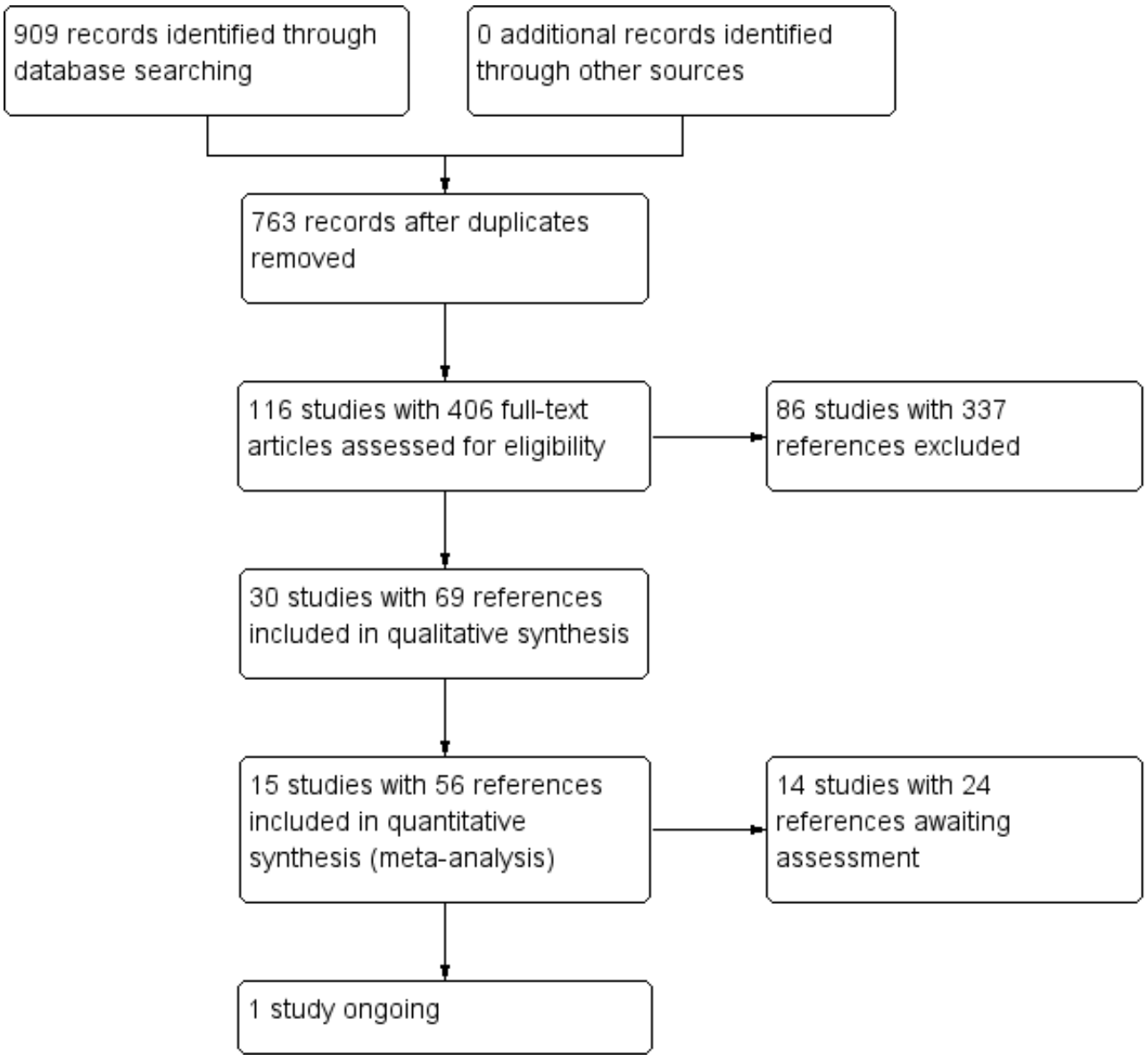
For a substantial description of each study, please refer to the relevant tables:Characteristics of included studies, Characteristics of excluded studies, Characteristics of ongoing studies.

Results of the search

The initial search resulted in 815 citations. We were able to include 42 references, relating to only 10 studies from which we could extract useable data. We used information regarding unpublished data from trials on risperidone available to the Cochrane Schizophrenia Group from drug companies. The update searches run in 2013 and 2015 yielded 94 citations, of which 5 new studies were included.

In total up to the current update, 909 citations were identified from the search process in total. After removing duplicates, 763 unique records were screened by viewing titles and abstracts. A total number of 116 studies with 406 full-text articles were screened for eligibility. Finally, 86 studies with 337 references were excluded, 14 studies with 24 references are awaiting assessment due to lack of full-texts and one study was onging trial, which resulted in 15 studies with 56 references being included in the data and analysis (see Figure 2 for study flow diagram).

Figure 2. Study flow diagram.



Included studies

1. Length of trials

Fourteen studies reported data on short-term follow-up, and only 1 study reported medium-term outcomes (Bachmann 2003), but even that was only at 16 weeks. Two studies were of 4 weeks duration (Potkin 1997; Potkin 2003), 6 studies were 6-weeks long (Borison 1992; Geffen 2010; Heisterberg 2007; Potkin 2006; Potkin 2007; Yagcioglu 2005), 3 studies were 8 weeks from start to finish (Chouinard 1992; Honer 2006; Marder 1994a), 2 studies were 9 weeks from start to finish (Downing 2014; Durgam 2014) and 1 study was 12 weeks in duration (Pai 2002).

2. Participants

Amongst our included studies, two included participants with no clear operational diagnostic criteria and simply stated

"schizophrenia" (Potkin 1997; Potkin 2007). Nine studies included people with a sole diagnosis of schizophrenia as per Diagnostic Statistical Manual of Mental Disorders (DSM) criteria (Borison 1992; Chouinard 1992; Downing 2014; Durgam 2014; Geffen 2010; Heisterberg 2007; Marder 1994a; Pai 2002; Yagcioglu 2005), and the remaining four studies included participants with a diagnosis of schizophrenia or schizoaffective disorder as per DSM criteria (Bachmann 2003; Honer 2006; Potkin 2003; Potkin 2006).

Potkin 2007 did not report the sex of participants in the study. All other studies included both men and women, but the majority of participants were male. Most participants were aged between late 30s and early 40s.

Two studies did not have definitive exclusion criteria (Heisterberg 2007; Potkin 1997). The remaining studies excluded people with alcohol and substance misuse, as well as pregnant or breastfeeding women. Yagcioglu 2005 excluded people who were intolerant to risperidone in the past, Potkin 2003 excluded people being treated with risperidone at baseline, and Potkin 2006 excluded people who had received risperidone within the last seven days. Marder 1994a excluded people with schizoaffective disorder, and Potkin 2006 excluded people with borderline personality disorder. Potkin 2007 excluded people who had made a recent suicide attempt and who had serious suicidal thoughts.

3. Setting

Eight of the included studies took place in the inpatient setting (Borison 1992; Chouinard 1992; Downing 2014; Durgam 2014; Geffen 2010; Marder 1994a; Potkin 2003; Potkin 2006). Three studies involved both inpatients and outpatients (Bachmann 2003; Honer 2006; Yagcioglu 2005). We could not find any explicit information on setting for the remaining four studies (Heisterberg 2007; Pai 2002; Potkin 1997; Potkin 2007).

Studies were conducted in the USA (Bachmann 2003; Borison 1992; Geffen 2010; Marder 1994a; Potkin 1997; Potkin 2003; Potkin 2006; Potkin 2007), Canada (Chouinard 1992; Honer 2006), India (Geffen 2010), Romania (Geffen 2010), Denmark (Heisterberg 2007), and Turkey (Yagcioglu 2005). One studies recruited participants internationally from 65 study centres in the United States, India, Russia, Ukraine, and Malaysia.

4. Study size

The largest study was Downing 2014, which randmised 1009 people to four groups, among which, 437 participants were assigned to either resperidone or placebo group. Heisterberg 2007 randomised 303 people to receive either risperidone or placebo. Durgam 2014 randomised 729 people to five groups, however, only 291 participants were assigned to either resperidone or placebo group. Where a study randomised different doses of risperidone in different arms, as well as having a separate placebo arm, we tried to take data from the risperidone arm that best fitted with the average doses across studies. For example, as the mean dose of risperidone for all the other trials was 5.5 mg per day, we took the 6 mg arm from the Marder 1994a and Chouinard 1992 trials for efficacy measures in the meta-analysis. In Potkin 1997, which had two risperidone arms of 4 mg and 8 mg, we took the 4 mg arm for efficacy measures in the meta-analysis, as this was closer than the 8 mg arm to the mean of 5.5 mg. Potkin 2006 randomised 226 people, Potkin 2003 202, Marder 1994a 130, Chouinard 1992 44, and Potkin 1997 168. The rest of the studies ranged between 24 and 121 participants.

5. Interventions

5.1 Risperidone

The dose of risperidone administered by the trialists varied from 2 mg up to 10 mg per day.

5.2 Placebo

All studies had a placebo arm, and most had another arm with an active treatment in addition to risperidone. Borison 1992, Marder 1994a, and Chouinard 1992 had an arm for haloperidol. Downing 2014 had two arms for LY2140023 with low dosage or high dosage. Durgam 2014 had three arms of cariprazine with low, medium or high dosage. Geffen 2010 had two additional arms for a low dose and a high dose of BL-1020. Marder 1994a and Chouinard 1992 also had four different risperidone arms with daily doses of 2 mg, 6 mg, 10 mg, and 16 mg. We used the 6 mg arm from the Marder 1994a and Chouinard 1992 trials for efficacy measures in the meta-analysis and the 4 mg arm data from Potkin 1997. Heisterberg 2007 used bifeprunox as the other arm, Potkin 2003 aripiprazole, Potkin 2006 quetiapine, and Potkin 2007 asenapine.

5.3 Augmentation

In three studies the risperidone and placebo arms were combined with clozapine (Bachmann 2003; Honer 2006; Yagcioglu 2005).

6. Outcomes

Our primary outcome measures were mental state and service utilisation; no data were available for service utilisation. Other outcomes of interest were leaving the study early, global state, adverse effects, and quality of life.

6.1 Mental state

The trials used several different rating scales to report on mental state. Heisterberg 2007 did not report useable data on mental state, and we could not use the Positive and Negative Symptom Scale (PANSS) data from Potkin 2007 as this trial had more than 50% attrition. Downing 2014 only reported means of PANSS score in each group, therefore we are unable to use the data. All other trials used either the PANSS or the Brief Psychiatric Rating Scale to measure this outcome. Wherever possible, we used the binary data from these measures, but the validity of dichotomising these measures, although widely accepted, is, nevertheless, unclear.

6.2 Leaving the study early

All included trials provided useable data on the number of participants leaving the study early.

6.3 Global state

Five of the included studies reported global change using the Clinical Global Impression (CGI) scale (Durgam 2014, Honer 2006, Marder 1994a, Potkin 2003, Potkin 2006). Yagcioglu 2005 used both the CGI and the Global Assessment of Functioning Scale.

6.4 Adverse effects

Adverse effects are an important outcome measure from any trial. We were able to pool data on adverse effects from the majority of trials; some data was skewed and is presented in additional tables.

6.5 Quality of life

were only presented by Only Yagcioglu 2005 presented quality of life data.

6.6 Missing outcomes

No data were available for service utilisation or economic outcomes.

6.7 Outcome scales

6.7.1 Global state scales

6.7.1.1 Clinical Global Impression (Guy 1976)
The CGI scale was used to assess both severity of illness and clinical improvement by comparing the conditions of the person standardised against other people with the same diagnosis. It is a seven-point scoring system with low scores showing decreased severity or overall improvement, or both.

6.7.1.2 Global Assessment of Functioning Scale (DSM-IV-TR)
The GAF scale is a numeric scale (0 through 100) used by mental-health clinicians and doctors to rate the social, occupational, and psychological functioning of adults. The scale is presented and described in the DSM-IV-TR on page 32 (Table 2).

6.7.2 Mental state scales

6.7.2.1 Positive and Negative Syndrome Scale (Kay 1986)
The PANSS is used for measuring symptom severity of people with schizophrenia. It is widely used in the study of antipsychotic therapy. The name refers to the two types of symptoms in schizophrenia, as defined by the American Psychiatric Association: positive symptoms, which refer to an excess or distortion of normal functions, and negative symptoms, which represent a diminution or loss of normal functions.

6.7.2.2 Brief Psychiatric Rating Scale (Overall 1962)
The BPRS consists of 18 items on a 7-point severity scale. Initially published as a 16-item scale in 1962, the standard 18-item version has been used since 1967 to successfully demonstrate efficacy of antidepressants, anti-anxiety drugs, and antipsychotics, including the newer 'atypical' antipsychotics. The BPRS has also been used in epidemiological studies, geropsychiatric research, and to compare diagnostic concepts between countries. It is most frequently used in schizophrenia. When using BPRS, rater training is a must and the use of a standardised interview is highly recommended in order to ascertain consistent results.

6.7.2.3 Calgary Depression Scale for Schizophrenia (Addington 1993)
Developed at the University of Calgary, the CDSS specifically assesses the level of depression in schizophrenia. It has been extensively evaluated in both relapsed and remitted patients and appears sensitive to change.

6.7.2.4 Scale for the Assessment of Negative Symptoms (Andreasen 1981)
The SANS assesses affective blunting, alogia, avolition/apathy, anhedonia/asociality, and disturbance of attention to measure negative symptoms in schizophrenia.

6.7.3 Adverse effects scales

6.7.3.1 Barnes Akathisia Scale (Barnes 1989)
The Barnes Akathisia Scale (commonly known as BAS or BARS) is a four-item rating scale administered by physicians to assess the severity of drug-induced akathisia. The most widely used scale for akathisia, it includes both objective items (e.g. observed restlessness) and subjective items (e.g. patient's awareness of restlessness and related distress), together with a global clinical assessment of akathisia. Global assessment is made on a scale of 0 to 5, with comprehensive definitions provided for each anchor point on the scale: 0 = absent; 1 = questionable; 2 = mild akathisia; 3 = moderate akathisia; 4 = marked akathisia; 5 = severe akathisia.

6.7.3.2 Extrapyramidal Symptom Rating Scale (Chouinard 1993)
The ESRS is a physician-rated scale for measuring extrapyramidal adverse effects from antipsychotic medication. It takes approximately 10 minutes and involves 6 questions about the person's subjective experience of extrapyramidal features (slowness, stiffness, and tremor); a standardised procedure for physical examination; and 7 rater-assessed items that address parkinsonian features (rigidity and tremor). The instrument may not differentiate effectively between dyskinesia and dystonia.

6.7.3.3 Simpson Angus Scale (Simpson 1970)
The SAS is a 10-item instrument used to evaluate the presence and severity of parkinsonian symptomatology specifically in patients who may be experiencing drug-induced parkinsonism and other extrapyramidal effects. For the past 25 years it has been the most commonly used rating scale for parkinsonism in clinical trials. The 10 items focus on rigidity rather than bradykinesia, and do not assess subjective rigidity or slowness. Items are rated for severity on a 0 to 4 scale, with definitions given for each anchor point.

6.7.3.4 Abnormal Involuntary Movement Scale (Guy 1976)
The AIMS is a 12-item clinician-rated scale to assess severity of dyskinesias including orofacial movements, extremity and truncal movements in patients taking neuroleptic medications.

6.7.3.5 The UKU side effect rating scale (Lingjaerde 1987)

UKU is a 48 item clinician-rated scale to assess the side effects of psychopharmacological medications. The interview takes anywhere from 10-30 minutes depending on the number of symptoms reported, the complexity of the symptoms, and the patient's ability to provide good report.

6.7.4 Quality of life scales

6.7.4.1 Quality of Life Scale (Carpenter 1994)
The QLS is a 21-item scale rated from a semistructured interview providing information on symptoms and functioning during the preceding 4 weeks. It is intended to be administered by a trained clinician and requires about 45 minutes to complete. Each item is rated on a 7-point scale and, in all but 2 cases, requires a judgement by the clinician/interviewer. Each item is comprised of 3 parts: (1) a brief descriptive statement to focus the interviewer on the judgement to be made; (2) a set of suggested probes; and (3) the 7-point scale with descriptive anchors for every other point. The specific descriptions vary among items, but the high end of the scales (scores 5 and 6) reflects normal or unimpaired functioning, and the low end of the scales (scores 0 and 1) reflects severe impairment of the function in question. The interviewer is instructed to probe around each item until he or she has an adequate basis for making the required judgement, and is encouraged to go beyond the suggested probes with questions

tailored for the individual patient. Thus the experience of both the patient and interviewer is similar to a careful clinical interview.

6.7.5 Cognitive function scales

6.7.5.1 Groton Maze Learning Test (Pietrzak 2008) (used in an ongoing study)
The GMLT assesses processing speed, working memory, and aspects of executive function in healthy adults. Performance on GMLT outcome measures can be compared to performance on tests of psychomotor speed, working memory, and learning from the Cogstate computerized cognitive test battery. Studies suggest that the GMLT measures of spatial learning efficiency and error monitoring correlate with Cogstate measures of attention, working memory, and learning. Exploratory factor analyses have yielded a two-factor solution of error monitoring and learning efficiency, which have been stable across repeated assessments.

6.8 Of note

Borison 1992: In 1997 the first author and his colleague, Diamond, were convicted in the US courts (AHRP 2006; CBS News 2000CBS News 2000 AHRP 2006). For example, one website states: “Diamond, a Ph.D. pharmacologist who had performed more than 300 trials over the course of his career on patients who assumed he was an M.D., was convicted in 1997 on 53 criminal counts, including practicing medicine without a license, theft, prescribing medications without a license, fraud, false statements, tax evasion and bribery. Although he admitted to a growing greed that led to some of his illegal practices, Diamond maintained that the pair had never fabricated research data.” We have continued to include data from this small study.

Excluded studies

We excluded 86 studies, 7 of which were not randomised (David 2000; Davis 2001; Baker 2012; Castle 2015; Kinon 2015; Marder 1991; Pikalov 2012). We excluded seven studies due to their populations not including people with schizophrenia (Anwunah 1999; Ayd 2001; NCT00088075; NCT00305474; Siever 2002; Anwunah 1999; Schmechtig 2010). The remaining excluded studies did not directly compare oral risperidone with placebo.

Ongoing studies

We identified one ongoing study. NCT00174200 is assessing the effects of risperidone (2 mg daily) on the differential sensitivity of two spatial working memory tests in non-agitated, drug-naive people suffering from first-episode schizophrenia or schizophreniform disorder. They intend to enrol 20 patients for the trial. Pfizer is sponsoring the study.

Awaiting assessment

Fourteen studies are awaiting assessment as sufficient information is not currently available (Anon 2010; Litman 2014; NCT 00694707; Vanover 2014; Nisenbaum 2013; Xu 2009; Bose 2010a; Cavazzoni 2002; DeMartinis 2012; GlaxoSmithKline 2006; NCT01086748; NCT01175135; NCT01363349; Rujescu 2009).

Risk of bias in included studies

Pharmaceutical companies funded 8 out of the 15 included trials. We did our best to collect as much information as possible from different sources about the types of biases that could have occurred during these trials, and have presented the results of our investigations in the following paragraphs. Figure 3 and Figure 4 presents the summary of risk of bias in included studies.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

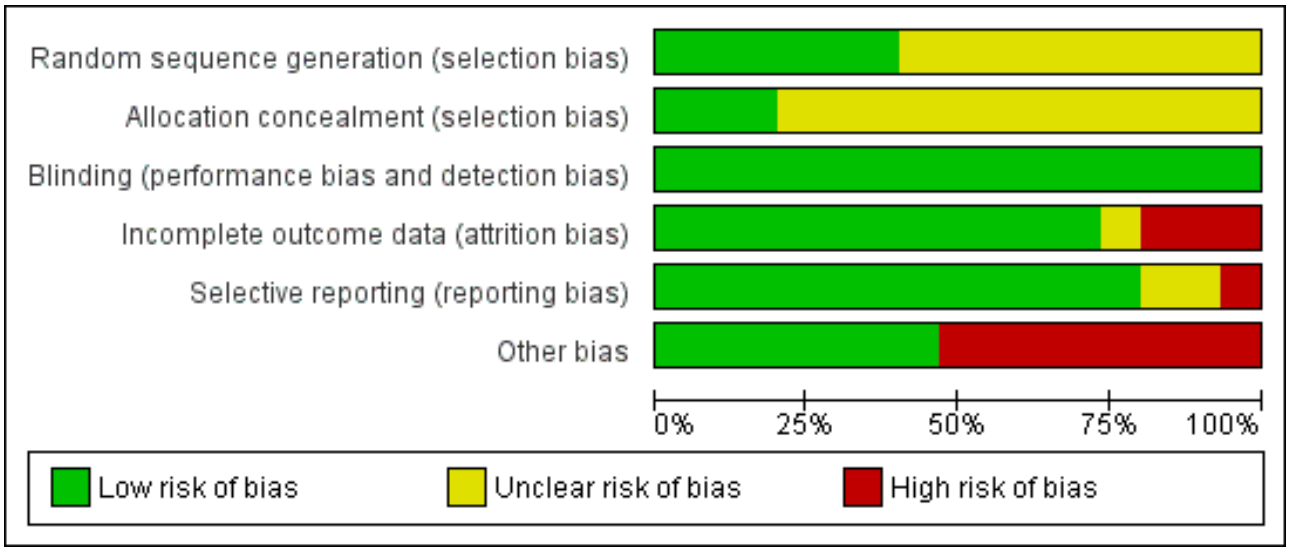
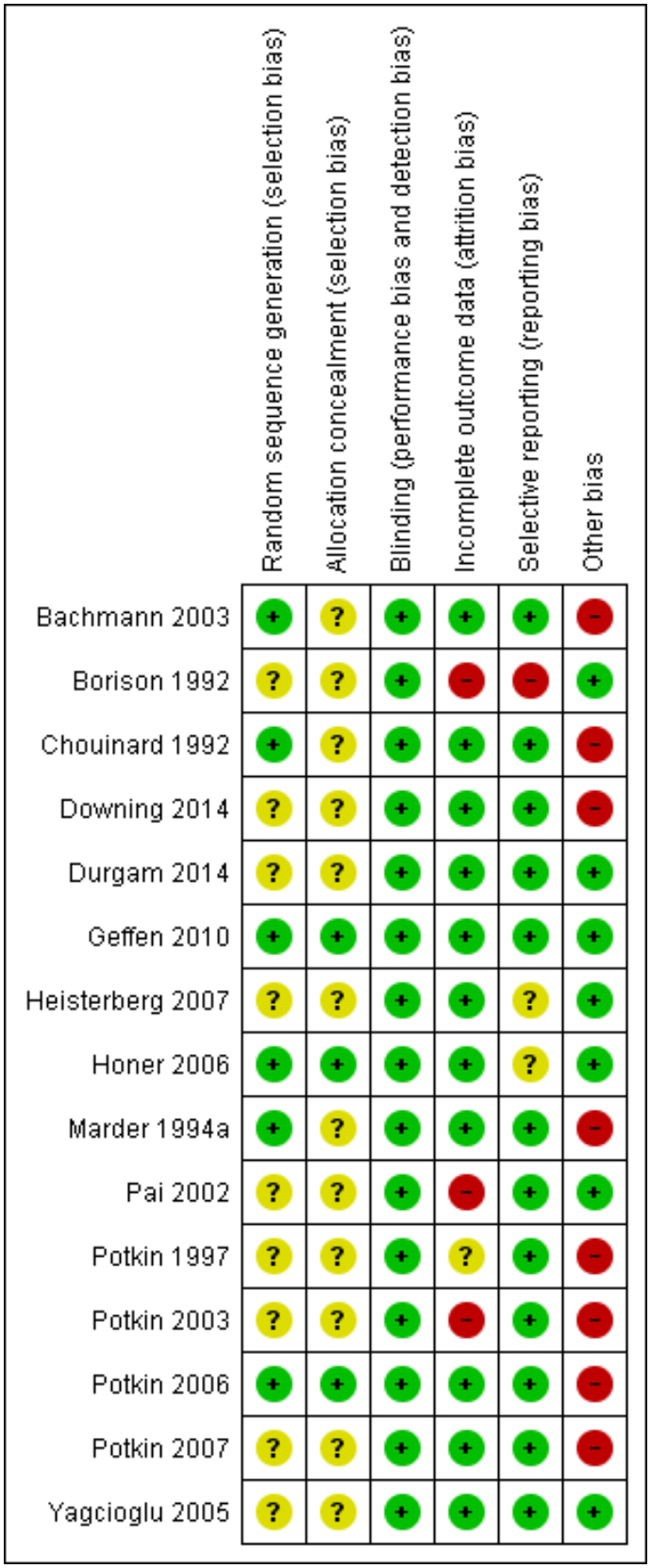


Figure 4. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

All included studies were said to be randomised, but many did not explicitly describe the method by which this was undertaken. Bachmann 2003 utilised randomisation that was stratified by inpatient status; no further details were provided. Honer 2006 used a computer-generated schedule with a permuted-block design to generate sequences. Marder 1994a and Chouinard 1992 undertook randomisation in blocks of 12. Geffen 2010 and Potkin 2006 both used a centralised interactive voice response system for allocation concealment. Although Yagcioglu 2005 used a pre-assigned random sequence for each of their study sites that was developed before the start of their study no further details were provided. The rest of the studies provided no information about the process of randomisation (Borison 1992; Downing 2014; Durgam 2014; Heisterberg 2007; Pai 2002; Potkin 1997; Potkin 2003; Potkin 2007; Potkin 2003; Potkin 1997; Pai 2002; Heisterberg 2007; Borison 1992), despite this having been repeatedly shown to be of key importance in excluding selection biases (Juni 2001).

Blinding

All the included studies were described as double blind, with some describing how this was achieved. Blinding is important for minimising observation bias and, because many of the outcomes were subjective.

Incomplete outcome data

Bachmann 2003, Downing 2014, Durgam 2014, Geffen 2010, Heisterberg 2007, Marder 1994a, Chouinard 1992, and Potkin 2006 used an intention-to-treat (ITT) analysis. Honer 2006, Yagcioglu 2005 and Durgam 2014 used the ITT principle in a mixed-model analysis. Potkin 2007 used ITT for the efficacy data and last observation carried forward (LOCF) for safety data.

We judged Pai 2002 and Borison 1992 to have a high risk of bias, as they did not consider in their analysis the data of participants who left early. We judged Potkin 1997 to be at unclear risk of bias, as no information about loss to follow-up was provided. Potkin 2003 used the LOCF method to manage their loss to follow-up, but as they had over 40% loss, we downgraded this category because such a high attrition rate makes data prone to bias. None of the trials attempted to validate assumptions by following up participants who did leave early.

Selective reporting

We were unable to obtain original study protocol, however, the included studies appear to have reported the results for all the outcomes listed in their methods sections. Based on the information available, we did not detect any obvious act of selective reporting.

Other potential sources of bias

1. Poor reporting

We could not use much data because of poor reporting. Findings that are presented as graphs, in percentiles, or simply reported as inexact P values were of little use to us as review authors. Many studies failed to provide standard deviations (SDs) when reporting mean changes. We are seeking further data from the first authors of relevant trials.

2. Industry

Pharmaceutical companies funded 8 out of the 13 included trials, with the majority of these funded by a company that would profit from finding beneficial effects of risperidone.

Effects of interventions

See: **Summary of findings for the main comparison** RISPERIDONE compared to PLACEBO for schizophrenia; **Summary of findings 2** RISPERIDONE + CLOZAPINE compared to PLACEBO + CLOZAPINE for schizophrenia

Studies relevant to this review fall into three comparisons. We identified 15 randomised trials from which it is possible to extract numerical data.

1. COMPARISON 1: RISPERIDONE versus PLACEBO

This comparison has 20 outcomes.

1.1 Mental state: no clinically significant response in psychotic symptoms (defined by various scale total score change) - short term (up to 12 weeks)

1.1.1 defined by PANSS < 30% decline

Three trials with a total of 707 participants provided data for this subset . We did find evidence that 'risperidone' was clearly different in its effects compared with 'placebo' (RR 0.74, 95% CI 0.67 to 0.83) (Analysis 1.1).

1.1.2 defined by PANSS/BPRS < 20% decline

Six trials with a total of 864 participants provided data for this subset. We did find evidence that 'risperidone' was clearly different in its effects compared with 'placebo' (RR 0.64, 95% CI 0.52 to 0.78). This subgroup had important levels of heterogeneity (Chi^2 = 12.27; df = 5.0; P = 0.03; I^2 = 59%) (Analysis 1.1).

1.2 Leaving the study early - short term (up to 12 weeks)

1.2.1 any reason

There were 12 relevant trials, with a total of 2261 participants providing data for numbers leaving the study early for any reason. We did find evidence that 'risperidone' was clearly different in its effects compared with 'placebo' (RR 0.69, 95% CI 0.62 to 0.78). There are moderate levels of heterogeneity (Chi^2 = 14.73; df = 11; P = 0.20; I^2 = 25%) (Analysis 1.2).

1.2.2 due to adverse events

There were 10 relevant trials, with a total of 2081 participants, providing data for this subset. There was not a clear difference between 'risperidone' and 'placebo' (RR 0.78, 95% CI 0.59 to 1.03) (Analysis 1.2).

1.2.3 due to lack of efficacy

Eleven trials, with a total of 2211 participants provided data for this subset We found evidence of a clear difference between 'risperidone' and 'placebo' (RR 0.39, 95% CI 0.29 to 0.51). There are moderate levels of heterogeneity (Chi^2 = 14.70; df = 10; P = 0.14; I^2 = 32%) (Analysis 1.2).

1.2.4 due to non-compliance

We found 4 trials to be relevant to this subset, with a total of 534 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 1.15, 95% CI 0.33 to 4.05) (Analysis 1.2).

1.2.5 lost to follow-up

We found 6 trials to be relevant to this subset, with a total of 1545 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 0.79, 95% CI 0.25 to 2.56). This subset had important levels of heterogeneity (Chi^2 = 11.97; df = 4.0; P = 0.02; I^2 = 67%) (Analysis 1.2).

1.2.6 protocol violation

We found 4 trials to be relevant to this subset, with a total of 1257 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 0.79, 95% CI 0.39 to 1.62) (Analysis 1.2).

1.2.7 reported death

There were 10 relevant trials in this subset, with a total of 1532 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 3.07, 95% CI 0.13 to 74.28) (Analysis 1.2).

1.2.8 withdrawal of consent

We found 7 trials to be relevant to this subset, with a total of 1589 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 1.12, 95% CI 0.80 to 1.56) (Analysis 1.2).

1.2.9 other

There were 3 relevant trials in this subset, with a total of 615 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 1.03, 95% CI 0.68 to 1.57) (Analysis 1.2).

1.3 Global state: 1. average endpoint scores of CGI severity scale (high = poor) - short term (up to 12 weeks)

We identified 3 studies relevant to this outcome, with a total of 457 participants. This outcome had no subsets. We found evidence of a clear difference between 'risperidone' and 'placebo' (MD -0.81, 95% CI -0.89 to -0.73) (Analysis 1.3).

1.4 Global state: 2. no significant clinical improvement - short term (up to 12 weeks)

For this outcome we found 4 relevant studies involving 594 participants. There were no subsets in this outcome. We found evidence of a clear difference between 'risperidone' and 'placebo' (RR 0.69, 95% CI 0.57 to 0.83). For this outcome heterogeneity was moderately high (Chi^2 = 5.43; df = 3.0; P = 0.14; I^2 = 44%) (Analysis 1.4).

1.5 Global state: 3. needing additional medication - short term (up to 12 weeks)

For this outcome we found six relevant studies, the data from which we divided into seven subsets.

1.5.1 benzodiazepine

There was a single trial in this subset, with a total of 42 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 0.96, 95% CI 0.77 to 1.2) (Analysis 1.5).

1.5.2 benzodiazepine derivatives - lorazepam

There were 2 relevant trials in this subset, with a total of 228 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 0.93, 95% CI 0.68 to 1.27) (Analysis 1.5).

1.5.3 benzodiazepine derivatives - Nitrazepam

There was a single trial in this subset, with a total of 184 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 0.51, 95% CI 0.10 to 2.72) (Analysis 1.5).

1.5.4 benzodiazepine related drugs - Zolpidem

We found 1 trial to be relevant to this subset, with a total of 184 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 0.81, 95% CI 0.53 to 1.23) (Analysis 1.5).

1.5.5 sedative/hypnotic

We found 2 trials to be relevant to this subset, with a total of 230 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 0.86, 95% CI 0.69 to 1.06) (Analysis 1.5).

1.5.6 antiparkinsonian

There were 2 relevant trials in this subset, with a total of 172 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 1.21, 95% CI 0.79 to 1.86) (Analysis 1.5).

1.5.7 psychotropics

We found 1 trial to be relevant to this subset, with a total of 186 participants. We found evidence of a clear difference between 'risperidone' and 'placebo' within this subset (RR 0.62, 95% CI 0.45 to 0.85) (Analysis 1.5).

1.6 Mental state: 1. average endpoint scores on various scales on psychotic symptoms (high = poor) - short term (up to 12 weeks)

We identified three studies relevant to this outcome, the data from which we divided into five subsets.

1.6.1 BPRS total

We found 2 trials to be relevant to this subset, with a total of 171 participants. We found evidence of a clear difference between 'risperidone' and 'placebo' within this subset (MD -12.69, 95% CI -17.06 to -8.32) (Analysis 1.6).

1.6.2 PANSS total

We found 3 trials to be relevant to this subset, with a total of 457 participants. For this outcome, within this subset, we did find evidence that 'risperidone' was clearly different in its effects

compared with 'placebo' (MD -17.81, 95% CI -18.17 to -17.45) (Analysis 1.6).

1.6.3 PANSS general pathology

There was a single trial in this subset, with a total of 44 participants. For this outcome, within this subset, we did find evidence that 'risperidone' was clearly different in its effects compared with 'placebo' (MD -13.20, 95% CI -20.15 to -6.25) (Analysis 1.6).

1.6.4 PANSS negative symptom

There were 3 relevant trials in this subset, with a total of 457 participants. We found evidence of a clear difference between 'risperidone' and 'placebo' within this subset (MD -3.10, 95% CI -3.19 to -3.01) (Analysis 1.6).

1.6.5 PANSS positive symptom

We found 3 trials to be relevant to this subset, with a total of 457 participants. For this outcome, within this subset, we did find evidence that 'risperidone' was clearly different in its effects compared with 'placebo' (MD -5.49, 95% CI -6.18 to -4.80) (Analysis 1.6).

1.7 Mental state: 2. skewed data - short term (up to 12 weeks)

These continuous data, from two trials were skewed. Therefore we have reported these data in a separate data table (Analysis 1.7) .

1.8 Adverse effects: 1a. extrapyramidal - various effects - short term (up to 12 weeks)

We identified 11 studies relevant to this outcome, the data from which we divided into 12 subsets.

1.8.1 general - any significant extrapyramidal symptom

We found 7 trials to be relevant to this subset, with a total of 1511 participants. We found evidence of a clear difference between 'risperidone' and 'placebo' within this subset (RR 1.56, 95% CI 1.13 to 2.15) (Analysis 1.8).

1.8.2 general - no improvement on AIMS score

There was a single trial in this subset, with a total of 42 participants. We found evidence of a clear difference between 'risperidone' and 'placebo' within this subset (RR 0.30, 95% CI 0.15 to 0.61) (Analysis 1.8).

1.8.3 general - no improvement on BAS score

There was a single trial in this subset, with a total of 226 participants. For this outcome, within this subset, we did find evidence that 'risperidone' was clearly different in its effects compared with 'placebo' (RR 1.14, 95% CI 1.01 to 1.28) (Analysis 1.8).

1.8.4 general - needing medication for EPS

We found 2 trials to be relevant to this subset, with a total of 94 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 1.14, 95% CI 0.78 to 1.67) (Analysis 1.8).

1.8.5 specific - akathisia

We found 5 trials to be relevant to this subset, with a total of 1204 participants. We found evidence of a clear difference between 'risperidone' and 'placebo' within this subset (RR 2.58, 95% CI 1.41 to 4.72). For this subset heterogeneity was moderately high (Chi^2 = 5.63; df = 4.0; P = 0.23; I^2 = 29%). (Analysis 1.8).

1.8.6 specific - bradykinesia

We found 2 trials to be relevant to this subset, with a total of 485 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 0.87, 95% CI 0.6 to 1.24) (Analysis 1.8).

1.8.7 specific - dyskinesia

We found 1 trial to be relevant to this subset, with a total of 303 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 0.32, 95% CI 0.01 to 7.86) (Analysis 1.8).

1.8.8 specific - dystonia

There were 3 relevant trials in this subset, with a total of 687 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 3.40, 95% CI 0.26 to 44.46). This subset had important levels of heterogeneity (Chi^2 = 13.09; df = 2.0; P = 0.001; I^2 = 84%) (Analysis 1.8).

1.8.9 specific - hypertonia

There were 3 relevant trials in this subset, with a total of 505 participants. We found evidence of a clear difference between 'risperidone' and 'placebo' within this subset (RR 2.98, 95% CI 1.35 to 6.59). For this subset heterogeneity was moderately high (Chi^2 = 2.87; df = 2.0; P = 0.24; I^2 = 30%) (Analysis 1.8).

1.8.10 specific - parkinsonism

We found 2 trials to be relevant to this subset, with a total of 485 participants. We found evidence of a clear difference between 'risperidone' and 'placebo' within this subset (RR 7.64, 95% CI 1.4 to 41.59) (Analysis 1.8).

1.8.11 specific - tardive dyskinesia

There was a single trial in this subset, with a total of 303 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 6.77, 95% CI 0.35 to 130.03) (Analysis 1.8).

1.8.12 specific - tremor

We found 5 trials to be relevant to this subset, with a total of 1204 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 1.60, 95% CI 0.89 to 2.88). This subset had moderate levels of heterogeneity (Chi^2 = 5.86; df = 4.0; P = 0.21; I^2 = 32%) (Analysis 1.8).

1.9 Adverse effects: 1b. extrapyramidal - AIMS average endpoint score - short term (up to 12 weeks)

For this outcome we found a single study. A greater reduction in AIMS scores were seen for people in the risperidone arm compared to the placebo arm (1 RCT, N=42, MD -5.50 95% CI -8.60 to -2.40) (Analysis 1.9).

1.10 Adverse effects: 1c. extrapyramidal - skewed data (various scales) - short term (up to 12 weeks)

These continuous data (four RCTs) had such large SDs as to suggest that analysis within RevMan would be inadvisable. Therefore, we have reported these data in a separate table (Analysis 1.10).

1.11 Adverse effects: 2. any adverse event - short term (up to 12 weeks)

For this outcome we found 9 relevant studies and categorised data into 16 subsets.

1.11.1 any adverse event

There were 7 relevant trials in this subset, with a total of 1610 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 1.05, 95% CI 0.96 to 1.15). This subset had important levels of heterogeneity (Chi^2 = 14.46; df = 6.0; P = 0.02; I^2 = 58%) (Analysis 1.11).

1.11.2 asthenia

There were 2 trials in this subset, with a total of 639 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 1.93, 95% CI 0.62 to 6.02) (Analysis 1.11).

1.11.3 back pain

There was a single trial in this subset, with a total of 202 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 1.04, 95% CI 0.38 to 2.86) (Analysis 1.11).

1.11.4 blurred vision

There was a single trial in this subset, with a total of 202 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 4.16, 95% CI 0.47 to 36.59) (Analysis 1.11).

1.11.5 cogwheel rigidity

We found 1 trial to be relevant to this subset, with a total of 226 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 5.25, 95% CI 0.69 to 39.88) (Analysis 1.11).

1.11.6 death

We found 1 trial to be relevant to this subset, with a total of 182 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 3.13, 95% CI 0.13 to 75.92) (Analysis 1.11).

1.11.7 dental disorder

There was a single trial in this subset, with a total of 202 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 3.64, 95% CI 0.78 to 17.11) (Analysis 1.11).

1.11.8 dysmenorrhoea

There were two trials in this subset, with a total of 495 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 1.10, 95% CI 0.04 to 30.00) (Analysis 1.11).

1.11.9 fatigue

There were two trial in this subset, with a total of 558 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 2.23, 95% CI 0.69 to 7.22) (Analysis 1.11).

1.11.10 fever

We found 1 trial to be relevant to this subset, with a total of 130 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 9.28, 95% CI 0.51 to 168.9) (Analysis 1.11).

1.11.11 infection

We found 1 trial to be relevant to this subset, with a total of 202 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 0.52, 95% CI 0.10 to 2.78) (Analysis 1.11).

1.11.12 salivation - increased

There was a single trial in this subset, with a total of 202 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 7.28, 95% CI 0.38 to 139.15) (Analysis 1.11).

1.11.13 pyrexia

We found 1 trial to be relevant to this subset, with a total of 182 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 1.19, 95% CI 0.45 to 3.16) (Analysis 1.11).

1.11.14 pain

There was a single trial in this subset, with a total of 121 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 1.58, 95% CI 0.47 to 5.31) (Analysis 1.11).

1.11.15 rash (skin)

There was a single trial in this subset, with a total of 202 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 1.19, 95% CI 0.45 to 3.16) (Analysis 1.11).

1.11.16 vaginitis

There was a single trial in this subset, with a total of 58 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 1.07, 95% CI 0.07 to 16.32) (Analysis 1.11).

1.12 Adverse effects: 3. cardiovascular - short term (up to 12 weeks)

For this outcome we found four relevant studies and categorised data into seven subsets.

1.12.1 dizziness - orthostatic

There was a single trial in this subset, with a total of 44 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 3.0, 95% CI 0.13 to 69.87) (Analysis 1.12).

1.12.2 ECG abnormal

We found 1 trial to be relevant to this subset, with a total of 182 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 9.40, 95% CI 0.51 to 172.11) (Analysis 1.12).

1.12.3 heart rate decreased

We found 1 trial to be relevant to this subset, with a total of 182 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 0.52, 95% CI 0.05 to 5.66) (Analysis 1.12).

1.12.4 heart rate increased

There was a single trial in this subset, with a total of 182 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 0.85, 95% CI 0.37 to 1.96) (Analysis 1.12).

1.12.5 hypotension - postural

There was a single trial in this subset, with a total of 44 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 3.00, 95% CI 0.13 to 69.87) (Analysis 1.12).

1.12.6 corrected QT interval > 450 milliseconds or > 10% increase from baseline

We found 2 trials to be relevant to this subset, with a total of 380 participants. We found evidence of a clear difference between 'risperidone' and 'placebo' within this subset (RR 8.46, 95% CI 1.07 to 67.07) (Analysis 1.12).

1.12.7 tachycardia

We found 2 trials to be relevant to this subset, with a total of 332 participants. We found evidence of a clear difference between 'risperidone' and 'placebo' within this subset (RR 12.22, 95% CI 2.33 to 64.1) (Analysis 1.12).

1.13 Adverse effects: 4. central nervous system - short term (up to 12 weeks)

We identified ten studies relevant to this outcome, the data from which we divided into eight subsets.

1.13.1 agitation

There were 8 relevant trials in this subset, with a total of 1388 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 0.93, 95% CI 0.75 to 1.17) (Analysis 1.13).

1.13.2 anxiety

We found 6 trials to be relevant to this subset, with a total of 1225 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 1.04, 95% CI 0.73 to 1.48) (Analysis 1.13).

1.13.3 dizziness

There were 5 relevant trials in this subset, with a total of 970 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 1.41, 95% CI 0.65 to 3.05). This subset had moderate levels of heterogeneity (Chi^2 = 7.37; df = 4.0; P = 0.12; I^2 = 46%) (Analysis 1.13).

1.13.4 headache

We found 10 trials to be relevant to this subset, with a total of 1905 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 0.99, 95% CI 0.81 to 1.21) (Analysis 1.13).

1.13.5 insomnia

We found 10 trials to be relevant to this subset, with a total of 1905 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 1.16, 95% CI 0.97 to 1.39) (Analysis 1.13).

1.13.6 sedation

There were two trials in this subset, with a total of 517 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 1.84, 95% CI 0.52 to 6.50) (Analysis 1.13).

1.13.7 somnolence

We found 6 trials to be relevant to this subset, with a total of 951 participants. We found evidence of a clear difference between 'risperidone' and 'placebo' within this subset (RR 1.61, 95% CI 1.06 to 2.45) (Analysis 1.13).

1.13.8 restlessness

There were two trials in this subset, with a total of 619 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 1.16, 95% CI 0.49 to 2.74) (Analysis 1.13).

1.14 Adverse effects: 5. endocrine - serum prolactin increase above reference range (23 ng/ml) - short term (up to 12 weeks)

For this outcome we found 2 relevant studies, with a total of 323 participants. There were no subsets in this outcome. We found evidence of a clear difference between 'risperidone' and 'placebo' (RR 12.14, 95% CI 4.38 to 33.68). For this outcome heterogeneity was high (Chi^2 = 2.14; df = 1.0; P = 0.14; I^2 = 53%).

1.15 Adverse effects: 6. gastrointestinal system - short term (up to 12 weeks)

For this outcome we found ten relevant studies and categorised data into six subsets.

1.15.1 constipation

We found 8 trials to be relevant to this subset, with a total of 1695 participants. We found evidence of a clear difference between 'risperidone' and 'placebo' within this subset (RR 1.88, 95% CI 1.19 to 2.96) (Analysis 1.15).

1.15.2 diarrhoea

There was a single trial in this subset, with a total of 202 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 0.92, 95% CI 0.37 to 2.3) (Analysis 1.15).

1.15.3 dry mouth

We found 1 trial to be relevant to this subset, with a total of 202 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 2.43, 95% CI 0.65 to 9.12) (Analysis 1.15).

1.15.4 dyspepsia

There were 5 relevant trials in this subset, with a total of 1058 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 1.24, 95% CI 0.64 to 2.40) (Analysis 1.15).

1.15.5 nausea

There were 6 relevant trials in this subset, with a total of 1225 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 1.18, 95% CI 0.75 to 1.86) (Analysis 1.15).

1.15.6 vomiting

There were 5 relevant trials in this subset, with a total of 1181 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 1.16, 95% CI 0.65 to 2.07) (Analysis 1.15).

1.16 Adverse effects: 7a. metabolic - weight gain - short term (up to 12 weeks)

For this outcome we found six relevant studies, the data from which we divided into two subsets.

1.16.1 any gain

We found 3 trials to be relevant to this subset, with a total of 910 participants. For this outcome, within this subset, we did find evidence that 'risperidone' was clearly different in its effects compared with 'placebo' (RR 3.77, 95% CI 1.34 to 10.63) (Analysis 1.16).

1.16.2 > 7% increase from baseline

We found 3 trials to be relevant to this subset, with a total of 606 participants. For this outcome, within this subset, we did find evidence that 'risperidone' was clearly different in its effects compared with 'placebo' (RR 3.47, 95% CI 1.64 to 7.33) (Analysis 1.16).

1.17 Adverse effects: 7b. metabolic - skewed data - average change value on lipid profile - short term (up to 12 weeks)

These continuous data (two RCTs) had such large SDs as to suggest that analysis within RevMan would be inadvisable. Therefore, we presented them in an separate table (Analysis 1.17).

1.18 Adverse effects: 8. musculoskeletal system - short term (up to 12 weeks)

We identified one study relevant to this outcome and categorised data into two subsets.

1.18.1 myalgia

We found 1 trial to be relevant to this subset, with a total of 202 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 0.69, 95% CI 0.12 to 4.06). (Analysis 1.18).

1.18.2 joint disorder

We found 1 trial to be relevant to this subset, with a total of 202 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 2.6, 95% CI 0.52 to 13.1) (Analysis 1.18).

1.19 Adverse effects: 9. physiology - short term (up to 12 weeks)

For this outcome we found two studies and categorised data into four subsets.

1.19.1 alanine aminotransferase increased

There was a single trial in this subset, with a total of 182 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 1.04, 95% CI 0.07 to 16.45) (Analysis 1.19).

1.19.2 aspartate aminotransferase increased

There was a single trial in this subset, with a total of 182 participants. No increase occured in either group. (Analysis 1.19).

1.19.3 blood creatine phosphokinase increased

We found 2 trials to be relevant to this subset, with a total of 619 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 0.67, 95% CI 0.23 to 1.95) (Analysis 1.19).

1.19.4 blood pressure increased

There was a single trial in this subset, with a total of 182 participants. There was not a clear difference between 'risperidone' and 'placebo' within this subset (RR 1.04, 95% CI 0.15 to 7.26) (Analysis 1.19).

1.20 Adverse effects: 10. respiratory system - short term (up to 12 weeks)

For this outcome we found four relevant studies and categorised data into three subsets.

1.20.1 upper respiratory infection

There were 2 relevant trials in this subset, with a total of 323 participants. We found evidence of a clear difference between 'risperidone' and 'placebo' within this subset (RR 2.83, 95% CI 1.03 to 7.74) (Analysis 1.20).

1.20.2 pharyngitis

There was a single trial in this subset, with a total of 202 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 0.42, 95% CI 0.08 to 2.1) (Analysis 1.20).

1.20.3 rhinitis

There were 2 relevant trials in this subset, with a total of 306 participants. For this outcome, within this subset, we found evidence that 'risperidone' was clearly different in its effects compared with 'placebo' (RR 10.81, 95% CI 2.58 to 45.29) (Analysis 1.20).

1.20.4 Sinusitis

There were 1 relevant trial in this subset, with a total of 437 participants. For this outcome, we did not find evidence of a clear difference between the two treatments (RR 1.04, 95% CI 0.09 to 11.36) (Analysis 1.20).

2. COMPARISON 2: RISPERIDONE plus CLOZAPINE versus PLACEBO plus CLOZAPINE

This particular comparison had 23 outcomes.

2.1 Mental state: no clinically significant response in psychotic symptoms (defined by PANSS/BPRS < 20% decline) - short term (up to 12 weeks)

For this outcome two relevant studies found no clear difference between treatments (2 RCTS, N = 98, RR 1.15, 95% CI 0.93 to 1.42 Analysis 2.1)

2.2 Leaving the study early - short term (up to 12 weeks)

For this outcome we found three relevant studies and categorised data into nine subsets.

2.2.1 any reason

We found 3 trials to be relevant to this subset, with a total of 167 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 1.13, 95% CI 0.53 to 2.42) (Analysis 2.2).

2.2.2 due to adverse events

There were 2 relevant trials in this subset, with a total of 137 participants. There was not a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (RR 4.11, 95% CI 0.47 to 36.24) (Analysis 2.2).

2.2.3 due to lack of efficacy

We found 1 trial to be relevant to this subset, with a total of 69 participants. There was not a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (RR 0.55, 95% CI 0.11 to 2.78) (Analysis 2.2).

2.2.4 due to noncompliance

We found 1 trial to be relevant to this subset, with a total of 69 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 0.36, 95% CI 0.02 to 8.61) (Analysis 2.2).

2.2.5 lost to follow-up

We found 1 trial to be relevant to this subset, with a total of 69 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 0.36, 95% CI 0.02 to 8.61) (Analysis 2.2).

2.2.6 reported death

There was a single trial in this subset, with a total of 68 participants. No deaths were reported. (Analysis 2.2).

2.2.7 withdrawal of consent

There were 3 relevant trials in this subset, with a total of 167 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 1.41, 95% CI 0.28 to 7.09) (Analysis 2.2).

2.2.8 administrative reasons

We found 1 trial to be relevant to this subset, with a total of 69 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 5.44, 95% CI 0.27 to 109.34) (Analysis 2.2).

2.2.9 abnormal lab results

We found 1 trial to be relevant to this subset, with a total of 69 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 0.36, 95% CI 0.02 to 8.61) (Analysis 2.2).

2.3 Global state: 1. average endpoint scores of CGI severity scale (high = poor) - short term (up to 12 weeks)

We identified 1 study relevant to this outcome involving 65 participants. This outcome had no subsets. We did not find evidence of a clear difference between the two treatments in this comparison (MD 0.51, 95% CI 0.02 to 1.00).

2.4 Global state: 2. no significant clinical improvement - short term (up to 12 weeks)

We identified 1 study relevant to this outcome, with a total of 68 participants. There were no subsets in this outcome. We did not find evidence of a clear difference between the two treatments in this comparison (RR 1.12, 95% CI 0.87 to 1.44) (Analysis 2.4).

2.5 Global state: 3. general functioning - average endpoint GAF score (high = good) - short term (up to 12 weeks)

We identified 1 study relevant to this outcome involving 30 participants. This outcome had no subsets. We found evidence of a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' (MD -4.50, 95% CI -8.38 to -0.62) (Analysis 2.5).

2.6 Mental state: 1. average endpoint scores on various scales on psychotic symptoms (high = poor) - short term (up to 12 weeks)

For this outcome we found two relevant studies and categorised data into five subsets.

2.6.1 PANSS total

We found 2 trials to be relevant to this subset, with a total of 95 participants. We found evidence of a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (MD 5.56, 95% CI 1.59 to 9.53) (Analysis 2.6).

2.6.2 PANSS general pathology

There was a single trial in this subset, with a total of 30 participants. There was not a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (MD 2.50, 95% CI 0.03 to 4.97) (Analysis 2.6).

2.6.3 PANSS delusion

We found 1 trial to be relevant to this subset, with a total of 30 participants. There was not a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (MD 0.70, 95% CI 0.09 to 1.31) (Analysis 2.6).

2.6.4 PANSS negative symptom

We found 2 trials to be relevant to this subset, with a total of 95 participants. For this subset, we did not find evidence of a clear difference between the two treatments (MD 0.69, 95% CI -0.68 to 2.05) (Analysis 2.6).

2.6.5 PANSS positive symptom

We found 2 trials to be relevant to this subset, with a total of 95 participants. For this subset, we did not find evidence of a clear difference between the two treatments (MD 2.30, 95% CI 0.98 to 3.62) (Analysis 2.6).

2.7 Mental state: 2. average endpoint scores on various scales on psychotic symptoms (high = poor) - medium term (up to 26 weeks)

For this outcome we found a single study, the data from which we divided into four subsets.

2.7.1 BPRS total

We found 1 trial to be relevant to this subset, with a total of 53 participants. We found evidence of a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (MD -4.60, 95% CI -9.88 to 0.68) (Analysis 2.7).

2.7.2 BPRS positive symptom

There was a single trial in this subset, with a total of 53 participants. For this subset, we did not find evidence of a clear difference between the two treatments (MD -0.90, 95% CI -2.81 to 1.01) (Analysis 2.7).

2.7.3 BPRS anxiety/depression factor

There was a single trial in this subset, with a total of 53 participants. We found evidence of a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (MD -1.00, 95% CI -2.80 to 0.80) (Analysis 2.7).

2.7.4 SANS total

We found 1 trial to be relevant to this subset, with a total of 53 participants. There was not a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (MD -3.10, 95% CI -10.30 to 4.10) (Analysis 2.7).

2.8 Mental state: 3. skewed data - short term (up to 12 weeks)

These continuous data (two RCTs) had such large SDs as to suggest that analysis within RevMan would be inadvisable. Therefore, we have presented them in a separate data table (Analysis 2.8).

2.9 Adverse effects: 1a. extrapyramidal - average endpoint SAS score - short term (up to 12 weeks)

For this outcome we found a single study. People in the risperidone + clozapine arm were less likely to experience extrapyramidal adverse events as reported on the SAS than those in the placebo + clozapine arm (1 RCT, N=30, MD -0.90 95% CI -1.97 to 0.17) (Analysis 2.9).

2.10 Adverse effects: 1b. extrapyramidal - skewed data (various scales) - short term (up to 12 weeks)

These continuous data (two RCTs) had such large SDs as to suggest that analysis within RevMan would be inadvisable. Therefore, we have presented them in a separate data table (Analysis 2.10).

2.11 Adverse effects: 1c. extrapyramidal - skewed data (various scales) - medium term (up to 26 weeks)

These continuous data (one RCT) were too skewed to report in a graphic. Therefore, we have reported these data in a separate data table (Analysis 2.11).

2.12 Adverse effects: 2. any adverse event - short term (up to 12 weeks)

We identified one study relevant to this outcome and categorised data into nine subsets.

2.12.1 any adverse event

We found 1 trial to be relevant to this subset, with a total of 64 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 1.14, 95% CI 0.83 to 1.58) (Analysis 2.12).

2.12.2 amenorrhoea

There was a single trial in this subset, with a total of 64 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 3.00, 95% CI 0.13 to 71.0) (Analysis 2.12).

2.12.3 asthenia

There was a single trial in this subset, with a total of 64 participants. There was not a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (RR 1.08, 95% CI 0.61 to 1.91) (Analysis 2.12).

2.12.4 depression

We found 1 trial to be relevant to this subset, with a total of 64 participants. There was not a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (RR 1.20, 95% CI 0.61 to 2.37) (Analysis 2.12).

2.12.5 emotional indifference

We found 1 trial to be relevant to this subset, with a total of 64 participants. There was not a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (RR 1.11, 95% CI 0.52 to 2.37) (Analysis 2.12).

2.12.6 fatigue

We found 1 trial to be relevant to this subset, with a total of 64 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 1.08, 95% CI 0.61 to 1.91) (Analysis 2.12).

2.12.7 failing memory

There was a single trial in this subset, with a total of 64 participants. There was not a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (RR 0.67, 95% CI 0.32 to 1.41) (Analysis 2.12).

2.12.8 increased duration of sleep

We found 1 trial to be relevant to this subset, with a total of 64 participants. There was not a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (RR 1.00, 95% CI 0.51 to 1.97) (Analysis 2.12).

2.12.9 salivation - increased

We found 1 trial to be relevant to this subset, with a total of 64 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 1.25, 95% CI 0.81 to 1.94) (Analysis 2.12).

2.13 Adverse effects: 3a. cardiovascular - short term (up to 12 weeks)

For this outcome we found a single study and categorised data into three subsets (in keeping with our protocol).

2.13.1 dizziness - orthostatic

We found 1 trial to be relevant to this subset, with a total of 64 participants. There was not a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (RR 1.00, 95% CI 0.43 to 2.34) (Analysis 2.13).

2.13.2 palpitation

There was a single trial in this subset, with a total of 64 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 1.00, 95% CI 0.27 to 3.66) (Analysis 2.13).

2.13.3 tachycardia

We found 1 trial to be relevant to this subset, with a total of 64 participants. There was not a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (RR 1.00, 95% CI 0.27 to 3.66) (Analysis 2.13).

2.14 Adverse effects: 3b. cardiovascular - corrected QT interval - short term (up to 12 weeks)

For this outcome we found a single study, with a total of 30 participants. There were no subsets in this outcome. We did not find evidence of a clear difference between the two treatments in this comparison (MD -19.70, 95% CI -42.08 to 2.68).

2.15 Adverse effects: 4. central nervous system - short term (up to 12 weeks)

For this outcome we found a single study and categorised data into three subsets.

2.15.1 sedation

There was a single trial in this subset, with a total of 64 participants. There was not a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (RR 1.46, 95% CI 0.88 to 2.43) (Analysis 2.15).

2.15.2 somnolence

We found 1 trial to be relevant to this subset, with a total of 64 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 1.00, 95% CI 0.51 to 1.97) (Analysis 2.15).

2.15.3 tension

We found 1 trial to be relevant to this subset, with a total of 64 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 1.23, 95% CI 0.71 to 2.12) (Analysis 2.15).

2.16 Adverse effects: 5. gastrointestinal system - short term (up to 12 weeks)

For this outcome we found a single study and categorised data into one subset.

2.16.1 constipation

We found 1 trial to be relevant to this subset, with a total of 64 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 0.71, 95% CI 0.25 to 2.02) (Analysis 2.16).

2.17 Adverse effects: 6a. haematological - short term (up to 12 weeks)

We identified two studies relevant to this outcome and categorised data into three subsets.

2.17.1 neutrophil count

There was a single trial in this subset, with a total of 57 participants. For this subset, we did not find evidence of a clear difference between the two treatments (MD 0.37, 95% CI -0.42 to 1.16) (Analysis 2.17).

2.17.2 prolactin level, ng/mL

We found 1 trial to be relevant to this subset, with a total of 30 participants. For this outcome, within this subset, we did find evidence that 'risperidone plus clozapine' was clearly different in its effects compared with 'placebo plus clozapine' (MD 60.1, 95% CI 46.52 to 73.68) (Analysis 2.17).

2.17.3 white cell count

There was a single trial in this subset, with a total of 61 participants. For this subset, we did not find evidence of a clear difference between the two treatments (MD 0.66, 95% CI -0.20 to 1.52) (Analysis 2.17).

2.18 Adverse effects: 6b. haematological - medium term (up to 26 weeks)

For this outcome we found a single study, the data from which we divided into two subsets.

2.18.1 prolactin level ng/mL

There was a single trial in this subset, with a total of 44 participants. We found evidence of a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (MD 34.1, 95% CI 17.63 to 50.57) (Analysis 2.18).

2.18.2 fasting glucose

There was a single trial in this subset, with a total of 40 participants. There was not a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (MD -4.60, 95% CI -17.09 to 7.89) (Analysis 2.18).

2.19 Adverse effects: 7a. metabolic - weight gain - short term (up to 12 weeks)

There was a single trial in this subset, with a total of 64 participants. For this subset, we did not find evidence of a clear difference between the two treatments (RR 1.00, 95% CI 0.40 to 2.52) (Analysis 2.19).

2.20 Adverse effects: 7a. metabolic - weight gain - medium term (up to 26 weeks)

We found 1 trial to be relevant to this subset, with a total of 48 participants. There was not a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (RR 0.20, 95% CI 0.01 to 3.96) (Analysis 2.20).

2.21 Adverse effects: 7b. metabolic - average endpoint value on lipid profile - short term (up to 12 weeks)

For this outcome we found a single study and categorised data into four subsets.

2.21.1 cholesterol - total (mg/dl)

We found 1 trial to be relevant to this subset, with a total of 56 participants. For this subset, we did not find evidence of a clear difference between the two treatments (MD -6.60, 95% CI -29.05 to 15.85) (Analysis 2.21).

2.21.2 high-density lipoprotein cholesterol (mg/dl)

We found 1 trial to be relevant to this subset, with a total of 52 participants. For this subset, we did not find evidence of a clear difference between the two treatments (MD 0.00, 95% CI -8.44 to 8.44) (Analysis 2.21).

2.21.3 low-density lipoprotein cholesterol (mg/dl)

There was a single trial in this subset, with a total of 53 participants. There was not a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (MD -6.90, 95% CI -26.02 to 12.22) (Analysis 2.21).

2.21.4 triglycerides (mg/dl)

There was a single trial in this subset, with a total of 56 participants. For this subset, we did not find evidence of a clear difference between the two treatments (MD 6.20, 95% CI -57.57 to 69.97) (Analysis 2.21).

2.22 Adverse effects: 7c. metabolic - average endpoint value - short term (up to 12 weeks)

We identified two studies relevant to this outcome, the data from which we divided into four subsets.

2.22.1 body mass index

We found 1 trial to be relevant to this subset, with a total of 63 participants. There was not a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (MD 1.70, 95% CI -0.99 to 4.39) (Analysis 2.22).

2.22.2 fasting glucose (mg/dl)

We found 1 trial to be relevant to this subset, with a total of 51 participants. There was not a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (MD 16.20 95% CI -3.12 to 35.52) (Analysis 2.22).

2.22.3 waist circumference (cm)

There was a single trial in this subset, with a total of 61 participants. There was not a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' within this subset (MD 5.10, 95% CI -4.14 to 14.34) (Analysis 2.22).

2.22.4 weight gain

We found 2 trials to be relevant to this subset, with a total of 94 participants. For this subset, we did not find evidence of a clear difference between the two treatments (MD 0.34, 95% CI -0.84 to 1.53) (Analysis 2.22).

2.23 Adverse effects: 8. sleep - skewed data - average change score (UKU) - short term (up to 12 weeks)

These continuous data, from a single trial, had such large SDs as to suggest that analysis within RevMan would be inadvisable. Therefore, we have presented them in a separate data table (Analysis 2.23).

2.24 Quality of life: average endpoint score (QLS, high = good) - short term (up to 12 weeks)

We identified 1 study relevant to this outcome involving 30 participants. There were no subsets in this outcome. There was not a clear difference between 'risperidone plus clozapine' and 'placebo plus clozapine' (MD 0.80, 95% CI -5.44 to 7.04) (Analysis 2.24).

3. COMPARISON 3: SENSITIVITY ANALYSIS: RISPERIDONE versus PLACEBO (based on attrition)

This particular comparison had only one outcome.

3.1 Mental state: 1. no clinically significant response (defined by PANSS/BPRS) - short term (up to 12 weeks)

We identified six studies relevant to this outcome and categorised data into two subsets (in keeping with our protocol).

3.1.1 defined by PANSS/BPRS < 20% decline

We found 6 trials to be relevant to this subset, with a total of 864 participants. We found evidence of a clear difference between 'sensitivity analysis: risperidone' and 'placebo (based on attrition)' within this subset (RR 0.64, 95% CI 0.52 to 0.78). For this outcome heterogeneity was high (Chi^2 = 12.27; df = 5.0; P = 0.03; I^2 = 59%) (Analysis 3.1).

3.1.2 defined by PANSS/BPRS < 20% decline (without studies with > 50% leaving the study early)

There were 3 relevant trials in this subset, with a total of 589 participants. We found evidence of a clear difference between 'sensitivity analysis: risperidone' and 'placebo (based on attrition)' within this subgroup (RR 0.77, CI 0.67 to 0.88) (Analysis 3.1).

DISCUSSION

Summary of main results

1. COMPARISON 1: RISPERIDONE versus PLACEBO

All of the included studies contributed data towards the comparison of risperidone versus placebo. Despite there being data from 15 studies in total, more often than not only a few studies contributed useable data towards each outcome. Most of the findings were based on few data, which in the majority of cases was of poor quality. The ratings within the Summary of findings table 1 reflect this, as we have judged the overall quality of evidence to be low or very low for each of the four main clinically relevant outcomes.

There is a clear difference in the treatment effect favouring risperidone group. Compared to placebo, people who received risperidone has a 36% risk reduction (very low quality of evidence) in not achieving clinically significant improvement in psychotic symptoms. The effect withstood, even when three studies with >50% attrition rate were removed from the analysis (3 RCTs, N = 589, RR 0.77, CI 0.67 to 0.88). Risperidone group also achieved greater reduction on BPRS score (a reduction of 12.69 compared to placebo group) and PANSS score (a reduction of 17.81 compared to placebo group). However the quality of evidence is compromised due to risk of bias of included studies, the slight heterogeneity and the involvement of industry sponsorship. Similarly, risperidone group are more likely to achieve significant clinical improvement than placebo group (a risk reduction of 31% in risperidone group, very low quality of evidence).

A variety of reasons have caused people to leave the study early, but most showed no clear difference between groups. However, placebo group had significantly more people left the study early due to lack of efficacy (a risk reduction of 61% if one receives risperidone, low quality evidence). Overall, risperidone group is 31% less likely to drop out early compared to placebo group (low quality evidence). The participants have also experienced a range of adverse events, but most had similar incidence rate between groups, but some clearly favoured placebo group including, EPS (1.56 times less likely compared to risperidone group), akathisia (2.58 times times less likely compared to risperidone group), hypertonia (2.98 times times less likely compared to risperidone group) and parkinsonism (7.64 times times less likely compared to risperidone group), somnolence (1.61 times times less likely compared to risperidone group), constipation (1.88 times less likely), weight gain (3.77 times less likely), upper respiratory infection (2.83 times less likely), rhinitis (10.81 times less likely).

2. COMPARISON 2: RISPERIDONE plus CLOZAPINE versus PLACEBO plus CLOZAPINE

When combined with clozapine, there was no obvious difference between groups in achieving clinically significant response in psychotic symptoms (low quality evidence). However, placebo plus clozapine group achieved greater reduction in PANSS score (MD = 5.56, 95% CI 1.59 to 9.53), while risperidone plus clozapine group appeared to produce more improvement in general functioning as assessed by GAF (MD = -4.5, 95% CI -8.38 to -0.62). Participants left the study early for a variety of reasons, but none of which discriminated against any interventions (very low quality of evidence). Similarly, we did not find any clear difference in the adverse events experienced between groups.

Overall completeness and applicability of evidence

The review included 15 studies (n = 2428) of relatively short duration, between 8 and 16 weeks, hence limiting the applicability of the results of this review to long term use of risperidone. All participants in included trials were adults diagnosed with schizophrenia or schizoaffective disorder. The studies took place in both primary and secondary care settings, however, most were conducted in high income countries, hence the evidence should be applied with care in developing countries. There was a lack of data in included studies on the following outcome, including service utilisation and quality of life.

Issue of placebo-controlled trials

Placebo-controlled trials have been used as a licensing requirement by the US Food and Drug Administration (FDA) and other regulatory authorities for some time. Since 1964, the Helsinki Ethical Principles for Medical Research Involving Human Subjects WMA 2008 have been considered a benchmark for trialists around the world (WMA 2008). However, recently it has been argued that it is unethical to conduct trials involving placebo arms for conditions that have an established standard treatment. Also recently, the FDA has adopted the less rigorous Good Clinical Practice as an alternative to the Helsinki declaration, although this has invited numerous criticisms (Lurie 1997; Lurie 2005). Nevertheless, placebo trials do still have an important place, and some ethical bodies around the world do approve of trial methodologies with placebo arms. We suggest that the findings of this review support the continued need for placebo-controlled studies. risperidone is a widely used drug. That many of the effects of this compound are not that different from a placebo is important and would not have been highlighted but for the use of this type of study.

Quality of the evidence

The quality of reporting in most studies could have been much better (Figure 4). Well over half of the included studies have concerns in sequence generation and allocation concealment. There has also been some controversy over the trials conducted by Borison, with the author being accused of scientific fraud (see Included studies). Although, the trialists have not been found to have fabricated research data, this cast a shadow to the findings of his trials (AHRP 2006; CBS News 2000CBS News 2000 AHRP 2006).

Now, years after the first Consolidated Standards of Reporting Trials (CONSORT) statement (Begg 1996), it is expected that all relevant details of methodology that are likely to influence outcome, such as means of allocation and concealment of allocation, are documented and reported. Only 5 out of 13 studies provided information about sequence generation, and 3 out of 13 provided any details about allocation concealment. Good randomisation methodology is essential, and more so for smaller trials, as it ensures that confounding variables are as equally distributed as possible between the intervention and control groups. Poor quality or inadequate randomisation procedures would instead produce imbalance between groups in terms of participant selection and could potentially bias the result.

Potential biases in the review process

The authors of this review made every effort to minimise bias in the review process by strictly following the Cochrane Handbook and conduct expectations. The majority of data in this review

were collected from published reports. Even though we identified substantial number of conference proceedings and unpublished reports, however, we were not able to extract much data from these reports due to either poor reporting or lack of collection at trial stage, therefore, could not be used in this review. For example, in some studies trialists reported mean without standard deviation. Our attempts to contact authors of trials for additional data were unsuccessful. This directly results in

2. Omission of relevant data or studies

As defined in our protocol, we had to omit efficacy measures from studies that had attrition rates of higher than 50% at study endpoint in a sensitivity analysis for our main outcomes. We are not sure if this is correct, but have identified no ready solution to the problem of missing data and when assumptions become too much and undermine credibility (Xia 2009). Certainly, high attrition rates, poor reporting, and poor methodology, combined with the rules we had set ourselves within our protocol, limited the information available for us to use. We feel that people can leave the trials for several reasons, most of which are not specified in the reports. Many studies carried the last observation of such people to the end of the trial period and used those data as if things stayed stable beyond leaving the study. This may or may not be correct but has gone untested. We have taken a conservative approach in presentation of the available data.

Agreements and disagreements with other studies or reviews

This review substantially updates the previous work in the area of risperidone. It also completes the series of direct comparison of risperidone with other drugs (Gilbody 2000; Hosalli 2003; Hunter 2003; Jayaram 2006; Kennedy 2000; Komossa 2007; Li 2009). The findings of this review were similar to the findings of other reviews involving risperidone.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia

Risperidone has a positive effect on the mental state of people with schizophrenia, but data in this review are of low to very low quality, suggesting that future research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

2. For clinicians

While mental state and global state outcomes favoured risperidone, when used alone, there is a high amount of uncertainty regarding this these data and, even if credible, their direct clinical meaning is unclear. Due in large part to poor reporting, we are very uncertain about the effects of risperidone on adverse effects.

3. For managers/policymakers

We found some low quality evidence, which supported the efficacy of risperidone compared to placebo. Based on the same body of evidence, it appears risperidone also causes more adverse events than placebo, and from the available evidence, it is unclear if the benefit out weight the harm. In summary, there is insufficient evidence from this review to support preferential use of risperidone over placebo. Policymakers are encouraged to allocate resources to fund bigger trials with greater methodological quality.

Implications for research

1. General

Strict adherence to the CONSORT statement may well have resulted in this review having more data. Full availability of all data from each study could greatly help future review authors. Many of the studies included in this review did not always clearly present denominator data, did not mention allocation concealment, and frequently described results as "significant" without original data. Multiple publications is another concern. Authors of this review inspectd a large number of publications, which eventually were identified as salami publication of the same trial. Multiple publication poses a risk for reviewers, as if not discovered, the data could be double counted which inadvertently results in biased summary. If mutiple publication is unavoidable, quoting specific trial identifiers such as the International Standard Randomised Controlled Trial Number would greatly reduce confusion over identification of the source of trial.

2. Specific

Many excluded trials could find a place in new or existing systematic reviews, and although many of the 'risperidone versus (other antipsychotic)' reviews have been undertaken, there are many others still to do before a full overview of the effects of risperidone in every comparison is complete (Table 3).

More independent well-planned, well-conducted, and well-reported RCTs of longer duration are needed to address important, unanswered clinically relevant outcomes. In Table 4, we have a recommended study design for future trials. Even though we included 15 studies in this review, we could present few clinically meaningful results. As a result, we are uncertain of the short-, medium-, and long-term efficacy of using this popular treatment.

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Parts of this review were generated using RevMan HAL v 4.2. You can find more information about RevMan HAL here.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Bachmann 2003

Methods	Allocation: randomised. Blindness: double. Duration: 16 weeks. Setting: inpatients and outpatients, USA. Design: parallel groups.
Participants	Diagnosis: people with schizophrenia or schizoaffective (DSM-IV). N = 69 Age: 18-65 years. Sex: male and female (data only available for completers). Inclusion criteria: Those who met DSM-IV criteria for schizophrenia or schizoaffective disorder were selected for study entry. BPRS total score of > 45 or CGI severity of illness item score of > 4; and BPRS positive symptom item total score of > 8, with 1 or more item rated > 4. They were required to have had an adequate clozapine trial, defined as clozapine treatment for > 6 months on a dose that produced a clozapine plasma level of X350 ng/ml or a clozapine + norclozapine plasma level of X450 ng/ml. Exclusion criteria: Participants who met DSM-IV diagnosis of alcohol or substance abuse (other than nicotine) within the past month, alcohol or substance dependence (other than nicotine) within the past 6 months, mental retardation, unstable medical condition, or those treated previously with adjunctive risperidone at X8 mg/day for at least 6 weeks.
Interventions	1. Risperidone (dose 4 mg) plus clozapine (dose not reported). N = 33. 2. Placebo plus clozapine (dose not reported). N =36.
Outcomes	Mental state: BPRS, SANS. Leaving the study early (the week that participants left the study early were reported; all left before 12 weeks). Adverse effects: metabolic, extrapyramidal, haematological.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Bachmann 2003 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Randomization was stratified by in-patient status" (p2276).
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding (performance bias and detection bias) All outcomes	Low risk	"All raters were blind to treatment assignment" (p2275). "Risperidone 4mg (two 2mg capsules) or placebo (two capsules)" (p2276).
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis and completers-only analysis undertaken.
Selective reporting (reporting bias)	Low risk	Outcomes listed in paper all reported.
Other bias	High risk	Double-blind medications were provided by Ortho-McNeil-Janssen Scientific Affairs, LLC. Authors have associations with Eli Lilly, Astra-Zeneca, Pfizer, GlaxoSmithKline, Cephalon, Otsuka, Bioscience, Abbott, Cypress, Merck, Organon, Sanofi-Aventis, Bristol-Myers Squibb, Janssen, Solvay, Wyeth, Zeneca, and Roche either as employees, stockholders, or members of advisory boards.

Borison 1992

Methods	Allocation: randomised. Blindness: double. Duration: 3 days washout period for oral medications plus 6 weeks treatment course (2 weeks for depot medications). Setting: inpatients. Design: parallel groups.
Participants	Diagnosis: schizophrenia (DSM-III-R). N = 160. Age: 18-65 years. Sex: male = 154 and female = 6. Length of illness: ranged from 10 to 17 years. Inclusion criteria: BPRS score more than 30. Exclusion criteria: poor general health, cardiopulmonary disease, head trauma or epilepsy, or drug or alcohol abuse in the last year.
Interventions	1. Risperidone: dose 2 mg/day to 10 mg/day, N = 53. 2. Haloperidol: dose 4 mg/day to 20 mg/day, N = 53*. 3. Placebo: N = 54.
Outcomes	Mental state. Leaving the study early. Global state: needing additional medication. Adverse effects: any, gastrointestinal, central nervous system, respiratory. Unable to use: Global state: CGI (SD not reported). Mental state: BPRS (SD not reported), SANS (SD not reported).

Borison 1992 *(Continued)*

	Adverse effects: AIMS, ESRS (SD not reported). Use of medication for EPS is reported as percentage, but we are unclear at which point the data was measured or the N number, thus unable to convert the data into binary outcome. Physiological measures: vital signs, ECG, blood and urine chemistries (no data reported).
Notes	No information available on funding, but one of the papers has a Janssen logo. *We did not use the data from this group, as the intervention is not relevant. The 'leaving the study early rate' was high in this trial, but the overall leaving the study early rate was less than 50%.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no further information.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	26/53 participants left from the risperidone group, 37/54 left from the placebo group.
Selective reporting (reporting bias)	High risk	All outcomes measured were reported, but without SD.
Other bias	Low risk	None obvious.

Chouinard 1992

Methods	Allocation: randomised. Blindness: double blind. Duration: 7-day single-blind placebo washout period plus 8-week treatment period. Setting: inpatients, at six centres in Canada. Design: multicentre, parallel group.
Participants	Diagnosis: chronic schizophrenia (DSM III-R). N = 135. Age: 19-67 years. Sex: male and female. Length of illness: mean ˜ 2.0 years, SD ˜ 3.4 years. Inclusion criteria: total PANSS score between 60 and 120. Exclusion criteria: pregnant or lactating women or women without adequate contraception, mental disorders other than schizophrenia, neurological disorders, psychoactive substance use or alcohol abuse.
Interventions	1. Risperidone: dose 2 mg/day, N = 24.* 2. Risperidone: dose 6 mg/day, N = 22. 3. Risperidone: dose 10 mg/day, N = 22.

Chouinard 1992 *(Continued)*

	4. Risperidone: dose 16 mg/day, N = 24. 5. Placebo, N = 22. 6. Haloperidol: dose 20 mg/day, N = 21.
Outcomes	Mental state: PANSS, BPRS. Leaving the study early. Global state: CGI. Adverse effects: ESRS, UKU Side Effect Rating Scale, concomitant sedative/hypnotic use. Unable to use: Physiological measures: blood pressure, heart rate in supine and standing positions, ECG, biochemistry, hematology, urine analysis (no data reported).
Notes	*Fixed dose. We included data only from the 6 mg/day arm, as this was the closest dose to what would be used in routine clinical practice. This arm had a differential leaving the study early rate with 45% in the risperidone arm leaving the study early compared to 68% in the placebo arm (overall participants leaving the study early was greater than 50%).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, blocks of 12.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind: "identical tablets" (p27).
Incomplete outcome data (attrition bias) All outcomes	Low risk	LOCF, ITT analysis used.
Selective reporting (reporting bias)	Low risk	Outcomes listed in papers all reported.
Other bias	High risk	Supported by a grant from the Janssen Research Foundation.

Downing 2014

Methods	Allocation: multicenter, randomised. Blindness: double blind; Quote: 'the raters were blind to the study design, entrance criteria, and patient treatment assignment.' p.3) Duration: 2 weeks study entry + 7 days placebo lead-in treatment phrase + 6 weeks treatment duration. Settings: inpatients. Design: parallel.
Participants	Diagnosis: schizophrenia (historical documentation and Structured Clinical Interview for DSM-IV Disorders [SCID] interview). N = 1009. (1013 participants were randomised, however, the author analysed data on an Intention-to-treat basis) Age: mean ˜ 39.8 years, SD ˜ 11.4 years.

Downing 2014 *(Continued)*

	Sex: male 647, female 362. Length of illness: mean ˜ 14.5 years, SD ˜ 10.7 years. Inclusion criteria: those with an accurate and reliable diagnosis of schizophrenia (based upon historical documentation and Structured Clinical Interview for DSMIV Disorders [SCID] interview), who experienced an exacerbation of their illness 2 weeks prior to study entry (Visit 1), leading to a need for intensification of psychiatric care. Patients could be antipsychotic treatment naive or have had prior exposure to antipsychotic medications and were not treatment refractory in the opinion of the investigator. Exclusion criteria: those who had any other current Axis I psychiatric diagnoses in addition to schizophrenia, a diagnosis of substance dependence or substance abuse, a history of one or more seizures, answered yes to any suiciderelated behaviors within 1 month of Visit 1, participated in any clinical trial for which they received a studyrelated medication in the 6 months prior to Visit 1, were treatment refractory, or had demonstrated an inadequate response to treatment with risperidone, or for whom treatment with risperidone, LY2140023, or placebo was contraindicated.
Interventions	1. Risperidone: 2 mg/d on the first day and 4mg/d therafter, N = 142. 2. Placebo: placebo tablets or capsules identical to LY2140023 and risperidone, N = 295. 3. LY2140023 low dose: twice daily, 40 mg/d, N = 292*. 4. LY2140023 high dose: twice daily, 80 mg/d, N = 280*.
Outcomes	Leaving the study early. Adverse effects**. Unable to use Mental state: PANSS (only means of change score were reported).
Notes	*We did not use the data from these groups, as the interventions are not relevant. **For the concomitant medications rate reported in this study, we only extracted 2 drugs mentioned in our protocol.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no further information. Quote: "multicenter, randomized, doubleblind, parallel..." (p.2).
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: 'the raters were blind to the study design, entrance criteria, and patient treatment assignment.' (p.3)
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis was performed.
Selective reporting (reporting bias)	Low risk	All the measured outcomes were reported.
Other bias	High risk	All authors were from Eli Lilly and Company.

Durgam 2014

Methods	Allocation: multinational, randomised. Blindness: double blind, but unclear who is blinded. Duration: 9 weeks duration including 7 days wash out period, 6 weeks treatment period and 2 weeks safety follow up. Settings: inpatients, 65 study centres in the United States, India, Russia, Ukraine, and Malaysia. Design: parallel.
Participants	Diagnosis: schizophrenia (DSM-IV-TR). N = 729. Age: mean ˜ 36 years, SD ˜ 10.8 years. Sex: male 502, female 227. Length of illness: mean ˜ 11.6 years, SD ˜ 9.7 years. Inclusion criteria: 18-60 years old, atients had the diagnosis for at least 1 year, current exacerbation less than 2 weeks' duration, and at least 1 psychotic episode requiring hospitalization/antipsychotic medication change/intervention during the preceding year. PANSS total score between 80 and 120, a score ≥4 (moderate) on at least 2 of 4 PANSS positive symptoms (delusions, hallucinatory behavior, conceptual disorganization, suspiciousness/persecution); CGI-S rating ≥4; Body mass index (BMI) between 18 and 35. Exclusion criteria: first episode of psychosis; diagnosis of various DSM-IV-TR disorders (e.g., schizoaffective, schizophreniform, bipolar I and II); alcohol/ substance abuse/dependence (within 3 months); treatment-resistant schizophrenia (poor response to ≥2 antipsychotics of adequate dose and duration) or suicidal or homicidal attempt/intent (active or preceding 2 years). Typical treatment-related, concomitant medication, and medical/physical exclusions were applied.
Interventions	1. Risperidone: 4 mg/d , N = 140. 2. Placebo: once daily, N = 151. 3. Cariprazine low dose: 1.5 mg/d, N = 145*. 4. Cariprazine medium dose: 3 mg/d, N = 146*. 5. Cariprazine high dose: 4.5 mg/d, N = 147*.
Outcomes	Mental state: no clinical response**, PANSS, Negative Symptom Assessment (NSA-16). Leaving the study early. Global state: Clinical Global Impressions-Improvement (CGI-I). Adverse effects***: Treatment-emergent adverse events (TEAEs). Unable to use: physical examination, laboratory evaluations, vital signs, weight, and 12-lead ECG.
Notes	*We did not use the data from these groups, as the interventions are not relevant. **defined as the decrease rate of PANSS score < 30% improvement from baseline) ***For the concomitant medications rate reported in this study, we only extracted 2 drugs mentioned in our protocol.

Risk of bias

Bias	Authors' judgement	Support for judgement

Durgam 2014 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomised, no further information. Quote: "A 9-week, multinational, randomized, double-blind..." (p.451).
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Seventy-two out of 151 participants left the study early from placebo group, while 39 out of 140 participants left the study early from risperidone group. Intention to treat analysis was used to analyzed the data and sensitivity analysis was also conducted by using mixed effects model for repeated measures.
Selective reporting (reporting bias)	Low risk	All the measured outcomes were reported.
Other bias	Low risk	None obvious.

Geffen 2010

Methods	Allocation: randomised, a central randomisation scheme. Blindness: double blind, but unclear who is blinded. Duration: 5-14 days suspension of other antipsychotics plus 6 weeks treatment period. Settings: inpatients, 40 sites in India, Romania, and USA. Design: parallel.
Participants	Diagnosis: schizophrenia (DSM-IV-TR). N = 363. Age: mean ˜ 34.2 years, SD ˜ 10.34 years. Sex: male 245, female 118. Length of illness: mean ˜ 8.26 years, SD ˜ 8.92 years. Inclusion criteria: 18-65 years old, acute exacerbation within 30 days, PANSS total score ≥ 70, at least 4 on any 2 of PANSS items (delusions, hallucinatory behaviours, conceptual disorganization, or suspiciousness/persecution), CGI ≥ 4. Exclusion criteria: a score of greater than 9 on the modified ISST, treatment refractory psychosis following 2 years of exposure to a therapeutic dose of antipsychotics, substance abuse, TD, use of mood stabilisers, history of blood cell disorder.
Interventions	1. Risperidone: 2 mg/d to 8 mg/d, N = 91. 2. Placebo: no details, N = 93. 3. BL-1020 low dose: 10 mg/d, N = 90*. 4. BL-1020 high dose: 20 mg/d to 30 mg/d, N = 89*.
Outcomes	Mental state. Leaving the study early. Global state: needing additional medication. Adverse effects**. Unable to use:

Geffen 2010 *(Continued)*

	Clinical response. Global state: CGI-I, CGI-S. Mental state: PANSS score. Cognitive function: Mean and SD of each outcome were not reported.
Notes	*We did not use the data from these groups, as the interventions are not relevant. **For the concomitant medications rate reported in this study, we only extracted 2 drugs mentioned in our protocol. Overall leaving the study early rate is less than 50%.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed via an interactive voice system. Quote: "Randomisation was performed using an interactive voice response system, one randomisation scheme was generated across all sites (i.e. a central randomisation scheme)". (p1169)
Allocation concealment (selection bias)	Low risk	Allocation sequence was concealed by the "voice response system". Quote: "when the drug was dispensed, the investigator called the interactive voice response system to assign the treatment code. This code number was used to identify the medication kit to be dispensed to the patient". (p1169)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind. Quote: "This was a 6-week, randomised, double-blind, placebo-controlled, parallel group phase 2 study". (p1168)
Incomplete outcome data (attrition bias) All outcomes	Low risk	20 participants in risperidone group and 37 participants in placebo group did not complete the trial, but ITT analysis was applied.
Selective reporting (reporting bias)	Low risk	All the measured outcomes were reported.
Other bias	Low risk	None obvious.

Heisterberg 2007

Methods	Allocation: randomised. Blindness: double. Duration: 6 weeks. Setting: no information available. Design: multicentre, parallel groups.
Participants	Diagnosis: schizophrenia as per DSM-IV-TR. N = 599. Age: 18-69 years. Sex: male and female. History: having an acute exacerbation of schizophrenia. Inclusion criteria: baseline PANSS score of 70 to 120 and CGI score of ≥ 4. Exclusion criteria: no information available.
Interventions	1. Risperidone: dose 6 mg/day, N = 154.

Heisterberg 2007 *(Continued)*

	2. Placebo: N = 149. 3. Bifeprunox: N = 296.
Outcomes	Adverse events: lipid parameters*, EPS. Leaving the study early. Unable to use: Adverse effects: weight change (no SD reported).
Notes	Study attrition was 60% at the end of 6 weeks -- no data included in efficacy analysis. *We reported this data as the paper used LOCF to account for missing values.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no further information. Quote: "...patients with acutely exacerbated schizophrenia were randomly assigned to..."
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis done.
Selective reporting (reporting bias)	Unclear risk	Outcomes listed in the methods were reported.
Other bias	Low risk	None obvious.

Honer 2006

Methods	Allocation: randomised. Blindness: double. Duration: 8 weeks. Setting: inpatient and community settings. Design: multicentre, parallel-group study.
Participants	Diagnosis: schizophrenia or schizoaffective disorder (DSM-IV). N = 68. Age: 18-65 years. Sex: male and female. History: poor response to clozapine. Inclusion criteria: all participants on clozapine at a stable dose of 400 mg or more for at least 12 weeks, baseline PANSS score of 80 or greater, baseline CGI score of 4 or greater, baseline SOFAS score of 40 or less. Exclusion criteria: alcohol or substance misuse in the past 3 months, pregnant, breastfeeding, people needing anticonvulsants, developmental disabilities, current treatment with clozapine for the primary indication of movement disorder.

Honer 2006 *(Continued)*

Interventions	1. Risperidone (3 mg/day) combined with clozapine (400 mg or more/day), N = 34. 2. Placebo combined with clozapine (400 mg or more/day), N = 34.
Outcomes	Mental state: PANSS. Leaving the study early. Global state: CGI-S. Adverse effects: ESRS, BAS, dystonia, dyskinesia, parkinsonism, lipid profile, weight, waist circumference, BMI, fasting blood glucose, white cell count, neutrophil count. Unable to use: Cognitive functions: frontal lobe cognitive functions (no data reported). Verbal working-memory index (not peer-reviewed scale). Adverse effects: UKU Side Effect Rating Scale (no data reported).
Notes	Supported by Stanley Medical Research Institute. The investigators had assessed 595 people for eligibility for the study, of which 458 (77%) did not meet the inclusion criteria and 69 (12%) declined to participate. Leaving the study early rate is less than 50%.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated schedule with a permuted-block design. Quote: "randomisation was performed according to a computer-generated schedule with a permuted-block design. The fixed block size was four patients". p473.
Allocation concealment (selection bias)	Low risk	Quote: "the site investigators did not know the block size. The person generating the randomization schedule was not involved in determining patients' eligibility, administering treatment, or determining outcome." p473.
Blinding (performance bias and detection bias) All outcomes	Low risk	Triple blinding (participants, investigator, and assessor blind) done but not tested out. Quote: "randomly assigned to double-blind treatment with risperidone or a placebo of identical appearance". p473.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT principle using mixed-model analysis.
Selective reporting (reporting bias)	Unclear risk	Outcomes listed in the methods were reported.
Other bias	Low risk	Janssen-Ortho, Canada, provided the risperidone and matching placebo and reviewed the protocol, but no request for amendment. The data were analysed and the manuscript was written solely by the listed authors.

Marder 1994a

Methods	Allocation: randomised. Blindness: double. Duration: 7-day single-blind placebo washout period plus 8-week treatment period. Setting: inpatients, 20 centres in USA. Design: parallel-group study.

Marder 1994a *(Continued)*

Participants	Diagnosis: schizophrenia (DSM III-R). N = 388*. Age: 18-67 years. Sex: male and female. Inclusion criteria: total PANSS score between 60 and 120. Exclusion criteria: pregnant or lactating women or women without adequate contraception, mental disorders other than schizophrenia, neurological disorders, psychoactive substance use or alcohol abuse, and schizoaffective disorder.
Interventions	1. Risperidone: dose 2 mg/day, N = 63**. 2. Risperidone: dose 6 mg/day, N = 64**. 3. Risperidone: dose 10 mg/day, N = 65. 4. Risperidone: dose 16 mg/day, N = 64. 5. Placebo: N = 66. 6. Haloperidol: dose 20 mg/day, N = 66.
Outcomes	Mental state: PANSS*. Leaving the study early***. Global state: CGI*. Adverse effects: ESRS, UKU Side Effect Rating Scale*.
Notes	*Data from a subset of participating centre, where leaving the study early was not reported (risperidone N = 64; placebo N = 66). **Fixed dose. We included data only from the 6 mg/day arm, as this was the closest dose to what would be used in routine clinical practice. This arm had a differential leaving the study early rate with 45% in the risperidone arm leaving the study early compared to 68% in the placebo arm. ***Data from a wider set of participating centres (risperidone N = 86; placebo N = 88).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation in blocks of 12.
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis was used.
Selective reporting (reporting bias)	Low risk	All outcomes measured were reported.
Other bias	High risk	Supported by a grant from the Janssen Research Foundation.

Pai 2002

Methods	Allocation: randomised.

Pai 2002 *(Continued)*

	Blindness: double blind, a placebo with an identical appearance to the risperidone, but unclear who is blinded. Duration: 12 weeks. Settings: not stated. Design: parallel.
Participants	Diagnosis: schizophrenia (DSM-IV). N = 50*. Age: mean ~ 50.2 years, SD ~ 9.6 years. Sex: male = 20 and female = 10. Length of illness: mean 11.86 years, SD 10.1 years. Inclusion criteria: age between 18 and 65 years, maintenance on conventional antipsychotics for more than 1 year with an equivalent dosage of less than 200 mg/day of chlorpromazine, BPRS total scores of less than 20, and no record of any violent or aggressive behavior within the last 6 months, to minimise the risk of psychotic exacerbation after withdrawing antipsychotics. Exclusion criteria: comorbidity of organic mental disorder or major physical illness, ever being prescribed any atypical antipsychotic, and neuroleptic depot administration within the last 6 months.
Interventions	1. Risperidone: titration period 6 weeks from 2 mg/d to 6 mg/d, then with fixed dosage of 6 mg/d for the remaining 6 weeks, N = 22. 2. Placebo: titration period 6 weeks from 2 mg/d to 6 mg/d, then with fixed dosage of 6 mg/d for the remaining 6 weeks, N = 20.
Outcomes	Mental state: BPRS. Leaving the study early. Global state: needing additional medication; CGI. Adverse effects: ESRS-parkinsonism score, ESRS-dystonia score, AIMS total score, concomitant with benzodiazepine, concomitant with antiparkinsonism drug. Unable to use: The number of participants leaving the study early in each group was not reported. Change score of ESRS, change score of AIMS. Change scores were not used, as endpoint scores of the same scales were available.
Notes	*2 of the references reported N = 50, 1 reference reported N = 49. We assume N = 50 in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no further information: Quote: "subjects were randomly assigned to the risperidone or placebo groups". (Bai 2003, p1343)
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind, a placebo with an identical appearance to the risperidone, but unclear who is blinded." (p1343)
Incomplete outcome data (attrition bias) All outcomes	High risk	42 participants completed the 12-week study and 7 participants withdrew. 4 participants left the study early due to psychotic symptom exacerbation, another 3 participants withdrew due to a medical condition.

Pai 2002 *(Continued)*

Selective reporting (reporting bias)	Low risk	All the measured outcomes were reported.
Other bias	Low risk	None obvious.

Potkin 1997

Methods	Allocation: randomised. Blindness: double blind. Duration: 4 weeks. Setting: multicentre, USA. Design: parallel.
Participants	Diagnosis: schizophrenia. N = 246. Age: no information available. Sex: male and female. Inclusion criteria: PANSS score of 80 to 120, ≥ 8 on at least 2 items on the PANSS positive subscale. Exclusion criteria: no information available.
Interventions	1. Risperidone: dose 4 mg/day, N = 85. 2. Risperidone: dose 8 mg/day, N = 78*. 3. Placebo: N = 83.
Outcomes	Mental state: PANSS. Leaving the study early. Adverse effects: any adverse event. Unable to use: Adverse effects: ESRS (SD not reported).
Notes	*We adopted data from the 4 mg arm, as it's more representative of the dosage used in a normal clinical setting.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no further description.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information available.
Selective reporting (reporting bias)	Low risk	All outcomes measured were reported.

Potkin 1997 *(Continued)*

Other bias	High risk	Funded by Janssen Research Foundation.

Potkin 2003

Methods	Allocation: randomised. Blindness: double. Duration: 4 weeks. Setting: inpatients, 40 centres in USA. Design: parallel.
Participants	Diagnosis: schizophrenia and schizoaffective disorder (DSM-IV). N = 404. Age: the mean age for each treatment group ranged from 38.1 to 40.2 years. Sex: male = 283, female = 121. Length of illness: not reported. Inclusion criteria: men and non-pregnant, non-lactating women, evidence of responsiveness to antipsychotic medications (were not refractory to antipsychotics and had previously shown an improvement with an antipsychotic drug other than clozapine and had been an outpatient for at least 1 3-month period during the last year, PANSS score of at least 60 and a minimum score of 4 (moderate) on at least 2 items of the psychotic item subscale. Exclusion criteria: history of violence, recent history of suicide attempt or serious suicide thoughts, neurological disorders other than TD or EPS, psychoactive substance dependence or history of drug or alcohol abuse within 1 month, treatment with an investigational drug within 4 weeks of the investigational period, any acute or unstable medical condition.
Interventions	1. Risperidone: dose 6 mg/day N = 99. 2. Aripiprazole: dose 20 mg/day N = 101*. 3. Aripiprazole: dose 30 mg/day N = 101*. 4. Placebo: N = 103.
Outcomes	Mental State: PANSS. Leaving the study early. Adverse effects. Unable to use: Global State: CGI (no SD reported). Mental state: BPRS, PANSS change score (no SD reported). Adverse effects: EPS, SAS, BAS, AIMS (no data reported). Body weight, serum prolactin, corrected QT (no SD reported). Pain was reported as "pain", "extremity pain", and "back pain"; since we are unsure if participants overlapped in these categories, we selected "back pain" to report to avoid double counting.
Notes	Lorazepam was used for anxiety and insomnia. Intramuscular lorazepam was used for agitation. Benztropine up to 6 mg per day was permitted for EPS. Psychotropics other than those prescribed by the study protocol were prohibited. *Data from these 2 arms were not used in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement

Potkin 2003 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "This was a randomised, 4-week, inpatient, double-blind, placebo-controlled, parallel-group study". (p682).
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "This was a randomised, 4-week, inpatient, double-blind, placebo-controlled, parallel-group study". (p682)
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was 40% (162/242) in this study. Although 392 participants were included in efficacy analysis using LOCF and 403 were included in safety analysis, we feel that the high attrition rate made any results from this trial prone to bias.
Selective reporting (reporting bias)	Low risk	All outcomes measured were reported.
Other bias	High risk	Supported by Bristol-Myers Squibb and Otsuka Pharmaceutical.

Potkin 2006

Methods	Allocation: randomised. Blindness: double. Duration: 6 weeks*. Setting: inpatients, 30 sites, USA. Design: parallel.
Participants	Diagnosis: schizophrenia or schizoaffective disorder (DSM-IV). N = 381. Age: mean ˜ 34.8 years, SD ˜ 9.7 years. Sex: male = 228 and female = 153. Length of illness: not reported. Inclusion criteria: 18-64 years old, acute exacerbation of schizophrenia of recent onset (within 4 weeks), have a score of ≥ 4 at least 2 of the following items on the PANSS: Hostility, Excitment, Tension, Uncooperativeness, and Poor Impulse Control, and a total score on the 5 items of at least 17, CGI ≥ 5. Exclusion criteria: comorbid Axis 1 diagnosis with the exception of substance abuse/dependence, borderline personality disorder, mental retardation or clinically significant medical illness, also excluded were people who received risperidone or quetiapine within 7 days of baseline, clozapine within 60 days, or depot antipsychotic or electroconvulsive therapy within the study period.
Interventions	1. Risperidone: dose 4.7 ± 0.9 mg/day, N = 153. 2. Quetiapine: dose 579.5 ± 128.9 mg/day, N = 156. 3. Placebo: N = 73. Zolpidem, zopiclone, and zaleplon used to treat insomnia. Injectable lorazepam, sodium amytal, or midazolam used for treating agitation or restlessness. Benztropine mesylate or an equivalent treatment for movement disorder was permitted throughout study as needed.
Outcomes	Mental state: PANSS. Leaving the study early. Global state: CGI-Severity, CGI-Change. Adverse effects: SAS, BAS, prolactin, EPS.

Potkin 2006 *(Continued)*

	Unable to use: Readiness for discharge questionnaire (not a validated scale). Study medication satisfaction (not a validated scale).
Notes	*2 weeks monotherapy phase followed by a 4-week additive therapy phase. In the additive therapy phase, all the participants in the 3 groups received other antipsychotic drugs. As the data in these two phases is reported separately, we only use the data from the 2-week monotherapy phase.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using a centralised interactive voice response system. Quote: "A non-centralised randomisation strategy was used to ensure that subjects were balanced across the three treatments within each investigate site... subjects were assigned to a double blind treatment using a centralized interactive voice response system (IVRS)" (p255)
Allocation concealment (selection bias)	Low risk	Concealed with centralised IVRS.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind by using a centralised IVRS (p255)
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis was used.
Selective reporting (reporting bias)	Low risk	All outcomes measured were reported.
Other bias	High risk	Supported by Janssen Pharmaceutica.

Potkin 2007

Methods	Allocation: randomised. Blindness: double. Duration: 6 weeks. Setting: 21 sites in USA. Design: parallel.
Participants	Diagnosis: schizophrenia. N = 180. Age: 18 to 65 years. Sex: not reported. History: participants with acute exacerbation were included in the trial. Inclusion criteria: baseline PANSS score > 60. Exclusion criteria: recent history of suicide attempt or serious suicide thoughts, neurological disorders other than TD or EPS, psychoactive substance dependence or history of drug or alcohol abuse within 1 month.
Interventions	1. Risperidone: dose 6 mg/day, N = 59. 2. Placebo: N = 62.

Potkin 2007 *(Continued)*

	3. Asenapine: dose 10 mg/day, N = 59.
Outcomes	Leaving the study early. Adverse effects. Unable to use: Global state: CGI (> 50% loss to follow-up, thus data was not reported). Mental state: PANSS (> 50% loss to follow-up, thus data was not reported). Function: battery of neurocognitive test (no SD reported), WCST (no data reported).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no further information.
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double dummy placebo design was employed to maintain blinding. Quote: "this double-blind, double-dummy, 3-arm, fixed-dose..." (p1493).
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT for efficacy data and LOCF for safety data.
Selective reporting (reporting bias)	Low risk	All outcomes measured were reported.
Other bias	High risk	Funded by Organon USA Inc and Pfizer Inc.

Yagcioglu 2005

Methods	Allocation: randomised. Blindness: double. Duration: 6 weeks. Setting: inpatients and outpatients, 2 sites in Turkey. Design: parallel.
Participants	Diagnosis: schizophrenia (DSM-IV). N = 30. Age: 18 to 55 years. Sex: male = 20 and female = 10. Length of illness: mean ˜ 14.4 years, SD ˜ 9.1 years. Inclusion criteria: patients had been receiving clozapine treatment (300 mg/d to 900 mg/d) for at least 6 months prior to the study; people diagnosed as having residual schizophrenia in whom negative symptoms were more prominent than positive symptoms; failed to respond adequately; positive symptoms was stable by clinical criteria and reported in written notes for at least 3 months prior to study entry; PANSS ≥ 72, CGI-S ≥ 4, a score of at least 3 on any one of the PANSS POS items.

Yagcioglu 2005 *(Continued)*

	Exclusion criteria: concomitantly receiving mood stabilisers, including lithium carbonate, antidepressants, and antipsychotic medication other than clozapine; alcohol or substance dependence; history of intolerance to risperidone for reasons other than EPS.
Interventions	1. Risperidone combined with clozapine: dose 2 mg/day to 6 mg/day, N = 16. 2. Placebo combined with clozapine, N = 14.
Outcomes	Clinical response*. Leaving the study early. Global state: CGI-S. Functioning: GAF. Mental state: PANSS, CDS. Adverse effect: weight gain, serum prolactin, SAS, BAS, AIMS score. Quality of life: QLS.
Notes	*no clinical improvement: PANSS positive subscale score < 20%.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear how the "pre-assigned random sequence" was achieved. Quote: "Randomisation was planned by one of the unblinded investigators prior to the initiation of the study in a 1:1 ratio, and pre-assigned random sequence was determined for each site. The patients arriving at each site were assigned the study medication according to this sequence in order with their enrolment." (p65)
Allocation concealment (selection bias)	Unclear risk	Not stated. Quote: "pre-assigned random sequence was determined for each site." (p65)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind, investigators were blinded, no further information.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant in the risperidone group withdrew consent just prior to final visit ratings. This is unlikely to have any significant impact on the outcome assessment.
Selective reporting (reporting bias)	Low risk	All the outcomes were reported.
Other bias	Low risk	None obvious.

AIMS: Abnormal Involuntary Movement Scale

BACS: Brief Assessment of Cognition in Schizophrenia

BAS: Barnes Akathisia Scale
BMI: body mass index

BPRS: Brief Psychiatric Rating Scale

CDS: Calgary Depression Scale

CGI: Clinical Global Impression

DSM: Diagnostic and Statistical Manual of Mental Disorders
ECG: electrocardiogram

EPS: extrapyramidal symptom

ESRS: Extrapyramidal Symptom Rating Scale
GAF: Global Assessment of Functioning

HAM-D: Hamilton Rating Scale for Depression
ISST: InterSePT Scale for Suicidal Thinking
ITT: intention to treat
IVRS: interactive voice response system
LOCF: last observation carried forward

PANSS: Positive and Negative Syndrome Scale
QLS: Quality of Life Scale

SANS: Scale for the Assessment of Negative Symptoms

SAS: Simpson Angus Scale
SD: standard deviation
SOFAS: Social and Occupational Functioning Assessment Scale

TD: tardive dyskinesia

WCST: Wisconsin Card Sorting Test

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

Study	Reason for exclusion
Adler 1999	Allocation: randomised. Participants: people with non-organic psychosis. Interventions: vitamin E versus placebo.
Akhondzadeh 2005	Allocation: randomised. Participants: people with chronic schizophrenia. Interventions: risperidone plus lamotrigine versus risperidone plus placebo.
Akhondzadeh 2007	Allocation: randomised. Participants: people with chronic schizophrenia. Interventions: risperidone plus celecoxib versus risperidone plus placebo.
Anwunah 1999	Allocation: randomised. Participants: people with schizotypal personality disorder.
Ayd 2001	Allocation: randomised. Participants: people with schizotypal personality disorder.
Azorin 2002	Allocation: randomised. Participants: people with schizophrenia. Interventions: risperidone versus sertindole.
Azorin 2006	Allocation: randomised. Participants: people with schizophrenia. Interventions: risperidone versus sertindole.

Study	Reason for exclusion
Bai 2005	Allocation: randomised. Participants: people with schizophrenia. Intervention: risperidone versus other atypicals (no placebo arm).
Baker 2012	Allocation: not RCT but pooled data from RCTs.
Basson 2001	Allocation: randomised. Participants: people with schizophrenia. Intervention: olanzapine versus haloperidol versus risperidone.
Beasley 1996	Allocation: randomised. Participants: people with schizophrenia. Intervention: olanzapine versus placebo versus haloperidol.
Bondolfi 1998	Allocation: randomised. Participants: people with resistant schizophrenia. Intervention: clozapine versus risperidone.
Borison 1992a	Allocation: randomised. Participants: people with chronic schizophrenia. Intervention: risperidone versus haloperidol.
Boyer 1995	Allocation: randomised. Participants: people with negative schizophrenia. Intervention: amisulpride versus placebo.
Brecher 1998	Allocation: randomised. Participants: people with schizophrenia. Interventions: risperidone versus olanzapine.
Cada 2004	Allocation: randomised. Participants: people with schizophrenia. Intervention: risperidone long-acting injection versus placebo.
Carson 2002	Allocation: randomised. Participants: people with schizophrenia. Intervention: aripiprazole versus haloperidol versus placebo.
Casey 2003	Allocation: randomised. Participants: people with schizophrenia. Intervention: aripiprazole versus placebo.
Castle 2015	Allocation: not RCT but pooled data from RCTs.
Chan 2007	Allocation: randomised. Participants: people with schizophrenia. Interventions: risperidone versus aripiprazole.
Chue 2002	Allocation: randomised. Participants: people with schizophrenia. Interventions: risperidone long-acting injection versus olanzapine.
Ciliberto 2005	Allocation: randomised. Participants: people with schizophrenia. Interventions: risperidone long-acting injection versus placebo.
Citrome 2004	Allocation: randomised.

Study	Reason for exclusion
	Participants: people with schizophrenia. Intervention: antipsychotic monotherapy versus antipsychotic plus valproate.
Claus 1992	Allocation: randomised. Participants: people with schizophrenia. Interventions: risperidone versus haloperidol.
Conley 1998	Allocation: randomised. Participants: people with schizophrenia. Intervention: risperidone versus olanzapine.
Cooper 1997	Allocation: randomised. Participants: people with schizophrenia. Interventions: risperidone versus olanzapine versus quetiapine.
Cornblatt 2002	Allocation: randomised. Participants: people with schizophrenia. Intervention: aripiprazole versus olanzapine.
Crawford 1997	Allocation: randomised. Participants: people with schizophrenia. Intervention: olanzapine versus haloperidol versus placebo.
Csernansky 1999	Allocation: randomised. Participants: people with schizophrenia. Interventions: risperidone versus haloperidol.
David 2000	Allocation: not randomised.
Davis 2001	Allocation: not randomised.
Dossenbach 1997	Allocation: randomised. Participants: people with schizophrenia. Interventions: olanzapine versus fluphenazine.
Dubitsky 2002	Allocation: randomised. Participants: people with schizophrenia. Intervention: aripiprazole versus risperidone.
Edgell 2000	Allocation: randomised. Participants: people with schizophrenia. Intervention: risperidone versus olanzapine.
Fleming 2007a	Allocation: randomised. Participants: people with schizophrenia. Intervention: asenapine versus risperidone versus placebo.
Friedman 2000	Allocation: randomised. Participants: people with schizophrenia. Interventions: risperidone versus haloperidol.
Gismondi 2004	Allocation: randomised. Participants: people with schizophrenia. Interventions: aripiprazole versus perphenazine.
Gregor 2000	Allocation: randomised.

Study	Reason for exclusion
	Participants: people with schizophrenia. Interventions: olanzapine versus haloperidol.
Harvey 2001	Allocation: randomised. Participants: people with schizophrenia and schizoaffective disorder. Interventions: risperidone versus olanzapine.
Hwang 2003	Allocation: randomised. Participants: people with schizophrenia. Interventions: risperidone versus amisulpride.
Hwang 2005	Allocation: randomised. Participants: people with schizophrenia. Interventions: risperidone versus aripiprazole.
Kane 2005	Allocation: randomised. Participants: people with schizophrenia. Interventions: risperidone, sertindole, and aripiprazole.
Kinon 1998	Allocation: randomised. Participants: people with schizophrenia. Interventions: olanzapine versus haloperidol.
Kinon 2015	Allocation: not RCT, but pooled data from five RCTs.
Lauriello 2005	Allocation: randomised. Participants: people with schizophrenia. Interventions: risperidone long-acting injection versus placebo.
Lemmens 1994	Allocation: randomised. Participants: people with schizophrenia. Intervention: risperidone versus zuclopenthixol dihydrochloride.
Lieberman 2005	Allocation: randomised. Participants: people with schizophrenia. Interventions: olanzapine versus haloperidol.
Lindstrom 1994	Allocation: randomised. Participants: people with schizophrenia. Intervention: risperidone versus haloperidol.
Loo 1997	Allocation: randomised. Participants: people with deficit schizophrenia. Interventions: amisulpride versus placebo.
Lopez 1996	Allocation: randomised. Participants: people with schizophrenia. Interventions: risperidone versus haloperidol.
Lopez-Ibor 1992	Allocation: randomised. Participants: people with schizophrenia. Intervention: risperidone versus haloperidol.
Luo 2011	Allocation: randomised. Participants: people with schizophrenia. Intervention: paliperidone versus olanzapine versus placebo.

Study	Reason for exclusion
Marder 1991	Allocation: not RCT, but pooled data from two RCTs.
McClellan 2009	Allocation: randomised. Participants: people with schizophrenia. Interventions: risperidone versus olanzapine or molindone.
McClure 2009	Allocation: randomised. Patients: Schizotypal personality disorder.
McKenna 2004	Allocation: randomised. Participants: people with refractory schizophrenia. Intervention: clozapine versus clozapine plus risperidone.
Nasrallah 2004a	Allocation: randomised. Participants: people with schizophrenia. Intervention: risperidone long-acting injection versus placebo.
NCT 02109562	Allocation: randomised. Participants: people with schizophrenia. Interventions: resperidone injections versus placebo.
NCT00034892	Allocation: randomised. Participants: people with schizophrenia, schizophreniform disorder, and schizoaffective disorder. Interventions: risperidone versus quetiapine versus olanzapine.
NCT00088075	Allocation: randomised. Participants: adolescents with schizophrenia.
NCT00202007	Allocation: randomised. Participants: people with schizophrenia. Interventions: risperidone versus aripiprazole.
NCT00249119	Allocation: randomised. Participants: people with schizophrenia. Interventions: risperidone long-acting injection versus placebo.
NCT00253136	Allocation: randomised. Participants: people with schizophrenia. Interventions: risperidone versus haloperidol.
NCT00305474	Allocation: randomised. Participants: non-psychotic relatives of people with schizophrenia.
Peuskens 1995	Allocation: randomised. Participants: people with schizophrenia. Intervention: risperidone versus haloperidol.
Peuskens 2001	Allocation: randomised. Participants: people with schizophrenia. Intervention: risperidone versus amisulpride.
Peuskens 2001a	Allocation: randomised. Participants: people with schizophrenia.

Study	Reason for exclusion
	Intervention: risperidone versus amisulpride plus haloperidol.
Pikalov 2012	Allocation: not RCT, but pooled data from seven RCTs.
Rabinowitz 2001	Allocation: randomised. Participants: people with schizophrenia. Intervention: risperidone versus haloperidol.
Rein 2002	Allocation: randomised. Participants: people with schizophrenia. Intervention: risperidone versus amisulpride.
Revicki 1996	Allocation: randomised. Participants: people with schizophrenia. Interventions: olanzapine versus haloperidol.
Riedel 2003	Allocation: randomised. Participants: people with schizophrenia. Intervention: risperidone plus celecoxib versus risperidone plus placebo.
Schmechtig 2010	Allocation: randomised. Participants: health volunteers.
Siever 2002	Allocation: randomised. Participants: people with schizotypal personality disorder.
Tollefson 1996	Allocation: randomised. Participants: people with schizophrenia. Intervention: olanzapine versus risperidone.
Tran 1997	Allocation: randomised. Participants: people with schizophrenia. Intervention: risperidone versus olanzapine.
Tsai 2004	Allocation: randomised. Participants: people with schizophrenia. Intervention: risperidone plus sarcosine versus risperidone plus placebo.
Tsai 2006	Allocation: randomised. Participants: people with schizophrenia. Intervention: risperidone plus D-alanine versus risperidone plus placebo.
Urioste 2004	Allocation: randomised. Participants: people with schizophrenia and schizoaffective disorder. Intervention: risperidone long-acting injection versus placebo.
Wang 2003	Allocation: randomised. Participants: people with schizophrenia. Intervention: risperidone plus valproate versus risperidone plus placebo.
Weickert 2003	Allocation: randomised. Participants: people with schizophrenia. Intervention: antipsychotic drugs (risperidone, olanzapine, quetiapine) versus placebo.
Weiden 2005	Allocation: randomised. Participants: schizophrenia with obesity. Intervention: sibutramin vs placebo

Study	Reason for exclusion
Wirshing 1995	Allocation: randomised. Participants: people with schizophrenia. Intervention: risperidone versus haloperidol.
Yamawaki 1996	Allocation: randomised. Participants: people with schizophrenia. Intervention: risperidone versus clocapramine (an atypical antipsychotic of the imidobenzyl class).
Zhang 2002	Allocation: randomised. Participants: people with schizophrenia. Intervention: risperidone plus antioxidants versus risperidone plus placebo.
Zhong 2006	Allocation: randomised. Participants: people with schizophrenia. Intervention: risperidone plus buflomedil versus risperidone plus placebo.

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

Anon 2010

Methods	Allocation: no information.
Participants	Diagnosis: schizophrenia.
Interventions	1. Risperidone. 2. Placebo.
Outcomes	Long-term efficacy.
Notes	Awaiting for full text.

Bose 2010a

Methods	Randomised.
Participants	People with schizophrenia.
Interventions	Placebo versus cariprazine versus risperidone
Outcomes	no useable data reported.
Notes	The paper didn't report any data relevant to pre-defined outcomes of this review. We have contacted trial authors for further data, but haven't received any reply.

Cavazzoni 2002

Methods	Randomised.
Participants	People with schizophrenia.

Cavazzoni 2002 *(Continued)*

Interventions	Risperidone versus olanzapine versus clozapine versus placebo.
Outcomes	No useable data.
Notes	The paper didn't report any data relevant to pre-defined outcomes of this review. We have contacted trial authors for further data, but haven't received any reply.

DeMartinis 2012

Methods	Randomised.
Participants	People with schizophrenia.
Interventions	Placebo versus risperidone versus PF-02545920.
Outcomes	No useable data reported.
Notes	The paper didn't report any data relevant to pre-defined outcomes of this review. We have contacted trial authors for further data, but haven't received any reply.

GlaxoSmithKline 2006

Methods	Randomised.
Participants	People with schizophrenia.
Interventions	Talnetant (a neurokinin 3 receptor antagonist) versus placebo versus risperidone.
Outcomes	No usable data.
Notes	The paper didn't report any data relevant to pre-defined outcomes of this review. We have contacted trial authors for further data, but haven't received any reply.

Litman 2014

Methods	Allocation: randomised. Blindness: double blind. Duration: 28 days. Design: parallel.
Participants	Diagnosis: people with schizophrenia. N = 151. Age: not reported. Sex: not reported.
Interventions	1. Risperidone: 4 mg. 2. Placebo.

Litman 2014 *(Continued)*

	3. AZD8529: 40 mg.
Outcomes	Unable to use: PANSS, CGI.
Notes	Full text is not available.

NCT 00694707

Methods	Allocation: randomised. Blindness: double. Duration: 6 weeks. Design: parallel.
Participants	Diagnosis: people with schizophrenia.
Interventions	1. Risperidone: dose 4 mg/day. 2. Placebo. 3. Cariprazine 1.5 mg/d. 4. Cariprazine 3 mg/d. 5. Cariprazine 4.5 mg/d.
Outcomes	Not reported.
Notes	Awaiting for full text.

NCT01086748

Methods	Randomised.
Participants	People with schizophrenia.
Interventions	Risperidone versus placebo versus LY2140023. (no further detail of the drug was available)
Outcomes	No usable data available.
Notes	The paper didn't report any data relevant to pre-defined outcomes of this review. We have contacted trial authors for further data, but haven't received any reply.

NCT01175135

Methods	Randomised.
Participants	People with schizophrenia.
Interventions	Risperidone versus placebo versus PF-02545920. (no further detail of the drug was available).

NCT01175135 *(Continued)*

Outcomes	No useable data available.
Notes	The paper didn't report any data relevant to pre-defined outcomes of this review. We have contacted trial authors for further data, but haven't received any reply.

NCT01363349

Methods	Randomised
Participants	People with schizophrenia.
Interventions	Risperidone versus placebo versus BL-1020.
Outcomes	No useable data*.
Notes	*This trial has terminated with the following reason stated: Pre-planned interim analysis of the Phase II/III CLARITY trial of BL-1020 indicate that the trial would not meet the pre-specified primary efficacy endpoint We have contacted trial authors for data, but not received any reply yet.

Nisenbaum 2013

Methods	Allocation: randomised. Blindness: double blind, but unclear who is blinded. Duration: 6 weeks. Design: parallel.
Participants	Diagnosis: schizophrenia (DSM-IV). N = 100. Age: 18-65 years old. Sex: not reported. Length of illness: not reported. Inclusion criteria: not reported. Exclusion criteria: not reported.
Interventions	1. Risperidone: 3 mg/d, N = 38. 2. Placebo: not reported, N = 78. 3. Pomaglumetad methionil: N = 83.
Outcomes	Unable to use: PANSS total score.
Notes	Full text is not available.

Rujescu 2009

Methods	Randomised.

Rujescu 2009 *(Continued)*

Participants	People with schizophrenia.
Interventions	Riluzole (a drug used to treat amyotrophic lateral sclerosis) versus risperidone versus placebo.
Outcomes	No useable data. (The grant was terminated due to slow enrolment.)
Notes	The paper didn't report any data relevant to pre-defined outcomes of this review. We have contacted trial authors for further data, but haven't received any reply.

Vanover 2014

Methods	Allocation: randomised. Blindness: double blind. Duration: 28 days. Design: parallel.
Participants	Diagnosis: acute exacerbated schizophrenia (DSM-IV). N = not reported. Age: not reported. Sex: not reported. Length of illness: not reported. Inclusion criteria: not reported. Exclusion criteria: not reported.
Interventions	1. Risperidone: 4 mg/d. 2. Placebo. 3. ITI-007 60 mg/d. 4. ITI-007 120 mg/d.
Outcomes	Uable to use: PANSS, CDSS.
Notes	No full text available, we contacted the author (Kimberly Vanover, Ph.D. kvanover@intracellulartherapies.com) but havn't received a reply yet.

Xu 2009

Methods	Allocation: randomised. Blindness: double blind, but unclear who is blinded. Duration: 90 days. Design: parallel.
Participants	Diagnosis: schizophrenia (DSM-IV). N = 200. Age: not reported. Sex: not reported. Length of illness: not reported. Inclusion criteria: not reported. Exclusion criteria: not reported.

Xu 2009 *(Continued)*

Interventions	1. Risperidone: 3 mg/d to 6 mg/d. 2. Placebo. 3. LDXGW plus risperidone 3 mg/d to 6 mg/d. 4. LDXGW plus risperidone < 3 mg/d.
Outcomes	Unable to use: CGI, BPRS, SANS, SAPS.
Notes	No full text available, we contacted the author but did not receive a reply.

BPRS: Brief Psychiatric Rating Scale
CGI: Clinical Global Impression
DSM: Diagnostic and Statistical Manual of Mental Disorders
PANSS: Positive and Negative Syndrome Scale
SANS: Scale for the Assessment of Negative Symptoms
SAPS: Scale for the Assessment of Positive Symptoms
CDSS: the Calgary Depression Scale for Schizophrenia

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

NCT00174200

Trial name or title	Study to assess differential sensitivity of 2 spatial working memory tests in people with schizophrenia treated with risperidone.
Methods	Allocation: randomised. Blindness: double.
Participants	Diagnosis: people with schizophrenia.
Interventions	1. Risperidone: dose 2 mg/day. 2. Placebo.
Outcomes	Cognitive functions: GMLT. Adverse effects: ESRS. Mental state: PANSS.
Starting date	July 2007.
Contact information	Pfizer CT.gov Call Center, Study Director, Pfizer.
Notes	Study ID: A9001229.

ESRS: Extrapyramidal Symptom Rating Scale
GMLT: Groton Maze Learning Test
PANSS: Positive and Negative Syndrome Scale

DATA AND ANALYSES

Comparison 1. RISPERIDONE vs PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental state: no clinically significant response in psychotic symptoms (defined by various scale total score change) - short term (up to 12 weeks)	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 defined by PANSS<30% decline	3	707	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.67, 0.83]
1.2 defined by PANSS/BPRS <20% decline	6	864	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.52, 0.78]
2 Leaving the study early - short term (up to 12 weeks)	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 any reason	12	2261	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.62, 0.78]
2.2 due to adverse events	10	2081	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.59, 1.03]
2.3 due to lack of efficacy	11	2211	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.29, 0.51]
2.4 due to noncompliance	4	534	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.33, 4.05]
2.5 lost to follow-up	6	1545	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.25, 2.56]
2.6 protocol violation	4	1257	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.39, 1.62]
2.7 reported death	10	1532	Risk Ratio (M-H, Random, 95% CI)	3.07 [0.13, 74.28]
2.8 withdrawal of consent	7	1589	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.80, 1.56]
2.9 other	3	615	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.68, 1.57]
3 Global state: 1. average endpoint scores of CGI severity scale (high=poor) - short term (up to 12 weeks)	3	457	Mean Difference (IV, Random, 95% CI)	-0.81 [-0.89, -0.73]
4 Global state: 2. no significant clinical improvement CGI - short term (up to 12 weeks)	4	594	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.57, 0.83]
5 Global state: 3. needing additional medication - short term (up to 12 weeks)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 benzodiazepine	1	42	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.77, 1.20]
5.2 benzodiazepine derivatives - Lorazepam	2	228	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.68, 1.27]
5.3 benzodiazepine derivatives - Nitrazepam	1	184	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.10, 2.72]
5.4 benzodiazepine related drugs - Zolpidem	1	184	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.53, 1.23]
5.5 sedative/hypnotic	2	230	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.69, 1.06]
5.6 antiparkinsonian	2	172	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.79, 1.86]
5.7 psychotropics	1	186	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.45, 0.85]
6 Mental state: 1. average endpoint scores on various scales on psychotic symptoms (high=poor) - short term (up to 12 weeks)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 BPRS total	2	171	Mean Difference (IV, Random, 95% CI)	-12.69 [-17.06, -8.32]
6.2 PANSS total	3	457	Mean Difference (IV, Random, 95% CI)	-17.81 [-18.17, -17.45]
6.3 PANSS general pathology	1	44	Mean Difference (IV, Random, 95% CI)	-13.20 [-20.15, -6.25]
6.4 PANSS negative symptom	3	457	Mean Difference (IV, Random, 95% CI)	-3.10 [-3.19, -3.01]
6.5 PANSS positive symptom	3	457	Mean Difference (IV, Random, 95% CI)	-5.49 [-6.18, -4.80]
7 Mental state: 2. skewed data - short term (up to 12 weeks)			Other data	No numeric data
7.1 average endpoint score BPRS total (high=poor)			Other data	No numeric data
7.2 average change score of CGI-C (larger decline=good)			Other data	No numeric data
7.3 average change score of CGI-SI (larger decline=good)			Other data	No numeric data
7.4 average change score of HAM-D-17 (larger decline=good)			Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.5 average change score of PANSS total (larger decline=good)			Other data	No numeric data
7.6 average change score of PANSS negative symptom (larger decline=good)			Other data	No numeric data
7.7 average change score of PANSS positive symptom (larger decline=good)			Other data	No numeric data
8 Adverse effects: 1a. extrapyramidal - various effects - short term (up to 12 weeks)	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 general - any significant EPS	7	1511	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.13, 2.15]
8.2 general - no improvement on AIMS score	1	42	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.15, 0.61]
8.3 general - no improvement on BAS score	1	226	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.01, 1.28]
8.4 general - needing medication for EPS	2	94	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.78, 1.67]
8.5 specific - akathisia	5	1204	Risk Ratio (M-H, Random, 95% CI)	2.58 [1.41, 4.72]
8.6 specific - bradykinesia	2	485	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.60, 1.24]
8.7 specific - dyskinesia	1	303	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.86]
8.8 specific - dystonia	3	687	Risk Ratio (M-H, Random, 95% CI)	3.40 [0.26, 44.46]
8.9 specific - hypertonia	3	505	Risk Ratio (M-H, Random, 95% CI)	2.98 [1.35, 6.59]
8.10 specific - parkinsonism	2	485	Risk Ratio (M-H, Random, 95% CI)	7.64 [1.40, 41.59]
8.11 specific - tardive dyskinesia	1	303	Risk Ratio (M-H, Random, 95% CI)	6.77 [0.35, 130.03]
8.12 specific - tremor	5	1204	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.89, 2.88]
9 Adverse effects: 1b. extrapyramidal - AIMS average endpoint score - short term (up to 12 weeks)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Adverse effects: 1c. extrapyramidal - skewed data (various scales) - short term (up to 12 weeks)			Other data	No numeric data
10.1 average change score of AIMS			Other data	No numeric data
10.2 average change score of CGI severity dyskinesia			Other data	No numeric data
10.3 average change score of CGI severity parkinsonism			Other data	No numeric data
10.4 average change score of ESRS			Other data	No numeric data
10.5 average change score of ESRS - akathisia			Other data	No numeric data
10.6 average change score of ESRS - dystonia			Other data	No numeric data
10.7 average change score of ESRS - dyskinesia			Other data	No numeric data
10.8 average change score of ESRS - parkinsonism			Other data	No numeric data
11 Adverse effects: 2. any adverse event - short term (up to 12 weeks)	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 any adverse event	7	1610	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.96, 1.15]
11.2 asthenia	2	639	Risk Ratio (M-H, Random, 95% CI)	1.93 [0.62, 6.02]
11.3 back pain	1	202	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.38, 2.86]
11.4 blurred vision	1	202	Risk Ratio (M-H, Random, 95% CI)	4.16 [0.47, 36.59]
11.5 cogwheel rigidity	1	226	Risk Ratio (M-H, Random, 95% CI)	5.25 [0.69, 39.88]
11.6 death	1	182	Risk Ratio (M-H, Random, 95% CI)	3.13 [0.13, 75.92]
11.7 dental disorder	1	202	Risk Ratio (M-H, Random, 95% CI)	3.64 [0.78, 17.11]
11.8 dysmenorrhoea	2	495	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.04, 30.00]
11.9 fatigue	2	558	Risk Ratio (M-H, Random, 95% CI)	2.23 [0.69, 7.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.10 fever	1	130	Risk Ratio (M-H, Random, 95% CI)	9.28 [0.51, 168.90]
11.11 infection	1	202	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.10, 2.78]
11.12 salivation - increased	1	202	Risk Ratio (M-H, Random, 95% CI)	7.28 [0.38, 139.15]
11.13 pyrexia	1	182	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.45, 3.16]
11.14 pain	1	121	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.47, 5.31]
11.15 rash (skin)	1	202	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.45, 3.16]
11.16 vaginitis	1	58	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.07, 16.32]
11.17 hyperhidrosis	1	437	Risk Ratio (M-H, Random, 95% CI)	10.35 [0.50, 214.17]
12 Adverse effects: 3. cardiovascular - short term (up to 12 weeks)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 dizziness - orthostatic	1	44	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 69.87]
12.2 ECG abnormal	1	182	Risk Ratio (M-H, Random, 95% CI)	9.40 [0.51, 172.11]
12.3 heart rate decreased	1	182	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.05, 5.66]
12.4 heart rate increased	1	182	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.37, 1.96]
12.5 hypotension - postural	1	44	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 69.87]
12.6 QTc > 450 milliseconds or > 10% increase from baseline	2	380	Risk Ratio (M-H, Random, 95% CI)	8.46 [1.07, 67.07]
12.7 tachycardia	2	332	Risk Ratio (M-H, Random, 95% CI)	12.22 [2.33, 64.10]
13 Adverse effects: 4. central nervous system - short term (up to 12 weeks)	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 agitation	8	1388	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.75, 1.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.2 anxiety	6	1225	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.73, 1.48]
13.3 dizziness	5	970	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.65, 3.05]
13.4 headache	10	1905	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.81, 1.21]
13.5 insomnia	10	1905	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.97, 1.39]
13.6 sedation	2	517	Risk Ratio (M-H, Random, 95% CI)	1.84 [0.52, 6.50]
13.7 somnolence	6	951	Risk Ratio (M-H, Random, 95% CI)	1.61 [1.06, 2.45]
13.8 restlessness	2	619	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.49, 2.74]
14 Adverse effects: 5. endocrine - serum prolactin increase above reference range (23 ng/ml) - short term (up to 12 weeks)	2	323	Risk Ratio (M-H, Random, 95% CI)	12.14 [4.38, 33.68]
15 Adverse effects: 6. gastrointestinal system - short term (up to 12 weeks)	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 constipation	8	1695	Risk Ratio (M-H, Random, 95% CI)	1.88 [1.19, 2.96]
15.2 diarrhoea	1	202	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.37, 2.30]
15.3 dry mouth	1	202	Risk Ratio (M-H, Random, 95% CI)	2.43 [0.65, 9.12]
15.4 dyspepsia	5	1058	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.64, 2.40]
15.5 nausea	6	1225	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.75, 1.86]
15.6 vomiting	5	1181	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.65, 2.07]
16 Adverse effects: 7a. metabolic - weight gain - short term (up to 12 weeks)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.1 any gain	3	910	Risk Ratio (M-H, Random, 95% CI)	3.77 [1.34, 10.63]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.2 >7% increase from baseline	3	606	Risk Ratio (M-H, Random, 95% CI)	3.47 [1.64, 7.33]
17 Adverse effects: 7b. metabolic - skewed data - average change value on lipid profile - short term (up to 12 weeks)			Other data	No numeric data
17.1 cholesterol - total			Other data	No numeric data
17.2 HDL			Other data	No numeric data
17.3 LDL			Other data	No numeric data
17.4 triglycerides			Other data	No numeric data
17.5 VLDL			Other data	No numeric data
18 Adverse effects: 8. musculoskeletal system - short term (up to 12 weeks)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
18.1 myalgia	1	202	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.12, 4.06]
18.2 Joint disorder	1	202	Risk Ratio (M-H, Random, 95% CI)	2.60 [0.52, 13.10]
19 Adverse effects: 9. physiology - short term (up to 12 weeks)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
19.1 ALT increased	1	182	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.07, 16.45]
19.2 AST increased	1	182	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
19.3 blood CPK increased	2	619	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.23, 1.95]
19.4 blood pressure increased	1	182	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.15, 7.26]
20 Adverse effects: 10. respiratory system - short term (up to 12 weeks)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.1 upper respiratory infection	2	323	Risk Ratio (M-H, Random, 95% CI)	2.83 [1.03, 7.74]
20.2 pharyngitis	1	202	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.08, 2.10]
20.3 rhinitis	2	306	Risk Ratio (M-H, Random, 95% CI)	10.81 [2.58, 45.29]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.4 sinusitis	1	437	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.09, 11.36]

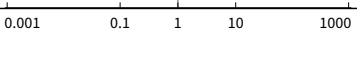
Analysis 1.1. Comparison 1 RISPERIDONE vs PLACEBO, Outcome 1 Mental state: no clinically significant response in psychotic symptoms (defined by various scale total score change) - short term (up to 12 weeks).

Study or subgroup	Risperidone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 defined by PANSS<30% decline					
Durgam 2014	78/138	120/148		45.39%	0.7[0.59,0.82]
Potkin 2003	57/95	79/103		32.56%	0.78[0.64,0.95]
Potkin 2006	76/152	45/71		22.05%	0.79[0.62,1]
Subtotal (95% CI)	**385**	**322**		**100%**	**0.74[0.67,0.83]**
Total events: 211 (Risperidone), 244 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.08, df=2(P=0.58); I^2=0%					
Test for overall effect: Z=5.2(P<0.0001)					
1.1.2 defined by PANSS/BPRS <20% decline					
Borison 1992	18/51	37/53		13.72%	0.51[0.33,0.76]
Chouinard 1992	6/22	19/22		6.68%	0.32[0.16,0.64]
Marder 1994a	27/63	50/64		17.87%	0.55[0.4,0.75]
Potkin 1997	30/85	44/83		16.11%	0.67[0.47,0.95]
Potkin 2003	57/95	79/103		23.94%	0.78[0.64,0.95]
Potkin 2006	76/152	45/71		21.69%	0.79[0.62,1]
Subtotal (95% CI)	**468**	**396**		**100%**	**0.64[0.52,0.78]**
Total events: 214 (Risperidone), 274 (Placebo)					
Heterogeneity: Tau^2=0.04; Chi^2=12.27, df=5(P=0.03); I^2=59.26%					
Test for overall effect: Z=4.33(P<0.0001)					
Test for subgroup differences: Chi^2=1.75, df=1 (P=0.19), I^2=42.74%					

Favours risperidone — Favours placebo

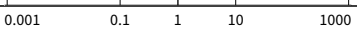
Analysis 1.2. Comparison 1 RISPERIDONE vs PLACEBO, Outcome 2 Leaving the study early - short term (up to 12 weeks).

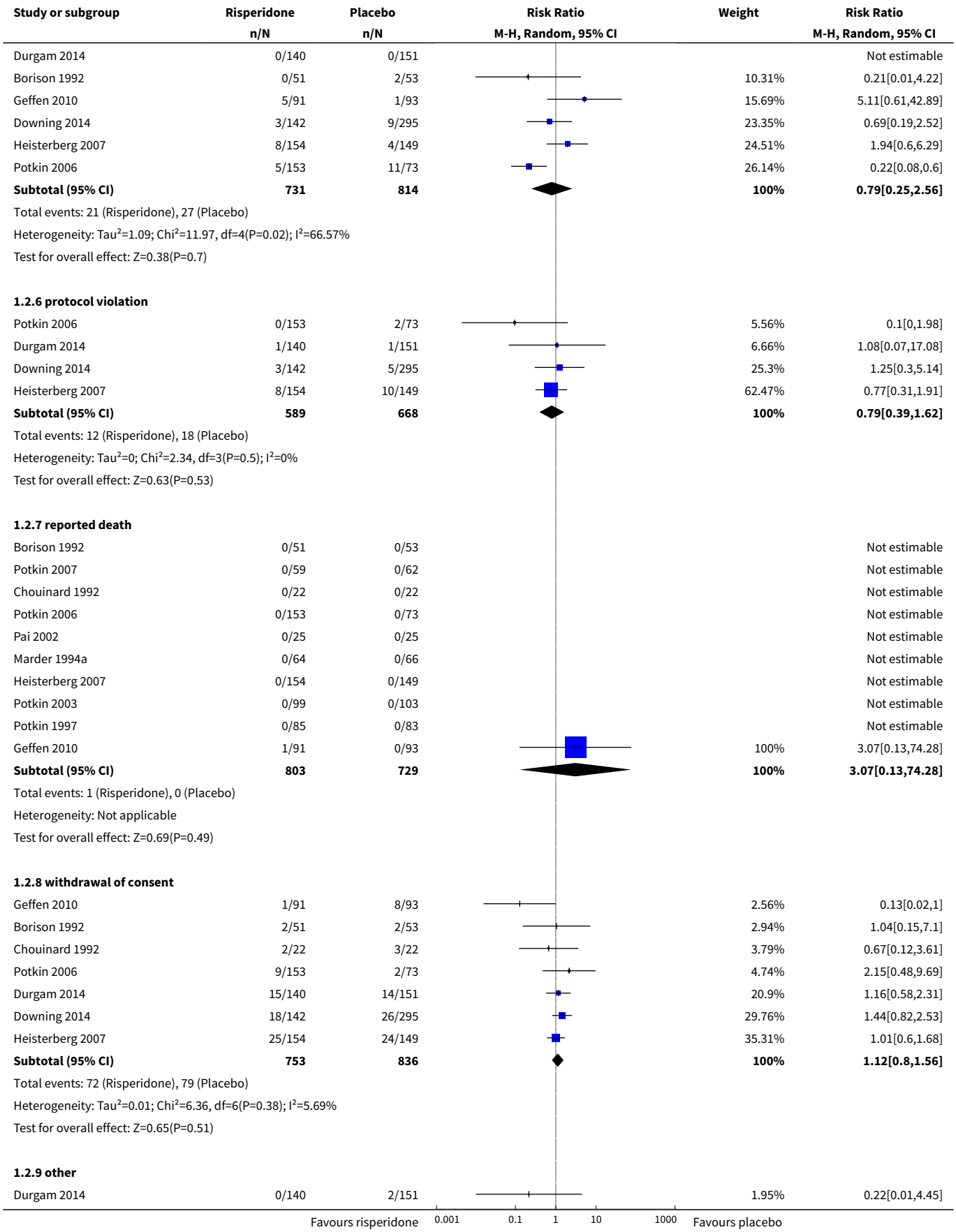
Study or subgroup	Risperidone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 any reason					
Pai 2002	3/25	5/25		0.78%	0.6[0.16,2.25]
Chouinard 1992	5/22	16/22		1.99%	0.31[0.14,0.7]
Geffen 2010	20/91	37/93		5.5%	0.55[0.35,0.88]
Potkin 2006	27/153	28/73		5.75%	0.46[0.29,0.72]
Potkin 1997	27/85	27/83		5.96%	0.98[0.63,1.52]
Marder 1994a	28/64	44/66		9.5%	0.66[0.47,0.91]
Borison 1992	26/51	37/53		9.67%	0.73[0.53,1.01]
Potkin 2003	37/99	51/103		9.72%	0.75[0.55,1.04]
Durgam 2014	39/140	72/151		10%	0.58[0.43,0.8]



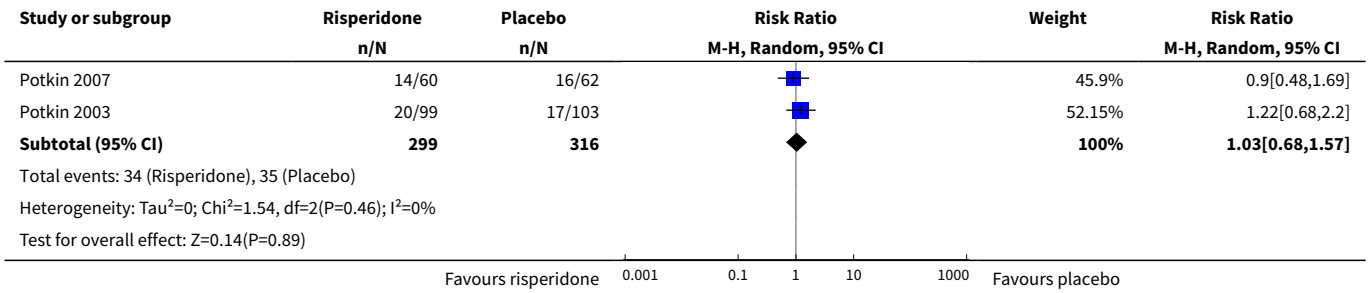
Favours risperidone — Favours placebo

Study or subgroup	Risperidone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Potkin 2007	34/60	41/62		11.52%	0.86[0.65,1.14]
Downing 2014	46/142	124/295		12.15%	0.77[0.59,1.01]
Heisterberg 2007	74/154	100/149		17.47%	0.72[0.59,0.87]
Subtotal (95% CI)	**1086**	**1175**		**100%**	**0.69[0.62,0.78]**
Total events: 366 (Risperidone), 582 (Placebo)					
Heterogeneity: Tau^2=0.01; Chi^2=14.73, df=11(P=0.2); I^2=25.32%					
Test for overall effect: Z=6.07(P<0.0001)					
1.2.2 due to adverse events					
Potkin 1997	6/85	0/83		0.96%	12.7[0.73,221.87]
Chouinard 1992	1/22	1/22		1.07%	1[0.07,15]
Potkin 2006	7/153	1/73		1.82%	3.34[0.42,26.64]
Potkin 2007	4/60	7/62		5.66%	0.59[0.18,1.91]
Borison 1992	6/51	7/53		7.52%	0.89[0.32,2.47]
Geffen 2010	9/91	7/93		8.78%	1.31[0.51,3.38]
Potkin 2003	8/99	17/103		12.43%	0.49[0.22,1.08]
Durgam 2014	13/140	22/151		18.77%	0.64[0.33,1.22]
Downing 2014	12/142	33/295		19.76%	0.76[0.4,1.42]
Heisterberg 2007	18/154	22/149		23.22%	0.79[0.44,1.41]
Subtotal (95% CI)	**997**	**1084**		**100%**	**0.78[0.59,1.03]**
Total events: 84 (Risperidone), 117 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=8.9, df=9(P=0.45); I^2=0%					
Test for overall effect: Z=1.76(P=0.08)					
1.2.3 due to lack of efficacy					
Chouinard 1992	1/22	10/22		1.9%	0.1[0.01,0.72]
Potkin 2006	4/153	9/73		5.01%	0.21[0.07,0.67]
Potkin 1997	4/85	11/83		5.32%	0.36[0.12,1.07]
Geffen 2010	4/91	18/93		5.82%	0.23[0.08,0.65]
Potkin 2003	8/99	17/103		8.81%	0.49[0.22,1.08]
Borison 1992	8/51	20/53		10%	0.42[0.2,0.86]
Durgam 2014	10/140	33/151		11.08%	0.33[0.17,0.64]
Downing 2014	10/142	48/295		11.46%	0.43[0.23,0.83]
Potkin 2007	16/60	18/62		13.33%	0.92[0.52,1.63]
Marder 1994a	11/64	40/66		13.34%	0.28[0.16,0.5]
Heisterberg 2007	15/154	40/149		13.95%	0.36[0.21,0.63]
Subtotal (95% CI)	**1061**	**1150**		**100%**	**0.39[0.29,0.51]**
Total events: 91 (Risperidone), 264 (Placebo)					
Heterogeneity: Tau^2=0.07; Chi^2=14.7, df=10(P=0.14); I^2=31.99%					
Test for overall effect: Z=6.66(P<0.0001)					
1.2.4 due to noncompliance					
Potkin 2003	1/99	0/103		13.12%	3.12[0.13,75.69]
Geffen 2010	0/91	3/93		14.94%	0.15[0.01,2.79]
Chouinard 1992	1/22	2/22		21.64%	0.5[0.05,5.12]
Borison 1992	9/51	4/53		50.3%	2.34[0.77,7.12]
Subtotal (95% CI)	**263**	**271**		**100%**	**1.15[0.33,4.05]**
Total events: 11 (Risperidone), 9 (Placebo)					
Heterogeneity: Tau^2=0.5; Chi^2=4.18, df=3(P=0.24); I^2=28.23%					
Test for overall effect: Z=0.22(P=0.83)					
1.2.5 lost to follow-up					

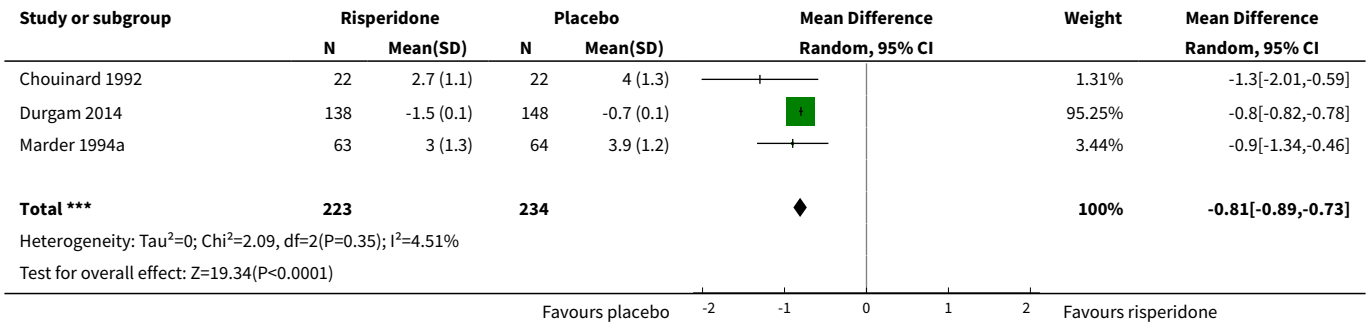




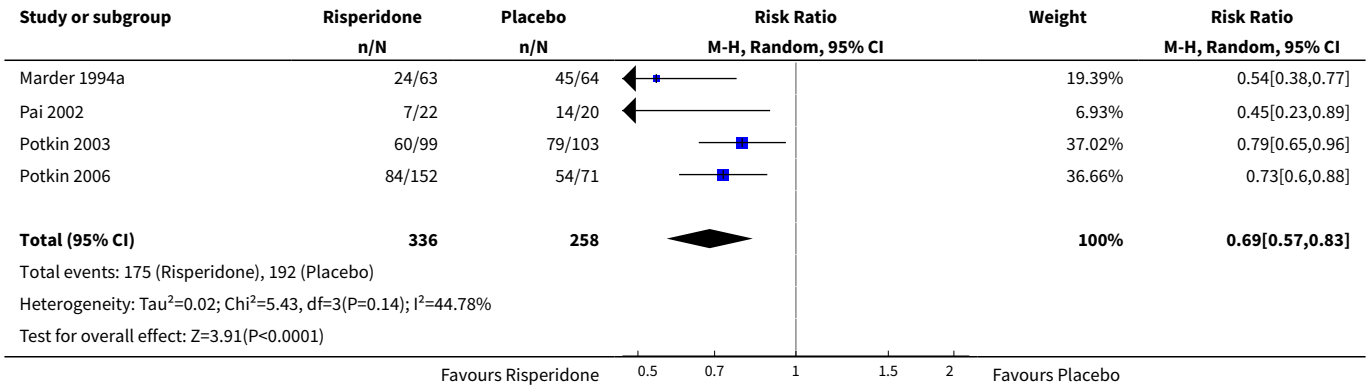
Study or subgroup	Risperidone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Durgam 2014	0/140	0/151			Not estimable
Borison 1992	0/51	2/53		10.31%	0.21[0.01,4.22]
Geffen 2010	5/91	1/93		15.69%	5.11[0.61,42.89]
Downing 2014	3/142	9/295		23.35%	0.69[0.19,2.52]
Heisterberg 2007	8/154	4/149		24.51%	1.94[0.6,6.29]
Potkin 2006	5/153	11/73		26.14%	0.22[0.08,0.6]
Subtotal (95% CI)	**731**	**814**		**100%**	**0.79[0.25,2.56]**
Total events: 21 (Risperidone), 27 (Placebo)					
Heterogeneity: Tau²=1.09; Chi²=11.97, df=4(P=0.02); I²=66.57%					
Test for overall effect: Z=0.38(P=0.7)					
1.2.6 protocol violation					
Potkin 2006	0/153	2/73		5.56%	0.1[0,1.98]
Durgam 2014	1/140	1/151		6.66%	1.08[0.07,17.08]
Downing 2014	3/142	5/295		25.3%	1.25[0.3,5.14]
Heisterberg 2007	8/154	10/149		62.47%	0.77[0.31,1.91]
Subtotal (95% CI)	**589**	**668**		**100%**	**0.79[0.39,1.62]**
Total events: 12 (Risperidone), 18 (Placebo)					
Heterogeneity: Tau²=0; Chi²=2.34, df=3(P=0.5); I²=0%					
Test for overall effect: Z=0.63(P=0.53)					
1.2.7 reported death					
Borison 1992	0/51	0/53			Not estimable
Potkin 2007	0/59	0/62			Not estimable
Chouinard 1992	0/22	0/22			Not estimable
Potkin 2006	0/153	0/73			Not estimable
Pai 2002	0/25	0/25			Not estimable
Marder 1994a	0/64	0/66			Not estimable
Heisterberg 2007	0/154	0/149			Not estimable
Potkin 2003	0/99	0/103			Not estimable
Potkin 1997	0/85	0/83			Not estimable
Geffen 2010	1/91	0/93		100%	3.07[0.13,74.28]
Subtotal (95% CI)	**803**	**729**		**100%**	**3.07[0.13,74.28]**
Total events: 1 (Risperidone), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					
1.2.8 withdrawal of consent					
Geffen 2010	1/91	8/93		2.56%	0.13[0.02,1]
Borison 1992	2/51	2/53		2.94%	1.04[0.15,7.1]
Chouinard 1992	2/22	3/22		3.79%	0.67[0.12,3.61]
Potkin 2006	9/153	2/73		4.74%	2.15[0.48,9.69]
Durgam 2014	15/140	14/151		20.9%	1.16[0.58,2.31]
Downing 2014	18/142	26/295		29.76%	1.44[0.82,2.53]
Heisterberg 2007	25/154	24/149		35.31%	1.01[0.6,1.68]
Subtotal (95% CI)	**753**	**836**		**100%**	**1.12[0.8,1.56]**
Total events: 72 (Risperidone), 79 (Placebo)					
Heterogeneity: Tau²=0.01; Chi²=6.36, df=6(P=0.38); I²=5.69%					
Test for overall effect: Z=0.65(P=0.51)					
1.2.9 other					
Durgam 2014	0/140	2/151		1.95%	0.22[0.01,4.45]



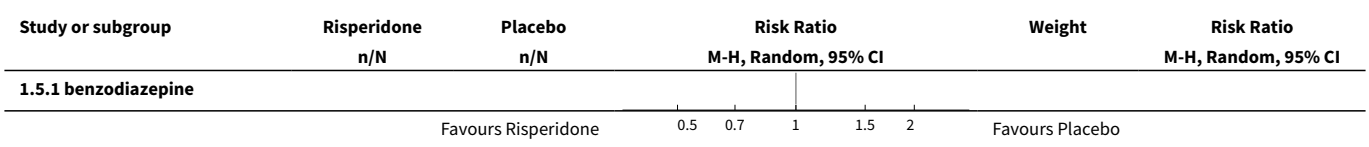
Analysis 1.3. Comparison 1 RISPERIDONE vs PLACEBO, Outcome 3 Global state: 1. average endpoint scores of CGI severity scale (high=poor) - short term (up to 12 weeks).

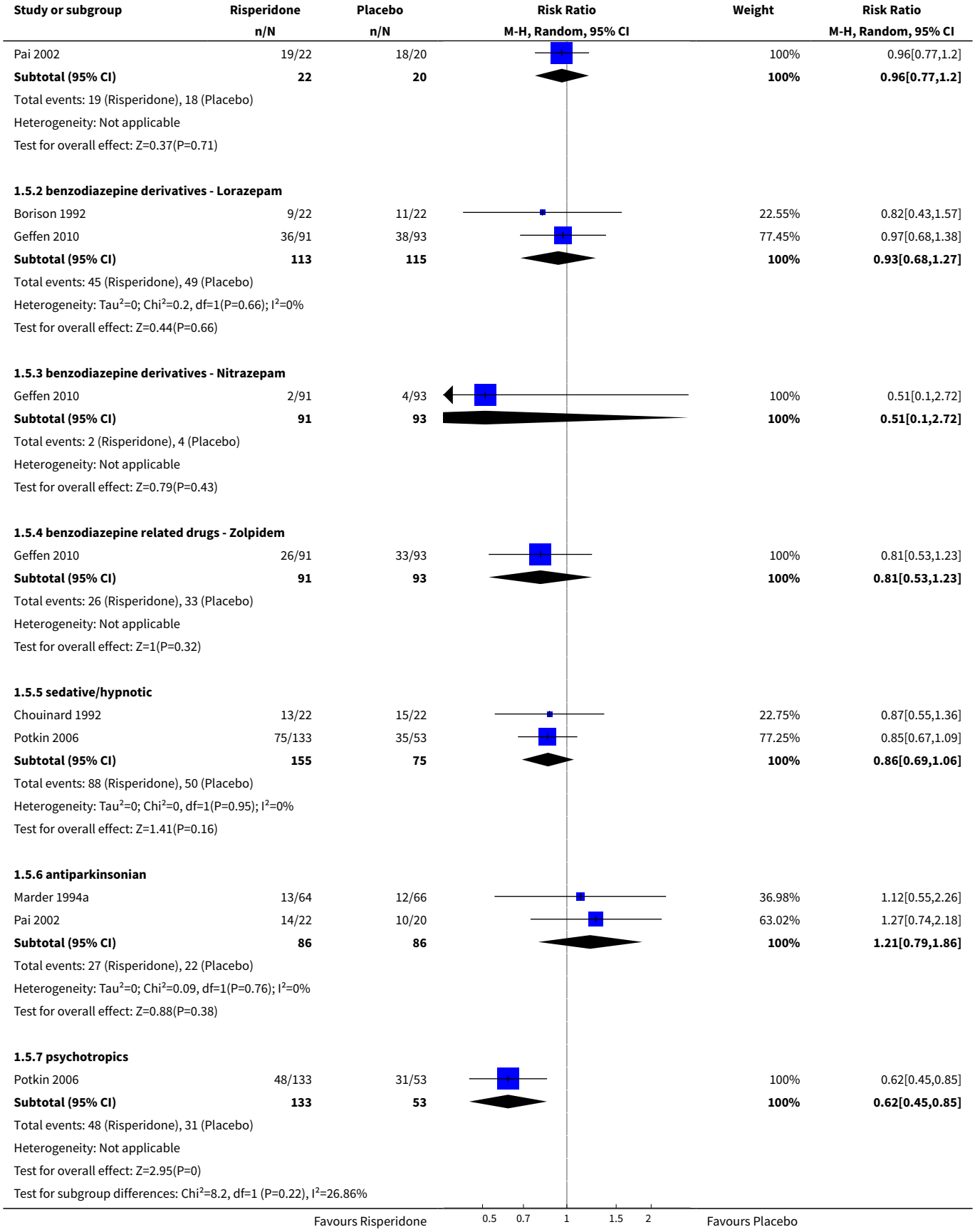


Analysis 1.4. Comparison 1 RISPERIDONE vs PLACEBO, Outcome 4 Global state: 2. no significant clinical improvement CGI - short term (up to 12 weeks).



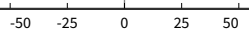
Analysis 1.5. Comparison 1 RISPERIDONE vs PLACEBO, Outcome 5 Global state: 3. needing additional medication - short term (up to 12 weeks).





Analysis 1.6. Comparison 1 RISPERIDONE vs PLACEBO, Outcome 6 Mental state: 1. average endpoint scores on various scales on psychotic symptoms (high=poor) - short term (up to 12 weeks).

Study or subgroup	Risperidone N	Risperidone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.6.1 BPRS total							
Chouinard 1992	22	41.5 (12.5)	22	57.6 (15.6)		27.39%	-16.1[-24.45,-7.75]
Marder 1994a	63	44.6 (14.7)	64	56 (14.8)		72.61%	-11.4[-16.53,-6.27]
Subtotal ***	**85**		**86**			**100%**	**-12.69[-17.06,-8.32]**
Heterogeneity: Tau^2=0; Chi^2=0.88, df=1(P=0.35); I^2=0%							
Test for overall effect: Z=5.69(P<0.0001)							
1.6.2 PANSS total							
Chouinard 1992	22	72.3 (20.1)	22	98.3 (25.3)		0.07%	-26[-39.5,-12.5]
Durgam 2014	138	-29.6 (1.6)	148	-11.8 (1.5)		99.75%	-17.8[-18.16,-17.44]
Marder 1994a	63	77.7 (24.3)	64	95.5 (24)		0.18%	-17.8[-26.2,-9.4]
Subtotal ***	**223**		**234**			**100%**	**-17.81[-18.17,-17.45]**
Heterogeneity: Tau^2=0; Chi^2=1.42, df=2(P=0.49); I^2=0%							
Test for overall effect: Z=97.04(P<0.0001)							
1.6.3 PANSS general pathology							
Chouinard 1992	22	35.3 (10)	22	48.5 (13.3)		100%	-13.2[-20.15,-6.25]
Subtotal ***	**22**		**22**			**100%**	**-13.2[-20.15,-6.25]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.72(P=0)							
1.6.4 PANSS negative symptom							
Chouinard 1992	22	20.4 (5.7)	22	24.4 (6.9)		0.06%	-4[-7.74,-0.26]
Durgam 2014	138	-5.1 (0.4)	148	-2 (0.4)		99.81%	-3.1[-3.19,-3.01]
Marder 1994a	63	21.9 (7.8)	64	24.2 (6.9)		0.13%	-2.3[-4.86,0.26]
Subtotal ***	**223**		**234**			**100%**	**-3.1[-3.19,-3.01]**
Heterogeneity: Tau^2=0; Chi^2=0.6, df=2(P=0.74); I^2=0%							
Test for overall effect: Z=65.54(P<0.0001)							
1.6.5 PANSS positive symptom							
Chouinard 1992	22	16.6 (7)	22	25.5 (8.7)		2.14%	-8.9[-13.57,-4.23]
Durgam 2014	138	-9.5 (0.5)	148	-4.1 (0.5)		91.94%	-5.4[-5.52,-5.28]
Marder 1994a	63	18.8 (8)	64	24.4 (7.8)		5.92%	-5.6[-8.35,-2.85]
Subtotal ***	**223**		**234**			**100%**	**-5.49[-6.18,-4.8]**
Heterogeneity: Tau^2=0.13; Chi^2=2.18, df=2(P=0.34); I^2=8.25%							
Test for overall effect: Z=15.57(P<0.0001)							



Favours risperidone — Favours placebo

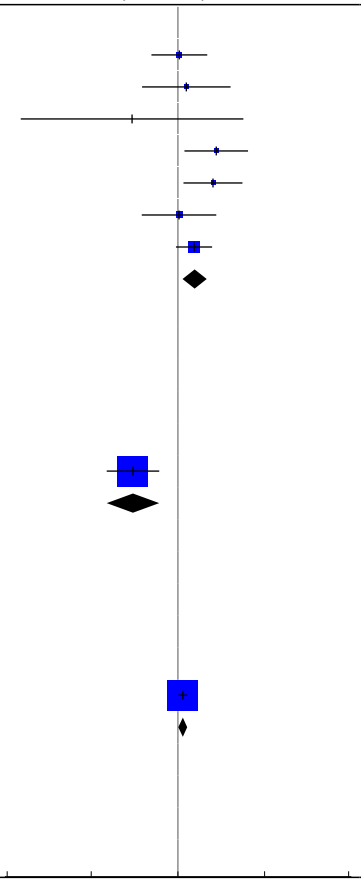
Analysis 1.7. Comparison 1 RISPERIDONE vs PLACEBO, Outcome 7 Mental state: 2. skewed data - short term (up to 12 weeks).

Mental state: 2. skewed data - short term (up to 12 weeks)				
Study	**Intervention**	**Mean**	**SD**	**N**
average endpoint score BPRS total (high=poor)				
Pai 2002	Resperidone	14.7	7.4	22
Pai 2002	Placebo	19.0	12.2	20
average change score of CGI-C (larger decline=good)				

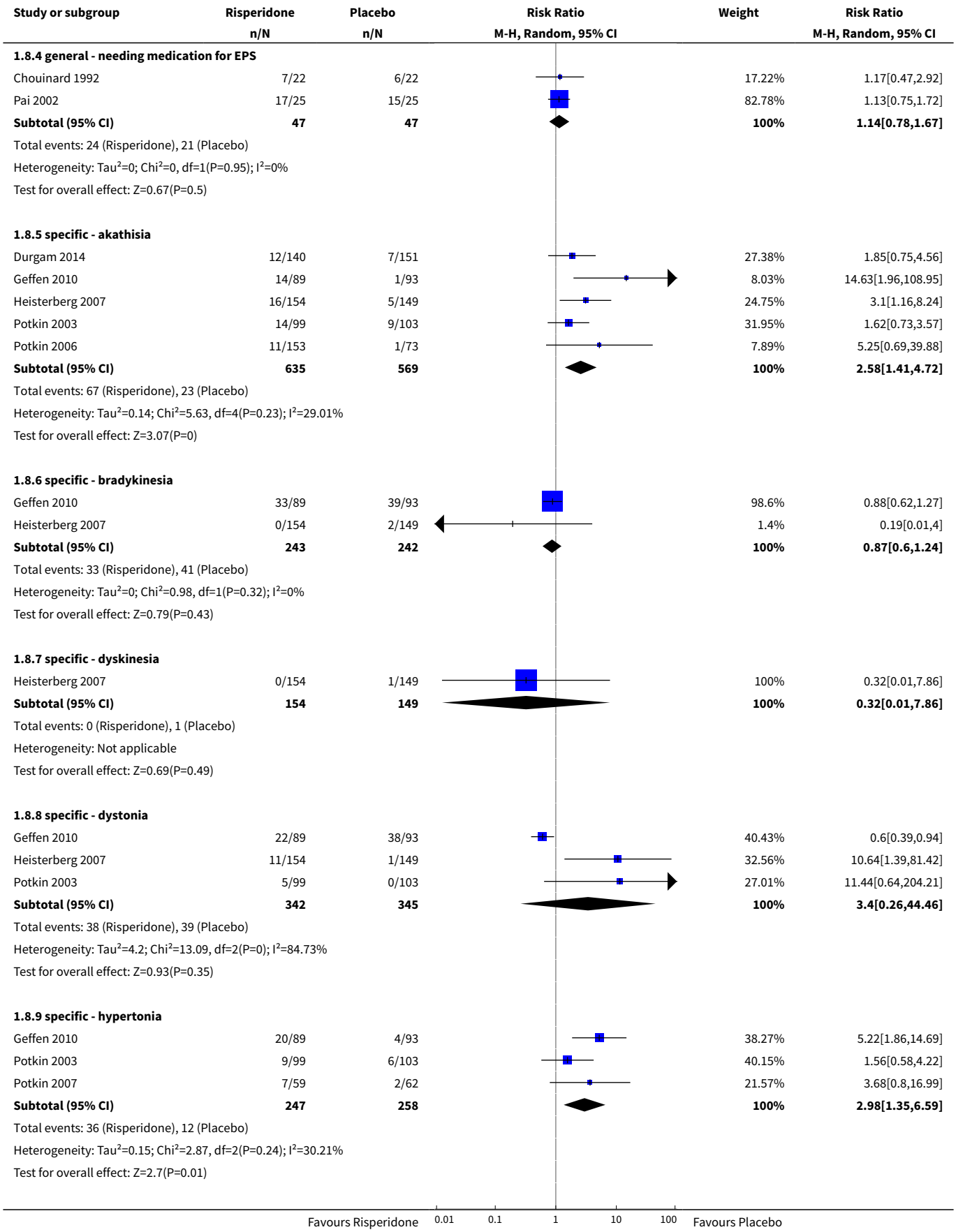
Mental state: 2. skewed data - short term (up to 12 weeks)				
Study	**Intervention**	**Mean**	**SD**	**N**
Potkin 2006	Resperidone	2.4	1.23	152
Potkin 2006	Placebo	2.9	0.84	71
average change score of CGI-SI (larger decline=good)				
Potkin 2006	Resperidone	-1.84	1.23	152
Potkin 2006	Placebo	-1.1	0.84	71
average change score of HAM-D-17 (larger decline=good)				
Potkin 2006	Resperidone	-5.6	4.93	152
Potkin 2006	Placebo	-4.4	4.21	71
average change score of PANSS total (larger decline=good)				
Potkin 2006	Resperidone	-27.7	18.49	152
Potkin 2006	Placebo	-20.2	16.85	71
average change score of PANSS negative symptom (larger decline=good)				
Potkin 2006	Resperidone	-4.0	4.93	152
Potkin 2006	Placebo	-3.5	5.06	71
average change score of PANSS positive symptom (larger decline=good)				
Potkin 2006	Resperidone	-8.7	6.16	152
Potkin 2006	Placebo	-5.3	5.9	71

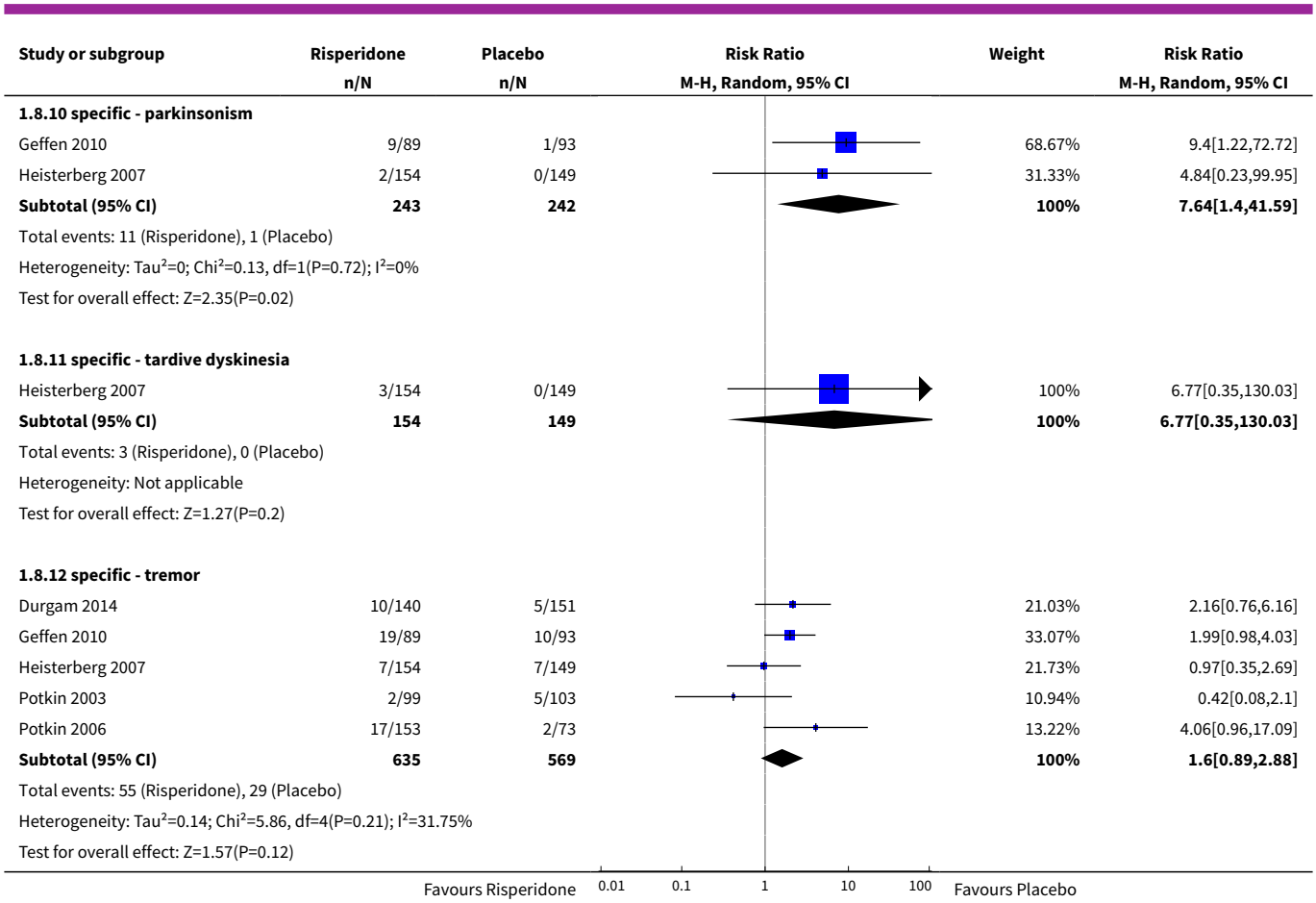
Analysis 1.8. Comparison 1 RISPERIDONE vs PLACEBO, Outcome 8 Adverse effects: 1a. extrapyramidal - various effects - short term (up to 12 weeks).

Study or subgroup	Risperidone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 general - any significant EPS					
Borison 1992	11/51	11/53		16.97%	1.04[0.49,2.18]
Chouinard 1992	5/22	4/22		7.18%	1.25[0.39,4.05]
Downing 2014	0/142	3/295		1.17%	0.3[0.02,5.69]
Durgam 2014	18/140	7/151		13.46%	2.77[1.19,6.44]
Heisterberg 2007	21/154	8/149		15.41%	2.54[1.16,5.55]
Marder 1994a	7/64	7/66		9.95%	1.03[0.38,2.77]
Potkin 2003	31/99	21/103		35.86%	1.54[0.95,2.48]
Subtotal (95% CI)	**672**	**839**		**100%**	**1.56[1.13,2.15]**
Total events: 93 (Risperidone), 61 (Placebo)					
Heterogeneity: Tau²=0.01; Chi²=6.48, df=6(P=0.37); I²=7.44%					
Test for overall effect: Z=2.72(P=0.01)					
1.8.2 general - no improvement on AIMS score					
Pai 2002	6/22	18/20		100%	0.3[0.15,0.61]
Subtotal (95% CI)	**22**	**20**		**100%**	**0.3[0.15,0.61]**
Total events: 6 (Risperidone), 18 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.35(P=0)					
1.8.3 general - no improvement on BAS score					
Potkin 2006	143/153	60/73		100%	1.14[1.01,1.28]
Subtotal (95% CI)	**153**	**73**		**100%**	**1.14[1.01,1.28]**
Total events: 143 (Risperidone), 60 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.2(P=0.03)					



Favours Risperidone — Favours Placebo





Analysis 1.9. Comparison 1 RISPERIDONE vs PLACEBO, Outcome 9 Adverse effects: 1b. extrapyramidal - AIMS average endpoint score - short term (up to 12 weeks).

Analysis 1.10. Comparison 1 RISPERIDONE vs PLACEBO, Outcome 10 Adverse effects: 1c. extrapyramidal - skewed data (various scales) - short term (up to 12 weeks).

Adverse effects: 1c. extrapyramidal - skewed data (various scales) - short term (up to 12 weeks)

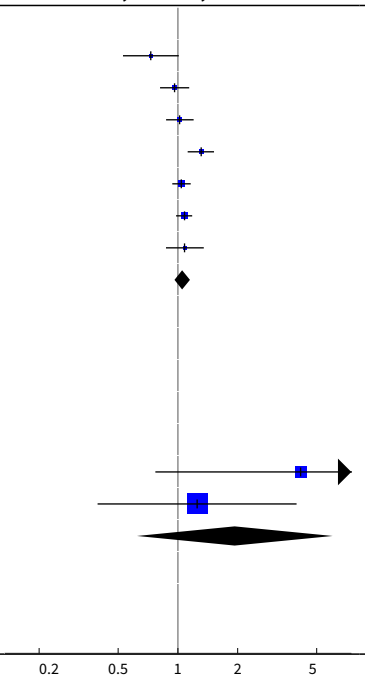
Study	Intervention	Mean	SD	N
		average change score of AIMS		
Potkin 2006	Risperidone	0.3	2.47	153
Potkin 2006	Placebo	-0.1	2.56	73
		average change score of CGI severity dyskinesia		
Chouinard 1992	Risperidone	0.3	3.3	22
Chouinard 1992	Placebo	3.5	5.3	22
		average change score of CGI severity parkinsonism		
Chouinard 1992	Risperidone	0.9	1.5	22
Chouinard 1992	Placebo	0.4	1.3	22

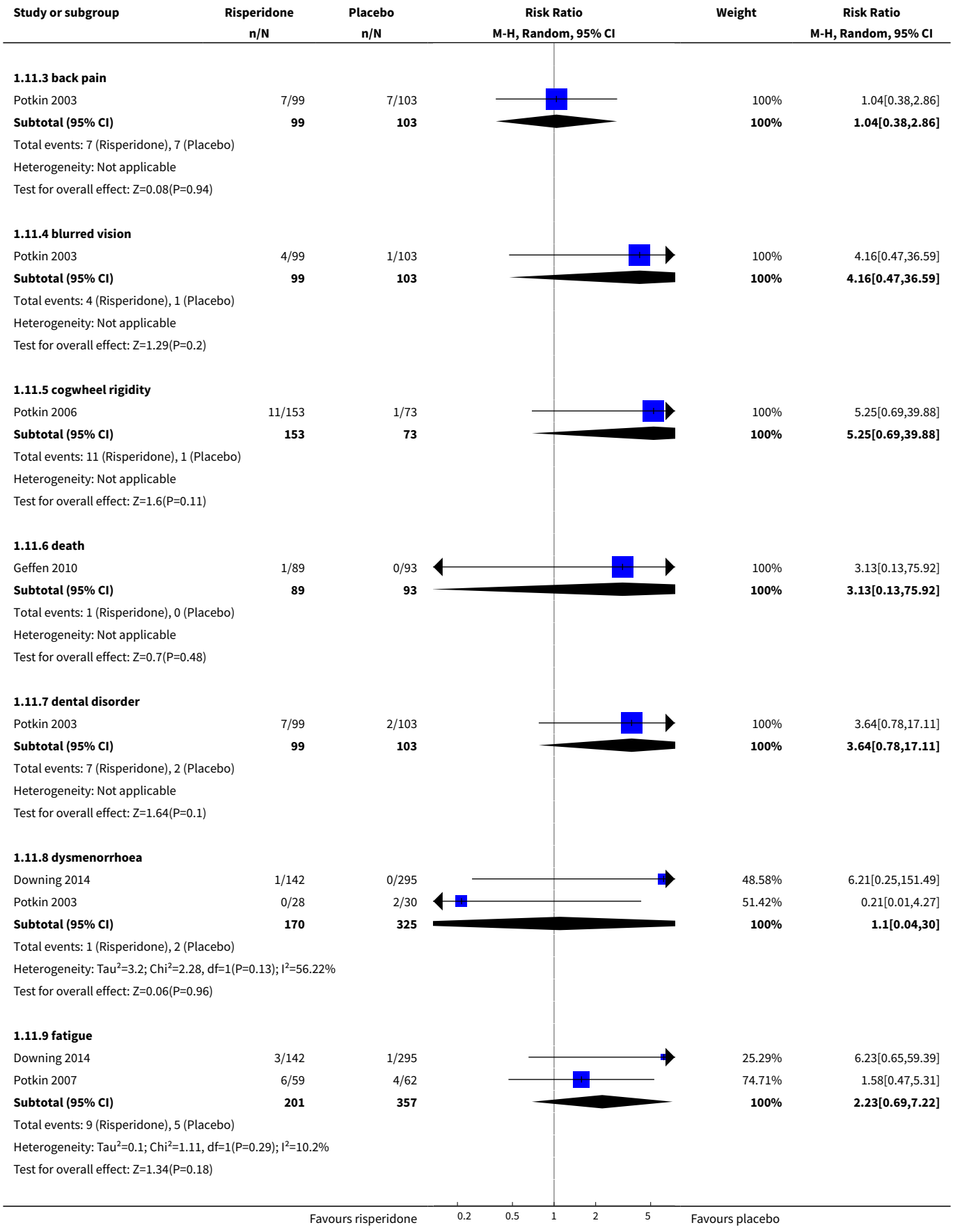
Adverse effects: 1c. extrapyramidal - skewed data (various scales) - short term (up to 12 weeks)

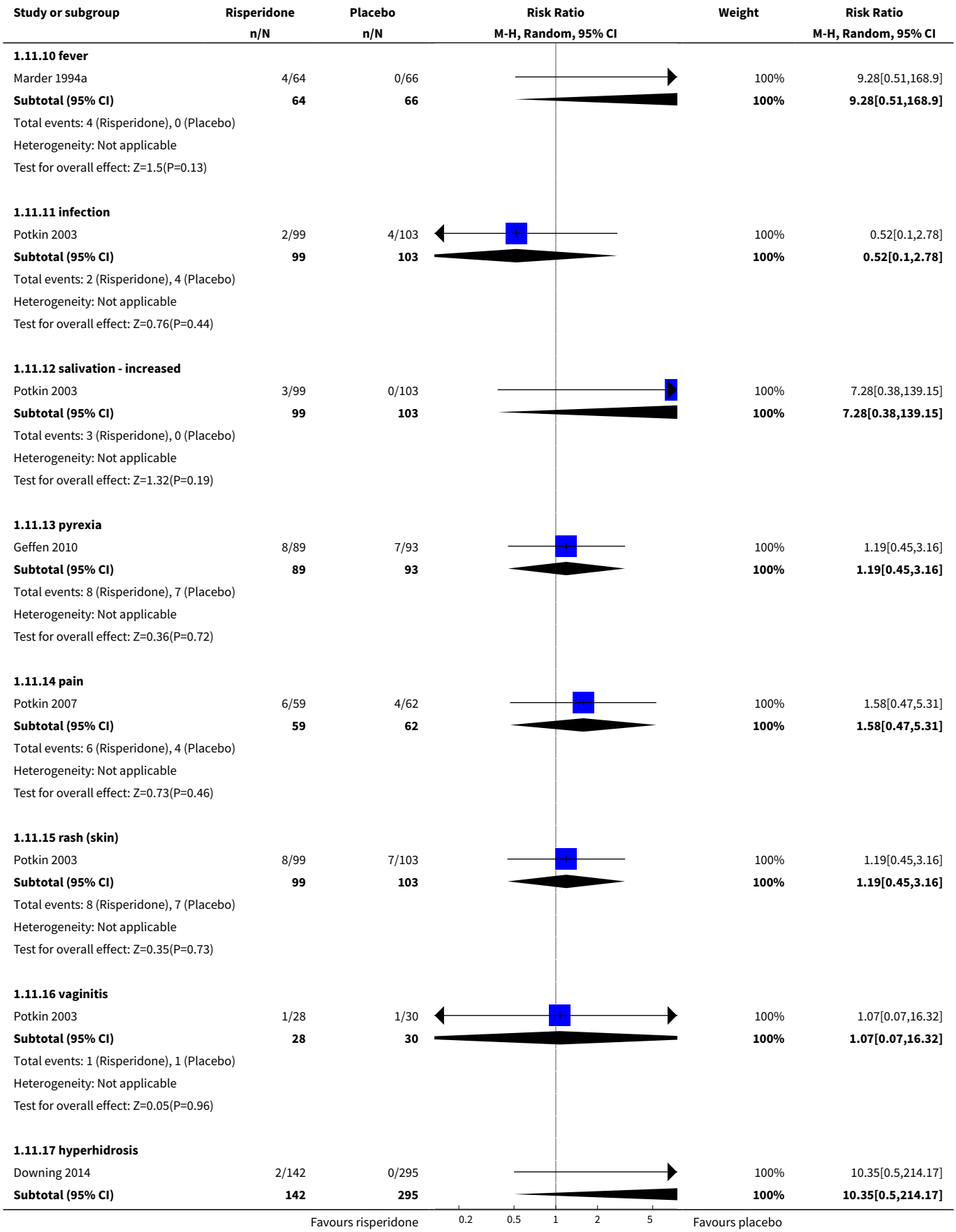
Study	Intervention	Mean	SD	N
		average change score of ESRS		
Marder 1994a	Risperidone	2.9	5.7	63
Marder 1994a	Placebo	2.4	5.8	65
		average change score of ESRS - akathisia		
Marder 1994a	Risperidone	0.6	1.1	63
Marder 1994a	Placebo	0.6	1.6	65
		average change score of ESRS - dystonia		
Chouinard 1992	Risperidone	0.3	0.8	22
Chouinard 1992	Placebo	1.0	2.3	22
Marder 1994a	Risperidone	1.3	1.3	63
Marder 1994a	Placebo	1.6	1.5	64
Pai 2002	Risperidone	2.1	1.7	22
Pai 2002	Placebo	2.8	1.8	20
		average change score of ESRS - dyskinesia		
Chouinard 1992	Risperidone	2.6	4.5	22
Chouinard 1992	Placebo	5.7	7.2	SD
Marder 1994a	Risperidone	0.6	1.1	63
Marder 1994a	Placebo	0.5	1.1	65
		average change score of ESRS - parkinsonism		
Chouinard 1992	Risperidone	2.1	7.5	22
Chouinard 1992	Placebo	2.3	8.7	22
Marder 1994a	Risperidone	0.6	1.1	63
Marder 1994a	Placebo	0.5	1.1	65
Pai 2002	Risperidone	2.1	1.3	22
Pai 2002	Placebo	2.5	1.5	20

Analysis 1.11. Comparison 1 RISPERIDONE vs PLACEBO, Outcome 11 Adverse effects: 2. any adverse event - short term (up to 12 weeks).

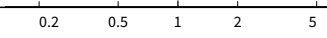
Study or subgroup	Risperidone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 any adverse event					
Borison 1992	26/51	37/53		6.12%	0.73[0.53,1.01]
Downing 2014	82/142	177/295		13.87%	0.96[0.81,1.14]
Durgam 2014	95/140	100/151		14.48%	1.02[0.87,1.2]
Geffen 2010	80/89	64/93		15.11%	1.31[1.12,1.52]
Potkin 1997	77/85	72/83		19.28%	1.04[0.94,1.16]
Potkin 2003	92/99	89/103		20.7%	1.08[0.98,1.18]
Potkin 2006	100/153	44/73		10.44%	1.08[0.87,1.35]
Subtotal (95% CI)	**759**	**851**		**100%**	**1.05[0.96,1.15]**
Total events: 552 (Risperidone), 583 (Placebo)					
Heterogeneity: Tau^2=0.01; Chi^2=14.46, df=6(P=0.02); I^2=58.49%					
Test for overall effect: Z=1.1(P=0.27)					
1.11.2 asthenia					
Downing 2014	4/142	2/295		36.43%	4.15[0.77,22.42]
Potkin 2003	6/99	5/103		63.57%	1.25[0.39,3.96]
Subtotal (95% CI)	**241**	**398**		**100%**	**1.93[0.62,6.02]**
Total events: 10 (Risperidone), 7 (Placebo)					
Heterogeneity: Tau^2=0.18; Chi^2=1.33, df=1(P=0.25); I^2=24.89%					
Test for overall effect: Z=1.14(P=0.25)					







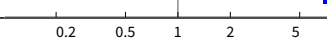
Study or subgroup	Risperidone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 2 (Risperidone), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.51(P=0.13)					
Test for subgroup differences: Chi^2=16.44, df=1 (P=0.42), I^2=2.71%					



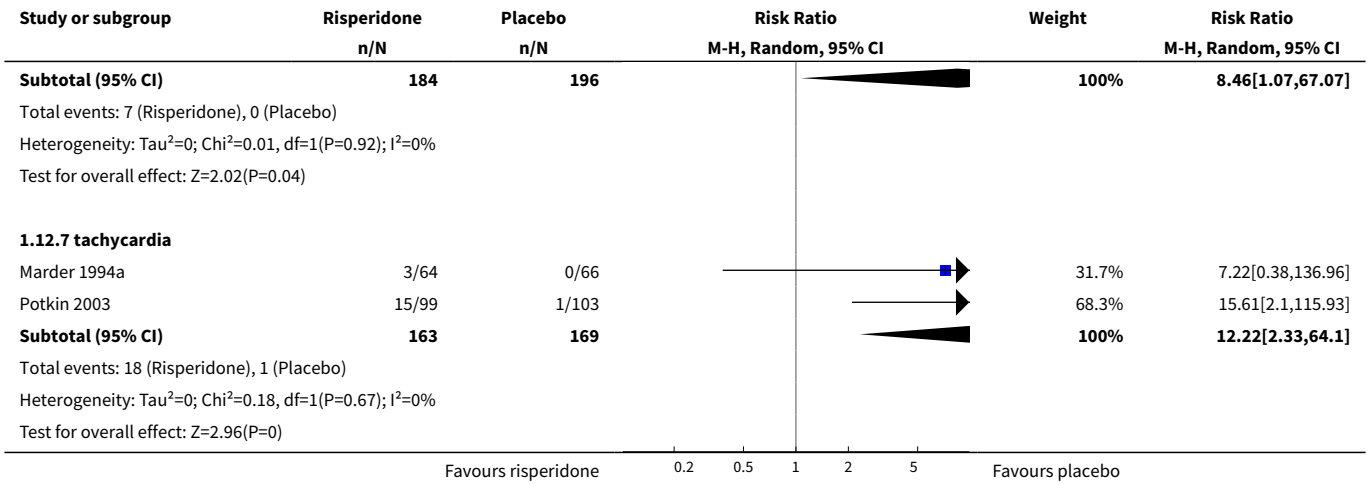
Favours risperidone Favours placebo

Analysis 1.12. Comparison 1 RISPERIDONE vs PLACEBO, Outcome 12 Adverse effects: 3. cardiovascular - short term (up to 12 weeks).

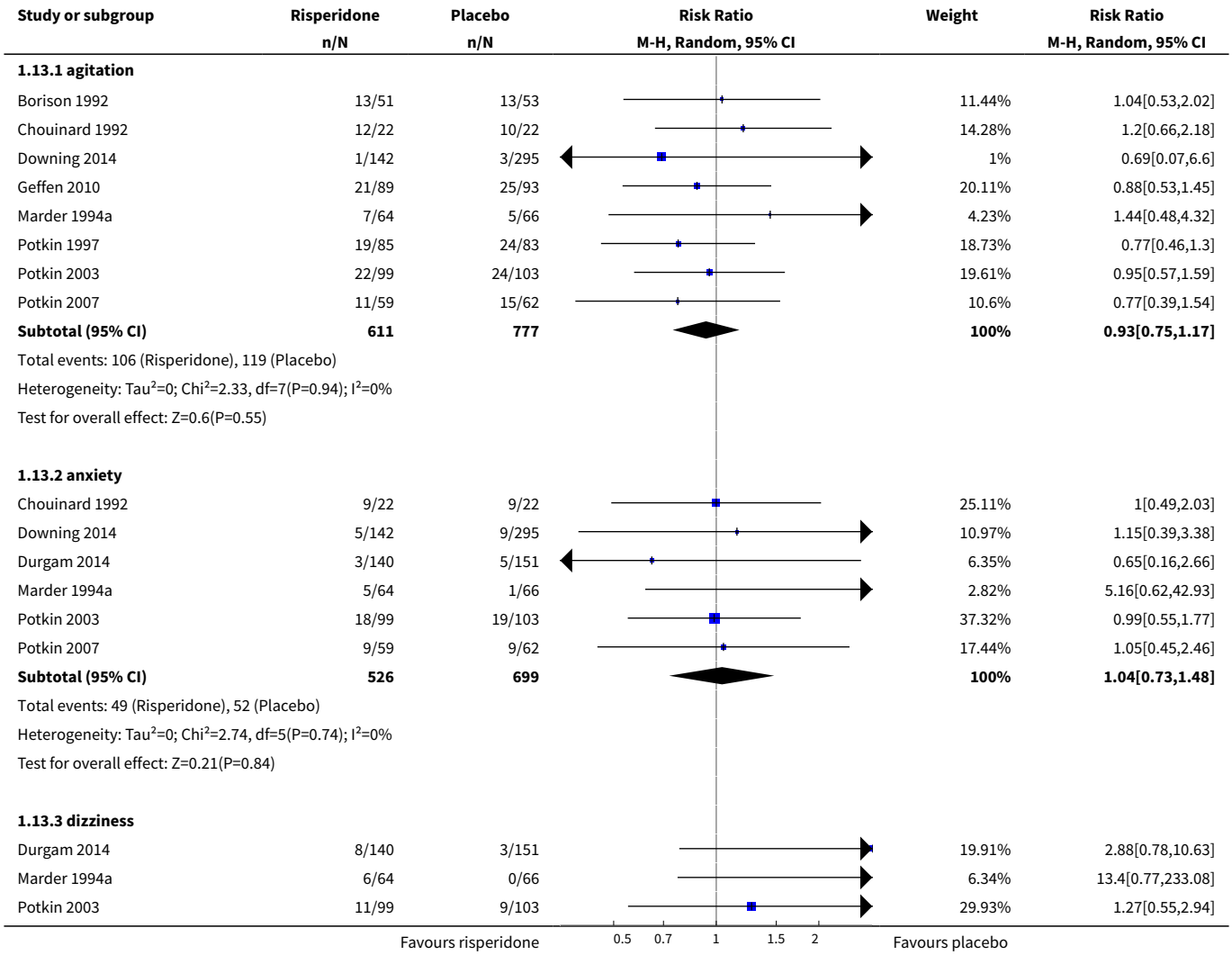
Study or subgroup	Risperidone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 dizziness - orthostatic					
Chouinard 1992	1/22	0/22		100%	3[0.13,69.87]
Subtotal (95% CI)	**22**	**22**		**100%**	**3[0.13,69.87]**
Total events: 1 (Risperidone), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.49)					
1.12.2 ECG abnormal					
Geffen 2010	4/89	0/93		100%	9.4[0.51,172.11]
Subtotal (95% CI)	**89**	**93**		**100%**	**9.4[0.51,172.11]**
Total events: 4 (Risperidone), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.51(P=0.13)					
1.12.3 heart rate decreased					
Geffen 2010	1/89	2/93		100%	0.52[0.05,5.66]
Subtotal (95% CI)	**89**	**93**		**100%**	**0.52[0.05,5.66]**
Total events: 1 (Risperidone), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.53(P=0.59)					
1.12.4 heart rate increased					
Geffen 2010	9/89	11/93		100%	0.85[0.37,1.96]
Subtotal (95% CI)	**89**	**93**		**100%**	**0.85[0.37,1.96]**
Total events: 9 (Risperidone), 11 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.37(P=0.71)					
1.12.5 hypotension - postural					
Chouinard 1992	1/22	0/22		100%	3[0.13,69.87]
Subtotal (95% CI)	**22**	**22**		**100%**	**3[0.13,69.87]**
Total events: 1 (Risperidone), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.49)					
1.12.6 QTc > 450 milliseconds or > 10% increase from baseline					
Geffen 2010	4/89	0/93		50.73%	9.4[0.51,172.11]
Potkin 2003	3/95	0/103		49.27%	7.58[0.4,144.91]

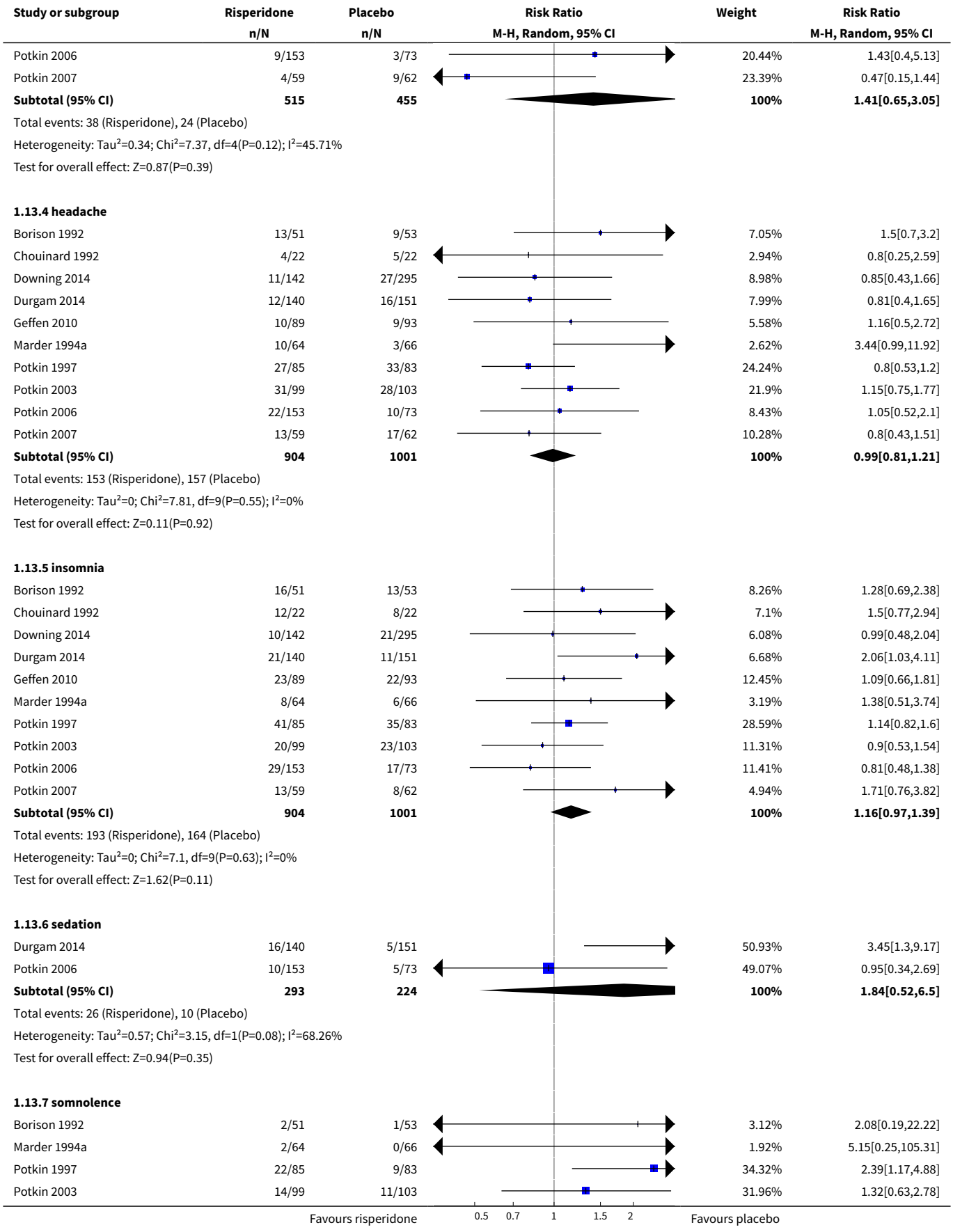


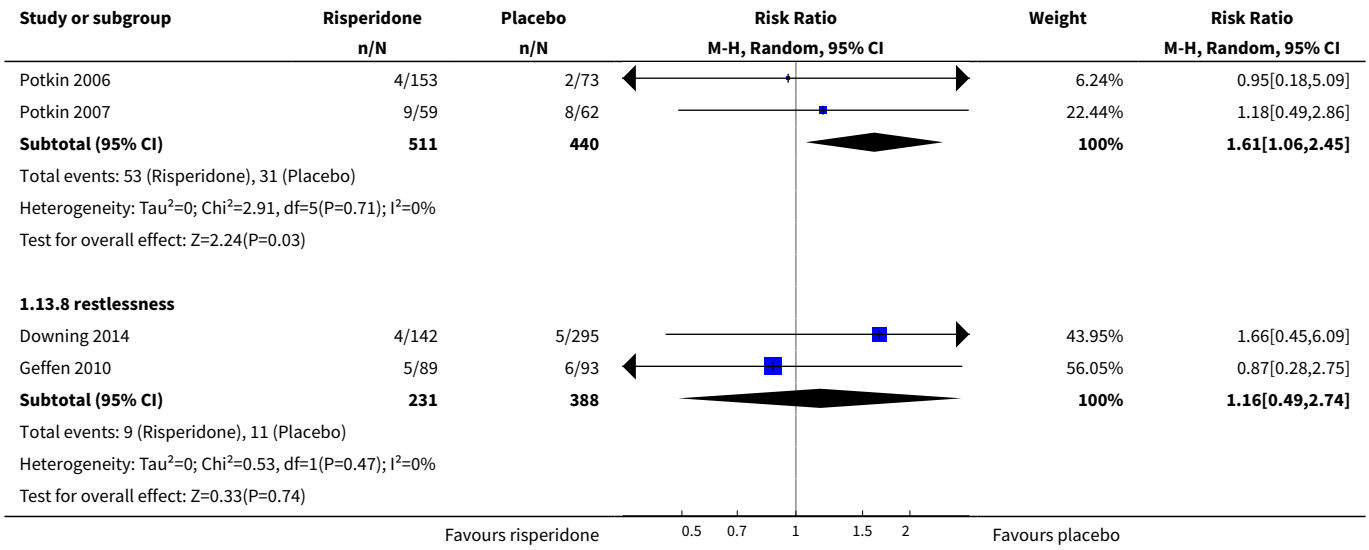
Favours risperidone Favours placebo



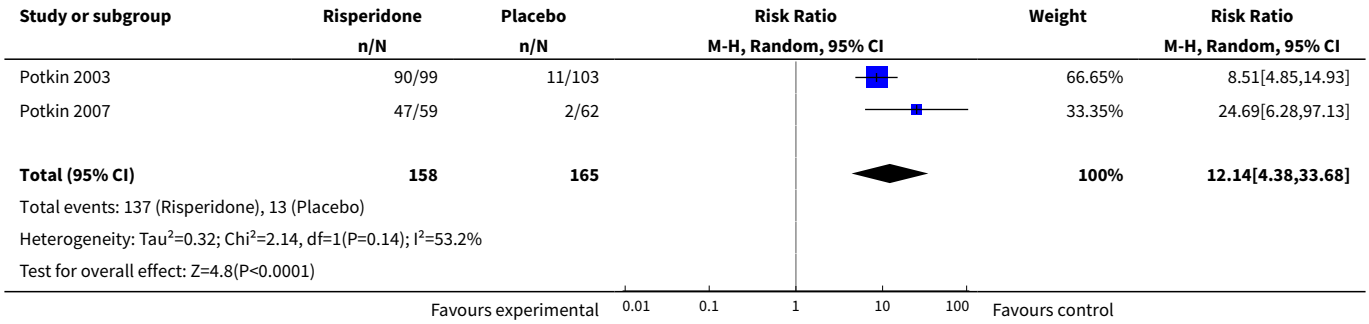
Analysis 1.13. Comparison 1 RISPERIDONE vs PLACEBO, Outcome 13 Adverse effects: 4. central nervous system - short term (up to 12 weeks).



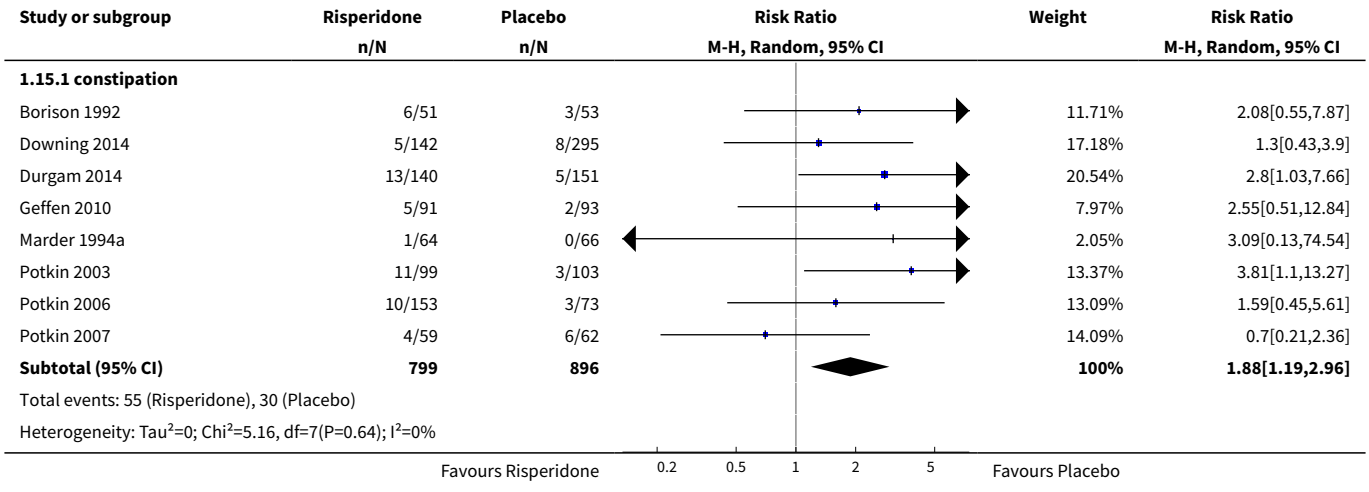




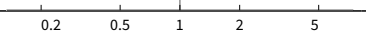
Analysis 1.14. Comparison 1 RISPERIDONE vs PLACEBO, Outcome 14 Adverse effects: 5. endocrine - serum prolactin increase above reference range (23 ng/ml) - short term (up to 12 weeks).



Analysis 1.15. Comparison 1 RISPERIDONE vs PLACEBO, Outcome 15 Adverse effects: 6. gastrointestinal system - short term (up to 12 weeks).



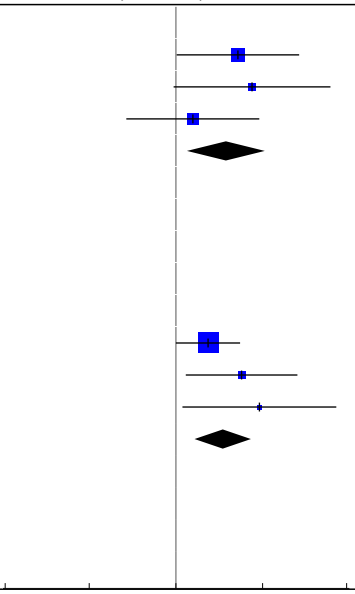
Study or subgroup	Risperidone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=2.71(P=0.01)					
1.15.2 diarrhoea					
Potkin 2003	8/99	9/103		100%	0.92[0.37,2.3]
Subtotal (95% CI)	**99**	**103**		**100%**	**0.92[0.37,2.3]**
Total events: 8 (Risperidone), 9 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.17(P=0.87)					
1.15.3 dry mouth					
Potkin 2003	7/99	3/103		100%	2.43[0.65,9.12]
Subtotal (95% CI)	**99**	**103**		**100%**	**2.43[0.65,9.12]**
Total events: 7 (Risperidone), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.31(P=0.19)					
1.15.4 dyspepsia					
Downing 2014	8/142	5/295		18.22%	3.32[1.11,9.98]
Marder 1994a	6/64	3/66		14.62%	2.06[0.54,7.9]
Potkin 1997	8/85	9/83		21.75%	0.87[0.35,2.14]
Potkin 2003	12/99	22/103		27.05%	0.57[0.3,1.08]
Potkin 2007	7/59	5/62		18.36%	1.47[0.49,4.38]
Subtotal (95% CI)	**449**	**609**		**100%**	**1.24[0.64,2.4]**
Total events: 41 (Risperidone), 44 (Placebo)					
Heterogeneity: Tau^2=0.31; Chi^2=9.21, df=4(P=0.06); I^2=56.58%					
Test for overall effect: Z=0.62(P=0.53)					
1.15.5 nausea					
Chouinard 1992	2/22	1/22		3.82%	2[0.2,20.49]
Downing 2014	5/142	14/295		20.62%	0.74[0.27,2.02]
Durgam 2014	8/140	5/151		17.29%	1.73[0.58,5.15]
Marder 1994a	4/64	0/66		2.45%	9.28[0.51,168.9]
Potkin 2003	12/99	10/103		32.9%	1.25[0.57,2.76]
Potkin 2007	7/59	8/62		22.92%	0.92[0.36,2.38]
Subtotal (95% CI)	**526**	**699**		**100%**	**1.18[0.75,1.86]**
Total events: 38 (Risperidone), 38 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.76, df=5(P=0.58); I^2=0%					
Test for overall effect: Z=0.72(P=0.47)					
1.15.6 vomiting					
Downing 2014	5/142	6/295		23.66%	1.73[0.54,5.58]
Durgam 2014	4/140	5/151		19.44%	0.86[0.24,3.15]
Marder 1994a	4/64	1/66		7.08%	4.13[0.47,35.92]
Potkin 2003	8/99	6/103		30.69%	1.39[0.5,3.85]
Potkin 2007	3/59	7/62		19.14%	0.45[0.12,1.66]
Subtotal (95% CI)	**504**	**677**		**100%**	**1.16[0.65,2.07]**
Total events: 24 (Risperidone), 25 (Placebo)					
Heterogeneity: Tau^2=0.01; Chi^2=4.11, df=4(P=0.39); I^2=2.66%					
Test for overall effect: Z=0.51(P=0.61)					



Favours Risperidone — Favours Placebo

Analysis 1.16. Comparison 1 RISPERIDONE vs PLACEBO, Outcome 16 Adverse effects: 7a. metabolic - weight gain - short term (up to 12 weeks).

Study or subgroup	Risperidone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.16.1 any gain					
Downing 2014	5/142	2/295		40.64%	5.19[1.02,26.44]
Durgam 2014	7/140	1/151		24.82%	7.55[0.94,60.59]
Geffen 2010	3/89	2/93		34.54%	1.57[0.27,9.16]
Subtotal (95% CI)	**371**	**539**		**100%**	**3.77[1.34,10.63]**
Total events: 15 (Risperidone), 5 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.54, df=2(P=0.46); I^2=0%					
Test for overall effect: Z=2.51(P=0.01)					
1.16.2 >7% increase from baseline					
Heisterberg 2007	17/154	7/149		63.25%	2.35[1,5.5]
Potkin 2003	11/99	2/103		23.8%	5.72[1.3,25.17]
Potkin 2007	8/47	1/54		12.95%	9.19[1.19,70.81]
Subtotal (95% CI)	**300**	**306**		**100%**	**3.47[1.64,7.33]**
Total events: 36 (Risperidone), 10 (Placebo)					
Heterogeneity: Tau^2=0.04; Chi^2=2.17, df=2(P=0.34); I^2=7.75%					
Test for overall effect: Z=3.25(P=0)					
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.9), I^2=0%					

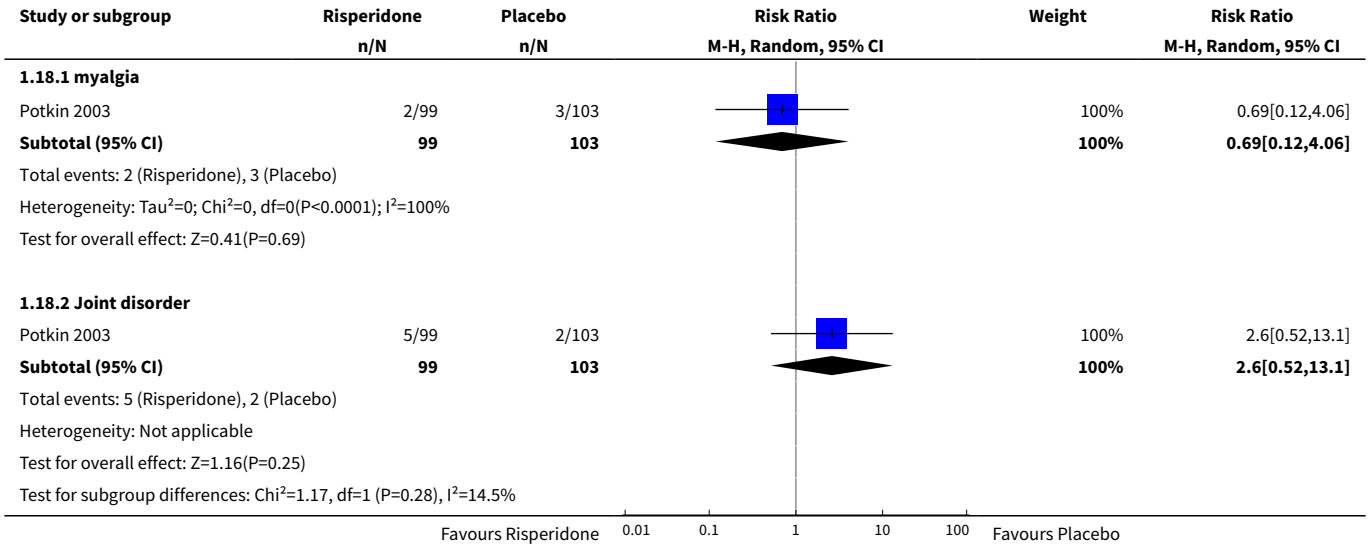


Analysis 1.17. Comparison 1 RISPERIDONE vs PLACEBO, Outcome 17 Adverse effects: 7b. metabolic - skewed data - average change value on lipid profile - short term (up to 12 weeks).

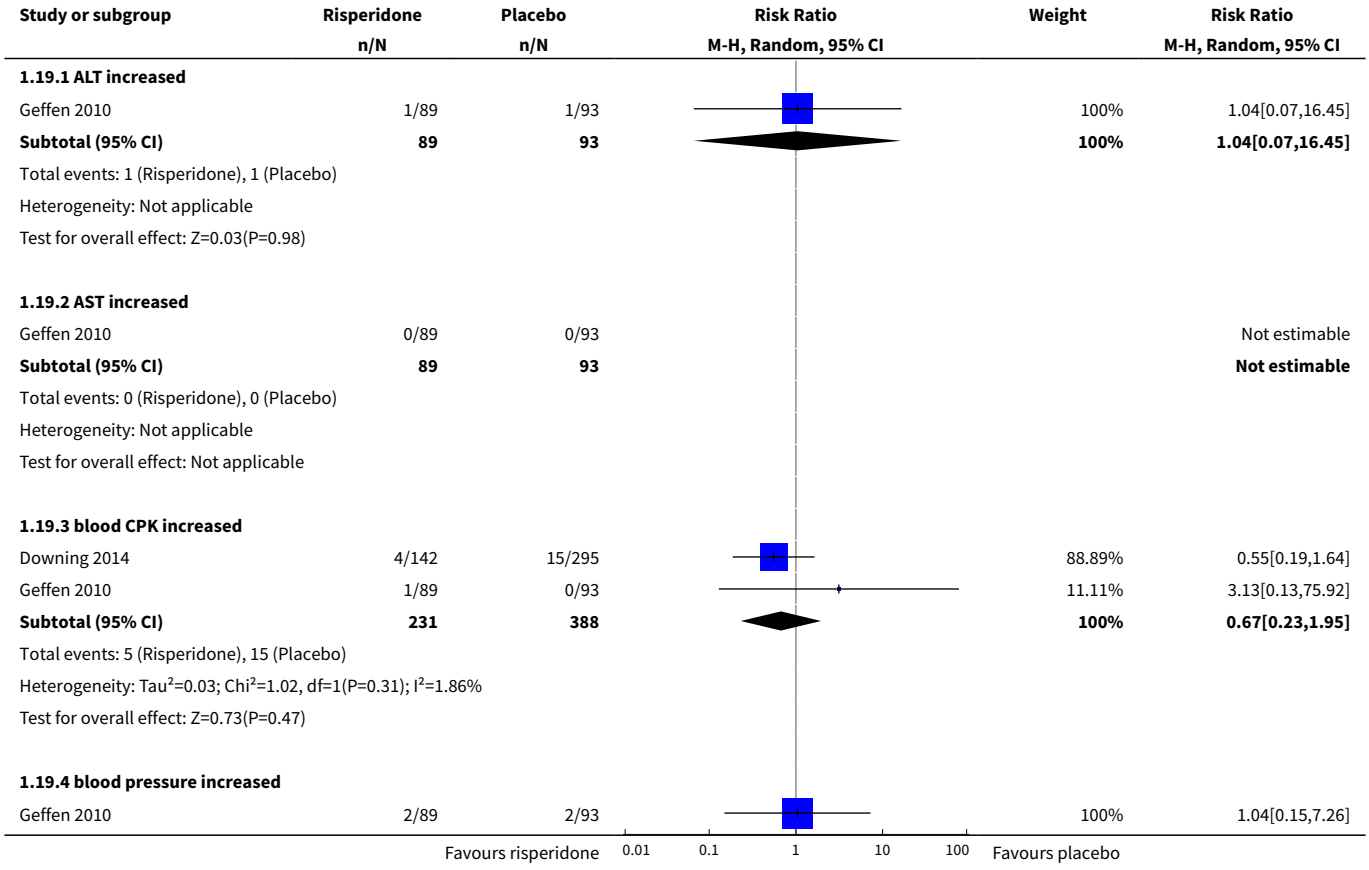
Adverse effects: 7b. metabolic - skewed data - average change value on lipid profile - short term (up to 12 weeks)

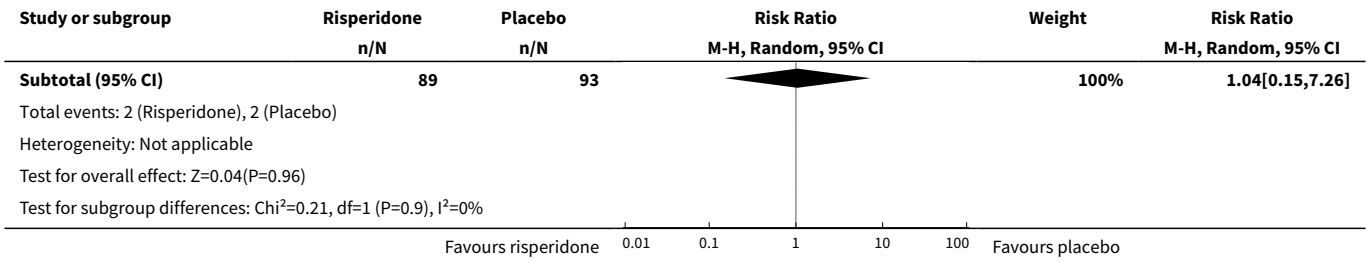
Study	Intervention	Mean	SD	N
		cholesterol - total		
Durgam 2014	Risperidone	4.6	34.6	140
Durgam 2014	Placebo	-1.3	30.4	151
Heisterberg 2007	Risperidone	-2.2	31.4	154
Heisterberg 2007	Placebo	-14.2	32.0	149
		HDL		
Durgam 2014	Risperidone	-0.6	10.1	140
Durgam 2014	Placebo	-1.1	9.4	151
Heisterberg 2007	Risperidone	2.1	10.3	154
Heisterberg 2007	Placebo	-0.7	6.8	149
		LDL		
Durgam 2014	Risperidone	3.8	30.6	140
Durgam 2014	Placebo	-0.1	25.3	151
Heisterberg 2007	Risperidone	-2.8	28.8	154
Heisterberg 2007	Placebo	-7.5	29.8	149
		triglycerides		
Durgam 2014	Risperidone	6.3	84.2	140
Durgam 2014	Placebo	-3.1	59.9	151
Heisterberg 2007	Risperidone	-6.7	136.2	154
Heisterberg 2007	Placebo	-27.9	104.4	149
		VLDL		
Heisterberg 2007	Risperidone	-1.4	17.7	154
Heisterberg 2007	Placebo	-3.7	16.9	149

Analysis 1.18. Comparison 1 RISPERIDONE vs PLACEBO, Outcome 18 Adverse effects: 8. musculoskeletal system - short term (up to 12 weeks).

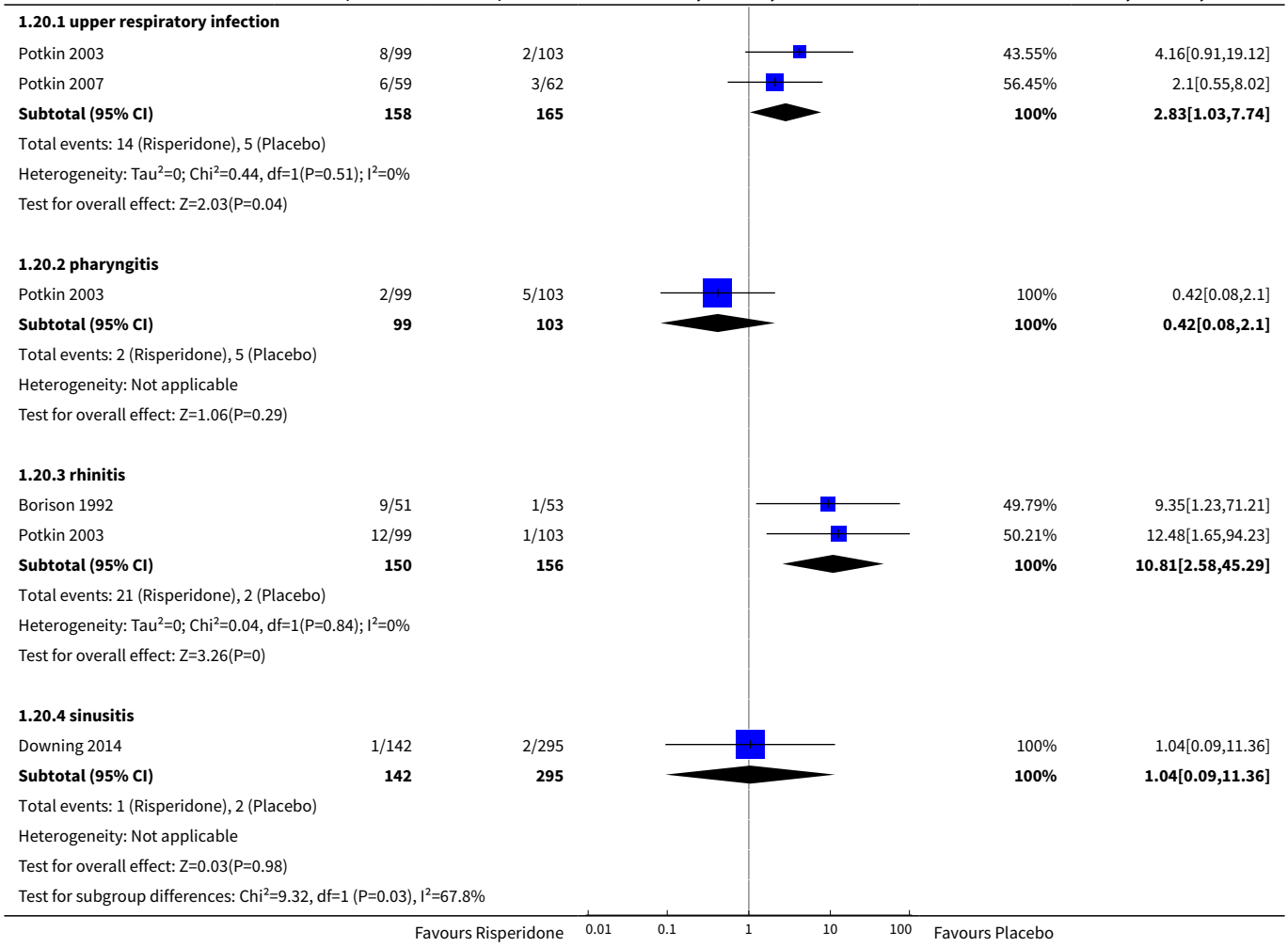


Analysis 1.19. Comparison 1 RISPERIDONE vs PLACEBO, Outcome 19 Adverse effects: 9. physiology - short term (up to 12 weeks).





Analysis 1.20. Comparison 1 RISPERIDONE vs PLACEBO, Outcome 20 Adverse effects: 10. respiratory system - short term (up to 12 weeks).



Comparison 2. RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental state: no clinically significant response in psychotic symptoms (defined by PANSS/BPRS<20% decline) - short term (up to 12 weeks)	2	98	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.93, 1.42]
2 Leaving the study early - short term (up to 12 weeks)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 any reason	3	167	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.53, 2.42]
2.2 due to adverse events	2	137	Risk Ratio (M-H, Random, 95% CI)	4.11 [0.47, 36.24]
2.3 due to lack of efficacy	1	69	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.11, 2.78]
2.4 due to noncompliance	1	69	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.02, 8.61]
2.5 lost to follow-up	1	69	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.02, 8.61]
2.6 reported death	1	68	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.7 withdrawal of consent	3	167	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.28, 7.09]
2.8 administrative reasons	1	69	Risk Ratio (M-H, Random, 95% CI)	5.44 [0.27, 109.34]
2.9 abnormal lab results	1	69	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.02, 8.61]
3 Global state: 1. average endpoint scores of CGI severity scale (high=poor) - short term (up to 12 weeks)	1	65	Mean Difference (IV, Random, 95% CI)	0.51 [0.02, 1.00]
4 Global state: 2. no significant clinical improvement CGI - short term (up to 12 weeks)	1	68	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.87, 1.44]
5 Global state: 3. general functioning - average endpoint GAF score (high=good) - short term (up to 12 weeks)	1	30	Mean Difference (IV, Random, 95% CI)	-4.5 [-8.38, -0.62]
6 Mental state: 1. average endpoint scores on various scales on psychotic symptoms (high=poor) - short term (up to 12 weeks)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 PANSS total	2	95	Mean Difference (IV, Random, 95% CI)	5.56 [1.59, 9.53]
6.2 PANSS general pathology	1	30	Mean Difference (IV, Random, 95% CI)	2.5 [0.03, 4.97]
6.3 PANSS delusion	1	30	Mean Difference (IV, Random, 95% CI)	0.70 [0.09, 1.31]
6.4 PANSS negative symptom	2	95	Mean Difference (IV, Random, 95% CI)	0.69 [-0.68, 2.05]
6.5 PANSS positive symptom	2	95	Mean Difference (IV, Random, 95% CI)	2.30 [0.98, 3.62]
7 Mental state: 2. average endpoint scores on various scales on psychotic symptoms (high=poor) - medium term (up to 26 weeks)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 BPRS total	1	53	Mean Difference (IV, Random, 95% CI)	-4.60 [-9.88, 0.68]
7.2 BPRS positive symptom	1	53	Mean Difference (IV, Random, 95% CI)	-0.90 [-2.81, 1.01]
7.3 BPRS anxiety/depression factor	1	53	Mean Difference (IV, Random, 95% CI)	-1.0 [-2.80, 0.80]
7.4 SANS total	1	53	Mean Difference (IV, Random, 95% CI)	-3.10 [-10.30, 4.10]
8 Mental state: 3. skewed data - short term (up to 12 weeks)			Other data	No numeric data
8.1 average endpoint score of CDS total (high=poor)			Other data	No numeric data
8.2 average endpoint score on verbal working memory (SD, high=good)			Other data	No numeric data
9 Adverse effects: 1a. extrapyramidal - average endpoint SAS score - short term (up to 12 weeks)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
10 Adverse effects: 1b. extrapyramidal - skewed data (various scales) - short term (up to 12 weeks)			Other data	No numeric data
10.1 average endpoint score of AIMS			Other data	No numeric data
10.2 average change score of Barnes akathisia rating scale			Other data	No numeric data
10.3 average change score of ESRS			Other data	No numeric data

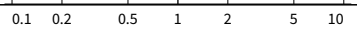
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.4 average change score of ESRS - dystonia			Other data	No numeric data
10.5 average change score of ESRS - dyskinesia			Other data	No numeric data
10.6 average change score of ESRS - parkinsonism			Other data	No numeric data
11 Adverse effects: 1c. extrapyramidal - skewed data (various scales) - medium term (up to 26 weeks)			Other data	No numeric data
11.1 average endpoint score of AIMS			Other data	No numeric data
11.2 average endpoint score of SAS			Other data	No numeric data
12 Adverse effects: 2. any adverse event - short term (up to 12 weeks)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 any adverse event	1	64	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.83, 1.58]
12.2 amenorrhoea	1	64	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 71.00]
12.3 asthenia	1	64	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.61, 1.91]
12.4 depression	1	64	Risk Ratio (M-H, Random, 95% CI)	1.2 [0.61, 2.37]
12.5 emotional indifference	1	64	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.52, 2.37]
12.6 fatigue	1	64	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.61, 1.91]
12.7 failing memory	1	64	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.32, 1.41]
12.8 increased duration of sleep	1	64	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.51, 1.97]
12.9 salivation - increased	1	64	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.81, 1.94]
13 Adverse effects: 3a. cardiovascular - short term (up to 12 weeks)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 dizziness - orthostatic	1	64	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.43, 2.34]
13.2 palpitation	1	64	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.27, 3.66]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.3 tachycardia	1	64	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.27, 3.66]
14 Adverse effects: 3b. cardiovascular - QTc interval - short term (up to 12 weeks)	1	30	Mean Difference (IV, Random, 95% CI)	-19.70 [-42.08, 2.68]
15 Adverse effects: 4. central nervous system - short term (up to 12 weeks)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 sedation	1	64	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.88, 2.43]
15.2 somnolence	1	64	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.51, 1.97]
15.3 tension	1	64	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.71, 2.12]
16 Adverse effects: 5. gastrointestinal system - short term (up to 12 weeks)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.1 constipation	1	64	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.25, 2.02]
17 Adverse effects: 6a. haematological - short term (up to 12 weeks)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
17.1 neutrophil count	1	57	Mean Difference (IV, Random, 95% CI)	0.37 [-0.42, 1.16]
17.2 prolactin level, ng/mL	1	30	Mean Difference (IV, Random, 95% CI)	60.10 [46.52, 73.68]
17.3 white cell count	1	61	Mean Difference (IV, Random, 95% CI)	0.66 [-0.20, 1.52]
18 Adverse effects: 6b. haematological - medium term (up to 26 weeks)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
18.1 prolactin level ng/mL	1	44	Mean Difference (IV, Random, 95% CI)	34.1 [17.63, 50.57]
18.2 fasting glucose	1	40	Mean Difference (IV, Random, 95% CI)	-4.60 [-17.09, 7.89]
19 Adverse effects: 7a. metabolic - weight gain - short term (up to 12 weeks)	1	64	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.40, 2.52]
20 Adverse effects: 7a. metabolic - weight gain - medium term (up to 26 weeks)	1	48	Risk Ratio (M-H, Random, 95% CI)	0.2 [0.01, 3.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21 Adverse effects: 7b. metabolic - average endpoint value on lipid profile - short term (up to 12 weeks)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
21.1 cholesterol - total (mg/dl)	1	56	Mean Difference (IV, Random, 95% CI)	-6.60 [-29.05, 15.85]
21.2 HDL cholesterol (mg/dl)	1	52	Mean Difference (IV, Random, 95% CI)	0.0 [-8.44, 8.44]
21.3 LDL cholesterol (mg/dl)	1	53	Mean Difference (IV, Random, 95% CI)	-6.90 [-26.02, 12.22]
21.4 triglycerides (mg/dl)	1	56	Mean Difference (IV, Random, 95% CI)	6.20 [-57.57, 69.97]
22 Adverse effects: 7c. metabolic - average endpoint value - short term (up to 12 weeks)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
22.1 body mass index	1	63	Mean Difference (IV, Random, 95% CI)	1.70 [-0.99, 4.39]
22.2 fasting glucose (mg/dl)	1	51	Mean Difference (IV, Random, 95% CI)	16.20 [-3.12, 35.52]
22.3 waist circumference (cm)	1	61	Mean Difference (IV, Random, 95% CI)	5.10 [-4.14, 14.34]
22.4 weight gain	2	94	Mean Difference (IV, Random, 95% CI)	0.34 [-0.84, 1.53]
23 Adverse effects: 8. sleep - skewed data - average change score (UKU) - short term (up to 12 weeks)			Other data	No numeric data
24 Quality of life: average endpoint score (QLS, high=good) - short term (up to 12 weeks)	1	30	Mean Difference (IV, Random, 95% CI)	0.80 [-5.44, 7.04]

Analysis 2.1. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 1 Mental state: no clinically significant response in psychotic symptoms (defined by PANSS/BPRS<20% decline) - short term (up to 12 weeks).

Study or subgroup	Risperidone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Honer 2006	28/34	25/34		68.95%	1.12[0.87,1.44]
Yagcioglu 2005	14/16	10/14		31.05%	1.23[0.84,1.79]
Total (95% CI)	**50**	**48**		**100%**	**1.15[0.93,1.42]**
Total events: 42 (Risperidone), 35 (Placebo)					



Favours risperidone — Favours placebo

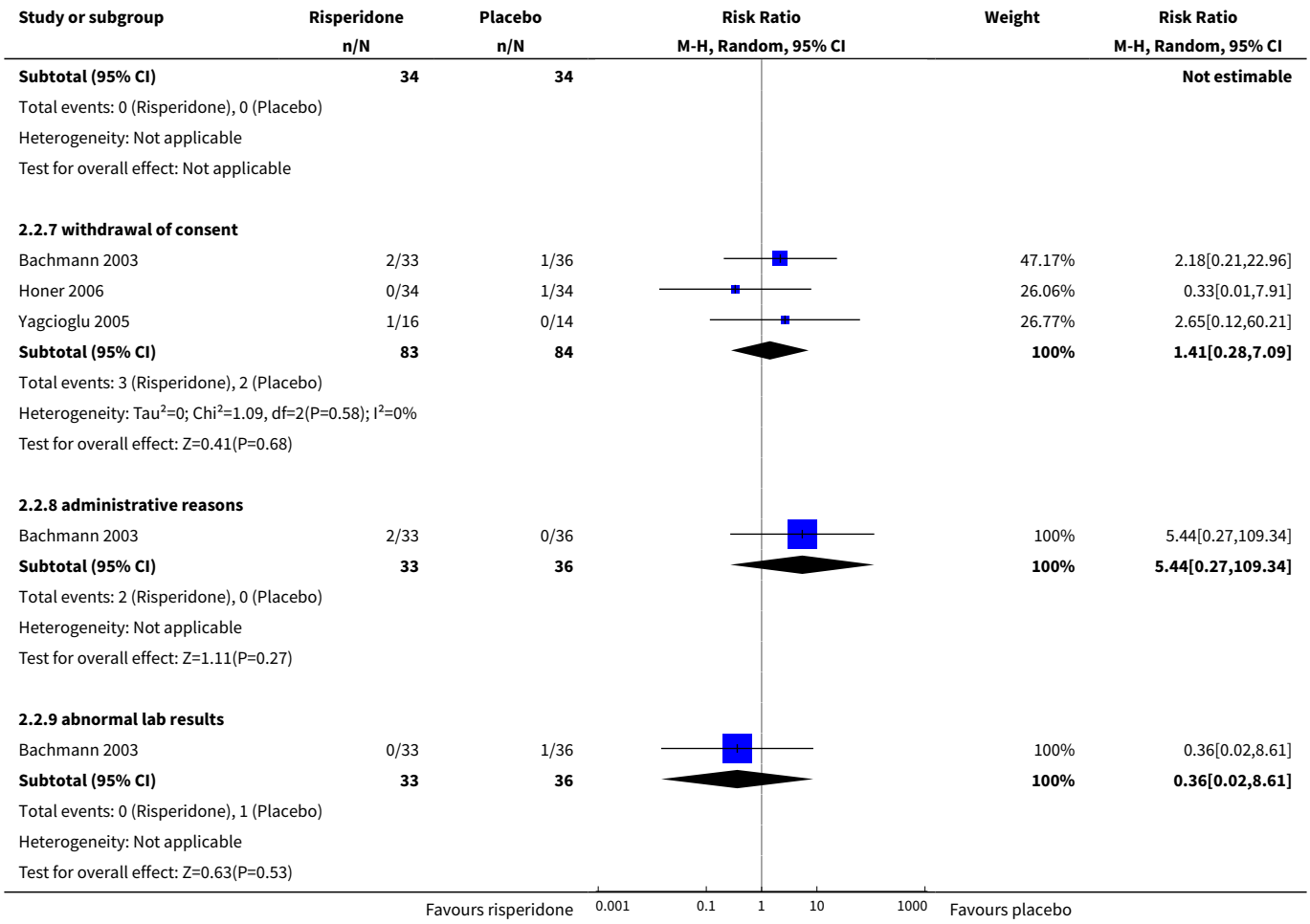
Study or subgroup	Risperidone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=0.15, df=1(P=0.7); I²=0%					
Test for overall effect: Z=1.31(P=0.19)					

Favours risperidone 0.1 0.2 0.5 1 2 5 10 Favours placebo

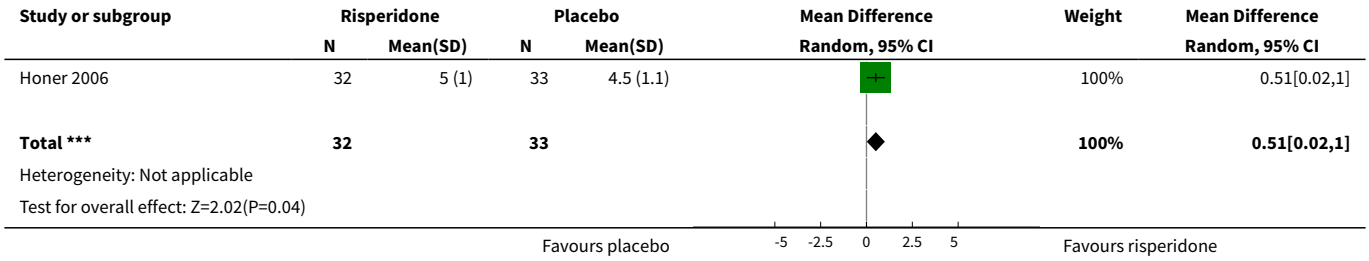
Analysis 2.2. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 2 Leaving the study early - short term (up to 12 weeks).

Study or subgroup	Risperidone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 any reason					
Bachmann 2003	8/33	8/36		78.16%	1.09[0.46,2.57]
Honer 2006	2/34	2/34		15.94%	1[0.15,6.7]
Yagcioglu 2005	1/16	0/14		5.9%	2.65[0.12,60.21]
Subtotal (95% CI)	**83**	**84**		**100%**	**1.13[0.53,2.42]**
Total events: 11 (Risperidone), 10 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.31, df=2(P=0.86); I²=0%					
Test for overall effect: Z=0.32(P=0.75)					
2.2.2 due to adverse events					
Bachmann 2003	2/33	0/36		52.68%	5.44[0.27,109.34]
Honer 2006	1/34	0/34		47.32%	3[0.13,71.15]
Subtotal (95% CI)	**67**	**70**		**100%**	**4.11[0.47,36.24]**
Total events: 3 (Risperidone), 0 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.07, df=1(P=0.79); I²=0%					
Test for overall effect: Z=1.27(P=0.2)					
2.2.3 due to lack of efficacy					
Bachmann 2003	2/33	4/36		100%	0.55[0.11,2.78]
Subtotal (95% CI)	**33**	**36**		**100%**	**0.55[0.11,2.78]**
Total events: 2 (Risperidone), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.73(P=0.47)					
2.2.4 due to noncompliance					
Bachmann 2003	0/33	1/36		100%	0.36[0.02,8.61]
Subtotal (95% CI)	**33**	**36**		**100%**	**0.36[0.02,8.61]**
Total events: 0 (Risperidone), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					
2.2.5 lost to follow-up					
Bachmann 2003	0/33	1/36		100%	0.36[0.02,8.61]
Subtotal (95% CI)	**33**	**36**		**100%**	**0.36[0.02,8.61]**
Total events: 0 (Risperidone), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					
2.2.6 reported death					
Honer 2006	0/34	0/34			Not estimable

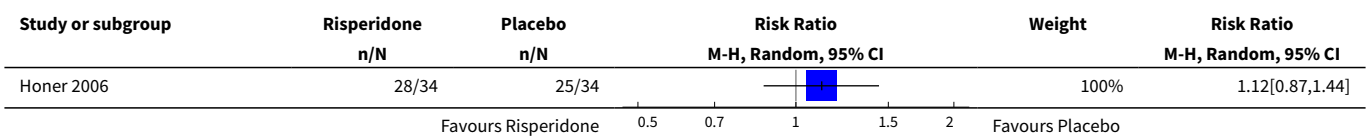
Favours risperidone 0.001 0.1 1 10 1000 Favours placebo

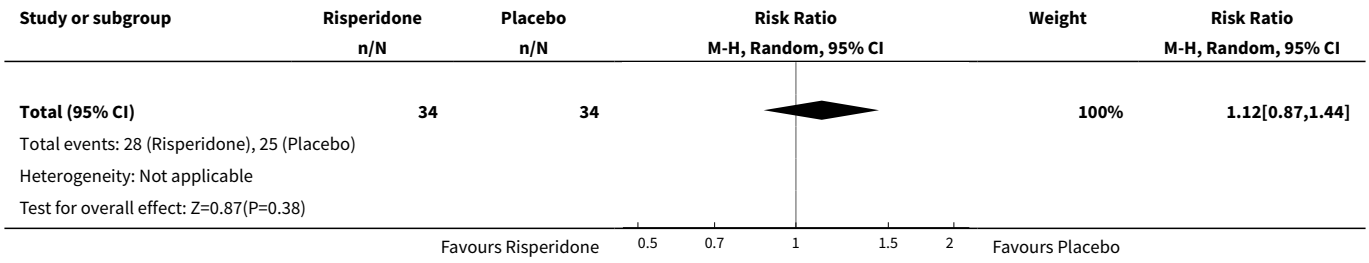


Analysis 2.3. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 3 Global state: 1. average endpoint scores of CGI severity scale (high=poor) - short term (up to 12 weeks).

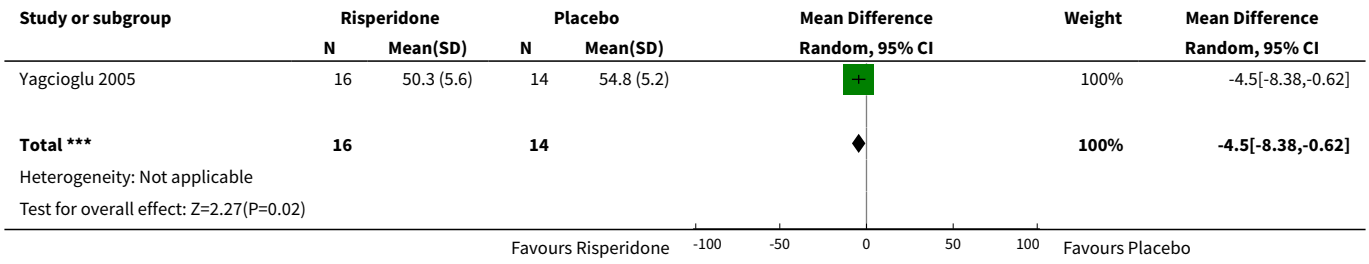


Analysis 2.4. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 4 Global state: 2. no significant clinical improvement CGI - short term (up to 12 weeks).

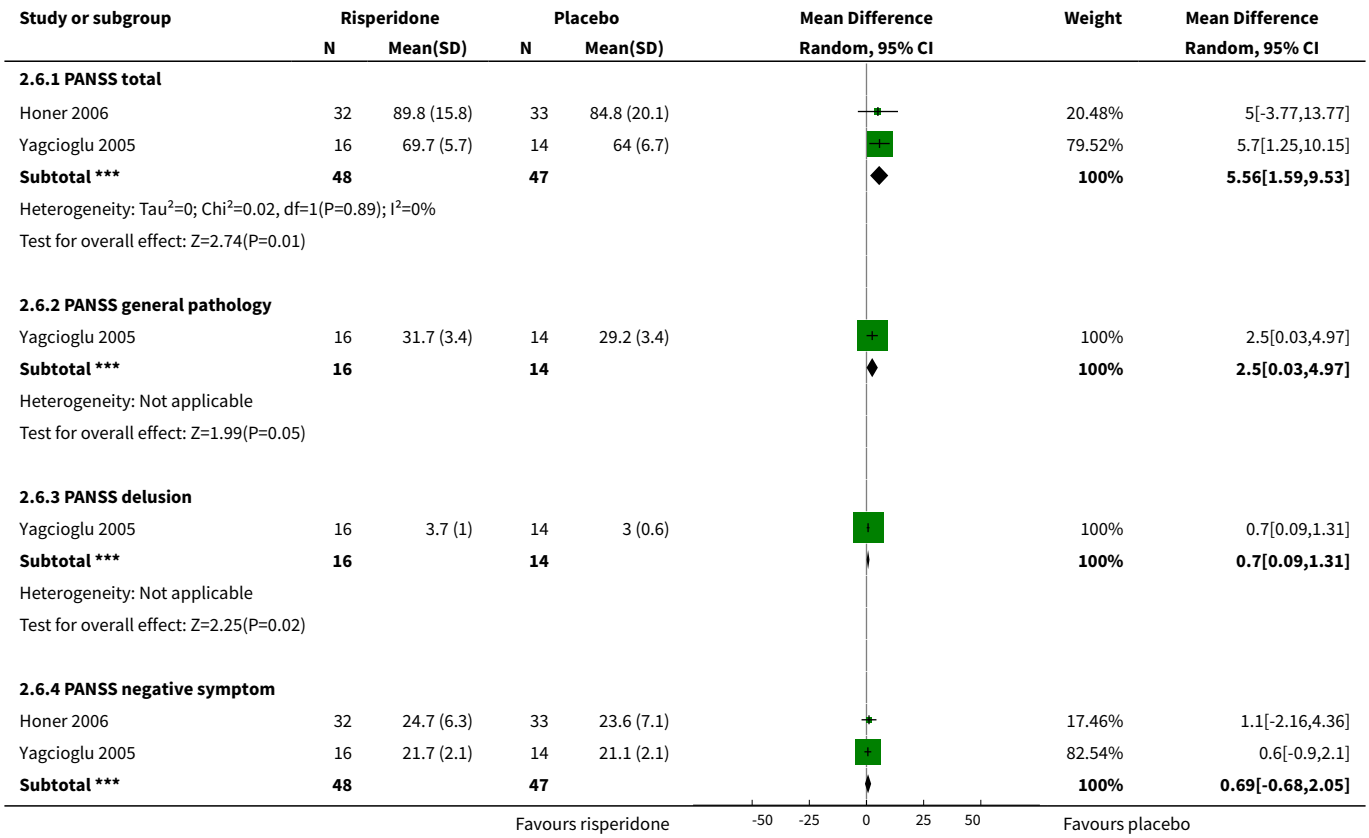


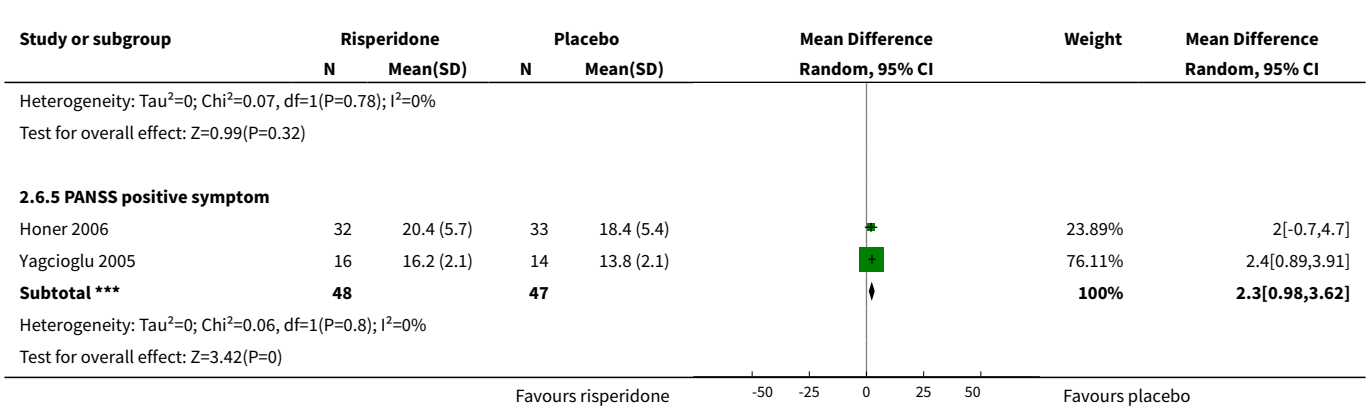


Analysis 2.5. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 5 Global state: 3. general functioning - average endpoint GAF score (high=good) - short term (up to 12 weeks).

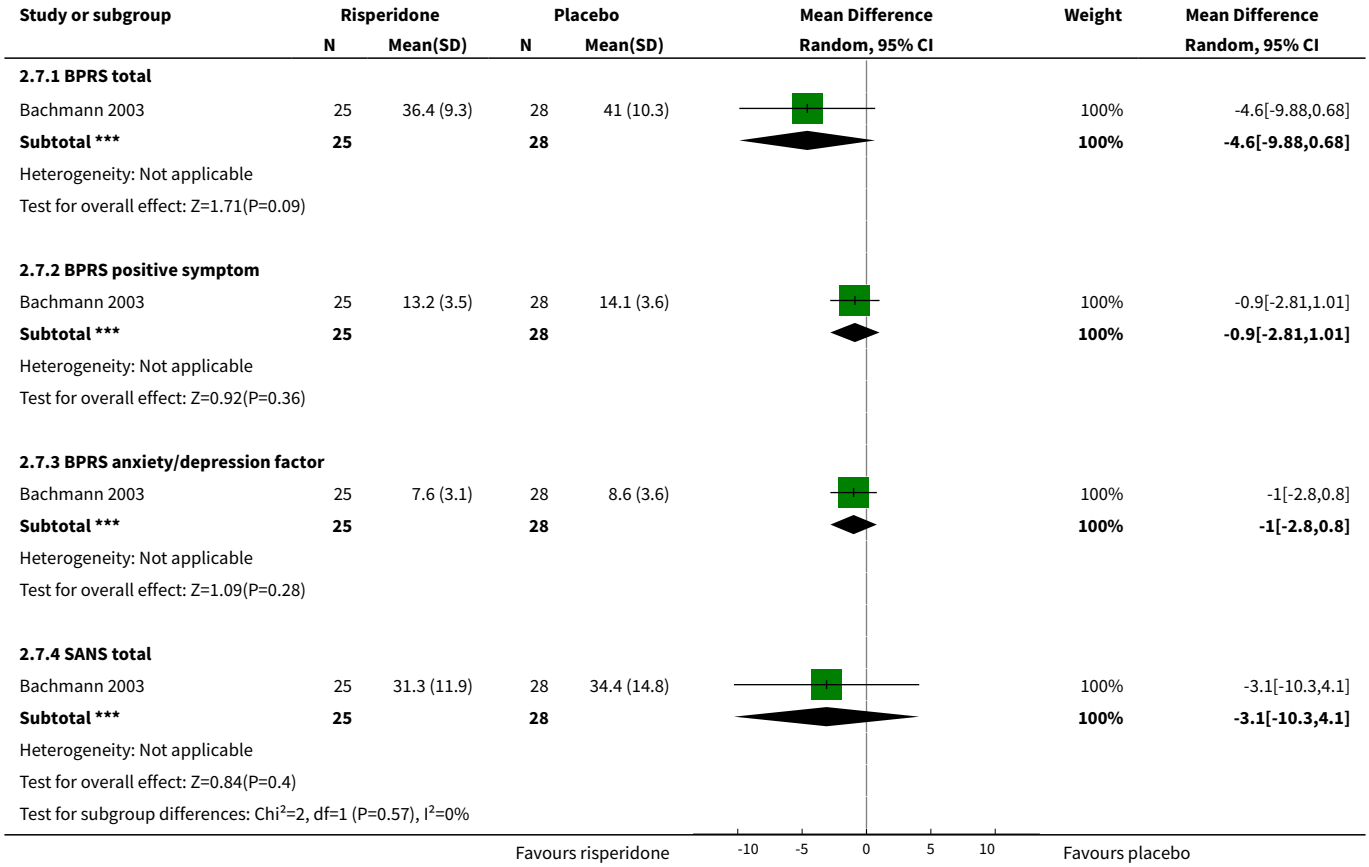


Analysis 2.6. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 6 Mental state: 1. average endpoint scores on various scales on psychotic symptoms (high=poor) - short term (up to 12 weeks).





Analysis 2.7. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 7 Mental state: 2. average endpoint scores on various scales on psychotic symptoms (high=poor) - medium term (up to 26 weeks).



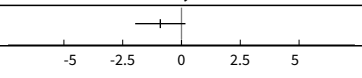
Analysis 2.8. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 8 Mental state: 3. skewed data - short term (up to 12 weeks).

Mental state: 3. skewed data - short term (up to 12 weeks)				
Study	**Intervention**	**Mean**	**SD**	**N**
average endpoint score of CDS total (high=poor)				
Yagcioglu 2005	Resperidone	1.6	2	16

Mental state: 3. skewed data - short term (up to 12 weeks)				
Study	**Intervention**	**Mean**	**SD**	**N**
Yagcioglu 2005	Placebo	1.4	1.9	14
average endpoint score on verbal working memory (SD, high=good)				
Honer 2006	Resperidone	0.08	0.99	152
Honer 2006	Placebo	0.14	0.83	71

Analysis 2.9. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 9 Adverse effects: 1a. extrapyramidal - average endpoint SAS score - short term (up to 12 weeks).

Study or subgroup	Risperidone		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Yagcioglu 2005	16	12.3 (1.5)	14	13.2 (1.5)		0%	-0.9[-1.97,0.17]



Analysis 2.10. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 10 Adverse effects: 1b. extrapyramidal - skewed data (various scales) - short term (up to 12 weeks).

Adverse effects: 1b. extrapyramidal - skewed data (various scales) - short term (up to 12 weeks)				
Study	**Intervention**	**Mean**	**SD**	**N**
average endpoint score of AIMS				
Yagcioglu 2005	Risperidone	1.3	0.88	16
Yagcioglu 2005	Placebo	1.0	0.86	14
average change score of Barnes akathisia rating scale				
Honer 2006	Risperidone	0.5	0.7	32
Honer 2006	Placebo	0.4	0.8	33
Yagcioglu 2005	Risperidone	0.18	0.6	16
Yagcioglu 2005	Placebo	0.72	0.6	14
average change score of ESRS				
Honer 2006	Risperidone	9.3	6.9	32
Honer 2006	Placebo	7.8	7.0	32
average change score of ESRS - dystonia				
Honer 2006	Risperidone	0.2	0.7	32
Honer 2006	Placebo	0.1	0.5	33
average change score of ESRS - dyskinesia				
Honer 2006	Risperidone	2.4	4.1	32
Honer 2006	Placebo	2.1	4.2	33
average change score of ESRS - parkinsonism				
Honer 2006	Risperidone	6.7	4.3	32
Honer 2006	Placebo	5.5	4	32

Analysis 2.11. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 11 Adverse effects: 1c. extrapyramidal - skewed data (various scales) - medium term (up to 26 weeks).

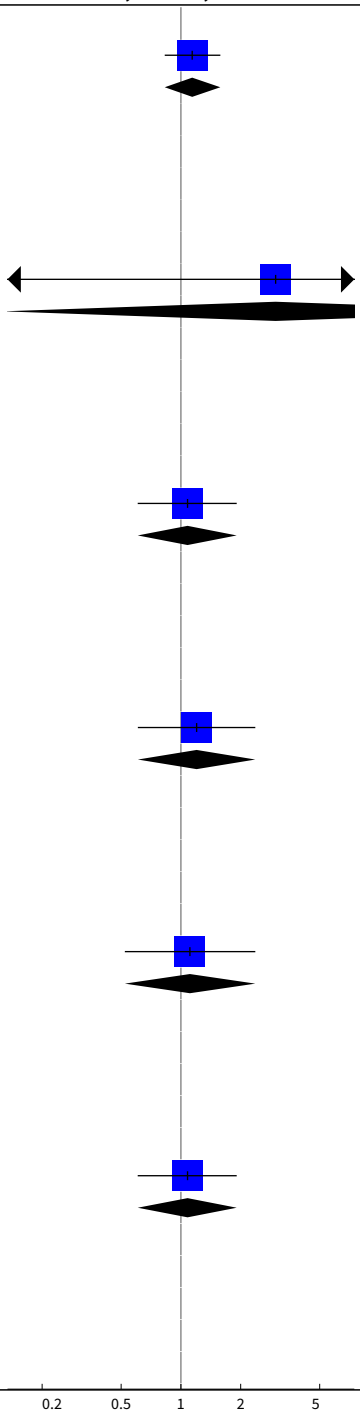
Adverse effects: 1c. extrapyramidal - skewed data (various scales) - medium term (up to 26 weeks)				
Study	**Intervention**	**Mean**	**SD**	**N**
average endpoint score of AIMS				
Bachmann 2003	Risperidone	3.5	5.5	25
Bachmann 2003	Placebo	2.2	2.8	28
average endpoint score of SAS				
Bachmann 2003	Risperidone	1.8	3.4	25

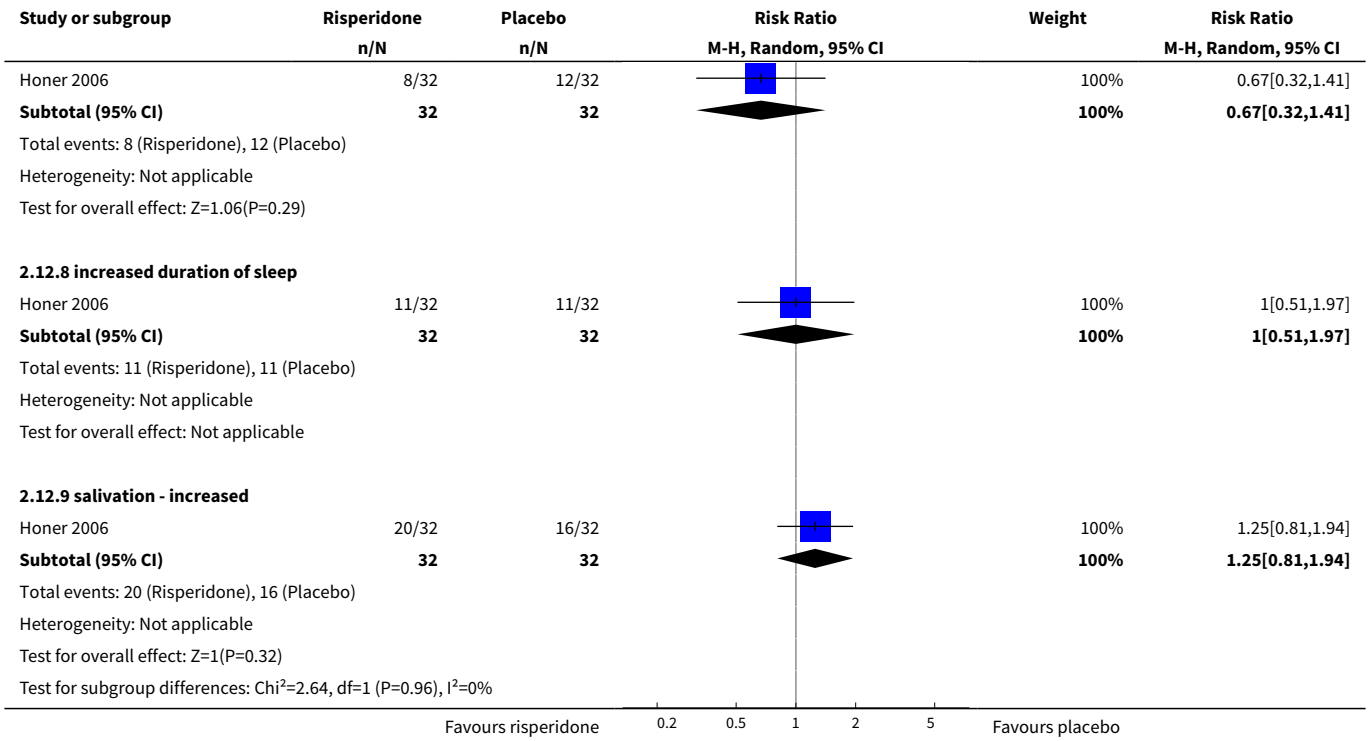
Adverse effects: 1c. extrapyramidal - skewed data (various scales) - medium term (up to 26 weeks)

Study	Intervention	Mean	SD	N
Bachmann 2003	Placebo	1.8	2.5	28

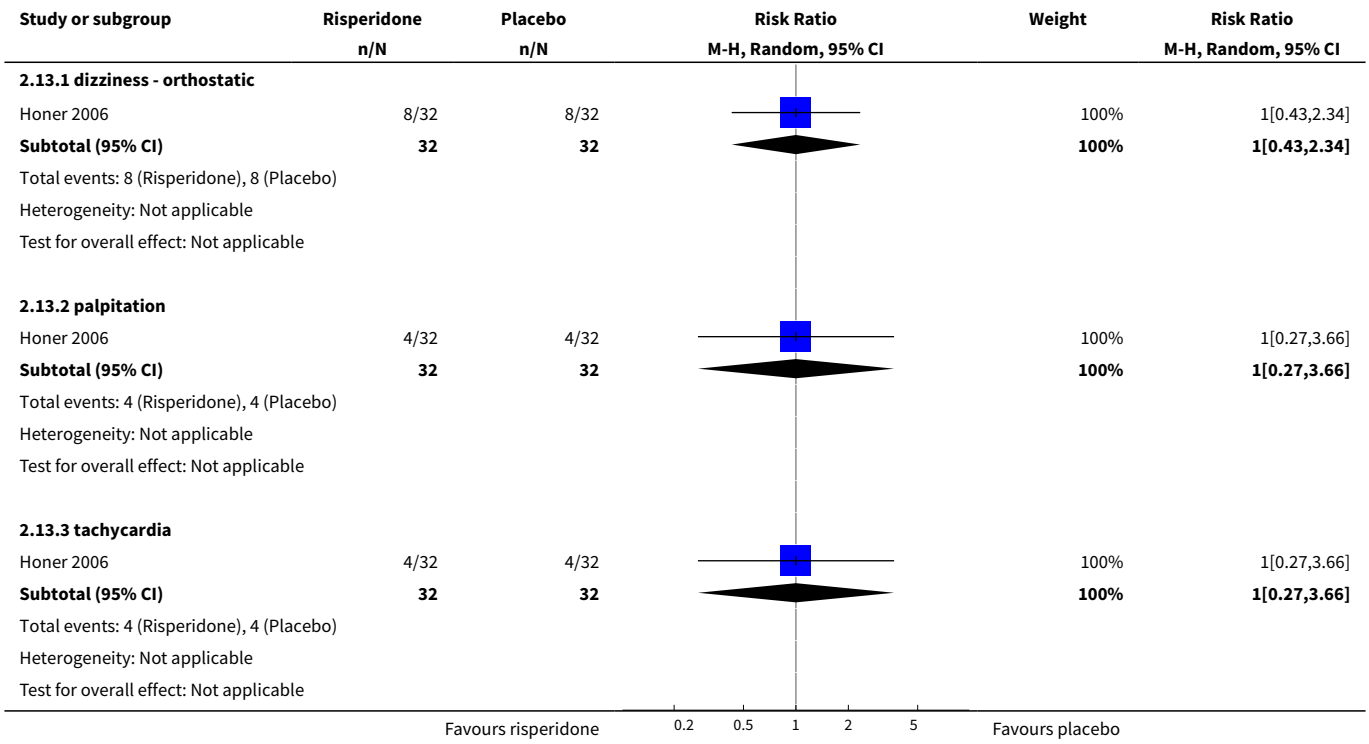
Analysis 2.12. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 12 Adverse effects: 2. any adverse event - short term (up to 12 weeks).

Study or subgroup	Risperidone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.12.1 any adverse event					
Honer 2006	24/32	21/32		100%	1.14[0.83,1.58]
Subtotal (95% CI)	**32**	**32**		**100%**	**1.14[0.83,1.58]**
Total events: 24 (Risperidone), 21 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.82(P=0.41)					
2.12.2 amenorrhoea					
Honer 2006	1/32	0/32		100%	3[0.13,71]
Subtotal (95% CI)	**32**	**32**		**100%**	**3[0.13,71]**
Total events: 1 (Risperidone), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.5)					
2.12.3 asthenia					
Honer 2006	14/32	13/32		100%	1.08[0.61,1.91]
Subtotal (95% CI)	**32**	**32**		**100%**	**1.08[0.61,1.91]**
Total events: 14 (Risperidone), 13 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.25(P=0.8)					
2.12.4 depression					
Honer 2006	12/32	10/32		100%	1.2[0.61,2.37]
Subtotal (95% CI)	**32**	**32**		**100%**	**1.2[0.61,2.37]**
Total events: 12 (Risperidone), 10 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.52(P=0.6)					
2.12.5 emotional indifference					
Honer 2006	10/32	9/32		100%	1.11[0.52,2.37]
Subtotal (95% CI)	**32**	**32**		**100%**	**1.11[0.52,2.37]**
Total events: 10 (Risperidone), 9 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.27(P=0.78)					
2.12.6 fatigue					
Honer 2006	14/32	13/32		100%	1.08[0.61,1.91]
Subtotal (95% CI)	**32**	**32**		**100%**	**1.08[0.61,1.91]**
Total events: 14 (Risperidone), 13 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.25(P=0.8)					
2.12.7 failing memory					

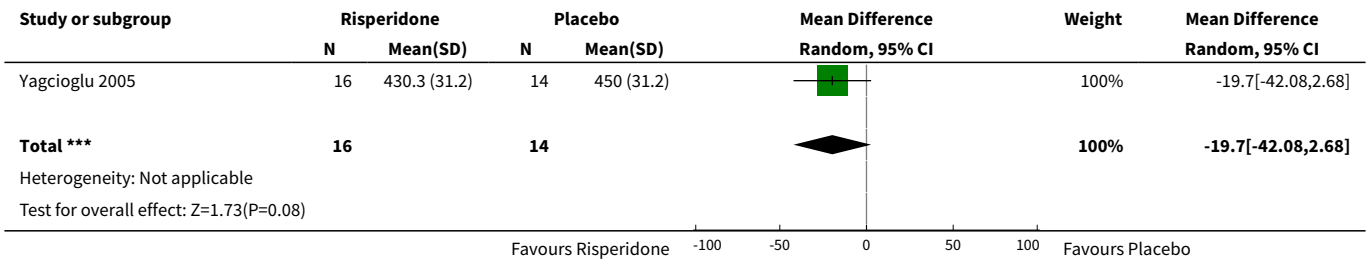




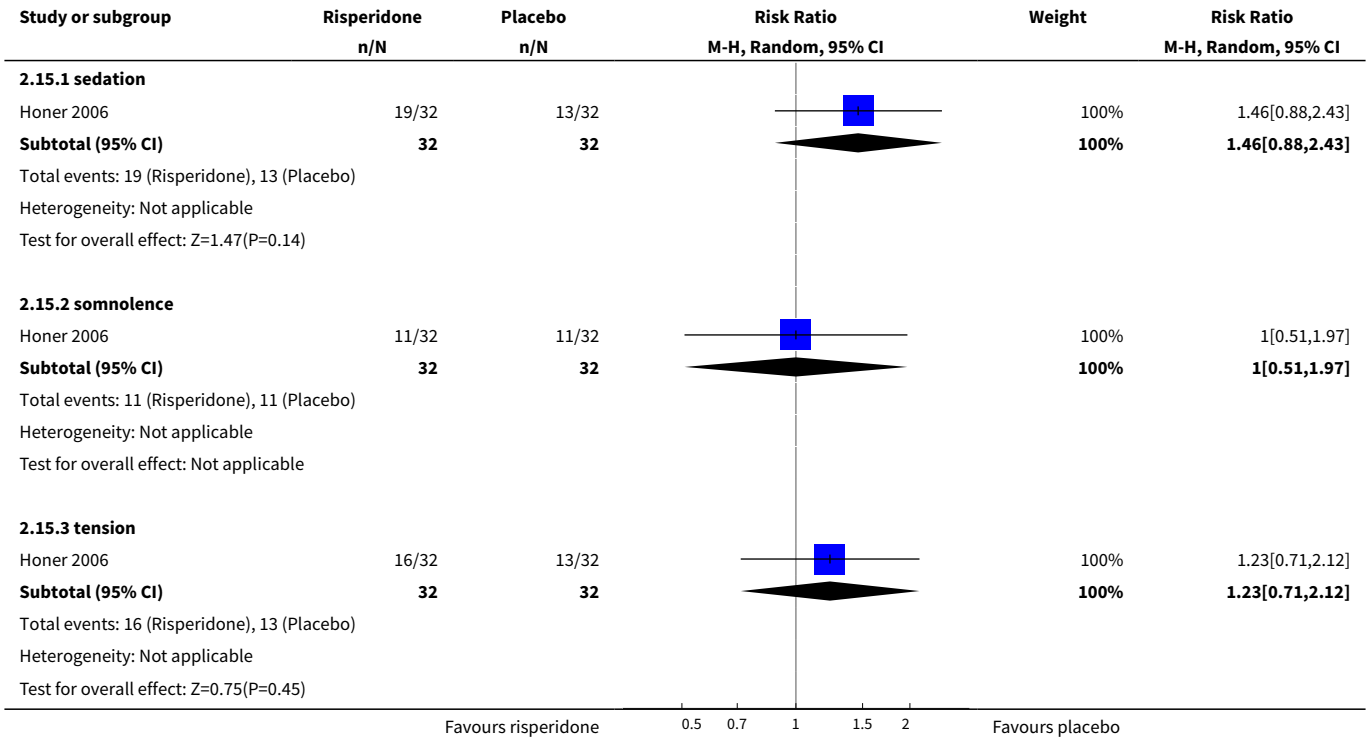
Analysis 2.13. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 13 Adverse effects: 3a. cardiovascular - short term (up to 12 weeks).



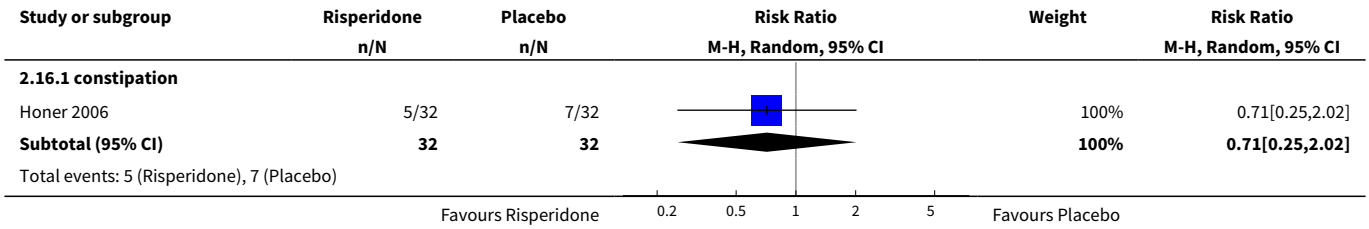
Analysis 2.14. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 14 Adverse effects: 3b. cardiovascular - QTc interval - short term (up to 12 weeks).

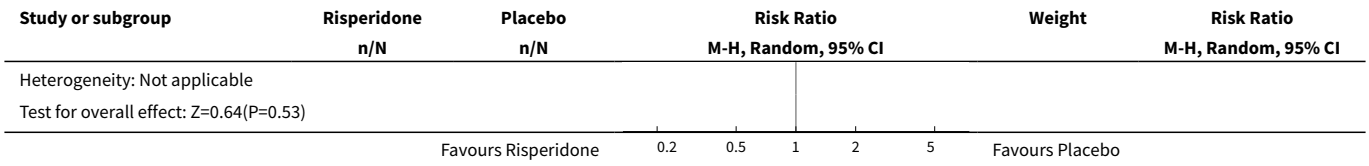


Analysis 2.15. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 15 Adverse effects: 4. central nervous system - short term (up to 12 weeks).

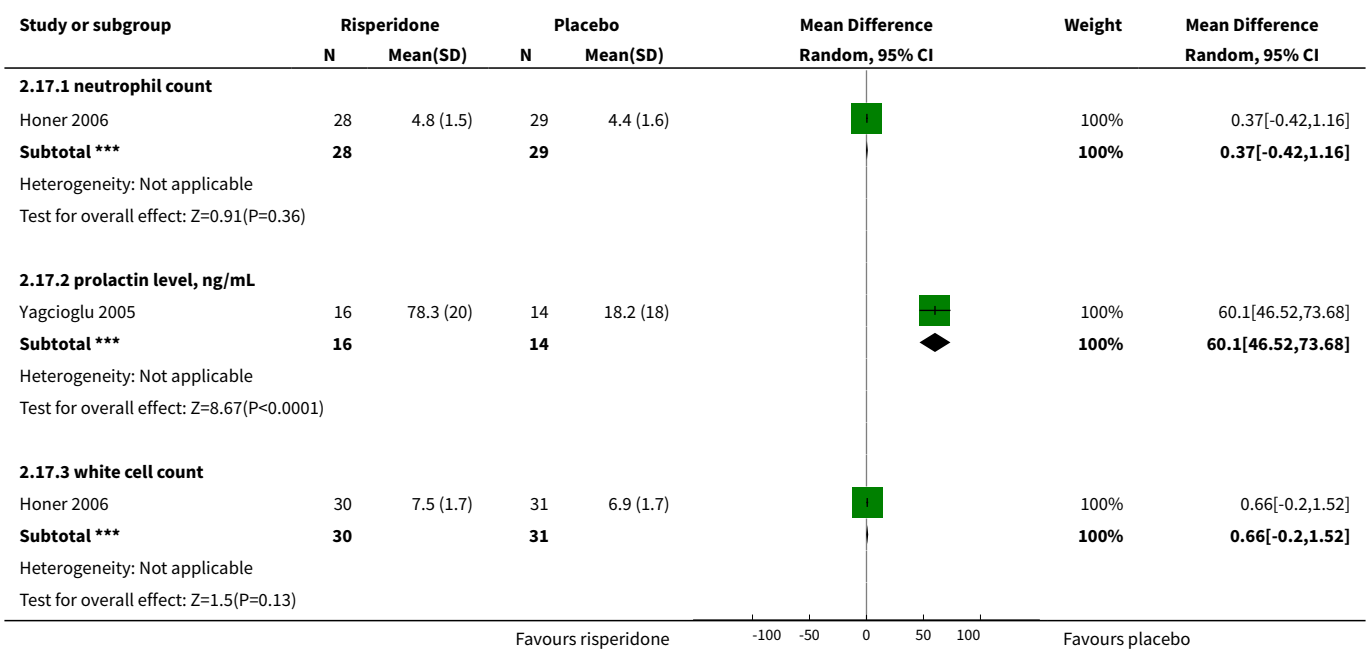


Analysis 2.16. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 16 Adverse effects: 5. gastrointestinal system - short term (up to 12 weeks).

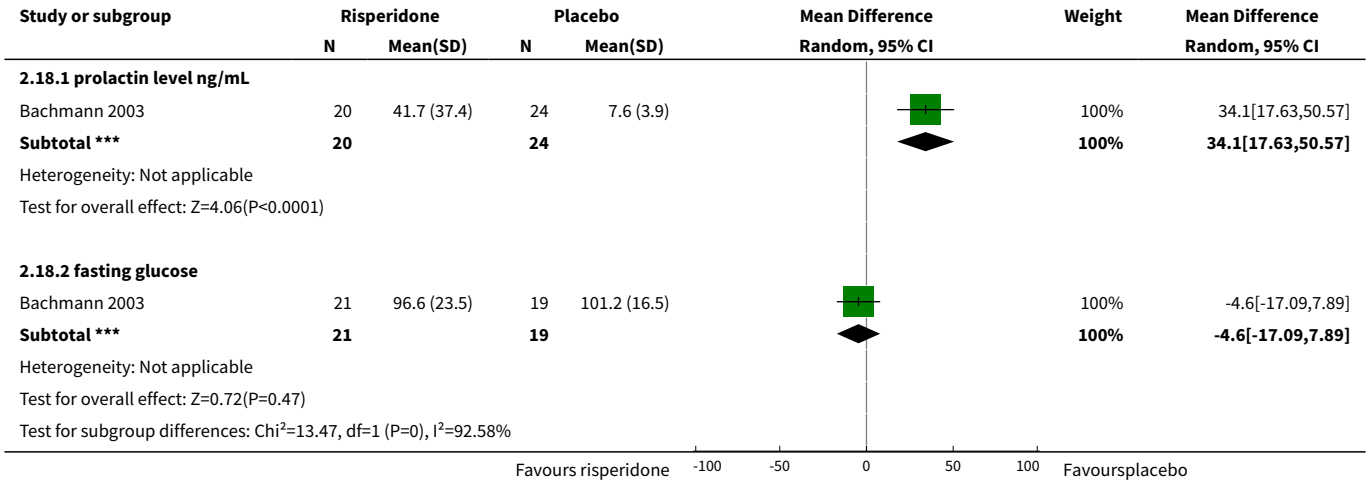




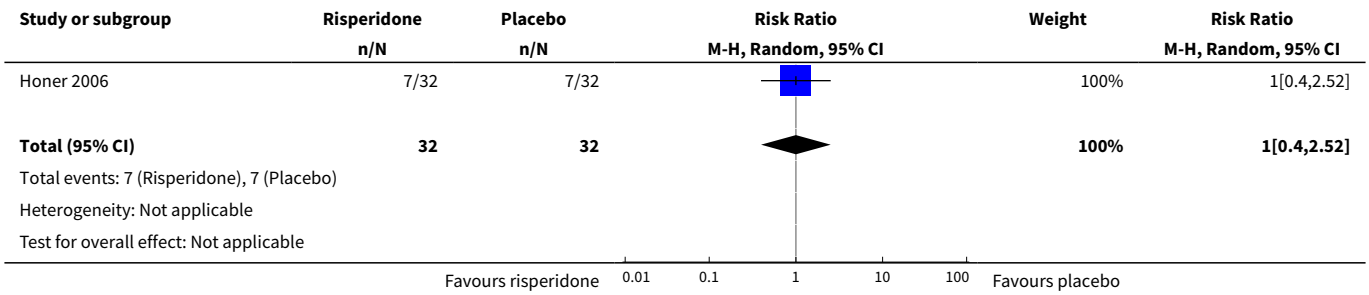
Analysis 2.17. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 17 Adverse effects: 6a. haematological - short term (up to 12 weeks).



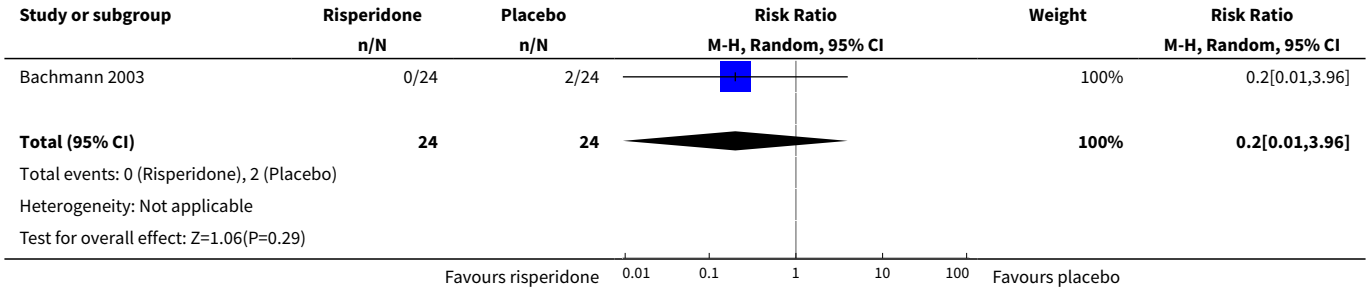
Analysis 2.18. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 18 Adverse effects: 6b. haematological - medium term (up to 26 weeks).



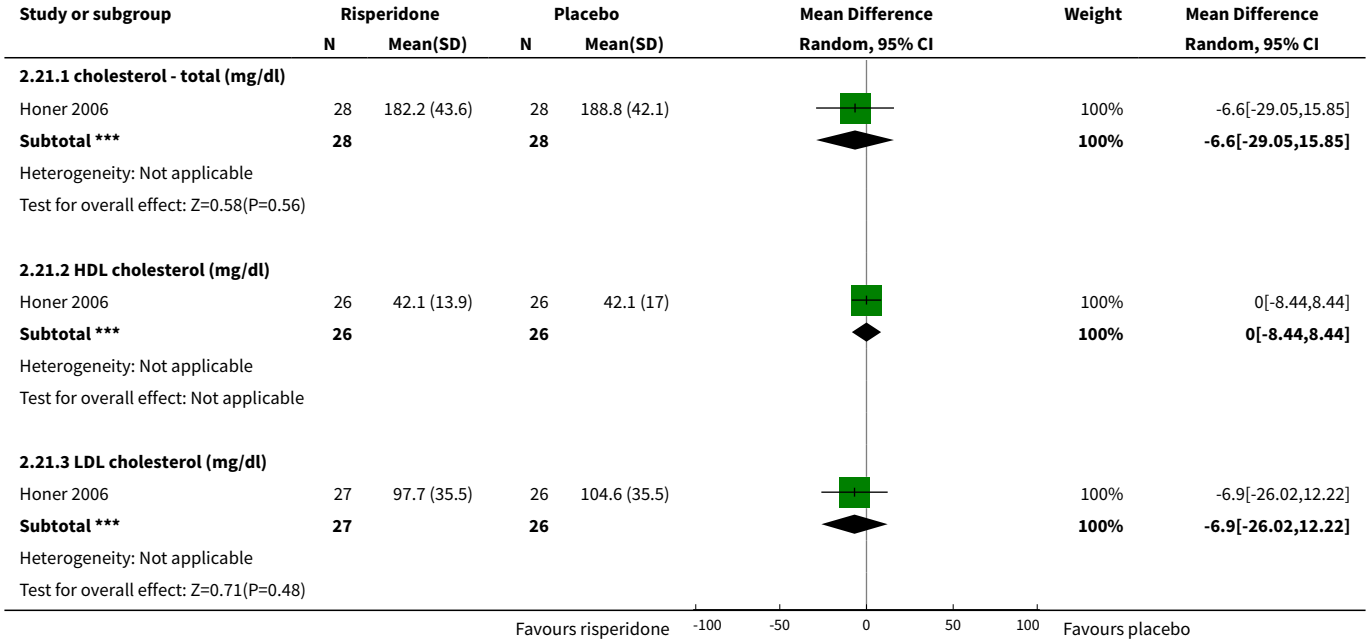
Analysis 2.19. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 19 Adverse effects: 7a. metabolic - weight gain - short term (up to 12 weeks).

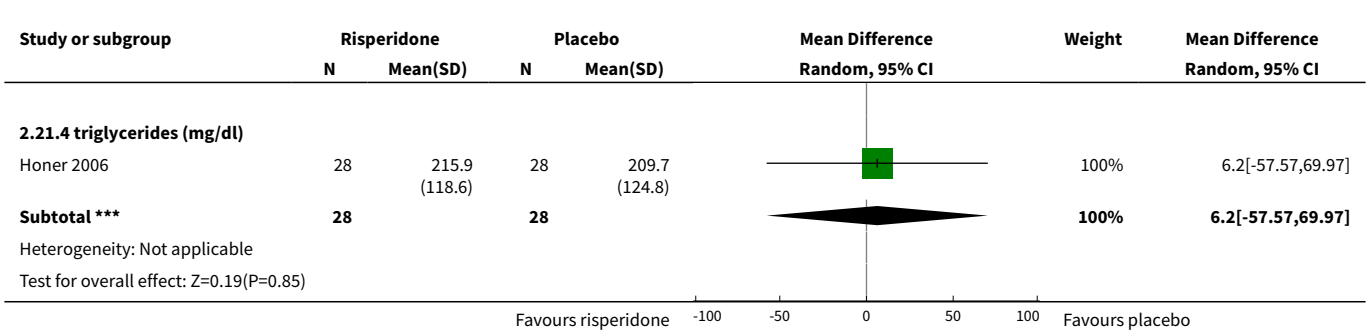


Analysis 2.20. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 20 Adverse effects: 7a. metabolic - weight gain - medium term (up to 26 weeks).

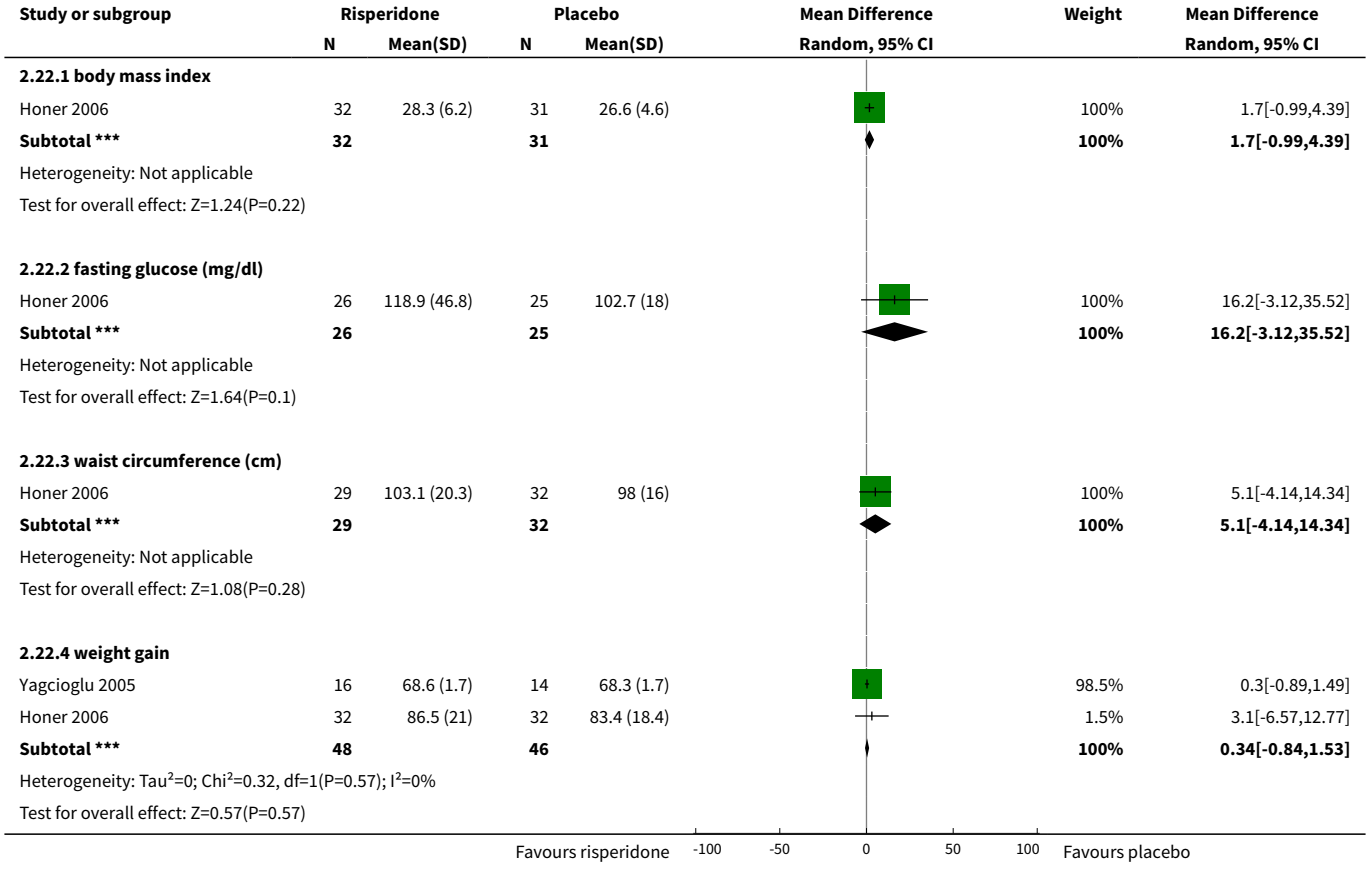


Analysis 2.21. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 21 Adverse effects: 7b. metabolic - average endpoint value on lipid profile - short term (up to 12 weeks).





Analysis 2.22. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 22 Adverse effects: 7c. metabolic - average endpoint value - short term (up to 12 weeks).

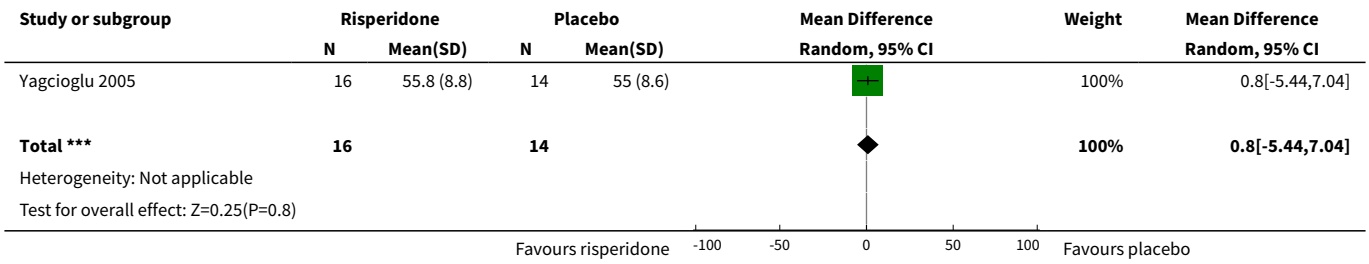


Analysis 2.23. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 23 Adverse effects: 8. sleep - skewed data - average change score (UKU) - short term (up to 12 weeks).

Adverse effects: 8. sleep - skewed data - average change score (UKU) - short term (up to 12 weeks)

Study	Intervention	Mean	SD	N
Yagcioglu 2005	Risperidone	0.7	0.36	16
Yagcioglu 2005	Placebo	0.2	0.37	14

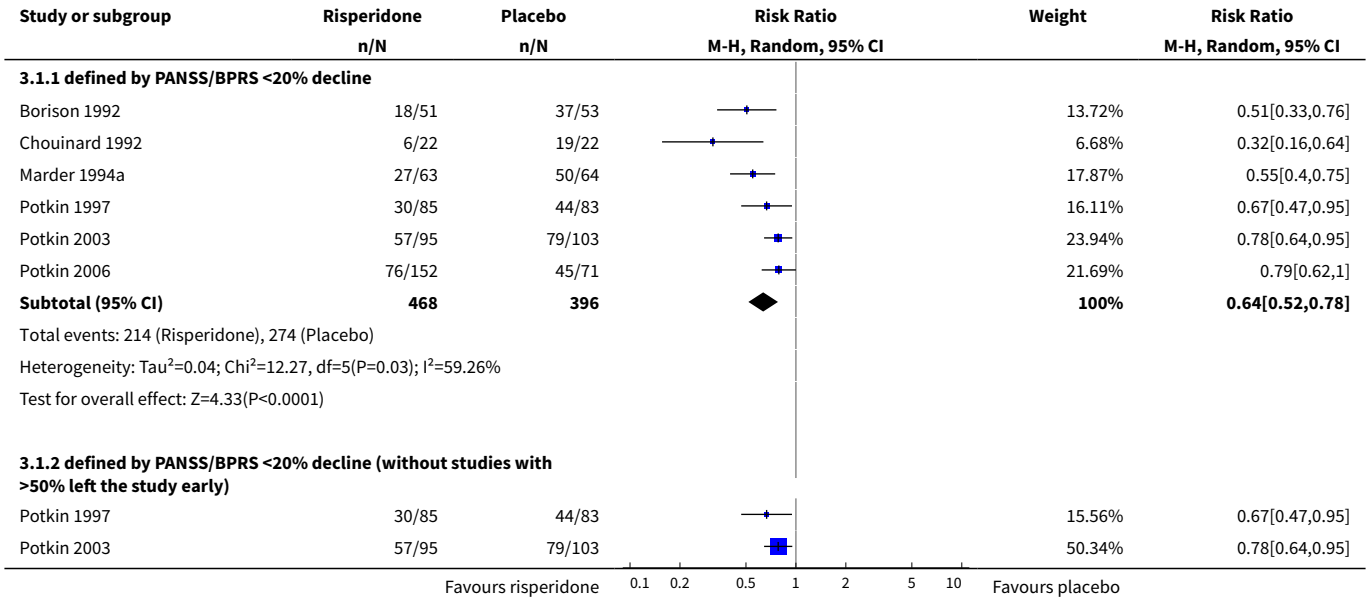
Analysis 2.24. Comparison 2 RISPERIDONE + CLOZAPINE vs PLACEBO + CLOZAPINE, Outcome 24 Quality of life: average endpoint score (QLS, high=good) - short term (up to 12 weeks).

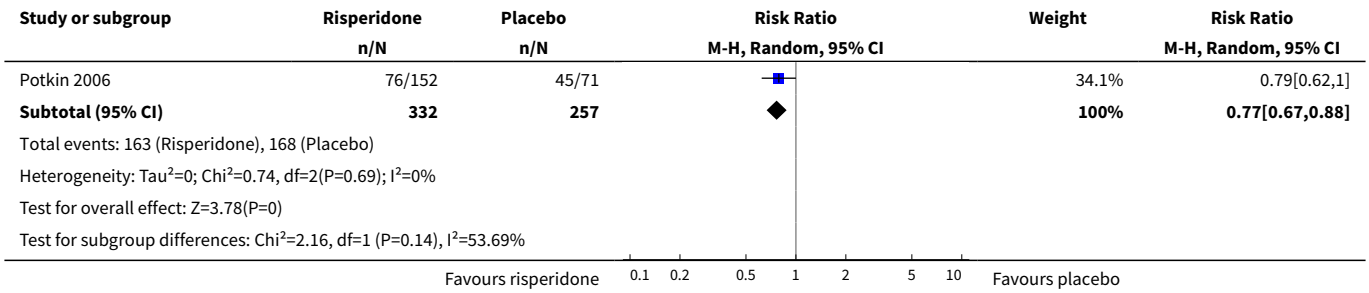


Comparison 3. SENSITIVITY ANALYSIS: RISPERIDONE vs PLACEBO (based on attrition)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental state: 1. no clinically significant response (defined by PANSS/BPRS) - short term (up to 12 weeks)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 defined by PANSS/BPRS <20% decline	6	864	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.52, 0.78]
1.2 defined by PANSS/BPRS <20% decline (without studies with >50% left the study early)	3	589	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.67, 0.88]

Analysis 3.1. Comparison 3 SENSITIVITY ANALYSIS: RISPERIDONE vs PLACEBO (based on attrition), Outcome 1 Mental state: 1. no clinically significant response (defined by PANSS/BPRS) - short term (up to 12 weeks).





ADDITIONAL TABLES

Table 1. Risperidone reviews

Comparison		Reference
Oral risperidone	vs other atypical drugs	Gilbody 2000; Komossa 2007
	vs olanzapine	Jayaram 2006
	vs typical drugs	Kennedy 2000; Hunter 2003
Depot risperidone		Hosalli 2003
Risperidone dose		Li 2009
Risperidone for acute aggression		Ahmed 2011

Table 2. Global Assessment of Functioning scale

Score	Judgement
91-100	Superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his or her many qualities. No symptoms.
81-90	Absent or minimal symptoms, good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns.
71-80	If symptoms are present they are transient and expectable reactions to psychosocial stresses; no more than slight impairment in social, occupational, or school functioning.
61-70	Some mild symptoms OR some difficulty in social, occupational, or school functioning, but generally functioning pretty well, has some meaningful interpersonal relationships.
51-60	Moderate symptoms OR any moderate difficulty in social, occupational, or school functioning.
41-50	Serious symptoms OR any serious impairment in social, occupational, or school functioning.
31-40	Some impairment in reality testing or communication OR major impairment in several areas, such as work or school, family relations, judgement, thinking, or mood.

Table 2. Global Assessment of Functioning scale *(Continued)*

21-30	Behavior is considerably influenced by delusions or hallucinations OR serious impairment in communications or judgment OR inability to function in all areas.
11-20	Some danger of hurting self or others OR occasionally fails to maintain minimal personal hygiene OR gross impairment in communication.
1-10	Persistent danger of severely hurting self or others OR persistent inability to maintain minimum personal hygiene OR serious suicidal act with clear expectation of death.
0	Not enough information available to provide GAF.

Table 3. Reviews suggested by excluded studies

Broad category of comparison	Intervention		Control	Excluded study/studies	Existing Cochrane reviews
Augmentation [of]	risperidone	by	antioxidants	Zhang 2002	-
			buflomedil	Zhong 2006	
			celecoxib	Riedel 2003	
			D-alanine	Tsai 2006	
			sarcosine	Tsai 2004	
			valproate	Wang 2003	
	clozapine		risperidone	McKenna 2004, Peuskens 2001a	
Long-acting preparation	depot risperidone	versus	olanzapine	Chue 2002	Hosalli 2003
			placebo	Cada 2004, Ciliberto 2005, Lauriello 2005, Nasrallah 2004a, Urioste 2004, NCT00249119	
Experimental compound	risperidone	versus	BL-1020	NCT01363349a	-
			LY2140023	NCT01086748a	
			PF-02545920	DeMartinis 2012a, NCT01175135a	
Versus another antipsychotic	risperidone	versus	amisulpride	Hwang 2003, Rein 2002, Peuskens 2001	Komossa 2010; Komossa 2007
			aripiprazole	Dubitsky 2002, Chan 2007, Hwang 2005, NCT00202007, Kane 2005	Khanna 2014; Komossa 2007
			asenapine	Fleming 2007a	Komossa 2007
			cariprazine	Bose 2010b	Protocol underway

Table 3. Reviews suggested by excluded studies *(Continued)*

			clozapine	Bondolfi 1998, Cavazzoni 2002a	Komossa 2007
			clocapramine	Yamawaki 1996	-
			haloperidol	Claus 1992, Friedman 2000, Lindstrom 1994, Lopez 1996, Lopez-Ibor 1992, NCT00253136, Peuskens 1995, Rabinowitz 2001, Wirshing 1995, Borison 1992a, Csernansky 1999	Hunter 2003
			molindone	McClellan 2009	Bagnall 2007
			olanzapine	Tollefson 1996, Edgell 2000, Tran 1997, Conley 1998, Harvey 2001, Brecher 1998, McClellan 2009, Cavazzoni 2002a, Cooper 1997, NCT00034892	Komossa 2007; Jayaram 2007
			quetiapine	Cooper 1997, NCT00034892	Asmal 2013; Komossa 2007
			sertindole	Kane 2005	Komossa 2009; Komossa 2007
			zuclopenthixol dihydrochloride	Lemmens 1994	Hunter 2003; Kumar 2005
Not risperidone	amisulpride	versus	placebo	Boyer 1995, Loo 1997	Mota 2002
	aripiprazole		haloperidol	Carson 2002	Bhattacharjee 2008
			olanzapine	Cornblatt 2002	Khanna 2014
			perphenazine	Gismondi 2004	Bhattacharjee 2008
			placebo	Carson 2002, Casey 2003	Belgamwar 2011
	haloperidol		placebo	Beasley 1996, Carson 2002, Crawford 1997	Adams 2013
	olanzapine		fluphenazine	Dossenbach 1997	Duggan 2005
			haloperidol	Beasley 1996, Crawford 1997, Gregor 2000, Kinon 1998, Lieberman 2005, Revicki 1996	
			paliperidone	Luo 2011	Komossa 2007; Nussbaum 2012
			placebo	Beasley 1996, Crawford 1997, Luo 2011	Protocol underway
	paliperidone		placebo	Luo 2011	Nussbaum 2012

Table 3. Reviews suggested by excluded studies *(Continued)*

Single vs polypharmacy	risperidone	versus	amisulpride + haloperidol	Peuskens 2001a	-
Miscellaneous	antipsychotic drugs	versus	miscellaneous (risperidone, olanzapine, quetiapine)	Weickert 2003	
	risperidone		valproate + miscellaneous antipsychotic drugs	Citrome 2004	
			riluzole (a drug used to treat amyotrophic lateral sclerosis)	Rujescu 2009a	
			talnetant (a neurokinin 3 receptor antagonist)	GlaxoSmithKline 2006a	

Table 4. Suggested design of study

Methods	Allocation: randomised, clearly described and concealed. Blinding: double, tested. Duration: 1 year or more.
Participants	Diagnosis: schizophrenia, schizotypal, schizoaffective, delusional disorder, acute psychosis, comorbid alcohol problems, and substance misuse. N = 300. Age: adults. Sex: men or women. History: perhaps once an early episode of moderate severity has subsided and after a period of stable washout of the medications used during the acute phase, living anywhere and not just in hospital.
Interventions	1. Risperidone: dose 4 mg/day or above. 2. Placebo.
Outcomes	Healthy days. Mental state: improved to important degree. Global state: improved to important degree, relapse. Service use: in hospital. Social functioning: employment status, relationships. Quality of life: improved to important degree. Economic outcomes: cost.
Notes	Free of all industry influence.

APPENDICES

Appendix 1. Previous search

The previous search phrases for the register via MeerKat (February 2008) were as follows:

[risperidone* or Risperdal* in title or *risperidone* or *risperdal* in abstract, index terms of REFERENCE] or [risperidone* in interventions of STUDY]

This register is compiled by systematic searches of major databases and their monthly updates, handsearches, and conference proceedings (see group module).

Appendix 2. Previous methods

Data collection and analysis

Selection of studies

We (RR, MJ) independently inspected all reports of identified studies. Any disagreements were resolved by consensus; where doubts remained, we acquired the full article. We independently decided whether these studies met the review criteria. We did not intend to blind the names of authors, institutions, and journal of publication. Again, we resolved any disagreements by consensus. When this was not possible, we sought further information and, in the interim, added these trials to the Studies awaiting classification list. RR and MJ independently inspected citations from the subsequent updated search (December 2007) and identified the relevant abstracts. We obtained and inspected full reports of the abstracts meeting the review criteria.

Data extraction and management

1. We (RR, MJ) independently extracted data and resolved any disagreements by discussion. When this was not possible, we sought further information from the trial authors.

1.1 Binary data
When summation was appropriate, with binary outcomes such as improved/not improved, we calculated the risk ratio statistic with a 95% confidence interval and used a random-effects model. In addition, as a measure of efficiency, we estimated the number needed to treat to benefit or the number needed to treat to harm from the pooled totals.

1.2. Continuous data
1.2.1 Normally distributed data
Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we applied the following standards to all data before inclusion: (a) standard deviations (SD) and means reported in the paper were obtained from the authors; (b) when a scale starts from the finite number 0, the SD, when multiplied by 2, is less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution) (Altman 1996); (c) if a scale started from a positive value (such as Positive and Negative Syndrome Scale, which can have values from 30 to 210), the calculation described above was modified to take the scale starting point into account. In these cases skew will be present if 2 SD > (S - S min), where S is the mean score and S min is the minimum score. Endpoint scores on scales often have a finite start and endpoint, and these rules can be applied to them. When continuous data are presented on a scale that includes a possibility of negative values (such as change on a scale), it is difficult to tell whether data are non-normally distributed (skewed) or not. We presented skewed data in the 'Other data' tables rather than included in the analysis.

For change data (endpoint minus baseline), the situation is even more problematic. In the absence of individual participant data, it is impossible to know if data are skewed, though this is likely. After consulting the ALLSTAT electronic statistics mailing list, we presented the change data in order to summarise the available information. In doing this, we assumed that data was not skewed or that the analyses can cope with the unknown degree of skew. Again, without individual participant data it was impossible to test this assumption. Where both change and endpoint data were available for the same outcome category, we presented only the endpoint data. We acknowledge that by doing this, much of the published change data can be excluded, but our argument is that endpoint data is more clinically relevant and that if change data were to be presented along with endpoint data, it would give undeserved equal prominence to both. We contacted the authors of studies that only reported change for endpoint figures.

1.2.2 Summary statistic
For continuous outcomes, we estimated a weighted mean difference between groups. Again, this was based on the random-effects model, as this took into account any differences between studies even if there was no statistically significant heterogeneity. We did not consider continuous data presented without use of summary statistics (that is mean, SD, standard error, median, interquartile range), although we noted the existence of these data in the text.

Assessment of risk of bias in included studies

Again working independently, review authors assessed risk of bias using the tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). This tool encourages consideration of how the sequence was generated, how allocation was concealed, the integrity of blinding at outcome, the completeness of outcome data, selective reporting, and other biases. We excluded studies where allocation was clearly not concealed.

We removed trials with high risk of bias (defined as at least three out of five domains categorised as 'no') from the 'included' category. When the raters disagreed, the final rating was made by consensus with the involvement of another review author. Where details of randomisation and other characteristics of trials were inadequate, we contacted authors of the studies to obtain further information. We reported non-concurrence in quality assessment.

Measures of treatment effect

Many rating scales are available to measure outcomes in mental health trials (Marshall 2000). These scales vary in quality, and many are poorly validated. It is generally accepted that measuring instruments should have the properties of reliability (the extent to which a test effectively measures anything at all) and validity (the extent to which a test measures that which it is supposed to measure). Before publication of an instrument, most scientific journals insist that its reliability and validity be demonstrated to the satisfaction of referees. As a minimum standard, we excluded data from unpublished rating scales. In addition, the rating scale was either: (i) a self report; or (ii) completed by an independent rater or relative. If continuous data were presented from different scales rating the same outcome, we presented all data without summation and inspected the general direction of effect.

Unit of analysis issues

To facilitate comparison between trials, we intended to convert variables (such as days in hospital) that can be reported in different metrics (mean days per year, per week, or per month) to a common metric (for example mean days per month). We converted weight gain reported in pounds to kilograms where possible.

Dealing with missing data

Where possible, we analysed the data on an intention-to-treat basis and assumed that those who had not been accounted for had the less positive outcome. We did not include this rule for the outcome of 'death'. We intended to test this assumption with a sensitivity analysis. For continuous data, which was impossible to manage in this way, we presented only the 'completer' data. Wherever feasible, we converted the continuous scores to dichotomous data.

If, for a given outcome (except adverse effects), more than 50% of the total numbers randomised were not accounted for, we did not present the results, as such data are impossible to interpret with authority. If, however, more than 50% of those in one arm of a study were lost, but the total loss was less than 50%, we marked such data with '*' to indicate that such result may well be prone to bias.

Assessment of heterogeneity

Firstly, we considered all the included studies within any comparison to judge clinical heterogeneity. We then visually inspected the graphs in order to investigate the possibility of statistical heterogeneity; to supplement this we used, primarily, the I^2 statistic, which provides an estimate of the percentage of variability due to heterogeneity rather than due to chance alone. Where the I^2 estimate was greater than or equal to 75%, we interpreted this as indicating the presence of high levels of heterogeneity (Higgins 2003). If inconsistency became high, we did not summate data, but presented it separately, and we investigated the reasons for heterogeneity.

Assessment of reporting biases

In order to investigate the likelihood of overt publication bias, we entered all data from all identified and selected trials into a funnel graph (trial effect against trial size) (Egger 1997).

Data synthesis

Where possible, we entered data in such a way that the area to the left of the line of no effect indicated a favourable outcome for risperidone. Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice), but analysis and pooling of clustered data pose problems. Firstly, authors often fail to account for intraclass correlation (ICC) in clustered studies, leading to a 'unit of analysis' error (Divine 1992), whereby P values are spuriously low, confidence intervals are unduly narrow, and statistical significance gets overestimated. This causes type I errors (Bland 1997, Gulliford 1999).

Where clustering was not accounted for in primary studies, we presented the data in a table with a (*) symbol to indicate the presence of a probable unit of analysis error. In subsequent versions of the review, we will seek out first authors of studies to obtain ICC of their clustered data and use accepted methods to adjust for this (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we also presented these data as if from a non-cluster randomised study, but adjusted for the clustering effect. We have sought statistical advice and have been advised that the binary data presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the ICC Design effect = 1 + (m - 1)*ICC (Donner 2002). If the ICC was

not reported, we assumed it to be 0.1 (Ukoumunne 1999). If cluster studies had been appropriately analysed, taking into account ICCs, and relevant data documented in the report, we synthesised these with other studies using the generic inverse variance technique.

Subgroup analysis and investigation of heterogeneity

If data were clearly heterogeneous, we checked that they had been extracted and entered correctly, and that we had made no unit of analysis errors. If the high levels of heterogeneity remained, we did not undertake a meta-analysis at this point, because if there is considerable variation in results, and particularly if there is inconsistency in the direction of effect, it may be misleading to quote an average value for the intervention effect. We prespecified no characteristics of studies that may be associated with heterogeneity except quality of trial method.

Sensitivity analysis

If studies had high attrition rates, we analysed the effect of including these studies in a sensitivity analysis, but we did not include any figures with more than 50% attrition in the analysis of efficacy. Where a trial was described as 'double-blind', but it was implied that the study was randomised, we intended to include such studies in the sensitivity analysis, but we did not come across any such studies.

F E E D B A C K

Response to comments, 21 February 2013

Summary

Hutton 2012 has highlighted the following issues regarding this review:

1. 'Fixed effect' analysis was used instead of 'random effects' analysis for the outcome of 20% change in total PANSS/BPRS scores.

2. Should not have included Marder 1994a in our analysis, as the overall attrition rate for this study was over 50%.

3. Should not have included Borison 1992 study in our analysis, as an internal confidential report by Janssen Pharmaceuticals reports a different leaving the study early rate than that of the original published paper.

4. It is incorrect to derive standard deviation from standard error in Chouinard 1992, and data were entered wrong way round for two outcomes: endpoint Brief Psychiatric Rating Scale (BPRS) total score and Positive and Negative Syndrome Scale (PANSS) positive symptom score.

5. Honer 2006 should not have contributed to outcome 'no clinically significant improvement (CGI-S)', as they had used only PANSS scores.

Reply

Thank you for your comments.

We have now repeated the analysis for the outcome 20% change in total PANSS/BPRS score by using 'random effects' model instead of fixed effects. With the 'fixed effects' analysis RR was 0.7 favouring risperidone and with 'random effect' analysis the RR is 0.68 favouring risperidone and hence there is no change in the overall outcome.

As regards the Marder 1994a study, it has an overall attrition rate of over 50%. However this study has three arms of risperidone and we included data from only the 6mg arm as this was closest to what is clinically most commonly used. This intervention arm of 6mg per day of risperidone had an attrition rate of 45% (page 828, American Journal of Psychiatry, 151:6 June 1994). The attrition rate for this particular arm was less than 50% and hence this was included.

The attrition rate in Borison 1992 as reported by the original published paper is zero. This did appear too good to be true, however our attempts to contact the authors were unsuccessful and we did not have access to any other data. We would be keen to have a look at the internal confidential report by Janssen if this indeed reports a different drop out rate and would be grateful if anyone with access to this can forward the data to the authors.

For data extraction from the Chouinard 1992 study, we have used formula recommended by the Cochrane Handbook to derive Standard Deviation Higgins 2008. The authors checked Chouinard 1992 data and are assured that we have reported it accurately in our review. The paper reports the figures for the number of patients showing more than 20% improvement in BPRS/PANSS but in our review we have extrapolated the figures for '<20% decrease in PANSS/BPRS total score'. Although the primary publication for Honer 2006 reports only the PANSS scores, we found additional published data (International Congress of Schizophrenia Research 2005, page 487) which provides data on CGI-S scores.

Contributors

Dr Ranganath Rattehalli and Dr Mahesh Jayaram

Response to email, 3 March 2013

Summary

Paul Hutton from the Psychosis Research Unit, Psychology Department, Greater Manchester West Mental Health Trust, UK, has sent an email to the authors of this review wherein he claims that the review authors should not have included the two clozapine augmentation studies in the review (Yagcioglu 2005 and Honer 2006), or should have analysed these separately.

Reply

We acknowledge that the two clozapine augmentation studies could have been analysed separately. We have thus now analysed our results with and without these two studies, and the results of this sensitivity analysis are as follows.

2.1 Leaving the study early - for any reason

With the clozapine augmentation studies the results are: 11 RCTs, N = 1363, RR 0.7 (0.57, 0.86), favours risperidone. Without the clozapine augmentation studies the results are: 9 RCTs, N = 1265, RR 0.69 (0.56, 0.85), still favours risperidone. Exclusion of clozapine augmentation studies makes no difference to this outcome.

2.2 Leaving study early - due to adverse effects

With the clozapine augmentation studies the results are: 6 RCTs, N = 829, RR 1.09 (0.43, 2.74), not statistically significant. Without the clozapine augmentation studies the results are: 5 RCTs, N = 761, RR 1.03 (0.38, 2.81), still not statistically significant. Exclusion of the clozapine augmentation studies makes no difference to this outcome.

2.3 Leaving the study early - due to withdrawal of consent

With the clozapine augmentation studies the results are: 4 RCTs, N = 368, RR 1.2 (0.44, 3.28), not statistically significant. Without the clozapine augmentation studies the results are: 3 RCTs, N = 300, RR 1.39 (0.48, 4.00), still not statistically significant. Exclusion of the clozapine augmentation study makes no difference to this outcome.

2.4 Global state - no clinically significant improvement (CGI-Severity)

With the clozapine augmentation studies the results are: 3 RCTs, N = 397, RR 0.8 (0.55, 1.15), not statistically significant. Without the clozapine augmentation studies the results are: 2 RCTs, N = 329, RR 0.67 (0.46, 0.98), favours risperidone. Exclusion of the clozapine augmentation study changes the result in favour of risperidone for this outcome.

2.5 Global state - average endpoint score (CGI-Severity)

With the clozapine augmentation studies the results are: 4 RCTs, N = 266, WMD -0.29 (-1.18, 0.59), not statistically significant. Without the clozapine augmentation studies the results are: 2 RCTs, N = 171, WMD -1.01 (-1.38, -0.64), favours risperidone. Exclusion of the clozapine augmentation study changes the result in favour of risperidone for this outcome.

2.6 Global state - average endpoint score (GAF score)

Akdede 2006 (clozapine augmentation study) is the only study favouring risperidone for this outcome.

2.7 Mental state - < 20% decline on PANSS total change score

With the clozapine augmentation studies the results are: 4 RCTs, N = 407, RR 0.64 (0.39, 1.04), not statistically significant. Without the clozapine augmentation studies the results are: 3 RCTs, N = 339, RR 0.54 (0.4 0.74), favours risperidone. Exclusion of clozapine augmentation study changes the result in favour of risperidone for this outcome.

2.8 Mental state - < 20% decrease in PANSS/BPRS total change score

With the clozapine augmentation studies the results are: 7 RCTs, N = 856, RR 0.7 (0.62, 0.79), favours risperidone. Without the clozapine augmentation studies the results are: 6 RCTs, N = 788, RR 0.66 (0.58, 0.76), favours risperidone. Exclusion of clozapine augmentation study makes no difference to this outcome.

2.9 Mental state - average endpoint score (PANSS Total score)

With the clozapine augmentation studies the results are: 4 RCTs, N = 266, WMD -7.55 (-22.04, 6.95), not statistically significant. Without the clozapine augmentation studies the results are: 2 RCTs, N = 171, WMD -20.13 (-27.33, ...), favours risperidone. Exclusion of the clozapine augmentation studies changes the result in favour of risperidone for this outcome.

2.10 Mental state - average endpoint score (PANSS General score)

With the clozapine augmentation studies the results are: 2 RCTs, N = 74, WMD -5 (-20.37, 10), not statistically significant. Without the clozapine augmentation studies the results are: 1 RCT, N = 44, WMD -13.2 (-20.15, ...), favours risperidone. Exclusion of the clozapine augmentation study leaves only one RCT for this outcome, which is in favour of risperidone.

2.11 Mental state - average endpoint score (PANSS Negative symptom score)

With the clozapine augmentation studies the results are: 4 RCTs, N = 266, WMD -0.9 (-3.06, 1.27), not statistically significant. Without the clozapine augmentation studies the results are: 2 RCTs, N = 171, WMD -2.84 (-4.96, -0.73), favours risperidone. Exclusion of the two clozapine augmentation studies changes this outcome in favour of risperidone.

2.12 Mental state - average endpoint score (PANSS Positive symptom score)

With the clozapine augmentation studies the results are: 4 RCTs, N = 266, WMD 1.67 (-2.93, 6.28), not statistically significant. Without the clozapine augmentation studies the results are: 2 RCTs, N = 171, WMD 1.52 (-12.69, 15.73), still not statistically significant. Exclusion of the two clozapine augmentation studies does not change this outcome.

Thus, in summary, exclusion of the two clozapine augmentation studies either makes no difference to the main outcomes or shifts the results slightly more in favour of risperidone on some of the outcomes related to mental state. These augmentation studies contribute to less than 20% of the data, and we feel that it is only fair to include them in the review, as in real life many more people with schizophrenia are going to be on a combination of antipsychotics.

Contributors

Dr Ranganath Rattehalli and Dr Mahesh Jayaram

WHAT'S NEW

Date	Event	Description
13 September 2016	New citation required but conclusions have not changed	Results of update searching added to review. Five new trials added to included studies table. Data from these new trials did not change overall results or conclusions of review.
19 October 2015	New search has been performed	Update search run and 25 references assessed, 2 new studies included.
15 October 2013	Amended	Update search carried out 2013, 69 references assessed, 3 new studies included.
15 March 2013	Feedback has been incorporated	Comments reported in Hutton 2012 regarding including trials with high attrition addressed, sensitivity analysis completed and added to feedback section. Overall results and conclusion of review are unaffected.

HISTORY

Protocol first published: Issue 1, 2008
Review first published: Issue 1, 2010

Date	Event	Description
3 March 2013	Amended	See feedback section for amendments.
21 February 2013	Amended	See feedback section for details.

CONTRIBUTIONS OF AUTHORS

RR: Initiated the review, developed the background and protocol, selected studies and extracted data, and wrote the findings of the original 2008 review, helped with 2015 update writing.
SZ: Screened search results, extracted data for the 2015 update search and wrote the report.
BL: Screened search results and extracted data for the 2015 update search.

MJ: Helped with developing the background and protocol, cross checked data extraction, and wrote the findings of the original 2008 review, draft checking 2015 update.
JX: Screened search results, extracted data, and participated in report writing for the 2015 update.
SS: Screened and data extraction for 2013 search.

DECLARATIONS OF INTEREST

RR: none known.
SZ: none known.
BL: none known.
MJ: none known.
JX: none known.
SS: none known.

SOURCES OF SUPPORT

Internal sources

- Leeds Partnerships NHS Foundation Trust, UK.

External sources

- University of Nottingham, UK.
- Cochrane Collaboration Programme Grant 2011, UK.

  Reference number: 10/4001/15

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The methods section of the protocol was updated to reflect the Cochrane Schizophrenia Group's standardised method section (see Appendix 2 for previous methods). We altered the structure of the protocol outcomes to match the structure in the data and analyses table; however, we have not changed outcomes.

NOTES

None

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Antipsychotic Agents [*administration & dosage] [adverse effects]; Placebos [therapeutic use]; Publication Bias; Randomized Controlled Trials as Topic; Risperidone [*administration & dosage] [adverse effects]; Schizophrenia [*drug therapy]

MeSH check words

Humans