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Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation) (Review)

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[Intervention Review]

Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

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ABSTRACT

Background

Aggressive, agitated or violent behaviour due to psychosis constitutes an emergency psychiatric treatment where fast-acting interventions are required. Risperidone is a widely accessible antipsychotic that can be used to manage psychosis-induced aggression or agitation.

Objectives

To examine whether oral risperidone alone is an effective treatment for psychosis-induced aggression or agitation.

Search methods

We searched the Cochrane Schizophrenia Group's Study-Based Register of Trials (up to April 2017); this 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. There are no language, date, document type, or publication status limitations for inclusion of records into the register.

Selection criteria

Randomised controlled trials (RCTs) comparing rapid use of risperidone and other drugs, combinations of drugs or placebo for people exhibiting aggression or agitation (or both) thought to be due to psychosis.

Data collection and analysis

We independently inspected all citations from searches, identified relevant abstracts, and independently extracted data from all included studies. For binary data we calculated risk ratio (RR) and for continuous data we calculated mean difference (MD), all with 95% confidence intervals (CI) and used a fixed-effect model. We assessed risk of bias for the included studies and used the GRADE approach to produce a 'Summary of findings' tables.

Main results

The review now contains data from nine trials (total n = 582) reporting on five comparisons. Due to risk of bias, small size of trials, indirectness of outcome measures and a paucity of investigated and reported 'pragmatic' outcomes, evidence was graded as very-low quality. None of the included studies provided useable data on our primary outcome 'tranquillisation or asleep' by 30 minutes, repeated need for tranquillisation or any economic outcomes. Data were available for our other main outcomes of agitation or aggression, needing restraint, and incidence of adverse effects.

Risperidone versus haloperidol (up to 24 hours follow-up)

For the outcome, specific behaviour - agitation, no clear difference was found between risperidone and haloperidol in terms of efficacy, measured as at least 50% reduction in the Positive and Negative Syndrome Scale - Psychotic Agitation Sub-score (PANSS-PAS) (RR 1.04, 95% CI 0.86 to 1.26; participants = 124; studies = 1; very low-quality evidence) and no effect was observed for need to use restraints (RR 2.00, 95% CI 0.43 to 9.21; participants = 28; studies = 1; very low-quality evidence). Incidence of adverse effects was similar between treatment groups (RR 0.94, 95% CI 0.54 to 1.66; participants = 124; studies = 1; very low-quality evidence).

Risperidone versus olanzapine

One small trial (n = 29) reported useable data for the comparison risperidone versus olanzapine. No effect was observed for agitation measured as PANSS-PAS endpoint score at two hours (MD 2.50, 95% CI -2.46 to 7.46; very low-quality evidence); need to use restraints at four days (RR 1.43, 95% CI 0.39 to 5.28; very-low quality evidence); specific movement disorders measured as Behavioural Activity Rating Scale (BARS) endpoint score at four days (MD 0.20, 95% CI -0.43 to 0.83; very low-quality evidence).

Risperidone versus quetiapine

One trial reported (n = 40) useable data for the comparison risperidone versus quetiapine. Aggression was measured using the Modified Overt Aggression Scale (MOAS) endpoint score at two weeks. A clear difference, favouring quetiapine was observed (MD 1.80, 95% CI 0.20 to 3.40; very-low quality evidence). No evidence of a difference between treatment groups could be observed for incidence of akathisia after 24 hours (RR 1.67, 95% CI 0.46 to 6.06; very low-quality evidence). Two participants allocated to risperidone and one allocated to quetiapine experienced myocardial ischaemia during the trial.

Risperidone versus risperidone + oxcarbazepine

One trial (n = 68) measured agitation using the Positive and Negative Syndrome Scale - Excited Component.(PANSS-EC) endpoint score and found a clear difference, favouring the combination treatment at one week (MD 2.70, 95% CI 0.42 to 4.98; very low-quality evidence), but no effect was observed for global state using Clinical Global Impression - Improvement (CGI-I) endpoint score at one week (MD -0.20, 95% CI -0.61 to 0.21; very-low quality evidence). Incidence of extrapyramidal symptoms after 24 hours was similar between treatment groups (RR 1.59, 95% CI 0.49 to 5.14; very-low quality evidence).

Risperidone versus risperidone + valproic acid

Two trials compared risperidone with a combination of risperidone plus valproic acid. No clear differences between the treatment groups were observed for aggression (MOAS endpoint score at three days: MD 1.07, 95% CI -0.20 to 2.34; participants = 54; studies = 1; very low-quality evidence) or incidence of akathisia after 24 hours: RR 0.75, 95% CI 0.28 to 2.03; participants = 122; studies = 2; very low-quality evidence).

Authors' conclusions

Overall, results for the main outcomes show no real effect for risperidone. The only data available for use in this review are from nine under-sampled trials and the evidence available is of very low quality. This casts uncertainty on the role of risperidone in rapid tranquillisation for people with psychosis-induced aggression. High-quality pragmatic RCTs are feasible and are needed before clear recommendations can be drawn on the use of risperidone for psychosis-induced aggression or agitation.

PLAIN LANGUAGE SUMMARY

Risperidone as a means of calming people who are aggressive or agitated due to psychosis

Background

People with psychosis may experience hearing voices (hallucinations) or abnormal thoughts (delusions), which can make the person frightened, distressed, and agitated. Experiencing such emotions can sometimes lead to aggressive behaviour. This poses a challenge and dilemma for staff. Mental health professionals have to diagnose and deliver the best available treatment to prevent the risk of harm to both the patient and/or others, the faster the better. Risperidone is a medication taken by mouth, widely used for treating people manage the symptoms of psychosis. As well as being an antipsychotic (preventing psychosis), it also could calm people down or help them to sleep.

Aim of the review

This review looks at whether the antipsychotic, risperidone, could be a fast, effective treatment for people who are agitated or aggressive as a result of having psychosis.

Searches

The Information Specialist of Cochrane Schizophrenia ran searches of their specialised register for randomised trials that looked at the effects of giving risperidone alone compared with giving either placebo (dummy treatment) or other treatments to people who are aggressive or agitated as a results of having psychosis. The latest date of searching was April 2017.

Results

Nine studies, with 582 participants, are included in the review but the information provided is poor in quality and tended to provide information only partially relevant to the main aim of this review, particularly a lack of information regarding immediate (i.e. under one hour after treatment) calming effects and the need for repeated tranquillisation. Economic data were also not reported. In the trials, risperidone was compared to other antipsychotics, which included haloperidol, olanzapine and quetiapine. The review found risperidone was no better or worse than haloperidol for calming aggression within 24 hours, and that two weeks after treatment, people receiving risperidone had higher (worse) scores on scales measuring levels of aggression than those receiving quetiapine. Both these results, however, were graded as very low-quality evidence. One small study found a combination of antipsychotics (risperidone plus oxcarbazepine) was better than risperidone alone at reducing levels of agitation but these data were collected after one week and again, this evidence was rated as very low quality. No clear differences in the incidence of side effects such as movement disorders were observed.

Conclusions

The review authors conclude that at the moment, there is weak, unclear evidence regarding the use of risperidone for calming people who are aggressive due to psychosis, and no firm conclusions can be made. Therefore, health professionals and people with mental health problems are left without clear evidence-based guidance. However, good quality trials are possible and more research is needed to help people dealing with psychosis-induced aggression consider and understand which medication is better at calming aggression, has fewer side effects and works quickly.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

RISPERIDONE compared to OTHER ANTIPSYCHOTIC: a. HALOPERIDOL for psychosis-induced aggression or agitation (rapid tranquillisation)

Patient or population: psychosis-induced aggression or agitation (rapid tranquillisation)
Setting: Psychiatric acute care units.
Intervention: RISPERIDONE
Comparison: OTHER ANTIPSYCHOTIC: a. HALOPERIDOL

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with OTHER ANTIPSYCHOTIC: a. HALOPERIDOL	Risk with RISPERIDONE				
Tranquillisation or asleep by 30 minutes - not measured	-	-	-	-	-	
Repeated need for tranquillisation within 24 hours - not measured	-	-	-	-	-	
Specific behaviour: agitation, up to 24 hours (PANSS-PAS response) assessed with: ≥50% reduction on PANSS-PAS baseline score	Study population		RR 1.04 (0.86 to 1.26)	124 (1 RCT)	⊕◯◯◯ VERY LOW [123]	
	758 per 1.000	788 per 1.000 (652 to 955)				
Global outcome: need for additional measures assessed with: use of restraints	Study population		RR 2.00 (0.43 to 9.21)	28 (1 RCT)	⊕◯◯◯ VERY LOW [2345]	
	143 per 1.000	286 per 1.000 (61 to 1.000)				

Adverse effects: up to 24 hours assessed with: one or more AEs	Study population		RR 0.94 (0.54 to 1.66)	124 (1 RCT)	⊕◯◯◯ VERY LOW [1,2,3]
	290 per 1.000	273 per 1.000 (157 to 482)			
Economic outcomes - not measured	-	-	-	-	-

*__The risk in the intervention group__ (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: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Risk of bias - rated 'very serious': high risk of performance and 'selective reporting' bias. Definition of the outcomes are not consistent between the multiple publications.
[2] Imprecision - rated 'serious': Optimal Information Size (OIS) criterion not met.
[3] Only one study available.
[4] Risk of bias - rated 'very serious': high risk of attrition bias and 'selective reporting' bias.
[5] Indirectness - rated 'serious': provided outcome is at a time point (4 days) different from those of primary importance in this setting.

BACKGROUND

Description of the condition

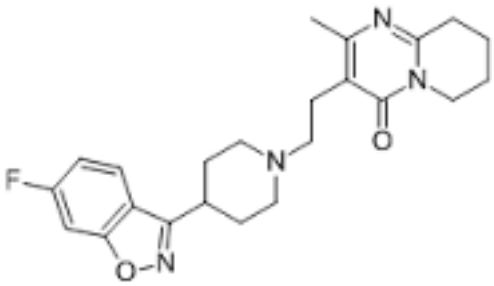
Aggression has been defined by NICE 2005 as a willingness to inflict harm, whether behavioural or verbally expressed, and regardless of whether physical harm is sustained. Violence has been described as the intentional use of physical force whether threatened or actual, against oneself, another person, a group, or community, that results in, or is likely to result in injury, death, psychological harm, maldevelopment or deprivation (WHO 2002; Wright 2002). Aggression is not a diagnosis in itself, but can be a feature of several mental health conditions. There is a well-established significant relationship between psychosis and violence (Arseneault 2000; Brennan 2000; Fazel 2006). Agitated or violent behaviour constitutes roughly 10% of all emergency psychiatric treatment (Tardiff 1982). Overall, the prevalence of violence in people who have schizophrenia, major depression or manic/bipolar disorder is about 11% to 13%. An even higher percentage of people with alcoholism (25%) or substance misuse (35%) have, at some stage, presented with violence or aggression. Even when additional factors such as alcohol and drug use are taken into account, psychotic symptoms such as delusions or hallucinations are significantly and strongly associated with aggressive and violent behaviour (Swanson 1990). Low GABA (gamma-aminobutyric acid) and serotonin levels in various parts of the brain have been suggested to be associated with aggressive behaviour whilst enhanced norepinephrine and dopamine levels with increased aggression (Bazire 2009).

Description of the intervention

There are many guidelines that describe the management of people with aggression and violence. (APA 2004; Addington 2005; NICE 2015). NICE guidelines recommend preventative measures such as observation, de-escalation and use of p.r.n. (i.e.: *pro re nata*, as needed) medication should initially be used. If these measures fail to calm the agitated individual, restrictive measures including seclusion and manual/mechanical restraint, may be pursued. Individuals unable or unwilling to consent to treatment may require rapid tranquillisation with lorazepam on its own or intramuscular haloperidol combined with intramuscular promethazine.

Risperidone was the first novel second-generation antipsychotic and has been widely available since the 1990s ($C_{23}H_{27}FN_4O_2$, Figure 1). The main pharmacological activities of risperidone include serotonin 5-HT2 receptor blockade and dopamine D2 antagonism (Megens 1994), and it has therefore been suggested that atypical antipsychotics could have an anti-aggressive effect (Buckley 1999). Risperidone is licensed in the UK for the treatment of psychotic conditions in which positive or negative symptoms are prominent, to maintain clinical improvement during continuation therapy in patients who have shown an initial treatment response, and for the treatment of mania in bipolar disorder (BNF 2017).

Figure 1. Risperidone structure



Risperidone and aripiprazole are the only two antipsychotics having FDA (Food and Drug Administration) approval for irritability associated with autistic disorder in children (Mathis 2009). Risperidone is also licensed in the UK for psychosis, persistent aggression in conduct disorder and severe aggression in autism in children (BNF 2017). A Cochrane review on atypical antipsychotics for aggression and psychosis in Alzheimer's disease found that the adverse events associated with risperidone may outweigh the benefits and suggested that risperidone should only be used for treating aggression in those with dementia when there is severe distress or risk of physical harm (Ballard 2006). Risperidone is now licensed in the UK at a low dose for the short-term management of aggression in Alzheimer dementia which is unresponsive to non-

pharmacological interventions (BNF 2017). Katz 1999 also found that 1 mg/day of risperidone was useful in controlling aggression in severe dementia.

Risperidone has atypical properties especially at lower doses but can become more 'conventional' at high doses (Stahl 2008). Risperidone has been found to be associated with more adverse effects such as extrapyramidal side effects, hyperprolactinaemia and sexual dysfunction than other antipsychotics (Tran 1997). A double-blind study looking at risperidone use in schizophrenia found that although hyperprolactinaemia is significantly associated with long-term risperidone use, symptoms related to high prolactin levels are rare (Conley 2001). Risperidone has been found to cause weight gain, but the link is not as significant as with olanzapine (Conley 2001) and clozapine (Wirshing 1999). Respiridone may cause a disproportionate increase in weight gain in adolescents compared to adults, which is a key area in non-compliance in this group (Fleischhaker 2007). Risperidone was the first atypical antipsychotic that became available in a long-term depot injectable formulation lasting for two weeks. Such dosage formulations may improve compliance, and if compliance is enhanced, may lead to better long-term outcomes. The difficulty is patient volunteers are generally co-operative and studies therefore do not address efficacy of depot injection in the non-compliant patient population. (Sampson 2016).

How the intervention might work

Among the atypical antipsychotics, risperidone has one of the simplest pharmacological profiles and comes closest to a serotonin-dopamine antagonist. Risperidone is a benzisoxazole derivative which blocks dopamine$_2$ receptors and 5HT$_2$ receptors (with a high ratio of serotonin to D2 receptor blockade). It also blocks alpha1 and alpha2 adrenoceptors, H1 receptors, and has no effect on beta adrenoceptors, muscarinic cholinoceptors or peptidergic receptors (Janssen 1988). Psychosis is considered to be associated with disturbances in the activity of neurotransmitters, dopamine in particular, in the brain. Risperidone has therefore been suggested to work by blocking the receptors in the brain that dopamine acts on, which prevents the excessive activity of dopamine and helps to control aggression or agitation. Czobor 1995 suggested that the combination of risperidone on the serotonergic and dopaminergic systems may underlie risperidone's effect on hostility.

Aleman 2001 found some evidence that risperidone is useful in reducing aggression in schizophrenia; although there is some conflicting evidence, risperidone may have less of a sedative effect than conventional antipsychotics, which in turn suggests the anti-aggressive effects of risperidone is not mediated by sedation. Compared with conventional antipsychotics such as haloperidol, risperidone produces some significantly better results according to Positive and Negative Syndrome Scale (PANSS) scores (Hunter 2003).

Why it is important to do this review

Mental health problems impose a significant burden in developing countries (Shah 2000). As about 1% of any population suffers from schizophrenia (Sartorius 1972), and around 80% of the world live in developing countries (CIA 2008), most care of people with serious mental illnesses such as schizophrenia must take place in these low- and middle-income country situations. There is no evidence that the prevalence of psychiatric emergencies differ across the globe and it seems reasonable to assume that most episodes of severe aggression and agitation in people with severe mental health problems will be taking place in low- and middle-income countries. In many of these countries expensive antipsychotic drugs may be available, but they are generally not affordable (WPA 2008).

Aronson 1997 conducted a review looking at the cost-effectiveness and quality of life of patients before and after commencing risperidone treatment and found that risperidone improved symptoms of psychosis, decreased the need for hospitalisation and improved quality of life. Viale 1997 also investigated the cost-effectiveness of risperidone before and after commencing treatment in patients with schizophrenia and found days in hospital were reduced by 26%, but there was a 3.4% increase in total psychiatric healthcare costs.

The fast-dissolving risperidone tablet formulation may be useful to ensure administration. These 'orodispersible' tablets are an option in acutely agitated psychosis (Normann 2006), and can be as effective as an alternative to intramuscular antipsychotics (Currier 2001). Despite being regularly used for the management of psychosis-induced agitation, we know of no systematic reviews on the use of risperidone in the emergency situation. This is one of a series of linked reviews (Table 1).

OBJECTIVES

To examine whether risperidone is an effective treatment for psychosis-induced aggression or agitation.

METHODS

Criteria for considering studies for this review

Types of studies

We included all relevant randomised controlled trials (RCTs). If a trial had been described as 'double-blind' but had implied randomisation and the demographic details of each group had been similar, we would have included it. We excluded quasi-randomised studies, such as those allocated by using alternate days of the week.

Types of participants

People exhibiting aggression or agitation (or both) thought to be due to psychosis, regardless of age and sex. Studies that also involved people with other diagnoses, such as drug or alcohol intoxication, organic problems including dementia, non-psychotic mental illnesses or learning disabilities, were included as long as the majority of participants (> 50%) were experiencing psychosis. We are interested in making sure that information is as relevant to the current care of people with schizophrenia as possible, so, if reported, would clearly highlight the current clinical state (acute, early post-acute, partial remission, remission) as well as the stage (prodromal, first episode, early illness, persistent). In addition, where possible, we would report whether the studies primarily focused on people with particular problems (for example, negative symptoms, treatment-resistant illnesses).

Types of interventions

1. Risperidone

Given alone, any dose and mode of administration.

2. Other antipsychotic medications

Given alone, any dose and mode of administration.

3. Placebo

Active or non-active.

Types of outcome measures

Where possible, we grouped outcomes by time: by 30 minutes, up to two hours, up to four hours, up to 24 hours, and over 24 hours.

Primary outcomes

1. Not tranquil or asleep

1.1 Not tranquil or asleep - by up to 30 minutes

2. Adverse events

Secondary outcomes

1. Tranquillisation or asleep

1.1 Not tranquil
1.2 Not asleep
1.3 Time to tranquillisation/sleep
1.4 Time to tranquillisation
1.5 Time to sleep

2. Specific behaviours

2.1 Self-harm, including suicide
2.2 Injury to others
2.3 Agitation
2.3.1 Another episode of agitation by 24 hours
2.3.2 No clinically important change in agitation
2.3.3 Any change in agitation
2.4 Aggression
2.4.1 Another episode of aggression by 24 hours
2.4.2 No clinically important change in aggression
2.4.3 No change in aggression
2.4.4 Average endpoint aggression score
2.4.5 Average change in aggression scores

3. Global outcomes

3.1 No overall improvement
3.2 Use of additional medication
3.3 Use of restraints/seclusion
3.4 Relapse - as defined by each study
3.5 Recurrence of violent incidents
3.6 Needing extra visits from the doctor
3.7 Refusing oral medication
3.8 Not accepting treatment
3.9 Average endpoint score
3.10 Average change score
3.11 Average dose of drug

4. Service outcomes

4.1 Duration of hospital stay
4.2 Re-admission
4.3 No clinically important engagement with services
4.4 No engagement with services
4.5 Average endpoint engagement score
4.6 Average change in engagement scores

5. Mental state

5.1 No clinically important change in general mental state
5.2 No change in general mental state
5.3 Average endpoint general mental state score
5.4 Average change in general mental state scores

6. Adverse effects

6.1 Death
6.2 Any general adverse effects
6.3 Any serious specific adverse effects
6.4 Average endpoint general adverse effect score
6.5 Average change in general adverse effect scores
6.6 Clinically important change in specific adverse effects
6.7 Any change in specific adverse effects
6.8 Average endpoint specific adverse effects
6.9 Average change in specific adverse effects

7. Leaving the study early

7.1 For specific reasons
7.2 For general reasons

8. Satisfaction with treatment

8.1 Recipient of treatment not satisfied with treatment
8.2 Recipient of treatment average satisfaction score
8.3 Recipient of treatment average change in satisfaction scores
8.4 Informal treatment provider not satisfied with treatment
8.5 Informal treatment providers' average satisfaction score
8.6 Informal treatment providers' average change in satisfaction scores
8.7 Professional providers not satisfied with treatment
8.8 Professional providers' average satisfaction score
8.9 Professional providers' average change in satisfaction scores

9. Acceptance of treatment

9.1 Not accepting treatment
9.2 Average endpoint acceptance score
9.3 Average change in acceptance score

10. Quality of life

10.1 No clinically important change in quality of life
10.2 Not any change in quality of life
10.3 Average endpoint quality of life score
10.4 Average change in quality of life scores
10.5 No clinically important change in specific aspects of quality of life
10.6 No change in specific aspects of quality of life
10.7 Average endpoint specific aspects of quality of life
10.8 Average change in specific aspects of quality of life

11. Economic outcomes

11.1 Direct costs
11.2 Indirect costs

Outcomes used for 'Summary of findings' table

We used the GRADE approach to interpret findings (Schünemann 2011) and used GRADEpro GDT to create 'Summary of findings' tables. These tables provide outcome-specific information concerning the overall quality of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rated as important to patient-care and decision making. We included the following outcomes in the 'Summary of findings' table:

1. tranquillisation or asleep - by 30 minutes;
2. repeated need for rapid tranquillisation - within 24 hours;
3. specific behaviours - agitation or aggression;
4. global state - needing restraints or seclusion;
5. adverse events - serious adverse effects (not death);
6. economic outcomes.

For assessments of the overall quality of evidence for each outcome that included pooled data from RCTs only, we downgraded the evidence from 'high quality' by one level for 'serious' (or by two for 'very serious') study limitations (risk of bias), indirectness of evidence, inconsistency, imprecision of effect estimates or potential publication bias.

Search methods for identification of studies

No language restriction was applied within the limitations of the search tools.

Electronic searches

Cochrane Schizophrenia Group Study-Based Register of Trials

The Information Specialist searched the register (up to 12 April 2017) using the following phrase:
(*rispe* or *9-OH-risperid* or *r 64766* in intervention of STUDY) AND (*aggress* or *violen* or *agitation* or *tranq* in title, abstract, index terms of REFERENCE or intervention of STUDY)
In such a study-based register, searching the major concept retrieves all the synonyms and relevant studies because all the studies have already been organised based on their interventions and linked to the relevant topics.
This 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' s Module). There are no language, date, document type, or publication status limitations for inclusion of records into the register.

Searching other resources

1. Reference searching

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

2. Personal contact

Where necessary, we contacted the first author of each included study for information regarding unpublished trials.

Data collection and analysis

Selection of studies

1. 2017 search

Review authors EGO and MH independently inspected all abstracts of studies identified as above to identify potentially relevant reports. Where disagreement occurred, we resolved it by discussion, or where there was still doubt, we acquired the full article for further inspection and further discussion with CEA. We acquired the full articles of relevant reports for re-assessment and to make a final decision on inclusion (see Criteria for considering studies for this review for this review). Once we had obtained the full articles, EGO and MH independently inspected all reports and independently decided whether they met the inclusion criteria. EGO and MH were not blinded to the names of the authors, institutions or journal of publication. Where difficulties or disputes arose, we discussed them with CEA and if a decision could not be reached, we added these studies to those awaiting assessment and contacted the authors of the papers for clarification.

2. 2015 search

Review author KM independently inspected all records identified in the search for potential relevance. Where difficulties or disputes arose, KM discussed them with CEA .

3. 2011 and 2013 searches

Review authors UA and FR independently inspected all abstracts of studies identified as above to identify potentially relevant reports. In addition, to ensure reliability, HJ (see Acknowledgements) inspected a random sample of these abstracts, comprising 10% of the total. Where disagreement occurred, we resolved it by discussion, or where there was still doubt, we acquired the full article for further inspection and further discussion with CEA. We acquired the full articles of relevant reports for re-assessment and to make a final decision on inclusion (see Criteria for considering studies for this review for this review). Once we had obtained the full articles, UA and FR independently inspected all reports and independently decided whether they met the inclusion criteria. UA and FR were not blinded to the names of the authors, institutions or journal of publication. Where difficulties or disputes arose, we discussed them with HJ and CEA and if we had been unable to reach a decision, we would have added these studies to those awaiting assessment and contacted the authors of the papers for clarification.

Data extraction and management

1. Extraction

1.1 2017 search

Review authors EGO and MH independently extracted data from all included studies. Again, any disagreement was discussed, decisions documented and, if necessary, we contacted the authors of studies for clarification. If there had been any remaining problems, we would have consulted with CEA to help clarify issues and these final decisions would have been documented. We extracted data presented only in graphs and figures whenever possible, but we only included the data if both EGO and MH independently had the same result; we used Plot Digitizer open source software for data extraction from figures, following instructions provided by Kadic 2016. We attempted to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. If studies had been multi-centre, where possible, we would have extracted data relevant to each component centre separately.

1.2 2011 and 2013 searches

Review authors UA and FR independently extracted data from all included studies. In addition, to ensure reliability, HJ independently extracted data from a random sample of these studies. Again, we discussed any disagreement, documented decisions and, if necessary, we contacted the authors of studies for clarification. With any remaining problems, CA helped to clarify issues and we documented these final 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 had the same result. We had also planned to attempt to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary, and to extract data relevant to each component of multi-centre studies separately if we had found such studies.

2. Management

2.1 Forms

We extracted data onto standard, pre-designed, 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);
b) the measuring instrument has not been written or modified by one of the trialists for that particular trial; and
c) the instrument should be a global assessment of an area of functioning and not sub-scores which are not, in themselves, validated or shown to be reliable. However there are exceptions, we included sub-scores from mental state scales measuring positive and negative symptoms of schizophrenia.

Ideally, the measuring instrument should either be i. a self-report or ii. completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly; in Description of studies we noted if this was the case or not.

2.3 Endpoint versus change data

There are advantages of both endpoint and change data: change data can remove a component of between-person variability from the analysis; however, calculation of change needs two assessments (baseline and endpoint), which can be difficult to obtain in unstable and difficult-to-measure conditions such as schizophrenia. We decided primarily to use endpoint data, and only use change data if the former were not available. If necessary, we combined endpoint and change data in the analysis, as we preferred to use mean differences (MDs) rather than standardised mean differences (SMDs) throughout (Deeks 2011).

2.4 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we applied the following standards to relevant continuous data before inclusion.
For endpoint data from studies including fewer than 200 participants:
a) when a scale started from the finite number zero, we subtracted the lowest possible value from the mean, and divided this by the standard deviation (SD). If this value was lower than one, it strongly suggests that the data are skewed. We excluded these data and entered them as 'other data'. If this ratio was higher than one but less than two, there is suggestion that the data are skewed: we entered these data and tested whether their inclusion or exclusion would change the results substantially. If such data changed the results we entered them as 'other data'; if they did not change the results substantially, we used these data in the analyses. Finally, if the ratio was larger than two, we included these data, because it is less likely that they are skewed (Altman 1996; Higgins 2011).
b) if a scale starts from a positive value (such as the Positive and Negative Syndrome Scale (PANSS), which can have values from 30 to 210 (Kay 1986)), we modified the calculation described above to take the scale starting point into account. In these cases skewed data are present if 2 SD > (S − S min), where S is the mean score and 'S min' is the minimum score.
Please note: we planned to enter all relevant data from studies of more than 200 participants in the analysis irrespective of the above rules, because skewed data pose less of a problem in large studies. We entered all relevant change data, as 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 or not data are skewed.

2.5 Common measurement

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

2.6 Conversion of continuous to binary

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

2.7 Direction of graphs

Where possible, we entered data in such a way that the area to the left of the line of no effect indicates a favourable outcome for risperidone. Where keeping to this made it impossible to avoid outcome titles with double-negatives (e.g. 'Not un-improved'), we reported data where the left of the line indicated an unfavourable outcome. If needed in order to improve readability, we switched labels on the X axis and stated it in a note accompanying the graph.

Assessment of risk of bias in included studies

For the 2017 search review authors EGO and MH independently assessed risk of bias within the included studies by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess trial quality (Higgins 2011a). This set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting.

If the raters had disagreed, we would have made the final rating by consensus, with the involvement of CEA. Where inadequate details of randomisation and other characteristics of trials were provided, we attempted to contact authors of the studies in order to obtain further information. If non-concurrence had occurred, we would have reported this.

We noted the level of risk of bias in the text of the review and in the text and 'Summary of findings' tables.

For the 2011 and 2013 searches, UA and FR undertook assessment of risk of bias as above.

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), as it has been shown that RR is more intuitive than odds ratios (Boissel 1999); and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). Although the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH), with their CIs are intuitively attractive to clinicians, they are problematic to calculate and interpret in meta-analyses (Hutton 2009). For binary data presented in the 'Summary of findings' tables we, where possible, we calculated illustrative comparative risks.

2. Continuous data

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

Unit of analysis issues

1. Cluster trials

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

If clustering had not been accounted for in primary studies, we would have presented data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. We would have attempted to contact the first authors of studies to obtain intra-class correlation coefficients (ICCs) for their clustered data and to adjust for this by using accepted methods (Gulliford 1999). If clustering had been incorporated into the analysis of primary studies, we would have presented these data as if from a non-cluster randomised study, but adjusted for the clustering effect. We have sought statistical advice and have been advised that the binary data as presented in a report should be divided by a 'design-effect'. This is calculated using the mean number of participants per cluster (m) and the ICC [Design effect = 1+(m-1)*ICC] (Donner 2002). If the ICC was not reported it was assumed to be 0.1 (Ukoumunne 1999). If cluster studies had been appropriately analysed taking into account ICCs and relevant data documented in the report, synthesis with other studies would have been possible using the generic inverse variance technique.

2. Cross-over trials

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

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up, data must lose credibility (Xia 2009). We chose that, for any particular outcome, should more than 50% of data be unaccounted for we would not reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a study were lost, but the total loss was less than 50%, we would address this within the 'Summary of findings' tables by down-rating quality. Finally, we would also downgraded quality within the 'Summary of findings' tables should the loss be 25% to 50% in total.

2. Binary

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

3. Continuous

3.1 Attrition

We used data where attrition for a continuous outcome was between 0% and 50%, and data only from people who completed the study to that point were reported.

3.2 Standard deviations

If standard deviations (SDs) were not reported, we tried to obtain the missing values from the authors. If these were not available, where there were missing measures of variance for continuous data, but an exact standard error (SE) and CIs available for group means, and either P value or t value available for differences in mean, we could calculate SDs according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). When only the SE is reported, SDs are calculated by the formula SD = SE * $\sqrt{}$(n). The *Cochrane Handbook for Systematic Reviews of Interventions* presents detailed formulae for estimating SDs from P, t or F values, CIs, ranges or other statistics (Higgins 2011). If these formulae do not apply, we could calculate the SDs according to a validated imputation method which is based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome and thus to lose information. Nevertheless, we would have examined the validity of the imputations in a sensitivity analysis that excludes imputed values.

3.3 Assumptions about participants who left the trials early or were lost to follow-up

Various methods are available to account for participants who left the trials early or were lost to follow-up. Some trials just present the results of study completers; others use the method of last observation carried forward (LOCF); while more recently, methods such as multiple imputation or mixed-effects models for repeated measurements (MMRM) have become more of a standard. While the latter methods seem to be somewhat better than LOCF (Leon 2006), we feel that the high percentage of participants leaving the studies early and differences between groups in their reasons for doing so is often the core problem in randomised schizophrenia trials. We therefore determined not to exclude studies based on the statistical approach used. However, by preference we planned to use the more sophisticated approaches, i.e. we would have used MMRM or multiple-imputation to LOCF, and would only have presented completer analyses if some kind of ITT data were not available at all. Moreover, we planned to address this issue in the item 'Incomplete outcome data' of the 'Risk of bias' tool.

Assessment of heterogeneity

1. Clinical heterogeneity

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

2. Methodological heterogeneity

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

3. Statistical heterogeneity

3.1 Visual inspection

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

3.2 Employing the I^2 statistic

We investigated heterogeneity between studies by considering the I^2 statistic alongside the Chi^2 P value. The I^2 statistic provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 depends on i. magnitude and direction of effects and ii. strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or a CI for I^2). An I^2 estimate greater than or equal to 50% accompanied by a statistically significant Chi^2 statistic, was interpreted as evidence of substantial levels of heterogeneity (Deeks 2011). Where substantial levels of heterogeneity were found in the primary outcome,

we explored reasons for the heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011).

1. Protocol versus full study

We tried to locate protocols of included randomised trials. If the protocol was available, we compared outcomes in the protocol and in the published report. If the protocol was not available, we compared outcomes listed in the methods section of the trial report with actually reported results.

2. Funnel plot

We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We decided not to use funnel plots for outcomes where there were 10 or fewer studies, or where all studies were of similar size. In future versions of this review, if funnel plots are possible, we will seek statistical advice in their interpretation.

Data synthesis

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

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

We did not anticipate any subgroup analyses.

2. Investigation of heterogeneity

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

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

Sensitivity analysis

We planned that if there were substantial differences in the direction or precision of effect estimates in any of the sensitivity analyses listed below, we would not add data from the lower-quality studies to the results of the higher-quality trials, but would present these data within a subcategory. If their inclusion did not result in a substantive difference, they would remain in the analyses.

1. Implication of randomisation

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

2. Assumptions for lost binary data

Where assumptions had to be made regarding people lost to follow-up (see Dealing with missing data), we compared the findings of the primary outcomes where we used our assumption compared with completer data only. If there was a substantial difference, we reported results and discussed them but continued to employ our assumption.

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

3. Risk of bias

We analysed the effects of excluding trials that were judged to be at high risk of bias across one or more of the domains of randomisation (see Assessment of risk of bias in included studies) for the meta-analysis of the primary outcome/s. If the exclusion of trials at high risk of bias did not substantially alter the direction of effect or the precision of the effect estimates, then we included data from these trials in the analysis.

4. Imputed values

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

5. Fixed and random effects

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

RESULTS

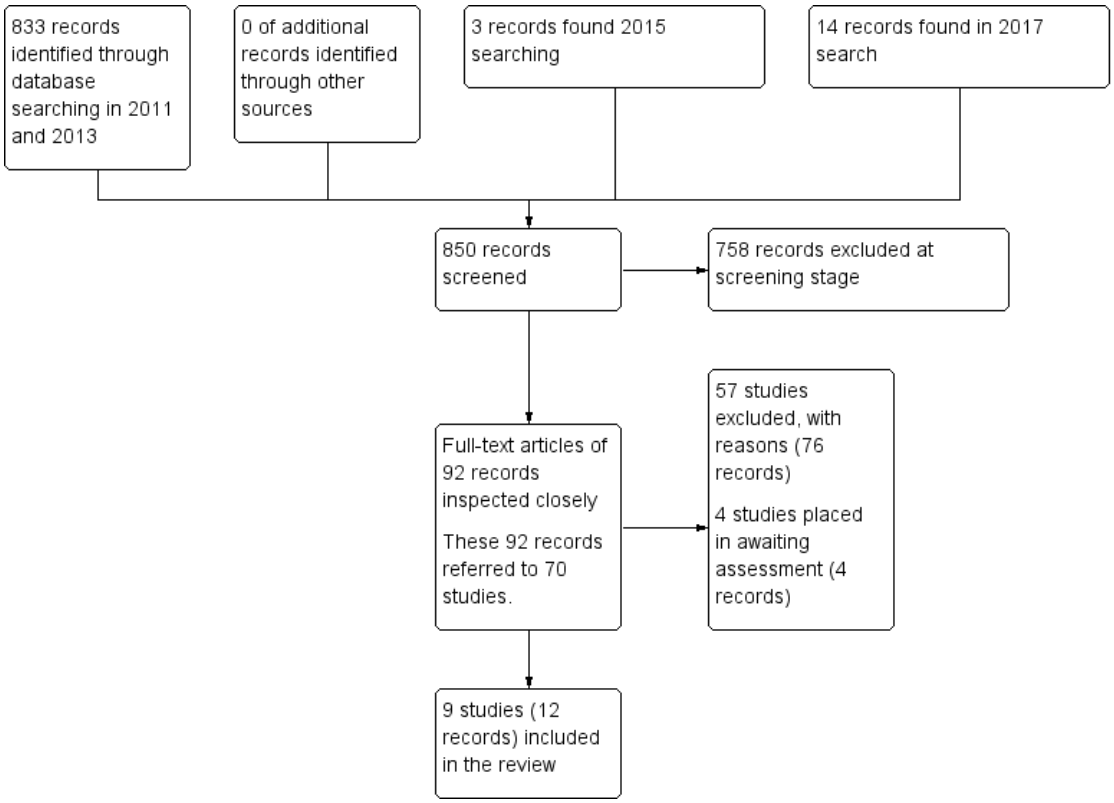
Description of studies

For substantive descriptions of studies please see the Characteristics of included studies, Characteristics of studies awaiting classification, and Characteristics of excluded studies.

Results of the search

Electronic searches up to April 2017 identified 850 records of potentially eligible studies. After an initial screening of these records (checking titles and abstracts), the full-text articles of 92 records (referring to 70 studies) were obtained. From these 70 studies, 57 (76 records) were excluded with reasons, four studies (four records were placed in awaiting assessment) and nine studies (12 records) were included. Please see Figure 2 for summary of the searches up to April 2017.

Figure 2. Search results - up to April 2017



Included studies

Details of the included studies in the review are provided in the Characteristics of included studies table. Searches undertaken between 2011 and 2015 identified three studies for inclusion (Lim 2010; Walther 2014; Yao 2010). In 2017, we identified six additional studies for inclusion (Dai 2012; Jin 2013; Li 2013; Wang 2012; Wang 2013; Zhou 2013).

1. Length of studies

The duration of the studies ranged from 24 hours (Lim 2010) to eight weeks (Dai 2012; Li 2013; Yao 2010).

2. Participants

2.1 Clinical state

Participants presented with acute exacerbation of psychotic symptoms. All the studies focused on people whose psychosis had primarily triggered agitation (Lim 2010; Walther 2014; Wang 2012; Zhou 2013) or aggressive behaviour (Dai 2012; Jin 2013; Li 2013; Wang 2013; Yao 2010).

2.2 Diagnosis

Eighty-nine per cent of participants (n = 520) had a diagnosis of schizophrenia. Other diagnosis included schizoaffective disorder (n = 6, 1%), bipolar I disorder with or without psychotic symptoms (n = 43, 7%), schizophreniform disorder (n = 10, 2%), and psychotic disorder not otherwise specified (n = 3, 1%).

2.3 Exclusions

Reported exclusion criteria included pregnant or lactating women, people with serious medical illnesses, people who had used certain medications (e.g. antipsychotics, long-acting antipsychotics, benzodiazepines) within a specified period prior to enrolment, people with a known allergy or hypersensitivity to the study drugs, and people with alcohol or psychoactive substance use disorder.

2.4 Age

Six studies reported age range and a mean age (Dai 2012; Jin 2013; Li 2013; Walther 2014; Wang 2012; Yao 2010), one study reported an age range (Lim 2010), and two studies reported a mean age (Wang 2013; Zhou 2013). Age ranges varied from the narrowest being 20-30 years (Dai 2012) to the largest one being of 18-65 (Jin 2013; Lim 2010); mean ages varied from the lowest being of 25.3 (Dai 2012) years to the highest 39.4 years (Jin 2013).

2.5 Sex

The studies included a total of 353 male participants and 229 female participants.

3. Study size

The study sizes varied with the smallest study having 40 participants (Dai 2012) and the largest randomising 124 people (Lim 2010).

4. Setting

In all the included studies, participants presented at psychiatric emergency departments and were newly admitted inpatients.

5. Interventions

A total of five comparisons were identified in the included studies: three comparisons involved a single drug whilst the other two comparisons involved a combination. Unfortunately, only two comparisons ('risperidone versus haloperidol', and 'risperidone versus valproic acid') could benefit from more than one study as source of data; moreover, as for the first comparison this held true for a single outcome only ('leaving the study early').
Involved daily doses of risperidone started from 1 mg (Dai 2012; Li 2013; Wang 2013; Yao 2010) or 2 mg (Lim 2010; Walther 2014) to a maximum of 4 mg (Zhou 2013) or 6 mg (Dai 2012; Li 2013; Lim 2010; Walther 2014; Wang 2013; Yao 2010). In one study (Wang 2012), authors declared a titration without a specification on the intended doses, reporting only a mean daily administered dose (4.2 mg ± 0.35mg). In Jin 2013 dosages were not specified.

5.1 Versus antipsychotics

Haloperidol intramuscular (IM) dose was in the 5 mg to 15 mg range (Lim 2010), whilst as for the oral formulation it was a fixed dose of 15 mg (Walther 2014). Olanzapine was given as a fixed dose of 20 mg, oral (Walther 2014). Quetiapine flexible dose started from 100 mg/day and then increased to 400 mg to 500 mg/day with a maximum dose of 750 mg/day (Dai 2012).

5.2 Versus combinations

In the risperidone + oxcarbazepine comparison (Wang 2012), daily administered dose of risperidone and oxcarbazepine were, respectively, of 4.1 mg ± 0.4 mg (oral formulation) and 1.20 g ± 0.42 g (oral formulation).

As for the risperidone + valproic acid comparison, magnesium valproate was administered at 500 mg/day (Yao 2010), within the 750 mg to 1000 mg/day range (Jin 2013; Li 2013), or with a mean dose of 800 mg ± 50 mg/day (Li 2013); sodium valproate daily administered dose was in the 600 mg to 1200 mg/day range (Wang 2013) or of 400 mg twice daily (intravenous formulation (Zhou 2013).

6. Outcomes

The majority of the included studies provided binary data with respect to "specific behaviour - agitation" outcome, "global state" outcome, "mental state" outcome, "adverse effects" outcome, and "leaving the study early" outcome. The majority of trials that employed continuous scales measured "specific behaviour - agitation" outcome, "specific behaviour - aggression" outcome, "mental state" outcome, and "adverse effects - movement disorders" outcome. The various rating scales, from which we were able to obtain usable data, are listed below.

6.1 Specific behaviour - agitation

a. Positive and Negative Syndrome Scale - Excited Component (PANSS-EC)

The PANSS-EC is a five-item scale (excitement, tension, hostility, uncooperativeness, and poor impulse control). The items are rated from one (not present) to seven (extremely severe). Scores range from five to 35, with mean scores $\geq$ 20 indicating agitation. A high score indicates high levels of agitation (Montoya 2011).

b. Positive and Negative Syndrome Scale - Psychotic Agitation Subscale (PANSS-PAS)

The PANSS-PAS is a five-item scale (excitement, hallucinatory behaviour, hostility, uncooperativeness, and poor impulse control). The items are rated from one (not present) to seven (extremely severe), with total scores ranging from five to 35. A high score indicates high levels of psychotic agitation (Currier 2000).

6.2 Specific behaviour - aggression

a. Modified Overt Aggression Scale (MOAS)

The OAS (Yudofsky 1986) is a 16-item rating scale which aims to measure the intensity of verbal and physical aggression. Clinicians are required to comment on the duration of the aggressive incident as well as the intervention required to control it. High scores are indicative of higher levels of aggression.

6.3 Global state

a. Clinical Global Impression (CGI)

The CGl (Guy 1976) is not a diagnostic tool but rather, enables clinicians to quantify the severity of symptoms of any mental health problem at one point in time. Clinicians are then able to use this to track whether there has been any improvement or worsening of symptoms over time. A seven-point rating scale is used with high scores indicating increased severity or less recovery.

b. Clinical Global Impression - Improvement (CGI-I)

The CGI-I (Guy 1976) enables clinicians to assess whether a person's symptoms have improved or worsened following an intervention. Based on the clinicians judgement, a rating on a seven-point scale is given from one (very much improved) to seven (very much worse). Low scores indicate greater improvement.

c. Clinical Global Impression - Severity (CGI-S)

The CGI-S (Guy 1976) requires clinicians to consider the severity of a person's symptoms in relation to the clinicians past experience of people with the same diagnosis. Clinicians then have to give a rating from one (normal) to seven (extremely ill). High scores indicate increased severity.

6.4 Mental state

a. Brief Psychiatric Rating Scale (BPRS)

The Brief Psychiatric Rating Scale was originally developed by Overall and Gorham (Overall 1962) as a 14-item scale to measure the severity of a range of psychiatric symptoms, including psychosis. This rating scale items evolved over time and now consists of 24 items which can be rated on a seven-point scale from 'not present' to 'extremely severe'. A high score would suggest poor mental health. It is not clear for the majority of the studies included in this review, which version of the BPRS was used.

b. Positive and Negative Syndrome Scale (PANSS)

The PANSS was developed and published by Kay, Flszbein and Opler (Kay 1986). The PANSS is designed as a brief interview, whereby the severity of 30 symptoms of schizophrenia can be assessed on a scale of one to seven. A high score would indicate more severe symptoms. The PANSS can be divided into separate sub scales by focusing on the statements relating to positive symptoms (e.g. hallucinations), negative symptoms (e.g. social withdrawal) or general psychopathology (e.g. anxiety and uncooperativeness).

6.5 Adverse effects

a. Abnormal Involuntary Movement Scale (AIMS)

The AIMS (Guy 1976) is a 12-items scale which records the occurrence of tardive dyskinesia. The first 10 items are rated from one to five, whilst the last two items are dichotomous items (yes, no).

b. Barnes Akathisia Scale (BAS)

The BAS scale was developed by Barnes 1989 and includes items which aim to rate both the observable symptoms which characterise akathisia such as restless movements and also the person's subjective experience, including any distress. The items are rated

from zero = normal to three = severe. There is also an item for rating global severity from zero (absent) to five (severe). A high score indicates high levels of akathisia.

c. Simpson-Angus Scale (SAS)

The SAS (Simpson 1970) is a 10-item scale which measures drug induced parkinsonism (extrapyramidal side effects). Each item is scored from zero to four. A high score would indicate increased levels of parkinsonism.

d. Treatment Emergent Symptom Scale (TESS)

The TESS (Guy 1976) is a six-item scale which is used to assess the occurrence and intensity of treatment-related adverse effects. A high score indicates worse symptoms.

7. Missing outcomes

Not one of the studies evaluated tranquillisation within 30 minutes, satisfaction with care, acceptance of treatment, quality of life, or economic outcomes.

8. Funders

One of the nine included studies received sponsorship from a pharmaceutical company.

Excluded studies

In total 59 studies had to be excluded: 12 studies were excluded based on their method of allocation (Beck 1997; Buckley 1997; Currier 2000; Greenspan 2005; Hatta 2008; Hovens 2005; Lewis 2006; Li 2014; Pei 2009; Potkin 2005; Schooler 2003; Villari 2008); 35 studies were excluded based on the characteristics of their participants, who were not experiencing a psychosis-induced aggression or agitation (Belenkaya 2005; Citrome 2001; Briken 2002; Buitelaar 2001; Citrome 2004; Chan 2013; Czobor 1995; Francey 2007; Han 2005; He 2005; Huaqiang 2009; ISRCTN11736448 2003; Kane 2003; Kirwan 2002; Kolivakis 2002; Lieberman 2001; Liu 2010; NCT00174200 2005; NCT00203775 2005; NCT00205699 2005; Citrome 2007; NCT00485498 2003; Ou 2007; Peng 2009; Swanson 2008; Tang 2007; Temputrn 2007; Tosic Golubovic Suzana 2009; Veser 2006; Wan 2005; Wang 2004; Wang 2006; Wei 2010; Xi 2010; Xuan 2007). For 11 studies the intervention under investigation did not meet our inclusion criteria (Conde 2011; Currier 2004; Fang 2012; Hong 2014; Hou 2011; Jiang 2012; Liu 2012; Wang 2015; Zhang 2012; Zheng 2010; Zhou 2012); one study was excluded because the study terminated too early due to difficulties in recruiting participants (NCT00418873 2007).

Risk of bias in included studies

Please see the relevant 'Risk of bias' tables in the Characteristics of included studies, Figure 3 and Figure 4.

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

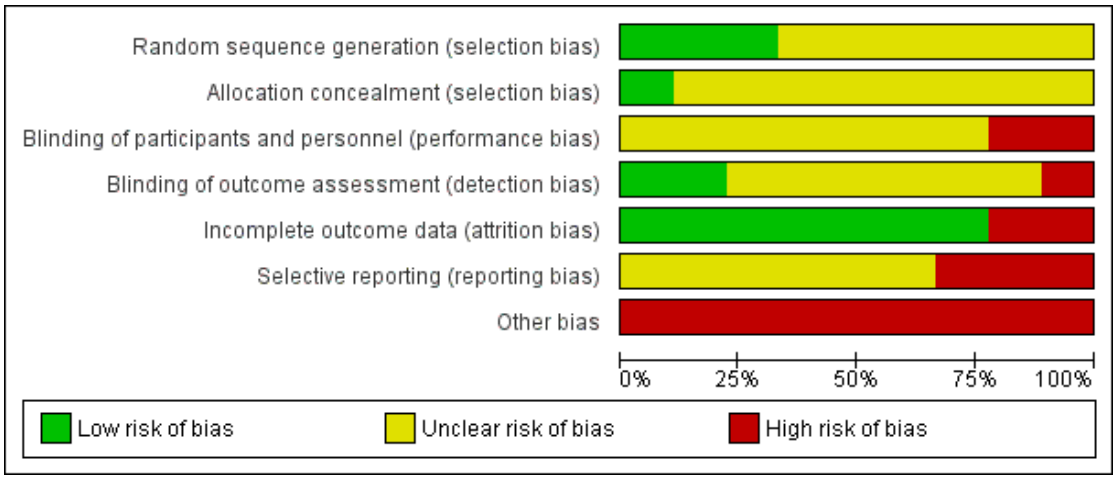
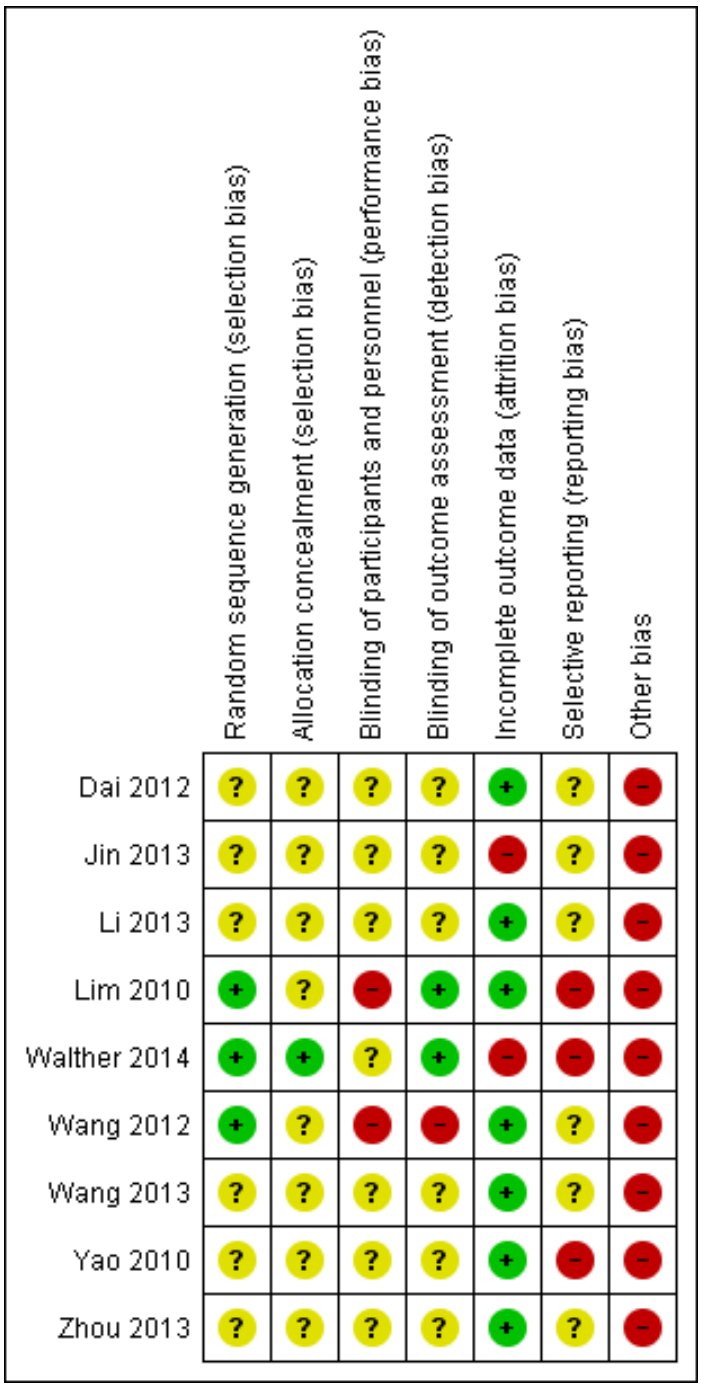


Figure 4. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All nine studies were reported as randomised. In Dai 2012, Jin 2013, Li 2013, Wang 2013, Yao 2010, and Zhou 2013 randomisation is stated but no informations on randomisation procedures and allocation process were given. For the studies that did report further details, methods are described as random number sequence (Wang 2012), pre-defined randomisation code (Lim 2010), and randomisation in blocks (Walther 2014).

Blinding

None of the studies were double-blind with two studies (Lim 2010 and Wang 2012) reporting to be open-label . Only two studies reported being rater-blind (Lim 2010; Walther 2014).

Incomplete outcome data

There was no evidence of attrition bias for seven studies (Dai 2012; Li 2013; Lim 2010; Wang 2012; Wang 2013; Yao 2010; Zhou 2013). In Jin 2013, two participants left the study early due to adverse effects (without any procedure in order to take into account attrition bias), whilst in Walther 2014, nine people were excluded due to refusal to provide post-hoc consent.

Selective reporting

In Lim 2010, Walther 2014 and Yao 2010, there was evidence of selective reporting, since several outcomes - despite being stated in the methods - are not reported or reported only partially.

Other potential sources of bias

A study being sponsored by a pharmaceutical company does not automatically indicate bias, but indicates a level of risk for uncertainty. One study was sponsored by Janssen Phamaceutica Korea (Lim 2010). Although Walther 2014 stated that their study was unfunded, several authors were affiliated with Novartis, AstraZeneca, Bristol-Myers Squibb, Janssen, Servier, Eli Lilly, Zeller Medical, and Sandoz. Eight out of the nine studies had a very small sample size (Dai 2012; Jin 2013; Li 2013; Walther 2014; Wang 2012; Wang 2013; Yao 2010; Zhou 2013).

Effects of interventions

See: **Summary of findings for the main comparison** RISPERIDONE compared to OTHER ANTIPSYCHOTIC: a. HALOPERIDOL for psychosis-induced aggression or agitation (rapid tranquillisation); **Summary of findings 2** RISPERIDONE compared to OTHER ANTIPSYCHOTIC: b. OLANZAPINE for psychosis-induced aggression or agitation (rapid tranquillisation); **Summary of findings 3** RISPERIDONE compared to OTHER ANTIPSYCHOTIC: c. QUETIAPINE for psychosis-induced aggression or agitation (rapid tranquillisation); **Summary of findings 4** RISPERIDONE compared to COMBINATION: a. RISPERIDONE + OXCARBAZEPINE for psychosis-induced aggression or agitation (rapid tranquillisation); **Summary of findings 5** RISPERIDONE compared to COMBINATION: b. RISPERIDONE + VALPROIC ACID for psychosis-induced aggression or agitation (rapid tranquillisation)
See: Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5.

1. COMPARISON 1: RISPERIDONE versus OTHER ANTIPSYCHOTIC: a. HALOPERIDOL

Two studies (n = 152) compared risperidone with haloperidol (Lim 2010; Walther 2014).

1.1 Specific behaviour - agitation

There were no clear differences in terms of Positive And Negative Syndrome Scale - Psychotic Agitation Sub-score (PANSS-PAS) response rate up to 24 hours (risk ratio (RR) 1.04, 95% confidence interval (CI) 0.86 to 1.26; participants = 124; studies = 1; Analysis 1.1) and PANSS-PAS rating scales up to two hours (mean difference (MD) 0.40, 95% CI -4.42 to 5.22; participants = 28; studies = 1; Analysis 1.2), up to 24 hours (MD 0.20, 95% CI -3.96 to 4.36; participants = 28; studies = 1; Analysis 1.3), and over 24 hours (at 48 hours, MD 1.50, 95% CI -1.36 to 4.36; participants = 28; studies = 1; at 72 hours, MD 1.40, 95% CI -1.62 to 4.42; participants = 28; studies = 1; at 96 hours, MD 2.90, 95% CI -0.34 to 6.14; participants = 28; studies = 1; Analysis 1.4).

1.2 Global outcome

No clear differences were identified in terms of need for benzodiazepines (RR 0.88, 95% CI 0.34 to 2.27; participants = 124; studies = 1), need for seclusion room (RR 0.33, 95% CI 0.01 to 7.55; participants = 28; studies = 1), and use of restraints (RR 2.00, 95% CI 0.43 to 9.21; participants = 28; studies = 1; Analysis 1.5).

1.3 Adverse effects

A similar proportion of participants experienced one or more adverse effects, thus resulting in no clear differences between treatment groups (RR 0.94, 95% CI 0.54 to 1.66; participants = 124; studies = 1; Analysis 1.7).

More people allocated to risperidone experienced insomnia, without clear differences (RR 13.00, 95% CI 0.75 to 225.90; participants = 124; studies = 1), while a similar number of patients experienced somnolence (RR 1.29, 95% CI 0.51 to 3.24; participants = 124; studies = 1; Analysis 1.8).

No clear differences resulted between risperidone and haloperidol in terms of movement disorders, both when considering the proportion of people experiencing extrapyramidal symptoms up to 24 hours (RR 0.63, 95% CI 0.22 to 1.80; participants = 124; studies = 1; Analysis 1.9), or continuous scale scores such as Behavioural Activity Rating Scale (BARS) (MD -0.60, 95% CI -1.56 to 0.36; participants = 28; studies = 1) and SAS (MD -0.40, 95% CI -3.00 to 2.20; participants = 28; studies = 1; Analysis 1.11).

Risperidone and haloperidol were similar for adverse events such as headache (RR 0.75, 95% CI 0.18 to 3.21; participants = 124; studies = 1) and dizziness (RR 1.00, 95% CI 0.26 to 3.82; participants = 124; studies = 1) up to 24 hours (Analysis 1.12).

1.4 Leaving the study early

A comparable proportion of participants left the study early due to any reason (RR 2.20, 95% CI 0.51 to 9.48; participants = 152; studies = 2; I^2 = 59%), due to adverse effects (RR 0.50, 95% CI 0.05 to 5.37; participants = 124; studies = 1), or due to lack of efficacy (RR 9.00, 95% CI 0.53 to 152.93; participants = 28; studies = 1; Analysis 1.13).

2. COMPARISON 2: RISPERIDONE versus OTHER ANTIPSYCHOTIC: b. OLANZAPINE

One study (n = 29) compared risperidone with olanzapine (Walther 2014). Unsurprisingly with such a small study, no difference between the compared drugs for any of the considered outcomes could be observed.

2.1 Specific behaviour - agitation

There were no clear differences in PANSS-PAS endpoint scores up to two hours (MD 2.50, 95% CI -2.46 to 7.46; participants = 29; studies = 1; Analysis 2.1), up to 24 hours (MD 0.90, 95% CI -3.40 to 5.20; participants = 29; studies = 1; Analysis 2.2), and over 24 hours (at 48 hours, MD -1.20, 95% CI -5.15 to 2.75; participants = 29; studies = 1; at 72 hours, MD -0.30, 95% CI -4.47 to 3.87; participants = 29; studies = 1; at 96 hours, MD 2.10, 95% CI -1.41 to 5.61; participants = 29; studies = 1; Analysis 2.3).

2.2 Global outcome

No clear differences were found when comparing risperidone and olanzapine in terms of need for seclusion room (RR 0.36, 95% CI 0.02 to 8.07; participants = 29; studies = 1) and use of restraints (RR 1.43, 95% CI 0.39 to 5.28; participants = 29; studies = 1; Analysis 2.4).

2.3 Adverse effects

Comparison in terms of BARS (MD 0.20, 95% CI -0.43 to 0.83; participants = 29; studies = 1) and SAS scores (MD 1.80, 95% CI -0.63 to 4.23; participants = 29; studies = 1) resulted in no clear difference (Analysis 2.6).

2.4 Leaving the study early

More people allocated to risperidone left the study early due to lack of efficacy, but there was no clear difference between treatment groups for this outcome (RR 2.14, 95% CI 0.46 to 9.93; participants = 29; studies = 1; Analysis 2.7).

3. COMPARISON 3: RISPERIDONE versus OTHER ANTIPSYCHOTIC: c. QUETIAPINE

One study (n = 40) compared risperidone with quetiapine (Dai 2012).

3.1 Specific behaviour - aggression

A clear difference at Modified Overt Aggression Scale (MOAS) endpoint score could be seen at two weeks favouring participants allocated to quetiapine (MD 1.80, 95% CI 0.20 to 3.40; participants = 40; studies = 1), whilst this was not the case at four weeks (MD 0.90, 95% CI -0.44 to 2.24; participants = 40; studies = 1), at six weeks (MD 0.70, 95% CI -0.29 to 1.69; participants = 40; studies = 1), and at eight weeks (MD 0.55, 95% CI -0.40 to 1.50; participants = 40; studies = 1). (Analysis 3.1).

3.2 Mental state

There was no clear difference observed in the 'no response' outcome of the PANSS rating scale at eight weeks (RR 1.00, 95% CI 0.16 to 6.42; participants = 40; studies = 1; Analysis 3.2). No clear differences were found as for the other dichotomous outcome (Analysis 3.3).

PANSS total endpoint scores and sub-scale endpoint scores (positive symptoms, negative symptoms, general psychopathology) were collected at two, four, six and eight weeks. Only PANSS positive symptoms sub-scale endpoint scores at four weeks resulted in a clear difference in favour of quetiapine (MD 1.70, 95% CI 0.01 to 3.39; participants = 40; studies = 1; Analysis 3.4).

3.3 Adverse effects

No clear differences could be observed between risperidone and quetiapine for a list of different adverse effects: blurred vision (RR 0.50, 95% CI 0.10 to 2.43; participants = 40; studies = 1; Analysis 3.5), somnolence (RR 0.60, 95% CI 0.17 to 2.18; participants = 40; studies = 1; Analysis 3.6), tachycardia (RR 4.00, 95% CI 0.49 to 32.72; participants = 40; studies = 1; Analysis 3.7), nausea

and vomiting (RR 1.00, 95% CI 0.07 to 14.90; participants = 40; studies = 1; Analysis 3.8), akathisia (RR 1.67, 95% CI 0.46 to 6.06; participants = 40; studies = 1), hypermyotonia (RR 7.00, 95% CI 0.95 to 51.80; participants = 40; studies = 1; Analysis 3.9), headache (RR 1.00, 95% CI 0.16 to 6.42; participants = 40; studies = 1), liver function tests (LFTs) elevation (RR 1.00, 95% CI 0.07 to 14.90; participants = 40; studies = 1), weight gain (RR 4.00, 95% CI 0.49 to 32.72; participants = 40; studies = 1), and agitation (RR 3.50, 95% CI 0.83 to 14.83; participants = 40; studies = 1; Analysis 3.10).

4. COMPARISON 4: RISPERIDONE versus COMBINATION: a. RISPERIDONE + OXCARBAZEPINE

One study (n = 68) compared risperidone with the 'risperidone + oxcarbazepine' combination (Wang 2012).

4.1 Specific behaviour - agitation

There was a clear difference in the Positive And Negative Syndrome Scale - Excited Component (PANSS-EC) endpoint scores at one week (MD 2.70, 95% CI 0.42 to 4.98; participants = 68; studies = 1; Analysis 4.1) in favour of the combination.

4.2 Global outcome

Comparison at one week in terms of Clinical Global Impression - Improvement (CGI-I) (MD -0.20, 95% CI -0.61 to 0.21; participants = 68; studies = 1) and Clinical Global Impression - Severity (CGI-S) endpoint scores (MD 0.20, 95% CI -0.25 to 0.65; participants = 68; studies = 1) resulted in no clear difference (Analysis 4.2).

4.3 Mental state

There was a clear difference between Brief Psychiatric Rating Scale (BPRS) endpoint scores at one week (MD 5.20, 95% CI 1.04 to 9.36; participants = 68; studies = 1) in favour of the combination (Analysis 4.5).

4.4 Adverse effects

In the combination group a total number of 47 adverse effects were registered compared to a total of 40 adverse effects in participants allocated to risperidone. (Analysis 4.6).

There was a clear difference in the number of participants experiencing excessive sedation in favour of risperidone. (RR 0.06, 95% CI 0.00 to 0.92; participants = 68; studies = 1; Analysis 4.8).

Risperidone and combination groups were comparable in terms of the number of participants that were experiencing various adverse effects at four weeks: dry mouth (RR 2.12, 95% CI 0.81 to 5.55; participants = 68; studies = 1) and constipation at four weeks (RR 1.30, 95% CI 0.62 to 2.72; participants = 68; studies = 1) (Analysis 4.7); tachycardia (RR 1.24, 95% CI 0.46 to 3.30; participants = 68; studies = 1; Analysis 4.9); nausea (RR 2.12, 95% CI 0.20 to 22.31; participants = 68; studies = 1; Analysis 4.10), extrapyramidal symptoms (EPS) (RR 1.59, 95% CI 0.49 to 5.14; participants = 68; studies = 1) and tremor (RR 0.85, 95% CI 0.25 to 2.89; participants = 68; studies = 1) (Analysis 4.11); headache (RR 0.07, 95% CI 0.00 to 1.19; participants = 68; studies = 1) and skin rash (RR 0.35, 95% CI 0.01 to 8.37; participants = 68; studies = 1) (Analysis 4.12).

5. COMPARISON 5: RISPERIDONE versus COMBINATION: b. RISPERIDONE + VALPROIC ACID

Five studies (n = 307) compared risperidone with the 'risperidone + valproic acid' combination (Jin 2013; Li 2013; Wang 2013; Yao 2010; Zhou 2013).

5.1 Specific behaviour - agitation

PANSS-EC endpoint scores were comparable between risperidone and combination at three days (MD -0.11, 95% CI -2.98 to 2.76; participants = 54; studies = 1); a clear difference in favour of the combination was identified at five days (MD 5.47, 95% CI 2.64 to 8.30; participants = 54; studies = 1) and seven days (MD 5.11, 95% CI 2.51 to 7.71; participants = 54; studies = 1; Analysis 5.1). Endpoint scores at PANSS-EC at two weeks (MD 0.09, 95% CI -0.90 to 1.08; participants = 63; studies = 1) and at four weeks (MD 0.17, 95% CI -0.85 to 1.19; participants = 63; studies = 1) could not show a difference between the compared drugs (Analysis 5.2).

5.2 Specific behaviour - aggression

Risperidone and 'risperidone + valproic acid' combination were comparable both at three days (MD 1.07, 95% CI -0.20 to 2.34; participants = 54; studies = 1) and five days (MD 0.38, 95% CI -0.83 to 1.59; participants = 54; studies = 1) in terms of Modified Overt Aggression Scale (MOAS) endpoint scores. A clear difference in favour of the combination could be identified at seven days (MD 3.32, 95% CI 2.07 to 4.57; participants = 54; studies = 1), at two weeks (MD 1.13, 95% CI 0.23 to 2.02; participants = 128; studies = 2; I^2 = 25%), at four weeks (MD 1.57, 95% CI 0.75 to 2.39; participants = 128; studies = 2; I^2 = 0%), and at six weeks (MD 1.47, 95% CI 0.83 to 2.11; participants = 68; studies = 1), whilst being comparable at eight weeks (MD 1.00, 95% CI -0.11 to 2.11; participants = 60; studies = 1;Analysis 5.2).

5.3 Mental state

Five participants allocated to risperidone and three participants allocated to the combination showed no clinical response based on the PANSS score (< 30% reduction from baseline score) at eight

weeks (RR 1.67, 95% CI 0.44 to 6.38; participants = 62; studies = 1; Analysis 5.3).

However, when looking at PANSS endpoint scores, a clear difference favouring the combination could be seen at two weeks (MD 3.48, 95% CI 1.88 to 5.08; participants = 253; studies = 4; I^2 = 80%), at four weeks (MD 5.45, 95% CI 3.81 to 7.08; participants = 253; studies = 4; I^2 = 70%), at six weeks (MD 9.90, 95% CI 7.42 to 12.37; participants = 130; studies = 2; I^2 = 92%) and at eight weeks (MD 5.83, 95% CI 4.12 to 7.54; participants = 122; studies = 2; I^2 = 58%).

High I^2 values that should be translated into inconsistency of findings between the studies; data at two, four and six weeks had Chi ^{2} P values statistically significant, showing evidence of substantial levels of heterogeneity (Assessment of heterogeneity; Section 9.5.2, Higgins 2011). We investigated for input errors and found that data were entered correctly. At the visual inspection of the forest plots we identified Wang 2013 as an outlying study for the two and four weeks pooled data analyses and removed it to see if homogeneity was restored. PANSS endpoint scores at two weeks (MD 2.50, 95% CI 0.78 to 4.21; participants = 185; studies = 3; I^2 = 62%, Chi^2 = 5.23, P = 0.07) showed a I^2 value > 50% with a Chi^2 P value non statistically significant, whilst at four weeks (MD 4.52, 95% CI 2.76 to 6.29; participants = 185; studies = 3; I^2 = 21%, Chi^2 = 2.55, P = 0.28) I^2 value resulted being <50% accompanied by a non statistically significant Chi^2 P value. Given the concordance of direction of effects, the summary effect resulting statistically significant even by removal of the outlying study, and that the relative weights of this last were 13.3% and 14.2%, (respectively, two and four weeks), we decided to present the pooled data (Subgroup analysis and investigation of heterogeneity).

Sub-scale continuous data showed a clear difference at PANSS positive symptoms sub-scale in favour of the combination at four weeks (MD 2.75, 95% CI 1.86 to 3.64; participants = 191; studies = 3; I^2 = 76%), six weeks (MD 4.40, 95% CI 1.40 to 7.40; participants = 68; studies = 1), and eight weeks (MD 1.70, 95% CI 0.71 to 2.69; participants = 60; studies = 1), despite being comparable at two weeks (MD 0.64, 95% CI -0.24 to 1.53; participants = 191; studies = 3; I^2 = 81%; Analysis 5.4).

Again, we investigated for input errors and that data were entered correctly. At the visual inspection of the graphs, Li 2013 could be identified as an hypothetical outlying study. By removing it, I^2 values resulted < 50% and Chi^2 P values resulted non statistically significant (two weeks: I^2 = 2%, Chi^2 = 1.02, P = 0.31; four weeks: I^2 = 0%, Chi^2 = 0.36, P = 0.55). Given the relative weights of the outlying study being 68.8% at two weeks and 69.8% at four weeks, we decided not to consider pooled data and wait for more studies and data.

PANSS negative symptoms sub-scale could not show clear differences at two weeks (MD 0.29, 95% CI -0.57 to 1.15; participants = 128; studies = 2; I^2 = 65%), four weeks (MD 1.23, 95% CI -0.16 to 2.62; participants = 128; studies = 2; I^2 = 59%), and eight weeks (MD 1.30, 95% CI -0.02 to 2.62; participants = 60; studies = 1); a clear difference was observed at six weeks only, favouring the combination (MD 3.80, 95% CI 1.07 to 6.53; participants = 68; studies = 1).

PANSS general psychopathology sub-scale showed clear differences in favour of the combination at four weeks (MD 1.14, 95% CI 0.04 to 2.23; participants = 128; studies = 2; I^2 = 50%), six weeks (MD 6.50, 95% CI 4.06 to 8.94; participants = 68; studies = 1), and eight weeks (MD 1.60, 95% CI 0.43 to 2.77; participants = 60; studies = 1); at two weeks data did not show a clear difference between the compared drugs (MD 0.93, 95% CI -0.07 to 1.93; participants = 128; studies = 2; I^2 = 66%) (Analysis 5.4).

5.4 Adverse effects

In the combination group a total number of 20 adverse effects were registered, compared to the 16 total adverse effects experienced by participants allocated to risperidone (Analysis 5.5).

Two participants allocated to risperidone and one allocated to the combination suffered from myocardial ischaemia (RR 2.00, 95% CI 0.19 to 20.93; participants = 62; studies = 1; Analysis 5.6).

Risperidone and combination groups resulted in comparable in terms of probability of experiencing blurred vision (RR 1.00, 95% CI 0.37 to 2.68; participants = 122; studies = 2; I^2 = 0%), dry mouth (RR 1.64, 95% CI 0.76 to 3.54; participants = 129; studies = 2; I^2 = 78%; Analysis 5.7); insomnia (RR 2.00, 95% CI 0.19 to 20.77; participants = 54; studies = 1), somnolence (RR 0.85, 95% CI 0.44 to 1.63; participants = 121; studies = 2; I^2 = 0%; Analysis 5.8); decreased blood pressure (RR 0.75, 95% CI 0.18 to 3.10; participants = 68; studies = 1), tachycardia (RR 1.48, 95% CI 0.83 to 2.67; participants = 251; studies = 4; I^2 = 35%), T-wave changes in ECG (RR 2.00, 95% CI 0.19 to 20.77; participants = 54; studies = 1; Analysis 5.9); constipation (RR 1.11, 95% CI 0.70 to 1.76; participants = 189; studies = 3; I^2 = 6%), nausea (RR 0.70, 95% CI 0.29 to 1.71; participants = 122; studies = 2; I^2 = 0%; Analysis 5.10); EPS (RR 1.35, 95% CI 0.76 to 2.39; participants = 121; studies = 2; I^2 = 91%), akathisia (RR 0.75, 95% CI 0.28 to 2.03; participants = 122; studies = 2; I^2 = 0%), tremor (RR 1.20, 95% CI 0.40 to 3.56; participants = 68; studies = 1; Analysis 5.11); headache (RR 0.94, 95% CI 0.53 to 1.68; participants = 243; studies = 4; I^2 = 0%), weight gain (RR 1.50, 95% CI 0.47 to 4.78; participants = 60; studies = 1), oedema (RR 0.34, 95% CI 0.01 to 8.13; participants = 63; studies = 1), leukopenia (RR 0.34, 95% CI 0.01 to 8.13; participants = 63; studies = 1), and liver function tests elevation (RR 0.60, 95% CI 0.15 to 2.40; participants = 116; studies = 2; I^2 = 0%; Analysis 5.13).

Treatment Emergent Symptom Scale (TESS) endpoint scores did not find a clear difference in movement disorders between the compared groups at three days (MD -0.04, 95% CI -1.35 to 1.27; participants = 54; studies = 1), five days (MD -0.11, 95% CI -1.55 to 1.33; participants = 54; studies = 1), and at seven days

(MD -0.51, 95% CI -1.88 to 0.86; participants = 54; studies = 1; Analysis 5.12).

5.5 Leaving the study early

Two participants allocated to the combination and none of those allocated to risperidone left the study early due to adverse effects (RR 0.21, 95% CI 0.01 to 4.13; participants = 63; studies = 1; Analysis 5.14).

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

RISPERIDONE compared to OTHER ANTIPSYCHOTIC: b. OLANZAPINE for psychosis-induced aggression or agitation (rapid tranquillisation)

Patient or population: psychosis-induced aggression or agitation (rapid tranquillisation)
Setting: Psychiatric acute care units.
Intervention: RISPERIDONE
Comparison: OTHER ANTIPSYCHOTIC: b. OLANZAPINE

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with OTHER ANTIPSYCHOTIC: b. OLANZAPINE	Risk with RISPERIDONE				
Tranquillisation or asleep by 30 minutes - not measured	-	-	-	-	-	
Repeated need for tranquillisation within 24 hours - not measured	-	-	-	-	-	
Specific behaviour: agitation, up to 2 hours assessed with: PANSS-PAS endpoint score		MD 2.5 higher (2.46 lower to 7.46 higher)	-	29 (1 RCT)	⊕◯◯◯ VERY LOW [123]	
Global outcome: need for additional measures assessed with: use of restraints	Study population 200 per 1.000	286 per 1.000 (78 to 1.000)	RR 1.43 (0.39 to 5.28)	29 (1 RCT)	⊕◯◯◯ VERY LOW [1234]	
Adverse effects: movement disorder assessed with: BARS endpoint score		MD 0.20 higher (0.43 lower to 0.83 higher)	-	29 (1 RCT)	⊕◯◯◯ VERY LOW [1234]	

Economic outcomes - not measured	-	-	-	-	-

*__The risk in the intervention group__ (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: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Risk of bias - rated 'very serious': high risk of attrition bias and 'selective reporting' bias.
[2] Only one study available.
[3] Imprecision - rated 'very serious': Optimal Information Size (OIS) criterion not met.
[4] Indirectness - rated 'serious': provided outcome is at a time point (4 days) different from those of primary importance in this setting.

RISPERIDONE compared to OTHER ANTIPSYCHOTIC: c. QUETIAPINE for psychosis-induced aggression or agitation (rapid tranquillisation)

Patient or population: psychosis-induced aggression or agitation (rapid tranquillisation)
Setting: Inpatient ward.
Intervention: RISPERIDONE
Comparison: OTHER ANTIPSYCHOTIC: c. QUETIAPINE

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with OTHER ANTIPSYCHOTIC: c. QUETIAPINE	Risk with RISPERIDONE				
Tranquillisation or asleep by 30 minutes - not measured	-	-	-	-	-	
Repeated need for tranquillisation within 24 hours - not measured	-	-	-	-	-	
Specific behaviour - aggression, over 24 hours assessed with: MOAS endpoint score at 2 weeks		MD 1.80 higher (0.20 higher to 3.40 higher)	-	40 (1 RCT)	⊕◯◯◯ VERY LOW [123]	
Global outcome - not measured	-	-	-	-	-	
Adverse effects: movement disorders over 24 hours assessed with: akathisia	Study population		RR 1.67 (0.46 to 6.06)	40 (1 RCT)	⊕◯◯◯ VERY LOW [123]	

	150 per 1.000	251 per 1.000 (69 to 909)			
Economic outcomes - not measured	-	-	-	-	-

*__The risk in the intervention group__ (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; **MD:** mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Only one study available.
[2] Indirectness - rated 'serious': provided outcome is at a time point (2 weeks) different from those of primary importance in this setting.
[3] Imprecision - rated 'very serious': Optimal Information Size (OIS) criterion not met.

RISPERIDONE compared to COMBINATION: a. RISPERIDONE + OXCARBAZEPINE for psychosis-induced aggression or agitation (rapid tranquillisation)

Patient or population: psychosis-induced aggression or agitation (rapid tranquillisation)
Setting: Inpatient ward.
Intervention: RISPERIDONE
Comparison: COMBINATION: a. RISPERIDONE + OXCARBAZEPINE

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with COMBINATION: a. RISPERIDONE + OXCARBAZEPINE	Risk with RISPERIDONE				
Tranquillisation or asleep by 30 minutes - not measured	-	-	-	-	-	
Repeated need for tranquillisation within 24 hours - not measured	-	-	-	-	-	
Specific behaviour: agitation, over 24 hours assessed with: PANSS-EC endpoint score		MD 2.70 higher (0.42 higher to 4.98 higher)	-	68 (1 RCT)	⊕◯◯◯ VERY LOW [1234]	
Global Outcome: average scores, over 24 hours assessed with: CGI-I endpoint score		MD 0.20 lower (0.61 lower to 0.21 higher)	-	68 (1 RCT)	⊕◯◯◯ VERY LOW [1234]	
Adverse effects: movement disorders, over 24 hours assessed with: EPS	Study population		RR 1.59 (0.49 to 5.14)	68 (1 RCT)	⊕◯◯◯ VERY LOW [1234]	

	114 per 1.000	182 per 1.000 (56 to 587)			
Economic outcomes - not measured	-	-	-	-	-

*__The risk in the intervention group__ (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; **MD:** mean difference;**RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Risk of bias - rated 'very serious': high risk for performance bias and detection bias.
[2] Only one study available.
[3] Indirectness - rated 'serious': provided outcome is at a time point (1 week) different from those of primary importance in this setting.
[4] Imprecision - rated 'very serious': Optimal Information Size (OIS) criterion not met.

RISPERIDONE compared to COMBINATION: b. RISPERIDONE + VALPROIC ACID for psychosis-induced aggression or agitation (rapid tranquillisation)

Patient or population: psychosis-induced aggression or agitation (rapid tranquillisation)
Setting: Inpatient ward.
Intervention: RISPERIDONE
Comparison: COMBINATION: b. RISPERIDONE + VALPROIC ACID

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with COMBINATION: b. RISPERIDONE + VALPROIC ACID	Risk with RISPERIDONE				
Tranquillisation or asleep by 30 minutes - not measured	-	-	-	-	-	
Repeated need for tranquillisation within 24 hours - not measured	-	-	-	-	-	
Specific behaviour - aggression, over 24 hours assessed with: MOAS endpoint score at 3 days	The mean specific behaviour - aggression, over 24 hours was 0	MD 1.07 higher (0.20 lower to 2.34 higher)	-	54 (1 RCT)	⊕◯◯◯ VERY LOW [123]	
Global outcome - not measured	-	-	-	-	-	
Adverse effects: movement disorders, over 24 hours assessed with: akathisia	Study population		RR 0.75 (0.28 to 2.03)	122 (2 RCTs)	⊕◯◯◯ VERY LOW [23]	

	66 per 1.000	49 per 1.000 (18 to 133)			
Economic outcomes - not measured	-	-	-	-	-

*__The risk in the intervention group__ (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;__MD:__ mean difference;__RR:__ Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Only one study available.
[2] Indirectness - rated 'serious': provided outcome is at a time point (3 days) different from those of primary importance in this setting.
[3] Imprecision - rated 'very serious': Optimal Information Size (OIS) criterion not met.

DISCUSSION

Summary of main results

1. COMPARISON 1: RISPERIDONE versus OTHER ANTIPSYCHOTIC: a. HALOPERIDOL

Two studies were included (Lim 2010; Walther 2014), with a total number of 152 participants (risperidone, n = 76; haloperidol, n = 76); although two potential sources of data were available, only one outcome could benefit from both ('leaving the study early'). We did expect to find more relevant studies since haloperidol has an historical role in drug development research and still could be indicated as the 'common comparator' when designing randomised controlled trials (RCTs). Moreover, available outcomes were rated of very low quality (Summary of findings for the main comparison), due to high risk of attrition and 'selective reporting' bias, small sample size and indirectness of outcome measures. No data concerning 'tranquillisation or asleep', repeated need for tranquillisation and economic outcomes were available.

1.1 Agitation, global outcome

Risperidone and haloperidol showed similar results in agitation measurement scales and global outcomes such as need for benzodiazepine, need for seclusion room or use of restraints.
Interestingly, dichotomous data on efficacy outcomes provided no strong evidence of a difference between oral risperidone and intramuscular administration of haloperidol; even if higher-quality evidence is needed to draw any firm conclusion, patients preference and best interest should be taken into consideration in treatment decision making when delivering a tailored therapy.

1.2 Adverse effects

Analyses provides no strong evidence that the intervention yielded any differences in terms of adverse effects.

1.3 Leaving the study early

A comparable number of participants allocated to either risperidone or haloperidol left the study early.

2. COMPARISON 2: RISPERIDONE versus OTHER ANTIPSYCHOTIC: b. OLANZAPINE

Only one study was included (Walther 2014), with a total number of 29 participants (risperidone, n = 14; olanzapine, n = 15). Due to high risk of attrition and 'selective reporting' bias, the small sample size and the indirectness of the outcome measures, available outcomes were rated of very low quality (Summary of findings 2). No data concerning 'tranquillisation or asleep', repeated need for rapid tranquillisation and economic outcomes were available.
Analyses provides no strong evidence that risperidone has an effect any different than olanzapine for any of the considered outcomes: 'specific behaviour - agitation', 'global outcome', 'adverse effects', 'leaving the study early'.

3. COMPARISON 3: RISPERIDONE versus OTHER ANTIPSYCHOTIC: c. QUETIAPINE

Only one study was included (Dai 2012), with a total number of 40 participants (risperidone, n = 20; quetiapine, n = 20). Due to small sample size and the indirectness of the outcome measures, available outcomes were rated of very low quality (Summary of findings 3). No data concerning 'tranquillisation or asleep', repeated need for rapid tranquillisation, 'global state' and economic outcomes were available. No data were available on the 'rapid tranquillisation' topic: the first time point at which data were collected was at two weeks.
Data analyses provide no strong evidence that risperidone has an effect clinically significantly different than quetiapine for almost all the outcomes: 'specific behaviour - aggression', 'mental state', 'adverse effects'.

4. COMPARISON 4: RISPERIDONE versus COMBINATION: a. RISPERIDONE + OXCARBAZEPINE

Only one study was included (Wang 2012), with a total number of 68 participants (risperidone, n = 33; risperidone + oxcarbazepine, n = 35). Due to high risk of performance and detection bias, small sample size and indirectness of outcome measures, available outcomes were rated of very low quality (Summary of findings 4); no data concerning 'tranquillisation or asleep', repeated need for tranquillisation and economic outcomes were available.

4.1 Agitation, global outcome, mental state

As for the available 'agitation' and 'mental state' outcomes (PANSS-EC and BPRS endpoint scores, respectively), we could find evidences of differences in favour of the combination, with no strong evidence of any difference for the 'global outcome'. However, it has to be noted that available data were collected at seven days, a timing far too late to be informative for the 'rapid tranquillisation' topic. Moreover, the quality of evidence was very low due to aforementioned risks.

4.2 Adverse effects

Very low quality of evidence was found that 'risperidone + oxcarbazepine' combination yielded to higher number of 'excessive sedation' adverse events (zero events occurred in the risperidone group, whilst nine events were reported for the combination group; Analysis 4.8). Interestingly, since we do not have further details on data and the latter have not been collected to multiple time points, we could not exclude that this evidence is just another way to read the higher efficacy one (Analysis 4.1; Analysis 4.5).

The ideal concept of 'tranquillisation' is to find a way to get people calm without causing sedation. Even if this last could be necessary within the first hours, it could not be justified in the later days (if no other aggression or agitation episodes occurred).
No strong evidence of any difference could be observed as for the other collected adverse events.

5. COMPARISON 5: RISPERIDONE versus COMBINATION: b. RISPERIDONE + VALPROIC ACID

Five studies were included (Jin 2013; Li 2013; Wang 2013; Yao 2010; Zhou 2013), with a total number of 307 participants (risperidone, n = 153; risperidone + valproic acid, n = 154). Available outcomes were rated of very low quality (Summary of findings 5), due to small sample size and indirectness of outcome measures. No data concerning 'tranquillisation or asleep', repeated need for tranquillisation and economic outcomes were available.

5.1 Agitation, aggression

As for available efficacy outcomes on agitation, continuous data analyses provides no strong evidence of different efficacy between risperidone and the 'risperidone + valproic acid' combination at three days; when focusing on later time points, a clear difference in favours of the combination at five and seven days, but not at two and four weeks, could be seen.
Concerning continuous data on aggression, evidence of a clear difference could be observed in favour of the combination at five and seven7 days, two, four, and six weeks. However, mean difference (MD) and confidence interval (CI) values should be taken into account to evaluate clinically significance. At eight weeks a strong evidence of any difference between the compared drugs could not be provided.

5.2 Mental state

Very low quality of evidence of a clear difference in PANSS endpoint scores favouring the combination could be observed (subgroup analyses were carried out for PANSS endpoint scores data at two and four weeks); this held true for the later time points (mainly six and eight weeks) of positive symptoms, negative symptoms and general psychopathology sub-scales; PANSS positive symptoms sub-scale endpoint scores data at two and four weeks could not be pooled due to high heterogeneity.
It has to be highlighted, however, that available data were measured starting from the second week: no evidence could be found concerning time points relevant to the 'rapid tranquillisation' topic.

5.3 Adverse effects

Data analyses provide no strong evidence of any difference in terms of adverse effects between risperidone and the 'risperidone + valproic acid' combination. However, in one study (Yao 2010), three episodes of myocardial ischaemia were observed: an association between the drug administration and the event could not be found throughout the relevant paper, nor more information about their cardiovascular baseline risk (presumably not high since age range of participants recruited in the study was between 17 and 42 years, with a mean age of 26.9 years).

5.4 Leaving the study early

No strong evidence of any difference in terms of 'leaving the study early' outcome could be observed.

Overall completeness and applicability of evidence

1. Completeness

We identified nine relevant studies and all reported only a few outcomes: only two comparisons could benefit from more than one study as data source and - even more surprisingly - as for the haloperidol comparison this held true only for a single outcome; the most represented comparison is the one comparing risperidone with 'risperidone + valproic acid' combination (five studies). No study reported data regarding the 'tranquillisation or asleep' outcome, service outcomes, satisfaction with treatment, acceptance of treatment, quality of life, or economic outcomes. Three included studies suffered from 'selective reporting' bias, thus further limiting available data. Protocols were not available for all the included studies.

2. Applicability

All of the included studies were more of the explanatory type of study rather the practical/pragmatic and easily applicable to real-world practice one (Thorpe 2009).
Included studies were conducted in three different countries (China, seven; Korea, one; Switzerland, one) and in psychiatric inpatient and emergency admission settings.
Rapid tranquillisation is often used to achieve a fast resolution of this clinical state that could otherwise result in injury to self or others, hence preventing prolonged physical restraint of people, which should be seen as the very last available resource. It was therefore surprising and disappointing that few studies measured agitation and aggression outcomes at time points that one would associate with 'rapid tranquillisation'. The first available time point is at two hours (Walther 2014), with seven studies having set time points greater than 24 hours (three days, Zhou 2013; one week, Wang 2012; two weeks, Dai 2012; Jin 2013; Li 2013; Wang 2013; Yao 2010). In Lim 2010, outcomes are stated to be measured as early as 30 minutes but, unfortunately, only 24 hours measurements were provided.

Quality of the evidence

1. General

All of the included studies were published after the first CONSORT guidance (1996); no studies complied with this internationally agreed standard. Disappointingly, a large proportion of data was rendered unusable, which could have been avoided had the trials been better reported.

2. Specific

All nine studies were randomised, but details were vaguely reported and none was double-blinded. Three studies suffered from 'selective reporting' bias. Data from more than one source were available for two comparisons only. These factors strongly limit the quality of the available evidence and this can be evinced in the 'Risk of bias' and 'Summary of findings' tables; all of the selected outcomes to be included in th 'Summary of findings' tables were rated as 'very low' quality.

Potential biases in the review process

We followed the protocol and conducted a thorough search and adhered to our pre-specified inclusion and exclusion criteria when inspecting citations. It is possible that we have failed to identify small relevant studies, but we feel that it is unlikely that we would have missed large studies that would make a substantial difference to the findings from this review. Given the small number of included studies, review authors EGO and MH independently inspected all citations obtained from the search and extracted the data to minimise bias.

In order to further limit the risk for potential biases and improve the overall quality of the work, we followed the recommendations of the Cochrane Editorial Unit (CEU) Screening Programme by Dr Nuala Livingstone and the Methodological Expectations of Cochrane Intervention Reviews (MECIR; Higgins 2016); the systematic review was checked and verified by using the CEU Screening Tool items. Previously excluded studies were checked for NROD exclusion bias (no relevant outcome data exclusion bias; Higgins 2016; Kirkham 2010): one study was retrieved.

Agreements and disagreements with other studies or reviews

The review authors are not aware of any other studies or systematic reviews that have focused solely on use of risperidone alone for people who are agitated or aggressive due to serious mental illnesses.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with an interest in psychosis-induced aggression or agitation

People during an acute episode of psychosis can be under tremendous distress; there is currently very limited high-quality research regarding effective and safe treatment for those episodes. It is essential that people receive appropriate care based on the best available evidence. The nine trials included in this review compared oral risperidone with intramuscular or oral single drugs (haloperidol, olanzapine, quetiapine) or combinations (risperidone + oxcarbazepine, risperidone + valproic acid). Data analyses could not provide strong evidence of any difference between the compared drugs when focusing on rapid tranquillisation (up to two hours, but ideally within the first 10 minutes after getting clinical attention). When checking for efficacy at medium-long terms, the combination of risperidone + oxcarbazepine yielded a greater improvement in terms of levels of agitation, even if the overall quality of evidence was rated as 'very low'. If people are at risk of needing such interventions, it would seem reasonable to expect better evidence than what research community has thus far provided.

2. For clinicians

Available evidence on the use of risperidone for people with psychosis-induced aggression or agitation is strongly limited. In terms of rapid tranquillisation of psychosis-induced aggression or agitation, no strong evidence could be observed between risperidone and compared drugs or combinations, including intramuscular administration of haloperidol. When widening the topic of the review to the phase after rapid tranquillisation, very low-quality evidence of a slight advantage up to one week in favour of the 'risperidone + oxcarbazepine' combination could be seen. Overall, data are very scarce: it is not possible to draw firm conclusions as to whether risperidone is more or less effective than other interventions for psychosis-induced aggression or agitation.

If researchers continue to let down the clinical community by avoiding pragmatic studies on such an important and relevant area like rapid tranquillisation in psychosis-induced aggression or agitation, clinicians should formally request such investigations: not to have good evidence in this area is always more often difficult to justify.

3. For policy makers

This is a greatly under researched area. Currently, the use of risperidone alone in the management of acutely agitated or aggressive patients could be efficacious but the evidence base for this is lacking. This underpins the need for high-quality trials in the rapid tranquillisation setting.

Implications for research

1. General

All nine studies identified for inclusion in this review were conducted after the Consolidated Standards of Reporting Trials (CONSORT, Moher 2001) statement was proposed, yet the reporting quality was rated as very-low quality due to high risk of performance, attrition and 'selective reporting' bias, small size of randomised populations, and indirectness of outcome measures. More transparency in the reporting of randomised controlled trials (RCTs) would enable readers to understand the design, conduct, analysis and interpretation, and to assess the validity of results. Although binary data are easier to interpret, where continuous data are used some measure of variance should be provided. Data presented in graphs should be accompanied by exact numbers and standard deviations (SDs) in the text.

2. Specific

Large pragmatic well-designed randomised trials led by independent researchers, which measure simple, meaningful and highly applicable outcomes such as 'being tranquil', 'being asleep', 'serious adverse effect', 'needing additional medication', 'further aggressive episodes', and 'economic outcomes' are still required. These studies just need modest financial support and firm help from ethics committees who should understand the need to produce good evidence for practice in this difficult area of health. See Table 2 for a suggested design for a study.

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

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Dai 2012

Methods	Allocation: randomised Blindness: not reported Duration: 8 weeks
Participants	Diagnosis: schizophrenia with aggressive behaviour (ICD-10) N = 40 Age: mean 25.3 years; range 20-30 years. Sex: 32 males, 8 females. History: mean length of illness of 1.45 years, range from 1 month to 3 years; history of aggressive behaviour (total score of Modified overt aggression scale more than 5 after admission for 1 week); type of schizophrenia: 29 participants with paranoid schizophrenia; 5 participants with hebephrenic schizophrenia; 6 participants with unclear type Excluded: organic psychosis, affective disorder or other psychogeny; body diseases, epilepsy, encephalosis, alcohol or drug dependence; women in gestational or suckling period Setting: Dalian, China (inpatient).
Interventions	1. Risperidone: initial dose of 1 mg/day, increased to 3 mg to 4 mg/day in 7 days, then dose adjusted according to illness condition within 1 month, maximum dose < 6 mg/day. N = 20 2. Quetiapine: initial dose of 100 mg/day, increased to 400 mg to 500 mg/day in 7 days, then dose adjusted according to illness condition within 1 month, maximum dose < 750 mg/day. N = 20 Trihexyphenidyl or benzodiazepines could be used as p.r.n. drugs
Outcomes	Specific behaviour: aggression - MOAS endpoint score (2, 4, 6, 8 weeks; Table 3 in p. 2063) Mental state: Clinical response (8 weeks; section 2.1 in p.2062), PANSS endpoint score (2, 4, 6, 8 weeks; Table 2 in p.2062), PANSS positive symptoms sub-scale endpoint score (2, 4, 6, 8 weeks; Table 2 in p.2062), PANSS negative symptoms sub-scale endpoint score (2, 4, 6, 8 weeks; Table 2 in p.2062), PANSS general psychopathology sub-scale endpoint score (2, 4, 6, 8 weeks; Table 2 in p.2062). Adverse events: specific adverse events (8 weeks; Table 4 in p.2063)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "All the cases were randomly assigned to two group…" (p.2061) Comments: the author described a random component, but no more detail about ran-

Dai 2012 (*Continued*)

		dom methods were given
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias
Selective reporting (reporting bias)	Unclear risk	Data on p.r.n. drugs usage not reported. Protocol not available; compared to the 'methods' section, no evidence of 'selective reporting' bias
Other bias	High risk	Small sample size

Jin 2013

Methods	Allocation: randomised Blindness: not reported Duration: 4 weeks
Participants	Diagnosis: schizophrenia with impulsive and aggressive behaviour (CCMD-3) N = 63 Age: mean 39.4 years; range 18-65 years. Sex: 32 males, 31 females. History: length of illness: mean 3.3 years; PANSS total score before treatment: mean 89.69; all patients received risperidone before enrolment Excluded: severe heart disease, hepatic disease, renal disease or physical ailments; drug allergies or leukopenia; epilepsy, alcohol and substance dependence Setting: Liaoning, China (inpatient).
Interventions	1. Risperidone: dosage not stated. N = 31. 2. Risperidone + magnesium valproate sustained release tablet: risperidone dosage not stated; magnesium valproate sustained release initial dose 500 mg/day, increased to 750 mg to 1000 mg/day over one week. N = 32 Trihexyphenidyl and propanolol could be used as p.r.n. drugs
Outcomes	Specific behaviour: agitation - PANSS-EC endpoint score (2, 4 weeks; Table 1 in p.161) . Mental state: PANSS endpoint score (2, 4 weeks; Table 1 in p.161), PANSS positive symptoms sub-scale endpoint score (2, 4 weeks; Table 1 in p.161). Adverse effects: specific adverse effects (4 weeks; Table 3 in p.161)

Jin 2013 (*Continued*)

	Unable to use: Adverse effects: TESS endpoint score (4 weeks; Table 2 in p.161)*.
Notes	* typo input error is likely

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "All the cases were randomly assigned to two group…" (p.161) Comments: the author described a random component, but no more detail about random methods were given
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Two participants left the study early due to adverse effects; these data were lost
Selective reporting (reporting bias)	Unclear risk	Data on p.r.n. drugs usage not reported. Protocol not available; compared to the 'methods' section, no evidence of 'selective reporting' bias
Other bias	High risk	Small sample size

Li 2013

Methods	Allocation: randomised Blindness: not reported Duration: 8 weeks
Participants	Diagnosis: schizophrenia with aggressive behaviour (ICD-10).N = 60 Age: mean 30 years; range 18-60 years. Sex: 31 males, 29 females History: length of illness: mean 5.3 years; education years: mean 8 years; PANSS total score before enrolment: mean 78.5; range more than 70; MOAS total score before enrolment: mean 8.8; range more than 4 Excluded: severe body diseases; drug dependence; women in gestational or suckling

Li 2013 (*Continued*)

	period Setting: Shanxi, China (outpatient).
Interventions	1. Risperidone: initial dose of 1 mg/day, maximum dose of 6 mg/day; mean dose of 3.3 ± 1.6 mg/day. N = 30 2. Risperidone + magnesium valproate sustained release: risperidone initial dose of 1 mg/day, maximum dose of 4 mg/day; mean dose of 2.5 mg ± 1.5 mg/day; magnesium valproate sustained release initial dose of 500 mg/day, maximum dose of 1000 mg/day; mean dose of 800 mg ±5 0 mg/day. N = 30 Benzodiazepines could be used as p.r.n. drugs.
Outcomes	Specific behaviour: agitation - MOAS endpoint score (2, 4, 8 weeks; Table 2 in p.70). Mental state: PANSS endpoint score (2, 4, 8 weeks; Table 1 in p.70), PANSS positive symptoms sub-scale endpoint score (2, 4, 8 weeks; Table 1 in p.70), PANSS negative symptoms endpoint score (2, 4, 8 weeks; Table 1 in p.70), PANSS general psychopathology endpoint score (2, 4, 8 weeks; Table 1 in p.70). Adverse effects: specific adverse events (4 weeks; section 2.3 in p.70) Unable to use: Adverse effects: gastrointestinal reaction (definition too vague)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "All the cases were randomly assigned to two group…" (p.69) Comments: the author described a random component, but no more detail about random methods
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias
Selective reporting (reporting bias)	Unclear risk	Data on p.r.n. drugs usage not reported. Protocol not available; compared to the 'methods' section, no evidence of 'selective reporting' bias

Li 2013 (*Continued*)

Other bias	High risk	Small sample size

Lim 2010

Methods	Allocation: randomised Blindness: open-label, rater blind. Duration: 24 hours
Participants	Diagnosis: DSM-IV diagnosis of schizophrenia (N = 78), bipolar disorder (N = 43), others (N = 3) N = 124 Age: range 18-65 years Sex: 66 males, 58 females History: "acute psychotic agitation in the emergency room or inpatient ward" (p.82) Excluded: neurological disorder, severe medical disease, alcohol or other psychoactive substance misusers, history of neuromalignant syndrome or hypersensitivity to trial medications, pregnant or lactating women, people treated with antipsychotics or benzodiazepines within 6 hours to the start of the trial or with depot antipsychotic within one treatment cycle of enrolment Setting: Korea (psychiatric emergency room inpatient ward).
Interventions	1. Risperidone: oral dose 2 mg, maximum 6 mg during 24 hours. N = 62 2. Haloperidol: IM dose 5 mg, maximum 15 mg during 24 hours. N = 62
Outcomes	Specific behaviour: no clinically important change in agitation (defined as PANSS-PAS* 50% reduction from the baseline score) Use of additional medication - lorazepam. Adverse events Leaving the study early Unable to use: Mental state: PANSS Total (mean, SE/SD not reported, P values of significant findings reported, overall F value) Mental state: YMRS Total (mean, SE/SD/CI not reported). Global state: CGI-S (mean, SE/SD not reported, P values of significant findings reported, overall F value) Specific behaviour: Behaviorally Anchored Rating Scale (mean, SE/SD/CI not reported)
Notes	4 participants allocated to risperidone and 17 participants allocated to haloperidol received more than previously stated maximum dose Intramuscular injection of 4 mg lorazepam or 2 mg of oral lorazepam was used as a rescue medicine if severe extrapyramidal symptoms (EPS) had occurred. Although paper gives information about use of additional lorazepam in 7 participants from risperidone and 8 from haloperidol group, it does not provide further details * Authors of the manuscript use the "PANSS-EC" term but provide the items list of PANSS-PAS; in other published studies they refers to this as an "5 item acute agitation cluster [...] from PANSS score"
Risk of bias	

Lim 2010 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were assigned "according to a predefined randomization code that was balanced to ensure even distribution of patients in each treatment group" (p.82)
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was an open-label study where one group received IM. and the other group received an orodispersible tablet
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study was rater-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	There is no evidence of incomplete outcome data. The authors give reasons for the participants who discontinued the study
Selective reporting (reporting bias)	High risk	Authors report that anti-parkinsonian drugs could be given at the lowest effective dose, however the amount administered is not described in the results. Several outcomes are not reported. Protocol not available
Other bias	High risk	Sponsored by Janssen Phamaceutica Korea. Authors state they used PANSS-EC but provide description for PANSS-PAS, while calling this scale a "5 item acute agitation cluster" in the other linked publications

Walther 2014

Methods	Allocation: randomised. Blindness: single. Duration: 96 hours.
Participants	Diagnosis: DSM-IV criteria for schizophrenia (n = 27), schizoaffective (n = 6), or schizophreniform disorder (n = 10) N = 43* Age: mean 34 years (SD 10), range 18-55 years. Sex: 31 males, 12 females. History: severely agitated, admitted to acute care inpatient unit Excluded: people who did not give post hoc informed consent, duration ill ~ 7 years, 84% free of antipsychotics or mood stabilisers at the time of study inclusion

Walther 2014 (*Continued*)

	Setting: Switzerland (acute care psychiatry units).
Interventions	1. Risperidone: 2 mg to 6 mg/day for 5 days, flexible dose, oral. N = 14 2. Haloperidol: 15 mg/day for 5 days, fixed dose, oral. N = 14 3. Olanzapine: 20 mg/day for 5 days, fixed dose, oral. N = 15 Additional use of up to 30 mg diazepam/day was permitted (day 1), up to 60 mg/day, days 2-5
Outcomes	Specific behaviour: PANSS-PAS score**, need for seclusion room Leaving the study early Lack of efficacy Adverse effects: movement disorders (AIMS for risperidone vs haloperidol, Barnes scale, SAS) Unable to use: Use of additional medication - diazepam/biperiden (data not reported by group) Adverse effects: movement disorders (AIMS for risperidone vs olanzapine: no SD)
Notes	* eligible patients were 52 patients but 9 refused to provide post-hoc consent ** scores and SE values were extracted from figures, see methods for further details; SD values were then calculated Authors were contacted (2nd July 2016, 9th July 2016).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was performed by creating 3 sets of random numbers between 1 and 60 using a computer-based research randomizer (www.randomizer.org)" (pg.125)
Allocation concealment (selection bias)	Low risk	" The order of inclusion determined allocation to treatment group. The randomisation list was locked in the office of the principal investigator [...], who was engaged neither in treatment nor in study assessments" (pg.125)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All ratings were performed by 1 of 2 raters who were blind to treatment allocation." (pg. 215)

Walther 2014 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	9 participants were excluded post-randomisation due to refusal to provide post-hoc consent; their treatment assignment was not provided. 6 participants dropped out but LOCF method was used to deal with attrition bias
Selective reporting (reporting bias)	High risk	PANSS-PAS scores at 24, 48, 72, and 96 hours not provided. PANSS scores at 96 hours not provided. Number of patients that needed additional BDZ not provided. Number of patients that needed additional biperiden not provided Protocol not available.
Other bias	High risk	Authors declare no conflicts of interest but all do have some affiliation with relevant companies Small sample size.

Wang 2012

Methods	Allocation: randomised Blindness: open-label Duration: 4 weeks
Participants	Diagnosis: schizophrenia with agitation (CCMD-3). N = 68 Age: mean 30.5 years; range 17~60 years. Sex: 57 males, 11 females. History: all patients did not receive clozapine; BPRS total score > = 35 before enrolment Excluded: severe body diseases, alcohol or drug dependence. Setting: Liaoning, China (inpatient)
Interventions	1. Risperidone: initial dose not stated, increased to treatment dosage in 7 to 10 days, then adjust dose according to illness condition; mean dose (4.2 ± 0.35) mg/day. N = 33 2. Risperidone + oxcarbazepine: initial dose not stated for both drugs. Risperidone increased to treatment dosage in 7 to 10 days, then adjust dose according to illness condition; mean dose (4.1 ± 0.4) mg/day. Oxcarbazepine: initial dose not stated, increased to 0.9~1.8 g/day in one week, then adjust dose according to illness condition; mean dose (1.20 ± 0.42) g/day. N = 35
Outcomes	Specific behaviour: agitation - PANSS-EC endpoint score (1, 2, 4 weeks; Table 1 in p. 2957). Mental state: BPRS endpoint score (1, 2, 4 weeks; Table 1 in p.2957). Global outcome: CGI endpoint score (1, 2, 4 weeks; Table 1 in p.2957). Adverse effects: specific adverse effects (4 weeks; 2.3 in p.2957)

Wang 2012 (*Continued*)

	Unable to use: No clinical response (4 weeks; 2.2 in p.2957), data is available at 4 weeks only which is not consistent with the "rapid tranquillisation" topic
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "All the cases were randomly assigned to two group according to random number table" (p.2061)
Allocation concealment (selection bias)	Unclear risk	The author did not describe the allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial. The blinding of participants and personnel not ensured
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open trial. The blinding of outcome assessment not ensured.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants (3/68, 4.4%) left study early due to poor clinical response (2 participants in risperidone alone group), however, the author used LOCF methodology to deal with missing data
Selective reporting (reporting bias)	Unclear risk	Protocol not available; compared to the 'methods' section, no evidence of 'selective reporting' bias
Other bias	High risk	Small sample size

Wang 2013

Methods	Allocation: randomised Blindness: not reported Duration: 6 weeks
Participants	Diagnosis: schizophrenia with aggressive behaviour (CCMD-3). N = 68 Age: mean 37.2 years. Sex: 43 males, 25 females.

	History: mean length of illness of 6 years, range from 6 months to 23 years; PANSS total score ≥ 60 before enrolment; MOAS total score ≥ 4 before enrolment Excluded: severe heart, liver and kidney or nervous system diseases, severe body diseases; endocrine disease, blood disease, hypertension; glaucoma; women in gestational or suckling period; with severe suicide risk; with poor compliance; allergy to study drugs Setting: Sichuan, China (inpatient).
Interventions	1. Risperidone: initial dose of 1 mg/day, dose range from 4 mg to 6 mg/day. N = 34 2. Risperidone + sodium valproate: risperidone initial dose of 1 mg/day, dose range from 4 mg to 6 mg/day. Sodium valproate initial dose of 4 mg/day, dose range from 600 mg to 1200 mg/day. N = 34 Additional treatment with benzodiazepines or benzhexol have been used as p.r.n. drugs
Outcomes	Specific behaviour: aggression - MOAS endpoint score (2, 4, 6 weeks; Table 2 in p.73). Mental state: PANSS endpoint score (2, 4, 6 weeks; Table 1 in p.73), PANSS positive symptoms sub-scale endpoint score (2, 4, 6 weeks; Table 1 in p.73), PANSS negative symptoms sub-scale endpoint score (2, 4, 6 weeks; Table1 in p.73), PANSS general psychopathology sub-scale endpoint score (2, 4, 6 weeks; Table 1 in p.73). Adverse events: specific adverse events (6 weeks; Table 3 in p.73)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "All the cases were randomly assigned to two group…" (p.73). Comments: the author described a randomised component, but no more detail about random methods were given
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome date
Selective reporting (reporting bias)	Unclear risk	Data on p.r.n. drugs usage not reported. Protocol not available; compared to the 'methods' section, no evidence of 'selective reporting' bias

Wang 2013 (*Continued*)

Other bias	High risk	Small sample size

Yao 2010

Methods	Allocation: randomised Blindness: not reported Duration: 8 weeks, follow-up 6 months on participants which had clinical response after treatment
Participants	Diagnosis: schizophrenia with aggressive behaviour (CCMD-3). N = 62 Age: mean 26.9 years; range 17-42 years. Sex: 33 males, 29 females. History: length of illness: not stated; marital status: 23 unmarried, 38 married; education: 3 illiterate, 53 less than Bachelor degree, 6 Bachelor degree or more Excluded: severe physical ailments; patients received antipsychotics within 2 weeks before enrolment; patients with positive family history Setting: Henan, China (inpatient).
Interventions	1. Risperidone: initial dose of 1 mg/day, increased to 4 mg to 6 mg/day in 7-15 days; mean (SD): 4.98 (1.07) mg/ay. N = 31 2. Risperidone + magnesium valproate sustained release tablet: risperidone initial dose of 1 mg/day, increased to 4 mg to 6 mg/day in 7-15 days; magnesium valproate sustained release tablet dose of 500 mg/day. N = 31 Benzodiazepines (alprazolam, 0.8 mg bed-time) could be used for participants with poor quality of sleep as p.r.n. drugs
Outcomes	Mental state: no clinical response at PANSS (8 weeks; section 2.1 in p.2714), PANSS endpoint score (2, 4, 6, 8 weeks; Table 1 in p.2714). Adverse effects: specific adverse effects. Unable to use: Global state: CGI endpoint score (not reported).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "… were randomly into…" (p. 2713) Comments: the author described a random component, but no more detail about random methods
Allocation concealment (selection bias)	Unclear risk	Not stated

Yao 2010 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not state
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of attrition bias
Selective reporting (reporting bias)	High risk	CGI endpoint score measured at 2, 4, 6, 8 weeks but not reported. Data on p.r.n. drugs usage not reported. Protocol not available
Other bias	High risk	Small sample size.

Zhou 2013

Methods	Allocation: randomised Blindness: not reported Duration: 7 days
Participants	Diagnosis: schizophrenia with agitation (CCMD-3) N = 54 Age: mean 26.0 years Sex: 28 males, 26 females. History: mean length of illness of 2.47 years; mean PANSS-EC baseline score of 21.98, range starting from 15; mean MOAS total baseline score of 8.37 Excluded: organic diseases, alcohol or drug dependence. Setting: Guangxi, China (inpatient).
Interventions	1. Risperidone: initial dose 1 mg/day, twice daily from day 1 to day 3, increased to 2 mg/day twice daily from the day 4 to day 7. N = 27 2. Risperidone + sodium valproate: Risperidone initial dose 1 mg/day twice daily from the day 1 to day 3, increased to 2 mg/day twice daily from the day 4 to the day 7. Sodium valproate: intravenous drip 400 mg twice daily from day 2 to day 4. N = 27 Benzhexol (2 mg/day) or alprazolam (0.4 mg to 0.8 mg/day) could be used when necessary
Outcomes	Specific behaviour - agitation: PANSS-EC endpoint score (3, 5, 7 days; Table 1 in p. 262), Specific behaviour - aggression: MOAS endpoint score (3, 5, 7 days; Table 1 in p. 262). Adverse events: TESS endpoint score (3, 5, 7 days; Table 2 in p.262), specific adverse events (7 days; 2.2 in p.262).
Notes	

Zhou 2013 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: " [...] were randomly divided into [...]" (p.261). Authors describe a random component, but no more detail about random methods were given
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Data on p.r.n. drugs usage not reported. Protocol not available; compared to the 'methods' section, no evidence of 'selective reporting' bias
Other bias	High risk	Small sample size

AIMS: Abnormal Involuntary Movement Scale.
BDZ: Benzodiazepine
BPRS: Brief Psychiatric Rating Scale.
CCMD: Chinese Classification of Mental Disorders.
CGI: Clinical Global Impression.
CGI-I: Clinical Global Impression - Improvement.
CGI-S: Clinical Global Impression - Severity.
CI: Confidence Interval.
DSM: Diagnostic and Statistical Manual of mental disorders.
ICD-10: International Classification of Diseases 10th edition.
IM: Intramuscular.
LOCF: Last Observation Carried Forward.
MOAS: Modified Overt Aggression Scale.
PANSS-EC: Positive and Negative Syndrome Scale - Excited Component.
PANSS-PAS: Positive and Negative Syndrome Scale - Psychotic Agitation Sub-score.
P.r.n.: Pro re nata (if needed).
SAS: Simpson-Angus Scale.
SD: Standard Deviation.
SE: Standard Error.

TESS: Treatment Emergent Symptom Scale.
YMRS: Young Mania Rating Scale.

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

Study	Reason for exclusion
Beck 1997	Allocation: quasi-randomised
Belenkaya 2005	Allocation: randomised Participants: patients with acute mania; not psychosis-induced aggression or agitation that required rapid tranquillisation
Briken 2002	Allocation: randomised Participants: schizophrenia or schizoaffective-disorder PANSS mean score of 2.00 (SD: 1.28) and a 3-day washout period suggests improbability on psychosis-induced aggression or agitation requiring rapid tranquillisation
Buckley 1997	Allocation: not randomised
Buitelaar 2001	Allocation: randomised Participants: adolescents with severe aggressive behaviour and borderline intelligence or mild mental retardation; not psychosis-induced aggression or agitation that required rapid tranquillisation
Chan 2013	Allocation: randomised Participants: schizophrenia; not psychosis-induced aggression or agitation that required rapid tranquillisation
Citrome 2001	Allocation: randomised Participants: schizophrenia and persistent aggressive behaviour; not psychosis-induced aggression or agitation that required rapid tranquillisation
Citrome 2004	Allocation: randomised Participants: acute exacerbation of schizophrenia; not psychosis-induced aggression or agitation that required rapid tranquillisation
Citrome 2007	Allocation: randomised Participants: schizophrenia patients who also exhibit problems with hostility; not psychosis-induced aggression or agitation that required rapid tranquillisation
Conde 2011	Allocation: randomised Participants: individuals with acute psychotic agitation. Intervention: risperidone + clonazepam vs haloperidol + clonazepam
Currier 2000	Allocation: not randomised

(*Continued*)

Currier 2004	Allocation: randomised Participants: individuals with schizophrenia, exhibiting agitation Intervention: risperidone + lorazepam vs haloperidol vs lorazepam
Czobor 1995	Allocation: randomised Participants: schizophrenia; not psychosis-induced aggression or agitation that required rapid tranquillisation
Fang 2012	Allocation: randomised Participants: schizophrenia exhibiting agitation Intervention: risperidone + clonazepam vs haloperidol
Francey 2007	Allocation: randomised Participants: first episode psychosis with low risk of self-harm or aggression; not psychosis-induced aggression or agitation that required rapid tranquillisation
Greenspan 2005	Allocation: not randomised
Han 2005	Allocation: randomised Participants: schizophrenia with agitation/aggression; not psychosis-induced aggression requiring rapid tranquillisation
Hatta 2008	Allocation: not randomised
He 2005	Allocation: randomised Participants: patients with schizophrenia; not psychosis-induced aggression or agitation that required rapid tranquillisation
Hong 2014	Allocation: randomised Participants: individuals with schizophrenia exhibiting agitation Intervention: risperidone + clonazepam vs MECT
Hou 2011	Allocation: randomised Participants: acute schizophrenia with excitement and agitation Intervention: risperidone + lorazepam vs haloperidol + promethazine
Hovens 2005	Allocation: not randomised
Huaqiang 2009	Allocation: randomised Participants: schizophrenia and schizophreniform psychosis and dominated with excitement and agitation; not psychosis-induced aggression or agitation that required rapid tranquillisation
ISRCTN11736448 2003	Allocation: randomised Participants: aggressive challenging behaviour and intellectual disability; not psychosis-induced aggression or agitation that required rapid tranquillisation

(*Continued*)

Jiang 2012	Allocation: randomised Participants: patients with schizophrenia exhibiting agitation or aggression Intervention: risperidone + clonazepam vs haloperidol
Kane 2003	Allocation: randomised Participants: patients with schizophrenia; not psychosis-induced aggression or agitation that required rapid tranquillisation
Kirwan 2002	Allocation: randomised Participants: nursing home patients with dementia; not psychosis-induced aggression or agitation that required rapid tranquillisation
Kolivakis 2002	Allocation: randomised Participants: schizophreniform disorder and early paranoid schizophrenia; not psychosis-induced aggression or agitation that required rapid tranquillisation
Lewis 2006	Allocation: not randomised
Li 2014	Allocation: not randomised (full text not consistent with abstract text)
Lieberman 2001	Allocation: randomised Participants: treatment resistant patients with schizophrenia; not psychosis-induced aggression or agitation that required rapid tranquillisation
Liu 2010	Allocation: randomised Participants: schizophrenia with excitement and agitation in the acute stage; not psychosis-induced aggression or agitation that required rapid tranquillisation
Liu 2012	Allocation: randomised Participants: patients with schizophrenia exhibiting agitation or aggression Intervention: risperidone + haloperidol vs risperidone + clonazepam vs haloperidol
NCT00174200 2005	Allocation: randomised Participants: antipsychotic-naive, non-agitated patients diagnosed with first-episode schizophrenia or schizophreniform disorder; not psychosis-induced aggression or agitation that required rapid tranquillisation
NCT00203775 2005	Allocation: randomised Participants: psychotic disorder; not psychosis-induced aggression or agitation that required rapid tranquillisation
NCT00205699 2005	Allocation: randomised Participants: not psychosis-induced aggression or agitation that required rapid tranquillisation
NCT00418873 2007	Allocation: randomised Participants: aggressive schizophrenic patients in an acute ward Intervention: risperidone vs zotepine Outcomes: study terminated due to difficulty in recruiting participants - no usable data

(*Continued*)

NCT00485498 2003	Allocation: randomised Participants: schizophrenia; not psychosis-induced aggression or agitation that required rapid tranquillisation
Ou 2007	Allocation: randomised Participants: schizophrenia with aggressive behavior; not psychosis-induced aggression or agitation that required rapid tranquillisation
Pei 2009	Allocation: quasi-randomised
Peng 2009	Allocation randomised Participants: people with schizophrenia who are hospitalised for the first time; not psychosis-induced aggression or agitation that required rapid tranquillisation
Potkin 2005	Allocation: not randomised
Schooler 2003	Allocation: not randomised
Swanson 2008	Allocation: randomised Participants: schizophrenia; not psychosis-induced aggression or agitation that required rapid tranquillisation
Tang 2007	Allocation: randomised Participants: acute excitement phase of schizophrenia; not psychosis-induced aggression or agitation
Temputrn 2007	Allocation: randomised Participants: schizoaffective disorder experiencing an acute exacerbation of psychotic symptoms; not psychosis-induced aggression or agitation that required rapid tranquillisation
Tosic Golubovic Suzana 2009	Allocation: randomised. Participants: people with schizophrenia or schizoaffective experiencing an acute psychotic episode; not psychosis-induced aggression or agitation that required rapid tranquillisation
Veser 2006	Allocation: randomised Participants: people with psychosis-induced agitation, however the study exclusion criteria included an inability to give informed consent; not psychosis-induced aggression or agitation that required rapid tranquillisation
Villari 2008	Allocation: quasi-randomised
Wan 2005	Allocation: randomised Participants: people with schizophrenia and agitation/aggression; not psychosis-induced aggression or agitation that required rapid tranquillisation
Wang 2004	Allocation: randomised Participants: acute agitation in schizophrenia; not psychosis-induced aggression or agitation that required rapid tranquillisation

(*Continued*)

Wang 2006	Allocation: randomised Participants: people with schizophrenia who are displaying aggressive behaviours, not acute agitation or aggressive episodes and thus not requiring rapid tranquillisation
Wang 2015	Allocation: randomised Participants: people with schizophrenia exhibiting agitation or aggression Intervention: risperidone + haloperidol vs risperidone + ECT
Wei 2010	Allocation: randomised Participants: adolescents with schizophrenia; not psychosis-induced aggression or agitation that required rapid tranquillisation
Xi 2010	Allocation: randomised Participants: schizophrenia with impulsive and aggressive symptoms; not psychosis-induced aggression or agitation that required rapid tranquillisation
Xuan 2007	Allocation: randomised Participants: people with acute schizophrenia with excitement/agitation and other behavioural disorders; not psychosis-induced aggression or agitation that required rapid tranquillisation
Zhang 2012	Allocation: randomised Participants: people with schizophrenia exhibiting agitation or aggression Intervention: risperidone + clonazepam vs haloperidol.
Zheng 2010	Allocation: randomised Participants: people with schizophrenia who have acute psychotic agitation Intervention: risperidone + clonazepam vs haloperidol
Zhou 2012	Allocation: randomised Participants: people with schizophrenia exhibiting agitation or aggression Intervention: risperidone + clonazepam vs haloperidol

ECT: electroconvulsive therapy.
MECT: modern electroconvulsive therapy.
PANSS: Positive And Negative Syndrome Scale.
SD: standard deviation.

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

Herrera 2005

Methods	Allocation: randomised. Blindness: double. Duration: not stated.
Participants	Diagnosis: psychosis with agitation and/or violence. N = 20. Age: not stated. Sex: not stated. History: not stated. Exclusion: not stated. Setting: psychiatric emergency department.
Interventions	1. Haloperidol: dose 10 mg/IM. 2. Risperidone: dose 2 mg/liquid.
Outcomes	Specific behaviour - agitation: PANSS-EC.
Notes	Conference abstract, full characteristics and outcome data not reported. Attempted to contact author

Hsu 2010

Methods	Allocation: randomised. Blindness: single. Duration: 24 hours.
Participants	Diagnosis: DSM-IV diagnosis of schizophrenia (N = 20), bipolar disorder (N = 18), schizoaffective disorder (N = 1) , delusional disorder or others (N = 3) N = 42. Age: range 18-65 years. Sex: 20 males and 22 females. History: within 24 hours of admission - previous psychiatric history not stated Exclusion: "pregnant or lactating women; patients with serious medical illnesses; patients with closed-angle glaucoma; patients with an allergic reaction to olanzapine, risperidone, or haloperidol; or patients who had received a long-acting antipsychotic agent injection within 30 days were excluded" Setting: Taiwan (acute medical centre).
Interventions	1. Haloperidol: dose 7.5 mg/IM. N = 11. 2. Risperidone: dose 3 mg/liquid. N = 10. 3. Olanzapine: dose 10 mg/IM. N = 11. 4. Olanzapine: dose 10 mg/velotab. N = 10.
Outcomes	Specific behaviour - agitation: PANSS-EC*.
Notes	* attempted to contact authors to ask for any usable data.

Lasic 2006

Methods	Allocation: randomised. Blindness: not stated. Duration: up to 3 months.
Participants	Diagnosis: ICD X diagnosis of acute exacerbation of schizophrenia or schizoaffective disorder, mania with psychotic features, acute paranoid reaction, or delusional disorders N = 60. Age: ≥18 years. Exclusion: "delirium, epilepsy, or mental retardation; intoxication or symptoms of withdrawal from alcohol or other psychoactive substances; clinical laboratory values indicating serious medical illness; treatment with any antipsychotic or benzodiazepine within 6 hours of screening; a history of neuroleptic malignant syndrome or known hypersensitivity to any of the trial medications; treatment with a depot antipsychotic within 1 treatment cycle of screening and use of disallowed medications" Setting: Croatia (acute psychiatric inpatient ward).
Interventions	1. Haloperidol IM (dose not reported). 2. Risperidol liquid (dose not reported).
Outcomes	Specific behaviour - agitation: BARS, PANSS agitation cluster. Mental state: PANSS. Global state: CGI-I. Adverse effects.
Notes	Conference abstract, full characteristics and outcome data not reported. Attempted to contact author

NCT00859872

Methods	Allocation: randomised. Blindness: single. Duration: 47 days.
Participants	Diagnosis: DSM-IV diagnosis of acute exacerbation of schizophrenia or schizoaffective disorder with agitation Age: range 18-45 years. Sex: males and females. History: not stated. Exclusion: pregnant or lactating women, serious medical illness, known sensitivity to study medication, treatment with a depot antipsychotic with 1 cycle of screening, use of disallowed medication, psychosis caused by "delirium, epilepsy, mental retardation and affective disorder; intoxication or symptoms of withdrawal from alcohol of other psychoactive substances." Setting: China (psychiatric inpatient ward).
Interventions	1. Haloperidol: dose 5 mg to 20 mg/IM/day. 2. Risperidone: dose 2 mg to 6 mg/oral/day + clonazepam: dose 4 mg to 8 mg/oral/day
Outcomes	Specific behaviour - agitation: PANSS-EC. Mental state: PANSS.
Notes	Protocol, full characteristics and outcome data not reported. Unable to establish contact details at this time

BARS: Behavioural Activity Rating Scale.
CGI-I: Clinical Global Impression - Improvement.
DSM: Diagnostic and Statistical Manual of mental disorders.
ICD: International Classification of Diseases.
IM: Intramuscular.
PANSS: Positive and Negative Syndrome Scale.
PANSS-EC: Positive and Negative Syndrome Scale - Excited Component.

DATA AND ANALYSES

Comparison 1. RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Specific behaviour: 1a. Agitation - Various measures	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 PANSS-PAS response up to 24 hours (≥ 50% reduction at PANSS-PAS score)	1	124	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.86, 1.26]
2 Specific behaviour: 1b. Agitation - Average scores - i. up to 2 hours	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Endpoint score (PANSS-PAS, high = worse)	1	28	Mean Difference (IV, Fixed, 95% CI)	0.40 [-4.42, 5.22]
3 Specific behaviour: 1c. Agitation - Average scores - ii. up to 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Endpoint score (PANSS-PAS, high = worse)	1	28	Mean Difference (IV, Fixed, 95% CI)	0.20 [-3.96, 4.36]
4 Specific behaviour: 1d. Agitation - Average scores - iii. over 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Endpoint score at 48 hours (PANSS-PAS, high = worse)	1	28	Mean Difference (IV, Fixed, 95% CI)	1.5 [-1.36, 4.36]
4.2 Endpoint score at 72 hours (PANSS-PAS, high = worse)	1	28	Mean Difference (IV, Fixed, 95% CI)	1.40 [-1.62, 4.42]
4.3 Endpoint score at 96 hours (PANSS-PAS, high = worse)	1	28	Mean Difference (IV, Fixed, 95% CI)	2.90 [-0.34, 6.14]
5 Global outcome: 1a. General - Need for additional measures	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Need for benzodiazepine up to 24 hours	1	124	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.34, 2.27]
5.2 Need for seclusion room	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.55]
5.3 Use of restraints	1	28	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.43, 9.21]
6 Global outcome: 1b. General - Need for additional medication (skewed data)			Other data	No numeric data
7 Adverse effects: 1. General	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 One or more AEs up to 24 hours	1	124	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.54, 1.66]
8 Adverse effects: 2a. Specific - Arousal level	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Insomnia up to 24 hours	1	124	Risk Ratio (M-H, Fixed, 95% CI)	13.0 [0.75, 225.90]

8.2 Somnolence up to 24 hours	1	124	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.51, 3.24]
9 Adverse effects: 2b. Specific - Movement disorder - i. Various	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 EPS up to 24 hours	1	124	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.22, 1.80]
10 Adverse effects: 2b. Specific - Movement disorder - ii. Need for biperiden			Other data	No numeric data
11 Adverse effects: 2b. Specific - Movement disorder - iii. Average scores (skewed data)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11.1 Endpoint scores at 96 hours (AIMS, high = worse)	1	28	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Endpoint scores at 96 hours (BARS, high = worse)	1	28	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.56, 0.36]
11.3 Endpoint scores at 96 hours (SAS, high = worse)	1	28	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.00, 2.20]
12 Adverse effects: 2c. Specific - Miscellaneous	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Headache up to 24 hours	1	124	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.18, 3.21]
12.2 Dizziness up to 24 hours	1	124	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.26, 3.82]
13 Leaving the study early	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 For any reason	2	152	Risk Ratio (M-H, Fixed, 95% CI)	2.2 [0.51, 9.48]
13.2 Due to adverse effects	1	124	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.37]
13.3 Lack of efficacy	1	28	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [0.53, 152.93]

Comparison 2. RISPERIDONE vs OTHER ANTIPSYCHOTIC: b. OLANZAPINE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Specific behaviour: 1. Agitation - Average scores - i. Up to 2 hours	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Endpoint score (PANSS-PAS, high = worse)	1	29	Mean Difference (IV, Fixed, 95% CI)	2.5 [-2.46, 7.46]
2 Specific behaviour: 1. Agitation - Average scores - ii. Up to 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Endpoint score (PANSS-PAS, high = worse)	1	29	Mean Difference (IV, Fixed, 95% CI)	0.90 [-3.40, 5.20]
3 Specific behaviour: 1. Agitation - Average scores - iii. over 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Endpoint score at 48 hours (PANSS-PAS, high = worse)	1	29	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-5.15, 2.75]

3.2 Endpoint score at 72 hours (PANSS-PAS, high= worse)	1	29	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-4.47, 3.87]
3.3 Endpoint score at 96 hours (PANSS-PAS, high = worse)	1	29	Mean Difference (IV, Fixed, 95% CI)	2.10 [-1.41, 5.61]
4 Global outcome: 1a. General - Need for additional measures	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Need for seclusion room	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.02, 8.07]
4.2 Use of restraints	1	29	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.39, 5.28]
5 Global outcome: 1b. General - Need for additional medication (skewed data)			Other data	No numeric data
6 Adverse effects: 1a. Specific - Movement disorder - i. Meed for biperiden			Other data	No numeric data
7 Adverse effects: 1b. Specific - Movement disorder - ii. Average scores (skewed data)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Endpoint score (BARS, high = worse)	1	29	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.43, 0.83]
7.2 Endpoint score (SAS, high = worse)	1	29	Mean Difference (IV, Fixed, 95% CI)	1.80 [-0.63, 4.23]
8 Leaving the study early	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Lack of efficacy	1	29	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [0.46, 9.93]

Comparison 3. RISPERIDONE vs OTHER ANTIPSYCHOTIC: c. QUETIAPINE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Specific behaviour: 1. Aggression - Average scores - i. Over 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Endpoint score at 2 weeks (MOAS, high = worse)	1	40	Mean Difference (IV, Fixed, 95% CI)	1.80 [0.20, 3.40]
1.2 Endpoint score at 4 weeks (MOAS, high = worse)	1	40	Mean Difference (IV, Fixed, 95% CI)	0.90 [-0.44, 2.24]
1.3 Endpoint score at 6 weeks (MOAS, high = worse)	1	40	Mean Difference (IV, Fixed, 95% CI)	0.70 [-0.29, 1.69]
1.4 Endpoint score at 8 weeks (MOAS, high = worse)	1	40	Mean Difference (IV, Fixed, 95% CI)	0.55 [-0.40, 1.50]
2 Mental state: 1a. No change in general mental state	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 No response at 8 weeks ($\leq$ 25% reduction at PANSS score)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.16, 6.42]
3 Mental state: 1b. Change in general mental state	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

3.1 Clinical response at 8 weeks (25 - 50% reduction at PANSS score)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.34, 5.21]
3.2 Clinical response at 8 weeks (50 - 75% reduction at PANSS score)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.39, 1.95]
3.3 Clinical response at 8 weeks (≥ 75% reduction at PANSS score)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.43, 2.33]
4 Mental state: 1c. Average scores - i. Over 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Endpoint score at 2 weeks (PANSS, high = worse)	1	40	Mean Difference (IV, Fixed, 95% CI)	2.40 [-2.15, 6.95]
4.2 Endpoint score at 4 weeks (PANSS, high = worse)	1	40	Mean Difference (IV, Fixed, 95% CI)	1.95 [-3.07, 6.97]
4.3 Endpoint score at 6 weeks (PANSS, high = worse)	1	40	Mean Difference (IV, Fixed, 95% CI)	5.75 [-0.09, 11.59]
4.4 Endpoint score at 8 weeks (PANSS, high = worse)	1	40	Mean Difference (IV, Fixed, 95% CI)	3.55 [-0.69, 7.79]
4.5 Endpoint score at 2 weeks (PANSS positive symptoms sub-scale, high = worse)	1	40	Mean Difference (IV, Fixed, 95% CI)	1.15 [-0.37, 2.67]
4.6 Endpoint score at 4 weeks (PANSS positive symptoms sub-scale, high = worse)	1	40	Mean Difference (IV, Fixed, 95% CI)	1.70 [0.01, 3.39]
4.7 Endpoint score at 6 weeks (PANSS positive symptoms sub-scale, high = worse)	1	40	Mean Difference (IV, Fixed, 95% CI)	2.05 [-0.15, 4.25]
4.8 Endpoint score at 8 weeks (PANSS positive symptoms sub-scale, high = worse)	1	40	Mean Difference (IV, Fixed, 95% CI)	2.25 [-0.36, 4.86]
4.9 Endpoint score at 2 weeks (PANSS negative symptoms sub-scale, high = worse)	1	40	Mean Difference (IV, Fixed, 95% CI)	1.30 [-0.07, 2.67]
4.10 Endpoint score at 4 weeks (PANSS negative symptoms sub-scale, high = worse)	1	40	Mean Difference (IV, Fixed, 95% CI)	1.31 [-0.04, 2.66]
4.11 Endpoint score at 6 weeks (PANSS negative symptoms sub-scale, high = worse)	1	40	Mean Difference (IV, Fixed, 95% CI)	1.70 [-0.12, 3.52]
4.12 Endpoint score at 8 weeks (PANSS negative symptoms sub-scale, high = worse)	1	40	Mean Difference (IV, Fixed, 95% CI)	2.05 [-0.06, 4.16]
4.13 Endpoint score at 2 weeks (PANSS general psychopathology sub-scale, high = worse)	1	40	Mean Difference (IV, Fixed, 95% CI)	-1.75 [-4.73, 1.23]

4.14 Endpoint score at 4 weeks (PANSS general psychopathology sub-scale, high = worse)	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-3.73, 2.53]
4.15 Endpoint score at 6 weeks (PANSS general psychopathology sub-scale, high = worse)	1	40	Mean Difference (IV, Fixed, 95% CI)	1.01 [-1.88, 3.90]
4.16 Endpoint score at 8 weeks (PANSS general psychopathology sub-scale, high = worse)	1	40	Mean Difference (IV, Fixed, 95% CI)	1.37 [-1.30, 4.04]
5 Adverse effects: 1a. Specific - Anticholinergic	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Blurred vision over 24 hours	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.10, 2.43]
6 Adverse effects: 1b. Specific - Arousal	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Somnolence over 24 hours	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.17, 2.18]
7 Adverse effects: 1c. Specific - Cardiovascular	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Tachycardia over 24 hours	1	40	Risk Ratio (M-H, Fixed, 95% CI)	4.0 [0.49, 32.72]
8 Adverse effects: 1d. Specific - Gastrointestinal	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Nausea and vomiting over 24 hours	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.90]
9 Adverse effects: 1e. Specific - Movement disorders	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Akathisia over 24 hours	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.46, 6.06]
9.2 Hypermyotonia over 24 hours	1	40	Risk Ratio (M-H, Fixed, 95% CI)	7.0 [0.95, 51.80]
10 Adverse effects: 1f. Specific - Miscellaneous	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Headache over 24 hours	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.16, 6.42]
10.2 Liver Function Tests (LFTs) elevation over 24 hours	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.90]
10.3 Weight gain over 24 hours	1	40	Risk Ratio (M-H, Fixed, 95% CI)	4.0 [0.49, 32.72]
10.4 Agitation over 24 hours	1	40	Risk Ratio (M-H, Fixed, 95% CI)	3.5 [0.83, 14.83]

Comparison 4. RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Specific behaviour: 1. Agitation - Average scores - i. over 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Endpoint score at 1 week (PANSS-EC, high = worse)	1	68	Mean Difference (IV, Fixed, 95% CI)	2.70 [0.42, 4.98]

1.2 Endpoint score at 2 weeks (PANSS-EC, high = worse)	1	68	Mean Difference (IV, Fixed, 95% CI)	2.40 [0.32, 4.48]
1.3 Endpoint score at 4 weeks (PANSS-EC, high = worse)	1	68	Mean Difference (IV, Fixed, 95% CI)	2.40 [0.53, 4.27]
2 Global Outcome: 1. Average scores - i. Over 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Endpoint score at 1 week (CGI-I, high = worse)	1	68	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.61, 0.21]
2.2 Endpoint score at 2 weeks (CGI-I, high = worse)	1	68	Mean Difference (IV, Fixed, 95% CI)	0.5 [0.07, 0.93]
2.3 Endpoint score at 4 weeks (CGI-I, high = worse)	1	68	Mean Difference (IV, Fixed, 95% CI)	0.50 [0.14, 0.86]
2.4 Endpoint score at 1 week (CGI-S, high = worse)	1	68	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.25, 0.65]
2.5 Endpoint score at 2 weeks (CGI-S, high = worse)	1	68	Mean Difference (IV, Fixed, 95% CI)	0.5 [0.07, 0.93]
2.6 Endpoint score at 4 weeks (CGI-S, high = worse)	1	68	Mean Difference (IV, Fixed, 95% CI)	0.5 [0.14, 0.86]
3 Mental state: 1a. No change in general mental state	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 No response at 4 weeks (< 50% reduction BPRS score)	1	68	Risk Ratio (M-H, Fixed, 95% CI)	10.61 [1.44, 78.36]
4 Mental state: 1b. Change in general mental state	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Clinical response at 4 weeks (50 - 75% reduction at BPRS score)	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.50, 0.97]
4.2 Clinical response at 4 weeks (≥ 75% reduction at BPRS score)	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.25, 2.89]
5 Mental state: 1c. Average scores - i. Over 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Endpoint score at 1 week (BPRS, high = worse)	1	68	Mean Difference (IV, Fixed, 95% CI)	5.20 [1.04, 9.36]
5.2 Endpoint score at 2 weeks (BPRS, high = worse)	1	68	Mean Difference (IV, Fixed, 95% CI)	6.20 [2.48, 9.92]
5.3 Endpoint score at 4 weeks (BPRS, high = worse)	1	68	Mean Difference (IV, Fixed, 95% CI)	5.40 [1.84, 8.96]
6 Adverse effects: 1. General - Total number of AEs			Other data	No numeric data
7 Adverse effects: 2a. Specific - Anticholinergic	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Dry mouth over 24 hours	1	68	Risk Ratio (M-H, Fixed, 95% CI)	2.12 [0.81, 5.55]
7.2 Constipation over 24 hours	1	68	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.62, 2.72]
8 Adverse effects: 2b. Specific - Arousal	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Excessive sedation over 24 hours	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.00, 0.92]
9 Adverse effects: 2c. Specific - Cardiovascular	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

9.1 Tachycardia over 24 hours	1	68	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.46, 3.30]
10 Adverse effects: 2d. Specific - Gastrointestinal	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Nausea over 24 hours	1	68	Risk Ratio (M-H, Fixed, 95% CI)	2.12 [0.20, 22.31]
11 Adverse effects: 2e. Specific - Movement disorders	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 EPS over 24 hours	1	68	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.49, 5.14]
11.2 Tremor over 24 hours	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.25, 2.89]
12 Adverse effects: 2f. Specific - Miscellaneous	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Headache over 24 hours	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.00, 1.19]
12.2 Skin rash over 24 hours	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.37]

Comparison 5. RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Specific behaviour: 1. Agitation - average scores - i. over 24 hours	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Endpoint score at 3 days (PANSS-EC, high = worse)	1	54	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-2.98, 2.76]
1.2 Endpoint score at 5 days (PANSS-EC, high = worse)	1	54	Mean Difference (IV, Fixed, 95% CI)	5.47 [2.64, 8.30]
1.3 Endpoint score at 7 days (PANSS-EC, high = worse)	1	54	Mean Difference (IV, Fixed, 95% CI)	5.11 [2.51, 7.71]
1.4 Endpoint score at 2 weeks (PANSS-EC, high = worse)	1	63	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.90, 1.08]
1.5 Endpoint score at 4 weeks (PANSS-EC, high = worse)	1	63	Mean Difference (IV, Fixed, 95% CI)	0.17 [-0.85, 1.19]
2 Specific behaviour: 1. Aggression - Average scores - i. over 24 hours	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Endpoint score at 3 days (MOAS, high = worse)	1	54	Mean Difference (IV, Fixed, 95% CI)	1.07 [-0.20, 2.34]
2.2 Endpoint score at 5 days (MOAS, high = worse)	1	54	Mean Difference (IV, Fixed, 95% CI)	0.38 [-0.83, 1.59]
2.3 Endpoint score at 7 days (MOAS, high = worse)	1	54	Mean Difference (IV, Fixed, 95% CI)	3.32 [2.07, 4.57]
2.4 Endpoint score at 2 weeks (MOAS, high = worse)	2	128	Mean Difference (IV, Fixed, 95% CI)	1.13 [0.23, 2.02]
2.5 Endpoint score at 4 weeks (MOAS, high = worse)	2	128	Mean Difference (IV, Fixed, 95% CI)	1.57 [0.75, 2.39]
2.6 Endpoint score at 6 weeks (MOAS, high = worse)	1	68	Mean Difference (IV, Fixed, 95% CI)	1.47 [0.83, 2.11]
2.7 Endpoint score at 8 weeks (MOAS, high = worse)	1	60	Mean Difference (IV, Fixed, 95% CI)	1.00 [-0.11, 2.11]

3 Mental state: 1. No change in general mental state	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 No clinical response at 8 weeks (< 30% reduction at PANSS score)	1	62	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.44, 6.38]
4 Mental state: 2. Average scores - i. over 24 hours	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Endpoint score at 2 weeks (PANSS, high = worse)	4	253	Mean Difference (IV, Fixed, 95% CI)	3.48 [1.88, 5.08]
4.2 Sub-group analysis: Endpoint score at 2 weeks (PANSS, high = worse)	3	185	Mean Difference (IV, Fixed, 95% CI)	2.50 [0.78, 4.21]
4.3 Endpoint score at 4 weeks (PANSS, high = worse)	4	253	Mean Difference (IV, Fixed, 95% CI)	5.45 [3.81, 7.08]
4.4 Sub-group analysis: Endpoint score at 4 weeks (PANSS, high = worse)	3	185	Mean Difference (IV, Fixed, 95% CI)	4.52 [2.76, 6.29]
4.5 Endpoint score at 6 weeks (PANSS, high = worse)	2	130	Mean Difference (IV, Fixed, 95% CI)	9.90 [7.42, 12.37]
4.6 Endpoint score at 8 weeks (PANSS, high = worse)	2	122	Mean Difference (IV, Fixed, 95% CI)	5.83 [4.12, 7.54]
4.7 Endpoint score at 2 weeks (PANSS positive symptoms sub-scale, high = worse)	3	191	Mean Difference (IV, Fixed, 95% CI)	0.64 [-0.24, 1.53]
4.8 Endpoint score at 4 weeks (PANSS positive symptoms sub-scale, high = worse)	3	191	Mean Difference (IV, Fixed, 95% CI)	2.75 [1.86, 3.64]
4.9 Endpoint score at 6 weeks (PANSS positive symptoms sub-scale, high = worse)	1	68	Mean Difference (IV, Fixed, 95% CI)	4.4 [1.40, 7.40]
4.10 Endpoint score at 8 weeks (PANSS positive symptoms sub-scale, high = worse)	1	60	Mean Difference (IV, Fixed, 95% CI)	1.70 [0.71, 2.69]
4.11 Endpoint score at 2 weeks (PANSS negative symptoms sub-scale, high = worse)	2	128	Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.57, 1.15]
4.12 Endpoint score at 4 weeks (PANSS negative symptoms sub-scale, high = worse)	2	128	Mean Difference (IV, Fixed, 95% CI)	1.23 [-0.16, 2.62]
4.13 Endpoint score at 6 weeks (PANSS negative symptoms sub-scale, high = worse)	1	68	Mean Difference (IV, Fixed, 95% CI)	3.80 [1.07, 6.53]
4.14 Endpoint score at 8 weeks (PANSS negative symptoms sub-scale, high = worse)	1	60	Mean Difference (IV, Fixed, 95% CI)	1.30 [-0.02, 2.62]

4.15 Endpoint score at 2 weeks (PANSS general psychopathology sub-scale, high = worse)	2	128	Mean Difference (IV, Fixed, 95% CI)	0.93 [-0.07, 1.93]
4.16 Endpoint score at 4 weeks (PANSS general psychopathology sub-scale, high = worse)	2	128	Mean Difference (IV, Fixed, 95% CI)	1.14 [0.04, 2.23]
4.17 Endpoint score at 6 weeks (PANSS general psychopathology sub-scale, high = worse)	1	68	Mean Difference (IV, Fixed, 95% CI)	6.5 [4.06, 8.94]
4.18 Endpoint score at 8 weeks (PANSS general psychopathology sub-scale, high = worse)	1	60	Mean Difference (IV, Fixed, 95% CI)	1.60 [0.43, 2.77]
5 Adverse effects: 1a. General - Total number of AEs			Other data	No numeric data
6 Adverse effects: 1b. General - Serious	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 myocardial ischaemia (at 8 weeks)	1	62	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.19, 20.93]
7 Adverse effects: 2a. Specific - Anticholinergic	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Blurred vision over 24 hours	2	122	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.37, 2.68]
7.2 Dry mouth over 24 hours	2	129	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.76, 3.54]
8 Adverse effects: 2b. Specific - Arousal	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Insomnia over 24 hours	1	54	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.19, 20.77]
8.2 Somnolence over 24 hours	2	121	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.44, 1.63]
9 Adverse effects: 2c. Specific - Cardiovascular	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Decreased blood pressure over 24 hours	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.18, 3.10]
9.2 Tachycardia over 24 hours	4	251	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.83, 2.67]
9.3 T-wave changes in ECG over 24 hours	1	54	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.19, 20.77]
10 Adverse effects: 2d. Specific - Gastrointestinal	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Constipation over 24 hours	3	189	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.70, 1.76]
10.2 Nausea over 24 hours	2	122	Risk Ratio (M-H, Fixed, 95% CI)	0.7 [0.29, 1.71]
11 Adverse effects: 2e. Specific - Movement disorders	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 EPS over 24 hours	2	121	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.76, 2.39]
11.2 Akathisia over 24 hours	2	122	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.28, 2.03]
11.3 Tremor over 24 hours	1	68	Risk Ratio (M-H, Fixed, 95% CI)	1.2 [0.40, 3.56]
12 Adverse effects: 2f. Specific - Movement disorders - Average scores - i. Over 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

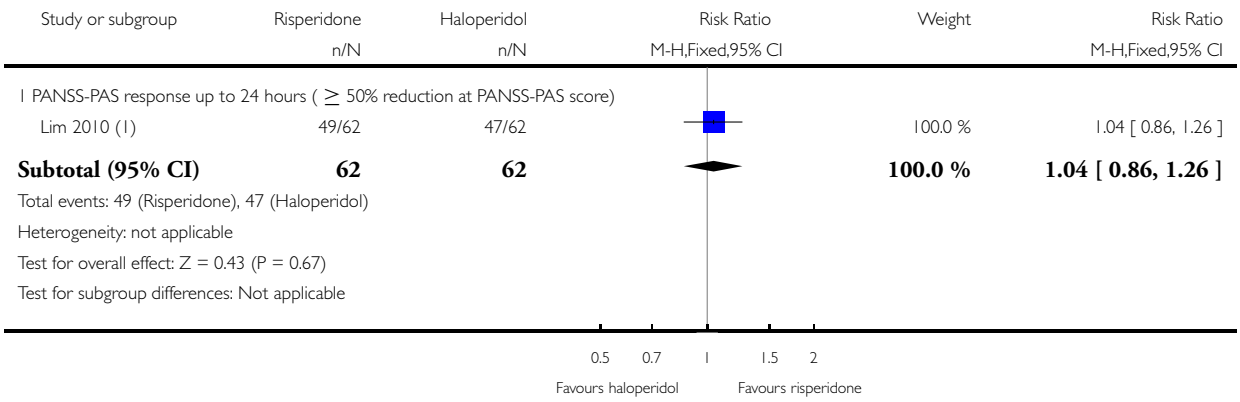
12.1 Endpoint score at 3 days (TESS, high = worse)	1	54	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-1.35, 1.27]
12.2 Endpoint score at 5 days (TESS, high = worse)	1	54	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-1.55, 1.33]
12.3 Endpoint score at 7 days (TESS, high = worse)	1	54	Mean Difference (IV, Fixed, 95% CI)	-0.51 [-1.88, 0.86]
13 Adverse effects: 2g. Specific - Miscellaneous	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Headache over 24 hours	4	243	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.53, 1.68]
13.2 Weight gain over 24 hours	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.47, 4.78]
13.3 Oedema over 24 hours	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.13]
13.4 Leukopenia over 24 hours	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.13]
13.5 Liver Function Tests (LFTs) elevation over 24 hours	2	116	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.15, 2.40]
14 Leaving the study early	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 For any reason	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.13]
14.2 Due to adverse effects	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.13]

Analysis 1.1. Comparison 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL, Outcome 1 Specific behaviour: 1a. Agitation - Various measures.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL

Outcome: 1 Specific behaviour: 1a. Agitation - Various measures



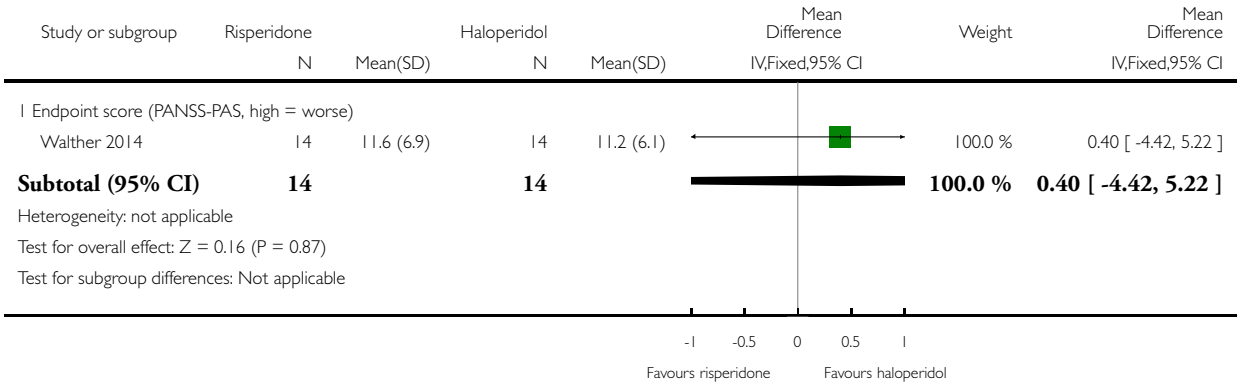
(1) Authors of the manuscript use the "PANSS-EC" term but provide the items list of PANSS-PAS; in other published studies they refers to this as an "5 item acute agitation cluster [...] from PANSS score". X-axis labels of the forest plot have been switched in order to improve readability.

Analysis 1.2. Comparison 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL, Outcome 2 Specific behaviour: 1b. Agitation - Average scores - i. up to 2 hours.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL

Outcome: 2 Specific behaviour: 1b. Agitation - Average scores - i. up to 2 hours

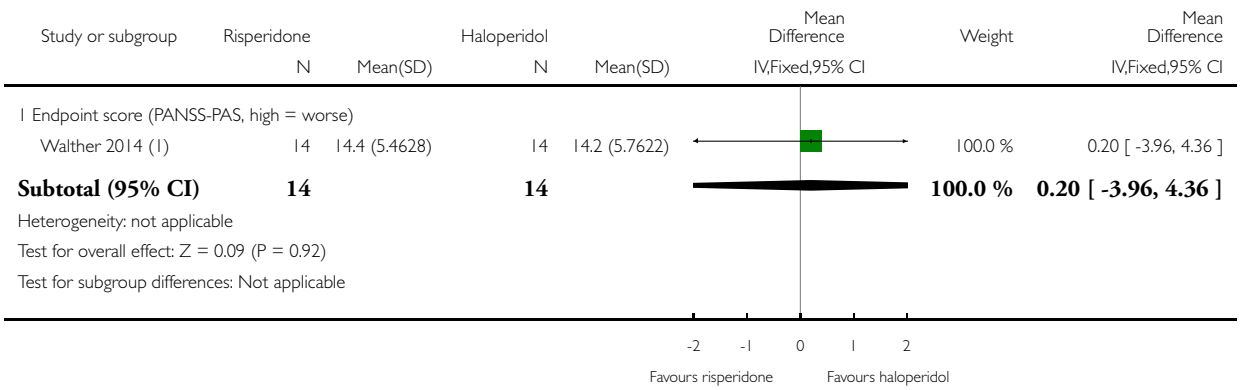


Analysis 1.3. Comparison 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL, Outcome 3 Specific behaviour: 1c. Agitation - Average scores - ii. up to 24 hours.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL

Outcome: 3 Specific behaviour: 1c. Agitation - Average scores - ii. up to 24 hours



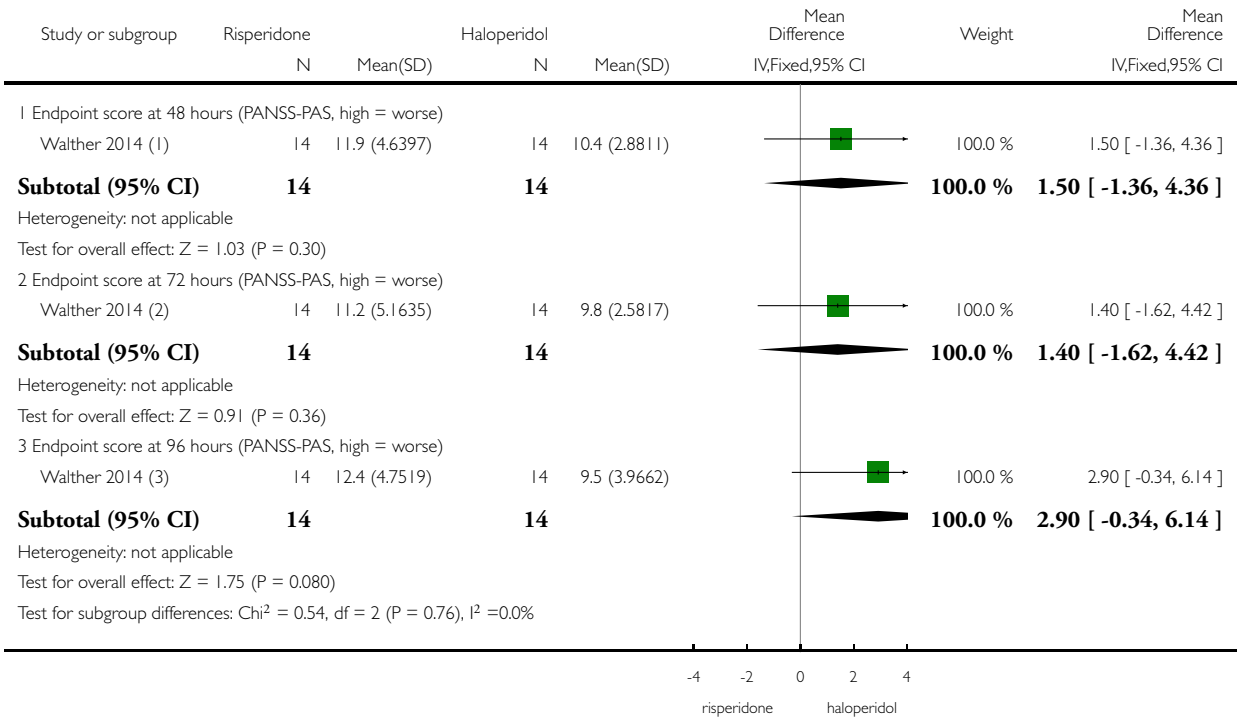
(1) Data were extracted from figure 1 (p.126); see methods for further details.

Analysis 1.4. Comparison 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL, Outcome 4 Specific behaviour: 1d. Agitation - Average scores - iii. over 24 hours.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL

Outcome: 4 Specific behaviour: 1d. Agitation - Average scores - iii. over 24 hours



(1) Data were extracted from figure 1 (p.126); see methods for further details.

(2) Data were extracted from figure 1 (p.126); see methods for further details.

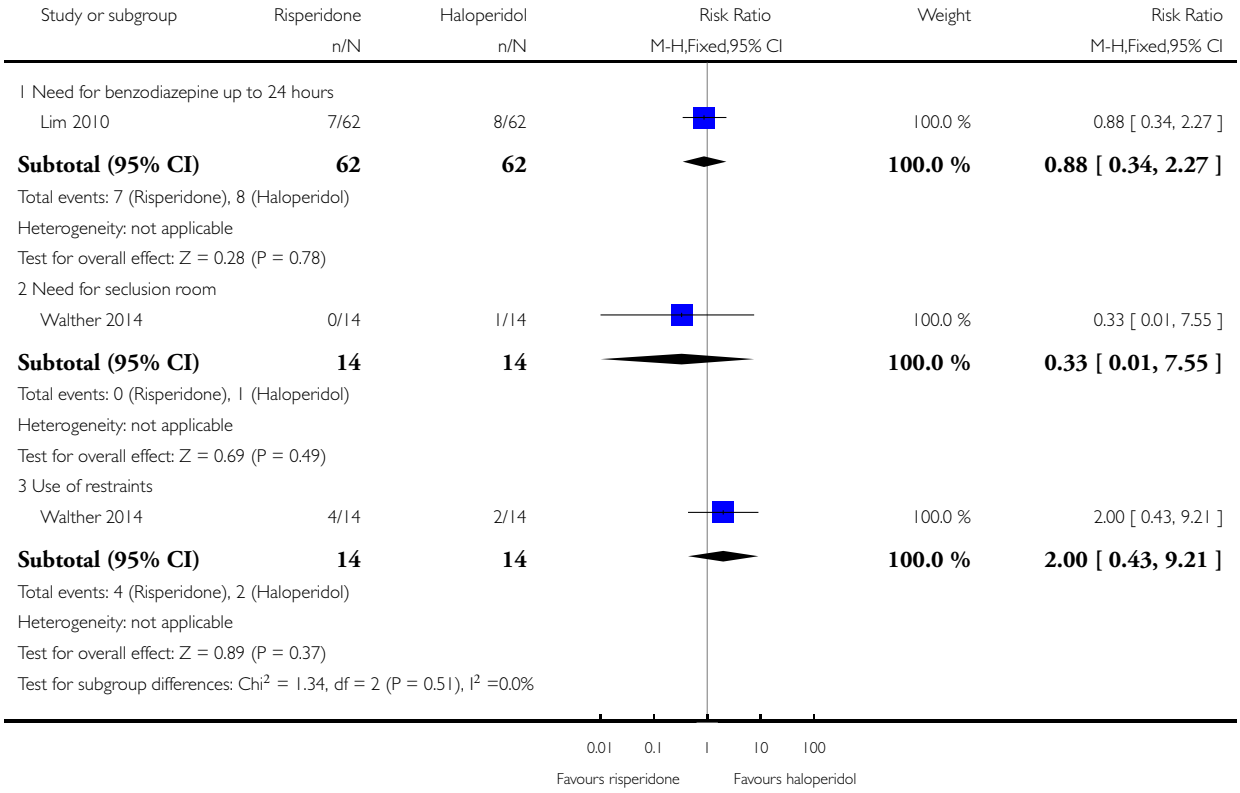
(3) Data were extracted from figure 1 (p.126); see methods for further details.

Analysis 1.5. Comparison 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL, Outcome 5 Global outcome: 1a. General - Need for additional measures.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL

Outcome: 5 Global outcome: 1a. General - Need for additional measures



Analysis 1.6. Comparison 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL, Outcome 6 Global outcome: 1b. General - Need for additional medication (skewed data).

Global outcome: 1b. General - Need for additional medication (skewed data)

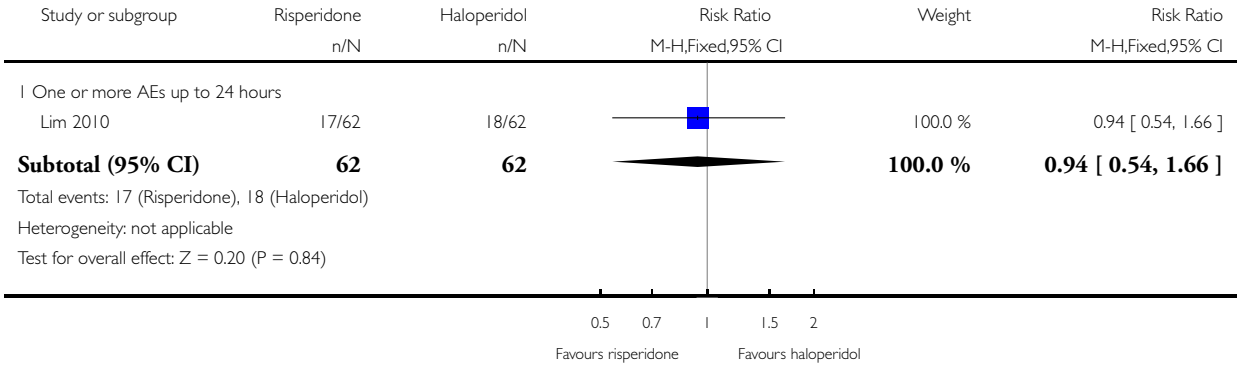
Study	Intervention	Mean (total mg of diazepam needed during the entire study per patient)	SD	N
Walther 2014	Risperidone	92.9	86.8	14
Walther 2014	Haloperidol	71.1	70.4	14

Analysis 1.7. Comparison 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL, Outcome 7 Adverse effects: 1. General.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL

Outcome: 7 Adverse effects: 1. General

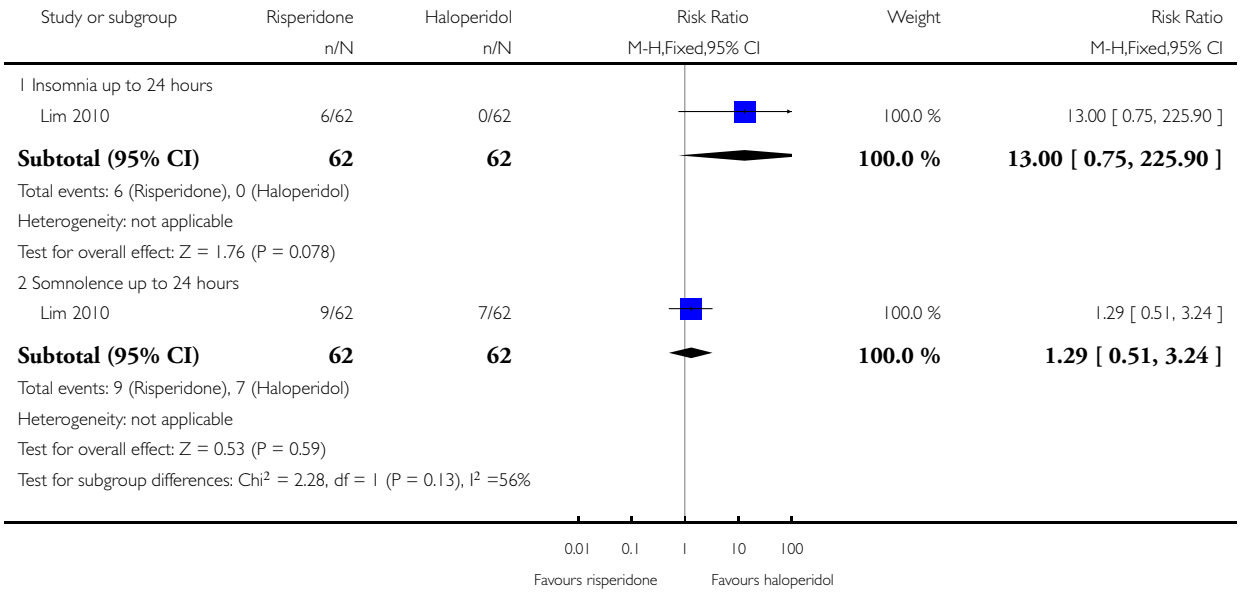


Analysis 1.8. Comparison 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL, Outcome 8 Adverse effects: 2a. Specific - Arousal level.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

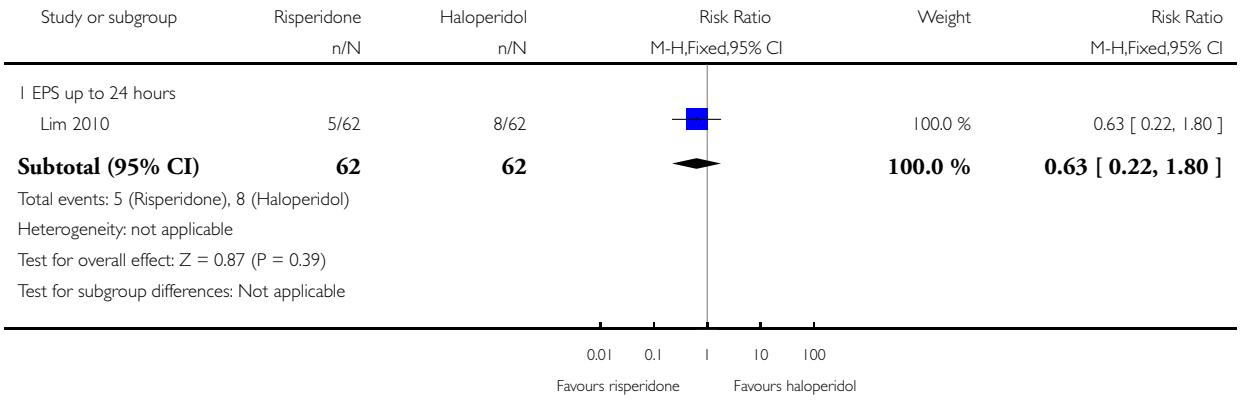
Comparison: 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL

Outcome: 8 Adverse effects: 2a. Specific - Arousal level



Analysis 1.9. Comparison 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL, Outcome 9 Adverse effects: 2b. Specific - Movement disorder - i. Various.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)
Comparison: 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL
Outcome: 9 Adverse effects: 2b. Specific - Movement disorder - i. Various



Analysis 1.10. Comparison 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL, Outcome 10 Adverse effects: 2b. Specific - Movement disorder - ii. Need for biperiden.

Adverse effects: 2b. Specific - Movement disorder - ii. Need for biperiden

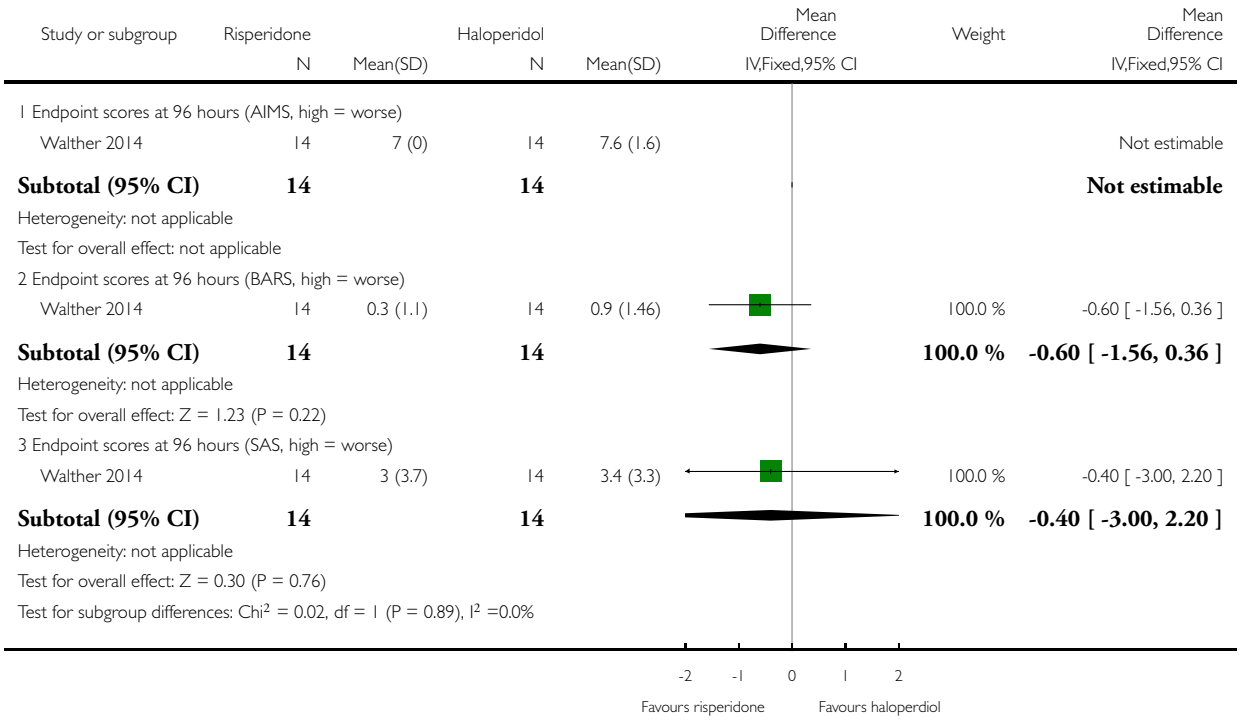
Study	Intervention	Mean (total mg of biperiden needed during the entire study per patient)	SD	N
Walther 2014	Risperidone	4.1	7.3	14
Walther 2014	Haloperidol	5.2	8.3	14

Analysis 1.11. Comparison 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL, Outcome 11 Adverse effects: 2b. Specific - Movement disorder - iii. Average scores (skewed data).

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL

Outcome: 11 Adverse effects: 2b. Specific - Movement disorder - iii. Average scores (skewed data)

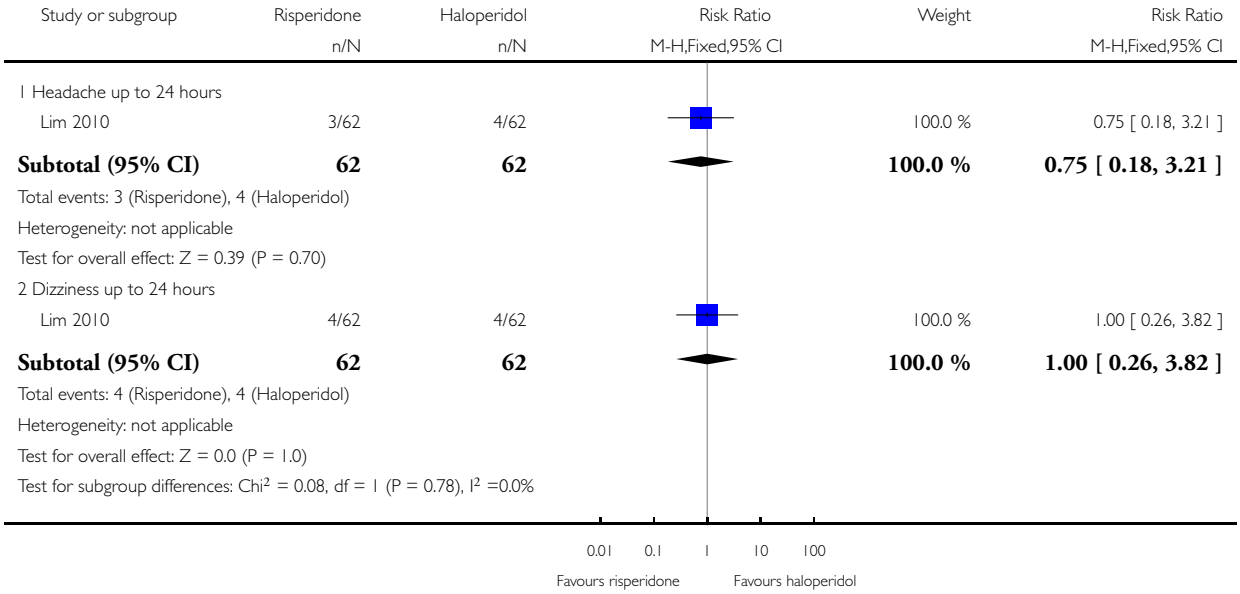


Analysis 1.12. Comparison 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL, Outcome 12 Adverse effects: 2c. Specific - Miscellaneous.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL

Outcome: 12 Adverse effects: 2c. Specific - Miscellaneous

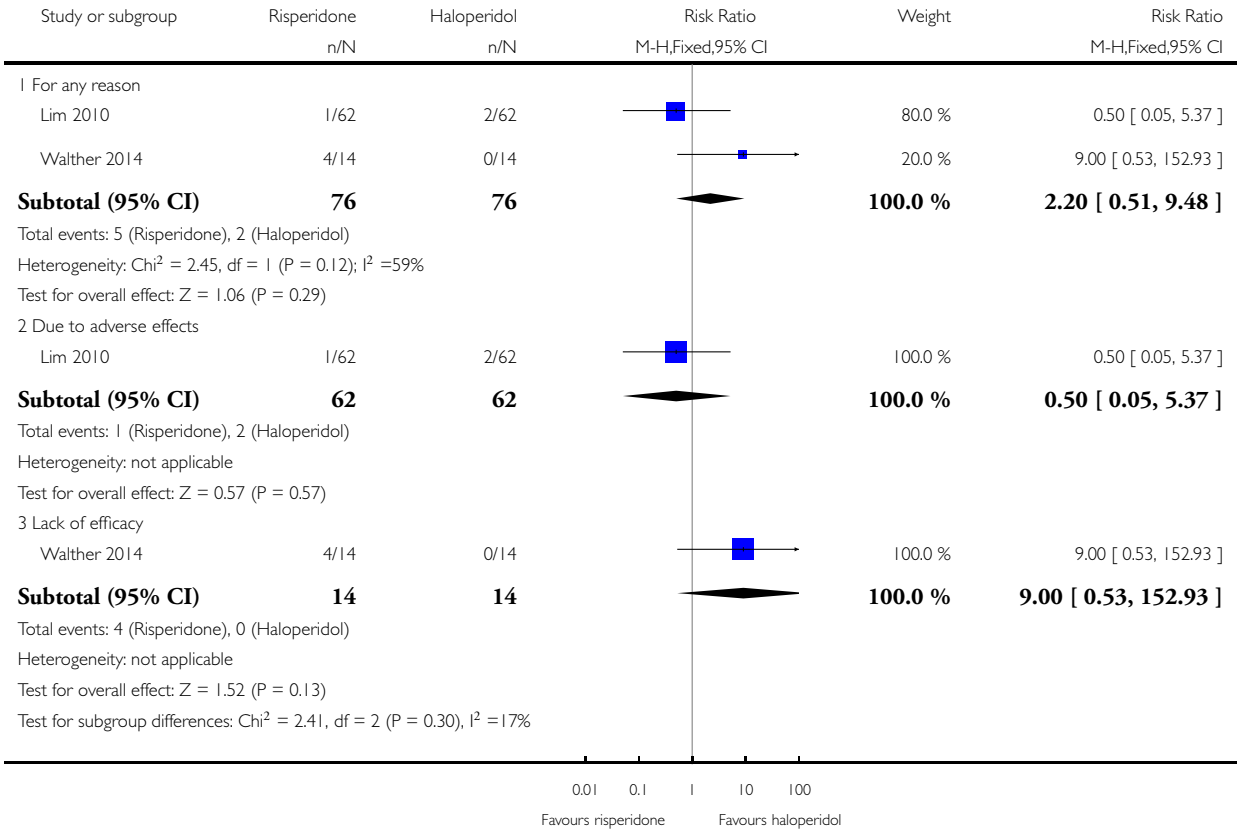


Analysis 1.13. Comparison 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL, Outcome 13 Leaving the study early.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 1 RISPERIDONE vs OTHER ANTIPSYCHOTIC: a. HALOPERIDOL

Outcome: 13 Leaving the study early

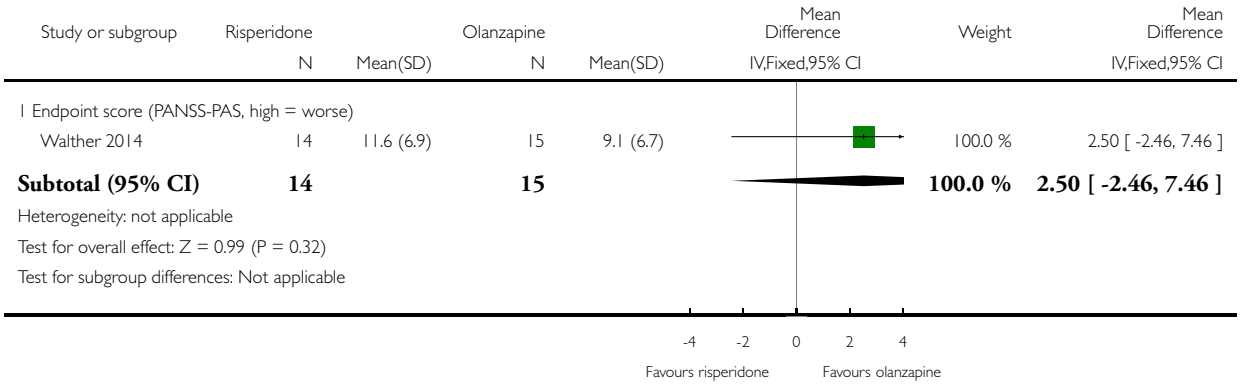


Analysis 2.1. Comparison 2 RISPERIDONE vs OTHER ANTIPSYCHOTIC: b. OLANZAPINE, Outcome 1 Specific behaviour: 1. Agitation - Average scores - i. Up to 2 hours.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 2 RISPERIDONE vs OTHER ANTIPSYCHOTIC: b. OLANZAPINE

Outcome: 1 Specific behaviour: 1. Agitation - Average scores - i. Up to 2 hours

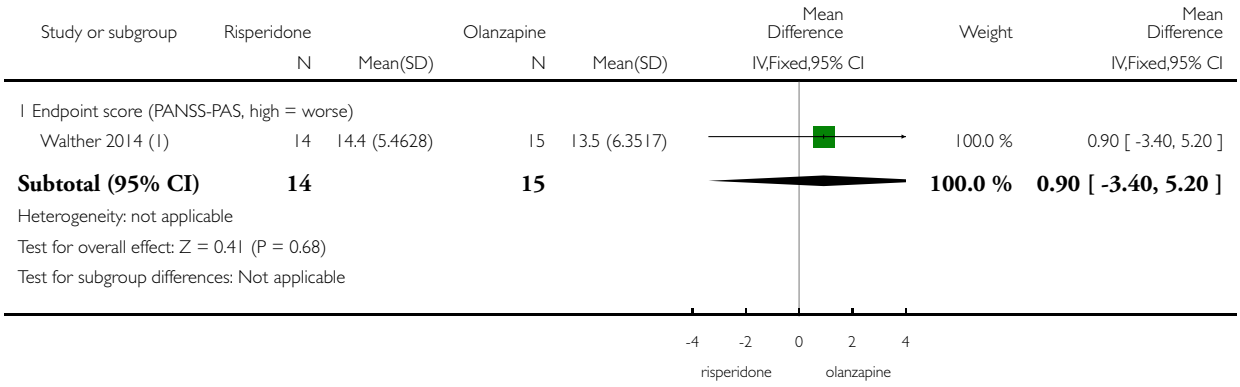


Analysis 2.2. Comparison 2 RISPERIDONE vs OTHER ANTIPSYCHOTIC: b. OLANZAPINE, Outcome 2 Specific behaviour: 1. Agitation - Average scores - ii. Up to 24 hours.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 2 RISPERIDONE vs OTHER ANTIPSYCHOTIC: b. OLANZAPINE

Outcome: 2 Specific behaviour: 1. Agitation - Average scores - ii. Up to 24 hours



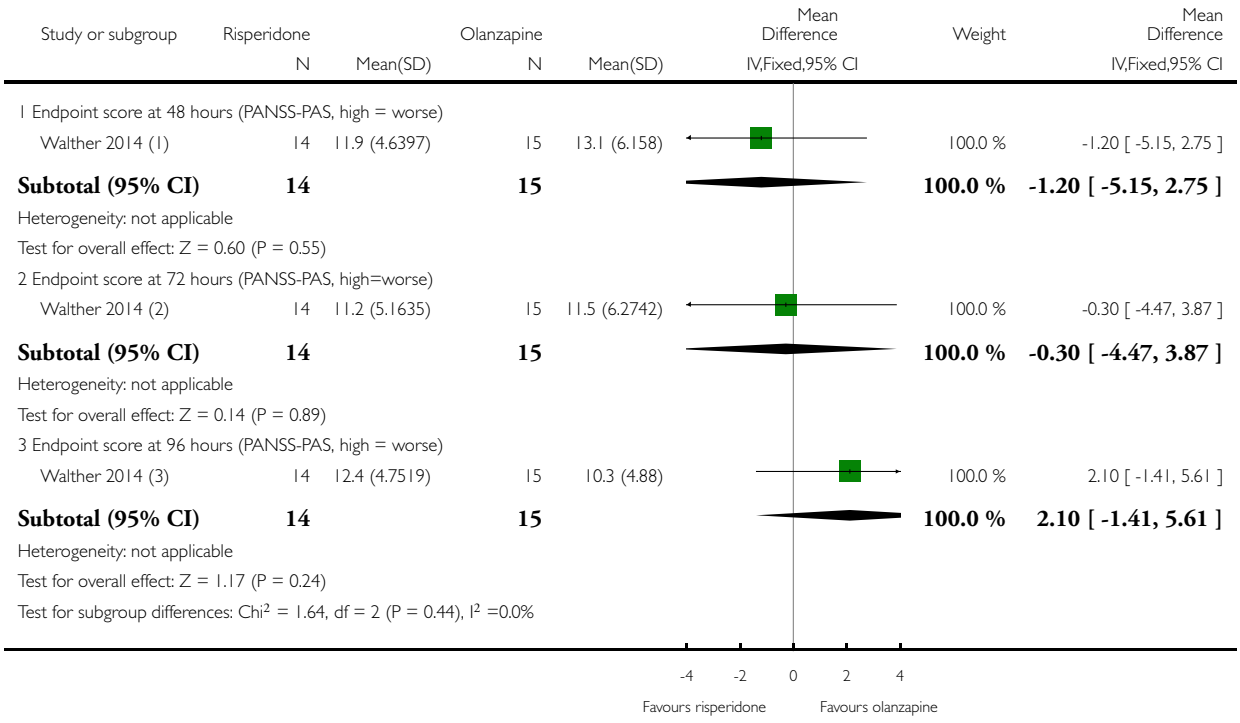
(1) Data were extracted from figure 1 (p.126); see methods for further details.

Analysis 2.3. Comparison 2 RISPERIDONE vs OTHER ANTIPSYCHOTIC: b. OLANZAPINE, Outcome 3 Specific behaviour: 1. Agitation - Average scores - iii. over 24 hours.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 2 RISPERIDONE vs OTHER ANTIPSYCHOTIC: b. OLANZAPINE

Outcome: 3 Specific behaviour: 1. Agitation - Average scores - iii. over 24 hours



(1) Data were extracted from figure 1 (p.126); see methods for further details.

(2) Data were extracted from figure 1 (p.126); see methods for further details.

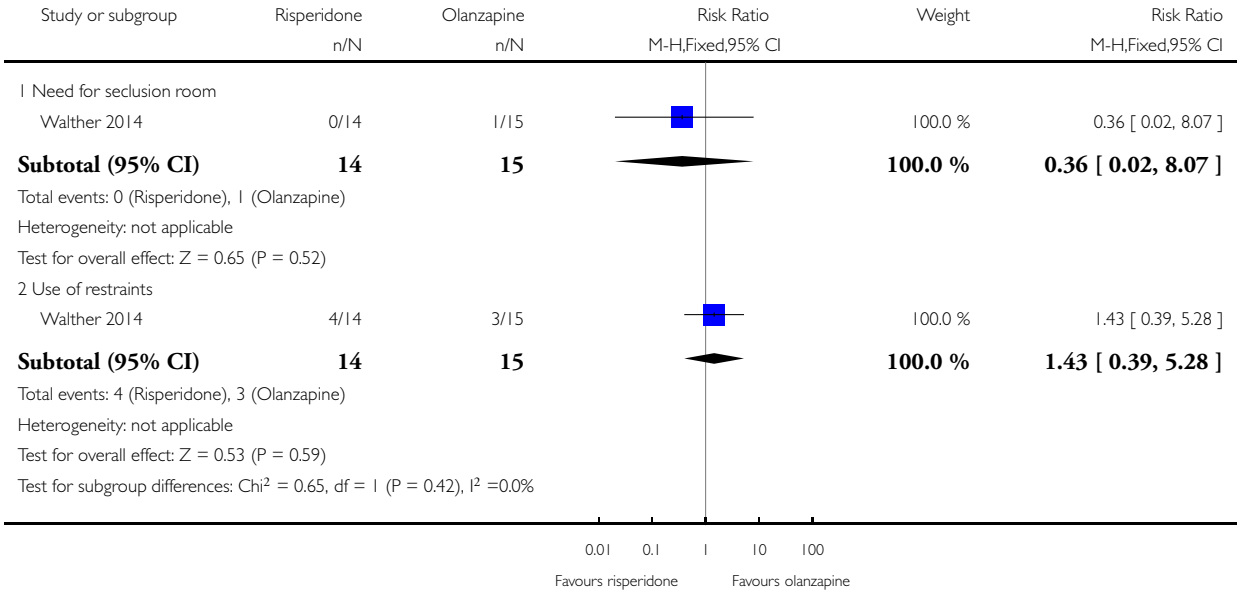
(3) Data were extracted from figure 1 (p.126); see methods for further details.

Analysis 2.4. Comparison 2 RISPERIDONE vs OTHER ANTIPSYCHOTIC: b. OLANZAPINE, Outcome 4 Global outcome: 1a. General - Need for additional measures.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 2 RISPERIDONE vs OTHER ANTIPSYCHOTIC: b. OLANZAPINE

Outcome: 4 Global outcome: 1a. General - Need for additional measures



Analysis 2.5. Comparison 2 RISPERIDONE vs OTHER ANTIPSYCHOTIC: b. OLANZAPINE, Outcome 5 Global outcome: 1b. General - Need for additional medication (skewed data).

Global outcome: 1b. General - Need for additional medication (skewed data)

Study	Intervention	Mean (total mg of diazepam needed during the entire study per patient)	SD	N
Walther 2014	Risperidone	92.9	86.8	14
Walther 2014	Olanzapine	114.0	79.5	15

Analysis 2.6. Comparison 2 RISPERIDONE vs OTHER ANTIPSYCHOTIC: b. OLANZAPINE, Outcome 6 Adverse effects: 1a. Specific - Movement disorder - i. Meed for biperiden.

Adverse effects: 1a. Specific - Movement disorder - i. Meed for biperiden

Study	Intervention	Mean (total mg of biperiden needed during the entire study per patient)	SD	N
Walther 2014	Risperidone	4.1	7.3	14
Walther 2014	Olanzapine	0.7	2.6	15

Analysis 2.7. Comparison 2 RISPERIDONE vs OTHER ANTIPSYCHOTIC: b. OLANZAPINE, Outcome 7 Adverse effects: 1b. Specific - Movement disorder - ii. Average scores (skewed data).

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 2 RISPERIDONE vs OTHER ANTIPSYCHOTIC: b. OLANZAPINE

Outcome: 7 Adverse effects: 1b. Specific - Movement disorder - ii. Average scores (skewed data)

Study or subgroup	Risperidone N	Mean(SD)	Olanzapine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Endpoint score (BARS, high = worse)							
Walther 2014	14	0.3 (1.1)	15	0.1 (0.5)		100.0 %	0.20 [-0.43, 0.83]
Subtotal (95% CI)	**14**		**15**			**100.0 %**	**0.20 [-0.43, 0.83]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.62 (P = 0.53)							
2 Endpoint score (SAS, high = worse)							
Walther 2014	14	3 (3.7)	15	1.2 (2.9)		100.0 %	1.80 [-0.63, 4.23]
Subtotal (95% CI)	**14**		**15**			**100.0 %**	**1.80 [-0.63, 4.23]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.45 (P = 0.15)							
Test for subgroup differences: Chi^2 = 1.56, df = 1 (P = 0.21), I^2 =36%							

Analysis 2.8. Comparison 2 RISPERIDONE vs OTHER ANTIPSYCHOTIC: b. OLANZAPINE, Outcome 8 Leaving the study early.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 2 RISPERIDONE vs OTHER ANTIPSYCHOTIC: b. OLANZAPINE

Outcome: 8 Leaving the study early

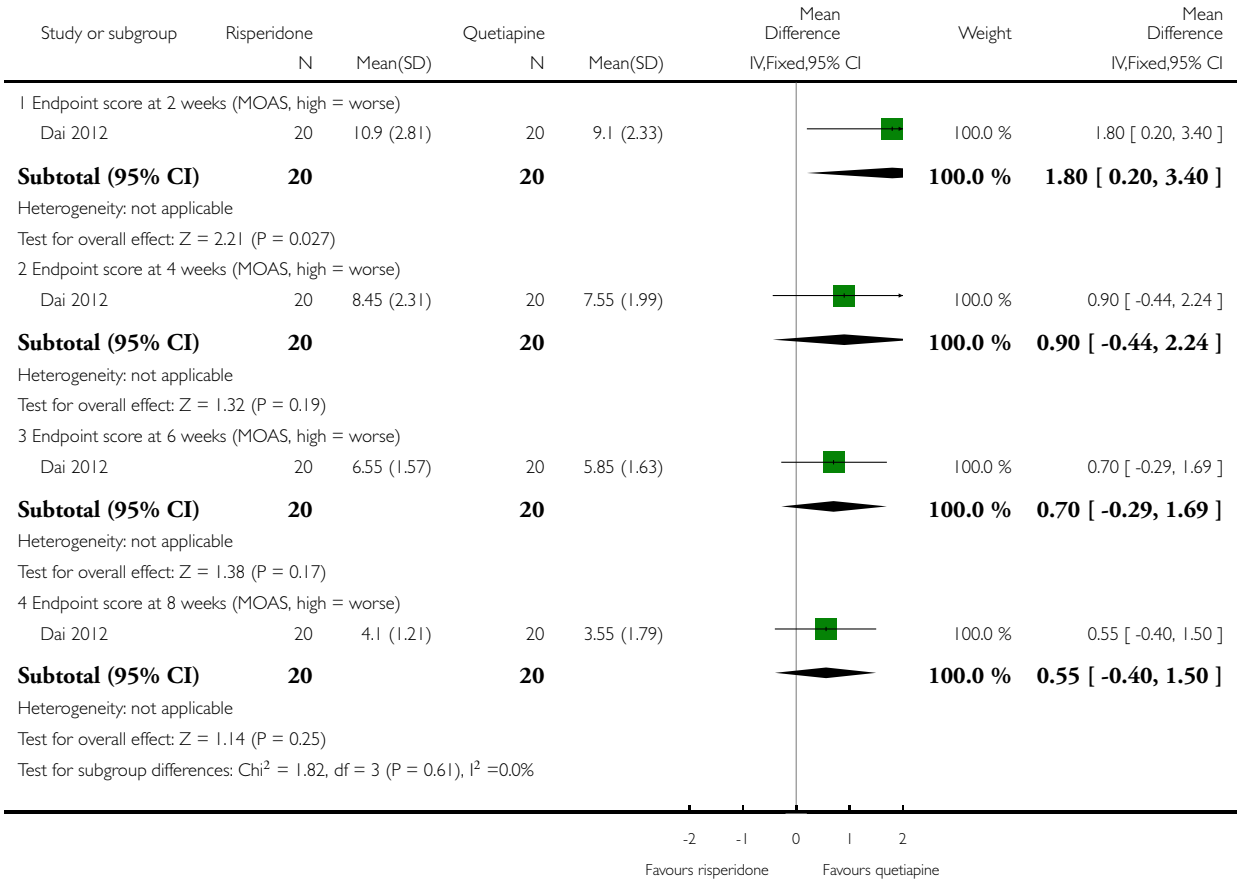
Study or subgroup	Risperidone n/N	Olanzapine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Lack of efficacy					
Walther 2014	4/14	2/15		100.0 %	2.14 [0.46, 9.93]
Subtotal (95% CI)	**14**	**15**		**100.0 %**	**2.14 [0.46, 9.93]**
Total events: 4 (Risperidone), 2 (Olanzapine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.97 (P = 0.33)					
Test for subgroup differences: Not applicable					

Analysis 3.1. Comparison 3 RISPERIDONE vs OTHER ANTIPSYCHOTIC: c. QUETIAPINE, Outcome 1 Specific behaviour: 1. Aggression - Average scores - i. Over 24 hours.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 3 RISPERIDONE vs OTHER ANTIPSYCHOTIC: c. QUETIAPINE

Outcome: 1 Specific behaviour: 1. Aggression - Average scores - i. Over 24 hours

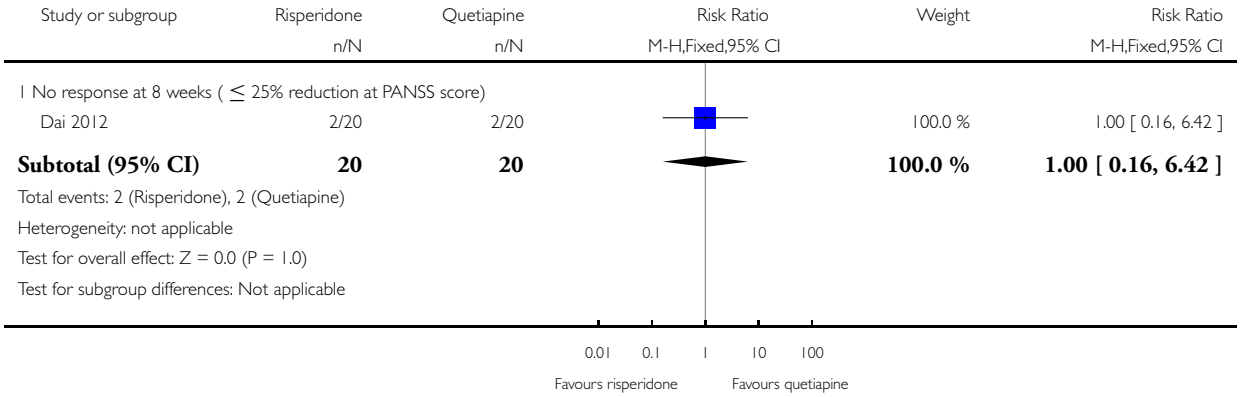


Analysis 3.2. Comparison 3 RISPERIDONE vs OTHER ANTIPSYCHOTIC: c. QUETIAPINE, Outcome 2 Mental state: 1a. No change in general mental state.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 3 RISPERIDONE vs OTHER ANTIPSYCHOTIC: c. QUETIAPINE

Outcome: 2 Mental state: 1a. No change in general mental state

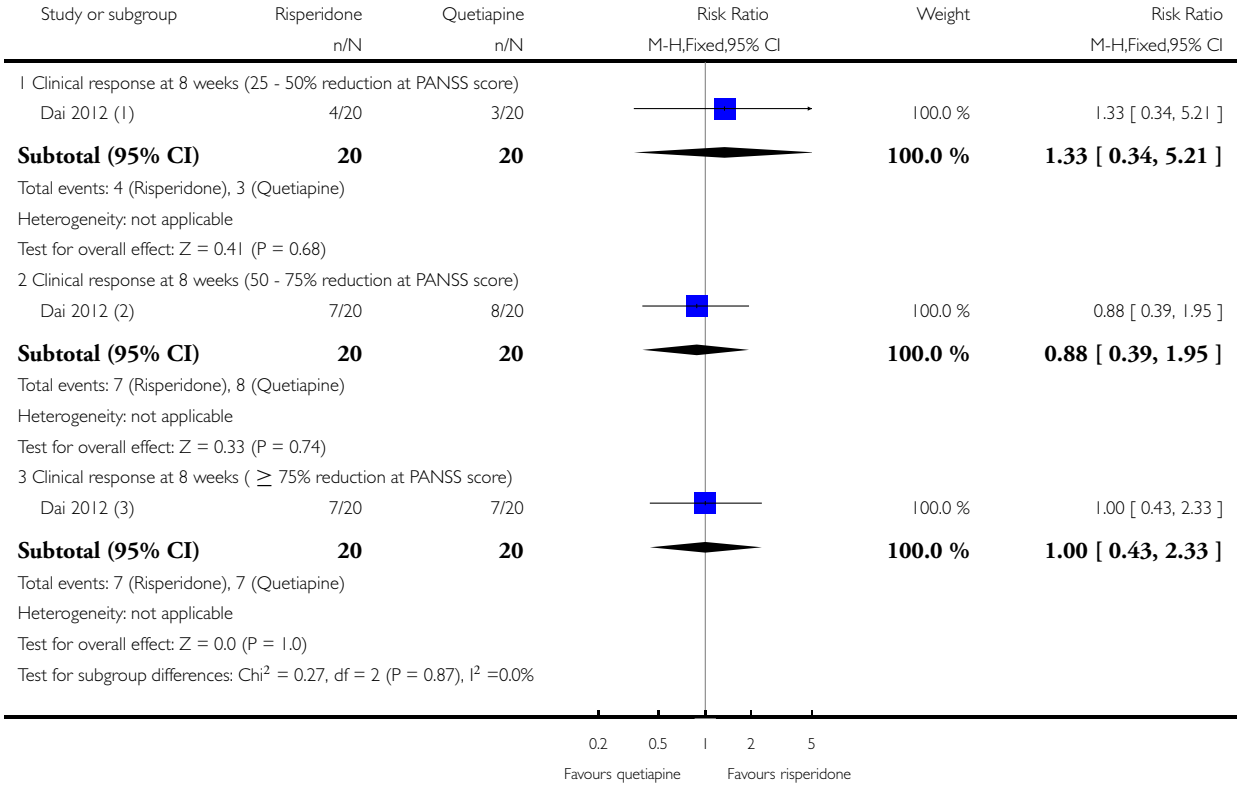


Analysis 3.3. Comparison 3 RISPERIDONE vs OTHER ANTIPSYCHOTIC: c. QUETIAPINE, Outcome 3 Mental state: 1b. Change in general mental state.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 3 RISPERIDONE vs OTHER ANTIPSYCHOTIC: c. QUETIAPINE

Outcome: 3 Mental state: 1b. Change in general mental state



(1) Axis labels have been switched in order to improve readability.

(2) Axis labels have been switched in order to improve readability.

(3) Axis labels have been switched in order to improve readability.

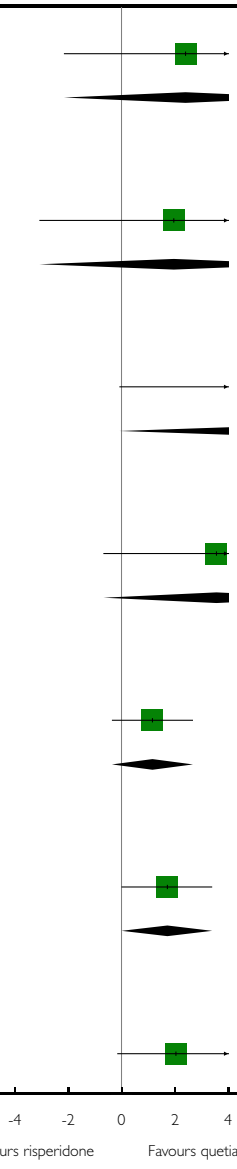
Analysis 3.4. Comparison 3 RISPERIDONE vs OTHER ANTIPSYCHOTIC: c. QUETIAPINE, Outcome 4 Mental state: 1c. Average scores - i. Over 24 hours.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 3 RISPERIDONE vs OTHER ANTIPSYCHOTIC: c. QUETIAPINE

Outcome: 4 Mental state: 1c. Average scores - i. Over 24 hours

Study or subgroup	Risperidone N	Risperidone Mean(SD)	Quetiapine N	Quetiapine Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Endpoint score at 2 weeks (PANSS, high = worse)							
Dai 2012	20	87.3 (6.7)	20	84.9 (7.93)		100.0 %	2.40 [-2.15, 6.95]
Subtotal (95% CI)	**20**		**20**			**100.0 %**	**2.40 [-2.15, 6.95]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.03 (P = 0.30)							
2 Endpoint score at 4 weeks (PANSS, high = worse)							
Dai 2012	20	76.9 (7.05)	20	74.95 (9.04)		100.0 %	1.95 [-3.07, 6.97]
Subtotal (95% CI)	**20**		**20**			**100.0 %**	**1.95 [-3.07, 6.97]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.76 (P = 0.45)							
3 Endpoint score at 6 weeks (PANSS, high = worse)							
Dai 2012	20	67.5 (7.36)	20	61.75 (11.11)		100.0 %	5.75 [-0.09, 11.59]
Subtotal (95% CI)	**20**		**20**			**100.0 %**	**5.75 [-0.09, 11.59]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.93 (P = 0.054)							
4 Endpoint score at 8 weeks (PANSS, high = worse)							
Dai 2012	20	52.25 (7.28)	20	48.7 (6.38)		100.0 %	3.55 [-0.69, 7.79]
Subtotal (95% CI)	**20**		**20**			**100.0 %**	**3.55 [-0.69, 7.79]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.64 (P = 0.10)							
5 Endpoint score at 2 weeks (PANSS positive symptoms sub-scale, high = worse)							
Dai 2012	20	27.2 (2.14)	20	26.05 (2.72)		100.0 %	1.15 [-0.37, 2.67]
Subtotal (95% CI)	**20**		**20**			**100.0 %**	**1.15 [-0.37, 2.67]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.49 (P = 0.14)							
6 Endpoint score at 4 weeks (PANSS positive symptoms sub-scale, high = worse)							
Dai 2012	20	23.8 (2.53)	20	22.1 (2.9)		100.0 %	1.70 [0.01, 3.39]
Subtotal (95% CI)	**20**		**20**			**100.0 %**	**1.70 [0.01, 3.39]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.98 (P = 0.048)							
7 Endpoint score at 6 weeks (PANSS positive symptoms sub-scale, high = worse)							
Dai 2012	20	19.75 (3.16)	20	17.7 (3.9)		100.0 %	2.05 [-0.15, 4.25]



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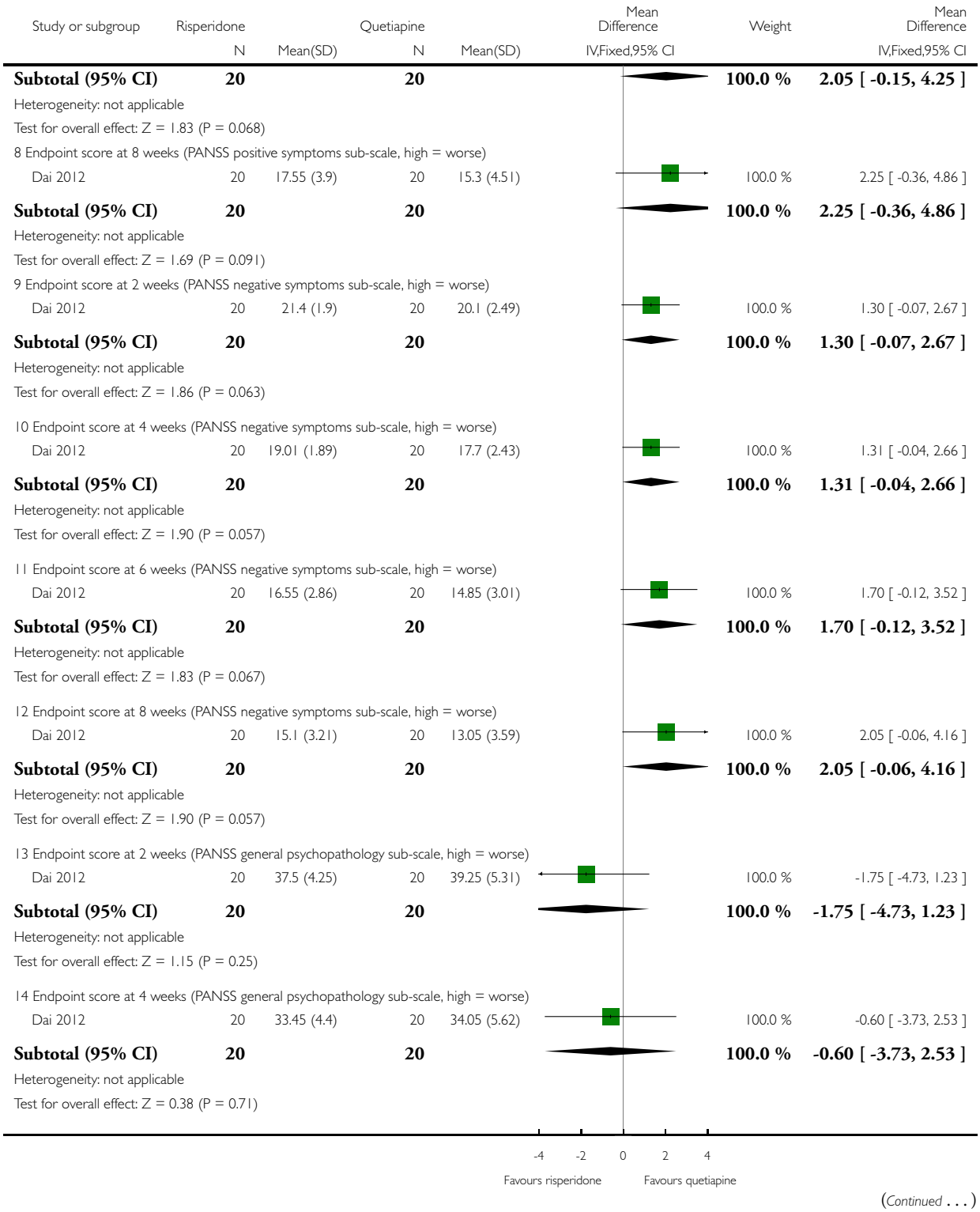

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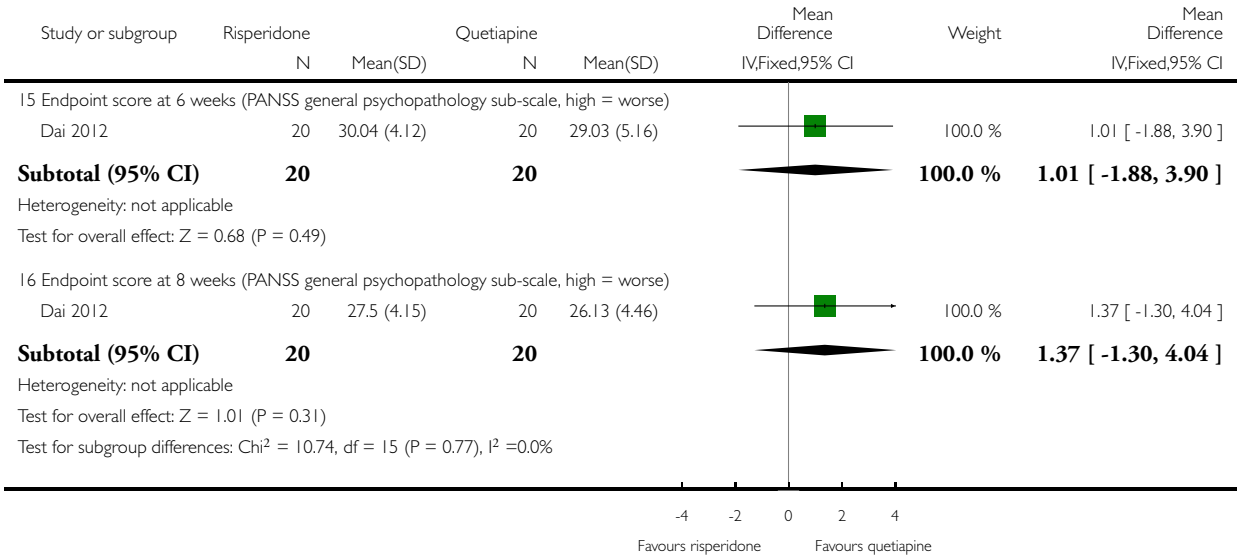
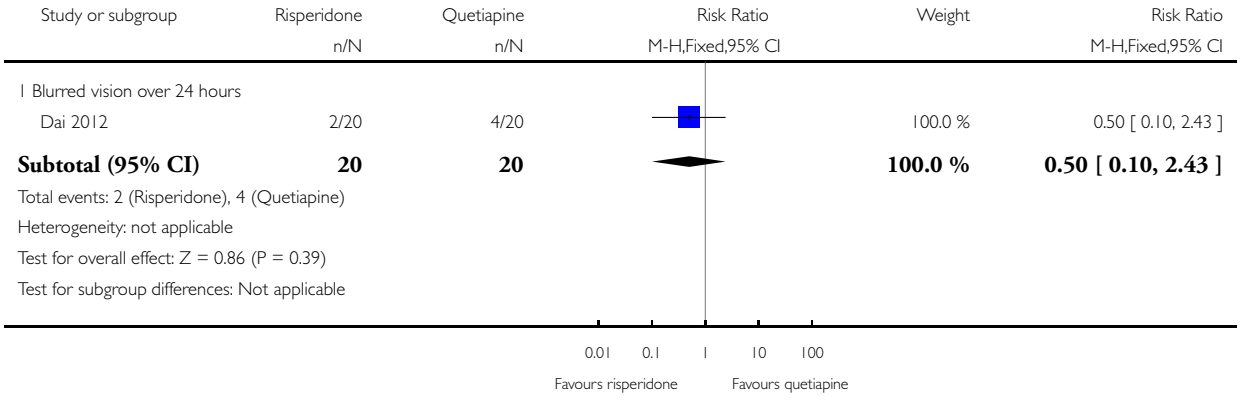


Analysis 3.5. Comparison 3 RISPERIDONE vs OTHER ANTIPSYCHOTIC: c. QUETIAPINE, Outcome 5 Adverse effects: 1a. Specific - Anticholinergic.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 3 RISPERIDONE vs OTHER ANTIPSYCHOTIC: c. QUETIAPINE

Outcome: 5 Adverse effects: 1a. Specific - Anticholinergic



Analysis 3.6. Comparison 3 RISPERIDONE vs OTHER ANTIPSYCHOTIC: c. QUETIAPINE, Outcome 6 Adverse effects: 1b. Specific - Arousal.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 3 RISPERIDONE vs OTHER ANTIPSYCHOTIC: c. QUETIAPINE

Outcome: 6 Adverse effects: 1b. Specific - Arousal

Study or subgroup	Risperidone n/N	Quetiapine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Somnolence over 24 hours					
Dai 2012	3/20	5/20		100.0 %	0.60 [0.17, 2.18]
Subtotal (95% CI)	**20**	**20**		**100.0 %**	**0.60 [0.17, 2.18]**
Total events: 3 (Risperidone), 5 (Quetiapine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.78 (P = 0.44)					
Test for subgroup differences: Not applicable					

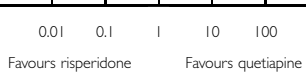
Analysis 3.7. Comparison 3 RISPERIDONE vs OTHER ANTIPSYCHOTIC: c. QUETIAPINE, Outcome 7 Adverse effects: 1c. Specific - Cardiovascular.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 3 RISPERIDONE vs OTHER ANTIPSYCHOTIC: c. QUETIAPINE

Outcome: 7 Adverse effects: 1c. Specific - Cardiovascular

Study or subgroup	Risperidone n/N	Quetiapine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Tachycardia over 24 hours					
Dai 2012	4/20	1/20		100.0 %	4.00 [0.49, 32.72]
Subtotal (95% CI)	**20**	**20**		**100.0 %**	**4.00 [0.49, 32.72]**
Total events: 4 (Risperidone), 1 (Quetiapine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.29 (P = 0.20)					
Test for subgroup differences: Not applicable					

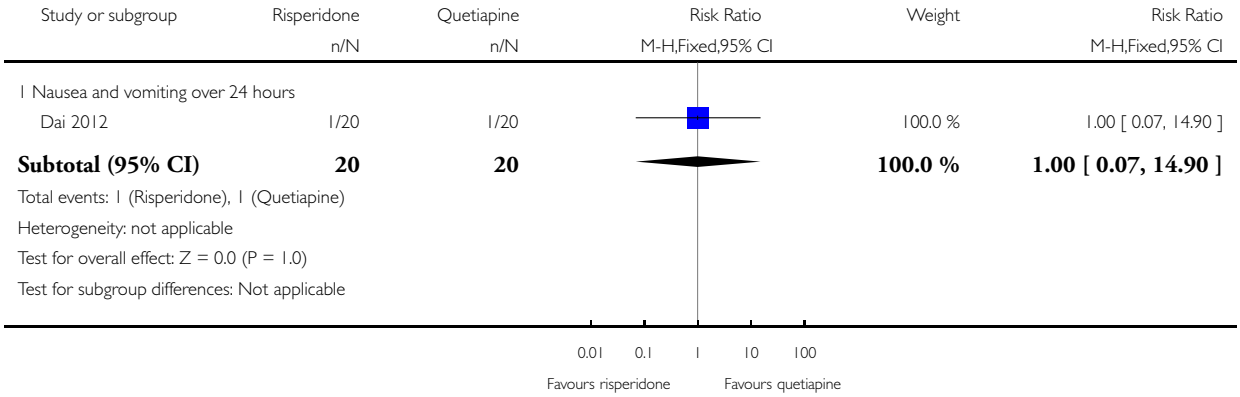


Analysis 3.8. Comparison 3 RISPERIDONE vs OTHER ANTIPSYCHOTIC: c. QUETIAPINE, Outcome 8 Adverse effects: 1d. Specific - Gastrointestinal.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 3 RISPERIDONE vs OTHER ANTIPSYCHOTIC: c. QUETIAPINE

Outcome: 8 Adverse effects: 1d. Specific - Gastrointestinal

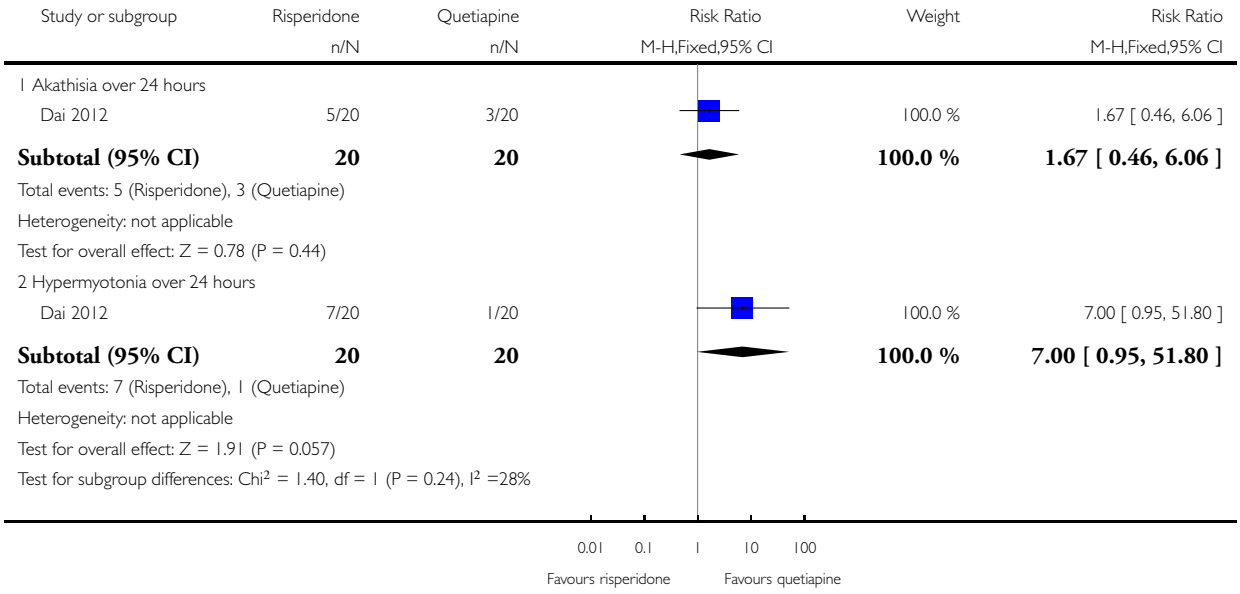


Analysis 3.9. Comparison 3 RISPERIDONE vs OTHER ANTIPSYCHOTIC: c. QUETIAPINE, Outcome 9 Adverse effects: 1e. Specific - Movement disorders.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 3 RISPERIDONE vs OTHER ANTIPSYCHOTIC: c. QUETIAPINE

Outcome: 9 Adverse effects: 1e. Specific - Movement disorders

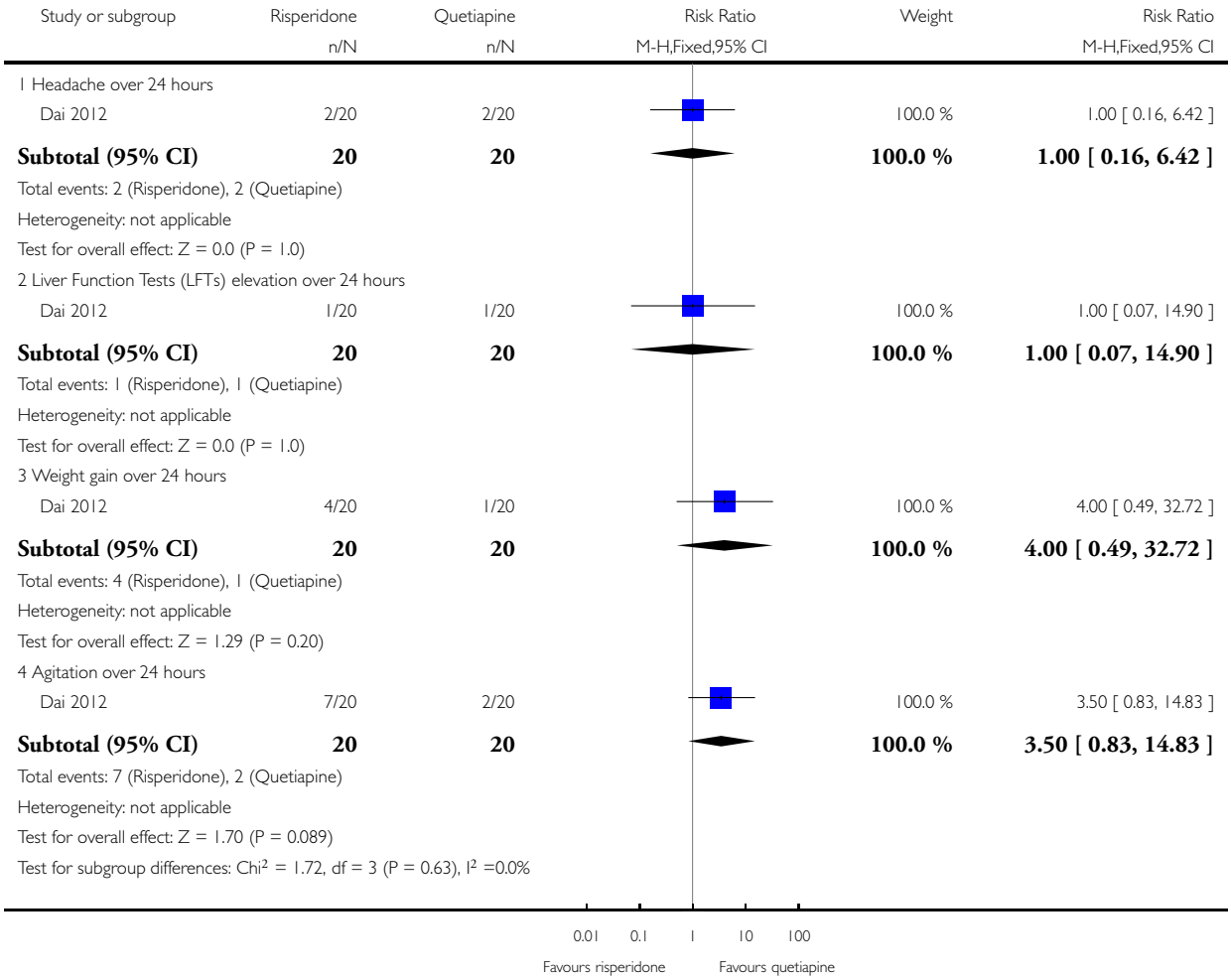


Analysis 3.10. Comparison 3 RISPERIDONE vs OTHER ANTIPSYCHOTIC: c. QUETIAPINE, Outcome 10 Adverse effects: 1f. Specific - Miscellaneous.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 3 RISPERIDONE vs OTHER ANTIPSYCHOTIC: c. QUETIAPINE

Outcome: 10 Adverse effects: 1f. Specific - Miscellaneous



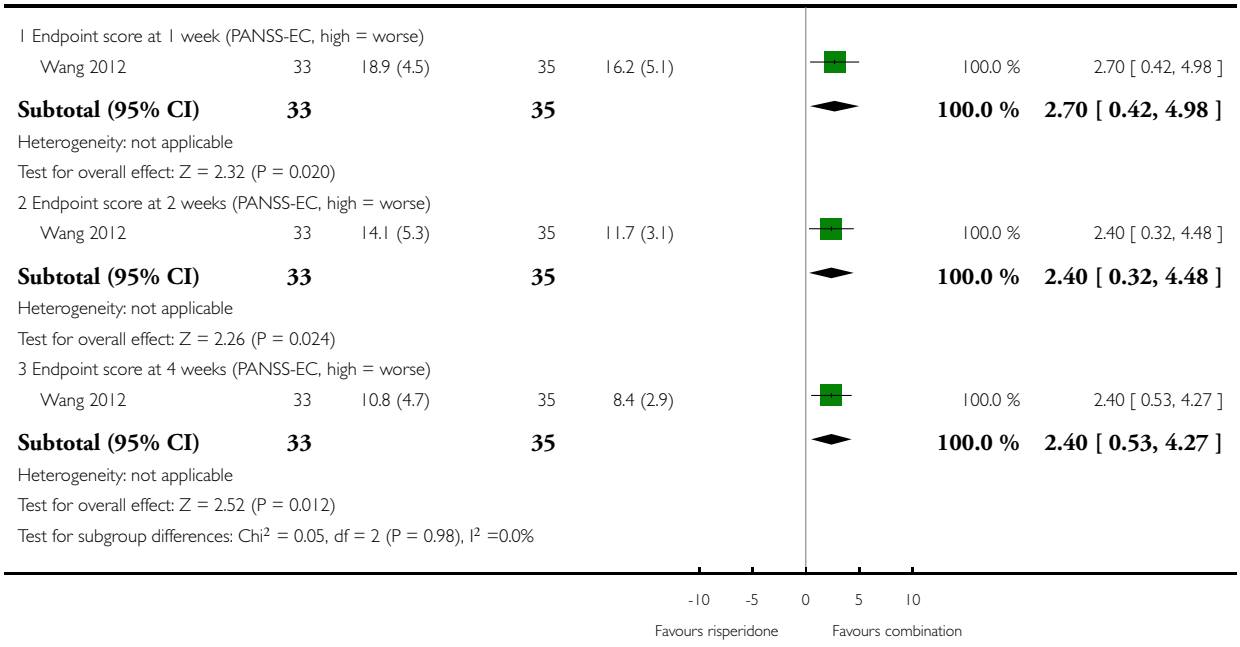
Analysis 4.1. Comparison 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE, Outcome 1 Specific behaviour: 1. Agitation - Average scores - i. over 24 hours.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE

Outcome: 1 Specific behaviour: 1. Agitation - Average scores - i. over 24 hours

Study or subgroup	Risperidone N	Mean(SD)	Combination N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Endpoint score at 1 week (PANSS-EC, high = worse)							
Wang 2012	33	18.9 (4.5)	35	16.2 (5.1)		100.0 %	2.70 [0.42, 4.98]
Subtotal (95% CI)	**33**		**35**			**100.0 %**	**2.70 [0.42, 4.98]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.32 (P = 0.020)							
2 Endpoint score at 2 weeks (PANSS-EC, high = worse)							
Wang 2012	33	14.1 (5.3)	35	11.7 (3.1)		100.0 %	2.40 [0.32, 4.48]
Subtotal (95% CI)	**33**		**35**			**100.0 %**	**2.40 [0.32, 4.48]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.26 (P = 0.024)							
3 Endpoint score at 4 weeks (PANSS-EC, high = worse)							
Wang 2012	33	10.8 (4.7)	35	8.4 (2.9)		100.0 %	2.40 [0.53, 4.27]
Subtotal (95% CI)	**33**		**35**			**100.0 %**	**2.40 [0.53, 4.27]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.52 (P = 0.012)							
Test for subgroup differences: Chi^2 = 0.05, df = 2 (P = 0.98), I^2 =0.0%							



Analysis 4.2. Comparison 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE, Outcome 2 Global Outcome: 1. Average scores - i. Over 24 hours.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE

Outcome: 2 Global Outcome: 1. Average scores - i. Over 24 hours

Study or subgroup	Risperidone N	Risperidone Mean(SD)	Combination N	Combination Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Endpoint score at 1 week (CGI-I, high = worse)							
Wang 2012	33	2.6 (0.7)	35	2.8 (1)		100.0 %	-0.20 [-0.61, 0.21]
Subtotal (95% CI)	**33**		**35**			**100.0 %**	**-0.20 [-0.61, 0.21]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.96 (P = 0.34)							
2 Endpoint score at 2 weeks (CGI-I, high = worse)							
Wang 2012	33	2.4 (1)	35	1.9 (0.8)		100.0 %	0.50 [0.07, 0.93]
Subtotal (95% CI)	**33**		**35**			**100.0 %**	**0.50 [0.07, 0.93]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.27 (P = 0.023)							
3 Endpoint score at 4 weeks (CGI-I, high = worse)							
Wang 2012	33	2.2 (0.8)	35	1.7 (0.7)		100.0 %	0.50 [0.14, 0.86]
Subtotal (95% CI)	**33**		**35**			**100.0 %**	**0.50 [0.14, 0.86]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.74 (P = 0.0062)							
4 Endpoint score at 1 week (CGI-S, high = worse)							
Wang 2012	33	4.2 (0.9)	35	4 (1)		100.0 %	0.20 [-0.25, 0.65]
Subtotal (95% CI)	**33**		**35**			**100.0 %**	**0.20 [-0.25, 0.65]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.87 (P = 0.39)							
5 Endpoint score at 2 weeks (CGI-S, high = worse)							
Wang 2012	33	3.4 (1)	35	2.9 (0.8)		100.0 %	0.50 [0.07, 0.93]
Subtotal (95% CI)	**33**		**35**			**100.0 %**	**0.50 [0.07, 0.93]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.27 (P = 0.023)							
6 Endpoint score at 4 weeks (CGI-S, high = worse)							
Wang 2012	33	3.2 (0.8)	35	2.7 (0.7)		100.0 %	0.50 [0.14, 0.86]
Subtotal (95% CI)	**33**		**35**			**100.0 %**	**0.50 [0.14, 0.86]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.74 (P = 0.0062)							
Test for subgroup differences: Chi^2 = 9.66, df = 5 (P = 0.09), I^2 =48%							

Analysis 4.3. Comparison 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE, Outcome 3 Mental state: 1a. No change in general mental state.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE

Outcome: 3 Mental state: 1a. No change in general mental state

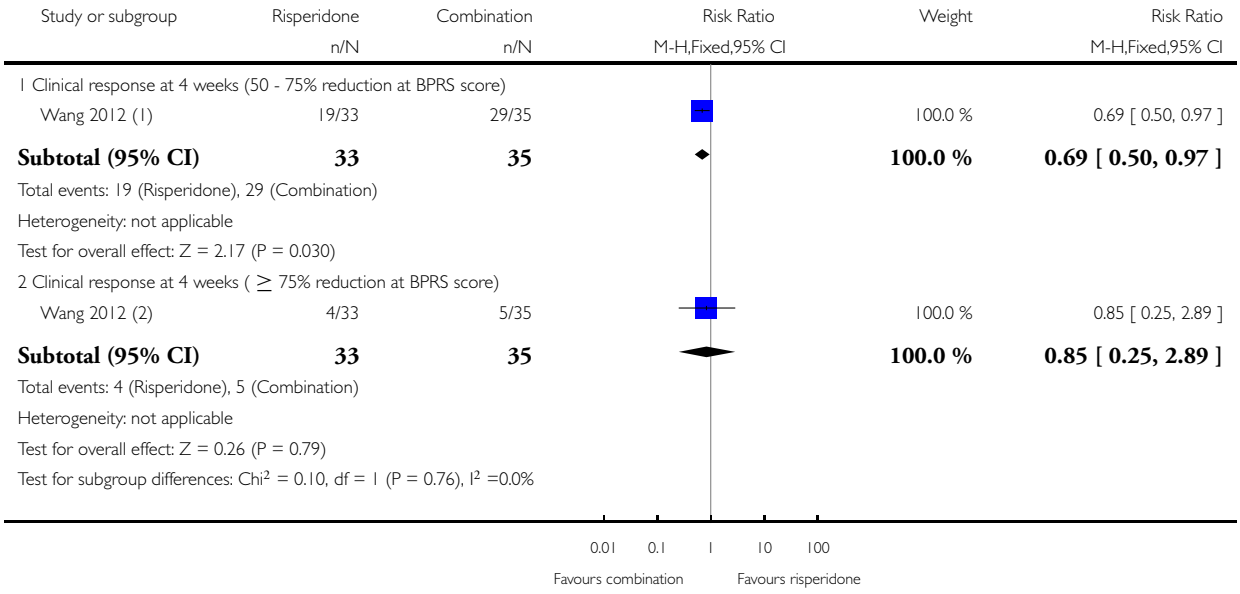
Study or subgroup	Risperidone n/N	Combination n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 No response at 4 weeks (< 50% reduction BPRS score)					
Wang 2012	10/33	1/35		100.0 %	10.61 [1.44, 78.36]
Subtotal (95% CI)	**33**	**35**		**100.0 %**	**10.61 [1.44, 78.36]**
Total events: 10 (Risperidone), 1 (Combination)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.31 (P = 0.021)					
Test for subgroup differences: Not applicable					

Analysis 4.4. Comparison 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE, Outcome 4 Mental state: 1b. Change in general mental state.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE

Outcome: 4 Mental state: 1b. Change in general mental state



(1) Axis labels have been switched in order to improve readability.

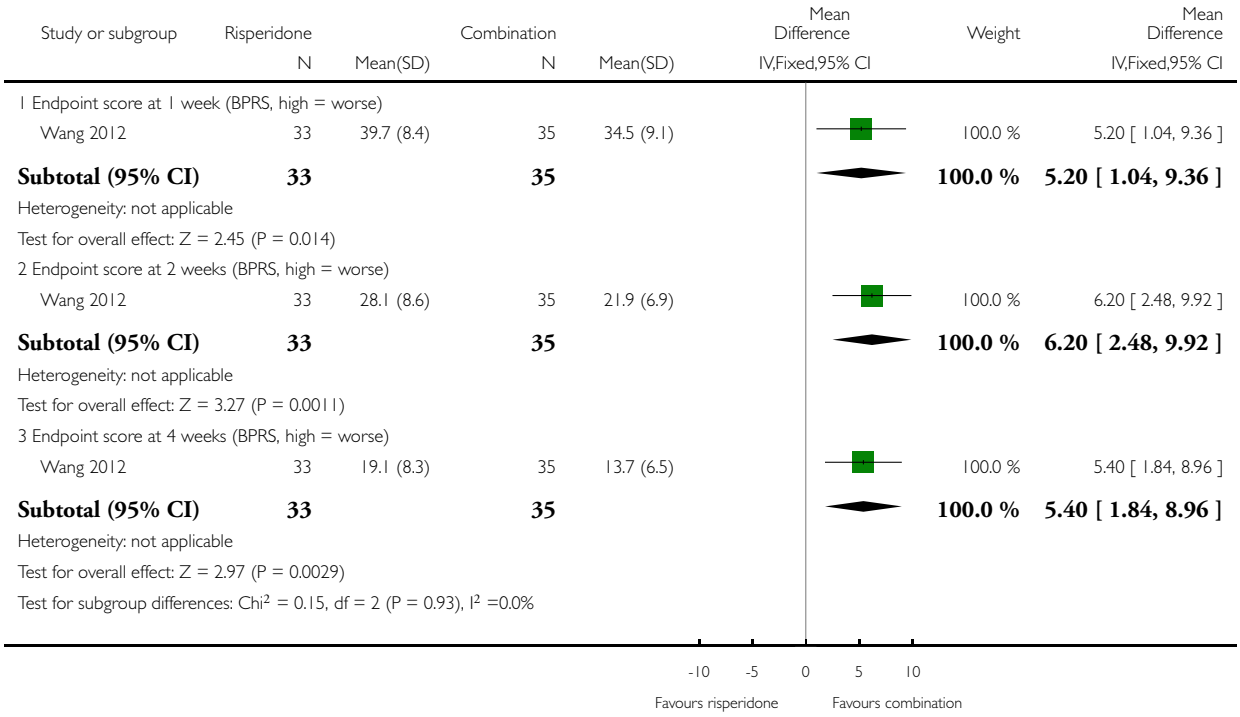
(2) Axis labels have been switched in order to improve readability.

Analysis 4.5. Comparison 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE, Outcome 5 Mental state: 1c. Average scores - i. Over 24 hours.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE

Outcome: 5 Mental state: 1c. Average scores - i. Over 24 hours



Analysis 4.6. Comparison 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE, Outcome 6 Adverse effects: 1. General - Total number of AEs.

Adverse effects: 1. General - Total number of AEs

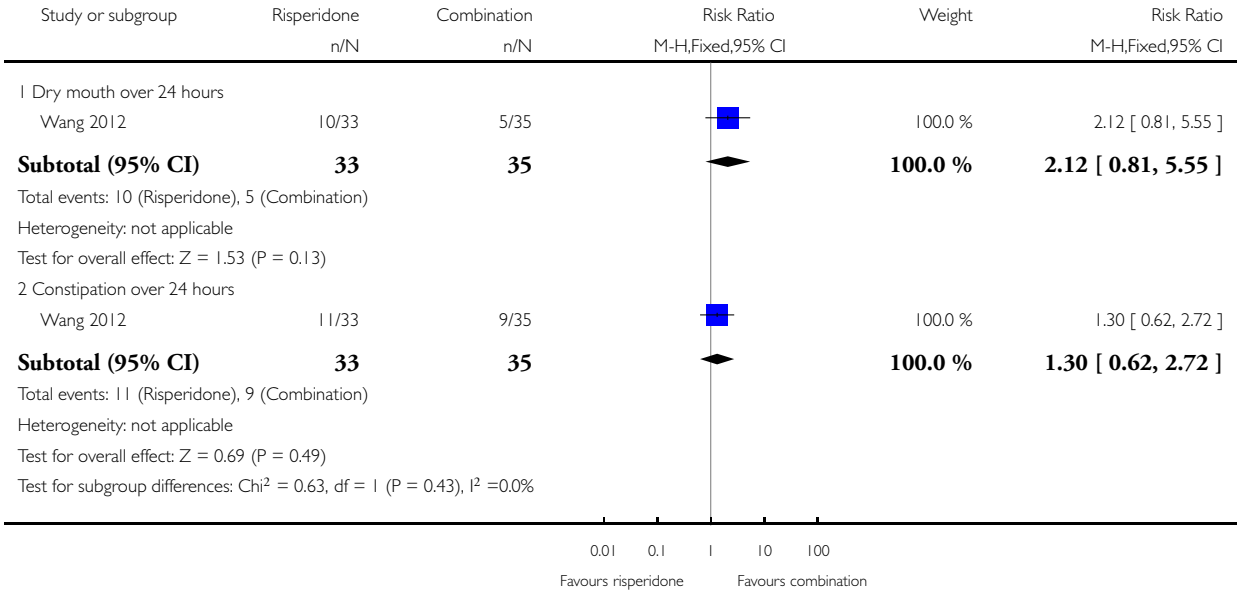
Study	AEs (*n*), *risperidone*	patients (*n*), *risperidone*	AEs (*n*), *combination*	patients (*n*), *combination*
Wang 2012	40	33	47	35

Analysis 4.7. Comparison 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE, Outcome 7 Adverse effects: 2a. Specific - Anticholinergic.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE

Outcome: 7 Adverse effects: 2a. Specific - Anticholinergic



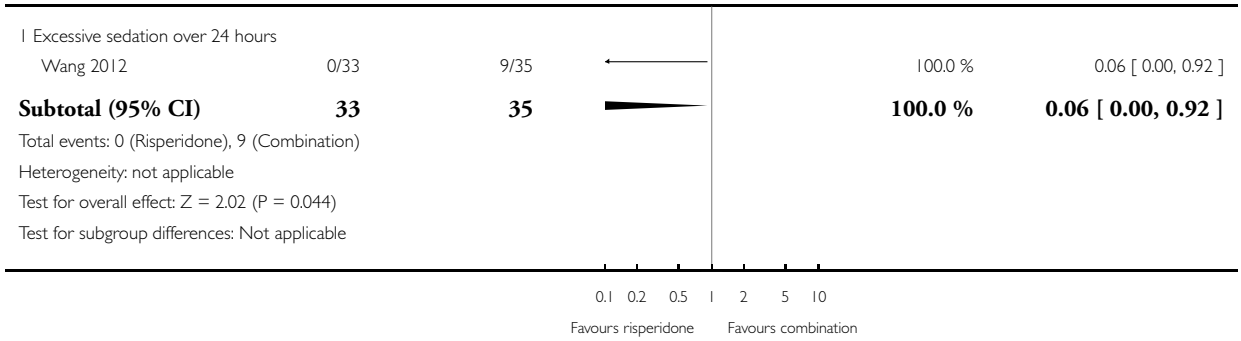
Analysis 4.8. Comparison 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE, Outcome 8 Adverse effects: 2b. Specific - Arousal.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE

Outcome: 8 Adverse effects: 2b. Specific - Arousal

Study or subgroup	Risperidone n/N	Combination n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Excessive sedation over 24 hours					
Wang 2012	0/33	9/35		100.0 %	0.06 [0.00, 0.92]
Subtotal (95% CI)	**33**	**35**		**100.0 %**	**0.06 [0.00, 0.92]**
Total events: 0 (Risperidone), 9 (Combination)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.02 (P = 0.044)					
Test for subgroup differences: Not applicable					



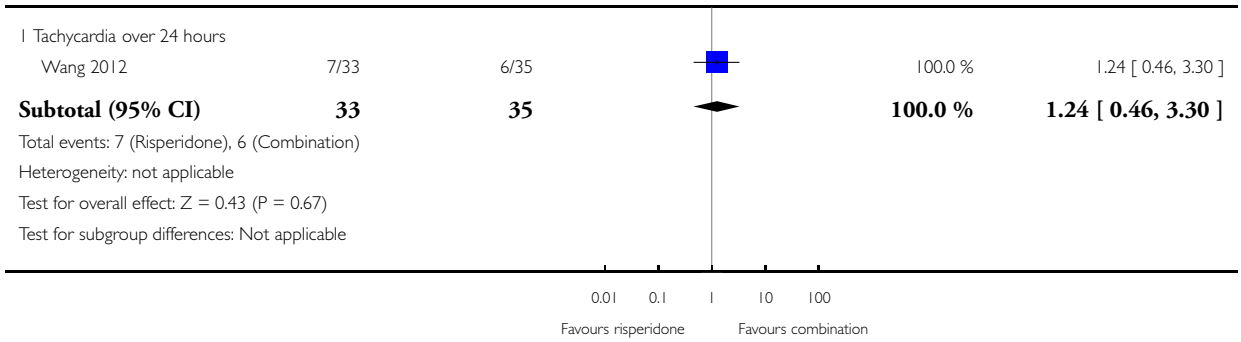
Analysis 4.9. Comparison 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE, Outcome 9 Adverse effects: 2c. Specific - Cardiovascular.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE

Outcome: 9 Adverse effects: 2c. Specific - Cardiovascular

Study or subgroup	Risperidone n/N	Combination n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Tachycardia over 24 hours					
Wang 2012	7/33	6/35		100.0 %	1.24 [0.46, 3.30]
Subtotal (95% CI)	**33**	**35**		**100.0 %**	**1.24 [0.46, 3.30]**
Total events: 7 (Risperidone), 6 (Combination)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					
Test for subgroup differences: Not applicable					



Analysis 4.10. Comparison 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE, Outcome 10 Adverse effects: 2d. Specific - Gastrointestinal.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE

Outcome: 10 Adverse effects: 2d. Specific - Gastrointestinal

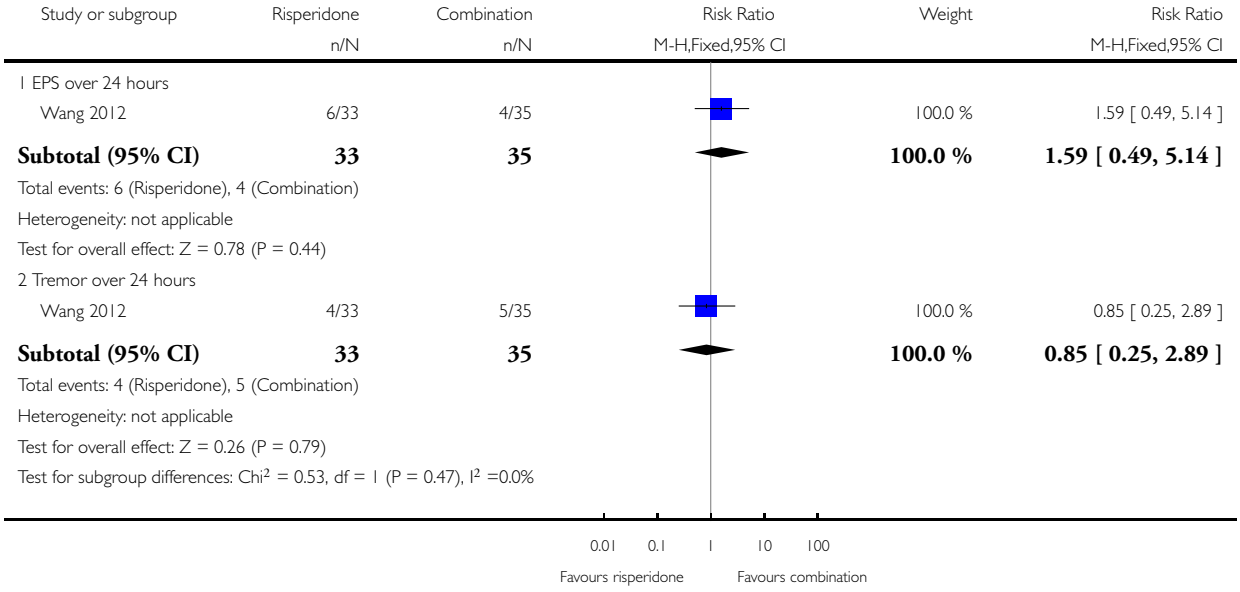
Study or subgroup	Risperidone n/N	Combination n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Nausea over 24 hours					
Wang 2012	2/33	1/35		100.0 %	2.12 [0.20, 22.31]
Subtotal (95% CI)	**33**	**35**		**100.0 %**	**2.12 [0.20, 22.31]**
Total events: 2 (Risperidone), 1 (Combination)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.63 (P = 0.53)					
Test for subgroup differences: Not applicable					

Analysis 4.11. Comparison 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE, Outcome 11 Adverse effects: 2e. Specific - Movement disorders.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE

Outcome: 11 Adverse effects: 2e. Specific - Movement disorders



Analysis 4.12. Comparison 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE, Outcome 12 Adverse effects: 2f. Specific - Miscellaneous.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 4 RISPERIDONE vs COMBINATION: a. RISPERIDONE + OXCARBAZEPINE

Outcome: 12 Adverse effects: 2f. Specific - Miscellaneous

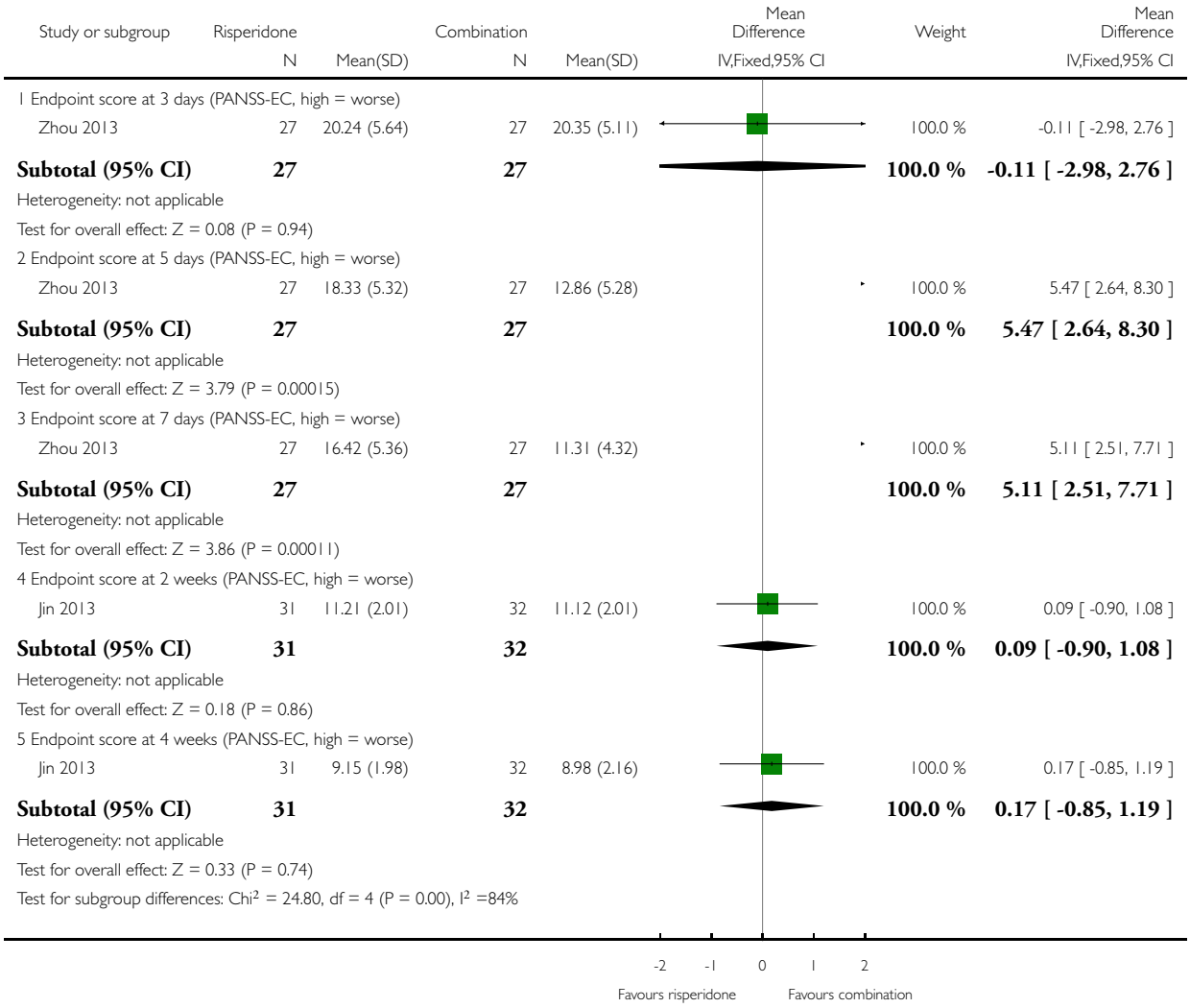
Study or subgroup	Risperidone n/N	Combination n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Headache over 24 hours					
Wang 2012	0/33	7/35		100.0 %	0.07 [0.00, 1.19]
Subtotal (95% CI)	**33**	**35**		**100.0 %**	**0.07 [0.00, 1.19]**
Total events: 0 (Risperidone), 7 (Combination)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.84 (P = 0.066)					
2 Skin rash over 24 hours					
Wang 2012	0/33	1/35		100.0 %	0.35 [0.01, 8.37]
Subtotal (95% CI)	**33**	**35**		**100.0 %**	**0.35 [0.01, 8.37]**
Total events: 0 (Risperidone), 1 (Combination)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.64 (P = 0.52)					
Test for subgroup differences: Chi^2 = 0.55, df = 1 (P = 0.46), I^2 =0.0%					

Analysis 5.1. Comparison 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID, Outcome 1 Specific behaviour: 1. Agitation - average scores - i. over 24 hours.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID

Outcome: 1 Specific behaviour: 1. Agitation - average scores - i. over 24 hours



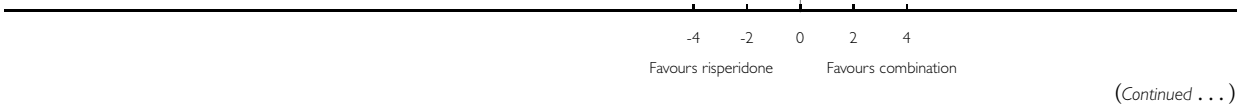
Analysis 5.2. Comparison 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID, Outcome 2 Specific behaviour: 1. Aggression - Average scores - i. over 24 hours.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID

Outcome: 2 Specific behaviour: 1. Aggression - Average scores - i. over 24 hours

Study or subgroup	Risperidone N	Risperidone Mean(SD)	Combination N	Combination Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Endpoint score at 3 days (MOAS, high = worse)							
Zhou 2013	27	7.42 (2.33)	27	6.35 (2.42)		100.0 %	1.07 [-0.20, 2.34]
Subtotal (95% CI)	**27**		**27**			**100.0 %**	**1.07 [-0.20, 2.34]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.66 (P = 0.098)							
2 Endpoint score at 5 days (MOAS, high = worse)							
Zhou 2013	27	6.24 (2.18)	27	5.86 (2.37)		100.0 %	0.38 [-0.83, 1.59]
Subtotal (95% CI)	**27**		**27**			**100.0 %**	**0.38 [-0.83, 1.59]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.61 (P = 0.54)							
3 Endpoint score at 7 days (MOAS, high = worse)							
Zhou 2013	27	6.56 (2.47)	27	3.24 (2.22)		100.0 %	3.32 [2.07, 4.57]
Subtotal (95% CI)	**27**		**27**			**100.0 %**	**3.32 [2.07, 4.57]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.19 (P < 0.00001)							
4 Endpoint score at 2 weeks (MOAS, high = worse)							
Li 2013	30	8 (2.4)	30	7.4 (2.6)		50.4 %	0.60 [-0.67, 1.87]
Wang 2013	34	6.94 (2.73)	34	5.28 (2.64)		49.6 %	1.66 [0.38, 2.94]
Subtotal (95% CI)	**64**		**64**			**100.0 %**	**1.13 [0.23, 2.02]**
Heterogeneity: Chi^2 = 1.34, df = 1 (P = 0.25); I^2 =25%							
Test for overall effect: Z = 2.45 (P = 0.014)							
5 Endpoint score at 4 weeks (MOAS, high = worse)							
Li 2013	30	5.6 (2.4)	30	3.8 (2.1)		51.5 %	1.80 [0.66, 2.94]
Wang 2013	34	5.29 (2.59)	34	3.96 (2.35)		48.5 %	1.33 [0.15, 2.51]
Subtotal (95% CI)	**64**		**64**			**100.0 %**	**1.57 [0.75, 2.39]**
Heterogeneity: Chi^2 = 0.32, df = 1 (P = 0.57); I^2 =0.0%							
Test for overall effect: Z = 3.76 (P = 0.00017)							
6 Endpoint score at 6 weeks (MOAS, high = worse)							
Wang 2013	34	3.65 (1.57)	34	2.18 (1.08)		100.0 %	1.47 [0.83, 2.11]
Subtotal (95% CI)	**34**		**34**			**100.0 %**	**1.47 [0.83, 2.11]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.50 (P < 0.00001)							



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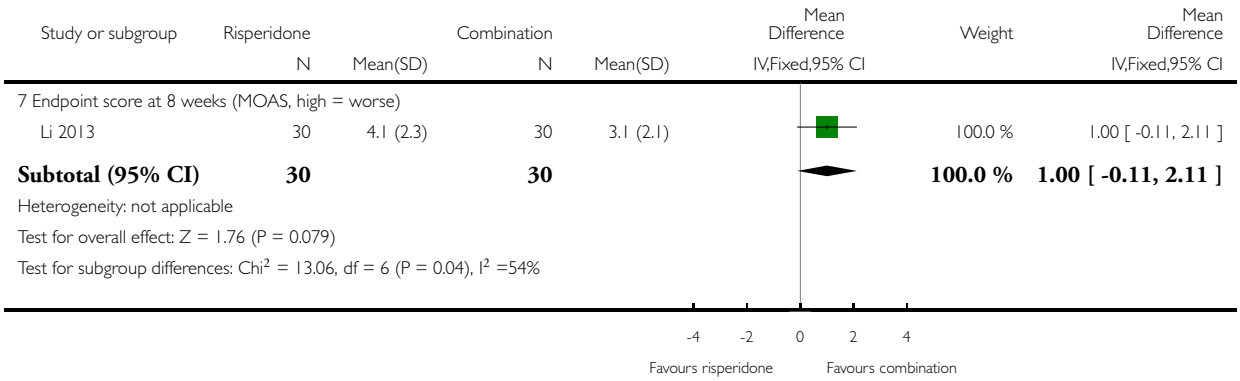
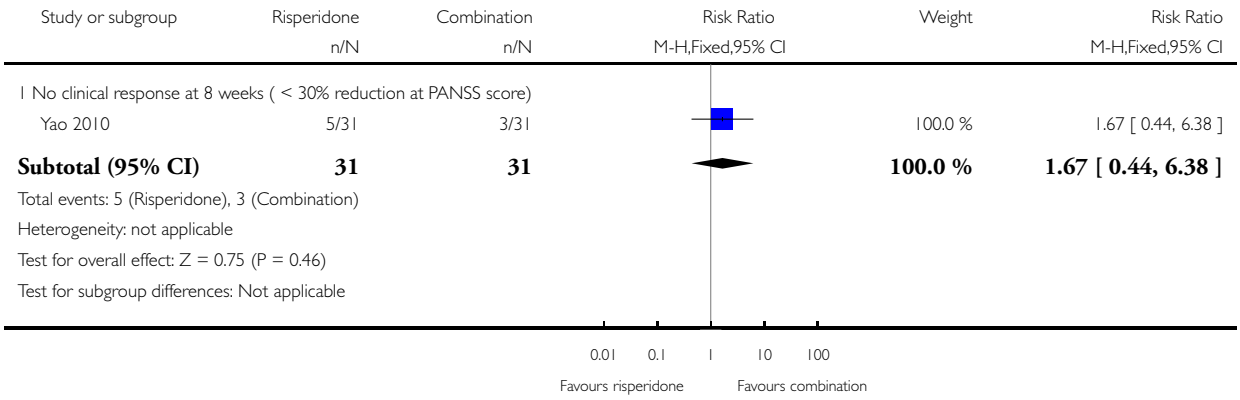


Analysis 5.3. Comparison 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID, Outcome 3 Mental state: 1. No change in general mental state.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID

Outcome: 3 Mental state: 1. No change in general mental state



Analysis 5.4. Comparison 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID, Outcome 4 Mental state: 2. Average scores - i. over 24 hours.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID

Outcome: 4 Mental state: 2. Average scores - i. over 24 hours

Study or subgroup	Risperidone N	Mean(SD)	Combination N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Endpoint score at 2 weeks (PANSS, high = worse)							
Jin 2013	31	80.49 (4.69)	32	75.63 (6.01)		36.2 %	4.86 [2.20, 7.52]
Li 2013	30	70.1 (5)	30	69.3 (5.1)		39.2 %	0.80 [-1.76, 3.36]
Wang 2013	34	75.7 (8.7)	34	65.8 (9.7)		13.3 %	9.90 [5.52, 14.28]
Yao 2010	31	79.13 (9.45)	31	78.34 (9.67)		11.3 %	0.79 [-3.97, 5.55]
Subtotal (95% CI)	**126**		**127**			**100.0 %**	**3.48 [1.88, 5.08]**
Heterogeneity: Chi² = 14.74, df = 3 (P = 0.002); I² =80%							
Test for overall effect: Z = 4.27 (P = 0.000020)							
2 Sub-group analysis: Endpoint score at 2 weeks (PANSS, high = worse)							
Jin 2013	31	80.49 (4.69)	32	75.63 (6.01)		41.8 %	4.86 [2.20, 7.52]
Li 2013	30	70.1 (5)	30	69.3 (5.1)		45.2 %	0.80 [-1.76, 3.36]
Yao 2010	31	79.13 (9.45)	31	78.34 (9.67)		13.0 %	0.79 [-3.97, 5.55]
Subtotal (95% CI)	**92**		**93**			**100.0 %**	**2.50 [0.78, 4.21]**
Heterogeneity: Chi² = 5.23, df = 2 (P = 0.07); I² =62%							
Test for overall effect: Z = 2.85 (P = 0.0044)							
3 Endpoint score at 4 weeks (PANSS, high = worse)							
Jin 2013	31	70.04 (4.23)	32	63.51 (8.62)		24.0 %	6.53 [3.19, 9.87]
Li 2013	30	56.4 (4.9)	30	53.1 (4.4)		48.1 %	3.30 [0.94, 5.66]
Wang 2013	34	64.8 (8.6)	34	53.8 (9.6)		14.2 %	11.00 [6.67, 15.33]
Yao 2010	31	61.68 (9.07)	31	56.37 (8.62)		13.8 %	5.31 [0.91, 9.71]
Subtotal (95% CI)	**126**		**127**			**100.0 %**	**5.45 [3.81, 7.08]**
Heterogeneity: Chi² = 9.91, df = 3 (P = 0.02); I² =70%							
Test for overall effect: Z = 6.53 (P < 0.00001)							
4 Sub-group analysis: Endpoint score at 4 weeks (PANSS, high = worse)							
Jin 2013	31	70.04 (4.23)	32	63.51 (8.62)		27.9 %	6.53 [3.19, 9.87]
Li 2013	30	56.4 (4.9)	30	53.1 (4.4)		56.0 %	3.30 [0.94, 5.66]
Yao 2010	31	61.68 (9.07)	31	56.37 (8.62)		16.0 %	5.31 [0.91, 9.71]
Subtotal (95% CI)	**92**		**93**			**100.0 %**	**4.52 [2.76, 6.29]**
Heterogeneity: Chi² = 2.55, df = 2 (P = 0.28); I² =21%							

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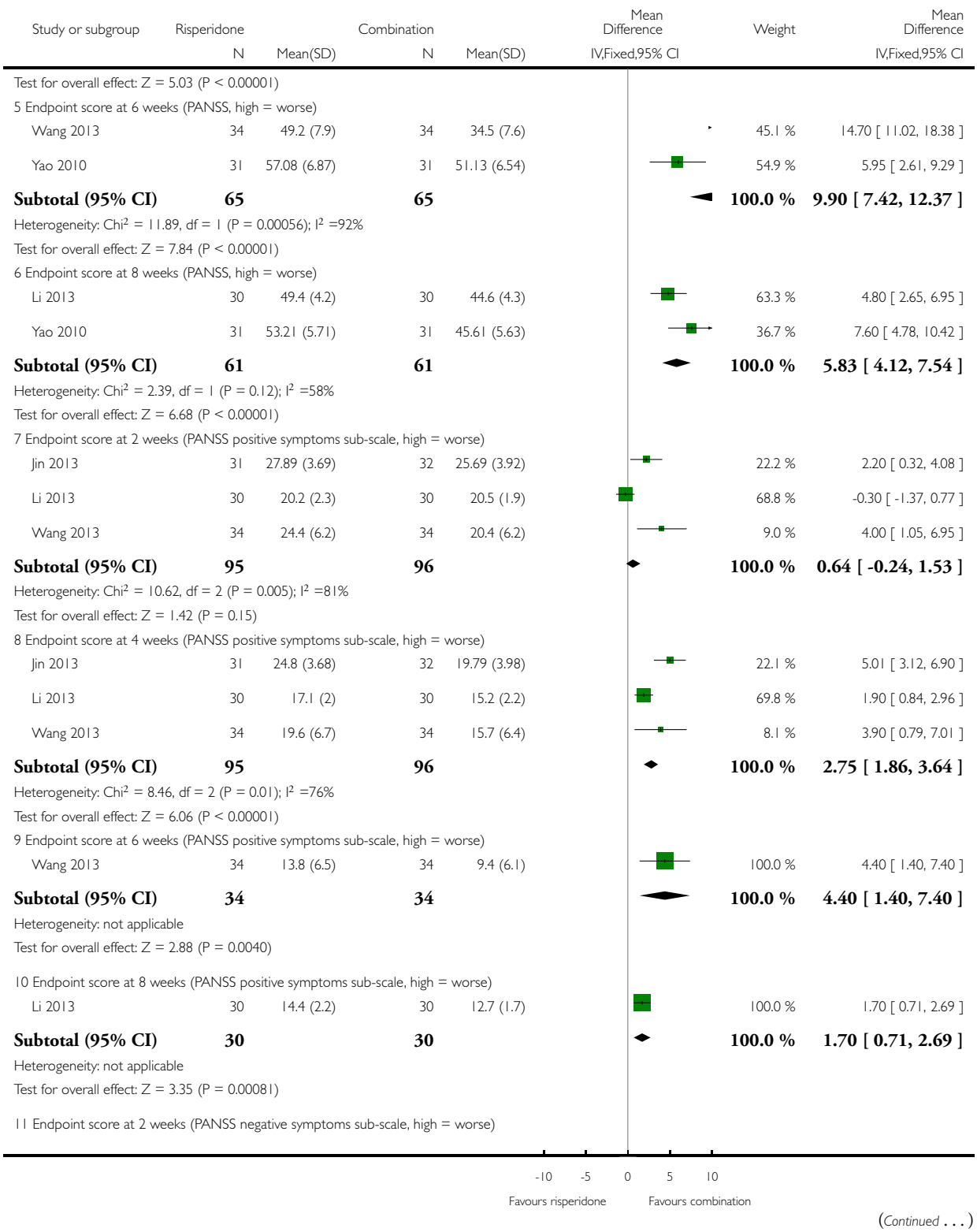

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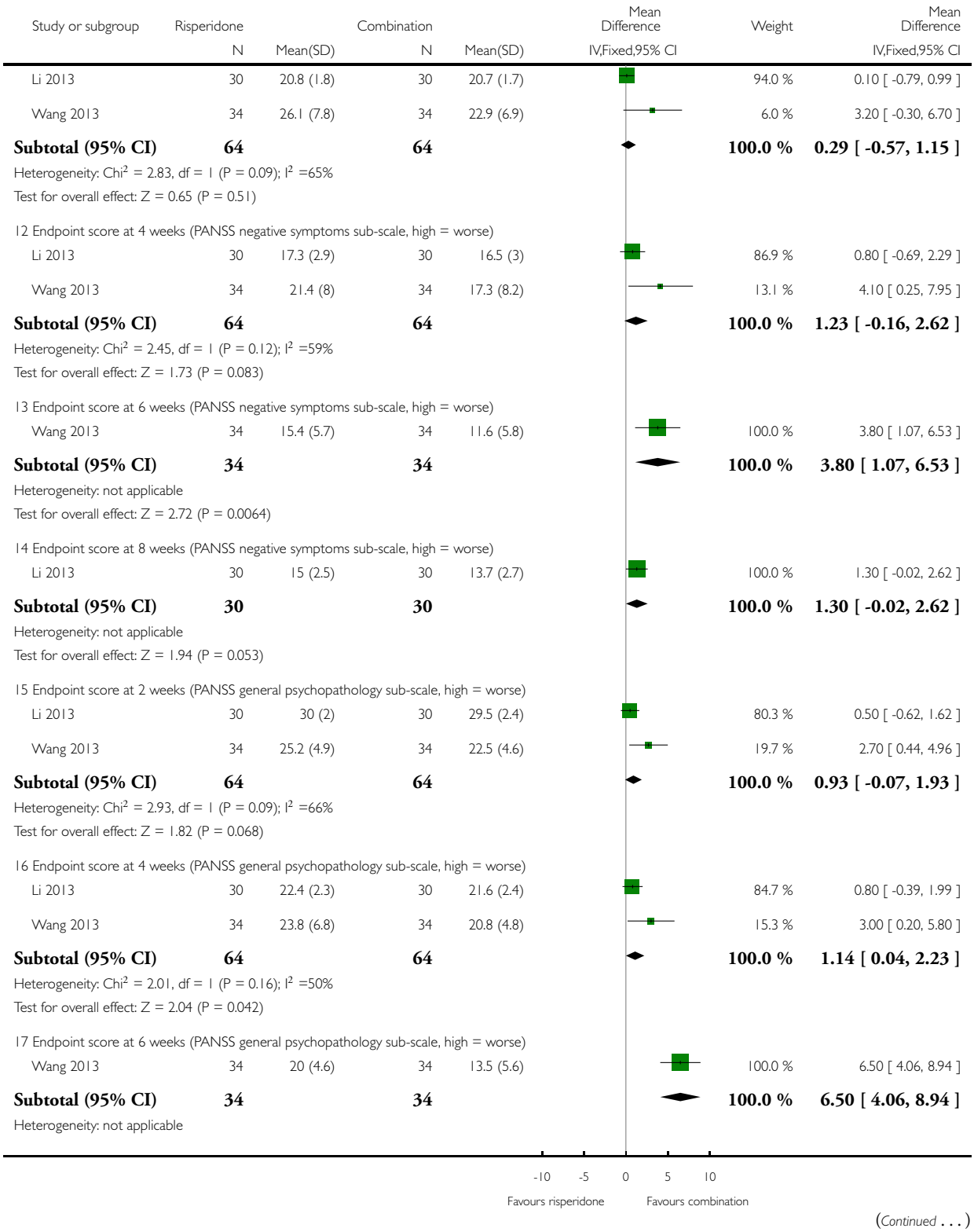

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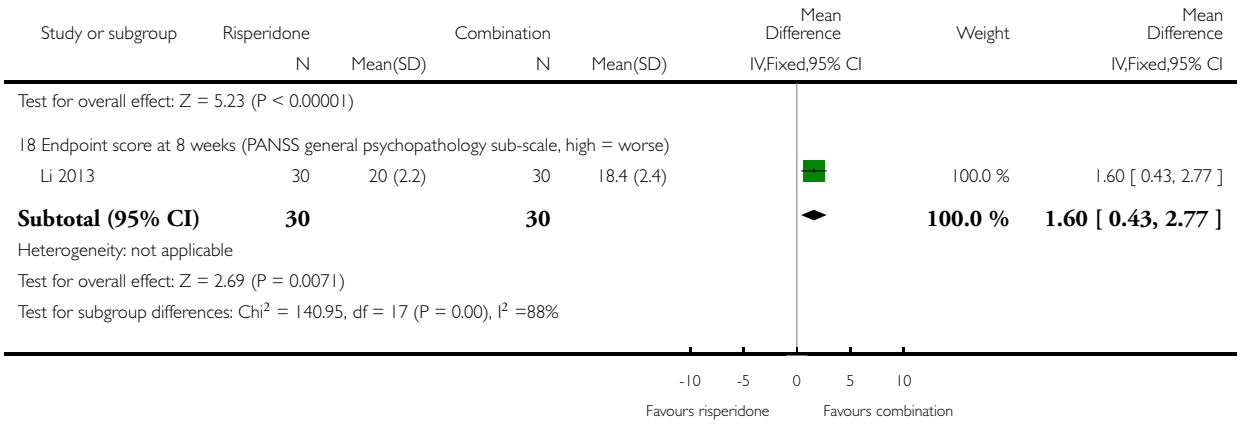

Analysis 5.5. Comparison 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID, Outcome 5 Adverse effects: 1a. General - Total number of AEs.

Adverse effects: 1a. General - Total number of AEs

Study	**AEs (*n*), *risperidone***	**patients (*n*), *risperidone***	**AEs (*n*), *combination***	**patients (*n*), *combination***
Wang 2012	16	27	20	27

Analysis 5.6. Comparison 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID, Outcome 6 Adverse effects: 1b. General - Serious.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID

Outcome: 6 Adverse effects: 1b. General - Serious

Study or subgroup	Risperidone n/N	Combination n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 myocardial ischaemia (at 8 weeks)					
Yao 2010	2/31	1/31		100.0 %	2.00 [0.19, 20.93]
Subtotal (95% CI)	**31**	**31**		**100.0 %**	**2.00 [0.19, 20.93]**
Total events: 2 (Risperidone), 1 (Combination)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.58 (P = 0.56)					
Test for subgroup differences: Not applicable					

Analysis 5.7. Comparison 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID, Outcome 7 Adverse effects: 2a. Specific - Anticholinergic.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID

Outcome: 7 Adverse effects: 2a. Specific - Anticholinergic

Study or subgroup	Risperidone n/N	Combination n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Blurred vision over 24 hours					
Wang 2013	4/34	3/34		42.9 %	1.33 [0.32, 5.51]
Zhou 2013	3/27	4/27		57.1 %	0.75 [0.19, 3.04]
Subtotal (95% CI)	**61**	**61**		**100.0 %**	**1.00 [0.37, 2.68]**
Total events: 7 (Risperidone), 7 (Combination)					
Heterogeneity: Chi^2 = 0.32, df = 1 (P = 0.57); I^2 =0.0%					
Test for overall effect: Z = 0.0 (P = 1.0)					
2 Dry mouth over 24 hours					
Jin 2013	10/31	2/30		22.5 %	4.84 [1.15, 20.28]

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Study or subgroup	Risperidone n/N	Combination n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wang 2013	5/34	7/34		77.5 %	0.71 [0.25, 2.03]
Subtotal (95% CI)	**65**	**64**		**100.0 %**	**1.64 [0.76, 3.54]**
Total events: 15 (Risperidone), 9 (Combination)					
Heterogeneity: Chi² = 4.63, df = 1 (P = 0.03); I² =78%					
Test for overall effect: Z = 1.26 (P = 0.21)					
Test for subgroup differences: Chi² = 0.60, df = 1 (P = 0.44), I² =0.0%					

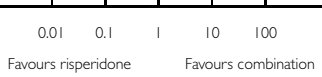
Analysis 5.8. Comparison 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID, Outcome 8 Adverse effects: 2b. Specific - Arousal.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID

Outcome: 8 Adverse effects: 2b. Specific - Arousal

Study or subgroup	Risperidone n/N	Combination n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Insomnia over 24 hours					
Zhou 2013	2/27	1/27		100.0 %	2.00 [0.19, 20.77]
Subtotal (95% CI)	**27**	**27**		**100.0 %**	**2.00 [0.19, 20.77]**
Total events: 2 (Risperidone), 1 (Combination)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.58 (P = 0.56)					
2 Somnolence over 24 hours					
Jin 2013	9/31	8/30		53.7 %	1.09 [0.48, 2.45]
Li 2013	4/30	7/30		46.3 %	0.57 [0.19, 1.75]
Subtotal (95% CI)	**61**	**60**		**100.0 %**	**0.85 [0.44, 1.63]**
Total events: 13 (Risperidone), 15 (Combination)					
Heterogeneity: Chi² = 0.84, df = 1 (P = 0.36); I² =0.0%					
Test for overall effect: Z = 0.49 (P = 0.62)					
Test for subgroup differences: Chi² = 0.48, df = 1 (P = 0.49), I² =0.0%					

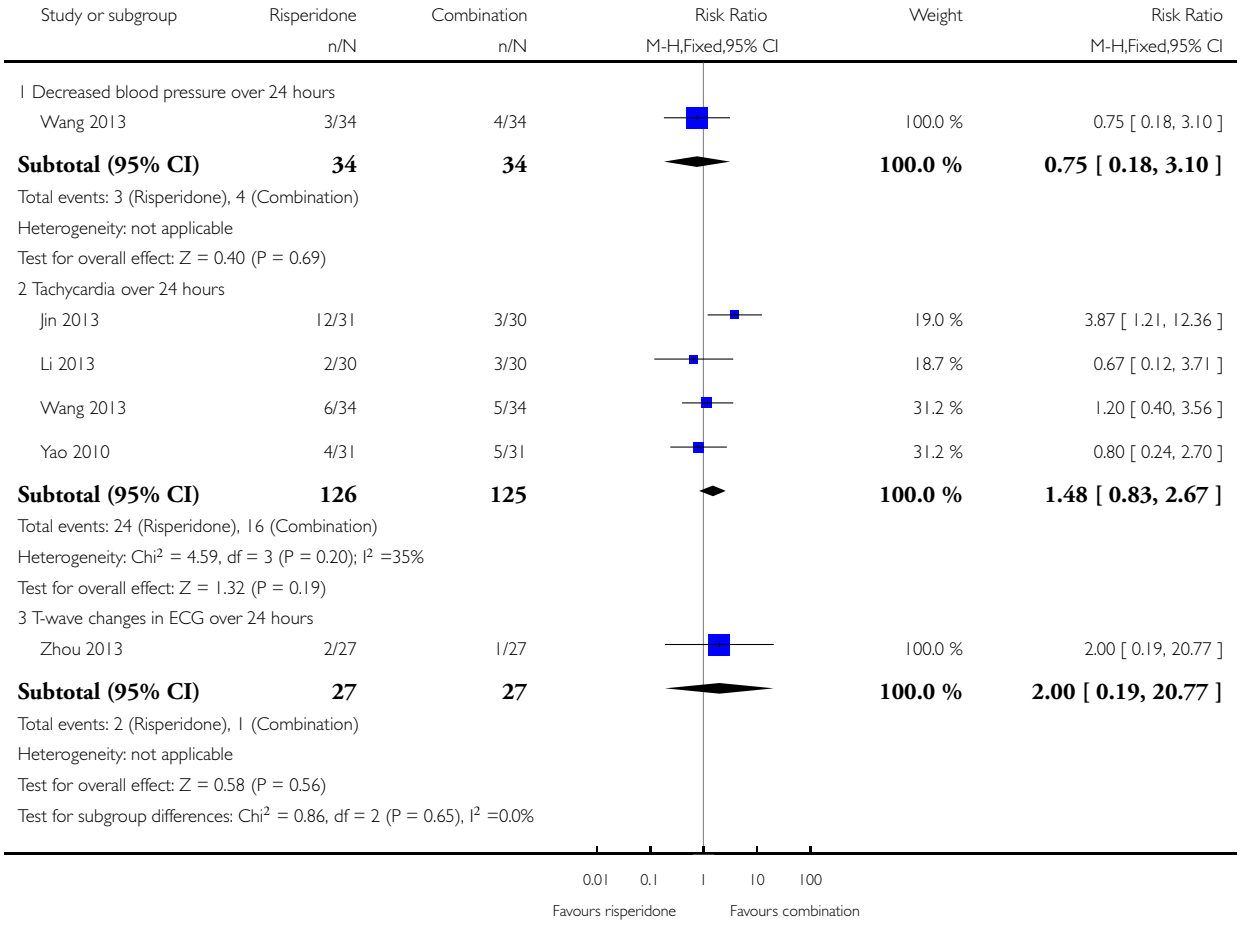


Analysis 5.9. Comparison 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID, Outcome 9 Adverse effects: 2c. Specific - Cardiovascular.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID

Outcome: 9 Adverse effects: 2c. Specific - Cardiovascular



Analysis 5.10. Comparison 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID, Outcome 10 Adverse effects: 2d. Specific - Gastrointestinal.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID

Outcome: 10 Adverse effects: 2d. Specific - Gastrointestinal

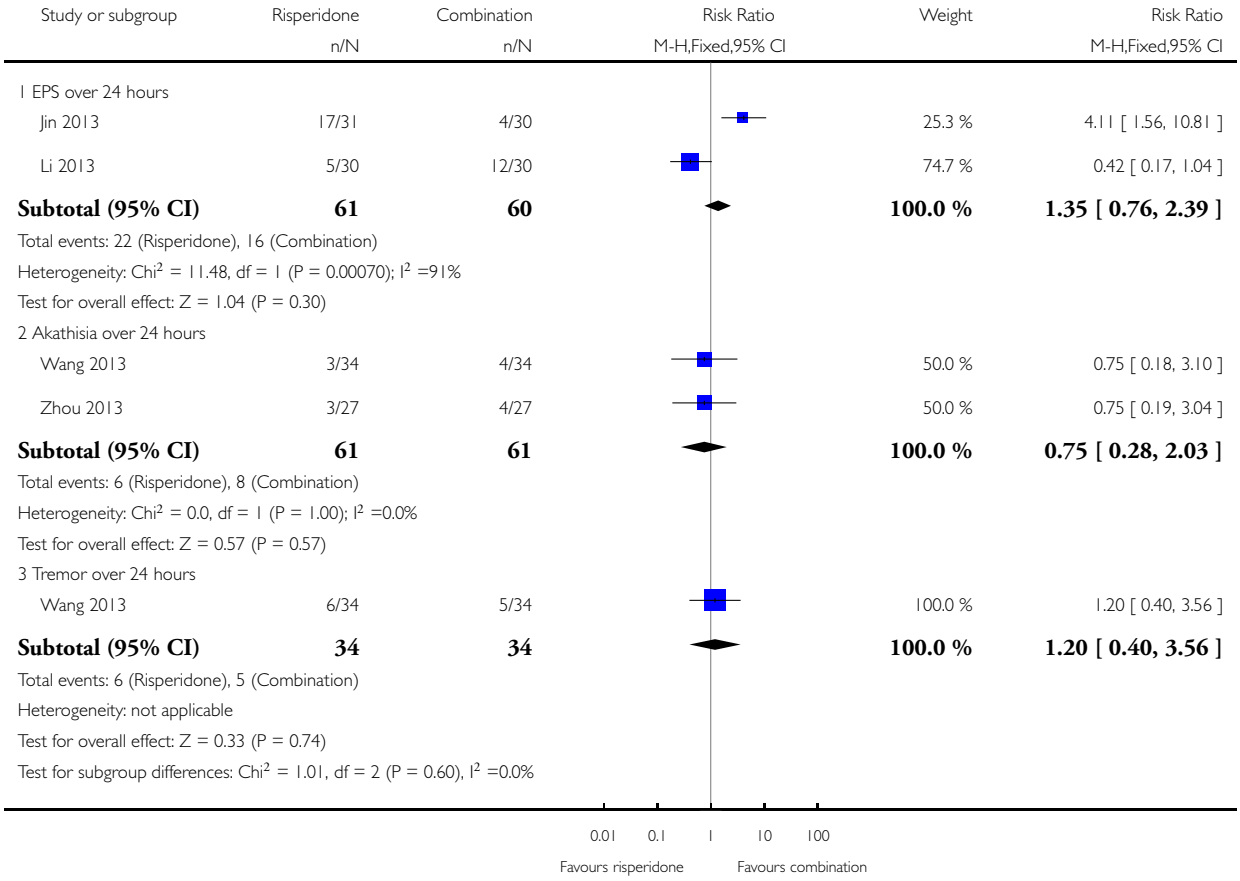
Study or subgroup	Risperidone n/N	Combination n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Constipation over 24 hours					
Jin 2013	13/31	8/30		33.7 %	1.57 [0.76, 3.24]
Li 2013	9/30	12/30		49.7 %	0.75 [0.37, 1.51]
Wang 2013	5/34	4/34		16.6 %	1.25 [0.37, 4.26]
Subtotal (95% CI)	**95**	**94**		**100.0 %**	**1.11 [0.70, 1.76]**
Total events: 27 (Risperidone), 24 (Combination)					
Heterogeneity: Chi^2 = 2.13, df = 2 (P = 0.34); I^2 =6%					
Test for overall effect: Z = 0.44 (P = 0.66)					
2 Nausea over 24 hours					
Wang 2013	5/34	7/34		70.0 %	0.71 [0.25, 2.03]
Zhou 2013	2/27	3/27		30.0 %	0.67 [0.12, 3.68]
Subtotal (95% CI)	**61**	**61**		**100.0 %**	**0.70 [0.29, 1.71]**
Total events: 7 (Risperidone), 10 (Combination)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%					
Test for overall effect: Z = 0.78 (P = 0.43)					
Test for subgroup differences: Chi^2 = 0.81, df = 1 (P = 0.37), I^2 =0.0%					

Analysis 5.11. Comparison 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID, Outcome 11 Adverse effects: 2e. Specific - Movement disorders.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID

Outcome: 11 Adverse effects: 2e. Specific - Movement disorders

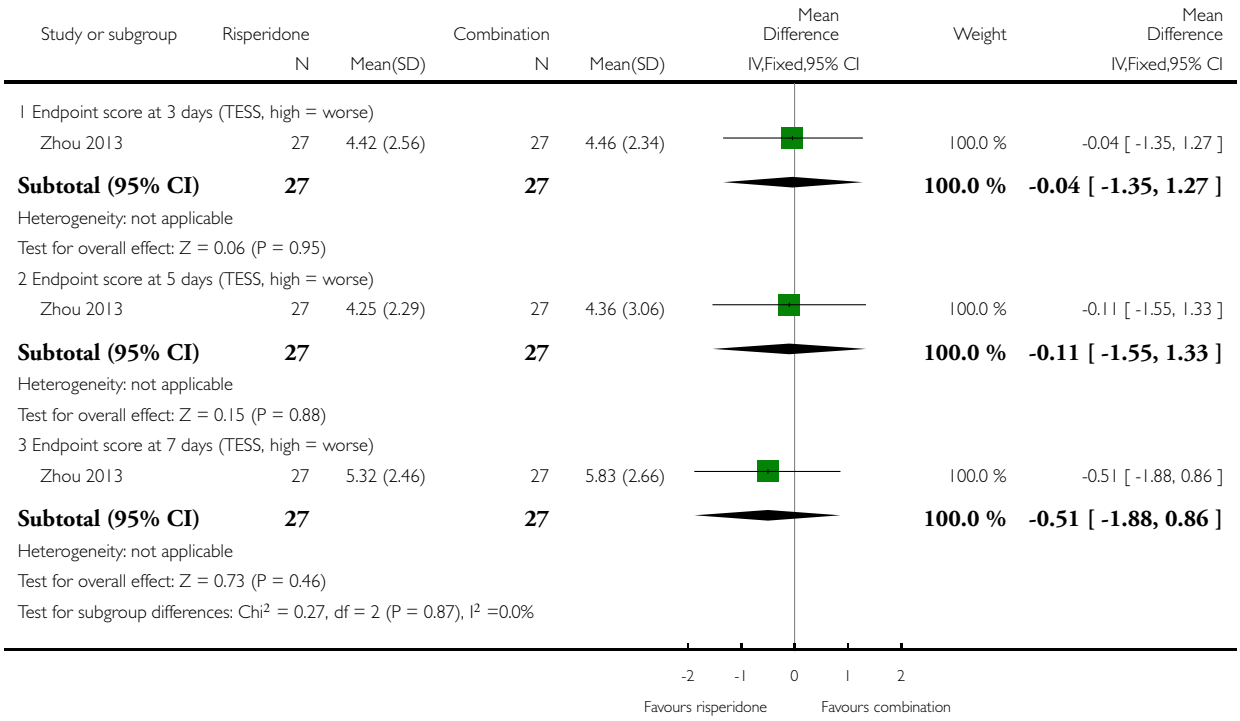


Analysis 5.12. Comparison 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID, Outcome 12 Adverse effects: 2f. Specific - Movement disorders - Average scores - i. Over 24 hours.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID

Outcome: 12 Adverse effects: 2f. Specific - Movement disorders - Average scores - i. Over 24 hours

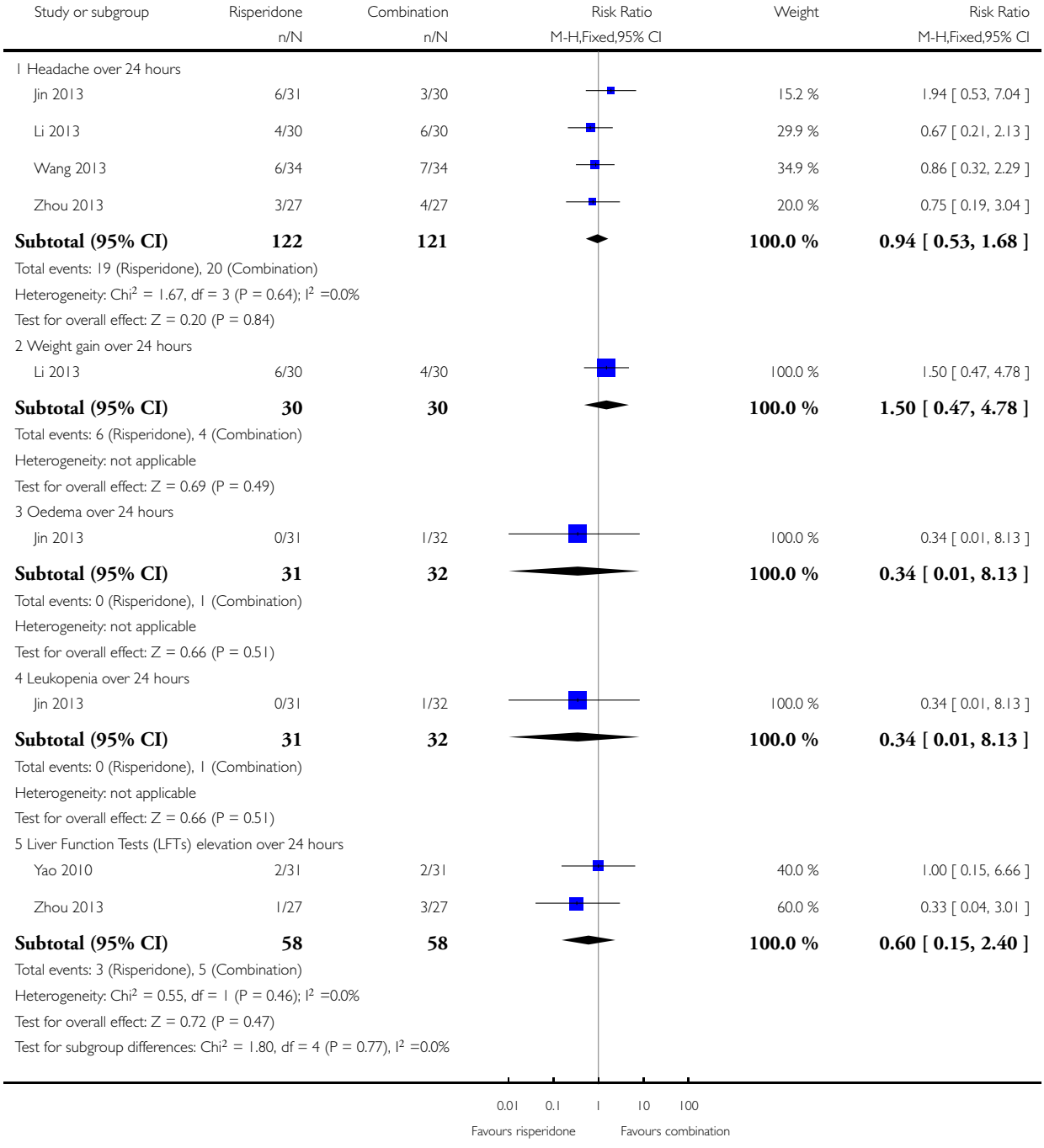


Analysis 5.13. Comparison 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID, Outcome 13 Adverse effects: 2g. Specific - Miscellaneous.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID

Outcome: 13 Adverse effects: 2g. Specific - Miscellaneous

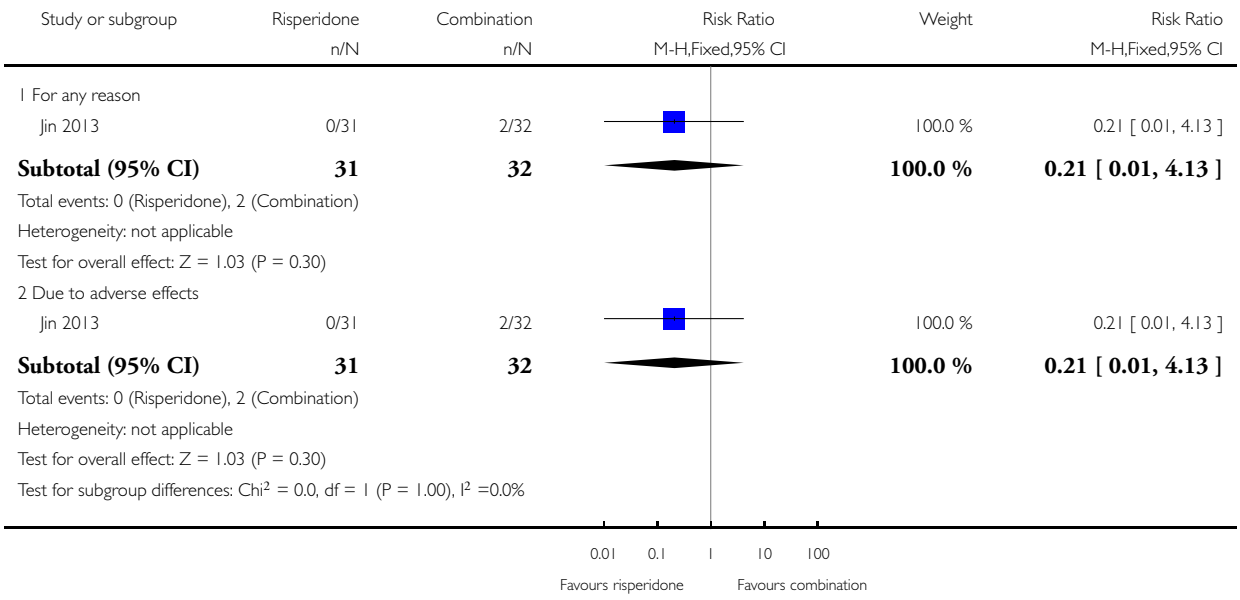


Analysis 5.14. Comparison 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID, Outcome 14 Leaving the study early.

Review: Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Comparison: 5 RISPERIDONE vs COMBINATION: b. RISPERIDONE + VALPROIC ACID

Outcome: 14 Leaving the study early



ADDITIONAL TABLES

Table 1. Linked reviews

Focus of review	Reference
Completed and maintained reviews	
Aripiprazole (intramuscular) for psychosis-induced aggression or agitation (rapid tranquillisation)	Ostinelli 2018
Benzodiazepines for psychosis-induced aggression or agitation	Zaman 2017

Table 1. Linked reviews (*Continued*)

Chlorpromazine for psychosis-induced aggression or agitation	Ahmed 2010
Containment strategies for people with serious mental illness	Muralidharan 2006
De-escalation techniques for psychosis-induced aggression or agitation	Du 2017
Droperidol for psychosis-induced aggression or agitation	Khokhar 2016
Haloperidol for psychosis-induced aggression or agitation (rapid tranquillisation)	Ostinelli 2017
Haloperidol plus promethazine for psychosis-induced aggression	Huf 2016
Olanzapine IM or velotab for acutely disturbed/agitated people with suspected serious mental illnesses	Belgamwar 2005
Zuclopenthixol acetate for acute schizophrenia and similar serious mental illnesses	Jayakody 2012
Reviews in the process of being completed	
Loxapine inhaler for psychosis-induced aggression	Vangala 2012
Quetiapine for psychosis-induced aggression	Wilkie 2012

Table 2. Suggested design for a trial

Methods	Allocation: randomised, clearly described and concealed. Blindness: double, described and tested. Duration: 2 weeks.
Participants	Diagnosis: thought to be psychosis. N = 300*. Age: any. Sex: both. History: acutely ill, aggressive and/or agitated.
Interventions	1. Risperidone: dose flexible within recommended limits. N = 150. 2. Comparison: dose flexible within recommended limits. N = 150
Outcomes	All outcomes are grouped by time: by 30 minutes, up to two hours, up to four hours, up to 24 hours, and over 24 hours. First outcome of interest could be as early as 20 minutes Tranquillisation or asleep - tranquil; asleep. Repeated need for tranquillisation - needing additional injections Specific behaviours - self-harm, including suicide, injury to others Global outcomes - patient satisfaction; use of restraint or seclusion

Table 2. Suggested design for a trial (*Continued*)

	Service outcomes - length of hospitalisation; readmission rate Mental state - effect of medication on mental state. Adverse effects - medication significant side effects. Leaving the study early - detailed reasons provided. Quality of life outcomes. Economic outcomes.
Notes	* Enough power to be able to identify a difference of ~20% between groups for primary outcome with adequate degree of certainty

HISTORY

Protocol first published: Issue 11, 2011

Review first published: Issue 4, 2018

Date	Event	Description
12 April 2017	Amended	Search re-run and 14 Studies were added to Studies awaiting classification section of the review
19 June 2015	Amended	Search re-run and two studies (three references) were added to 'Studies awaiting assessment' section of the review
1 November 2013	Amended	Search re-run in November 2013, and 56 studies were added to 'Studies awaiting assessment' section of the review
1 December 2011	Amended	Original search in December 2011.

CONTRIBUTIONS OF AUTHORS

Edoardo G Ostinelli - screened and retrieved papers (2017 search, checking again studies from previous searches) against eligibility criteria, appraised quality of papers, extracted data from papers, entered data into RevMan and analysed data, interpreted data and took the lead in writing the review.

Mohsin Hussein - screened and retrieved papers (2017 search, checking again studies from previous searches) against eligibility criteria, appraised quality of papers, extracted data from papers, entered data into RevMan and analysed data, interpreted data and helped in writing the review.

Uzair Ahmed - (2011 and 2013 searches) screened and retrieved papers against eligibility criteria, extracted data from papers, helped writing the protocol and review.

Fair-ur Rehman - (2011 and 2013 searches) screened and retrieved papers against eligibility criteria, extracted data from papers, helped writing the protocol and review.

Miramontes - extracted data from papers, helped writing the review (2015 search).

Clive E Adams - helped writing and provided advice for the protocol and all review versions.

DECLARATIONS OF INTEREST

Edoardo G Ostinelli: none known.

Mohsin Hussein: none known.

Uzair Ahmed: none known.

Faiz-ur Rehman: none known.

Krista Miramontes: none known.

Clive E Adams: none known.

SOURCES OF SUPPORT

Internal sources

- Università degli Studi di Milano, Milan, Italy.

Employs lead author Edoardo G Ostinelli.

- Queens Medical Centre, The University of Nottingham, UK.

Employs review author Mohsin Hussein.

- Rotherham, Doncaster and South Humber NHS Foundation Trust, Doncaster, UK.

Employed review author Uzair Ahmed at the time of writing the review.

- Buxton Health Centre, Buxton, UK.

Employed review author Faiz-ur Rehman at time of writing review.

- Cochrane Schizophrenia Group, The University of Nottingham, UK.

Employs review author Clive E Adams.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

As the latest searches were conducted some time after protocol publication, we used the latest Cochrane methods for each search and updated the methods section with the Cochrane Schizophrenia Methods template.

In addition, in order to conform this systematic review to the family of 'rapid tranquillisation' ones, the 'methods' section was amended as follows.

Title amendment

Title is now Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation), the previous title was Risperidone for psychosis induced aggression or agitation (rapid tranquillisation)

Types of interventions

The 'risperidone in combination with other drugs' potential comparisons were not taken in consideration, in order to have 'risperidone alone' as a common comparator.

Types of outcome measures - primary outcomes

The primary outcome 'not tranquil or asleep' has been specified with a relevant time point indication: 'by up to 30 minutes'.

Types of outcome measures - secondary outcomes

A list of secondary outcomes within the 'tranquillisation or asleep' subgroup was added.

Data extraction and management - extraction

A reference for data extraction from figures was added.

Data extraction and management - 'Summary of findings' table

The list of included outcomes was improved and listed within the 'type of outcome measures' section.

Data synthesis

We preferred to use a fixed-effect model; please note that this change was done before data extraction and studies analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Aggression [*drug effects; psychology]; Antipsychotic Agents [adverse effects; *therapeutic use]; Carbamazepine [analogs & derivatives; therapeutic use]; Psychomotor Agitation [*drug therapy]; Psychotic Disorders [*complications; drug therapy; psychology]; Quetiapine Fumarate [therapeutic use]; Randomized Controlled Trials as Topic; Risperidone [adverse effects; *therapeutic use]; Tranquilizing Agents [therapeutic use]; Valproic Acid [therapeutic use]

MeSH check words

Humans