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Antipsychotics for agitation and psychosis in people with Alzheimer's disease and vascular dementia (Review)

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[Intervention Review]

Antipsychotics for agitation and psychosis in people with Alzheimer's disease and vascular dementia

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ABSTRACT

Background

Typical and atypical antipsychotics are widely used to treat agitation and psychosis in dementia. However, whether or not they are beneficial is uncertain. Some trials have yielded negative results and effectiveness may be outweighed by harms.

Objectives

To assess the efficacy and safety of antipsychotics for the treatment of agitation and psychosis in people with Alzheimer's disease and vascular dementia.

Search methods

We searched ALOIS, the Cochrane Dementia and Cognitive Improvement Group's register, MEDLINE (Ovid Sp), Embase (Ovid SP), PsycINFO (Ovid SP), CINAHL (EBSCOhost), Web of Science Core Collection (ISI Web of Science), LILACS (BIREME), ClinicalTrials.gov and the World Health Organization's meta-register, and the International Clinical Trials Registry Portal on 7 January 2021. Two review authors independently screened the title and abstract of the hits, and two review authors assessed the full text of studies that got through this screening.

Selection criteria

We included randomised, placebo-controlled, parallel-arm trials comparing the effects of antipsychotics and placebo for the treatment of agitation or psychosis in people with dementia due to Alzheimer's disease or vascular dementia, or both, irrespective of age, severity of cognitive impairment, and setting. (The majority of) participants had to have clinically significant agitation (including aggression) or psychosis or both at baseline. We excluded studies about antipsychotics that are no longer available in the USA or EU, or that are used for emergency short-term sedation. We also excluded head-to-head trials and antipsychotic withdrawal trials.

Data collection and analysis

The primary outcomes were (1) reduction in agitation or psychosis in participants with agitation or psychosis, respectively at baseline, and (2) the number of participants with adverse events: somnolence, extrapyramidal symptoms, any adverse event, any serious adverse event (SAE), and death.

Two review authors independently extracted the necessary data and assessed risk of bias with the Cochrane risk of bias tool. We calculated the pooled effect on agitation and psychosis for typical and atypical antipsychotics separately, and the pooled risk of adverse effects independent of the target symptom (agitation or psychosis). We used RevMan Web for the analyses.

Main results

The search yielded 8233 separate hits. After assessing the full-text of 35 studies, we included 24 trials that met the eligibility criteria. Six trials tested a typical antipsychotic, four for agitation and two for psychosis. Twenty trials tested an atypical antipsychotic, eight for agitation and 12 for psychosis. Two trials tested both drug types. Seventeen of 26 comparisons were performed in patients with Alzheimer's disease specifically. The other nine comparisons also included patients with vascular dementia or mixed dementia. Together, the studies included 6090 participants (12 to 652 per study). The trials were performed in institutionalised, hospitalised and community-dwelling patients, or a combination of those.

For typical antipsychotics (e.g. haloperidol, thiothixene), we are uncertain whether these drugs improve agitation compared with placebo (standardised mean difference (SMD) -0.36, 95% confidence interval (CI) -0.57 to -0.15, 4 studies, n = 361); very low-certainty evidence, but typical antipsychotics may improve psychosis slightly (SMD -0.29, 95% CI -0.55 to -0.03, 2studies, n= 240; low-certainty evidence) compared with placebo. These drugs probably increase the risk of somnolence (risk ratio (RR) 2.62, 95% CI 1.51 to 4.56, 3 studies, n = 466; moderate-certainty evidence) and increase extrapyramidal symptoms (RR 2.26, 95% CI 1.58 to 3.23, 3 studies, n = 467; high-certainty) evidence. There was no evidence regarding the risk of any adverse event. The risks of SAEs (RR 1.32, 95% CI 0.65 to 2.66, 1 study, n = 193) and death (RR 1.46, 95% CI 0.54 to 4.00, 6 studies, n = 578) may be increased slightly, but these estimates were very imprecise, and the certainty was low. The effect estimates for haloperidol from five trials were in line with those of the drug class.

Atypical antipsychotics (e.g. risperidone, olanzapine, aripiprazole, quetiapine) probably reduce agitation slightly (SMD -0.21, 95% CI -0.30 to -0.12, 7 studies, n = 1971; moderate-certainty evidence), but probably have a negligible effect on psychosis (SMD -0.11, 95% CI -0.18 to -0.03, 12 studies, n = 3364; moderate-certainty evidence). These drugs increase the risk of somnolence (RR 1.93, 95% CI 1.57 to 2.39, 13 studies, n - 3878; high-certainty evidence) and are probably also associated with slightly increased risk of extrapyramidal symptoms (RR 1.39, 95% CI 1.14 to 1.68, 15 studies, n = 4180; moderate-certainty evidence), serious adverse events (RR 1.32, 95% CI 1.09 to 1.61, 15 studies, n= 4316; moderate-certainty evidence) and death (RR 1.36, 95% CI 0.90 to 2.05, 17 studies, n= 5032; moderate-certainty evidence), although the latter estimate was imprecise. The drugs probably have a negligible effect on the risk of any adverse event (RR 1.05, 95% CI 1.02 to 1.09, 11 studies, n = 2785; moderate-certainty evidence). The findings from seven trials for risperidone were in line with those for the drug class.

Authors' conclusions

There is some evidence that typical antipsychotics might decrease agitation and psychosis slightly in patients with dementia. Atypical antipsychotics reduce agitation in dementia slightly, but their effect on psychosis in dementia is negligible. The apparent effectiveness of the drugs seen in daily practice may be explained by a favourable natural course of the symptoms, as observed in the placebo groups. Both drug classes increase the risk of somnolence and other adverse events. If antipsychotics are considered for sedation in patients with severe and dangerous symptoms, this should be discussed openly with the patient and legal representative.

PLAIN LANGUAGE SUMMARY

Do antipsychotic medicines reduce agitated behaviour and psychotic symptoms in people with Alzheimer's disease and vascular dementia?

Key messages

It is uncertain whether older, first-generation or 'typical' antipsychotic medicines such as haloperidol have an effect on agitated behaviour (for example, restlessness and aggression); the effect is moderate at best. Typical antipsychotic medicines may decrease delusions and hallucinations slightly in people with dementia.

Newer, second-generation 'atypical' antipsychotic medicines, such as risperidone, probably reduce agitated behaviour slightly. Atypical antipsychotic medicines probably have no effect on psychotic symptoms.

Both first- and second-generation antipsychotic medicines increase the risk of drowsiness and other unwanted events. When patients' symptoms improve after antipsychotics have been prescribed, this is probably largely due to natural improvement in symptoms over time.

What are antipsychotic medicines?

Antipsychotics are medicines prescribed to treat psychotic symptoms and severely disturbed behaviour in some mental illnesses, such as schizophrenia, bipolar disorder and severe depression. Psychotic symptoms are delusions (very strongly held beliefs in something which is not true) and hallucinations (sensing – usually seeing or hearing - things which are not really there).

Antipsychotic medicines are often divided into two groups:

1. first-generation (older) or 'typical' antipsychotics, for example haloperidol;

2. second-generation (newer) or 'atypical' antipsychotics, for example risperidone.

Both types can cause unwanted effects, such as drowsiness, movement disorders (for example, involuntary or uncontrollable movements, tremors, muscle contractions) and weight gain.

Why do people with dementia need antipsychotics?

People with dementia quite often experience hallucinations and delusions during their illness for some time. Particularly in the later stages of the illness, they may also show agitated behaviours such as restlessness, shouting out or aggression towards others. It is important to try to understand what is driving these behaviours and there are many ways to manage them which do not involve drugs. However, antipsychotic medicines have often been prescribed to people with dementia for these problems. In many countries, they are prescribed less often than in the past but are still used when the symptoms are severe.

What did we want to find out?

We wanted to know how well antipsychotic medicines reduce the severity of agitation and psychotic symptoms in people with the two commonest types of dementia, namely dementia due to Alzheimer's disease and vascular dementia. We also wanted to know how many people experienced unwanted effects.

What did we do?

We searched for studies that investigated antipsychotic medicines currently available in the USA or European Union by comparing them with placebo (a 'dummy' pill), for treatment of persistent agitation or psychotic symptoms. People in the studies had to have Alzheimer's disease or vascular dementia. They could be any age and reside in a care home, a hospital, or the community. Most of the people in the studies had to be experiencing agitation (including aggression) or psychotic symptoms, or both, at the start of the study.

We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 24 studies with a total of 6090 people:

- six studies tested typical antipsychotics, mostly haloperidol;

- 20 studies tested atypical antipsychotics, such as risperidone, olanzapine, and aripiprazole; and

- two studies tested both typical and atypical antipsychotics.

All the studies compared antipsychotics with placebo. The people were living in institutions, hospitals, the community, or a combination of these settings.

Main results

Typical antipsychotics (haloperidol, thiothixene) compared with placebo:

- may improve symptoms of psychosis slightly (2 studies, 240 people), but we are uncertain about their effect on agitation (4 studies, 361 people);

- probably increase the risk of drowsiness (3 studies, 466 people), and movement disorders (3 studies, 467 people);

- may slightly increase the risk of serious unwanted effects (1 study, 193 people) and of death (6 studies, 578 people).

There was no evidence about the risk of non-serious and serious unwanted effects combined.

Atypical antipsychotics (risperidone, olanzapine, aripiprazole, quetiapine) compared with placebo:

- probably slightly reduce agitation (7 studies, 1971 people) and may slightly reduce aggression (1 study, 301 people), but probably make no important difference to symptoms of psychosis (12 studies, 3364 people);

- increase the risk of drowsiness (13 studies, 2878 people) and probably slightly increase movement disorders (15 studies, 4180 people);

- probably slightly increase the risk of experiencing any non-serious or serious unwanted effect combined, the risk of serious unwanted effects, and the risk of death (17 studies, 5032 people).

What are the limitations of the evidence?

Overall, our confidence in the evidence about typical antipsychotics is limited and our confidence in the evidence about atypical antipsychotics moderate. Typical antipsychotics have been investigated in just a few studies. In addition, the studies about typical and atypical antipsychotics did not always use the best methods to carry out their investigations, or did not report the results. Consequently, the effects on agitation or psychosis may have been overestimated, and the effects on adverse events underestimated.

How up to date is this evidence?

The evidence is up-to-date to 7 January 2021.

Summary of findings 1. Summary of findings - Typical antipsychotics compared to placebo in people with Alzheimer's disease and vascular dementia

Outcomes	Absolute mean change from baseline or absolute risk in each group		Comparison of mean changes or risks between groups (treatment effect)		Certainty of the evidence (GRADE)	Comments
	Placebo group	Antipsychotics group (95%CI)	Relative effect, RR (95% CI)	Absolute effect, MD or RD (95% CI)		
Agitation - presented in units on CMAI (higher is worse)[a] - 361 persons in 4 RCTs of 3 to 16 weeks	15.0 decrease	20.2 decrease (17.2 to 23.3)[b]	NA	5.2 greater decrease (2.2 to 8.2)	⊕⊝⊝⊝ Very low[c,d,e]	Baseline mean on CMAI was 58.8; SMD 0.36 less (0.57 to 0.15)
Response for agitation - as defined by authors of RCTs - 367 persons in 4 RCTs of 3 to 16 weeks	52 per 100	61 per 100 (52 to 71)	1.18 (1.01 to 1.38)	9 more per 100 (0 to 19)	⊕⊕⊕⊝ Moderate[c]	Example of response: improvement on CGIS
Psychosis - presented in units of NPI-NH P (higher is worse)[f] - 240 persons in 2 RCTs of 6 to 10 weeks	4.7 decrease	6.3 decrease (4.9 to 7.7)[g]	NA	1.6 greater decrease (0.2 to 3.0)	⊕⊕⊝⊝ Low[e,h]	Baseline mean on NPH-NH P was 11.2; SMD 0.29 less (0.55 to 0.03)
Response for psychosis - as defined by authors of RCTs - 259 persons in 2 RCTs of 6 to 10 weeks	27 per 100	35 per 100 (24 to 52)	1.31 (0.90 to 1.92)	8 more per 100 (3 less to 35 more)	⊕⊕⊝⊝ Low[e,h]	Example of response: improvement on CGIS
Extrapyramidal symptoms - assessed with different instruments - 467 persons in 3 RCTs of 3 to 16 weeks	15 per 100	33 per 100 (23 to 48)	2.26 (1.58 to 3.23)	18 more per 100 (8 to 33 more)	⊕⊕⊕⊕ High	-
Somnolence	7 per 100	19 per 100	2.62	12 more per 100	⊕⊕⊕⊝	-

- assessed with different instruments - 466 persons in 3 RCTs of 3 to 16 weeks		(11 to 33)	(1.51 to 4.56)	(4 to 26 more)	Moderate[d]	
Death - 578 persons in 6 RCTs of 3 to 16 weeks	25 per 1000	36 per 1000 (13 to 98)	1.46 (0.54 to 4.00)	11 more per 1000 (12 less to 73 more)	⊕⊕⊙⊙ Low[i]	-

CGIS: Clinical Global Impression scale; **CI:** confidence interval; **CMAI:** Cohen-Mansfield Agitation Inventory; **MD:** mean difference; **NA:** not applicable (to changes from baseline); **NPH-NH P:** NPH-NH psychosis subscale; **RR:** risk ratio; **RD:** risk difference; **RCT:** randomised controlled trial; **SMD:** standardised mean difference

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: 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 certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] The CMAI is a well-known and much used scale for agitation (possible range 29-203)

[b] The weighted average SD of change from baseline on the CMAI was 14.4 in the intervention groups

[c] Downgraded one level for risk of bias: all studies were rated at high risk of bias in at least one of the following domains: selection bias (comparability of study groups), attrition bias (incomplete outcome data), and other bias (use of a run-in period)

[d] Downgraded one level for inconsistency: pronounced statistical heterogeneity ($I^2 > 50\%$)

[e] Downgraded one level for imprecision: confidence interval indicates both an important effect and an effect with no clinical relevance

[f] NPH-NH P was the most frequently used scale (possible range 0-24)

[g] The weighted average SD of change from baseline on the NPI-NH psychosis subscale was 5.4 in the intervention groups

[h] Downgraded one level for risk of bias: all studies were rated at high risk of other bias (use of a run-in period)

[i] Downgraded two levels for imprecision: confidence interval encompasses an important harmful effect as well as a protective effect

Summary of findings 2. Summary of findings - Atypical antipsychotics compared to placebo in people with Alzheimer's disease and vascular dementia

Outcomes	Absolute mean change from baseline or absolute risk in each group		Comparison of mean changes or risks between groups (treatment effect)		Certainty of the evidence (GRADE)	Comments
	Placebo group	Antipsychotics group (95%CI)	Relative effect, RR (95% CI)	Absolute effect, MD or RD (95% CI)		
Agitation	15.0 decrease	18.0 decrease	NA	3.0 greater decrease	⊕⊕⊕⊙	Baseline mean on CMAI was 58.8;

- presented in units on CMAI (higher is worse)[a] - 1971 persons in 9 RCTs of 3 to 12 weeks		(19.3 to 16.7)[b]		(4.3 to 1.7)	Moderate[c]	SMD 0.21 less (0.30 to 0.12)[a]
Response for agitation - as defined by authors of RCTs - 1303 persons in 4 RCTs of 3 to 12 weeks	36 per 100	48 per 100 (42 to 54)	1.31 (1.16 to 1.48)	12 more per 100 (6 to 18 more)	⊕⊕⊕⊖ Moderate[c]	Example of response: improvement on CGIS
Psychosis - presented in units of NPI-NH P (higher is worse)[d] - 3364 persons in 12 RCTs of 3 to 12 weeks	4.7 decrease	5.3 decrease (5.7 to 4.9)[e]	NA	0.6 greater decrease (1.0 to 0.2)	⊕⊕⊕⊖ Moderate[c]	Baseline mean on NPH-NH P was 11.2; SMD 0.11 less (0.18 to 0.03)
Response for psychosis - as defined by authors of RCTs - 1958 persons in 7 RCTs of 3 to 12 weeks	49 per 100	56 per 100 (51 to 61)	1.13 (1.03 to 1.23)	7 more per 100 (2 to 12 more)	⊕⊕⊖⊖ Low[c,f]	Example of response: improvement on CGI
Extrapyramidal symptoms - assessed with different instruments - 4180 persons in 15 RCTs of 3 to 12 weeks	8 per 100	11 per 100 (9 to 14)	1.39 (1.14 to 1.68)	3 more per 100 (1 to 6 more)	⊕⊕⊕⊖ Moderate[c]	-
Somnolence - assessed with different instruments - 3878 persons in 13 RCTs of 3 to 12 weeks	7 per 100	14 per 100 (11 to 17)	1.93 (1.57 to 2.39)	7 more per 100 (4 to 10 more)	⊕⊕⊕⊕ High	-
Death - 5032 persons in 17 RCTs of 3 to 12 weeks	19 per 1000	26 per 1000 (17 to 39)	1.36 (0.90 to 2.05)	7 more per 1000 (2 less to 20 more)	⊕⊕⊕⊖ Moderate[g]	-

CGIS: Clinical Global Impression scale; **CI:** confidence interval; **CMAI:** Cohen-Mansfield Agitation Inventory; **MD:** mean difference; **NA:** not applicable (to changes from baseline); **NPH-NH P:** NPH-NH psychosis subscale; **RR:** risk ratio; **RD:** risk difference; **RCT:** randomised controlled trial; **SMD:** standardised mean difference

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[a] The CMAI is a well-known and much used scale for agitation (possible range 29-203)
[b] The weighted average SD of change from baseline on the CMAI was 14.4 in intervention the groups
[c] Downgraded one level for risk of bias: all studies were rated at high risk of bias in at least one of the following domains: selection bias (comparability of study groups), attrition bias (incomplete outcome data), and other bias (use of a run-in period)
d NPH-NH Psychosis subscale was the most frequently used scale (possible range 0-24)
e The weighted average SD of change from baseline on the NPI-NH psychosis subscale was 5.4 in the intervention groups
f Downgraded one level for inconsistency: pronounced statistical heterogeneity ($I^2 > 50\%$)
g Downgraded one level for imprecision: confidence interval encompasses a harmful effect as well as a protective effect

BACKGROUND

Description of the condition

Dementia is a clinical syndrome characterised by cognitive, neuropsychiatric, and functional symptoms. It involves cognitive deterioration, disturbances in language, psychological and psychiatric changes, and impairments in activities of daily living (ADL). Five per cent of people aged over 60 years (Prince 2015), and in 2015, an estimated 47 million people were living with dementia worldwide. The total number of people with dementia will most likely continue to rise as the age of the population increases. Alzheimer's disease is the most common type of dementia (Livingston 2017).

Neuropsychiatric symptoms, also known as behavioural and psychological symptoms of dementia (BPSD), or challenging behaviour are common features of dementia. About 90% of people with dementia experience agitation, psychosis, or other neuropsychiatric symptoms such as anxiety, depression, and apathy at some time during the course of the disease (Borsje 2018). Symptoms often co-occur. Agitation is difficult to define simply (Cummings 2015). It covers unsettled verbal, vocal, or motor activity that is or is not accompanied by aggression (Cohen-Mansfield 1996). Common symptoms include restlessness, wandering, verbal insults, and shouting. Agitation is often measured with the Cohen-Mansfield Agitation Inventory (CMAI), a scale that covers many different types of agitation. In clinical practice, simpler definitions are also used.

Psychosis in dementia is characterised by delusions and hallucinations. Simple delusions about theft or abandonment are typical symptoms in Alzheimer's disease (Murray 2014). Prevalence of psychosis in Alzheimer's disease varies from 25% to 50% and depends on the stage of the disease: the prevalence is lower in the early stage of the disease, and rises as the disease progresses (Murray 2014).

Agitation and psychosis are distressing for people with dementia and their carers, and make it more difficult to care for the patient (Gilley 1991; Livingston 2014a; Schmidt 2012). The symptoms are associated with greater functional impairment and poorer quality of life (Morris 2015; Scarmeas 2005; Wetzels 2010). They frequently trigger placement in residential care or use of psychotropic drugs and are associated with higher care costs (Testad 2010; Toot 2017).

Agitation and psychosis can occur as a result of other causes (superimposed on dementia). Therefore, a comprehensive assessment of possible precipitating somatic, psychosocial and environmental factors such as pain, delirium, unmet needs, and annoying sounds should be performed to rule out other treatable causes, before hypothesising that agitation and psychosis are due to the dementia syndrome and considering the use of antipsychotics.

Description of the intervention

Antipsychotics, also known as neuroleptics, are widely used to treat agitation and psychosis in dementia. Antipsychotic use in Western European nursing home residents ranges from 12% to 59% (Janus 2016). Factors influencing antipsychotic use in people with dementia in nursing homes are nurses' job satisfaction and their belief in positive treatment effects (Janus 2017).

Antipsychotics can be classified into two subgroups: typical (conventional, first-generation) and atypical (second-generation) agents. Haloperidol is the most commonly used typical antipsychotic and risperidone the most commonly used atypical antipsychotic for agitation and psychosis in dementia (Yohanna 2017). Other typical agents are chlorpromazine and thiothixene, and other atypical agents include olanzapine, quetiapine, clozapine, or aripiprazole. The US Food and Drug Administration (FDA) has not approved any antipsychotics for use in people with dementia; in the EU, only risperidone is licensed for short-term use for aggression in this patient population (; Almutairi 2018Tampi 2016).

Despite the wide use of antipsychotics for agitation and psychosis in dementia, their benefit is uncertain because some trials have yielded negative results and effectiveness may be outweighed by harms (Schneider 2006). Antipsychotics have various severe adverse effects such extrapyramidal symptoms (EPS), somnolence, and (further) cognitive decline (Ballard 2005; Kirchner 2001). Less frequent but serious adverse events (SAEs) are malignant neuroleptic syndrome, strokes, falls, and pneumonia (Banerjee 2010; Knol 2008; Lonergan 2002).

Regulatory agencies issued a warning about the use of atypical antipsychotics in people with dementia in the mid-2000s due to an increased risk of death and stoke in this population (EMA 2008; Kuehn 2005; MHRA 2009; Schneider 2005). Cohort studies have also shown an association between use of typical antipsychotics and an increased risk of mortality in older people (Arai 2016; Kales 2007; Kales 2012). However, it has also been postulated that this the co-occurrence of the use of typical antipsychotics and deaths might result from "confounding by indication" because many cohort studies included people with terminal illness and delirium, but did not adjust for severity of disease (Luijendijk 2016). This could also explain why mortality is highest during the first month of use (Luijendijk 2016).

Overprescribing of antipsychotics in people with dementia has become a major problem. Antipsychotic drugs are often prescribed inappropriately (unclear indication, presence of contraindications, or chronic use longer than necessary or advocated) and with little monitoring (Furniss 1998; Renom-Guiteras 2018). The use of antipsychotics in people with dementia has also provoked much debate due to the potential for SAEs. In addition, some consider the use of antipsychotics to be simply a chemical restraint, suggesting that antipsychotics are used to calm people down with the sedative effects rather than to treat agitation and psychosis specifically or searching for and remedying the triggers for these behaviours (Hughes 2008). Furthermore, it has been shown that long-term use of antipsychotics could be successfully discontinued in people with dementia (Van Leeuwen 2018).

How the intervention might work

Almost all typical antipsychotics are antagonists at the dopamine receptor. This effect is considered to reduce agitation and psychosis, but also cause adverse drug reactions, including motor EPS, sedation, and endocrine changes. Atypical antipsychotics also act on serotonergic, adrenergic, histaminergic and muscarinic receptors (Farah 2005). Serotonergic blockade could reduce negative symptoms of psychosis, but also cause EPS. Adrenergic blockade is related to hypotension and sedation, histaminergic blockade to sedation and weight gain, and muscarinergic blockade

to cognitive disorder, urinary retention, and obstipation (anticholinergic effects). Nevertheless, atypical antipsychotics have been marketed on the premise that they offer a better adverse effect profile than conventional antipsychotics, in particular fewer severe EPS (Pierre 2005)

Why it is important to do this review

In the current review, we have updated and combined two previous Cochrane Reviews. Both were published when concern about the use of antipsychotics began to emerge. The first concerned haloperidol for agitation in dementia (Lonergan 2002). This review did not cover psychosis in dementia. The second concerned atypical antipsychotics for neuropsychiatric symptoms (Ballard 2006). The present review will focus on agitation (with or without aggression) and psychosis.

In addition, we wish to present the evidence for atypical and typical antipsychotics in one review so that the reader can make an informed choice between the two types of drugs. This review will support decision-making for clinicians, carers, and patients. Finally, the widespread use of antipsychotics as well as the potentially unfavourable balance between benefits and harms call for an up-to-date review.

OBJECTIVES

To assess the efficacy and safety of antipsychotics for the treatment of agitation and psychosis in people with Alzheimer's disease and vascular dementia.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised, placebo-controlled trials comparing the effects of antipsychotics and placebo for the treatment of agitation or psychosis in people with dementia due to Alzheimer's disease or vascular dementia. We included full journal publications, online clinical trial results, summaries of otherwise unpublished clinical trials, and abstracts. We also included studies which report insufficient data for analysis and described the results narratively.

We excluded studies that were non-randomised, case reports, and clinical observations. We also excluded studies using antipsychotics that are no longer available on the US or EU market, studies of antipsychotics that are used for acute short-term sedation in emergency situations, studies comparing different antipsychotics head to head, and antipsychotic withdrawal trials.

There were no language restrictions.

Types of participants

We included trials in people with a diagnosis of dementia due to Alzheimer's disease, vascular dementia, or both, irrespective of age, severity of cognitive impairment, and setting. Diagnoses of dementia must have been made with established diagnostic criteria for Alzheimer's or vascular dementia. We also included studies with mixed dementia populations if at least 80% of the participants had Alzheimer's or vascular dementia. We excluded trials in people with other types of dementia, or delirium.

Participants must have clinically significant agitation (including aggression) or psychosis or both at baseline. We accepted definitions of clinically significant agitation or psychosis from the included trials based either on scores on validated measurement instruments or on reports of clinical relevance from informal carers or healthcare professionals. Validated measurement instruments often used to assess agitation are the Cohen-Mansfield Agitation Inventory (CMAI), the agitation subscale of the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), or the Neuropsychiatric Inventory (NPI). The psychosis subscale of BEHAVE-AD or NPI are frequently used to assess psychosis.

Types of interventions

We included all studies using typical and atypical antipsychotics that are presently available for use on the US or EU market.

As typical antipsychotics, we considered substances coded in the Anatomical Therapeutic Chemical Classification System (ATC) as N05AA, N05AB, N05AD, N05AF, and N05AG (e.g. chlorpromazine, chlorprothixene, flupentixol, fluphenazine, haloperidol, levomepromazine, perphenazine, pimozide, thiothixene, trifluoperazine, zuclopenthixol). Atypical antipsychotics are ATC coded as N05AE, N05AH, N05AL, and N05AX (e.g. amisulpride, aripiprazole, clozapine, lurasidone, olanzapine, quetiapine, risperidone, sertindole, sulpiride, zotepine, ziprasidone) (WHO 2017).

Types of outcome measures

Primary outcomes

- Efficacy:
  - severity of agitation in participants with agitation, or severity of psychosis in participants with psychosis.
- Adverse effects:
  - somnolence;
  - EPS;
  - any adverse event;
  - any SAE, which is defined by the FDA and EMA as resulting in death, being life-threatening, requiring hospitalisation, or causing prolongation of existing hospitalisation, resulting in persistent or significant disability/incapacity or requiring interventions to prevent permanent impairment or damage. This includes stroke, thromboembolism, and pneumonia;
  - death.

Secondary outcomes

- Responders for agitation or psychosis in trials that included participants with agitation or psychosis respectively at baseline (response according to definition of primary study authors, or improvement on Clinical Global Impression scale).
- Discontinuation (any reason).
- Discontinuation due to adverse events.
- Health-related quality of life.
- Functioning in activities of daily living (ADL).
- Cognitive functioning;.
- Carer burden or carer quality of life.

Search methods for identification of studies

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois), which is the Cochrane Dementia and Cognitive Improvement Group's (CDCIG) specialised register on 7 January 2021.

ALOIS is maintained by the Information Specialists for the CDCIG, and contains studies that fall within the areas of dementia prevention, dementia treatment and management, and cognitive enhancement in healthy elderly populations. The studies are identified through searching:

- the Cochrane Library's Central Register of Controlled Trials (CENTRAL);
- major healthcare databases: MEDLINE (OvidSP), Embase (OvidSP), CINAHL (EBSCOhost), and PsycINFO (OvidSP);
- trial registers: ClinicalTrials.gov and the World Health Organization's (WHO) International Clinical Trials Register Platform (ICTRP) which covers ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials; and the Netherlands National Trials Register, plus others;
- grey literature sources: ISI Web of Science Core Collection.

To view a list of all sources searched, see the ALOIS website (www.medicine.ox.ac.uk/alois).

Details of the search strategies run in healthcare bibliographic databases, used for the retrieval of reports of dementia, cognitive improvement, and cognitive enhancement trials, can be viewed on the CDCIG's website (dementia.cochrane.org/searches).

We ran additional searches in MEDLINE (OvidSP), Embase (OvidSP), PsycINFO (OvidSP), CINAHL (EBSCOhost), LILACs (Bireme), ClinicalTrials.gov, and the WHO Portal/ICTRP to ensure that the searches for this review are as comprehensive and up-to-date as possible. The search strategies used for the retrieval of reports of trials can be seen in Appendix 1.

Searching other resources

We searched relevant trial registers of pharmaceutical companies such as those listed in Section 6.2.3.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). In addition, we searched regulatory agency sources European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for relevant clinical study reports (Isojarvi 2018; Schroll 2015).

Data collection and analysis

Selection of studies

After removing duplicates, two review authors independently assessed eligibility of studies identified by the search with the defined inclusion criteria. Both review authors independently reviewed full texts of each study deemed possibly relevant. We used Covidence to facilitate the process. We resolved disagreements in consensus discussions or consultation of a third review author. We reported details of included studies in the Characteristics of included studies table and reasons for exclusion in the Characteristics of excluded studies table.

We collated multiple reports of the same study including retraction statements and errata, and other unpublished key information. We included a PRISMA flow chart in the full review showing the status of identified studies (Moher 2009), as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). We included studies irrespective of whether measured outcome data are reported in a 'usable' way.

Data extraction and management

Two review authors independently extracted data using Covidence. We collected the following data from the main article and other data sources.

- General study characteristics: drug and daily dose tested, setting, type of dementia, number randomised, indication (agitation or psychosis), and commercial funding. One author also extracted the mean age, proportion of women, and severity of dementia of the participants.
- Continuous outcomes (severity of agitation or psychosis, health-related quality of life, functioning in activities of daily living (ADL), cognitive functioning, carer burden or carer quality of life): we extracted mean changes per treatment group for continuous outcomes and accompanying standard deviations (SDs), preferably for all randomised participants or otherwise for all participants available at endpoint assessment. If standard deviations (SDs) were not available for the groups that we compared, we calculated them from reported data if possible.
- Binary outcomes (occurrence of somnolence, EPS, any adverse event, any SAE, death, response on agitation or psychosis, discontinuation (any reason), discontinuation due to adverse event): we extracted the number of participants with the outcome per treatment group, and the number of all randomised participants as denominator.

Clinical response was treated as a binary variable (present or not) and we used the definition of the study authors. If a response was not defined but measured with the Clinical Global Impression scale or a comparable instrument, we used the categories 'very much improved', 'much improved' and 'minimally improved'. Patients with missing data were regarded as not having a favourable response.

We resolved any disagreements by discussion and consensus using Covidence. After reaching consensus, we transferred data into RevMan Web (Review Manager 2019).

Assessment of risk of bias in included studies

We assessed risk of bias using the Cochrane risk of bias tool as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). Two review authors independently assessed and rated the methodological quality of the studies to identify any potential source of bias. We assessed the following aspects of trial design: selection bias (random sequence generation, concealment of allocation, comparability of groups at baseline); performance bias (blinding of personnel and participants); detection bias (blinding of outcome assessors); attrition bias (incomplete reporting of outcome data); reporting bias (selective reporting) and other bias (run-in period). We found very few protocols of studies that were published, and only assessed protocol deviations in terms of selective reporting. Commercial funding was one of the extracted general study

characteristics. We categorised studies as having low, high, or unclear risk of bias. The judgements were compared automatically so that discrepancies could be discussed and resolved.

Measures of treatment effect

Where possible, we expressed the treatment effect on a continuous outcome (change from baseline in psychosis or agitation) as pooled standardised mean difference (SMD) with 95% confidence interval (CIs). We included all reported measurement instruments for agitation and psychosis in these analyses, and ensured that higher scores have the same meaning across instruments.

We expressed the treatment effect on dichotomous outcomes as risk ratio (RR) with 95% CIs. Where informative, we performed meta-analyses to calculate the number needed to treat for an additional beneficial outcome (NNTB) or the number needed to harm for an additional harmful outcome (NNTH) based on pooled risk differences (RDs).

We performed the statistical analyses using RevMan Web (Review Manager 2019).

Unit of analysis issues

We combined data from multiple active drug groups within a trial if they tested the same drug (multiple dosages). We included cross-over studies using first-phase data only to avoid carry-over effects. We excluded groups treated with more than one drug in the same group or groups treated with other psychotropic drugs. If we included more than one study arm per study in the same analysis, we split the control group following the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* to avoid that it counted multiple times (Higgins 2019).

We included studies that had a run-in period before randomisation, even though some eligible participants who met inclusion criteria for the study at the start of the run-in period, might have been excluded from participation at the end of the run-in period (Hulshof 2020).

Dealing with missing data

Where possible, we contacted authors of the included studies to obtain missing data. We used data from intention-to-treat (ITT) analyses if available. Otherwise, we planned to also included data from per-protocol analyses but perform sensitivity analyses to assess for their effect, but this was not the case in any of the included studies.

Assessment of heterogeneity

We assessed heterogeneity of the treatment effect between the trials with the Chi^2 statistic. We used a fixed-effect model, unless the I^2 statistic was greater than 40%, in which case we used a random-effects model.

Assessment of reporting biases

We assessed reporting bias with a funnel plot if at least 10 studies were available for meta-analysis.

Data synthesis

We used RevMan Web (Review Manager 2019) to analyse the data. We calculated the pooled effects of typical and atypical antipsychotics on agitation and psychosis separately. When investigating adverse effects, we pooled data from studies independent of the indication investigated (agitation or psychosis). If meta-analysis was not suitable because of heterogeneity or insufficient data, we presented a narrative synthesis.

Subgroup analysis and investigation of heterogeneity

We reran all analyses including only haloperidol and risperidone studies, as these are the antipsychotics of first choice in many countries in 2019. We did not perform subgroup analyses related to participant characteristics.

We also conducted a post-hoc subgroup analysis among studies including patients with (any type of) agitation versus one trial that included only patients with physical aggression. In addition, in response to a reviewer's comment, we performed post-hoc analyses for quetiapine only.

Sensitivity analysis

We did not perform a pre-planned sensitivity analysis excluding trials with at least one rating of high risk of bias because all studies had a high risk of bias rating in at least one domain. We also did not perform the pre-planned sensitivity analysis excluding trials that only reported per-protocol analysis due to the lack of such studies.

Summary of findings and assessment of the certainty of the evidence

We assessed the overall quality of the body of evidence for the most important outcomes using the GRADE approach (Guyatt 2013a; Guyatt 2013b). This includes taking into account: risk of bias, inconsistency, indirectness, imprecision, and publication bias. For efficacy, bias away from the null was considered a threat to validity, and bias to the null for adverse effects. If a 95% confidence interval was so wide that it included no effect or a clinically negligible effect, the evidence would be downgraded one level for imprecision.

We described the results using a standardised wording that incorporates the certainty of evidence and the importance of benefits or harms as described in Chapter 15 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2020). High-certainty evidence is described as 'improves/reduces' the outcome (for important benefits or harm), 'improves/reduces slightly' (less important benefits or harm), and 'have little or no effect' (for no or negligible benefits or harm). Moderate-certainty evidence is described as 'probably improves/reduces' the outcome (for important benefits or harm), 'probably improves/reduces slightly' (less important benefits or harm), and 'probably have little or no effect' (for no or negligible benefits or harm). Low-certainty evidence is described as 'may improve/reduce' the outcome (for important benefits or harm), 'may improve/reduce slightly' (less important benefits or harm), or 'may have little or no effect' (for no or negligible benefits or harm). Very-low certainty evidence is described as 'we are uncertain whether...improves/reduces' the outcome.

Based on the available data, we presented the results of the following outcomes in the summary of findings tables for typical and atypical antipsychotics:

- agitation in trials that included patients with agitation;

- response for agitation in trials that included participants with agitation;
- psychosis in trials that included patients with psychosis;
- response for psychosis in trials that included patients with psychosis;
- EPS;
- somnolence;
- death.

To present the effects of the drug classes on the continuous outcomes agitation and psychosis in the summary of findings tables, we converted the SMDs to absolute changes from baseline in units of a representative measurement instrument for the placebo and antipsychotics groups **(**CMAI for agitation and NPI-NH psychosis subscale for psychosis). We calculated the average absolute change of the placebo groups in studies that used this instrument. We calculated the average absolute change of the antipsychotics group by multiplying the SMD with the weighted average SD of change in the antipsychotics groups of the studies that used this instrument, and adding this figure to the average absolute change of the placebo group. For the dichotomous outcomes response, EPS, somnolence, and death, we present the number of participants with the outcome per 100 patients. Absolute and relative effects of treatment that derive from the differences between the groups, expressed in changes or risks, are also shown in the summary of findings tables.

RESULTS

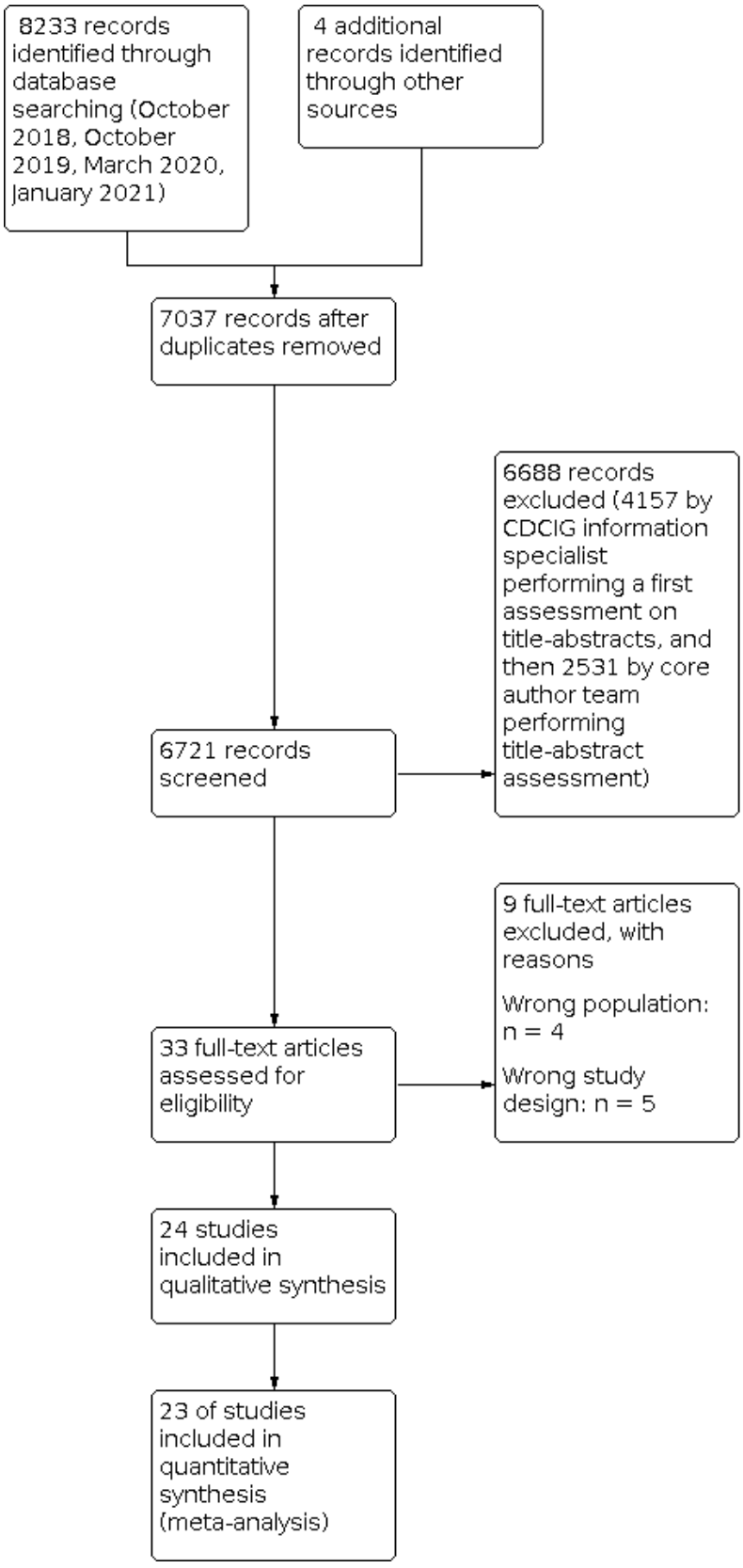
Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

The search retrieved 8233 records. After 1196 duplicates were excluded, we screened 7037 for potential eligibility. 7005 were excluded based on title and abstract. We excluded 9 studies and included 24 studies after full-text screening (Figure 1).

Figure 1. Study flow diagram.



Included studies

We included 24 randomised controlled trials with a total of 6090 participants. Six trials tested a typical antipsychotic (see table 1): five randomised controlled trials (RCTs) with 421 participants investigated the effect on agitation (Allain 2000; Auchus 1997;Devanand 1998; Finkel 1995; Teri 2000), and two trials with 350 participants the effect on psychosis (Devanand 1998; Tariot 2006). Five trials tested haloperidol, and one thiothixene. Mean ages ranged from 72.1 to 85 years and most patients were female (62.9% to 86%). In one study, the participants had mild-to-moderate dementia (Allain 2000), in two studies moderate dementia (Auchus 1997; Tariot 2006), and the other three studies moderate-to-severe dementia (Devanand 1998; Teri 2000 ; Finkel 1995).

For atypical antipsychotics, there were 20 trials (see table 2): Eight RCTs with 2320 participants tested the effect on agitation (Allain 2000; Ballard 2005; Brodaty 2003 RIS-AUS-05; Grossberg 2020a; Grossberg 2020b; Japic CTI 142578 2015; Schneider 2006 CATIE-AD; Zhong 2007), and 12 studies with 3589 participants the effect on psychosis (Ballard 2018; De Deyn 2005; Deberdt 2005 F1D MC HGGU; De Deyn 2004 F1D MC HGIV; RIS-INT-83 2003; Schneider 2003 RIS USA 63; Mintzer 2007; NCT00287742 2006; Paleacu 2008; Mintzer 2006 RIS USA 232; Streim 2008; Tariot 2006). The trials tested aripiprazole (4x), brexpiprazol (2x), olanzapine (3x), pimavanserin (1x), quetiapine (5x), risperidone (7x), and tiapride (1x).

One study included patients with psychosis (71.8%) or psychomotor agitation (78.9%) (Devanand 1998). Of the RIS-USA 63, only the subgroup of patients with psychosis was included (Schneider 2003 RIS USA 63). Two trials tested
both a typical and an atypical antipsychotic drug against placebo (Auchus 1997; Tariot 2006). One publication reported on two RCTs (Grossberg 2020a; Grossberg 2020b).

Mean ages ranged from 73.885.9 years and most patients were female (55.2 to 84.9%). Most studies included patients with moderate dementia (Deberdt 2005 F1D MC HGGU; De Deyn 2005; Mintzer 2006 RIS USA 232; Mintzer 2007; NCT00287742 2006; Paleacu 2008; Schneider 2006 CATIE-AD; Streim 2008; Tariot 2006) or severe dementia (Ballard 2005; Ballard 2018; Brodaty 2003 RIS-AUS-05; Schneider 2003 RIS USA 63; Zhong 2007). In one study, dementia was mild-to-moderate (Allain 2000), and in three studies mild-to-severe (De Deyn 2004 F1D MC HGIV; Grossberg 2020a; Grossberg 2020b). One study did not mention the severity of dementia (RIS-INT-83 2003).

Three studies were non-commercially funded (Auchus 1997; Devanand 1998; Schneider 2006 CATIE-AD). Nineteen trials were funded by pharmaceutical companies, and the funding source was unclear in two studies.

We found three studies that have not been published in a journal. A summary of results was reported on a trial registration website for NCT00287742 2006 and RIS-INT-83 2003. No results were reported for Japic CTI 142578 2015.

We obtained additional data about one trial (Paleacu 2008). All other data were extracted from published reports.

Table 1: Characteristics of included studies on typical antipsychotics

Study-ID	Setting	Condition	Indication	Scale	Drug	Daily dose	Duration, weeks	Number randomised
Finkel 1995	Nursing homes	AD, VD[a]	Agitation	CMAI	Thiothixene	0.25 mg to 18 mg	11	33
Auchus 1997	Community-dwelling	AD	Agitation	CMAI-SF	Haloperidol	3 mg	6	12
Teri 2000	Community-dwelling	AD	Agitation	CMAI	Haloperidol	0.5 mg to 3 mg	16	70
Allain 2000	Nursing home or hospitalised	AD, VD, mixed type	Agitation	MOSES[b]	Haloperidol	Up to 6 mg	3	306
Tariot 2006	Nursing homes	AD	Psychosis	NPI-NH psychosis[c]	Haloperidol	0.5mg to 12 mg	10	284
Devanand 1998	Community-dwelling	AD	Psychosis Agitation	BPRS psychosis[c] BSSD psychomotor agitation item	Haloperidol	0.5 mg to 0.75 mg or 2 mg to 3 mg	6	66

AD: Alzheimer's disease; **VD:** Vascular dementia; **CMAI(-SF):** Cohen-Mansfield Agitation Inventory(-short form); **MOSES:** Multidimensional Observation Scale for Elderly Subjects; **NPI-NH:** Neuropsychiatric Inventory-Nursing Home; **BPRS:** Brief Psychiatric Rating Scale; **BSSD:** Behavioural Syndromes Scale for Dementia; personal communication; irritability/aggressiveness subscore;subscale.

Table 2: Characteristics of included studies on atypical antipsychotics

Study-ID	Setting	Condition	Indication	Scale	Drug	Daily dose	Duration, weeks	Number randomised
Allain 2000	Nursing home or hospitalised	AD, VD, mixed type	Agitation	MOSES[a]	Tiapride	Up to 300 mg	3	306
Ballard 2005	Care facilities	AD	Agitation	CMAI	Quetiapine	50 mg to 100 mg	6	62
Zhong 2007	Nursing homes, assisted-living facilities	AD, VD	Agitation	PANSS-EC	Quetiapine	100 mg or 200 mg	10	333
Schneider 2006 CATIE-AD	Community-dwelling or assisted-living facilities	AD	Agitation	NPI agitation[b]	Olanzapine, Quetiapine or Risperidone	Flexible dose[c]	12	421
Brodaty 2003 RISAUS-05	Nursing homes	AD, VD, mixed type	Agitation	CMAI aggression[b]	Risperidone	up to 2 mg	12	345
Grossberg 2020a	Community-dwelling or care facility	AD	Agitation	CMAI	Brexpiprazole	0.5 mg, 1 mg and 2 mg	12	433
Grossberg 2020b	Community-dwelling or care facility	AD	Agitation	CMAI	Brexpiprazole	0.5 mg to 2 mg	12	270
Japic CTI 142578 2015	Hospital or care facilities	AD	Agitation	Not reported	Aripiprazole	2, 3 mg or 6 mg	10	150
Tariot 2006	Nursing homes	AD	Psychosis	NPI-NH psychosis[b]	Quetiapine	25 mg to 600 mg	10	284
Paleacu 2008	Not reported	AD	Psychosis	NPI-NH psychosis[b]	Quetiapine	50 mg to 300 mg	6	40
Ballard 2018	Nursing homes	AD	Psychosis	NPI-NH psychosis[b]	Pimavanserin	34 mg	12	181
De Deyn 2004 F1D MC HGIV	Nursing homes, continuing-care hospitals	AD	Psychosis	NPI-NH psychosis[b]	Olanzapine	1 mg, 2.5 mg, 5 mg or 7.5 mg	10	652
Deberdt 2005 F1D MC HGGU	Outpatients, nursing homes, assisted-living centres	AD, VD, mixed type	Psychosis	NPI(-NH) psychosis[b]	Olanzapine or	2.5 mg to 10 mg, respectively	10	494

					Risperidone	0.5 mg to 2 mg		
Mintzer 2006 RIS USA 232	Nursing homes, long-term care	AD, VD	Psychosis	BEHAVE-AD psychosis[b]	Risperidone	1 mg to 1.5 mg	8	473
NCT00287742 2006	In- or outpatients	AD	Psychosis	BEHAVE-AD psychosis[b]	Risperidone	0.5 mg to -2 mg	8	33
RIS-INT-83 2003	Nursing homes or long-term care	AD	Psychosis	BEHAVE-AD	Risperidone	1 mg to 1.5 mg	8	18
Schneider 2003 RIS USA 63	Nursing homes, hospital	AD, VD, mixed type	Psychosis	BEHAVE-AD psychosis[b]	Risperidone	1 mg, 2 mg or 3 mg	12	463 (psychosis subgroup)
Streim 2008	Institutionalised subjects	AD, VD	Psychosis	NPI-NH psychosis[b]	Aripiprazole	2 mg to 15 mg	10	256
Mintzer 2007	Nursing homes, assisted-living facilities	AD	Psychosis	NPI-NH psychosis[b]	Aripiprazole	2, 5 mg or 10 mg	10	487
De Deyn 2005	Community-dwelling	AD	Psychosis	NPI Psychosis[b]	Aripiprazole	2 mg to 15 mg	10	208

AD: Alzheimer's disease; **VD:** Vascular dementia; **MOSES**: Multidimensional Observation Scale for Elderly Subjects; **CMAI:** Cohen-Mansfield Agitation Inventory; **PANSS-EC:** Positive and Negative Syndrome Scale - Excitement Component; **NPI:** Neuropsychiatric Inventory; **NPI-NH:** Neuropsychiatric Inventory-Nursing Home; **BEHAVE-AD:** Behavioural Pathology in Alzheimer's Disease; irritability/aggressiveness subscore; [b]subscale; [c]Olanzapine: mean 5.5mg/day, Quetiapine: mean 56.5mg/day, Risperidone: mean 1.0mg/day.

Excluded studies

Nine studies were excluded. Reasons for exclusion were wrong study design (not placebo controlled Shin 2013; Trequattrini 2003; Holmes 2007; Meguro 2004,or no parallel groups Devanand 1989), wrong population (not Alzheimer's disease or vascular dementia NCT00043849 2002), or wrong indication (not specifically agitation or psychosis Street 2000 F1D MC HGEU; a broad range of neuropsychiatric symptoms (DeDeyn 1999 RIS-INT-24) or unclear how many participants were psychotic or agitated Pollock 2002).

Risk of bias in included studies

Most studies were at high risk of bias in at least one domain. Detailed information about the risk of bias in the included studies is presented in the table Characteristics of included studies. An overview is provided in Figure 2 and Figure 3.

Figure 2. Risk of bias summary

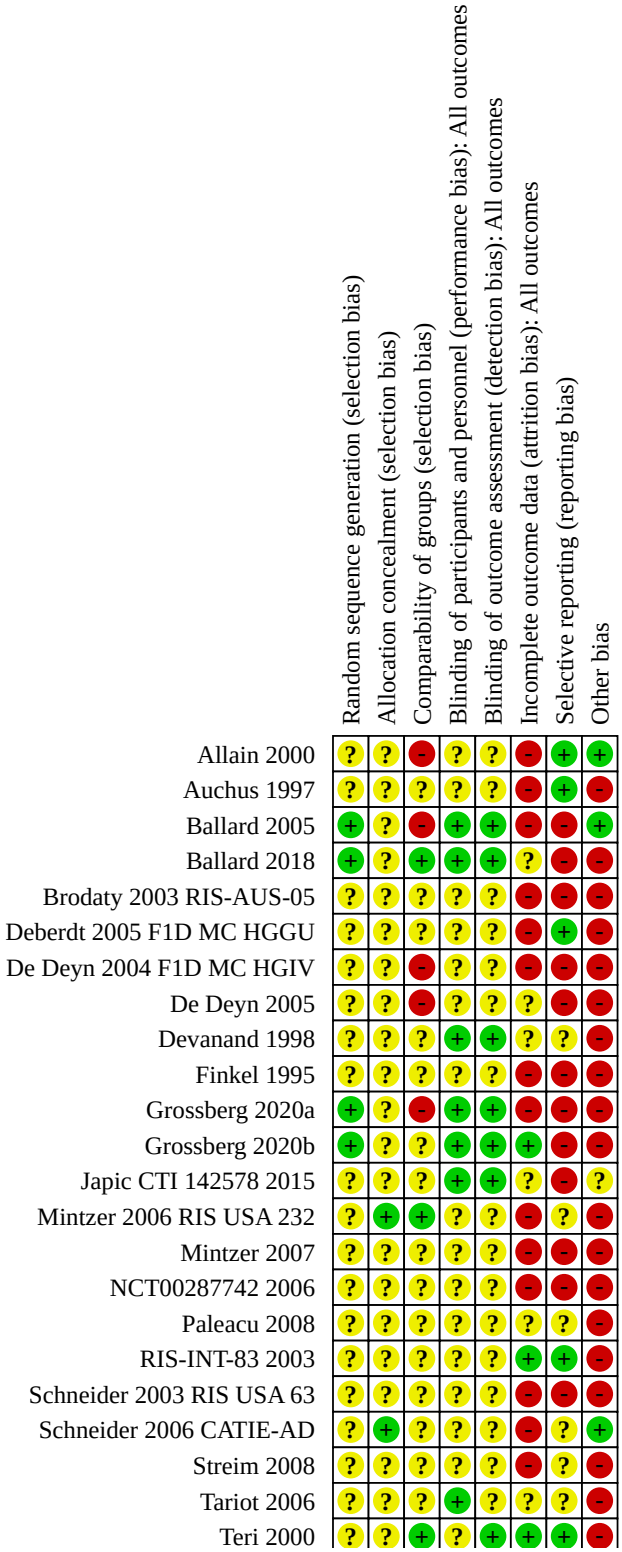


Figure 2. (Continued)

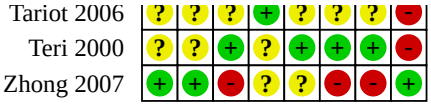
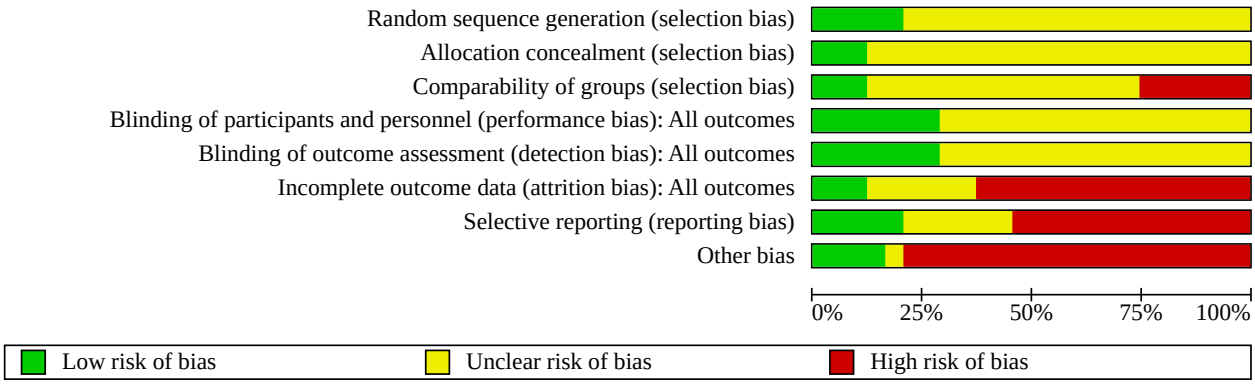


Figure 3. Risk of bias graph



Allocation

The randomisation sequence was adequately generated in five studies (Ballard 2005; Ballard 2018; Grossberg 2020b; Grossberg 2020a; Zhong 2007) and unclear in most studies. Allocation was concealed (non-predictable) in three studies (Mintzer 2006 RIS USA 232; Schneider 2006 CATIE-AD; Zhong 2007) and unclear in all other studies.

Despite randomisation in all trials, only three studies were judged to have comparable groups or adequate adjustment for baseline differences (Ballard 2018; Mintzer 2006 RIS USA 232; Teri 2000). Comparability of groups was limited in six studies (Allain 2000; Ballard 2005; De Deyn 2005; De Deyn 2004 F1D MC HGIV; Grossberg 2020a; Zhong 2007) and unclear in 15 studies (the baseline differences were not reported or there were small differences with unclear significance).

Blinding

Participants and personnel were blinded to the treatment status of the participants during the trial in seven studies (Ballard 2005; Ballard 2018; Devanand 1998; Grossberg 2020a; Grossberg 2020b; Japic CTI 142578 2015; Tariot 2006). Outcome assessors were blinded in seven studies (Ballard 2005; Ballard 2018; Devanand 1998; Grossberg 2020a; Grossberg 2020b;Japic CTI 142578 2015; Teri 2000). The persons who were blinded was unclear in the rest of studies.

Incomplete outcome data

Only three studies presented complete outcome data (Grossberg 2020b ;RIS-INT-83 2003; Teri 2000). Outcome data were incomplete in 15 studies, and data completeness was unclear in six studies.

Selective reporting

Selective reporting did not seem to be present in five studies (Allain 2000; Auchus 1997; Deberdt 2005 F1D MC HGGU; RIS-INT-83 2003; Teri 2000), was unclear in six studies and seemed present in 13 studies.

Funnel plots

Visual inspection of funnel plots for analyses of atypical antipsychotics in Figure 4 (outcome: psychosis); Figure 5 (outcome: somnolence); Figure 6 (outcome: extrapyramidal symptoms); Figure 7 (outcome: any adverse event); Figure 8 (outcome: any serious adverse event); Figure 9 (outcome: death); Figure 10 (outcome: discontinuation due to adverse events); Figure 11 (outcome: discontinuation (any reason)) and Figure 12 (outcome: cognitive function) do not show marked asymmetries. Therefore reporting bias is not clearly indicated, although some funnels plots may show a tendency towards some bias in favour of atypical antipsychotics.

Figure 4. Funnel plot: Analysis 3.2 (Psychosis, atypical antipsychotics)

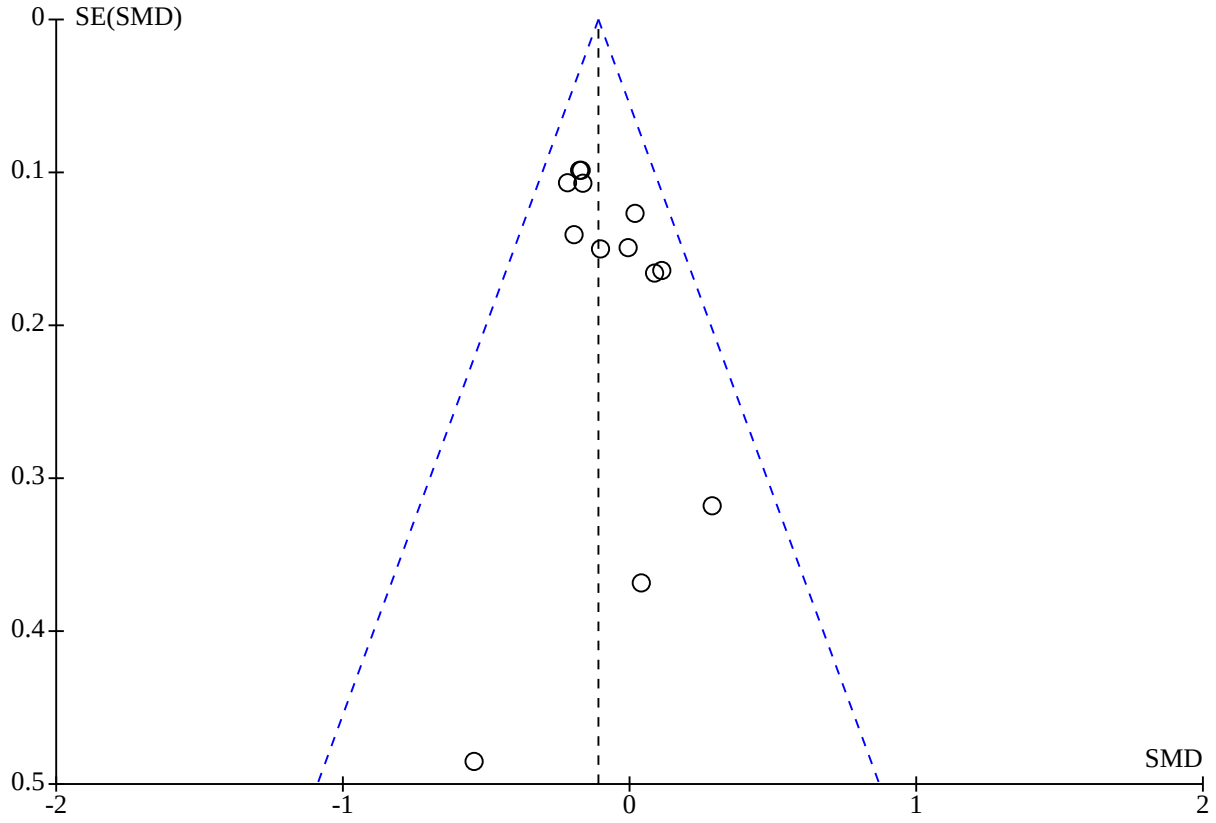


Figure 5. Funnel plot: Analysis 3.3 (Somnolence, atypical antipsychotics)

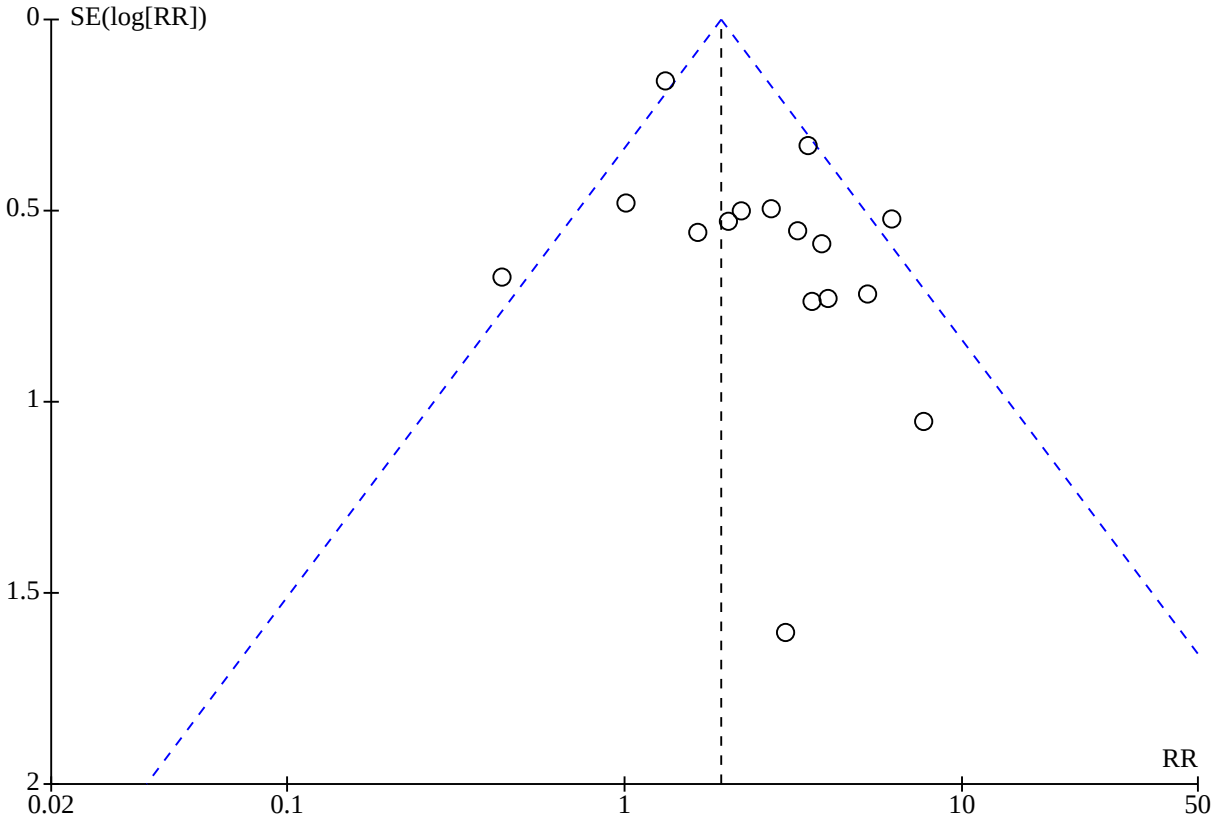


Figure 6. Funnel plot: Analysis 3.5 (Extrapyramidal symptoms, atypical antipsychotics)

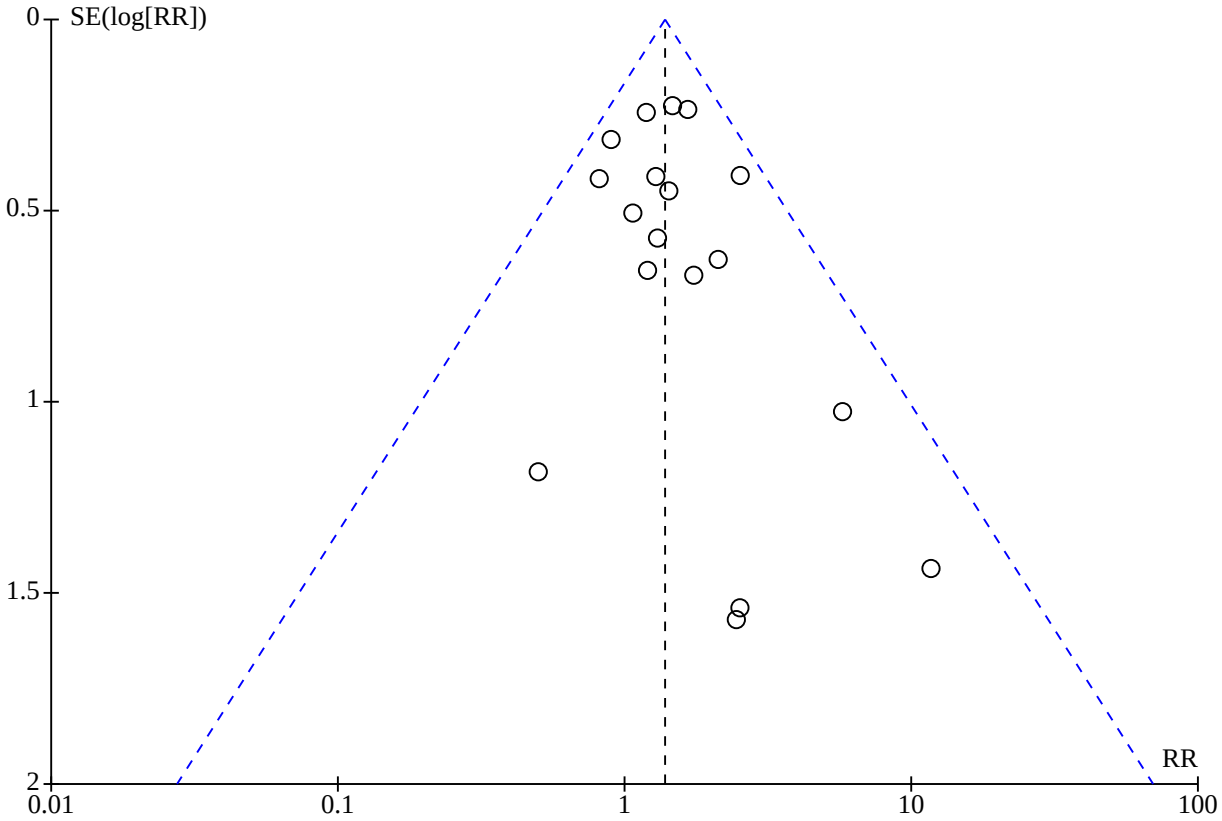


Figure 7. Funnel plot: Analysis 3.7 (Any adverse event, atypical antipsychotics)

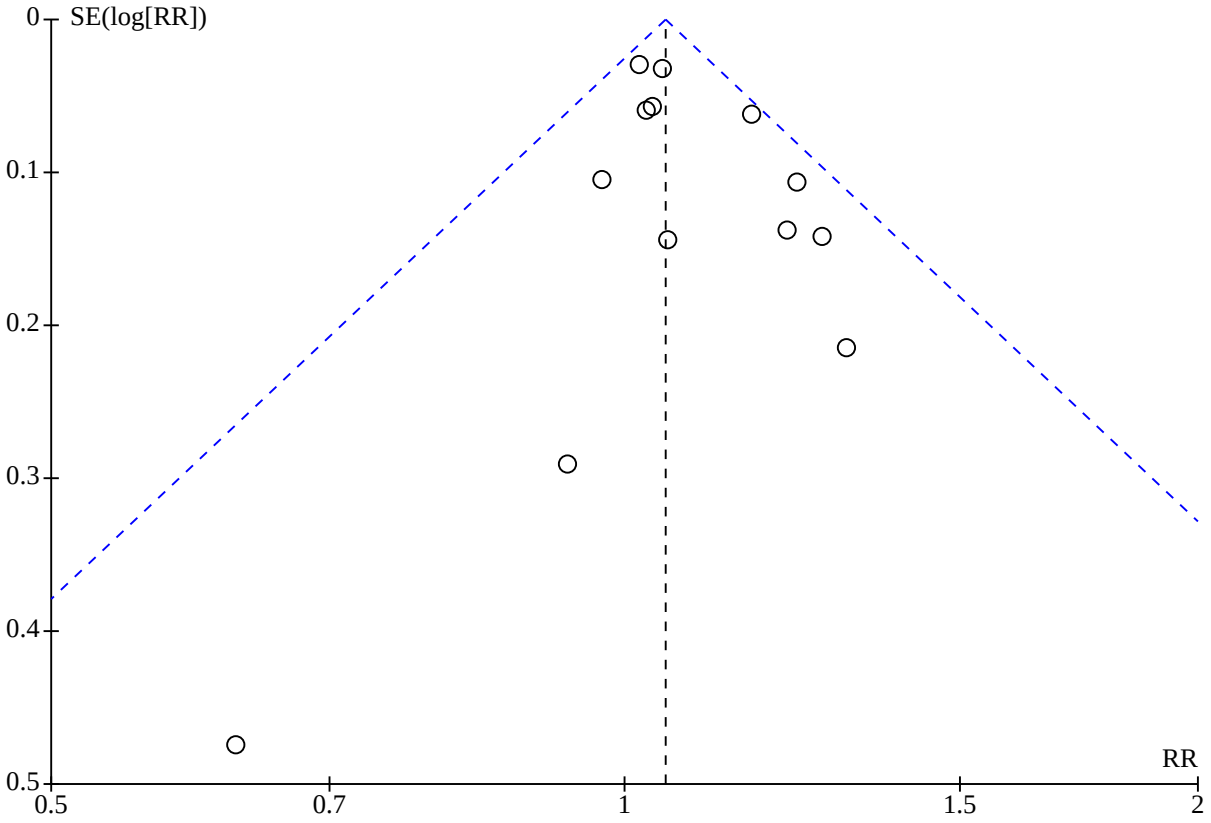


Figure 8. Funnel plot: Analysis 3.9 (Any serious adverse event, atypical antipsychotics)

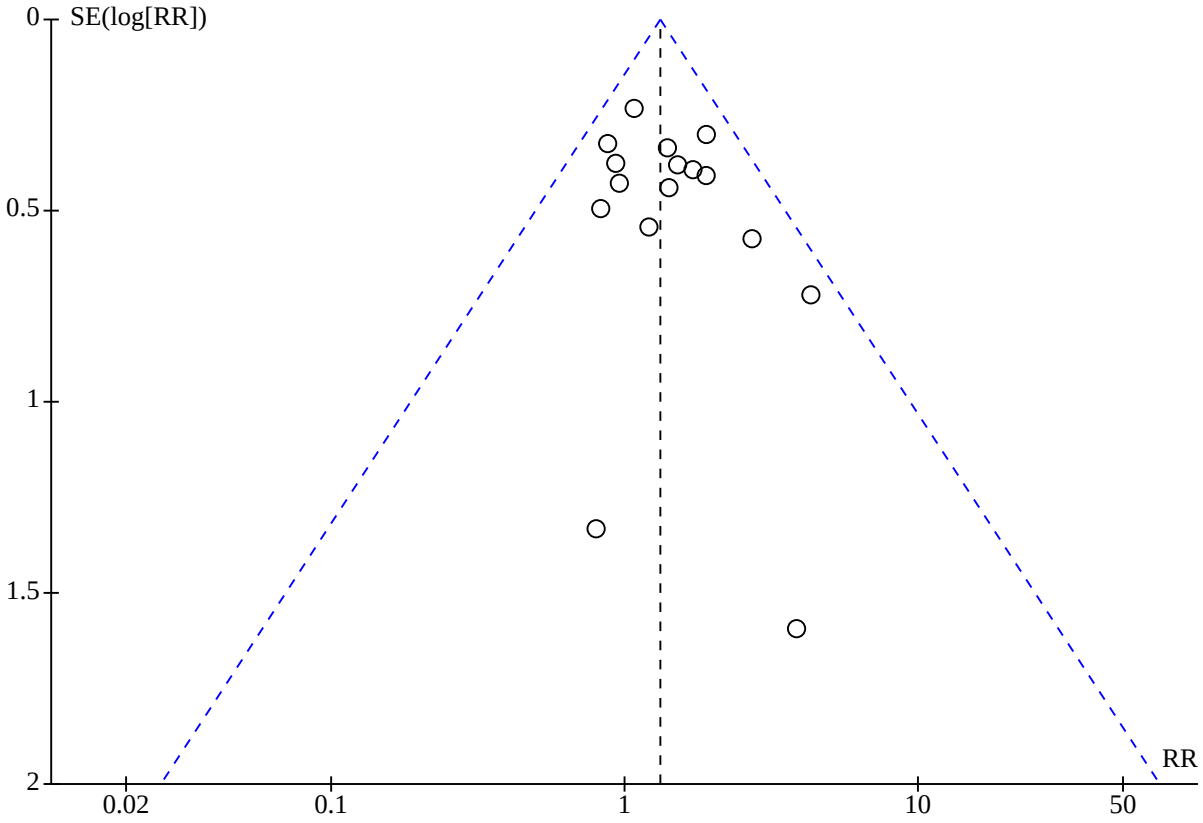


Figure 9. Funnel plot: Analysis 3.11 (Death, atypical antipsychotics)

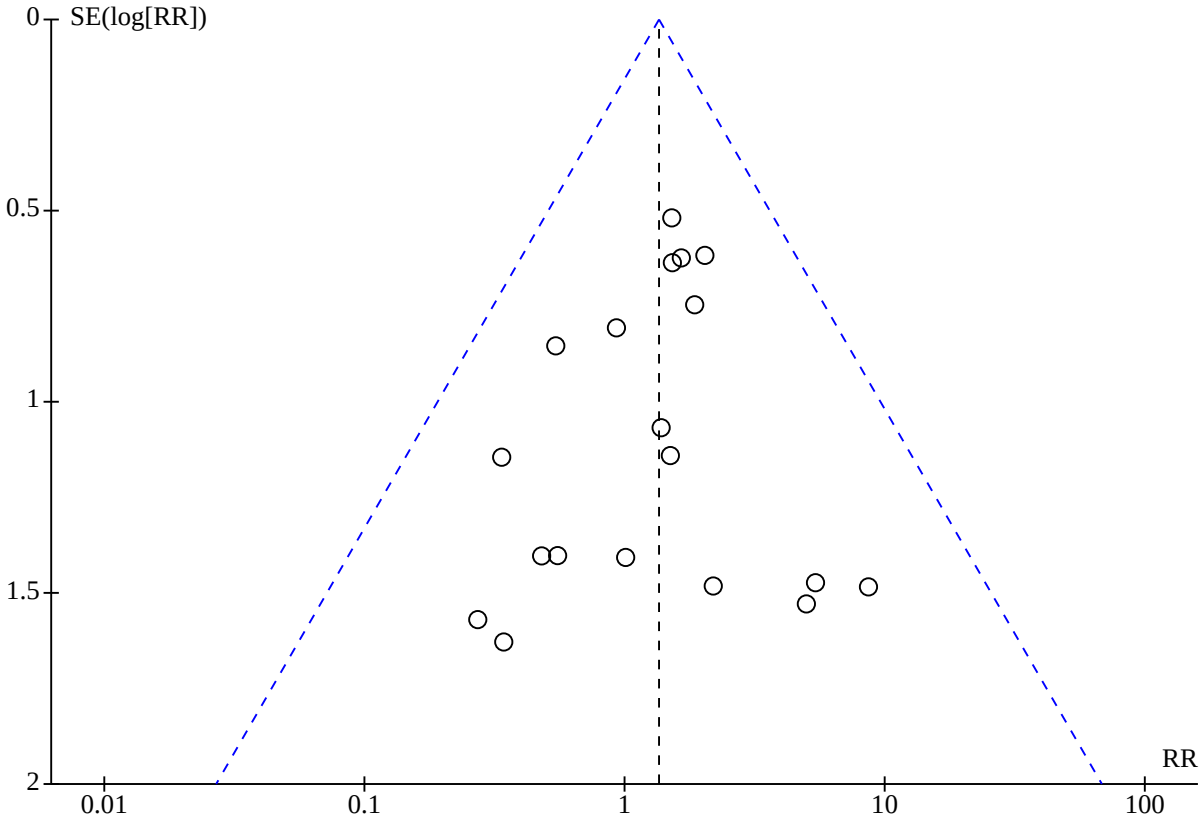


Figure 10. Funnel plot: Analysis 3.17 (Discontinuation due to adverse events, atypical antipsychotics)

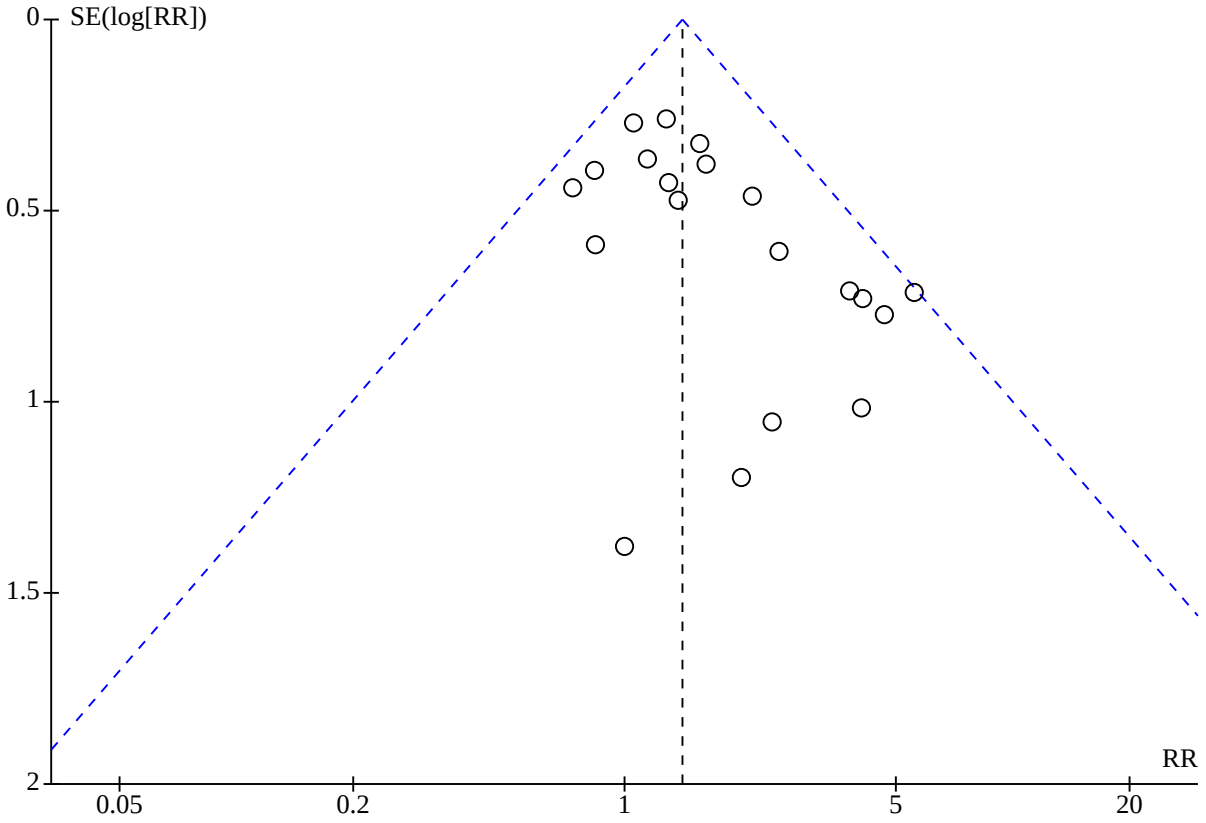


Figure 11. Funnel plot: Analysis 3.19 (Discontinuation (any reason), atypical antipsychotics)

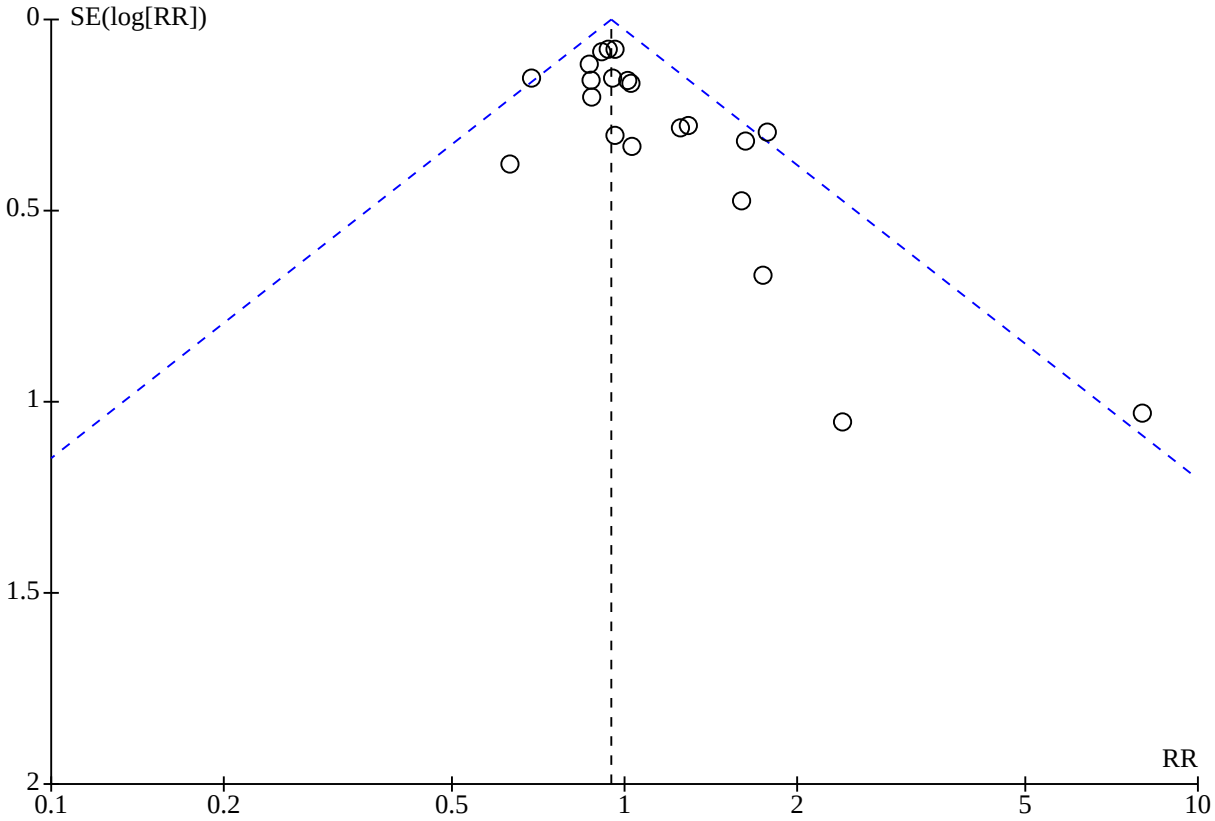
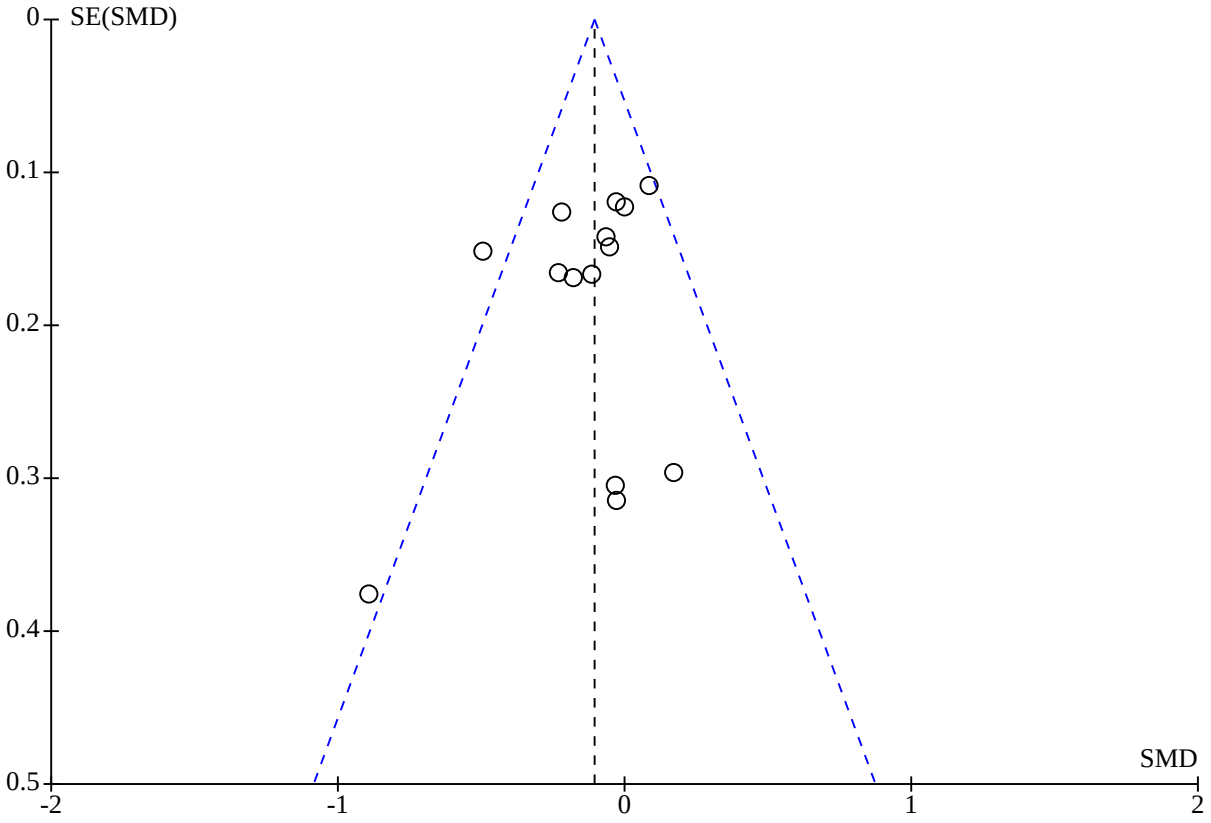


Figure 12. Funnel plot: Analysis 3.22 (Cognitive function, atypical antipsychotics)



Other potential sources of bias

Nineteen studies used a run-in period, which may introduce bias due to deselection of (eligible) patients with side effects before randomization. There were only four studies without a run-in period (Allain 2000; Ballard 2005; Schneider 2006 CATIE-AD; Zhong 2007), and there was no information about a run-in period in another study (Japic CTI 142578 2015).

Effects of interventions

See: **Summary of findings 1** Summary of findings - Typical antipsychotics compared to placebo in people with Alzheimer's disease and vascular dementia; **Summary of findings 2** Summary of findings - Atypical antipsychotics compared to placebo in people with Alzheimer's disease and vascular dementia

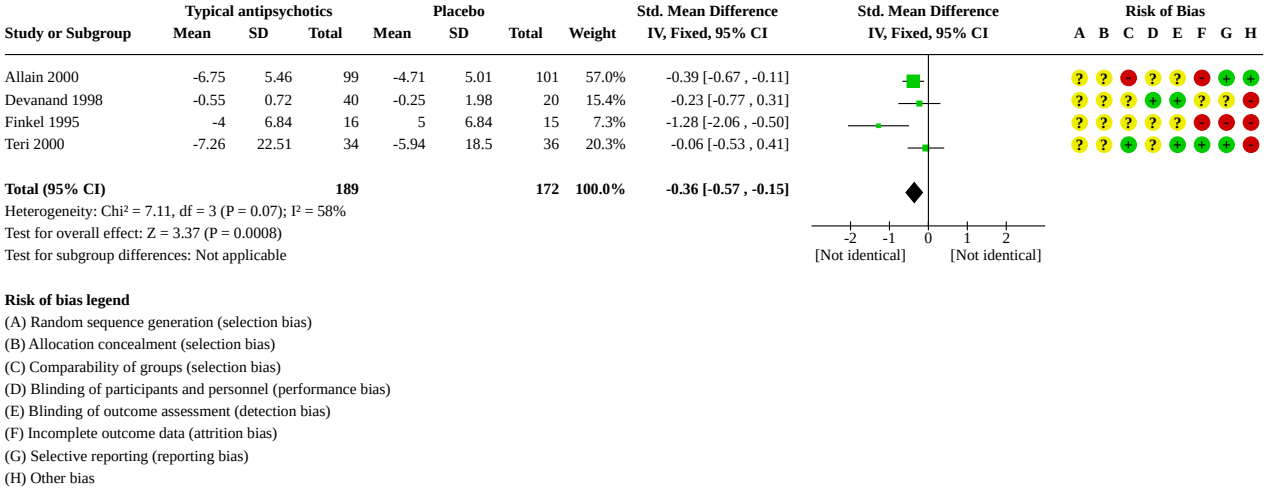
See Summary of findings 1 and Summary of findings 2.

Typical antipsychotics versus placebo

Efficacy

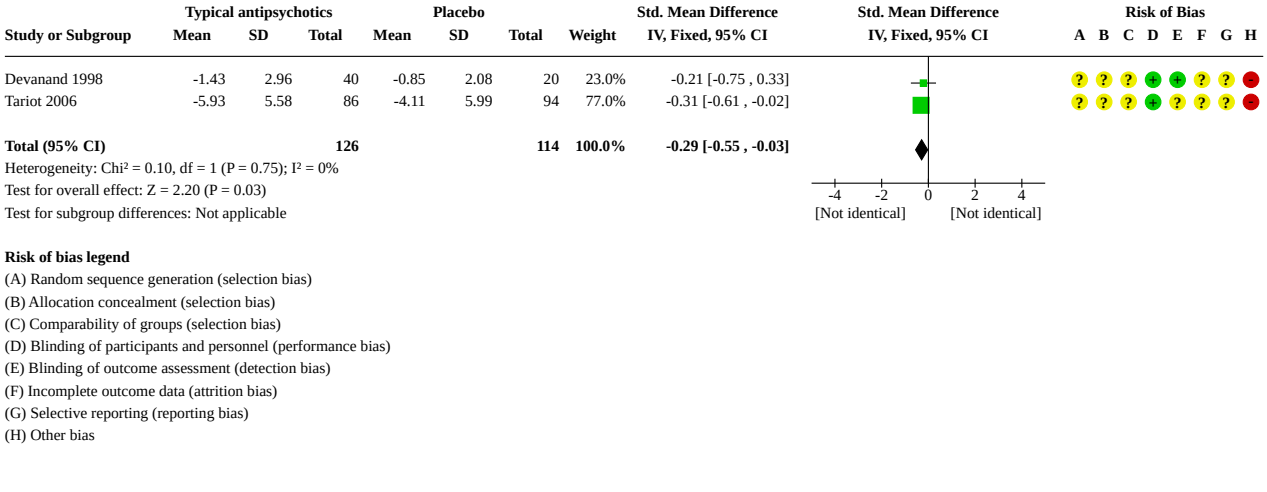
Five studies investigated the effect of typical antipsychotics on agitation and four could be pooled. Given the very low-certainty evidence, we are uncertain whether typical antipsychotics improve agitation compared with placebo (standardised mean difference (SMD) -0.36, 95% confidence interval (CI) -0.57 to -0.15; I^2 = 58%, n = 361; Analysis 1.1; Figure 13). The study that was not included in the meta-analysis reported no clinically meaningful difference between the antipsychotic and placebo group at the end of the study (the mean difference in decrease on the CMAI between the groups was -1.0, with a mean at baseline of 35.2 (range 25 to 44); Auchus 1997).

Figure 13. Forest plot (1.1 Agitation)



Two studies evaluated the effect of typical antipsychotics on psychosis. Low-certainty evidence showed that typical antipsychotics may improve psychosis slightly compared with placebo (SMD -0.29, 95% CI -0.55 to -0.03, n = 240; Analysis 1.2; Figure 14).

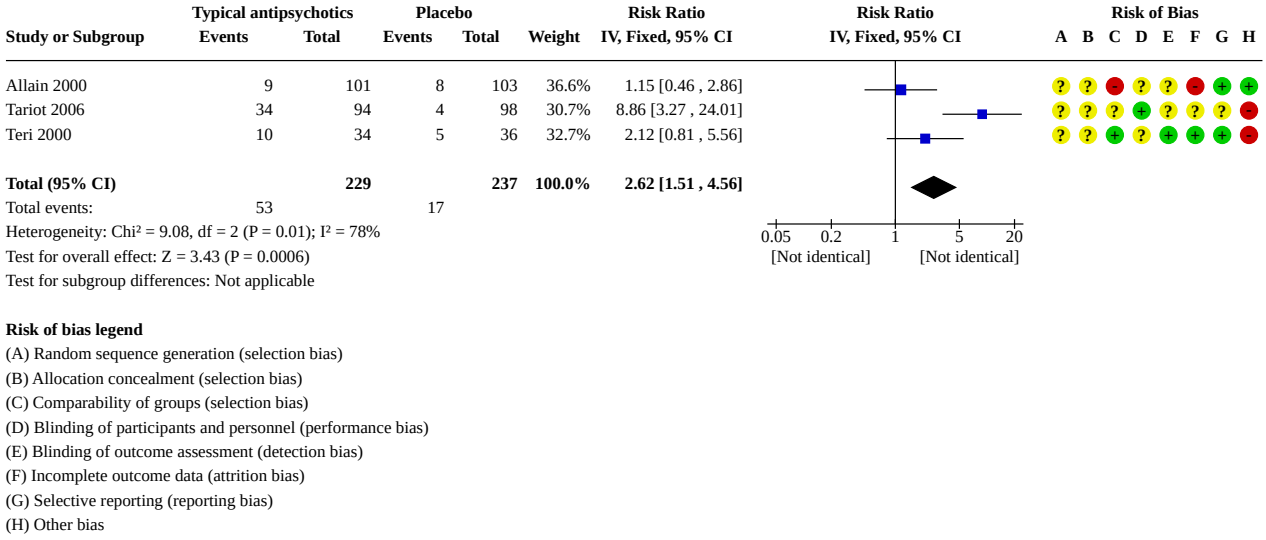
Figure 14. Forest plot (1.2 Psychosis)



Adverse events

Based on the moderate-certainty evidence, typical antipsychotics probably increase the risk of somnolence compared with placebo (risk ratio (RR) 2.62, 95% CI 1.51 to 4.56; I^2 = 78%, n = 466; Analysis 1.3; Figure 15). The corresponding risk difference was 0.12 (95% CI 0.06 to 0.18; NNTH = 8, n = 466; Analysis 1.4). Based on the high-certainty evidence, typical antipsychotics increase the risk of extrapyramidal symptoms compared with placebo (RR 2.26, 95% CI 1.58 to 3.23, n = 467; Analysis 1.5; Figure 16). The corresponding risk difference was 0.19 (95% CI 0.11 to 0.27, n = 467; NNTH: 5; Analysis 1.6).

Figure 15. Forest plot (1.3 Somnolence)

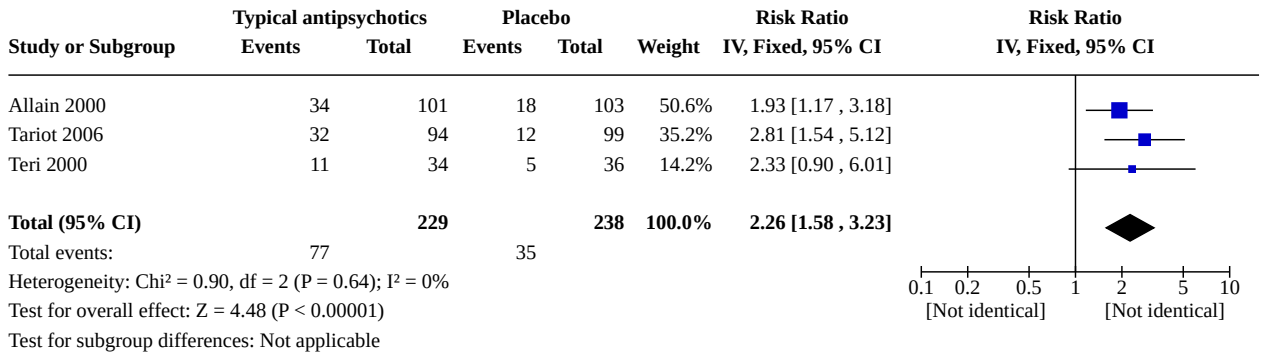


Study or Subgroup	Typical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Allain 2000	9	101	8	103	36.6%	1.15 [0.46 , 2.86]
Tariot 2006	34	94	4	98	30.7%	8.86 [3.27 , 24.01]
Teri 2000	10	34	5	36	32.7%	2.12 [0.81 , 5.56]
Total (95% CI)		**229**		**237**	**100.0%**	**2.62 [1.51 , 4.56]**
Total events:	53		17			

Heterogeneity: Chi² = 9.08, df = 2 (P = 0.01); I² = 78%
Test for overall effect: Z = 3.43 (P = 0.0006)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 16. Forest plot (1.5 Extrapyramidal symptoms)



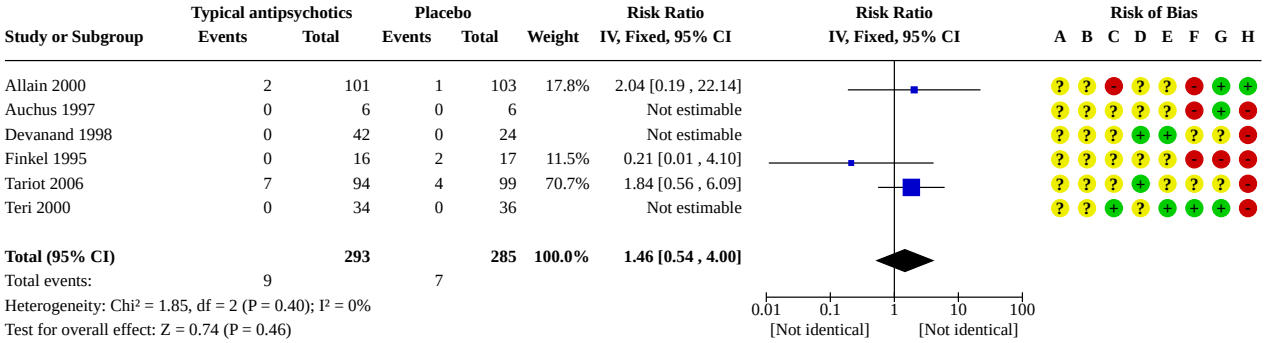
Study or Subgroup	Typical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Allain 2000	34	101	18	103	50.6%	1.93 [1.17 , 3.18]
Tariot 2006	32	94	12	99	35.2%	2.81 [1.54 , 5.12]
Teri 2000	11	34	5	36	14.2%	2.33 [0.90 , 6.01]
Total (95% CI)		**229**		**238**	**100.0%**	**2.26 [1.58 , 3.23]**
Total events:	77		35			

Heterogeneity: Chi² = 0.90, df = 2 (P = 0.64); I² = 0%
Test for overall effect: Z = 4.48 (P < 0.00001)
Test for subgroup differences: Not applicable

No study reported the number of participants with at least one adverse event and only one study reported serious adverse events (SAEs). Based on the low-certainty evidence, typical antipsychotics may increase the risk of SAE slightly compared with placebo (RR 1.32, 95% CI 0.65 to 2.66, n = 193; Analysis 1.7). The corresponding risk difference was 0.04 (95% CI -0.06 to 0.14, n = 193; Analysis 1.8).

Death was reported in six studies, and in three of those studies no events occurred (Auchus 1997; Devanand 1998; Teri 2000). The low-certainty evidence suggests that typical antipsychotics may increase the risk of mortality slightly (RR 1.46, 95% CI 0.54 to 4.00, n = 578; Analysis 1.9; Figure 17). The corresponding risk difference was 0.01 (95% CI -0.02 to 0.03, n = 578; Analysis 1.10).

Figure 17. Forest plot (1.9 Death)



Study or Subgroup	Typical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Allain 2000	2	101	1	103	17.8%	2.04 [0.19 , 22.14]
Auchus 1997	0	6	0	6		Not estimable
Devanand 1998	0	42	0	24		Not estimable
Finkel 1995	0	16	2	17	11.5%	0.21 [0.01 , 4.10]
Tariot 2006	7	94	4	99	70.7%	1.84 [0.56 , 6.09]
Teri 2000	0	34	0	36		Not estimable
Total (95% CI)		**293**		**285**	**100.0%**	**1.46 [0.54 , 4.00]**
Total events:	9		7			

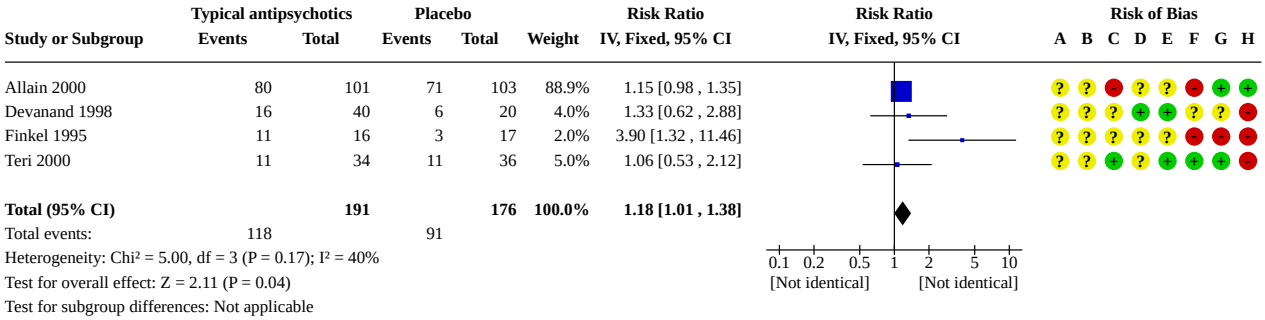
Heterogeneity: Chi² = 1.85, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Secondary outcomes

We found moderate-certainty evidence that typical antipsychotics probably increase the number of responders for agitation slightly (RR 1.18, 95% CI 1.01 to 1.38; I^2 = 40%, n = 367; Analysis 1.11; Figure 18). The corresponding risk difference was 0.13 (95% CI 0.04 to 0.22; I^2 = 62%, n = 367; NNTB = 7; Analysis 1.12). We found low-certainty evidence that typical antipsychotics may increase the number of responders for psychosis slightly (RR 1.31, 95% CI 0.90 to 1.92, n = 259; Analysis 1.13; Figure 19). The corresponding risk difference was 0.09 (95% CI -0.03 to 0.20, n = 259; NNTB = 11; Analysis 1.14).

Figure 18. Forest plot (1.11 Number of responders for agitation)

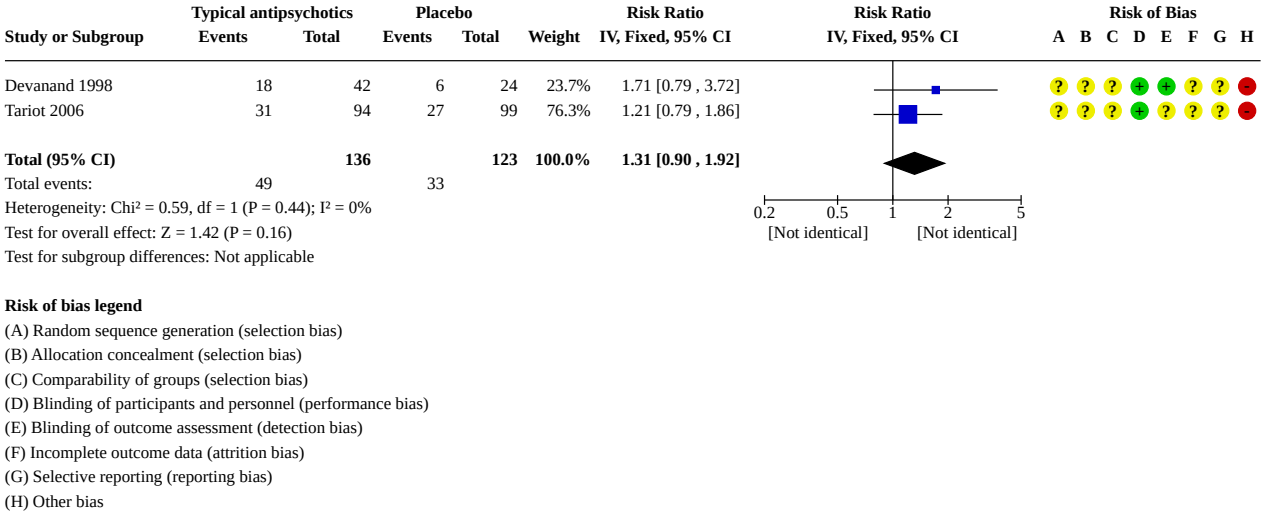


Study or Subgroup	Typical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Allain 2000	80	101	71	103	88.9%	1.15 [0.98 , 1.35]
Devanand 1998	16	40	6	20	4.0%	1.33 [0.62 , 2.88]
Finkel 1995	11	16	3	17	2.0%	3.90 [1.32 , 11.46]
Teri 2000	11	34	11	36	5.0%	1.06 [0.53 , 2.12]
Total (95% CI)		**191**		**176**	**100.0%**	**1.18 [1.01 , 1.38]**
Total events:	118		91			

Heterogeneity: Chi² = 5.00, df = 3 (P = 0.17); I² = 40%
Test for overall effect: Z = 2.11 (P = 0.04)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

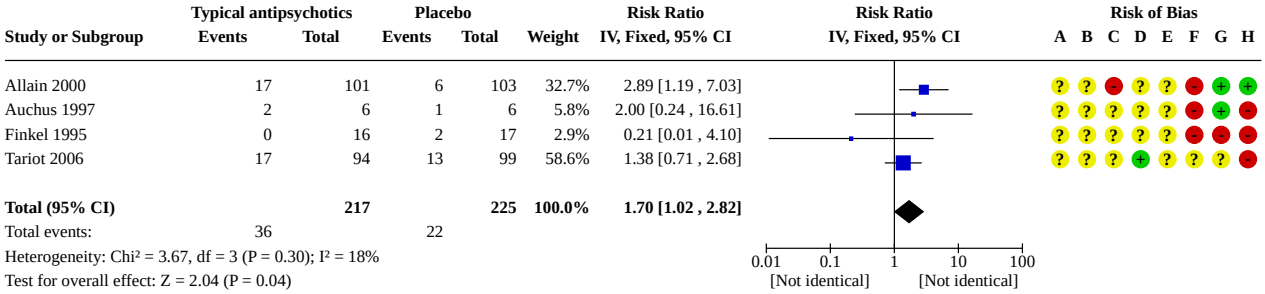
Figure 19. Forest plot (1.13 Number of responders for psychosis)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

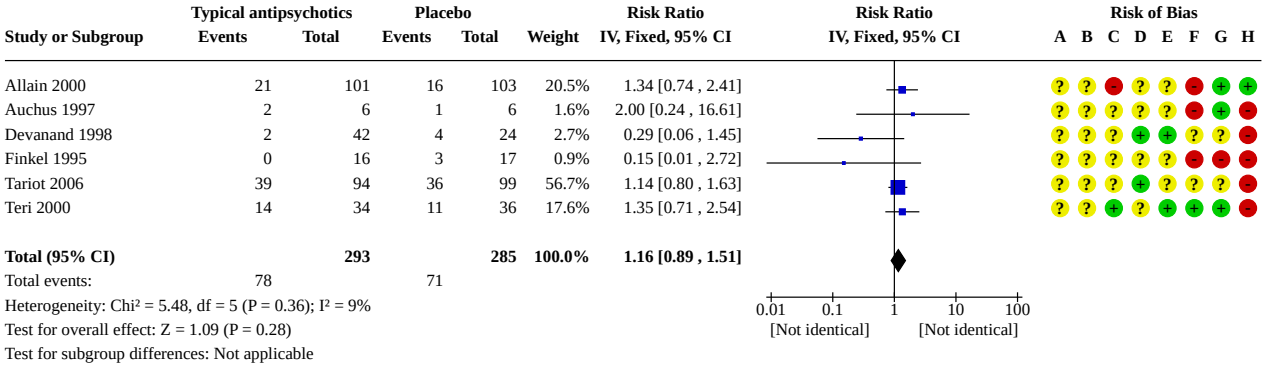
We found low-certainty evidence that typical antipsychotics may increase the risk of discontinuation due to adverse events (RR 1.70, 95% CI 1.02 to 2.82, n = 442; Analysis 1.15; Figure 20). The corresponding risk difference was 0.06 (95% CI 0.00 to 0.12; NNTH = 17; I^2 = 44%, n = 442; 4 studies; Analysis 1.16). We found moderate-certainty evidence that typical antipsychotics probably have little or no effect on discontinuation due to any reason (RR 1.16, 95% CI 0.89 to 1.51, n = 578; Analysis 1.17; Figure 21). The corresponding risk difference was 0.01 (95% CI -0.06 to 0.07; I^2 = 36%, n = 578; Analysis 1.18).

Figure 20. Forest plot (1.15 Discontinuation due to adverse events)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

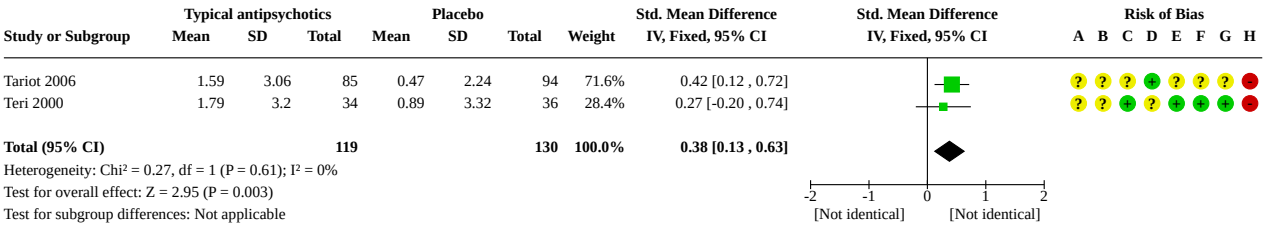
Figure 21. Forest plot (1.17 Discontinuation, any reason)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

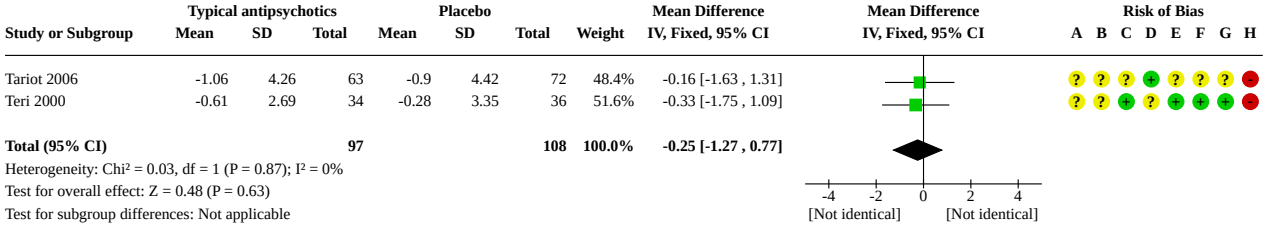
No studies reported having measured health-related quality of life. We found low-certainty evidence that typical antipsychotics may improve functioning slightly (SMD 0.38, 95% CI 0.13 to 0.63, n = 249; Analysis 1.19; Figure 22). We found low-certainty evidence that typical antipsychotics may have little (harmful) or no effect on cognitive functioning (MD -0.25 on Mini Mental State Examination (MMSE), 95% CI -1.27 to 0.77, n = 205; Analysis 1.20; Figure 23). For caregiver burden, we found low-certainty evidence from one study that typical antipsychotics may have little (beneficial) or no effect on caregiver burden (MD 0.70, 95% CI -3.65 to 5.05, n = 70; Analysis 1.21). One very small study that was not included in this meta-analysis (Auchus 1997) found an increase in caregiver stress in the typical antipsychotic and placebo group (14.0 and 18.6 on the Caregiver Strain Index (CSI), respectively, with a baseline mean of 165.4 and 116.2, respectively, n = 9).

Figure 22. Forest plot (1.19 Functioning (ADL))



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 23. Forest plot (1.20 Cognitive function)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

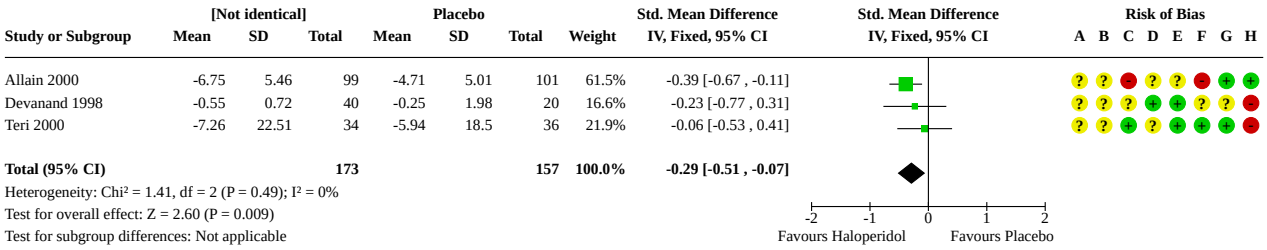
Subgroup analysis for haloperidol

In the pre-planned subgroup analysis for haloperidol, we found very low, low- and moderate-certainty evidence for the different outcomes.

Efficacy

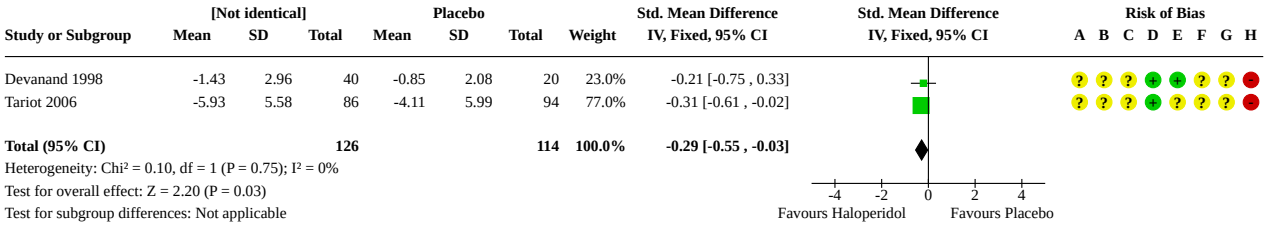
Haloperidol may reduce agitation slightly compared with placebo (SMD -0.29; 95% CI -0.51 to -0.07, n = 330; Analysis 2.1; Figure 24). We are uncertain whether typical antipsychotics improve psychosis compared to placebo (SMD -0.29; 05% CI -0.55 to -0.03, n = 240; Analysis 2.2; Figure 25).

Figure 24. Forest plot (2.1 Agitation)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 25. Forest plot (2.2 Psychosis)

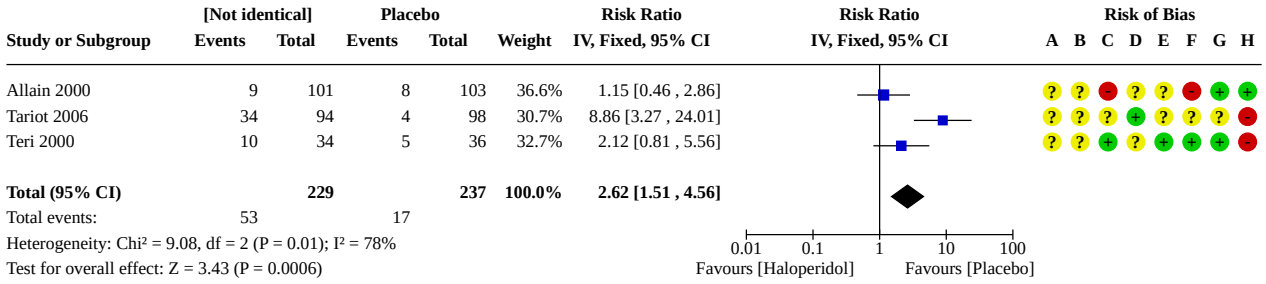


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Adverse events

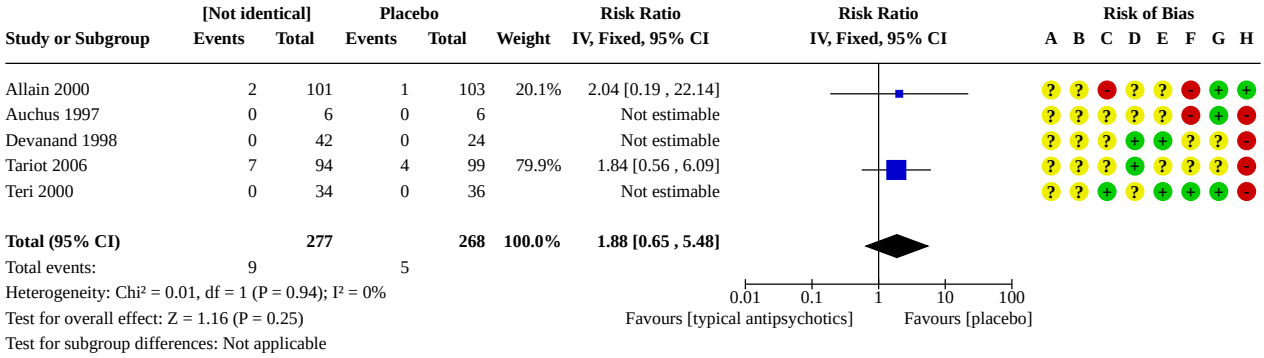
We found that haloperidol probably increased the risk of somnolence compared with placebo (RR 2.62, 95% CI 1.51 to 4.56, n = 466; Analysis 2.3; Figure 26). Haloperidol may increase the risk of extrapyramidal symptoms (RR 2.33, 95% CI 0.90 to 6.01, n = 70; Analysis 2.4). No study reported the number of participants with any adverse events. For serious adverse events, we found that haloperidol may increase the risk of serious adverse events slightly compared with placebo (RR 1.32, 95% CI 0.65 to 2.66, n = 193; Analysis 2.5). Death was assessed in five studies and in three of those studies no events occurred (Auchus 1997; Devanand 1998; Teri 2000). Based on the other studies, haloperidol may increase the risk of mortality (RR 1.88, 95% CI 0.65 to 5.48, n = 545; Analysis 2.6; Figure 27).

Figure 26. Forest plot (2.3 Somnolence)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 27. Forest plot (2.6 Death)

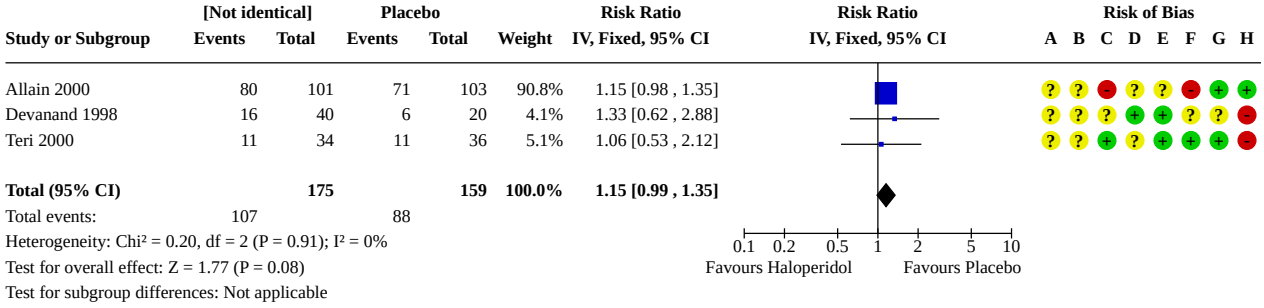


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Secondary outcomes

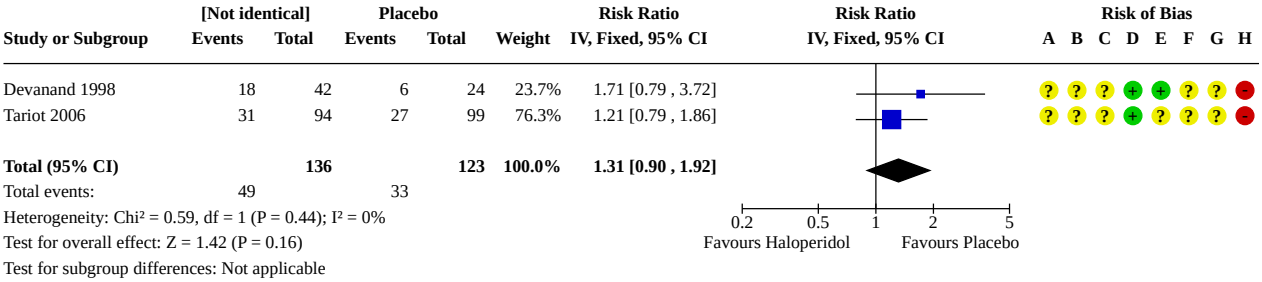
Haloperidol may have little or no effect on the number of responders for agitation (RR 1.16, 95% CI 0.99 to 1.35, n = 334; Analysis 2.7; Figure 28). Haloperidol may increase the number of responders for psychosis compared with placebo slightly (RR 1.31, 95% CI 0.90 to 1.92, n = 259; Analysis 2.8; Figure 29).

Figure 28. Forest plot (2.7 Number of responders for agitation)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

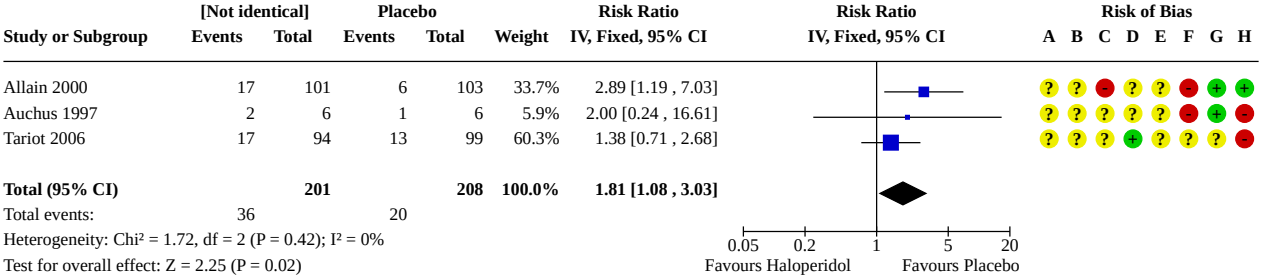
Figure 29. Forest plot (2.8 Number of responders for psychosis)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

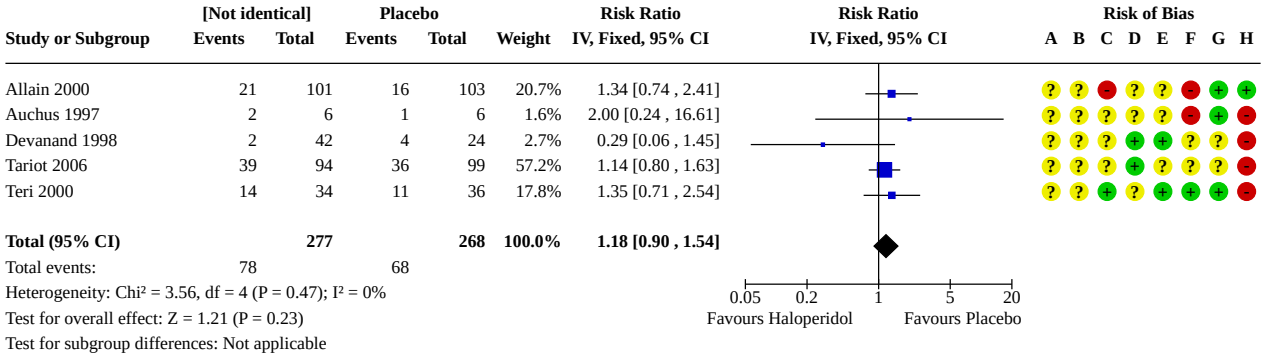
Haloperidol may increase discontinuation due to adverse events compared with placebo (RR 1.81, 95% CI 1.08 to 3.03, n = 409; Analysis 2.9; Figure 30). Haloperidol probably has little or no effect on discontinuation due to any reason (RR 1.18, 95% CI 0.90 to 1.54, n = 545; Analysis 2.10; Figure 31).

Figure 30. Forest plot (2.9 Discontinuation due to adverse events)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

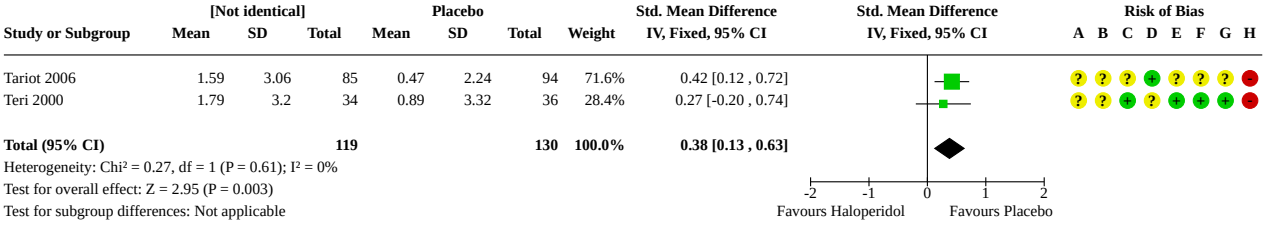
Figure 31. Forest plot (2.10 Discontinuation, any reason)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

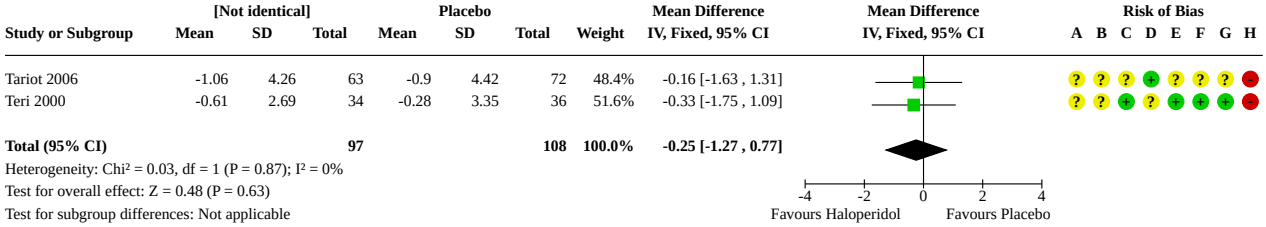
No study reported health-related quality of life. Haloperidol may improve functioning slightly (SMD 0.38, 95% CI 0.13 to 0.63, n = 249; Analysis 2.11; Figure 32). Haloperidol may have little or no effect on cognitive functioning (MD -0.25 on MMSE, 95% CI -1.27 to 0.77, n = 205; Analysis 2.12; Figure 33). For caregiver burden, we are uncertain what the effect of haloperidol is (MD 0.70, 95% CI -3.65 to 5.05, n = 70; Analysis 2.13).

Figure 32. Forest plot (2.11 Functioning (ADL))



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 33. Forest plot (2.12 Cognitive function)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

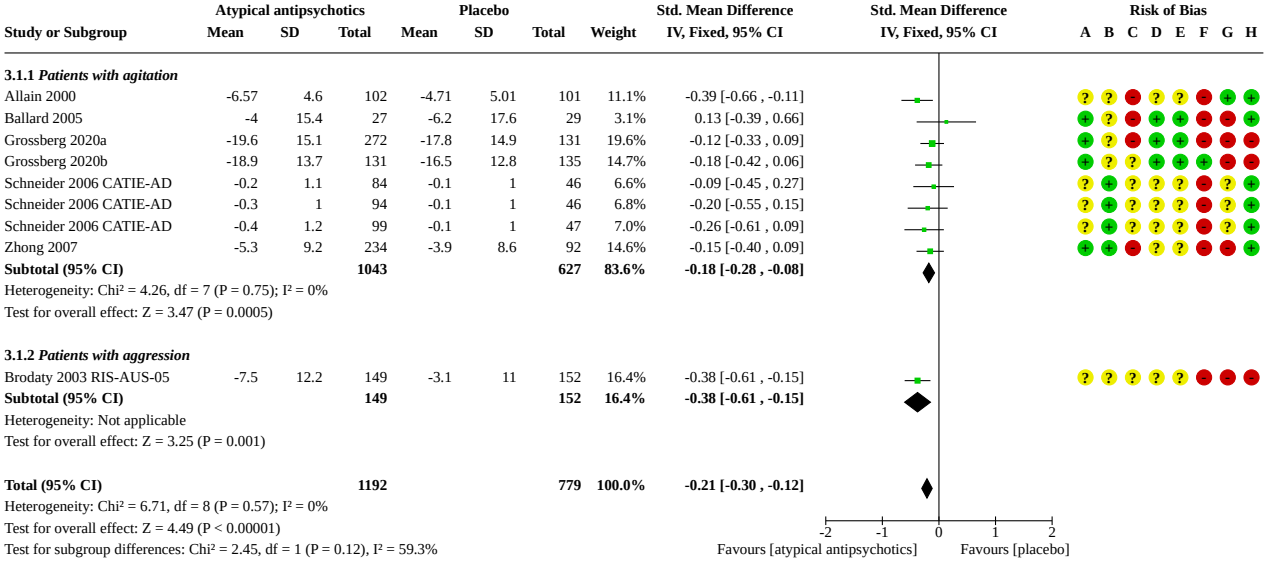
Atypical antipsychotics versus placebo

Efficacy

Moderate-certainty evidence indicates that atypical antipsychotics probably reduce agitation slightly compared with placebo (SMD -0.21, 95% CI -0.30 to -0.12, n = 1971; Analysis 3.1; Figure 34).

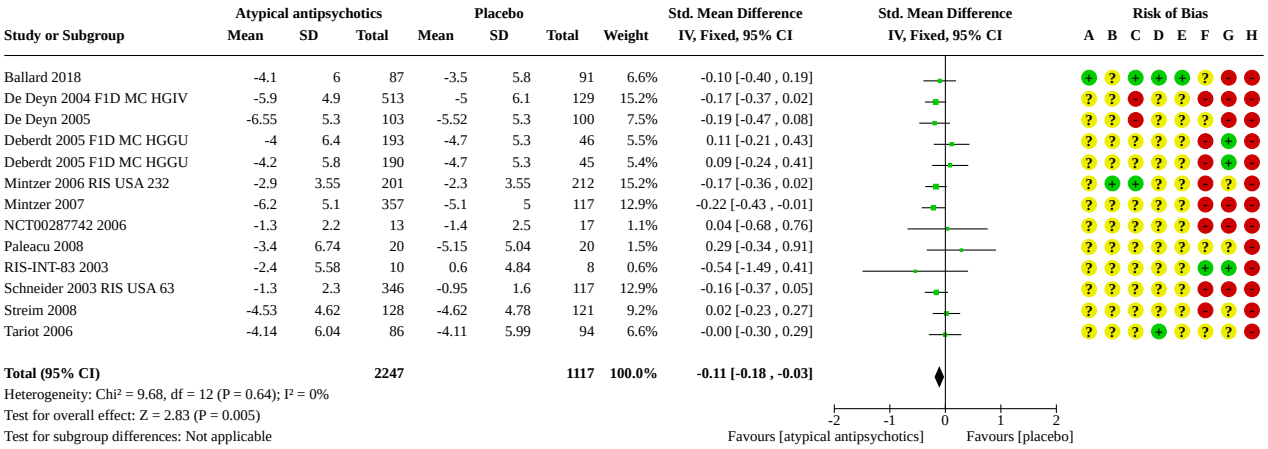
Evidence from one study indicates that atypical antipsychotic (in this study risperidone) may reduce aggression slightly as well (SMD -0.38, 95% CI -0.61 to -0.15, n = 301; Analysis 3.1; Figure 34). Moderate-certainty evidence indicated that atypical antipsychotics probably have a negligible effect on psychosis (SMD -0.11, 95% CI -0.18 to -0.03, n = 3364; Analysis 3.2; Figure 35).

Figure 34. Forest plot (3.1 Agitation)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 35. Forest plot (3.2 Psychosis)



Study or Subgroup	Atypical antipsychotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
Ballard 2018	-4.1	6	87	-3.5	5.8	91	6.6%	-0.10 [-0.40 , 0.19]	+ ? + + + ? - -
De Deyn 2004 F1D MC HGIV	-5.9	4.9	513	-5	6.1	129	15.2%	-0.17 [-0.37 , 0.02]	? ? - ? ? - - -
De Deyn 2005	-6.55	5.3	103	-5.52	5.3	100	7.5%	-0.19 [-0.47 , 0.08]	? ? - ? ? ? - -
Deberdt 2005 F1D MC HGGU	-4	6.4	193	-4.7	5.3	46	5.5%	0.11 [-0.21 , 0.43]	? ? ? ? ? - + -
Deberdt 2005 F1D MC HGGU	-4.2	5.8	190	-4.7	5.3	45	5.4%	0.09 [-0.24 , 0.41]	? ? ? ? ? - + -
Mintzer 2006 RIS USA 232	-2.9	3.55	201	-2.3	3.55	212	15.2%	-0.17 [-0.36 , 0.02]	? + + ? ? - ? -
Mintzer 2007	-6.2	5.1	357	-5.1	5	117	12.9%	-0.22 [-0.43 , -0.01]	? ? ? ? ? - - -
NCT00287742 2006	-1.3	2.2	13	-1.4	2.5	17	1.1%	0.04 [-0.68 , 0.76]	? ? ? ? ? - - -
Paleacu 2008	-3.4	6.74	20	-5.15	5.04	20	1.5%	0.29 [-0.34 , 0.91]	? ? ? ? ? ? ? -
RIS-INT-83 2003	-2.4	5.58	10	0.6	4.84	8	0.6%	-0.54 [-1.49 , 0.41]	? ? ? ? ? + + -
Schneider 2003 RIS USA 63	-1.3	2.3	346	-0.95	1.6	117	12.9%	-0.16 [-0.37 , 0.05]	? ? ? ? ? - - -
Streim 2008	-4.53	4.62	128	-4.62	4.78	121	9.2%	0.02 [-0.23 , 0.27]	? ? ? ? ? - ? -
Tariot 2006	-4.14	6.04	86	-4.11	5.99	94	6.6%	-0.00 [-0.30 , 0.29]	? ? ? + ? ? ? -
Total (95% CI)			**2247**			**1117**	**100.0%**	**-0.11 [-0.18 , -0.03]**	

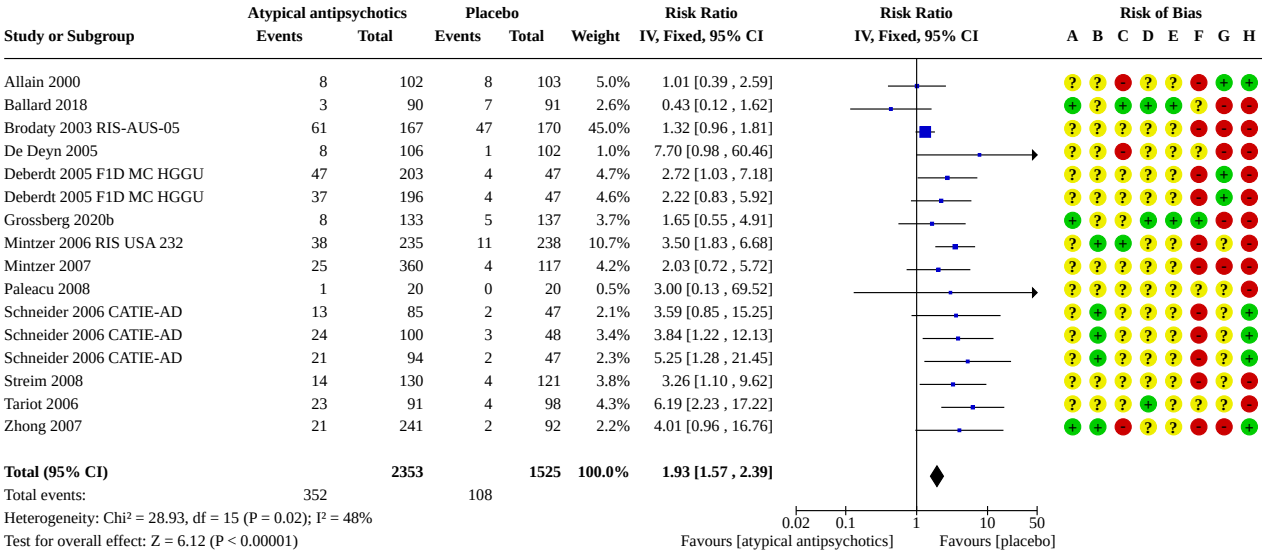
Heterogeneity: Chi² = 9.68, df = 12 (P = 0.64); I² = 0%
Test for overall effect: Z = 2.83 (P = 0.005)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Adverse events

We found high-certainty evidence that atypical antipsychotics increase the risk of somnolence compared with placebo (RR 1.93, 95% CI 1.57 to 2.39, n = 3878; Analysis 3.3; Figure 36). The corresponding risk difference was 0.07 (95% CI 0.05 to 0.08; I^2 = 65%, n = 3878; Analysis 3.4). We found moderate-certainty evidence that atypical antipsychotics probably increase extrapyramidal symptoms slightly (RR 1.39, 95% CI 1.14 to 1.68, n = 4180; Analysis 3.5; Figure 37). The corresponding risk difference was 0.03 (95% CI 0.02 to 0.05, n = 4180; Analysis 3.6).

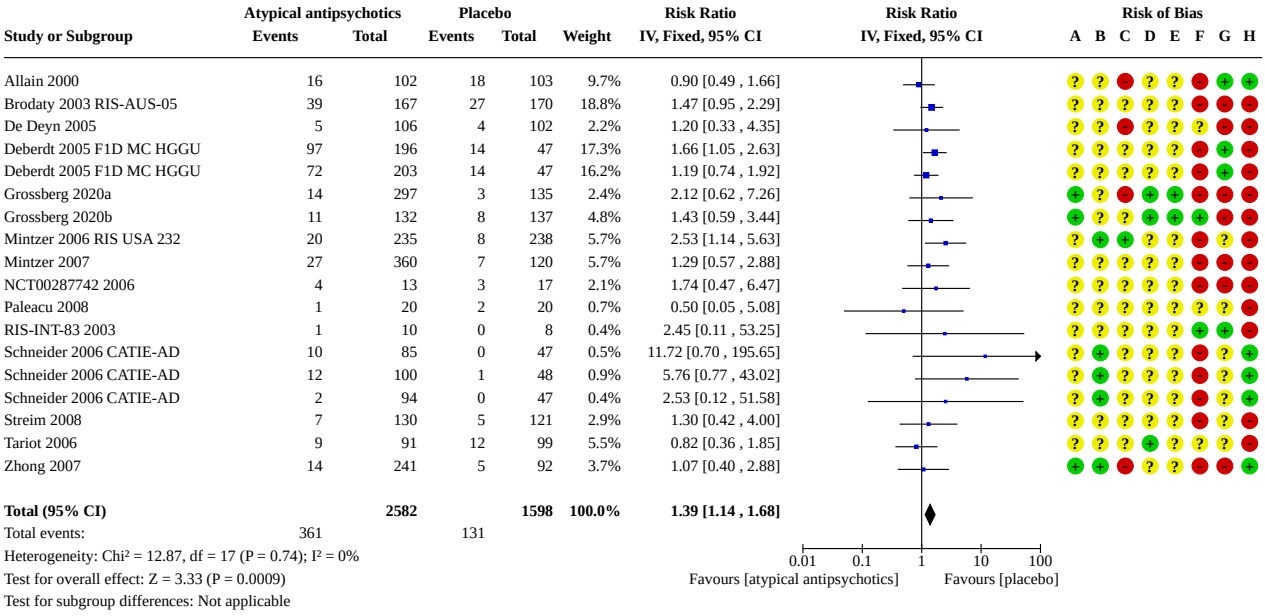
Figure 36. Forest plot (3.3 Somnolence)



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

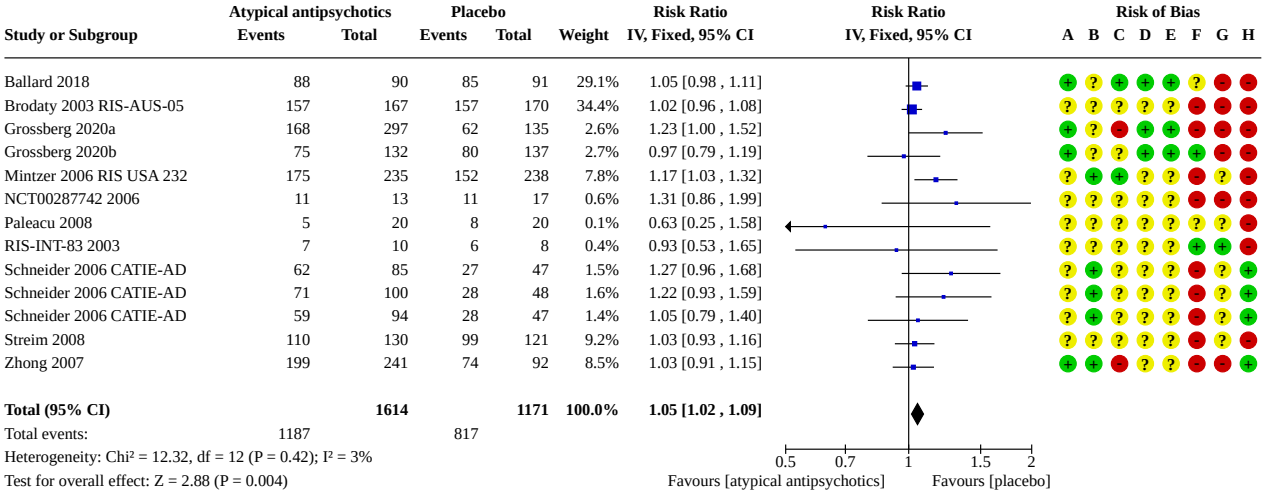
Figure 37. Forest plot (3.5 Extrapyramidal symptoms)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

We found moderate-certainty evidence that atypical antipsychotics probably have a negligible effect on the risk of any adverse events (RR 1.05, 95% CI 1.02 to 1.09, n = 2785; Analysis 3.7; Figure 38). The corresponding risk difference was 0.05 (95% CI 0.02 to 0.07, n = 2785; Analysis 3.8). We found moderate-certainty evidence that atypical antipsychotics probably increase the number of SAE slightly (RR 1.32, 95% CI 1.09 to 1.61, n = 4316; Analysis 3.9; Figure 39). The corresponding risk difference was 0.04 (95% CI 0.02 to 0.05, n = 4316; Analysis 3.10).

Figure 38. Forest plot (3.7 Any adverse event)

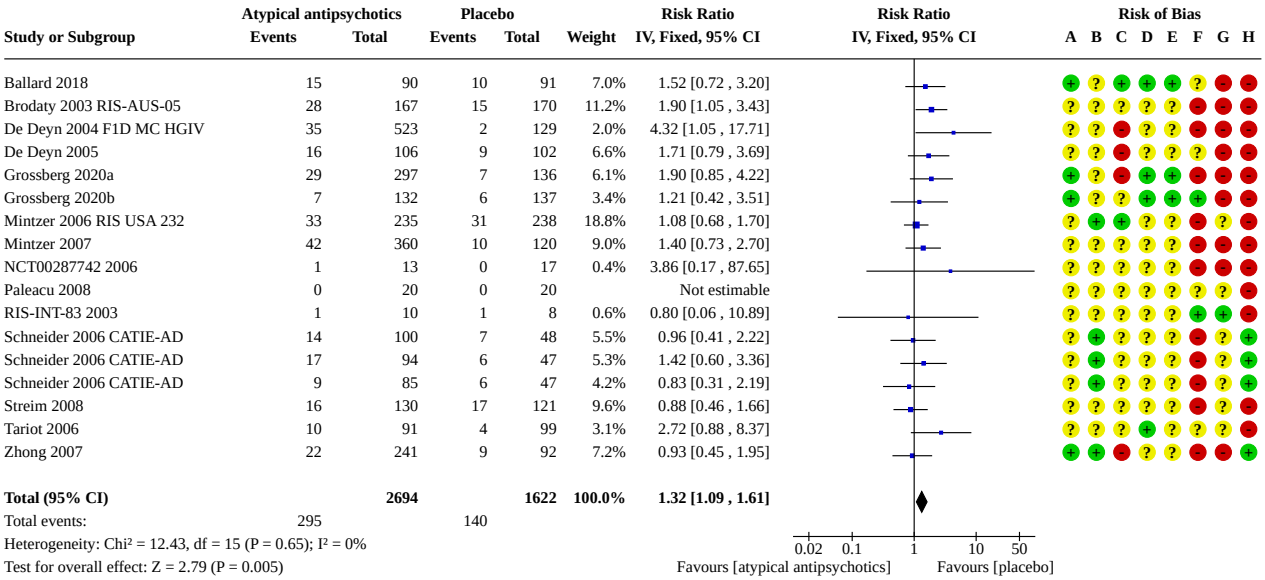


Study or Subgroup	Atypical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Ballard 2018	88	90	85	91	29.1%	1.05 [0.98 , 1.11]
Brodaty 2003 RIS-AUS-05	157	167	157	170	34.4%	1.02 [0.96 , 1.08]
Grossberg 2020a	168	297	62	135	2.6%	1.23 [1.00 , 1.52]
Grossberg 2020b	75	132	80	137	2.7%	0.97 [0.79 , 1.19]
Mintzer 2006 RIS USA 232	175	235	152	238	7.8%	1.17 [1.03 , 1.32]
NCT00287742 2006	11	13	11	17	0.6%	1.31 [0.86 , 1.99]
Paleacu 2008	5	20	8	20	0.1%	0.63 [0.25 , 1.58]
RIS-INT-83 2003	7	10	6	8	0.4%	0.93 [0.53 , 1.65]
Schneider 2006 CATIE-AD	62	85	27	47	1.5%	1.27 [0.96 , 1.68]
Schneider 2006 CATIE-AD	71	100	28	48	1.6%	1.22 [0.93 , 1.59]
Schneider 2006 CATIE-AD	59	94	28	47	1.4%	1.05 [0.79 , 1.40]
Streim 2008	110	130	99	121	9.2%	1.03 [0.93 , 1.16]
Zhong 2007	199	241	74	92	8.5%	1.03 [0.91 , 1.15]
Total (95% CI)		**1614**		**1171**	**100.0%**	**1.05 [1.02 , 1.09]**
Total events:	1187		817			

Heterogeneity: Chi² = 12.32, df = 12 (P = 0.42); I² = 3%
Test for overall effect: Z = 2.88 (P = 0.004)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 39. Forest plot (3.9 Any serious adverse event)



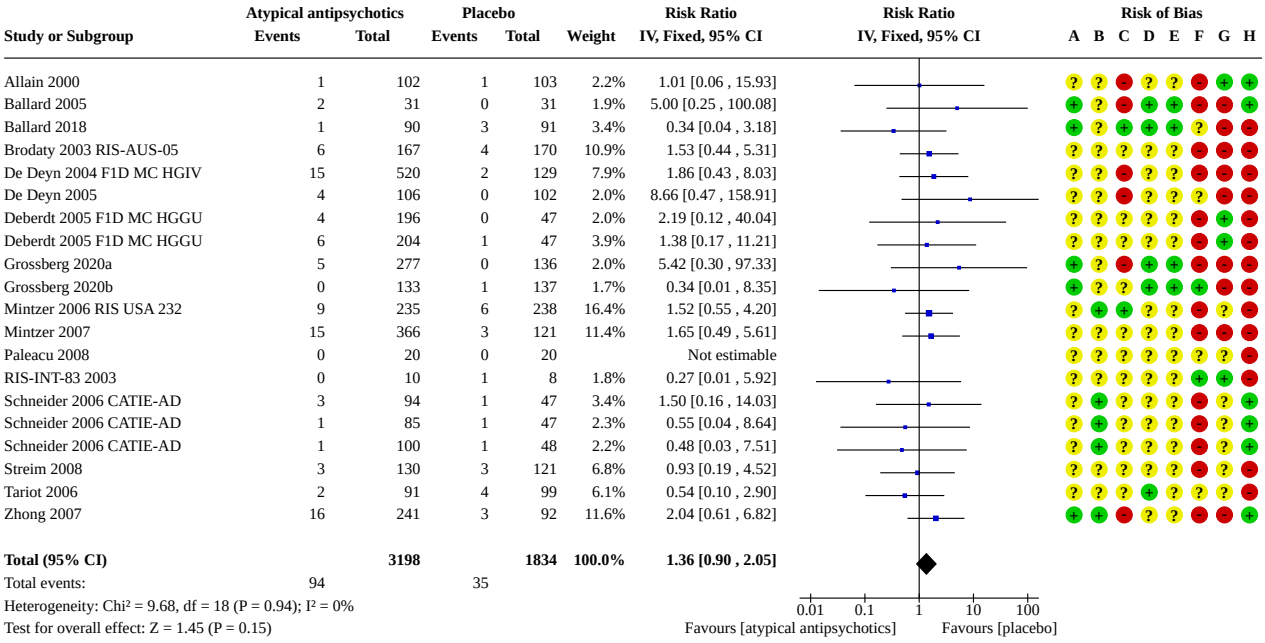
Study or Subgroup	Atypical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Ballard 2018	15	90	10	91	7.0%	1.52 [0.72 , 3.20]
Brodaty 2003 RIS-AUS-05	28	167	15	170	11.2%	1.90 [1.05 , 3.43]
De Deyn 2004 F1D MC HGIV	35	523	2	129	2.0%	4.32 [1.05 , 17.71]
De Deyn 2005	16	106	9	102	6.6%	1.71 [0.79 , 3.69]
Grossberg 2020a	29	297	7	136	6.1%	1.90 [0.85 , 4.22]
Grossberg 2020b	7	132	6	137	3.4%	1.21 [0.42 , 3.51]
Mintzer 2006 RIS USA 232	33	235	31	238	18.8%	1.08 [0.68 , 1.70]
Mintzer 2007	42	360	10	120	9.0%	1.40 [0.73 , 2.70]
NCT00287742 2006	1	13	0	17	0.4%	3.86 [0.17 , 87.65]
Paleacu 2008	0	20	0	20		Not estimable
RIS-INT-83 2003	1	10	1	8	0.6%	0.80 [0.06 , 10.89]
Schneider 2006 CATIE-AD	14	100	7	48	5.5%	0.96 [0.41 , 2.22]
Schneider 2006 CATIE-AD	17	94	6	47	5.3%	1.42 [0.60 , 3.36]
Schneider 2006 CATIE-AD	9	85	6	47	4.2%	0.83 [0.31 , 2.19]
Streim 2008	16	130	17	121	9.6%	0.88 [0.46 , 1.66]
Tariot 2006	10	91	4	99	3.1%	2.72 [0.88 , 8.37]
Zhong 2007	22	241	9	92	7.2%	0.93 [0.45 , 1.95]
Total (95% CI)		**2694**		**1622**	**100.0%**	**1.32 [1.09 , 1.61]**
Total events:	295		140			

Heterogeneity: Chi² = 12.43, df = 15 (P = 0.65); I² = 0%
Test for overall effect: Z = 2.79 (P = 0.005)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Moderate-certainty evidence indicated that atypical antipsychotics probably increase mortality slightly (RR 1.36, 95% CI 0.90 to 2.05, n = 5032; Analysis 3.11; Figure 40). The corresponding risk difference was 0.01 (95% CI -0.00 to 0.02, n = 5032; Analysis 3.12).

Figure 40. Forest plot (3.11 Death)

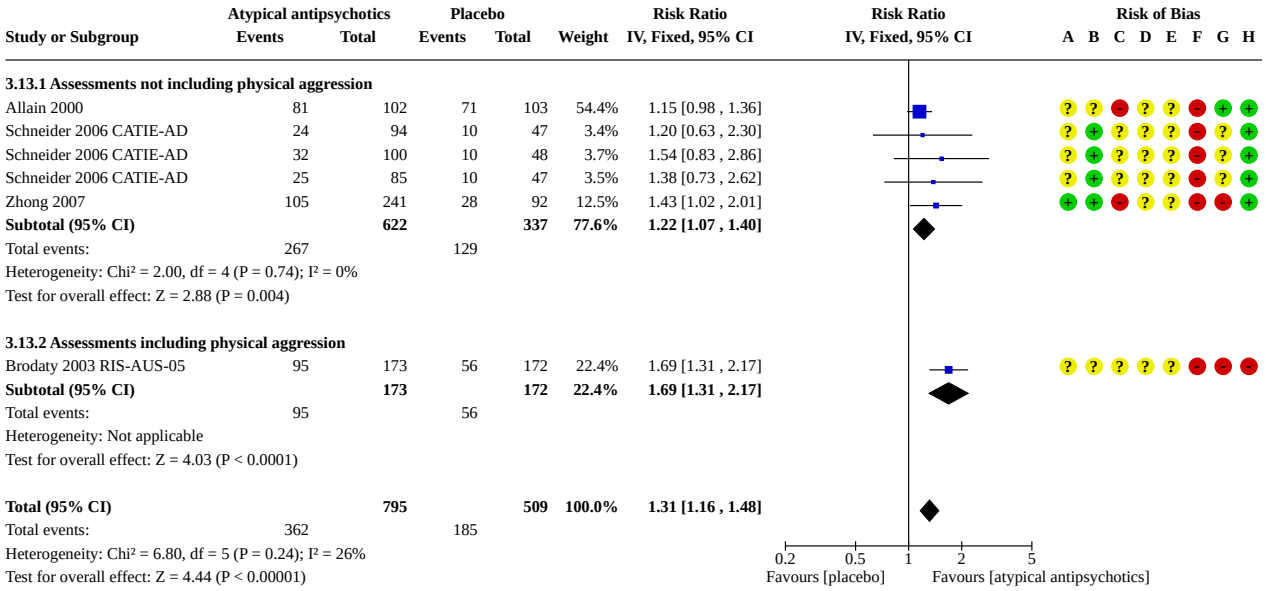


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Secondary outcomes

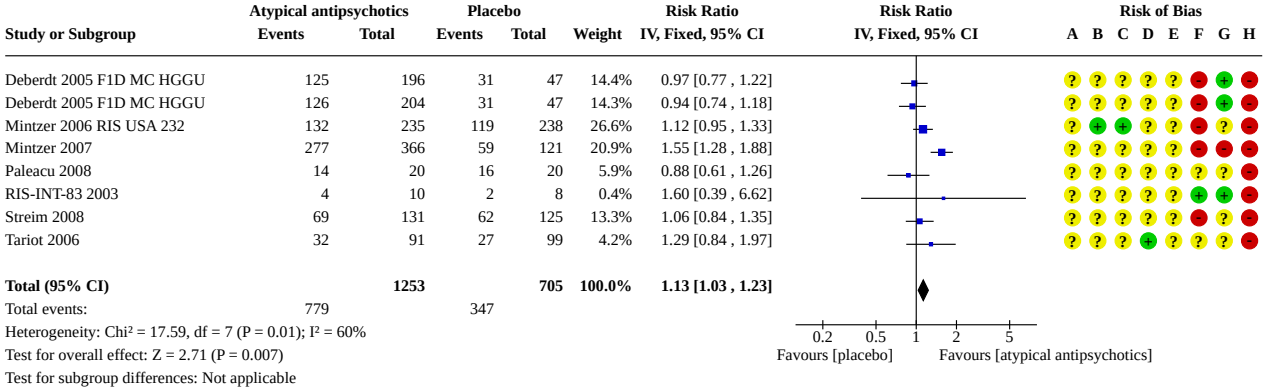
Moderate-certainty evidence indicated that atypical antipsychotics probably increase the number of responders for agitation slightly (RR 1.31, 95% CI 1.16 to 1.48, n = 1304; Analysis 3.13; Figure 41). The corresponding risk difference was 0.13 (95% CI 0.08 to 0.18, n = 1304; Analysis 3.14). Low-certainty evidence indicated that atypical antipsychotics may increase the risk of response for psychosis slightly compared with placebo (RR 1.13, 95% CI 1.03 to 1.23; I^2= 60%, n = 1958; Analysis 3.15; Figure 42). The corresponding risk difference was 0.08 (95% CI 0.04 to 0.13, n = 1958; Analysis 3.16).

Figure 41. Forest plot (3.13 Number of responders for agitation)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 42. Forest plot (3.15 Number of responders for psychosis)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

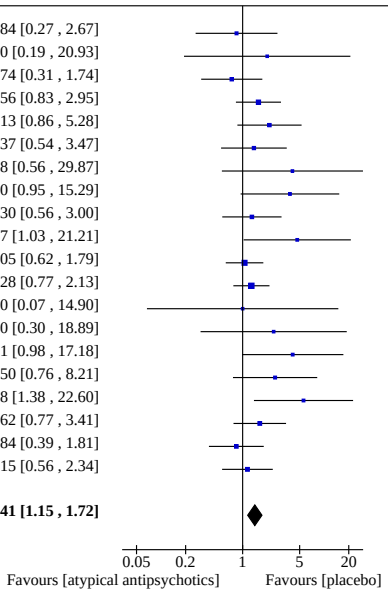
Moderate-certainty evidence indicated that atypical antipsychotics probably increase discontinuation due to adverse events slightly (RR 1.41, 95% CI 1.15 to 1.72, n = 5058; Analysis 3.17; Figure 43). The corresponding risk difference was 0.04 (95% CI 0.02 to 0.06, n =

5058; Analysis 3.18). Low-certainty evidence indicated that atypical antipsychotics may have little or no effect on discontinuation for any reason (RR 0.95, 95% CI 0.89 to 1.01, n = 5095; Analysis 3.19; Figure 44). The corresponding risk difference was -0.00 (95% CI -0.02 to 0.02, n = 5095; Analysis 3.20).

Figure 43. Forest plot (3.17 Discontinuation due to adverse events)

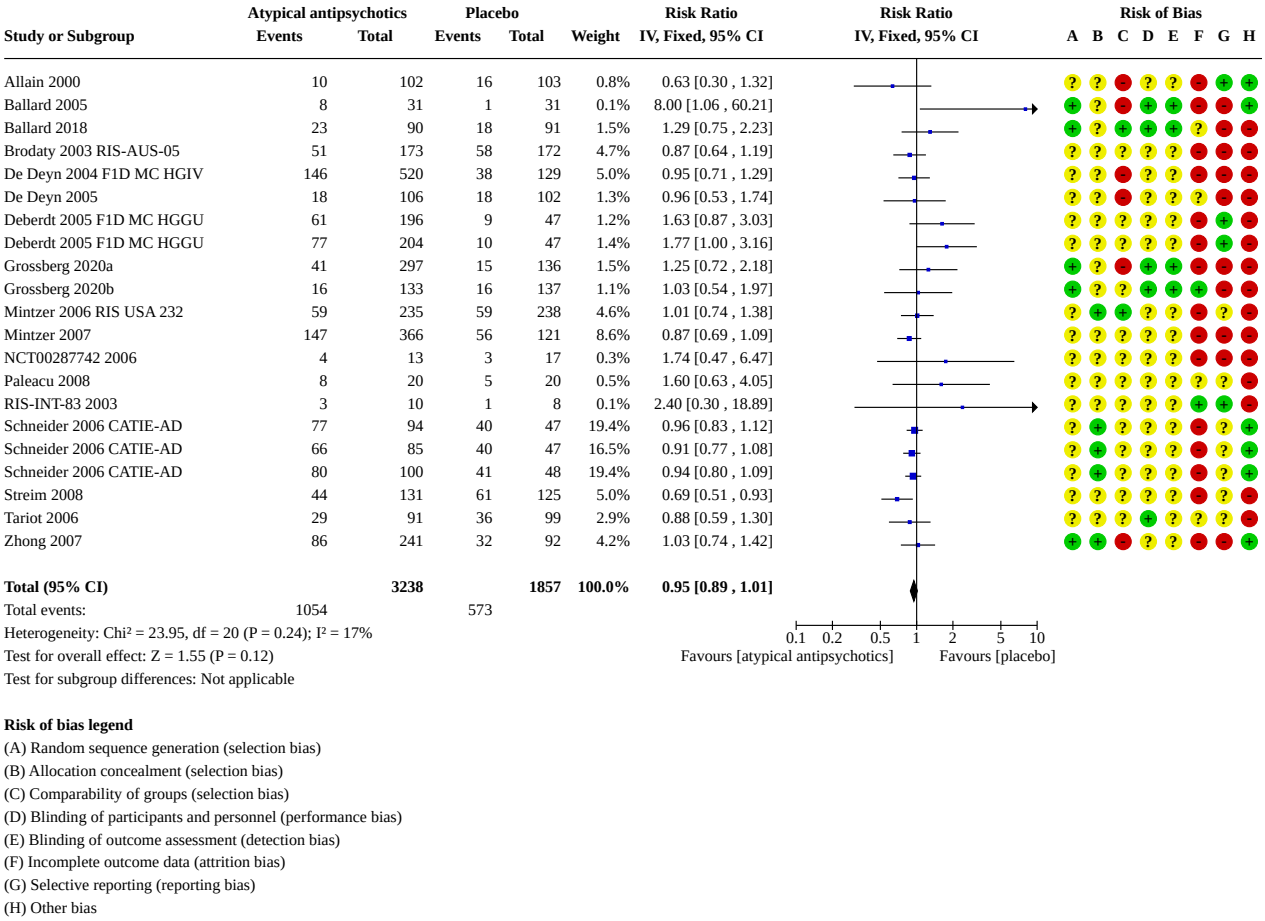
Study or Subgroup	Atypical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Allain 2000	5	102	6	103	3.0%	0.84 [0.27 , 2.67]
Ballard 2005	2	31	1	31	0.7%	2.00 [0.19 , 20.93]
Ballard 2018	8	90	11	91	5.4%	0.74 [0.31 , 1.74]
Brodaty 2003 RIS-AUS-05	22	173	14	172	10.0%	1.56 [0.83 , 2.95]
De Deyn 2004 F1D MC HGIV	43	520	5	129	4.9%	2.13 [0.86 , 5.28]
De Deyn 2005	10	106	7	102	4.7%	1.37 [0.54 , 3.47]
Deberdt 2005 F1D MC HGGU	17	196	1	47	1.0%	4.08 [0.56 , 29.87]
Deberdt 2005 F1D MC HGGU	33	204	2	47	2.1%	3.80 [0.95 , 15.29]
Grossberg 2020a	20	297	7	135	5.8%	1.30 [0.56 , 3.00]
Grossberg 2020b	9	132	2	137	1.8%	4.67 [1.03 , 21.21]
Mintzer 2006 RIS USA 232	25	235	24	238	14.4%	1.05 [0.62 , 1.79]
Mintzer 2007	62	366	16	121	15.6%	1.28 [0.77 , 2.13]
Paleacu 2008	1	20	1	20	0.6%	1.00 [0.07 , 14.90]
RIS-INT-83 2003	3	10	1	8	1.0%	2.40 [0.30 , 18.89]
Schneider 2006 CATIE-AD	15	84	2	46	2.0%	4.11 [0.98 , 17.18]
Schneider 2006 CATIE-AD	15	94	3	47	2.9%	2.50 [0.76 , 8.21]
Schneider 2006 CATIE-AD	24	99	2	46	2.1%	5.58 [1.38 , 22.60]
Streim 2008	17	131	10	125	7.4%	1.62 [0.77 , 3.41]
Tariot 2006	10	91	13	99	6.8%	0.84 [0.39 , 1.81]
Zhong 2007	27	241	9	92	7.9%	1.15 [0.56 , 2.34]
Total (95% CI)		**3222**		**1836**	**100.0%**	**1.41 [1.15 , 1.72]**
Total events:	368		137			

Heterogeneity: Chi² = 19.99, df = 19 (P = 0.40); I² = 5%
Test for overall effect: Z = 3.35 (P = 0.0008)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 44. Forest plot (3.19 Discontinuation, any reason)

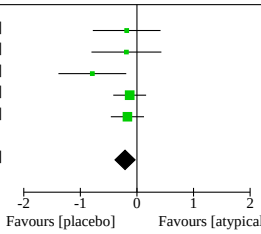


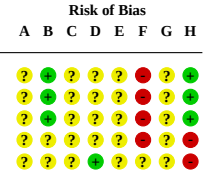
We found moderate-certainty evidence that atypical antipsychotics probably reduce functioning slightly (SMD -0.21, 95% CI -0.39 to -0.03, n = 514; Analysis 3.21; Figure 45), but probably have little or no effect on cognitive function compared with placebo (SMD -0.10, 95% CI -0.19 to -0.02, n = 2698; Analysis 3.22; Figure 46). One small study that was not included in the meta-analysis also found little or no effect of atypical antipsychotics on cognitive function (MD -1.40 on MMSE; 95% CI -5.89 to 3.09, n = 38; Analysis 3.23; Paleacu 2008). Based on very-low-certainty evidence from another study, we are uncertain whether atypical antipsychotics have an effect on health-related quality of life (MD 0.95, 95% CI -4.14 to 6.04, n = 151 assessed with Alzheimer's Disease-Related Quality of Life (ADRQL), range 0 to 100; Analysis 3.24; Schneider 2006 CATIE-AD). For the time that caregivers spend providing care (mean change in hours/day) we found low-certainty evidence from one study that atypical antipsychotics may have little or no effect compared with placebo (MD 0.08, 95% CI -1.39 to 1.55, n = 151; Analysis 3.25; Schneider 2006 CATIE-AD).

Figure 45. Forest plot (3.21 Functioning (ADL))

Study or Subgroup	Atypical antipsychotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Schneider 2006 CATIE-AD	-1.1	8.8	33	0.5	8.4	16	8.8%	-0.18 [-0.78 , 0.42]
Schneider 2006 CATIE-AD	-1	7.7	31	0.5	8.4	15	8.3%	-0.19 [-0.80 , 0.43]
Schneider 2006 CATIE-AD	-6.1	8.2	40	0.5	8.4	16	8.8%	-0.79 [-1.39 , -0.19]
Streim 2008	-0.83	4.94	93	-0.22	4.52	90	37.4%	-0.13 [-0.42 , 0.16]
Tariot 2006	-0.01	3.38	86	0.47	2.24	94	36.7%	-0.17 [-0.46 , 0.12]
Total (95% CI)			**283**			**231**	**100.0%**	**-0.21 [-0.39 , -0.03]**

Heterogeneity: Chi² = 3.98, df = 4 (P = 0.41); I² = 0%
Test for overall effect: Z = 2.32 (P = 0.02)
Test for subgroup differences: Not applicable



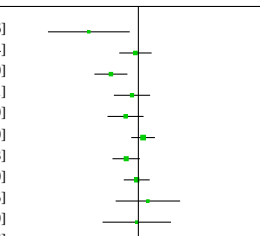


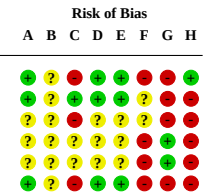
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 46. Forest plot (3.22 Cognitive function)

Study or Subgroup	Atypical antipsychotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Ballard 2005	-10.5	14.8	14	3.2	15.1	18	1.2%	-0.89 [-1.63 , -0.16]
Ballard 2018	-0.1	5.7	90	0.2	5.7	91	7.9%	-0.05 [-0.34 , 0.24]
De Deyn 2005	-0.81	2.7	94	0.53	2.7	86	7.6%	-0.49 [-0.79 , -0.20]
Deberdt 2005 F1D MC HGGU	-0.8	3.5	182	-0.4	3.4	45	6.3%	-0.11 [-0.44 , 0.21]
Deberdt 2005 F1D MC HGGU	-1.3	4	180	-0.4	3.4	46	6.4%	-0.23 [-0.56 , 0.09]
Grossberg 2020a	0.11	2.1	256	-0.07	2.1	127	14.9%	0.09 [-0.13 , 0.30]
Grossberg 2020b	-0.36	2	124	0.08	2	130	11.1%	-0.22 [-0.47 , 0.03]
Mintzer 2007	-1	3.5	299	-0.9	3.1	92	12.3%	-0.03 [-0.26 , 0.20]
Schneider 2006 CATIE-AD	-0.1	3.7	40	-0.7	2.7	16	2.0%	0.17 [-0.41 , 0.75]
Schneider 2006 CATIE-AD	-0.8	3.8	31	-0.7	2.7	15	1.8%	-0.03 [-0.64 , 0.59]
Schneider 2006 CATIE-AD	-0.8	3.2	33	-0.7	2.7	16	1.9%	-0.03 [-0.63 , 0.56]
Streim 2008	-0.77	2.99	106	-0.57	3.17	93	8.7%	-0.06 [-0.34 , 0.21]
Tariot 2006	-1.58	2.98	69	-0.9	4.42	72	6.2%	-0.18 [-0.51 , 0.15]
Zhong 2007	0	2.7	241	0	2	92	11.7%	0.00 [-0.24 , 0.24]
Total (95% CI)			**1759**			**939**	**100.0%**	**-0.10 [-0.19 , -0.02]**

Heterogeneity: Chi² = 17.99, df = 13 (P = 0.16); I² = 28%
Test for overall effect: Z = 2.49 (P = 0.01)
Test for subgroup differences: Not applicable





Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

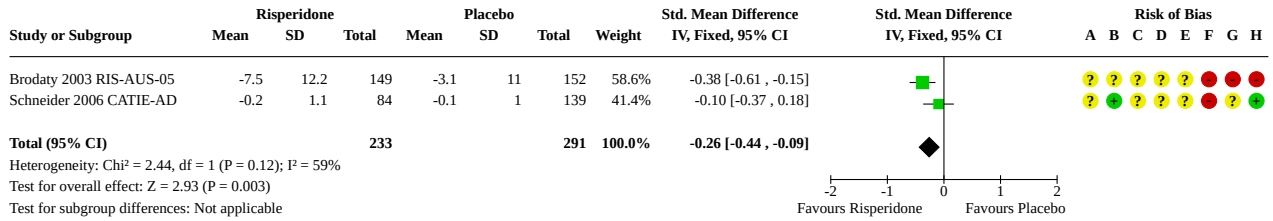
Subgroup analysis for risperidone

In the pre-planned subgroup analysis for risperidone, we found very low, low- and moderate-certainty evidence for the different outcomes.

Efficacy

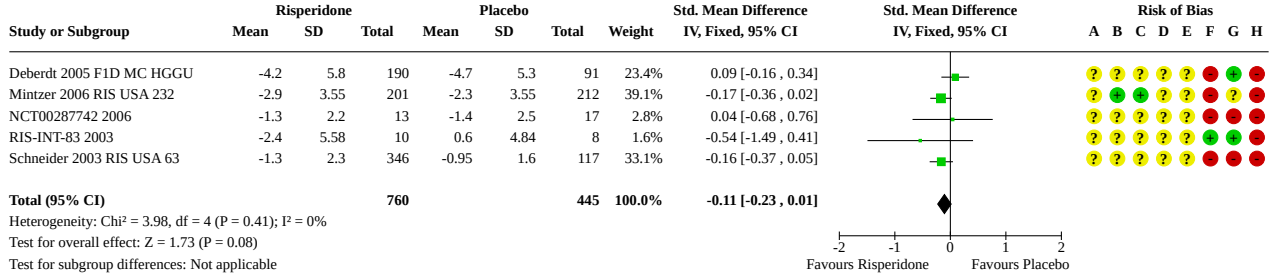
Risperidone may slightly reduce agitation compared to placebo (SMD -0.26, 95 % CI -0.44 to -0.09, n = 524; Analysis 4.1; Figure 47). Risperidone probably has little or no effect on psychosis (SMD -0.11, 95% CI -0.23 to 0.01, n = 1205; Analysis 4.2; Figure 48).

Figure 47. Forest plot (4.1 Agitation)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 48. Forest plot (4.2 Psychosis)

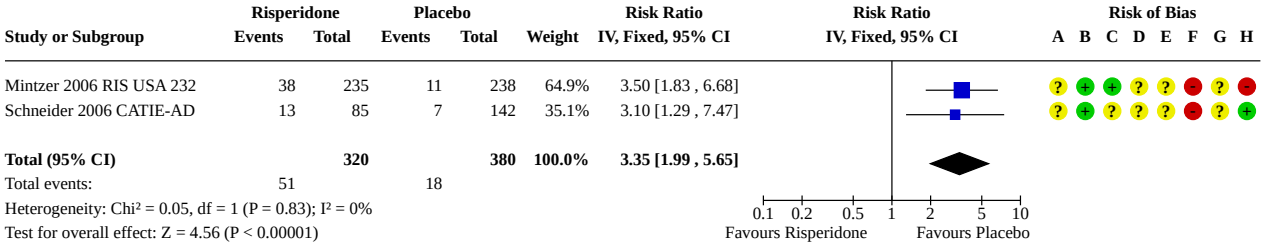


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Adverse events

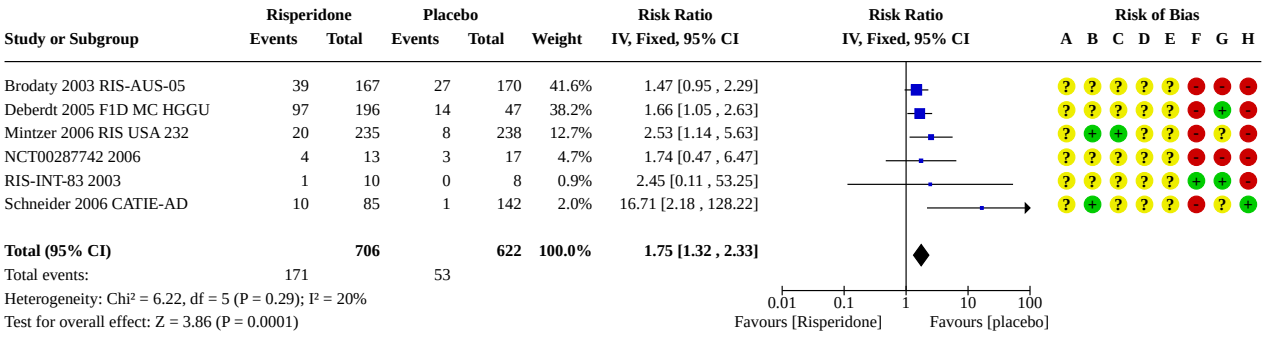
Risperidone probably increases the risk of somnolence compared with placebo (RR 3.35, 95% CI 1.99 to 5.65, n = 700; Analysis 4.3; Figure 49). Risperidone may increase extrapyramidal symptoms (RR 1.75, 95% CI 1.32 to 2.33, n = 1328; Analysis 4.4; Figure 50). Risperidone probably increase the risk of any adverse events slightly (RR 1.19, 95% CI 1.07 to 1.32, n = 700; Analysis 4.5; Figure 51). Risperidone may increase the risk of SAE slightly too (RR 1.21, 95% CI 0.88 to 1.67, n = 1085; Analysis 4.6; Figure 52) and the risk of mortality (RR 1.29, 95% CI 0.64 to 2.60, n = 1298; Analysis 4.7; Figure 53).

Figure 49. Forest plot (4.3 Somnolence)



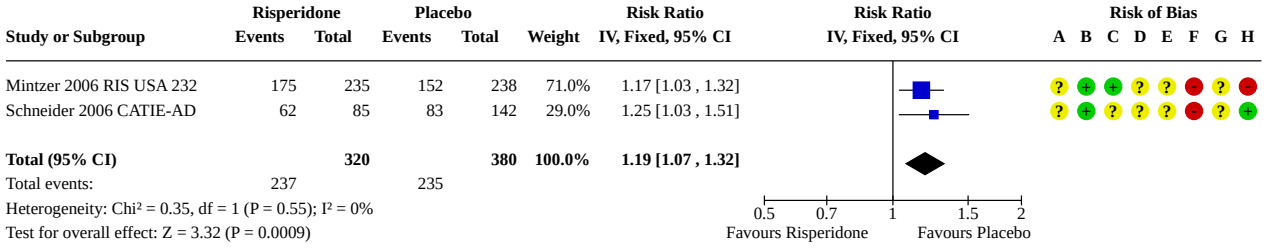
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 50. Forest plot (4.4 Extrapyramidal symptoms)



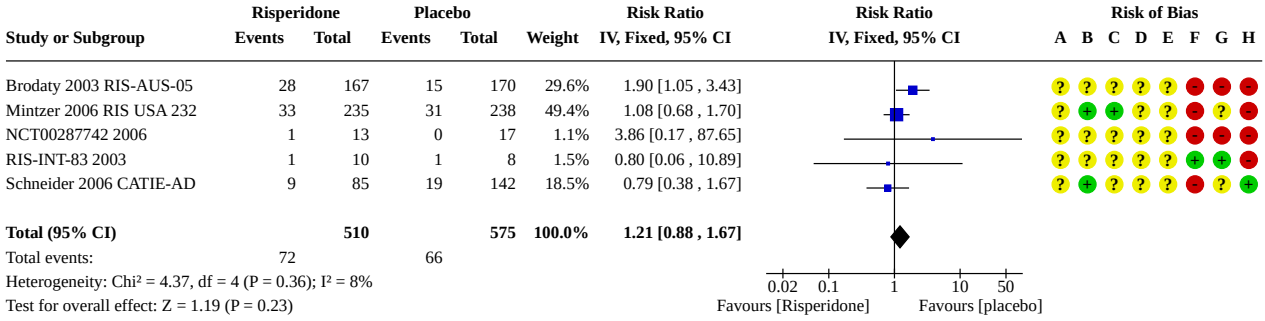
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 51. Forest plot (4.5 Any adverse event)



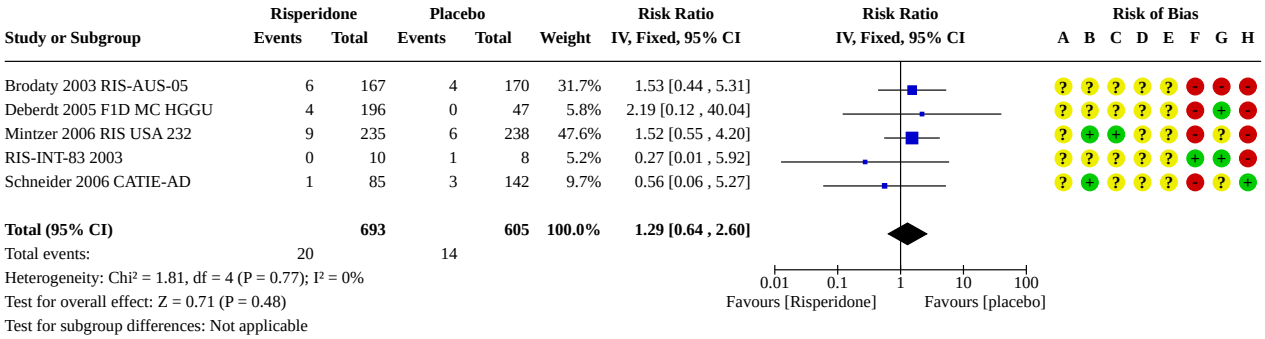
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 52. Forest plot (4.6 Any serious adverse event)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 53. Forest plot (4.7 Death)

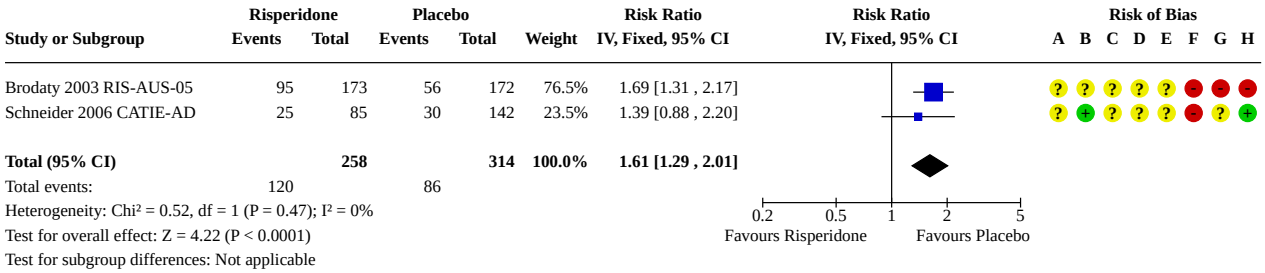


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Secondary outcomes

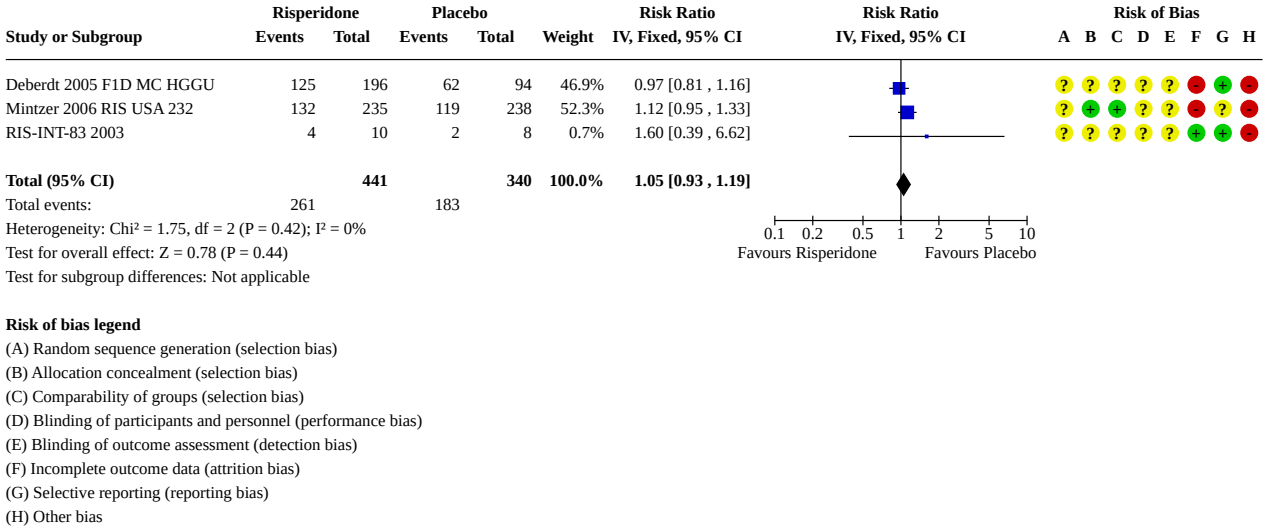
Risperidone probably increases the number of responders for agitation slightly compared with placebo (RR 1.61, 95% CI 1.29 to 2.01, n = 572; Analysis 4.8; Figure 54), but may have little or no effect on the number of responders for psychosis compared with placebo (RR 1.05, 95% CI 0.93 to 1.19, n = 781; Analysis 4.9; Figure 55).

Figure 54. Forest plot (4.8 Number of responders for agitation)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

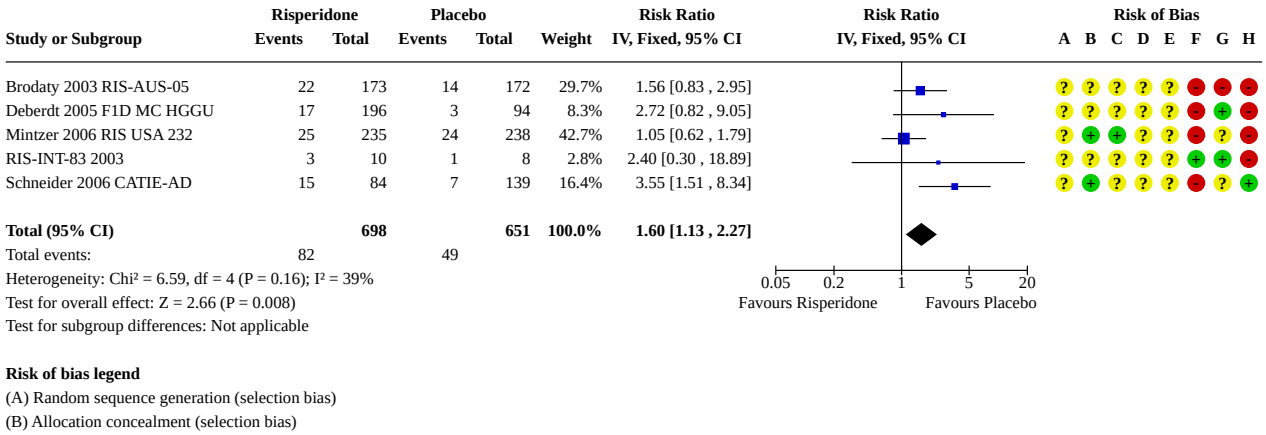
Figure 55. Forest plot (4.9 Number of responders for psychosis)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

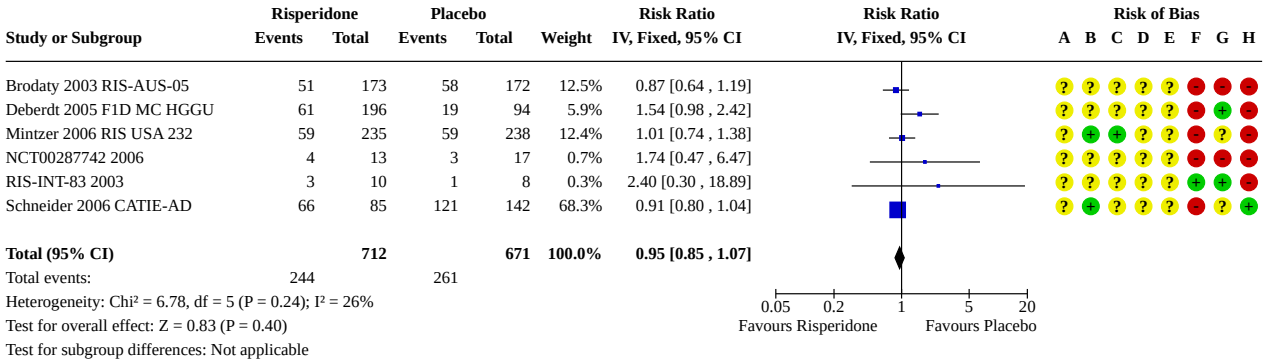
Risperidone may slightly increase discontinuation due to adverse events compared with placebo (RR 1.60, 95% CI 1.13 to 2.27, n = 1349; Analysis 4.10; Figure 56), but probably has little or no effect on discontinuation for any reason compared with placebo (RR 0.95, 95% CI 0.85 to 1.07, n = 1383; Analysis 4.11; Figure 57).

Figure 56. Forest plot (4.10 Discontinuation due to adverse events)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

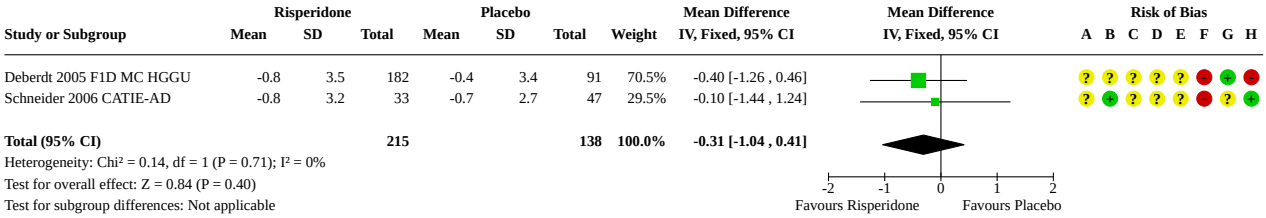
Figure 57. Forest plot (4.11 Discontinuation, any reason)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Risperidone probably has little or no effect on cognitive function compared with placebo (MD -0.31 on MMSE, 95% CI -1.04 to 0.41, n = 353; Analysis 4.12; Figure 58). Given the evidence from one study, we are uncertain whether risperidone has an effect on functioning (MD -1.60, 95% CI -5.44 to 2.24, n = 80; Analysis 4.13), on health-related quality of life (MD -2.00, 95% CI -8.12 to 4.12, assessed with ADRQL, range 0 to 100, n = 80; Analysis 4.14), or on the time that a caregiver spend on providing care (MD -0.50 hours/day, 95% CI -2.49 to 1.49, n = 80; Analysis 4.15).

Figure 58. Forest plot (4.12 Cognitive function)



Risk of bias legend
(A) Random sequence generation (selection bias)
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(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

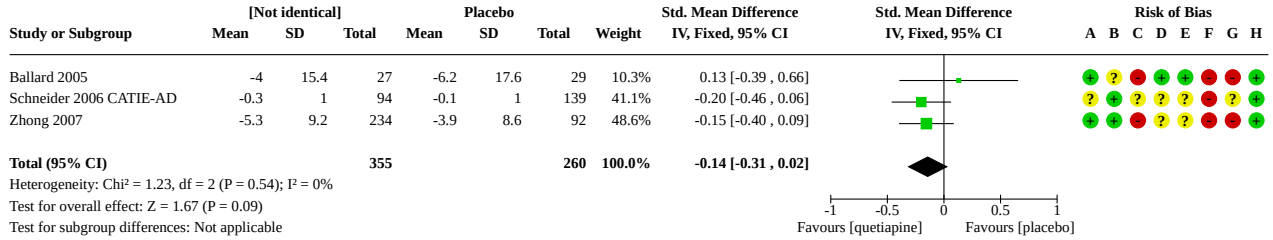
Subgroup analysis for quetiapine

We performed a post-hoc subgroup analysis for quetiapine, and we found very- low, low- and moderate-certainty evidence for the different outcomes.

Efficacy

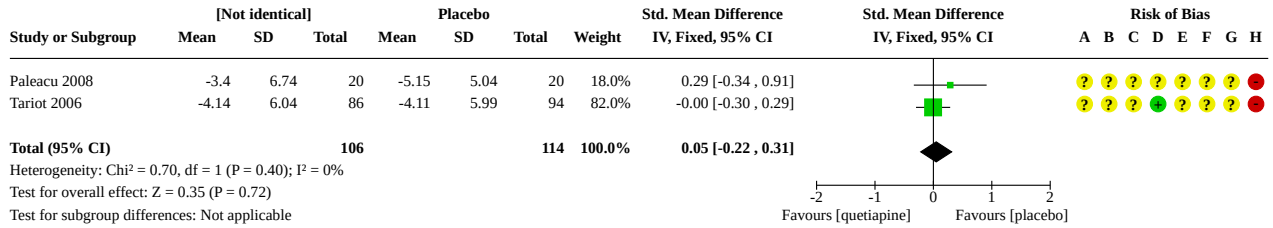
Quetiapine may have little or no effect on agitation (SMD -0.14, 95% CI -0.31 to 0.02, n = 615; Analysis 5.1; Figure 59) and probably has little or no effect on psychosis (SMD 0.05, 95% CI -0.22 to 0.31, n = 220; Analysis 5.2; Figure 60).

Figure 59. Forest plot (5.1 Agitation)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 60. Forest plot (5.2 Psychosis)

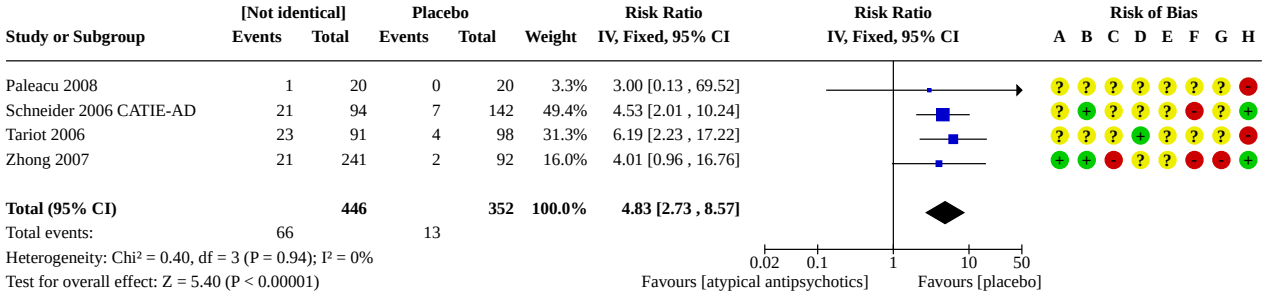


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Adverse events

Quetiapine probably increases the risk of somnolence compared with placebo (RR 4.83, 95% CI 2.73 to 8.57, n = 798; Analysis 5.3; Figure 61). Quetiapine may have little or no effect on extrapyramidal symptoms (RR 0.94, 95% CI 0.52 to 1.70, n = 799; Analysis 5.4; Figure 62). Quetiapine probably has little or no effect on any adverse events (RR 1.03, 95% CI 0.93 to 1.14, n = 609; Analysis 5.5; Figure 63), but may increase the risk of SAE slightly compared with placebo (RR 1.32, 95% CI 0.86 to 2.03, n = 799; Analysis 5.6; Figure 64). Quetiapine may also increase the risk of mortality (RR 1.48, 95% CI 0.67 to 3.31, n = 861; Analysis 5.7; Figure 65).

Figure 61. Forest plot (5.3 Somnolence)



Risk of bias legend
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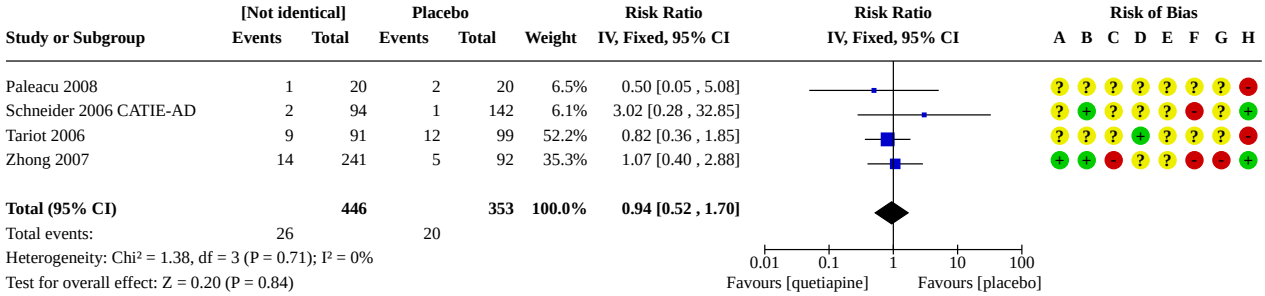
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 62. Forest plot (5.4 Extrapyramidal symptoms)



Risk of bias legend
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(B) Allocation concealment (selection bias)
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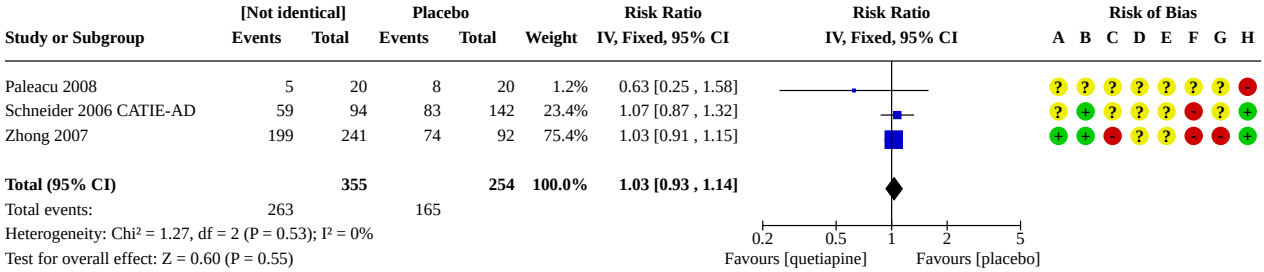
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 63. Forest plot (5.5 Any adverse event)



Risk of bias legend
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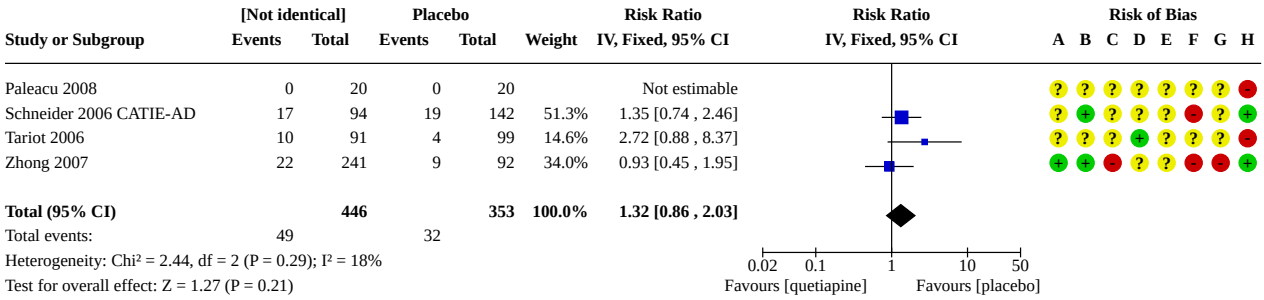
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 64. Forest plot (5.6 Any serious adverse event)



Risk of bias legend
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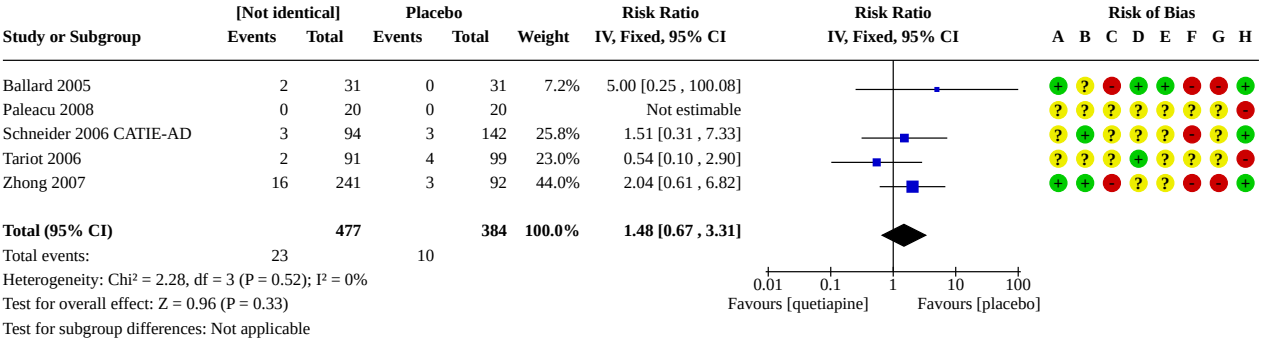
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 65. Forest plot (5.7 Death)



Risk of bias legend
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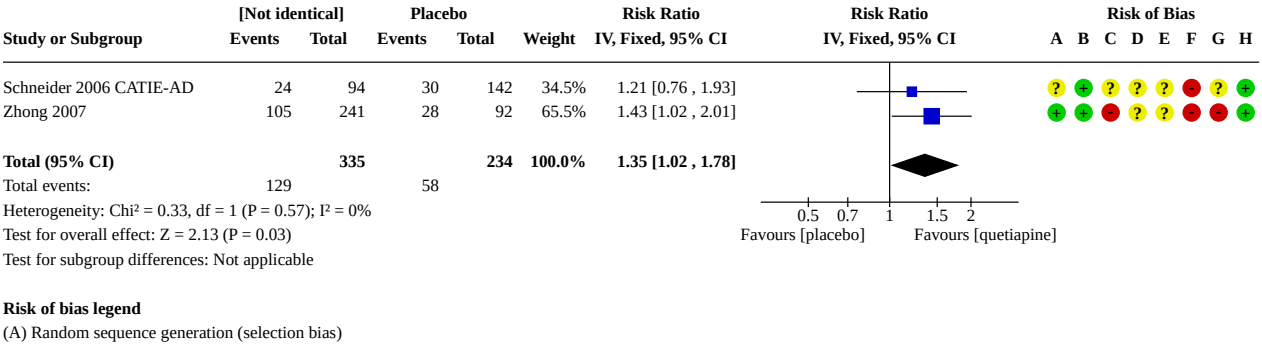
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Secondary outcomes

Quetiapine probably increases the number of responders for agitation slightly compared with placebo (RR 1.35, 95% CI 1.02 to 1.78, n = 569; Analysis 5.8; Figure 66), but may have little or no effect on the number of responders for psychosis (RR 1.03, 95% CI 0.7 to 1.36, n = 230; Analysis 5.9; Figure 67).

Figure 66. Forest plot (5.8 Number of responders for agitation)



Risk of bias legend
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(B) Allocation concealment (selection bias)
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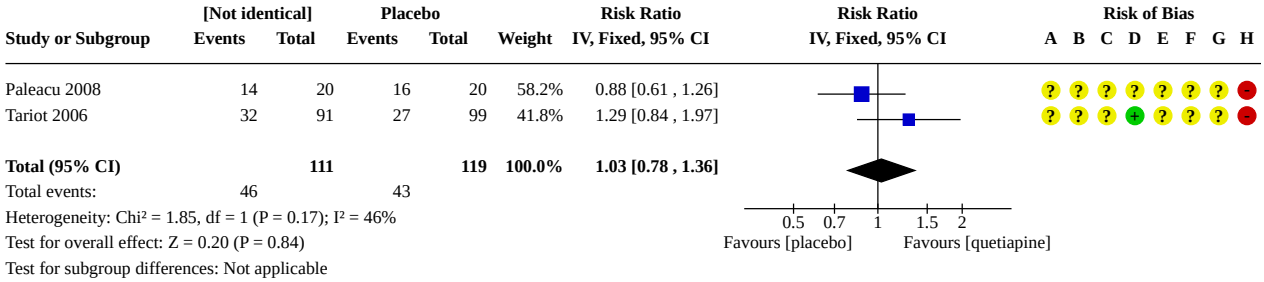
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 67. Forest plot (5.9 Number of responders for psychosis)



Risk of bias legend
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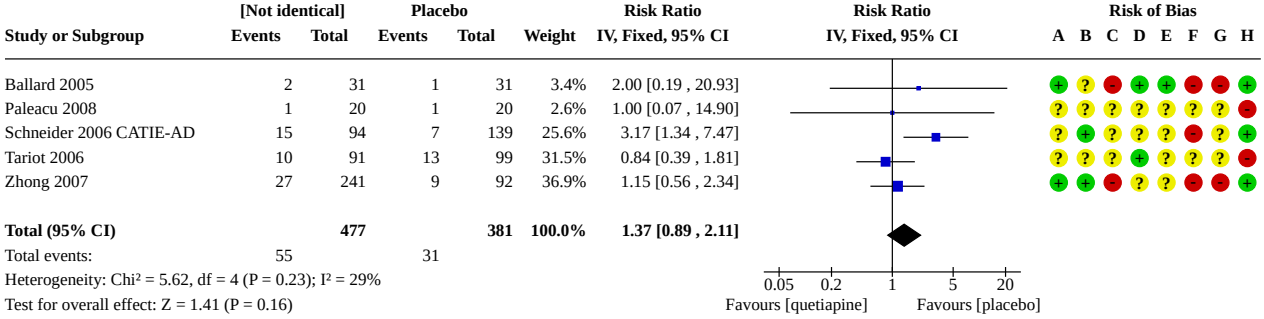
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Quetiapine may slightly increase discontinuation due to adverse events compared with placebo (RR 1.37, 95% CI 0.89 to 2.11, n = 858; Analysis 5.10; Figure 68), but probably has little or no effect on discontinuation for any reason compared with placebo (RR 0.97, 95% 0.88 to 1.08, n = 861; Analysis 5.11; Figure 69).

Figure 68. Forest plot (5.10 Discontinuation due to adverse events)



Risk of bias legend
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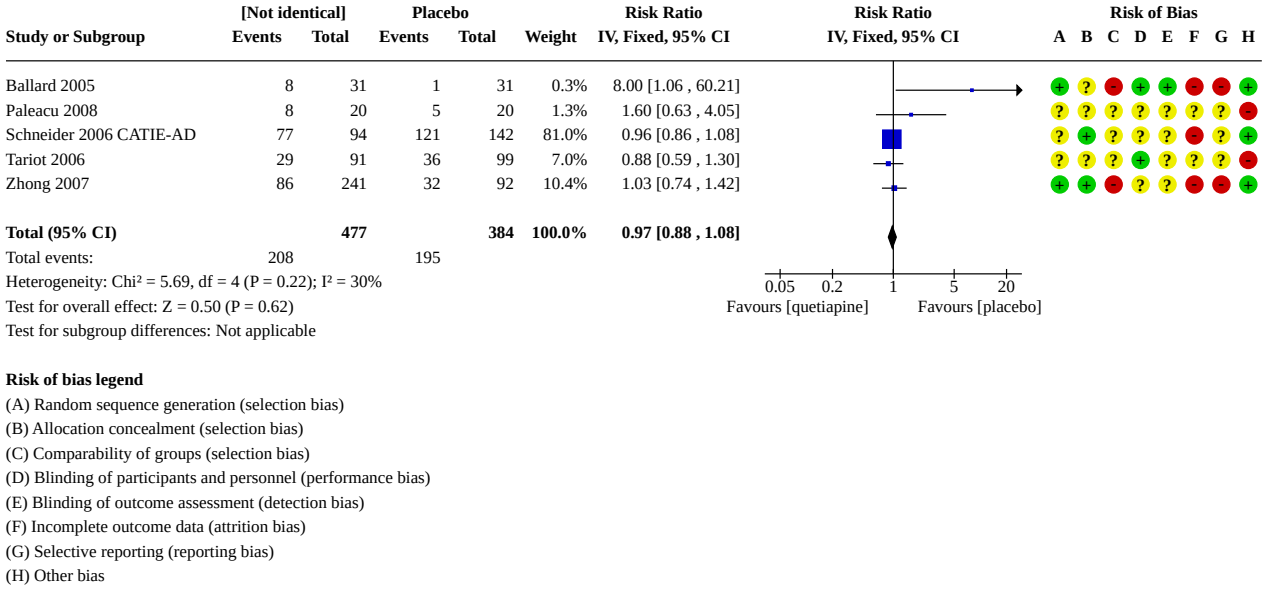
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 69. Forest plot (5.11 Discontinuation, any reason)



Risk of bias legend
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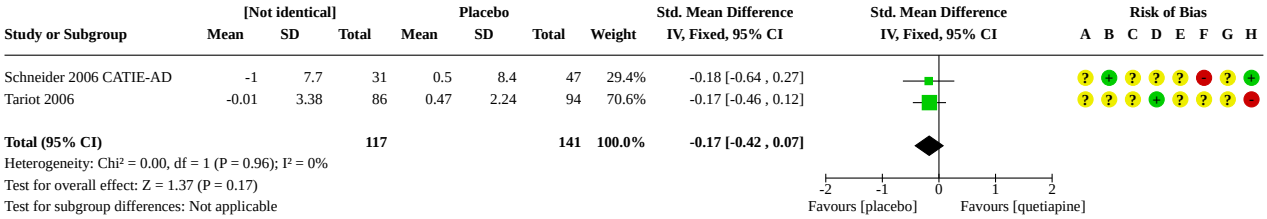
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

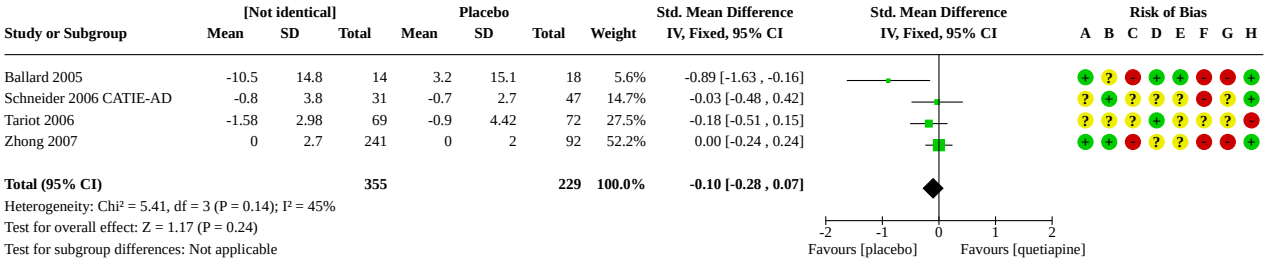
Quetiapine probably has little or no effect on functioning (SMD -0.17, 95% CI -0.42 to 0.07, n = 258; Analysis 5.12; Figure 70). Quetiapine probably has little or no effect on cognitive function compared with placebo (SMD -0.10, 95% CI -0.28 to 0.07, n = 584; Analysis 5.13; Figure 71; and results from one small study that was not included in the meta-analysis MD -1.40 on MMSE; 95% CI -5.89 to 3.09, n = 38; Analysis 5.14; Paleacu 2008). Given evidence from one study, we are uncertain whether quetiapine has an effect on health-related quality of life (MD 2.60, 95% CI -3.51 to 8.71, assessed with ADRQL, range 0 to 100, n = 78; Analysis 5.15), or on the time that a caregiver spend on providing care (MD -0.10 hours/day, 95% CI -2.01 to 1.81, n = 78; Analysis 5.16).

Figure 70. Forest plot (5.12 Functioning (ADL))



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 71. Forest plot (5.13 Cognitive function)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

DISCUSSION

In this systematic review, we included 24 randomised trials that tested the effect of one or more antipsychotics on agitation or psychosis in persons with dementia.

Summary of main results

We identified five trials that tested haloperidol and one that tested thiothixene. The pooled results indicate that typical antipsychotics might improve psychosis slightly compared with placebo, while the effect on agitation is uncertain. These drugs probably increase the risk of somnolence and extrapyramidal symptoms. There was no evidence regarding the risk of at least one adverse event, and a slight increase in the risk of a serious adverse event (SAE) or death. The effect estimates for haloperidol were in line with those of the drug class, although haloperidol may have a small effect on agitation.

In addition, we identified 20 trials that tested one of following atypical antipsychotics: aripiprazole, brexpiprazol, olanzapine, pimavanserin, quetiapine, risperidone, and tiapride. Atypical antipsychotics had a negligible effect on psychosis and a slight effect on agitation. These drugs probably increase the risk of somnolence and extrapyramidal symptoms. They probably increase the risk of any adverse event. The risk of a serious adverse event and the risk of death are slightly increased. The findings from seven trials for risperidone were in line with those for the drug class.

Overall completeness and applicability of evidence

There is low certainty about the effect of typical antipsychotics on psychosis in dementia, due to a small number of studies (only two studies). The number of studies and the number of participants included in the studies about the effect of typical antipsychotics on agitation were too small to provide a precise estimate (four studies). These drugs were developed when trials were not performed and published as often as nowadays. It is unlikely that new trials with haloperidol will be performed soon. The lack of evidence is unfortunate because the current estimates with high upper limit of the confidence intervals does not preclude the possibility that typical antipsychotics have a larger/more substantial effect on psychosis and moderate effect on agitation. Moreover, old studies used high doses of haloperidol that may have negatively affected the balance between beneficial and harmful effects. Compared to studies on atypical antipsychotics, studies on typical antipsychotics often lack elaborate documentation of adverse events. This is most probably due to the fact that most studies are fairly old and were conducted when reporting of adverse events was less regulated by marketing authorities.

In contrast, there was a large number of studies that tested the effect of atypical antipsychotics on psychosis and agitation in dementia (12 and eight studies, respectively), and most studies were relatively large. As a result, the effect estimates are very precise and give certainty that these drugs only have a small effect on agitation and little or no effect on psychosis. With mean SMDs of -0.21 and -0.11 for agitation and psychosis, respectively, one could seriously question the clinical relevance, as SMDs of 0.20 are defined by Cohen (Cohen 1988; Cohen 1992) as so small that they are not visible to the naked eye.

The negative results of this review for antipsychotics in general and more specific for haloperidol, risperidon, and quetiapine seem to contradict the widespread use of antipsychotics. There may be a number of explanations. First, patients treated with antipsychotics in daily practice may have more severe symptoms than patients enrolled in the trials in this review. In one trial among patients with aggression, i.e. severe agitation, the effect of risperidone was somewhat greater (SMD -0.38: -0.61 to -0.15) (Brodaty 2003 RIS-AUS-05) than that on agitation in the other six trials (SMD -0.18; -0.28 to -0.08). In these six trials, the severity of agitation at baseline varied. In the two trials among populations with the highest baseline agitation (given the range of the scale used), tiapride showed a somewhat greater effect as well (SMD -0.39: -0.66 to -0.11), but quetiapine did not (SMD -0.15; -0.40 to 0.09) (Allain 2000; Zhong 2007).

Secondly, hospitalised and institutionalised patients with severe and dangerous symptoms may have delirium, whether or not superimposed on dementia. Delirium is often missed (Wahid 2004), and most of the trials in our review did not exclude patients with delirium explicitly. As efficacy of antipsychotics is very low in delirium (Neufeld 2019), missed deliriums may explain a part of the negative results.

Thirdly, the relationship of dosage with efficacy and AEs is also relevant. Studies of typical antipsychotics allowed doctors to prescribe relatively high doses if deemed necessary. Hence, the doses cannot explain that our review found only a slight effect on agitation and psychosis. On the other hand, studies about atypical antipsychotics sometimes used relatively low maximum (fixed or flexible) doses. This might explain the lack of efficacy, although a previous review did not show dose-response effects (Ballard 2006). The differences in dosing between the drug classes may explain the apparent difference in risk of AEs between them.

Quality of the evidence

A limitation of the evidence is the patients enrolled in the identified trials were not representative of all patients for which antipsychotics are considered. First, the studies did not include many patients with vascular dementia. In addition, it is unclear whether the studies recruited patients who had not responded to non-pharmacological measures. Such measures are recommended by many guidelines as the treatment of first choice. Finally, the use of strict exclusion criteria in most trials may have decreased the representativeness of the study populations. For instance, some studies excluded patients with terminal disease.

Another limitation is that none of the included studies scored low risk of bias on all items. Randomisation procedures were frequently described poorly with just five studies reporting the method of sequence generation and three studies the method of concealment allocation. Despite randomisation, five studies showed clinically relevant baseline differences between groups that might have biased the results of the studies. Blinding procedures were not described well either. Just seven studies reported the explicit blinding of patients and personnel and/or outcome assessors. In the other studies, this was implied by the use of placebo. At least half of the studies showed a high risk of bias due to incomplete data, selective reporting, and commercial funding. Given the often unclear or high risk of bias, it cannot be ruled out that the reported effects of the drugs on agitation and psychosis were overestimated, and the risks of adverse events underestimated, and so were the pooled estimates that we present.

Although uncommon in Cochrane Reviews, we assessed the use of a run-in period, because it can affect the validity of the study results for the population of interest (as defined in the PICO). A run-in period takes place between screening and randomisation. Prohibited drugs or investigated drugs already in use can be washed out, a placebo can be given to identify placebo-responders, and sometimes the investigated drug is given. Participants are sometimes blinded, but clinical assessors and investigators are usually not blinded. Hence, participants that respond favourably to wash-out or placebo or unfavourably to introduction of an active drug can be deselected at the end of a run-in period. Use of a run-in period in trials about antipsychotics and antidepressants has been associated with overestimated treatment effects, and especially underestimated risks of adverse events (Bridge 2007; Hulshof 2020; Khan 1989). Most of the studies included in our review used a run-in period, and so bias may have been introduced.

Potential biases in the review process

We found three studies that have not been published in a journal. Therefore, these studies lacked external peer review as a quality criterion. Although we included many outcomes and did not correct for multiple testing, we do not think that this introduced bias because the conclusions of our review are mostly negative for beneficial effects, and positive for harmful effects.

Agreements and disagreements with other studies or reviews

One prior review assessed the effect of haloperidol on agitation in dementia (Lonergan 2002). The search was updated in 2010 and yielded no new evidence. It reported a negligible effect on agitation (SMD -0.12; 95% CI -0.31 to 0.08), and a small effect on aggression (SMD -0.31; 95% CI-0.49 to -0.13). This review included two trials among patients with diverse neuropsychiatric symptoms (DeDeyn 1999; Devanand 1998), which we excluded. The inclusion of these two trials might have diluted the effect of conventional antipsychotics on agitation. We found no published reviews of conventional antipsychotics on psychosis outcomes to compare to our results.

Another review of trials has addressed the mortality risk of typical antipsychotics in older patients (Hulshof 2015). It included 14 trials among patients with dementia (independent of type of neuropsychiatric symptoms) and three trials among patients with delirium. No increased risk of mortality was found: RR 1.07 (95% CI 0.54 to 2.13) and RD 0.1% (95% CI: -1.0% to 1.2%). The higher number of included trials could explain the difference with our results based on three trials: a slightly increased but imprecisely estimated risk of mortality (RR 1.46, 95% CI 0.54 to 4.00).

Two reviews studied the effect of atypical antipsychotics on behavioural symptoms in patients with dementia (Ballard 2006; Ma 2014). These reviews differentiated between individual antipsychotics and doses, which complicates direct comparison with our results. Nevertheless, those reviews reported modest effects on aggression (with or without other forms of agitation) and on psychosis. Around half of the trials pooled in those reviews had been conducted in patients with diverse neuropsychiatric symptoms, which we excluded, and that approach might have led to overestimated efficacy (Smeets 2018). A recent network meta-analysis found that there was no single most effective and safe atypical drug (Yunusa 2019).

Some reviews of trials about atypical antipsychotics addressed particular serious harms. Two reviews have reported an identical increased risk of mortality with data from 15 trials (OR 1.54; 95% CI 1.06-2.23) (Schneider 2005; Yeh 2019). According to these results, one in 100 patients treated with an atypical drug dies due to the drug use. We used data from 17 trials, but the estimate was less precise (RR 1.36; 95% CI 0.90-2.05), probably because we excluded a number of older and larger trials most of which showed an increased risk. These trials did not enrol patients with agitation or psychosis specifically. For the outcome mortality, it seems justifiable to include these trials, and the prior reviews provided valid evidence (Schneider 2005; Yeh 2019).

In response to the 2005 review about the mortality risk of atypical antipsychotics (Schneider 2005), many observational studies about the mortality risk of typical antipsychotics were performed. The studies showed that use of typical antipsychotics and especially haloperidol was related to an even higher increased risk of death (Luijendijk 2016). In these studies, sicker and older patients received typical antipsychotics more often than atypical antipsychotics. The risk of dying was especially high in the first

month of use, and when haloperidol was administered per injection or in high doses. However, none of the observational studies, all based on retrospective analyses of administrative data, had been adjusted for terminal illness (Luijendijk 2016). This could have resulted in an overestimated risk of mortality for typical antipsychotics versus atypical antipsychotics or no antipsychotic use.

AUTHORS' CONCLUSIONS

Implications for practice

There is some evidence that typical antipsychotics may decrease psychosis somewhat and that haloperidol may decrease agitation somewhat in patients with dementia. The increased risk of somnolence and other possible adverse events, should urge doctors to be reluctant to prescribe these drugs. Atypical antipsychotics are not effective for psychosis in dementia, and should not be used for this indication. The use of these atypical antipsychotic drugs should be kept to a minimum for agitation in dementia as well: these drugs may decrease agitation somewhat, but they also increase the risk of somnolence, extrapyramidal symptoms (EPS), any adverse events and serious adverse events.

Overall, the evidence shows that most of the decrease in agitation and psychosis seen in the drug groups can be attributed to a favourable natural course of these symptoms, as observed in the placebo groups. This finding explains the apparent effectiveness of the drugs seen in daily practice.

Due to the unfavourable balance between beneficial effects and risks of adverse events for both typical and atypical antipsychotics, it is advised to look at alternative therapeutic options. Treatment of the underlying possible psychosocial and somatic causes of agitation or psychosis should always be considered (Leng 2020; Livingston 2014a; Livingston 2014b). If antipsychotics are considered for sedation in patients with severe and dangerous symptoms nonetheless, and somnolence is the intended outcome, this should be discussed openly with the patient and legal representative.

Implications for research

The precise effect of haloperidol on psychosis and agitation in dementia is still unclear, and should be studied in sufficiently large well-designed trials. This also applies to some other frequently used typical antipsychotics such as pipamperon and zuclopentixol, and perhaps the relatively new atypical antipsychotic pimavanserin. Future studies should be carefully designed to address the interaction with co-medications and non-pharmacological interventions.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Allain 2000

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Study duration:** 3 weeks **Rescue medication:** not allowed; quote:"All psychotropics drug were excluded except benzodiazepines prescribed as hypnotics, zopiclone and zolpidem and antidepressants prescribed at low doses (less than a third of the usual dose for major depression). Such drugs could be continued during the study under the condition that doses remained unchanged for a month and during the period of the study."
Participants	**Number randomised:** 306 (101 haloperidol, 102 tiapride, 103 placebo) **Mean age:** 79.6 years

Allain 2000 *(Continued)*

	Sex (female): 64% **Type of dementia:** Alzheimer's disease, vascular dementia and mixed type dementia. **Severity of dementia:** mild-moderate **Indication:** Agitation (baseline MOSES: 20.2) **Setting:** nursing home or otherwise hospitalised patients **Country:** France, the Netherlands, Germany, Latvia and Portugal
Interventions	**Intervention characteristics** Haloperidol • *dosage*: 2 mg/day (1 mg twice a day). Haloperidol dose could be progressively increased from the sixth hour after the first drug intake to day 3 according to the patient's status and treatment acceptability. Maximum accepted dose was 6 mg/day haloperidol (6 capsules a day). From day 4 up to the end of the treatment (day 21), the recommended dose was 4 mg/day for haloperidol. Tiapride • *dosage*: 100 mg/day (50 mg twice a day). Tiapride dose could be progressively increased from the sixth hour after the first drug intake to day 3 according to the patient's status and treatment acceptability. Maximum accepted dose was 300 mg/day tiapride. From day 4 up to the end of the treatment (day 21), the recommended dose was 200 mg/day for tiapride. Placebo The active drug-treated patients received 175.45 ± 44.70 mg/day of tiapride or 3.53 ± 1.05 mg/day of haloperidol. Seven tiapride-treated patients (7%) and 13 haloperidol-treated patients (13%) received the maximum dose planned in the protocol (300 mg/day and 6 mg/day, respectively). Most of the patients received the recommended dose: 68 patients (67%) in the tiapride group (200 mg/day) and 58 patients (57%) in the haloperidol group (4 mg/day).
Outcomes	Agitation: Multidimensional Observation Scale for the Elderly Subjects (MOSES) Number of responders for agitation Extrapyramidal symptoms: "Udvalg for Kliniske Undersøgelser" (Task force for clinical investigations) (UKU scale) Somnolence: "Udvalg for Kliniske Undersøgelser" (Task force for clinical investigations) (UKU scale) Death Discontinuation due to adverse events Discontinuation (any reason)
Identification	
Notes	**Sponsorship source:** Unclear, but Laboratoires Synthélabo involved

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomly allocated to tiapride 100 mg/day (50 mg twice a day), haloperidol 2 mg/day (1 mg twice a day) or placebo.

Allain 2000 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not mentioned in study
Comparability of groups (selection bias)	High risk	There were group differences in age, sex, and agitation at baseline, which were not adjusted for. Baseline extrapyramidal symptoms and other UKU adverse events were not reported. Mean ages were, respectively, for the placebo, tiapride and haloperidol groups 78.6±7.3 years; 80.3±7.6 years; 79.9±7.9 years and sex distributions were 71 (69%) female and 32 (31%) male patients; 63 (62%) female and 39 (38%) male patients and 63 (62%) female and 38 (38%) male patients. MOSES irritability/aggressiveness subscores were: Placebo 20.28±2.85; tiapride 19.90±2.92; haloperidol 20.52±3.27.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double blind but no further information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double blind but no further information
Incomplete outcome data (attrition bias) All outcomes	High risk	Forty-seven patients (15%) dropped out from the study, ten in the tiapride group (adverse event five; lack of efficacy one; uncooperativeness three; recovery one), 21 in the haloperidol group (adverse event 17; lack of efficacy one; uncooperativeness two; concomitant medication one) and 16 in the placebo group (adverse event six; lack of efficacy eight; uncooperativeness two).
Selective reporting (reporting bias)	Low risk	All outcomes described in methods section are reported in the results section.
Other bias	Low risk	No run-in period.

Auchus 1997

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Study duration:** 6 weeks **Rescue medication:** no information provided
Participants	**Number randomised:** 12 (6 haloperidol 6 placebo) **Mean age:** 75.6 years **Sex (female):** 66% **Type of dementia:** Alzheimer's disease **Severity of dementia:** moderate **Indication:** Agitation (baseline CMAI 35.9) **Setting:** community-dwelling

Auchus 1997 *(Continued)*

	Country: USA
Interventions	**Intervention characteristics** Haloperidol • *dosage*: fixed 3 mg daily Placebo
Outcomes	Agitation: Cohen-Mansfield Agitation Inventory (CMAI) Death Discontinuation due to adverse events Discontinuation (any reason) Carer burden or carer quality of life: Caregiver Strain Index (CSI)
Identification	
Notes	**Sponsorship source:** Grant from Emory University Research Council (226-93) and Grant Alzheimer's Disease Core Center from the National Institute on Aging (P3OAG1O13O)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Comparability of groups (selection bias)	Unclear risk	Baseline characteristics are not presented per group for all randomized. Baseline outcome score differ greatly but direction of bias unclear. Unclear whether the difference has been adjusted for.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double blind", but it is not described if haloperidol and placebo tablets did look the same and no other actions to secure blinding of personnel and participants are described. Patients probably blinded but unclear if blinding of personnel was performed.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	High risk	High rate of drop-out: 2/6 haloperidol (33%) and 1/6 (17%) placebo treated patients drop-out.
Selective reporting (reporting bias)	Low risk	All outcomes reported in methods section are reported in the results section.
Other bias	High risk	Subjects in each group completed a 2-week washout period during which any current psychotropic medications were carefully withdrawn.

Ballard 2005

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Study duration:** 6 weeks **Rescue medication:** not mentioned
Participants	**Number randomised:** 62; 31 quetiapine 31 placebo **Mean age:** 83.6 years **Sex (female):** 82.3% **Type of dementia:** Alzheimer's disease **Severity of dementia:** severe **Indication:** = agitation (baseline CMAI 58.8) **Setting:** care facilities **Country:** UK
Interventions	**Intervention characteristics** Quetiapine • *dose*: 25 mg to 50 mg twice daily Placebo
Outcomes	Agitation: Cohen-Mansfield Agitation Inventory (CMAI) Death Discontinuation due to adverse events Discontinuation (any reason) Cognitive function: Severe Impairment Battery (SIB)
Identification	
Notes	**Sponsorship source:** general donations to CB's research programme and profits from previously completed commercially funded CT (by Astra Zeneca and Novartis), with additional support from the Alzheimer's Research Trust

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The allocations were computer generated with block randomisation (block sizes of three and six)."
Allocation concealment (selection bias)	Unclear risk	It is reported that: "The study statistician randomly assigned patients." "The randomising clinician faxed a form to the statistician, who communicated allocation to the pharmacy, ensuring concealment."The procedure is not clearly

Ballard 2005 *(Continued)*

		described because it first suggests that the statistician performs the randomisation, and later that the clinician randomises (which would be wrong).
Comparability of groups (selection bias)	High risk	Clear differences between groups at baseline, f.i. in % women (87.1 versus 77.4) and 5 with EPS (12.9 versus 6.5), and mean CMAI (59.1 versus 56.4) for quetiapine versus placebo. Only the latter was adjusted for in the analyses.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Design: Randomised double blind (clinician, patient, outcomes assessor) placebo controlled trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Assessors were blind to treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-out was: 8/31 in quetiapine group and 1/31 in placebo group. Modified ITT analysis (those who dropped out not included, and LOCF)
Selective reporting (reporting bias)	High risk	Few outcomes compared to what is common in these trials. ECG and full blood count not reported. Adverse events/ side effects missing in general.
Other bias	Low risk	No run-in period.

Ballard 2018

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Study duration:** 12 weeks **Rescue medication:** was allowed.
Participants	**Number randomised:** 181 (90 pimavanserin 91 placebo) **Mean age:** 85.9 years **Sex (female):** 80.9% **Type of dementia:** Alzheimer's disease **Severity of dementia: s**evere **Indication:** Psychosis (baseline Psychosis NPI-NH: 9.75) **Setting:** nursing homes **Country:** UK
Interventions	**Intervention characteristics** Pimavanserin • *dosage*: 2 x 17 mg tablets daily

Ballard 2018 *(Continued)*

	Placebo
Outcomes	Psychosis: Neuropsychiatric Inventory - Nursing Home Version (NPI-NH) Somnolence (**Notes**: reported only on clinicaltrials.gov) Death Any adverse event Any serious adverse event Discontinuation (any reason) Discontinuation due to adverse events Cognitive function: Mini-Mental State Examination (MMSE)
Identification	
Notes	**Sponsorship source:** ACADIA Pharmaceuticals Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"An independent statistician without any other involvement in the study generated the randomisation sequence with use of permuted block sizes of four, which was implemented using Trident software (version 1.2)."
Allocation concealment (selection bias)	Unclear risk	No information reported.
Comparability of groups (selection bias)	Low risk	Small baseline differences, which seem to be in favour of placebo.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"We masked participants, caregivers, the study sponsor, and study personnel at the clinic site to treatment assignment. We achieved masking of active treatment and placebo by using identical-appearing tablets."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	According to clinicaltrials.gov: Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	High risk	A lot of analyses with subscores and various weeks of follow-up. Primary outcome was reduction of psychotic symptoms at 12 weeks according to protocol in clinicaltrials.gov. In article, the primary outcome was reduction of psychotic symptoms at 6 weeks. There was not difference in symptoms at 12 weeks.
Other bias	High risk	This period also allowed for washout in participants taking antipsychotic medication. During screening, participants entered a 3-week period in which BPST was used to ensure that only individuals who required a pharmacological treat-

Ballard 2018 *(Continued)*

	ment progressed to randomisation in the study, to minimise subsequent placebo response.

Brodaty 2003 RIS-AUS-05

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Study duration:** 12 weeks **Rescue medication:** anticholinergic medication was allowed to treat EPS only if a reduction in trial medication dose was not effective. Treatment of urinary incontinence with low-dose tricyclic antidepressants or anticholinergic medication was allowed to continue. Low-dose oxazepam was permitted to treat agitation, provided that usage did not exceed 4 days in a 7-day period. Short-acting sedative/hypnotic agents prescribed chronically for insomnia at baseline were permitted if the clinician judged that they could not be discontinued. Under exceptional circumstances, initiation of night sedation for insomnia was allowed using a short-acting benzodiazepine (preferably oxazepam at the lowest effective dose). Narcotic analgesics were permitted, provided that the dosage had been stable for at least 3 months and that they were not prescribed to control agitation or aggression.
Participants	**Number randomised:** 345 (173 risperidone 172 placebo) **Mean age:** 83.5 years **Sex (female):** 84.9% **Type of dementia:** Alzheimer's disease, vascular dementia, mixed type dementia **Severity of dementia:** severe **Indication:** aggression (is subtype of agitation); subgroup analysis in patients with psychosis (additionally) was reported (Baseline CMAI total aggression: 33.5) **Setting:** nursing home **Country:** Australia and New Zealand
Interventions	**Intervention characteristics** Risperidone • *dose*: 0.25mg to 1 mg twice daily Placebo Mean risperidone dosage was 1.03 ± 0.61 mg/day.
Outcomes	Agitation: Cohen-Mansfield Agitation Inventory (CMAI) total aggression subscale Number of responders for agitation Extrapyramidal symptoms Somnolence Death Any adverse event

Brodaty 2003 RIS-AUS-05 *(Continued)*

	Any serious adverse event Discontinuation (any reason) Discontinuation due to adverse events
Identification	
Notes	**Sponsorship source:** Janssen-Cilag Australia and Johnson & Johnson, L.L.C.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Comparability of groups (selection bias)	Unclear risk	No baseline characteristics for all randomized per group are shown (n=156 instead of 172 for placebo; n=153 instead of 173 for risperidone). Small differences in the reported baseline characteristics, e.g. more aggression and NPS in risperidone group. Most are not adjusted for in the analyses. Unclear how the differences could have affected the estimated effects.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	High risk	Agitation: In the article, 152 for placebo and 149 for risperidone were reported instead of 170 and 167 who received at least once the study medication.
Selective reporting (reporting bias)	High risk	Results on all reported measures are reported. However, effect on MMSE and FAST not reported in numbers. Post-hoc subgroup analysis with respect to effect on psychosis.One site excluded. Only adjusted least square means are reported. Crude means are only mentioned in a figure without providing exact numbers. No CI or SD or SE are reported for the change from baseline. Only difference of LS between placebo and risperidone.
Other bias	High risk	The double-blind treatment period was preceded by a maximum 7-day, single-blind washout period, during which patients took 0.5 mL of placebo oral solution each evening while existing psychotropic medication was discontinued.

Deberdt 2005 F1D MC HGGU

Study characteristics

Methods	**Study design:** randomised controlled trial

Deberdt 2005 F1D MC HGGU *(Continued)*

	Study grouping: parallel group **Study duration:** 10 weeks **Rescue medication:** allowed for EPS as well as benzodiazepines.
Participants	**Number randomised:** 494 (204 olanzapine, 196 risperidone, 94 placebo) **Mean age:** 78.3 years **Sex (female):** 65.6% **Type of dementia:** Alzheimer's disease, vascular dementia, mixed type dementia **Severity of dementia:** moderate **Indication:** Psychosis (Baseline Psychosis NPI: 11.2) **Setting:** outpatients or nursing homes or assisted-living centres **Country:** USA
Interventions	**Intervention characteristics** Olanzapine • *dosage*: 2.5 mg to 10 mg/day Risperidone • *dosage*: 0.5 to 2.0 mg/day Placebo Half the patients assigned to olanzapine began treatment with 2.5 mg/day, which was increased to 5 mg/day at the end of the first week; the other half began treatment with 5 mg/day. Those assigned to risperidone began with 0.5 mg/day, which was increased to 1 mg/day at the end of the first week. The mean daily olanzapine dose was 5.2 mg and that for risperidone was 1.0 mg.
Outcomes	Psychosis: Neuropsychiatric Inventory–Nursing Home version (NPI-NH) psychosis score Number of responders for psychosis Extrapyramidal symptoms Somnolence Death Discontinuation (any reason) Discontinuation due to adverse events Cognitive function: Mini-Mental State Examination (MMSE)
Identification	
Notes	**Sponsorship source:** Lilly Research Laboratories, Indianapolis, IN (WGD, PDF, CAY, DPH, DLL, EKD, AB), the Geriatric Research, Education and Clinical Center Program, Veterans Affairs Medical Center; Minneapolis, MN (MWD), Agewell Ltd., Indianapolis, IN (SAR), and Eli Lilly G.m.b.H., Vienna, Austria (MD).

Risk of bias

Bias	Authors' judgement	Support for judgement

Deberdt 2005 F1D MC HGGU *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Comparability of groups (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was high (42%). Analyses not with all randomized. LOCF for missing data.
Selective reporting (reporting bias)	Low risk	"Any adverse events" and "serious adverse events" not reported, but reported measurement were all reported. Negative trial.
Other bias	High risk	"After a 3- to 14-day placebo/washout period (...)"

De Deyn 2004 F1D MC HGIV

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Study duration:** 10 weeks **Rescue medication:** allowed
Participants	**Number randomised:** 652 (520 olanzapine129 placebo) **Mean age:** 76.6 years **Sex (female):** 75% **Type of dementia:** Alzheimer's disease **Severity of dementia:** mild-severe **Indication:** Psychosis (baseline Psychosis NPI-NH: 9.7) **Setting:** long-term nursing homes or continuing-care hospitals **Country:** Europe, Australia, Israel, Lebanon, and South Africa
Interventions	**Intervention characteristics** Olanzapine

De Deyn 2004 F1D MC HGIV *(Continued)*

	• *dosage*: fixed 1.0, 2.5, 5.0, or 7.5 mg per day Placebo Patients randomly assigned to receive olanzapine 1.0mg or olanzapine 2.5mg were respectively given a single 1.0 mg or 2.5 mg capsule of olanzapine daily (at bedtime) throughout the study period. Patients assigned to receive olanzapine 5.0 mg or olanzapine 7.5 mg began therapy on 2.5 mg/day for the first week and were titrated to their final dose by 2.5 mg/week increments. Patients unable to tolerate the assigned olanzapine or placebo dose were discontinued from the study.
Outcomes	Psychosis: Neuropsychiatric Inventory–Nursing Home version (NPI-NH) Death Any serious adverse event Discontinuation (any reason) Discontinuation due to adverse events
Identification	
Notes	**Sponsorship source:** Eli Lilly and Company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Comparability of groups (selection bias)	High risk	Baseline characteristics were not reported per group and not for all randomized in the main results article (NPI). A limited set of characteristics (not the primary outcome) was reported in a clinical study report and showed clear differences in f.i. sex and smaller differences in other characteristics. Only baseline scores for outcomes were adjusted for.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	High risk	Total number randomized 652 does not agree with numbers randomized per group (520 and 129).
Selective reporting (reporting bias)	High risk	Many subanalyses, for instance with the individual NPI items. Post-hoc analyses. Each time for all four drug groups. No adjustment for multiple testing. Much missing data on adverse events (no information f.i. on somnolence, or just summary information, f.i. on cognitive function).
Other bias	High risk	"Following a placebo lead-in phase of up to a maximum of 14 days (...)"

De Deyn 2005

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Study duration:** 10 weeks **Rescue medication:** allowed for NPS, not for EPS
Participants	**Number randomised:** 208 (106 aripiprazole 102 placebo) **Mean age:** 81.5 years **Sex (female):** 72% **Type of dementia:** Alzheimer's disease **Severity of dementia:** moderate **Indication:** Psychosis (Baseline Psychosis NPI Psychosis: 12.4) **Setting:** assisted living facilities, adult communities or living with a caregiver **Country:** USA
Interventions	**Intervention characteristics** Aripiprazole • *dosage*: flexible, 2 mg to 15 mg per day Placebo Eligible patients were randomised to aripiprazole 2 mg/d or placebo, administered once daily for 10 weeks, in this multicentre, double-blind study. Aripiprazole could be titrated to higher doses (5, 10 mg, and 15 mg/day) at 2-week intervals (or more rapidly based on investigator's judgement) if the patient showed insufficient clinical response. At end point, the mean daily dose of aripiprazole was 10.0 mg.
Outcomes	Psychosis: Neuropsychiatric Inventory (NPI) Psychosis subscale Extrapyramidal symptoms Somnolence Death Any serious adverse event Discontinuation (any reason) Discontinuation due to adverse events Cognitive function: Mini-Mental State Examination (MMSE)
Identification	
Notes	**Sponsorship source:** Bristol-Myers Squibb and Otsuka Pharmaceutical Co., Ltd.
Risk of bias	

De Deyn 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No comments
Allocation concealment (selection bias)	Unclear risk	No comments
Comparability of groups (selection bias)	High risk	Judgement Comment: No baseline information in main article. A clinical study report provides data on age, sex, race and weight only: small differences that might or might not be in favour of the drug. They are not adjusted for. Baseline scores for outcomes are given for analysed (not all randomised) patients only, but are adjusted for.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No comments
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No comments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement Comment: Drop-out was just below 20% and did not differ >5% between groups.It seems that not all patients were included in the analyses (see table with results on outcomes). Missing data were imputed with LOCF.
Selective reporting (reporting bias)	High risk	Insufficient information about outcomes in the protocol. Lots of secondary outcomes.
Other bias	High risk	"Following screening and a minimum 7-day washout period for previous psychotropic medication (...)"

Devanand 1998

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over **Study duration:** 6 weeks **Rescue medication:** not allowed for NPS or EPS.
Participants	**Number randomised:** 66 (42 haloperidol, 24 placebo) **Mean age:** 72.1 years **Sex (female):** 64.8% **Type of dementia:** Alzheimer's disease **Severity of dementia:** moderate-severe **Indication:** diverse NPS, but the majority showed psychosis (71.8%), and psychomotor agitation (78.9%) (baseline psychosis BPRS: 6.8, psychomotor agitation BSS: 3.6)

Devanand 1998 *(Continued)*

	Setting: outpatients **Country:** USA
Interventions	**Intervention characteristics** Haloperidol • *dose*:low dose of 0.50 mg to 0.75 mg/day; or standard dose of 2 mg to 3 mg/day. Placebo After the first week the daily dose was raised from two capsules (haloperidol, 2 mg or 0.50 mg, or placebo) to three capsules (haloperidol, 3mg or 0.75 mg, or placebo). If side effects (e.g. extrapyramidal signs) were limiting, on the basis of the psychiatrist's clinical judgment, the dose was maintained at two capsules daily. Therefore, in both phases, patients were on a stable dose for 5 weeks before the endpoint evaluation of efficacy and side effects.
Outcomes	Psychosis: Brief Psychiatric Rating Scale (BPRS) psychosis subscale Number of responders for psychosis Death Discontinuation due to adverse events
Identification	
Notes	**Sponsorship source:** Supported in part by grants MH-44176, MH-50038, and MH-55735 from NIMH; grants AG-07370, AG-07232, and AG-08702 from the National Institute on Aging; NIH grant RR-00645; and the Charles S. Robertson Memorial Gift for Alzheimer's Disease Research from the Banbury Fund

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Comparability of groups (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Raters and patients were blind to the study design throughout phase A and phase B.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The blinded research psychiatrist (D.P.D.) who evaluated the patients was also in charge of treatment, including dose adjustment, at all time points in the study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-out was 9% overall. Results of completers analyses were shown in detail. "Intent-to-treat analyses were also conducted for the phase A sample, carrying forward the last observation", but results were not shown in detail. Apparently, they were not very different.

Devanand 1998 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	High risk	In the initial 1-week single-blind phase, all patients received placebo. At the end of this week, the patients who still met the entry criteria were eligible for phase A

Finkel 1995

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** gross-over **Study duration:** 11 weeks (until cross-over) **Rescue medication:** benztropine was allowed for 1-3 weeks, but unclear how many participants used this during the trial.
Participants	**Number randomised:** 33 (16 thiothixene, 17 placebo) **Mean age:** 85 years **Sex (female):** 86% **Type of dementia:** not specified in study, but according to personal communication Alzheimer's and vascular dementia **Severity of dementia:** severe **Indication:** agitation **Setting:** nursing homes **Country:** USA
Interventions	**Intervention characteristics** Thiothixene • *dosage*: flexible (attained mean 4.6mg/day with a range of 0.25 mg to18mg/day) twice daily Placebo Twice a day dosage could be adjusted by a maximum of 2 mg every 2 days on the basis of a psychiatrist's judgement of behavioural improvement or side-effects after examination of the patient, discussion with the nursing team and review of progress notes
Outcomes	Agitation: Cohen-Mansfield Agitation Inventory (CMAI) Number of responders for agitation Death Discontinuation (any reason) Discontinuation due to adverse events
Identification	

Finkel 1995 *(Continued)*

Notes	**Sponsorship source:** Weber Pharmaceuticals involved in trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Comparability of groups (selection bias)	Unclear risk	No baseline characteristics of all randomized per group reported, but apparently "unbalanced distributions" at baseline were adjusted for.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" trial, but persons blinded not specified. "...medication or placebo, which were dispensed twice a day either in 1 mg outwardly identical capsules or in a liquid form at an initial dose of 1 mg."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" trial, but persons blinded not specified. "...medication or placebo, which were dispensed twice a day either in 1 mg outwardly identical capsules or in a liquid form at an initial dose of 1 mg."
Incomplete outcome data (attrition bias) All outcomes	High risk	3 of 33 drop-out (9%), but all in one group (0% versus 18%). ITT seems to have been performed, but not mentioned explicitly.
Selective reporting (reporting bias)	High risk	All reported outcomes were reported, but all secondary outcomes including adverse events were only reported in terms of statistical significance. No means or percentages.
Other bias	High risk	"Patients were screened and, if they met criteria, entered a 1-week medication washout phase, after which a baseline assessment was obtained."

Grossberg 2020a

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Study duration:** 12 weeks **Rescue medication:** allowed: antidepressants (if the dose was stable for 30 days prior to randomisation and did not change during the study) and benzodiazepines (during the first 4 weeks of the randomised phase only (limited to 4 days/week with a maximum dose of 2 mg/day of lorazepam or equivalent)
Participants	**Number randomised:** 433 (297 brexpiprazole, 136 placebo) **Mean age:** 73.8 years **Sex (female):** 55.2% **Type of dementia:** Alzheimer's disease

Grossberg 2020a *(Continued)*

	Severity of dementia: mild-severe **Indication:** Agitation (baseline CMAI 70.9) **Setting**: care facility or community-dwelling, provided the patient was not living alone **Country**: Russia (29.1% of randomised patients), the USA (27.9%), Ukraine (14.8%), Serbia (12.2%), Croatia (8.5%), Spain (4.4%), and Germany (3.0%). Efficacy results of 1 study group (0.5mg/day) not reported
Interventions	Brexpiprazole: 0.5, 1 mg and 2 mg/day Placebo Doses were titrated over a period of 2−4 weeks (days 1−3, 0.25 mg/day; days 4−14, 0.5mg/day; days 15−28, 1 mg/day; day 29 onwards, assigned dose). Patients unable to tolerate their assigned dose (or matching placebo) were discontinued from the trial.
Outcomes	Agitation: Cohen-Mansfield Agitation Inventory (CMAI) Extrapyramidal symptoms Death Any adverse event Any serious adverse event Discontinuation (any reason) Discontinuation due to adverse events Cognitive function: Mini-Mental State Examination (MMSE)
Identification	
Notes	**Sponsorship Source:** Otsuka Pharmaceutical Development & Commercialization Inc (Princeton, NJ, USA) and H. Lundbeck A/S (Valby, Denmark).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Treatments were assigned by an interactive voice/web response system based on a fixed-block, computer-generated randomization code provided by the study sponsor and stratified by study center."
Allocation concealment (selection bias)	Unclear risk	No information provided
Comparability of groups (selection bias)	High risk	There were various differences between the study groups, including a higher score on the CMAI and on the MMSE in the placebo group than in (all three) drug groups. These differences were not (all) taken into account in the analysis
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Treatment assignments were blinded to patients, investigators, and sponsor personnel..." "Brexpiprazole and matching placebo tablets were provided by the sponsor, packaged in numbered, weekly blister cards."

Grossberg 2020a *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Treatment assignments were blinded to patients, investigators, and sponsor personnel..."
Incomplete outcome data (attrition bias) All outcomes	High risk	No efficacy data for one study group (0.5mg/day). Overall and differential drop-out low. No ITT analysis of efficacy.
Selective reporting (reporting bias)	High risk	Many outcomes reported on clinical trials.gov were not reported
Other bias	High risk	Run-in of 6 weeks to wash out of antipsychotics, and other types of medication

Grossberg 2020b

Study characteristics	
Methods	**Study design: r**andomised controlled trial **Group:** parallel group **Study duration:** 12 weeks **Rescue medication:** allowed: antidepressants (if the dose was stable for 30 days prior to randomisation and did not change during the study) and benzodiazepines (during the first 4 weeks of the randomized phase only (limited to 4 days/week with a maximum dose of 2 mg/day of lorazepam or equivalent)
Participants	**Number randomised:** 270 (133 brexpiprazole, 137 placebo) **Mean age:** 73.8 years **Sex (female):** 63.0% **Type of dementia:** Alzheimer's disease **Severity of dementia:** mild-severe **Indication:** agitation (baseline CMAI 69.9) **Setting:** care facility or community-dwelling, provided the patient was not living alone **Country:** Ukraine (28.9% of randomised patients), the USA (22.6%), Russia (19.3%), Bulgaria (17.8%), Canada (4.8%), France (3.3%), Slovenia (2.2%), the UK (0.7%), and Finland (0.4%)
Interventions	Brexpiprazole: flexible dose 0.5 m to 2mg/day, mean dose 1.54 mg/day. Placebo Brexpiprazole was initiated at 0.25 mg/day (days 1–3), increased to 0.5 mg/day (days 4–14), and further increased to a target dose of 1 mg/day (days 15–28; could be decreased back to 0.5 mg/day). An additional dose increase to 2 mg/day could be initiated from day 29 (week 4 visit) onwards. After week 4, stepwise dose decreases and increases could occur at any time (scheduled or unscheduled visits), based on the investigator's clinical evaluation of the patient's response and tolerability. Patients unable to tolerate brexpiprazole 0.5 mg/day (or matching placebo) were discontinued from the trial.
Outcomes	Agitation: Cohen-Mansfield Agitation Inventory (CMAI) Extrapyramidal symptoms Somnolence

Grossberg 2020b *(Continued)*

	Death
	Any adverse event
	Any serious adverse event
	Discontinuation (any reason)
	Discontinuation due to adverse events
	Cognitive function: Mini-Mental State Examination (MMSE)
Identification	
Notes	**Sponsorship Source:** Otsuka Pharmaceutical Development & Commercialization Inc. (Princeton, NJ, USA) and H. Lundbeck A/S (Valby, Denmark)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Treatments were assigned by an interactive voice/web response system based on a fixed-block, computer-generated randomization code provided by the study sponsor and stratified by study center."
Allocation concealment (selection bias)	Unclear risk	No information provided
Comparability of groups (selection bias)	Unclear risk	There are several small differences that were not taken into account, and might have influence the results
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Treatment assignments were blinded to patients, investigators, and sponsor personnel..." "Brexpiprazole and matching placebo tablets were provided by the sponsor, packaged in numbered, weekly blister cards."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Treatment assignments were blinded to patients, investigators, and sponsor personnel..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall and differential drop-out low. ITT not used, but given negative study results this was probably not problematic
Selective reporting (reporting bias)	High risk	Many outcomes mentioned on clinicaltrials.gov have not been reported
Other bias	High risk	6-week run-in for wash-out

Japic CTI 142578 2015

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group

Japic CTI 142578 2015 *(Continued)*

	Study duration: 10 weeks **Rescue medication:** no information
Participants	**Number randomised:** 150 **Type of dementia:** Alzheimer's disease **Indication:** agitation **Setting:** hospital or care facilities **Country:** Japan
Interventions	**Intervention characteristics** Aripiprazole • *dosage*: 2 mg/day, 3mg/day, or 6 mg/day Placebo
Outcomes	No outcomes reported
Identification	
Notes	**Sponsorship source:** Otsuka Pharmaceutical Co., Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Comparability of groups (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)" Use of placebo, but identical tablets not described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	High risk	The trial was early terminated after enrolment of 150 of 880 participants. The results have not been published. The company did not provide the data when one of the authors (HJL) requested them.
Other bias	Unclear risk	No information

Mintzer 2006 RIS USA 232

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Study duration:** 8 weeks **Rescue medication:** allowed
Participants	**Number randomised:** 473 (235 risperidone 238 placebo) **Mean age:** 83.3 years **Sex (female):** 77.0% **Type of dementia:** Alzheimer's disease, vascular dementia **Severity of dementia:** moderate **Indication:** psychosis (although 50 (included) patients with psychosis at screening were found not to have psychosis anymore at baseline) (baseline BEHAVE-AD psychosis: 7.4) **Setting:** nursing homes, long-term care facilities **Country:** USA
Interventions	**Intervention characteristics** Risperidone • *dose*: 1.0 mg to 1.5mg per day Placebo Medication was initiated at 0.50 mg (0.25-mg tablets twice daily) and increased after three days to 1.00 mg (0.5-mg tablets twice daily). For patients whose clinical response remained inadequate by day 13, medication was increased to 1.50 mg (0.75 mg twice daily). Subsequent adjustments were allowed in patients who experienced adverse events. The minimum treatment dosage was 0.50 mg daily for patients who achieved and maintained efficacy at this dose. After randomisation, the mean daily dosage of risperidone was 1.03 ± 0.24 mg (median: 1.00 mg/day, range: 0.40 mg to 1.90 mg/day), with a maximum daily risperidone dosage of 2.5 mg, which exceeded trial recommendations.
Outcomes	Psychosis: Behavioural Pathology in Alzheimer's Disease (BEHAVE-AD) psychosis subscale Number of responders for psychosis Extrapyramidal symptoms Somnolence Death Any adverse event Any serious adverse event Discontinuation (any reason) Discontinuation due to adverse events
Identification	

Mintzer 2006 RIS USA 232 *(Continued)*

Notes	**Sponsorship source:** Johnson & Johnson Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Low risk	"Investigators received sealed envelopes for each patient containing coded details of the treatment in this phase."
Comparability of groups (selection bias)	Low risk	(Small) baseline differences, f.i. in sex, type dementia and psychosis, but some are in favour of risperidone and others not. Only psychosis at baseline was adjusted for.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo-controlled with identical tablets, double-blind, but no reference to blinding of participants and personel specifically.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-out was high (>20%). Modified ITT (excluding patients without assessment after baseline). Handling of missing data not reported.
Selective reporting (reporting bias)	Unclear risk	Many subanalyses with primary outcome, but adverse events reported in more detail than usual.
Other bias	High risk	During the run-in phase, all patients received placebo for 1 week to wash out previously used psychotropic medications. The run-in length was reduced for patients not using psychotropic medications and for patients whose psychosis or agitation worsened.

Mintzer 2007

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Study duration:** 10 weeks **Rescue medication:** allowed for NPS and EPS
Participants	**Number randomised:** 487 (366 aripiprazole, 121 placebo) **Mean age:** 82.5 years **Sex (female):** 79% **Type of dementia:** Alzheimer's disease **Severity of dementia:** moderate

Mintzer 2007 *(Continued)*

	Indication: Psychosis (baseline NPI-NH psychosis: 11.6) **Setting:** nursing homes or residential assisted-living facilities **Country:** USA, Australia, Canada, South Africa, and Argentina
Interventions	**Intervention characteristics** Aripiprazole • *dosage*: fixed 2 mg/day, 5 mg/day, or 10 mg/day Placebo Nodose modification of study medication was allowed for tolerability reasons after titration during the acute phase. Patients unable to tolerate acute-phase study medication were discontinued from the study.
Outcomes	Psychosis: Neuropsychiatric Inventory–Nursing Home version (NPI-NH) psychosis subscale Number of responders for psychosis Extrapyramidal symptoms Somnolence Death Any serious adverse event Discontinuation (any reason) Discontinuation due to adverse events Cognitive function: Mini-Mental State Examination (MMSE)
Identification	
Notes	**Sponsorship source:** Alzheimer's Research & Clinical Programs, Medical University of South Carolina and the Ralph H. Johnson VA Medical Center, Charleston, SC (JEM); the Department of Psychiatry, Emory University, Atlanta, GA (LET); Bristol-Myers Squibb Company, Wallingford, CT (CDB, RNM); Bristol-Myers Squibb Company, Braine l'Alleud, Belgium (RS); and Otsuka Pharmaceutical Development & Commercialization, Princeton, NJ (RDM, AF).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Comparability of groups (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information

Mintzer 2007 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-out was very high (42%). Modified ITT with exclusion of patients who did not take at least one dose of study medication, and did not have at least one postbaseline evaluation within 7 days after the last medication was taken. Handling of missing data with LOCF.
Selective reporting (reporting bias)	High risk	Outcome was measured with several scales and presented for each drug group separately. Subanalyses of individual NPI items. No correction for multiple testing. % any adverse event per group missing. No study protocol available.
Other bias	High risk	Concomitant use of antipsychotics, mood stabilizers or sedatives (except trazodone [25–50 mg], zolpidem tartrate [2.5–5.0 mg] and temazepam [7.5–15.0 mg]) was prohibited during the study treatment period and the seven days prior to randomization.

NCT00287742 2006

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Study duration:** 8 weeks **Rescue medication:** no information provided
Participants	**Number randomised:** 33 (13 risperidone, 17 placebo, 3 unclear) **Mean age:** unclear, around 77 years **Sex (female):** 77% **Type of dementia:** Alzheimer's dementia **Severity of dementia:** moderate **Indication:** psychosis **Setting:** In- or outpatients **Country:** Japan
Interventions	**Intervention characteristics** Risperidone • *dosage*: flexible dose regimen of 0.5 mg to 2.0 mg daily in 2 doses Placebo
Outcomes	Psychosis: Behavioural Pathology in Alzheimer's Disease (BEHAVE-AD) psychotic symptom cluster score Extrapyramidal symptoms Any adverse event

NCT00287742 2006 *(Continued)*

	Any serious adverse event Discontinuation (any reason)
Identification	
Notes	**Sponsorship source:** Janssen Pharmaceutical K.K.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Comparability of groups (selection bias)	Unclear risk	Clear difference in psychosis between groups at baseline. Other characteristics not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" trial, but unclear who was blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" trial, but unclear who was blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout was 7 of 33 (21%) in total and differed for 18% between groups. Outcomes were provided for all participants at endpoint.
Selective reporting (reporting bias)	High risk	Only BEHAVE-AD Psychotic Symptom Cluster Score reported. Results for ADL and MMSE not reported. Early terminated trial. No full article.
Other bias	High risk	Single-blind (with placebo) run-in of 1 week.

Paleacu 2008

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Study duration:** 6 weeks **Rescue medication:** not allowed for NPS or EPS
Participants	**Number randomised:** 40 (20 quetiapine, 20 placebo) **Mean age:** 82.2 years **Sex (female):** 65% **Type of dementia:** Alzheimer's disease

Paleacu 2008 *(Continued)*

	Severity of dementia: moderate **Indication:** diverse NPS, but 68% had delusions, so majority was psychotic. **Setting:** not reported **Country:** Israel
Interventions	**Intervention characteristics** Quetiapine • *dosage*: 50 mg to 300 mg/day (in two doses) Placebo After initial screening visit, patients were given at visit 2 (baseline) quetiapine at a dose of 25 mg twice daily during the first week, and then increased to a target dose of 150 mg/day by increments of 50 mg every week. If at the target dose no NPI improvement was measured additional increments of 50 mg per week were continued until a maximal dose of 300 mg/day or until side effects were reported by the patient. Median total daily dose of quetiapine in the treatment group was 200 mg at week 6 (range: 75 mg to 300 mg/day).
Outcomes	Psychosis: Neuropsychiatric Inventory (NPI) items delusions and hallucinations only) Number of responders for psychosis Extrapyramidal symptoms Somnolence Death Any adverse event Any serious adverse event Discontinuation (any reason) Discontinuation due to adverse events Cognitive function: Mini-Mental State Examination (MMSE)
Identification	
Notes	**Sponsorship source:** Grant from AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Comparability of groups (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias)	Unclear risk	No information

Paleacu 2008 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall drop-out was 15%. Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups. But high discontinuation rate with a very small sample with a high rate of imputed data. Results included patients that dropped-out (ITT analysis), with LOCF for missing data.
Selective reporting (reporting bias)	Unclear risk	No detailed data for NPI total baseline to endpoint. For CGI-C no comparison data with placebo. The study report fails to include results for a key outcome (NPI total) that would be expected to have been reported for in the usual way (baseline to endpoint). No study protocol available.
Other bias	High risk	For those patients who received other antipsychotics before the trial a washout period of 2 weeks was mandatory.

RIS-INT-83 2003

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Study duration:** 8 weeks **Rescue medication:** no information provided
Participants	**Number randomised:** 18 (10 risperidone, 8 placebo) **Mean age:** unclear Sex (female): 72.2% **Type of dementia:** Alzheimer's disease **Severity of dementia:** unclear **Indication:** Psychosis (Baseline BEHAVE-AD Psychosis: 7.1) **Setting:** nursing homes or long-term care facilities **Country:** Israel
Interventions	**Intervention characteristics** Risperidone • *dosage*: 1 to 1.5 mg daily in 2 dosages Placebo
Outcomes	Psychosis: Behavioural Pathology in Alzheimer's Disease (BEHAVE-AD) Number of responders for psychosis

RIS-INT-83 2003 *(Continued)*

	Extrapyramidal symptoms
	Death
	Any adverse event
	Any serious adverse event
	Discontinuation (any reason)
	Discontinuation due to adverse events
Identification	
Notes	**Sponsorship source:** Johnson & Johnson Pharmaceutical Research& Development

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Comparability of groups (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out was 22%, but results were reported for all randomized.
Selective reporting (reporting bias)	Low risk	All outcomes seem to be reported.
Other bias	High risk	All eligible subjects first participated in a single-blind, placebo-controlled run-in phase of 7 days.

Schneider 2003 RIS USA 63

Study characteristics

Methods	**Study design:** randomised controlled trial
	Study grouping: parallel group
	Study duration: 12 weeks

Schneider 2003 RIS USA 63 *(Continued)*

	Rescue medication: allowed **Country:** USA
Participants	**Number randomised:** 463 (of 625 in main trial) **Mean age:** 83.3 years **Sex (female):** 72% **Type of dementia:** Alzheimer's disease, vascular dementia, mixed type dementia **Severity of dementia:** severe **Indication:** mixed for main trial, but results were reported for the subgroup with psychosis at baseline. **Setting:** nursing home or chronic disease hospital
Interventions	**Intervention characteristics** Risperidone • *dosage*: 2x0.5 mg, 2x1.0 mg or 2x2.0 mg daily Placebo
Outcomes	Psychosis: Behavioural Pathology in Alzheimer's Disease (BEHAVE-AD) psychosis subscale
Identification	
Notes	**Sponsorship source:** Janssen Research Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information for subgroup cohort
Allocation concealment (selection bias)	Unclear risk	No information for subgroup cohort
Comparability of groups (selection bias)	Unclear risk	No information for subgroup cohort
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Identically appearing risperidone (0.25, 0.5, and 1.0 mg) and placebo tablets were supplied by the sponsor. Each patient received 2 tablets twice daily. All trial drugs were appropriately labelled with a 2-part la- bel containing the visit, protocol, patient numbers, and directions for administration. The first part of the label remained attached to the medication carton and the second part (double-blind portion) was detached and placed in the case report form.Only says double blind but doesn't mention the persons who were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information if trained raters were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Modified (all patients who received at least one dose and one post baseline assessment) ITT analysis performed. Imputation LOCF. Discontinuation rates imbalanced across groups (range from 27% in the placebo group to 42% in the group receiving 2mg risperidone).

Schneider 2003 RIS USA 63 *(Continued)*

Selective reporting (reporting bias)	High risk	This is a secondary report of the trial based on the patients with psychosis only. Primary results are presented for the 1.0 and 2.0 group combined. Unclear why. Many outcomes that were reported in the main results paper based on all participants were not reported here.
Other bias	High risk	After a single-blind placebo washout period of 3 to 7 days, eligible patients were randomly assigned to placebo or to 0.5, 1.0, or 2.0 mg/day of risperidone

Schneider 2006 CATIE-AD

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Study duration:** 2 to 36 weeks, but endpoint for outcomes is 12 weeks **Rescue medication:** allowed
Participants	**Number randomised:** 421 (100 olanzapine 94 quetiapine 85 risperidone 142 placebo) **Mean age:** 77.9 years **Sex (female):** 56% **Type of dementia:** Alzheimer's disease **Severity of dementia:** moderate **Indication:** generic NPS, but 82% had delusions and 86% agitation. **Setting:** outpatients living at home or assisted- living facility with regular contact to caregiver **Country:** USA
Interventions	**Intervention characteristics** Olanzapine • *dose*: flexible, tablets of 2.5 mg and 5.0 mg. Mean last dose 5.5mg/day. Quetiapine • *dose*: flexible, tablets of 25 mg and 50 mg. Mean last dose 56.5mg/day. Risperidone • *dose*: flexible, tablets of 0.5 mg and 1.0 mg. Mean last dose 1.0mg/day. Placebo The treating physician could adjust the dosage, as indicated clinically, over the 36 weeks of the trial. The mean initially prescribed doses were 3.2 mg of olanzapine per day, 34.1 mg of quetiapine per day, and 0.7 mg of risperidone per day. The last prescribed mean dose in phase 1 was 5.5 mg of olanzapine per day, 56.5 mg of quetiapine per day, and 1.0 mg of risperidone per day.
Outcomes	Agitation: Neuropsychiatric Inventory (NPI) agitation Number of responders for agitation

Schneider 2006 CATIE-AD *(Continued)*

	Extrapyramidal symptoms Somnolence Death Any adverse event Any serious adverse event Discontinuation (any reason) Discontinuation due to adverse events Cognitive function: Mini-Mental State Examination (MMSE) Health-related quality of life: Alzheimer's Disease Related Quality of Life (ADRQL) Functioning in activities of daily living: Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (ADCS-ADL) Carer burden or carer quality of life: The Caregiver Activity Survey (CAS)
Identification	
Notes	**Sponsorship source:** Supported by a grant (NO1 MH9001) from the NIMH. AstraZeneca Pharmaceuticals, Forest Pharmaceuticals, Janssen Pharmaceutica, and Eli Lilly provided medications for the studies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided.
Allocation concealment (selection bias)	Low risk	"Randomization was performed with the use of permuted blocks of nine per site without stratification and was implemented with the use of an interactive voice-response telephone system."The use of blocks diminishes concealment, but the blocks are large and an interactive voice-response telephone system is used.
Comparability of groups (selection bias)	Unclear risk	Many small baseline differences varyingly in favour of a drug or placebo. Analyses were adjusted for differences in age, sex, MMSE score, and total BPRS score.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trials was "double-blind" and "Medications were dispensed at each visit in the form of identically appearing small and large capsules [...]". Persons blinded has not been specified.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was "double-blind" and "Medications were dispensed at each visit in the form of identically appearing small and large capsules [...]". Persons blinded has not been specified.
Incomplete outcome data (attrition bias) All outcomes	High risk	The overall rate of discontinuation of treatment at 12 weeks was 63% (primary outcome).Other outcomes are analysed with modified ITT (patients without an assessment after baseline are excluded).
Selective reporting (reporting bias)	Unclear risk	Study protocol available but no outcomes prespecified.

Schneider 2006 CATIE-AD *(Continued)*

Other bias	Low risk	Washout from previous treatment and run-in periods were not used because of the patients' acute clinical symptoms; instead, the study design allowed for rapid assignment and initiation of treatment to be consistent with clinical practice.

Streim 2008

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Study duration:** 10 weeks **Rescue medication:** allowed for NPS and EPS.
Participants	**Number randomised:** 256 (131 aripiprazole125 placebo) **Mean age:** 83.0 years **Sex (female):** 76% **Type of dementia:** Alzheimer's disease **Severity of dementia:** moderate **Indication:** psychosis (Psychosis NPI-NH: 10.6) **Setting:** institutionalised persons (i.e. residing in a nursing home or residential assisted-living facility) **Country:** USA
Interventions	**Intervention characteristics** Aripiprazole • *dosage*: flexible, 2 mg to 15 mg/ day Placebo Aripiprazole dosing was flexible, starting at 2 mg/day, with titration to higher doses (5 mg, 10 mg, and 15 mg/day) depending on the study physicians' clinical judgment. The recommended titration schedule was 2 mg/day for 1 week, increasing to 5 mg/day for 2 weeks, 10 mg/day for the next 2 weeks, and 15 mg/day for the remainder of the acute phase (Weeks 6 –10). The mean daily aripiprazole dose at Week 10 was 9.0 mg (range: 0.7 mg to 15.0 mg).
Outcomes	Psychosis: Neuropsychiatric Inventory–Nursing Home version (NPI-NH) psychosis score Number of responders for psychosis Extrapyramidal symptoms Somnolence Death Any adverse event Any serious adverse event Discontinuation (any reason)

Streim 2008 *(Continued)*

	Discontinuation due to adverse events Cognitive function: Mini-Mental State Examination (MMSE) Functioning in activities of daily living: Alzheimer's Disease Cooperative Study – Activities of Daily Living for Severe impairment (ADCS-ADL-SEV)
Identification	
Notes	**Sponsorship source:** Bristol-Myers Squibb Company, Wallingford, CT (CDB, Marcus); Bristol-Myers Squibb Company, Braine l'Alleud, Belgium (RS); Otsuka America Pharmaceutical Inc., Princeton, NJ (McQuade, WHC)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Comparability of groups (selection bias)	Unclear risk	Limited set of relevant baseline characteristics shown. Small differences in set shown. Outcome score at baseline is not given for all randomized, but adjusted for in the analyses.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-out was high (41%). Modified ITT was used excluding patients that did not receive one dose of study medication or an assessment after baseline (within 7 days after taking medication). Missing data was imputed with LOCF.
Selective reporting (reporting bias)	Unclear risk	Insufficient information. Study protocol is available but no outcomes prespecified. Two coprimary outcomes. Multiple scales for NPS. Many additional analyses including OC comparisons. Unusual cut-offs f.i. only weight increase of 7% or more included. Correction for multiple testing.
Other bias	High risk	Following screening and a minimum 7-day psychotropic medication washout period (...)

Tariot 2006

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Study duration:** 10 weeks

Tariot 2006 *(Continued)*

	Rescue medication: allowed for agitation, not for EPS
Participants	**Number randomised:** 284 (94 haloperidol 91 quetiapine 99 placebo) **Mean age:** 83.1 years **Sex (female):** 73.2% **Type of dementia:** Alzheimer's disease **Severity of dementia: m**oderate **Indication:** Psychosis (Baseline Psychosis NPI-NH: 10.0) **Setting:** nursing homes **Country:** USA
Interventions	**Intervention characteristics** Haloperidol • *dose*: 0.5 mg to 12 mg/ day Quetiapine • *dose*: 25 mg to 600 mg/day Placebo We initiated quetiapine at 25 mg per day, increased by 25 mg every four days to a target dosage of 100 mg per day by day 14. We started haloperidol at 0.5 mg per day, increased by 0.5 mg per day every four days through day 14. We had the ability to adjust dosages thereafter according to clinical response and tolerability to a maximum of 600 mg per day of quetiapine or 12 mg per day of haloperidol. The median of the mean daily dose of quetiapine was 96.9 mg; the median maximum was 125.0 mg. The median of the mean daily dose of haloperidol was 1.9mg; the median maximum was 2.0 mg.
Outcomes	Psychosis: Neuropsychiatric Inventory–Nursing Home version 2 (NPI-NH2) (delusion + hallucination items) Number of responders for psychosis Extrapyramidal symptoms Somnolence Deaths (Notes: Reported for all participants, not just for those with AD) Any serious adverse events Discontinuation (any reason) Discontinuation due to adverse events Cognitive function: Mini-Mental State Examination (MMSE) Functioning in activities of daily living (ADL): Physical Self-Maintenance Scale (PSMS)
Identification	
Notes	**Sponsorship source:** AstraZeneca Pharmaceuticals LP
Risk of bias	

Tariot 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Comparability of groups (selection bias)	Unclear risk	Some smaller and larger differences, of which it is unclear if and how they affected the results. Only baseline outcome score was adjusted for.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This was a "double-blind" trial. "Identically appearing capsules containing 25 mg quetiapine, 0.5 mg haloperidol, or placebo" were used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-out was high (29%), analyses were not based on all randomized, LOCF for missing data. However, it is a negative trial. In addition, missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.
Selective reporting (reporting bias)	Unclear risk	No protocol available. Insufficient information. 'Any adverse events' and 'serious adverse events' were not reported.
Other bias	High risk	Participants underwent a washout of ≥48 hours.

Teri 2000

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Study duration:** 16 weeks **Rescue medication:** not allowed for NPS or EPS.
Participants	**Number randomised:** 70 (34 haloperidol, 36 placebo) **Mean age:** 75.5 years **Sex (female):** 62.9% **Type of dementia:** Alzheimer's disease **Severity of dementia:** moderate-severe **Indication:** agitation **Setting:** community **Country:** USA

Teri 2000 *(Continued)*

Interventions	**Intervention characteristics** Haloperidol • *dosage*: 0.5 mg to 3.0mg/day Placebo Medication was provided in tablets of haloperidol 0.5 mg, treatment began with one tablet each day and increased at the next clinic visit by one tablet a day unless the subject was rated as moderately or markedly improved, significant adverse events were noted, or the maximum dose was reached (3 mg/day for haloperidol).Participants achieved a mean haloperidol dose of 1.861 mg/day (range, 0 to 3 mg/d)ay.
Outcomes	Agitation: Cohen-Mansfield Agitation Inventory (CMAI) Number of responders for agitation Extrapyramidal symptoms (**Notes**: Parkinsonian gait, rigidity, tremor, and bradykinesia are forms of EPS. Rigidity showed the largest contrast to avoid underestimating the risk of EPS: 33% (11) and 13% (5)). Somnolence Death Discontinuation (any reason) Cognitive function: Mini-Mental State Examination (MMSE) Functioning in activities of daily living (ADL): Instrumental Activities of Daily Living (IADL) Carer burden or carer quality of life: The Screen for Caregiver Burden (SCB)
Identification	
Notes	**Sponsorship source:** supported by a grant from the National Institute of Aging (AG-010483). Active study medications and corresponding placebos were provided by Purpac Pharmaceutical, Elizabeth, NJ

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	Not enough information provided.It was a "randomized" trial. "Treatments were assigned in randomized blocks of nine (for three arms) or 12 (for four arms)." Restriction methods could potentially affect allocation concealment.
Comparability of groups (selection bias)	Low risk	There were small differences between the treatment groups. The authors found that "None of the prestated potential confounding variables [patient age, patient gender, MMSE score, total CMAIscore, and caregiver gender] [...] was significantly related to primary outcome." And the trial was a negative trial.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not completely blinded, because one arm (behaviour management techniques) could not be blinded.

Teri 2000 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Assessments were conducted [...] by interviewers blind to treatment assignment." "To insure that interviewers remained blind to treatment assignment, caregivers did not discuss any aspect of their treatment with the interviewer. In no instance was the blinding compromised.""Medication was provided in [...] identically appearing tablets." "The primary outcome measure was [...] completed by a trained clinician blind to treatment assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall drop-out was high (36%).ITT-analysis: "Missing scores at posttreatment were imputed with last observation carried forward from discontinuation visit scores or, if those were not available, from midpoint visit scores. If no ADCS-CGIC score [primary outcome, rev] was available, a value of “worse” was assigned (n=12). The rationale for doing this was to assume the worst case scenario: subjects who dropped out did so because they became worse. In addition,we reviewed the reasons caregivers cited for dropping out of the study and in each instance our assignment of“worse” was confirmed. "
Selective reporting (reporting bias)	Low risk	All outcomes seem to be reported.
Other bias	High risk	Subjects receiving psychotropic medications were required to discontinue them at least 2 weeks before study enrolment.

Zhong 2007

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Study duration:** 10 weeks **Rescue medication:** allowed
Participants	**Number randomised:** 333 (241 quetiapine, 92 placebo) **Mean age:** 83.2 years **Sex (female):** 74.2% **Type of dementia:** Alzheimer's disease and vascular dementia **Severity of dementia:** severe **Indication:** Agitation (Baseline PANSS-EC: 23.0) **Setting:** nursing homes and assisted living facilities **Country:** USA
Interventions	**Intervention characteristics** Quetiapine • *dose*: 100 mg per day, or 200 mg per day Placebo Participants randomised to treatment with quetiapine initially received 25 mg/day. The dose was titrated in 25 mg increments every day to reach 100 mg/day on day 4 for both quetiapine treatment groups;

Zhong 2007 *(Continued)*

	those assigned to 100 mg/day were maintained on this dose, those randomised to 200 mg/day continued the titration in 25 mg increments daily to reach the target dose of 200 mg on day 8, after which the dose was held constant. Participants unable to tolerate the assigned treatment were discontinued from the study.
Outcomes	Agitation: Positive and Negative Syndrome Scale-Excitement Component (PANSS-EC) Number of responders for agitation Extrapyramidal symptoms Somnolence Death Any adverse event Any serious adverse event Discontinuation (any reason) Discontinuation due to adverse events Cognitive function: Mini-Mental State Examination (MMSE)
Identification	
Notes	**Sponsorship source:** AstraZeneca Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The centralized randomization schedule was generated using a random block size of 8 and was created using random seed and treatment allocation ratios of 3:3:2 and maintained blinded by the sponsor's randomization group.
Allocation concealment (selection bias)	Low risk	"The centralized randomization schedule was [...] maintained blinded by the sponsor's randomization group."
Comparability of groups (selection bias)	High risk	Limited table of baseline characteristics. Clear baseline differences in sex, race and type of dementia. Also somewhat more agitation at baseline in drug groups. Type of dementia and baseline outcome score were adjusted for.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was a "double-blind" trial. "Each [medication] kit contained 10 blister wallets with the same number of tablets and the same configuration of color, size, and shape. Study medication was administered twice daily from blister wallets."Personal not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was a "double-blind" trial. "Each [medication] kit contained 10 blister wallets with the same number of tablets and the same configuration of color, size, and shape. Study medication was administered twice daily from blister wallets."Personal not mentioned.
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-out was high (35%). Modified ITT analysis excluding patients that did not receive one dose of study medication or one assessment after baseline. LOCF was used for imputing missing data.
Selective reporting (reporting bias)	High risk	Various scale for the outcome have been used. The least commonly used is presented as the primary outcome. Results based on OC analyses and p-values are given undue attention f.i. in the abstract. Subgroup analyses for type of de-

Zhong 2007 *(Continued)*

		mentia. Protocol was submitted after publication and does not list pre-specified outcomes.
Other bias	Low risk	No run-in period

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

Study	Reason for exclusion
DeDeyn 1999 RIS-INT-24	Wrong patient population. Patients with a broad range of neuropsychiatric symptoms enrolled, not specific for agitation or psychosis.
Devanand 1989	Wrong study design. Placebo and haloperidol were not given in parallel groups. Each patient received both drugs consecutively (placebo - haloperidol - placebo).
Holmes 2007	Wrong study design. Wrong comparator, not placebo controlled
Meguro 2004	Wrong study design. Wrong comparator, not placebo controlled
NCT00043849 2002	Wrong patient population (not Alzheimer's or vascular dementia)
Pollock 2002	Wrong population. Unclear how many were psychotic or agitated. Many patients with Lewy body dementia included.
Shin 2013	Wrong study design (one study group only, not placebo controlled)
Street 2000 F1D MC HGEU	Wrong population. Description on the patient population far too vague and therefore unclear how many patients were psychotic or agitated
Trequattrini 2003	Wrong study design (one study group only, not placebo controlled)

DATA AND ANALYSES

Comparison 1. Typical antipsychotics versus placebo

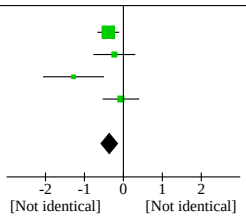
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Agitation	4	361	Std. Mean Difference (IV, Fixed, 95% CI)	-0.36 [-0.57, -0.15]
1.2 Psychosis	2	240	Std. Mean Difference (IV, Fixed, 95% CI)	-0.29 [-0.55, -0.03]
1.3 Somnolence	3	466	Risk Ratio (IV, Fixed, 95% CI)	2.62 [1.51, 4.56]
1.4 Somnolence (RD)	3	466	Risk Difference (IV, Fixed, 95% CI)	0.12 [0.06, 0.18]
1.5 Extrapyramidal symptoms	3	467	Risk Ratio (IV, Fixed, 95% CI)	2.26 [1.58, 3.23]

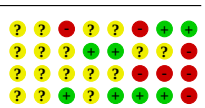
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6 Extrapyramidal symptoms (RD)	3	467	Risk Difference (IV, Fixed, 95% CI)	0.19 [0.11, 0.27]
1.7 Any serious adverse events	1	193	Risk Ratio (IV, Fixed, 95% CI)	1.32 [0.65, 2.66]
1.8 Any serious adverse events (RD)	1	193	Risk Difference (IV, Fixed, 95% CI)	0.04 [-0.06, 0.14]
1.9 Death	6	578	Risk Ratio (IV, Fixed, 95% CI)	1.46 [0.54, 4.00]
1.10 Death (RD)	6	578	Risk Difference (IV, Fixed, 95% CI)	0.01 [-0.02, 0.03]
1.11 Number of responders for agitation	4	367	Risk Ratio (IV, Fixed, 95% CI)	1.18 [1.01, 1.38]
1.12 Number of responders for agitation (RD)	4	367	Risk Difference (IV, Fixed, 95% CI)	0.13 [0.04, 0.22]
1.13 Number of responders for psychosis	2	259	Risk Ratio (IV, Fixed, 95% CI)	1.31 [0.90, 1.92]
1.14 Number of responders for psychosis (RD)	2	259	Risk Difference (IV, Fixed, 95% CI)	0.09 [-0.03, 0.20]
1.15 Discontinuation due to adverse events	4	442	Risk Ratio (IV, Fixed, 95% CI)	1.70 [1.02, 2.82]
1.16 Discontinuation due to adverse events (RD)	4	442	Risk Difference (IV, Fixed, 95% CI)	0.06 [0.00, 0.12]
1.17 Discontinuation (any reason)	6	578	Risk Ratio (IV, Fixed, 95% CI)	1.16 [0.89, 1.51]
1.18 Discontinuation (any reason) (RD)	6	578	Risk Difference (IV, Fixed, 95% CI)	0.01 [-0.06, 0.07]
1.19 Functioning (ADL)	2	249	Std. Mean Difference (IV, Fixed, 95% CI)	0.38 [0.13, 0.63]
1.20 Cognitive function	2	205	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-1.27, 0.77]
1.21 Carer burden	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Typical antipsychotics versus placebo, Outcome 1: Agitation

Study or Subgroup	Typical antipsychotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Allain 2000	-6.75	5.46	99	-4.71	5.01	101	57.0%	-0.39 [-0.67 , -0.11]
Devanand 1998	-0.55	0.72	40	-0.25	1.98	20	15.4%	-0.23 [-0.77 , 0.31]
Finkel 1995	-4	6.84	16	5	6.84	15	7.3%	-1.28 [-2.06 , -0.50]
Teri 2000	-7.26	22.51	34	-5.94	18.5	36	20.3%	-0.06 [-0.53 , 0.41]
Total (95% CI)			**189**			**172**	**100.0%**	**-0.36 [-0.57 , -0.15]**

Heterogeneity: Chi² = 7.11, df = 3 (P = 0.07); I² = 58%
Test for overall effect: Z = 3.37 (P = 0.0008)
Test for subgroup differences: Not applicable



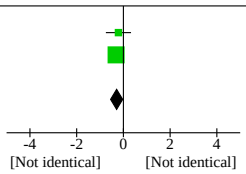


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.2. Comparison 1: Typical antipsychotics versus placebo, Outcome 2: Psychosis

Study or Subgroup	Typical antipsychotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Devanand 1998	-1.43	2.96	40	-0.85	2.08	20	23.0%	-0.21 [-0.75 , 0.33]
Tariot 2006	-5.93	5.58	86	-4.11	5.99	94	77.0%	-0.31 [-0.61 , -0.02]
Total (95% CI)			**126**			**114**	**100.0%**	**-0.29 [-0.55 , -0.03]**

Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 2.20 (P = 0.03)
Test for subgroup differences: Not applicable

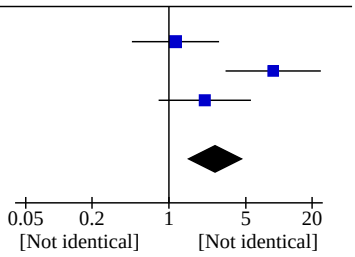


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.3. Comparison 1: Typical antipsychotics versus placebo, Outcome 3: Somnolence

Study or Subgroup	Typical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Allain 2000	9	101	8	103	36.6%	1.15 [0.46 , 2.86]
Tariot 2006	34	94	4	98	30.7%	8.86 [3.27 , 24.01]
Teri 2000	10	34	5	36	32.7%	2.12 [0.81 , 5.56]
Total (95% CI)		**229**		**237**	**100.0%**	**2.62 [1.51 , 4.56]**
Total events:	53		17			

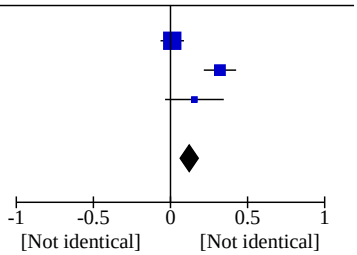
Heterogeneity: Chi² = 9.08, df = 2 (P = 0.01); I² = 78%
Test for overall effect: Z = 3.43 (P = 0.0006)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Typical antipsychotics versus placebo, Outcome 4: Somnolence (RD)

Study or Subgroup	Typical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
Allain 2000	9	101	8	103	59.4%	0.01 [-0.06 , 0.09]
Tariot 2006	34	94	4	98	31.2%	0.32 [0.22 , 0.43]
Teri 2000	10	34	5	36	9.4%	0.16 [-0.04 , 0.35]
Total (95% CI)		**229**		**237**	**100.0%**	**0.12 [0.06 , 0.18]**
Total events:	53		17			

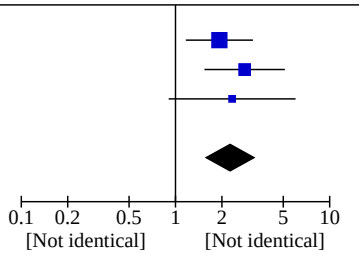
Heterogeneity: Chi² = 22.12, df = 2 (P < 0.0001); I² = 91%
Test for overall effect: Z = 4.07 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Typical antipsychotics versus placebo, Outcome 5: Extrapyramidal symptoms

Study or Subgroup	Typical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Allain 2000	34	101	18	103	50.6%	1.93 [1.17 , 3.18]
Tariot 2006	32	94	12	99	35.2%	2.81 [1.54 , 5.12]
Teri 2000	11	34	5	36	14.2%	2.33 [0.90 , 6.01]
Total (95% CI)		**229**		**238**	**100.0%**	**2.26 [1.58 , 3.23]**
Total events:	77		35			

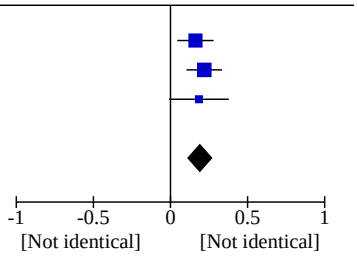
Heterogeneity: Chi² = 0.90, df = 2 (P = 0.64); I² = 0%
Test for overall effect: Z = 4.48 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Typical antipsychotics versus placebo, Outcome 6: Extrapyramidal symptoms (RD)

Study or Subgroup	Typical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
Allain 2000	34	101	18	103	41.5%	0.16 [0.04 , 0.28]
Tariot 2006	32	94	12	99	43.2%	0.22 [0.10 , 0.33]
Teri 2000	11	34	5	36	15.3%	0.18 [-0.01 , 0.38]
Total (95% CI)		**229**		**238**	**100.0%**	**0.19 [0.11 , 0.27]**
Total events:	77		35			

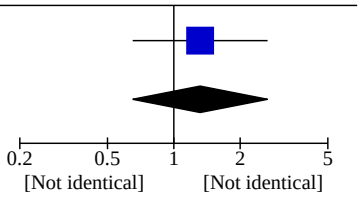
Heterogeneity: Chi² = 0.47, df = 2 (P = 0.79); I² = 0%
Test for overall effect: Z = 4.91 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Typical antipsychotics versus placebo, Outcome 7: Any serious adverse events

Study or Subgroup	Typical Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Tariot 2006	15	94	12	99	100.0%	1.32 [0.65 , 2.66]
Total (95% CI)		**94**		**99**	**100.0%**	**1.32 [0.65 , 2.66]**
Total events:	15		12			

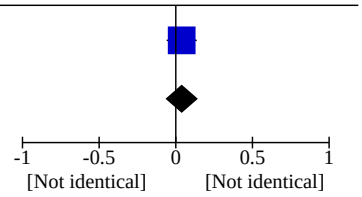
Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.44)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Typical antipsychotics versus placebo, Outcome 8: Any serious adverse events (RD)

Study or Subgroup	Typical Antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
Tariot 2006	15	94	12	99	100.0%	0.04 [-0.06 , 0.14]
Total (95% CI)		**94**		**99**	**100.0%**	**0.04 [-0.06 , 0.14]**
Total events:	15		12			

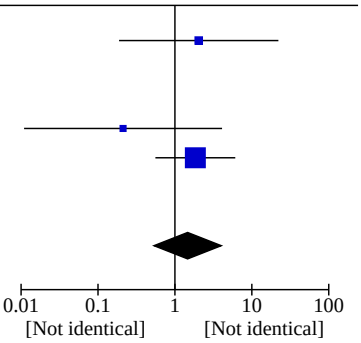
Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Typical antipsychotics versus placebo, Outcome 9: Death

Study or Subgroup	Typical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Allain 2000	2	101	1	103	17.8%	2.04 [0.19 , 22.14]
Auchus 1997	0	6	0	6		Not estimable
Devanand 1998	0	42	0	24		Not estimable
Finkel 1995	0	16	2	17	11.5%	0.21 [0.01 , 4.10]
Tariot 2006	7	94	4	99	70.7%	1.84 [0.56 , 6.09]
Teri 2000	0	34	0	36		Not estimable
Total (95% CI)		**293**		**285**	**100.0%**	**1.46 [0.54 , 4.00]**
Total events:	9		7			

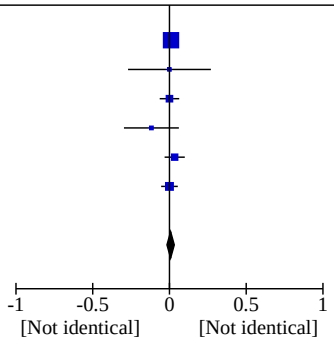
Heterogeneity: $Chi^2 = 1.85$, df = 2 (P = 0.40); $I^2 = 0\%$
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Typical antipsychotics versus placebo, Outcome 10: Death (RD)

Study or Subgroup	Typical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
Allain 2000	2	101	1	103	51.3%	0.01 [-0.02 , 0.04]
Auchus 1997	0	6	0	6	0.8%	0.00 [-0.27 , 0.27]
Devanand 1998	0	42	0	24	13.9%	0.00 [-0.06 , 0.06]
Finkel 1995	0	16	2	17	1.8%	-0.12 [-0.30 , 0.06]
Tariot 2006	7	94	4	99	13.0%	0.03 [-0.03 , 0.10]
Teri 2000	0	34	0	36	19.2%	0.00 [-0.05 , 0.05]
Total (95% CI)		**293**		**285**	**100.0%**	**0.01 [-0.02 , 0.03]**
Total events:	9		7			

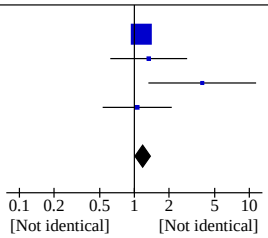
Heterogeneity: Chi² = 2.66, df = 5 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.62 (P = 0.53)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Typical antipsychotics versus placebo, Outcome 11: Number of responders for agitation

Study or Subgroup	Typical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Allain 2000	80	101	71	103	88.9%	1.15 [0.98 , 1.35]
Devanand 1998	16	40	6	20	4.0%	1.33 [0.62 , 2.88]
Finkel 1995	11	16	3	17	2.0%	3.90 [1.32 , 11.46]
Teri 2000	11	34	11	36	5.0%	1.06 [0.53 , 2.12]
Total (95% CI)		**191**		**176**	**100.0%**	**1.18 [1.01 , 1.38]**
Total events:	118		91			

Heterogeneity: Chi² = 5.00, df = 3 (P = 0.17); I² = 40%
Test for overall effect: Z = 2.11 (P = 0.04)
Test for subgroup differences: Not applicable

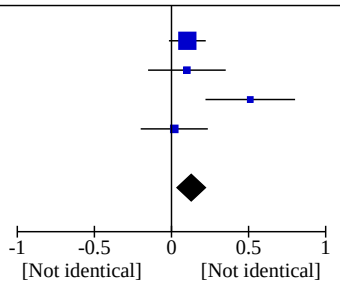


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.12. Comparison 1: Typical antipsychotics versus placebo, Outcome 12: Number of responders for agitation (RD)

Study or Subgroup	Typical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
Allain 2000	80	101	71	103	59.0%	0.10 [-0.02 , 0.22]
Devanand 1998	16	40	6	20	13.3%	0.10 [-0.15 , 0.35]
Finkel 1995	11	16	3	17	10.0%	0.51 [0.22 , 0.80]
Teri 2000	11	34	11	36	17.8%	0.02 [-0.20 , 0.24]
Total (95% CI)		**191**		**176**	**100.0%**	**0.13 [0.04 , 0.22]**
Total events:	118		91			

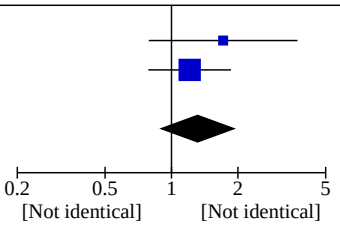
Heterogeneity: Chi² = 7.88, df = 3 (P = 0.05); I² = 62%
Test for overall effect: Z = 2.74 (P = 0.006)
Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1: Typical antipsychotics versus placebo, Outcome 13: Number of responders for psychosis

Study or Subgroup	Typical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Devanand 1998	18	42	6	24	23.7%	1.71 [0.79 , 3.72]
Tariot 2006	31	94	27	99	76.3%	1.21 [0.79 , 1.86]
Total (95% CI)		**136**		**123**	**100.0%**	**1.31 [0.90 , 1.92]**
Total events:	49		33			

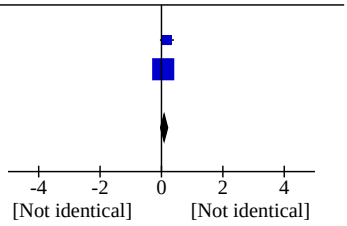
Heterogeneity: Chi² = 0.59, df = 1 (P = 0.44); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.16)
Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1: Typical antipsychotics versus placebo, Outcome 14: Number of responders for psychosis (RD)

Study or Subgroup	Typical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
Devanand 1998	18	42	6	24	24.2%	0.18 [-0.05 , 0.41]
Tariot 2006	31	94	27	99	75.8%	0.06 [-0.07 , 0.19]
Total (95% CI)		**136**		**123**	**100.0%**	**0.09 [-0.03 , 0.20]**
Total events:	49		33			

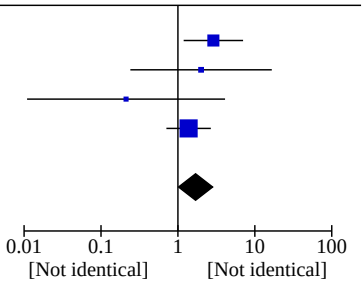
Heterogeneity: Chi² = 0.82, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 1.50 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1: Typical antipsychotics versus placebo, Outcome 15: Discontinuation due to adverse events

Study or Subgroup	Typical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Allain 2000	17	101	6	103	32.7%	2.89 [1.19 , 7.03]
Auchus 1997	2	6	1	6	5.8%	2.00 [0.24 , 16.61]
Finkel 1995	0	16	2	17	2.9%	0.21 [0.01 , 4.10]
Tariot 2006	17	94	13	99	58.6%	1.38 [0.71 , 2.68]
Total (95% CI)		**217**		**225**	**100.0%**	**1.70 [1.02 , 2.82]**
Total events:	36		22			

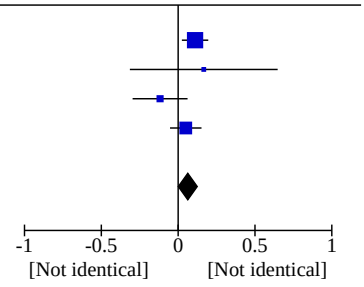
Heterogeneity: Chi² = 3.67, df = 3 (P = 0.30); I² = 18%
Test for overall effect: Z = 2.04 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 1.16. Comparison 1: Typical antipsychotics versus placebo, Outcome 16: Discontinuation due to adverse events (RD)

Study or Subgroup	Typical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
Allain 2000	17	101	6	103	50.9%	0.11 [0.02 , 0.20]
Auchus 1997	2	6	1	6	1.6%	0.17 [-0.31 , 0.65]
Finkel 1995	0	16	2	17	11.7%	-0.12 [-0.30 , 0.06]
Tariot 2006	17	94	13	99	35.8%	0.05 [-0.05 , 0.15]
Total (95% CI)		**217**		**225**	**100.0%**	**0.06 [0.00 , 0.12]**
Total events:	36		22			

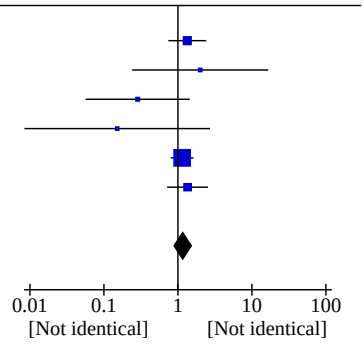
Heterogeneity: Chi² = 5.32, df = 3 (P = 0.15); I² = 44%
Test for overall effect: Z = 2.00 (P = 0.05)
Test for subgroup differences: Not applicable



Analysis 1.17. Comparison 1: Typical antipsychotics versus placebo, Outcome 17: Discontinuation (any reason)

Study or Subgroup	Typical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Allain 2000	21	101	16	103	20.5%	1.34 [0.74 , 2.41]
Auchus 1997	2	6	1	6	1.6%	2.00 [0.24 , 16.61]
Devanand 1998	2	42	4	24	2.7%	0.29 [0.06 , 1.45]
Finkel 1995	0	16	3	17	0.9%	0.15 [0.01 , 2.72]
Tariot 2006	39	94	36	99	56.7%	1.14 [0.80 , 1.63]
Teri 2000	14	34	11	36	17.6%	1.35 [0.71 , 2.54]
Total (95% CI)		**293**		**285**	**100.0%**	**1.16 [0.89 , 1.51]**
Total events:	78		71			

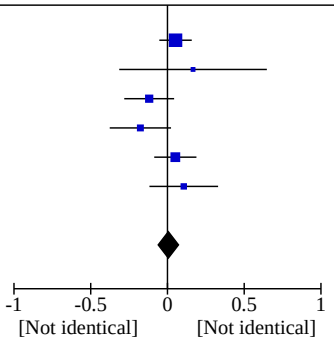
Heterogeneity: Chi² = 5.48, df = 5 (P = 0.36); I² = 9%
Test for overall effect: Z = 1.09 (P = 0.28)
Test for subgroup differences: Not applicable



Analysis 1.18. Comparison 1: Typical antipsychotics versus placebo, Outcome 18: Discontinuation (any reason) (RD)

Study or Subgroup	Typical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
Allain 2000	21	101	16	103	39.0%	0.05 [-0.05 , 0.16]
Auchus 1997	2	6	1	6	1.9%	0.17 [-0.31 , 0.65]
Devanand 1998	2	42	4	24	16.5%	-0.12 [-0.28 , 0.04]
Finkel 1995	0	16	3	17	10.9%	-0.18 [-0.38 , 0.02]
Tariot 2006	39	94	36	99	23.0%	0.05 [-0.09 , 0.19]
Teri 2000	14	34	11	36	8.7%	0.11 [-0.12 , 0.33]
Total (95% CI)		**293**		**285**	**100.0%**	**0.01 [-0.06 , 0.07]**
Total events:	78		71			

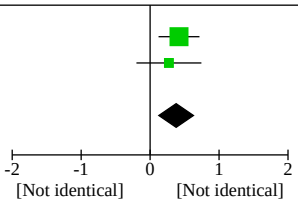
Heterogeneity: Chi² = 7.85, df = 5 (P = 0.16); I² = 36%
Test for overall effect: Z = 0.17 (P = 0.86)
Test for subgroup differences: Not applicable



Analysis 1.19. Comparison 1: Typical antipsychotics versus placebo, Outcome 19: Functioning (ADL)

Study or Subgroup	Typical antipsychotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Tariot 2006	1.59	3.06	85	0.47	2.24	94	71.6%	0.42 [0.12 , 0.72]
Teri 2000	1.79	3.2	34	0.89	3.32	36	28.4%	0.27 [-0.20 , 0.74]
Total (95% CI)		**119**				**130**	**100.0%**	**0.38 [0.13 , 0.63]**

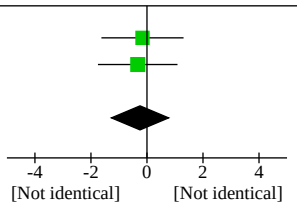
Heterogeneity: Chi² = 0.27, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 2.95 (P = 0.003)
Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1: Typical antipsychotics versus placebo, Outcome 20: Cognitive function

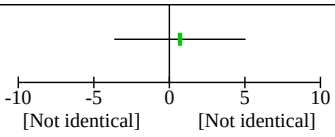
Study or Subgroup	Typical antipsychotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tariot 2006	-1.06	4.26	63	-0.9	4.42	72	48.4%	-0.16 [-1.63 , 1.31]
Teri 2000	-0.61	2.69	34	-0.28	3.35	36	51.6%	-0.33 [-1.75 , 1.09]
Total (95% CI)		**97**				**108**	**100.0%**	**-0.25 [-1.27 , 0.77]**

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable



Analysis 1.21. Comparison 1: Typical antipsychotics versus placebo, Outcome 21: Carer burden

Study or Subgroup	Typical antipsychotics Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Teri 2000	-1.88	8.89	34	-2.58	9.67	36	0.70 [-3.65 , 5.05]



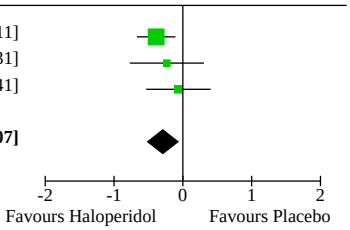
Comparison 2. Haloperidol versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Agitation	3	330	Std. Mean Difference (IV, Fixed, 95% CI)	-0.29 [-0.51, -0.07]
2.2 Psychosis	2	240	Std. Mean Difference (IV, Fixed, 95% CI)	-0.29 [-0.55, -0.03]
2.3 Somnolence	3	466	Risk Ratio (IV, Fixed, 95% CI)	2.62 [1.51, 4.56]
2.4 Extrapyramidal symptoms	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2.5 Serious adverse events	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2.6 Death	5	545	Risk Ratio (IV, Fixed, 95% CI)	1.88 [0.65, 5.48]
2.7 Number of responders for agitation	3	334	Risk Ratio (IV, Fixed, 95% CI)	1.15 [0.99, 1.35]
2.8 Number of responders for psychosis	2	259	Risk Ratio (IV, Fixed, 95% CI)	1.31 [0.90, 1.92]
2.9 Discontinuation due to adverse events	3	409	Risk Ratio (IV, Fixed, 95% CI)	1.81 [1.08, 3.03]
2.10 Discontinuation (any reason)	5	545	Risk Ratio (IV, Fixed, 95% CI)	1.18 [0.90, 1.54]
2.11 Functioning (ADL)	2	249	Std. Mean Difference (IV, Fixed, 95% CI)	0.38 [0.13, 0.63]
2.12 Cognitive function	2	205	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-1.27, 0.77]
2.13 Carer burden	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Haloperidol versus placebo, Outcome 1: Agitation

Study or Subgroup	[Not identical] Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Allain 2000	-6.75	5.46	99	-4.71	5.01	101	61.5%	-0.39 [-0.67 , -0.11]
Devanand 1998	-0.55	0.72	40	-0.25	1.98	20	16.6%	-0.23 [-0.77 , 0.31]
Teri 2000	-7.26	22.51	34	-5.94	18.5	36	21.9%	-0.06 [-0.53 , 0.41]
Total (95% CI)			**173**			**157**	**100.0%**	**-0.29 [-0.51 , -0.07]**

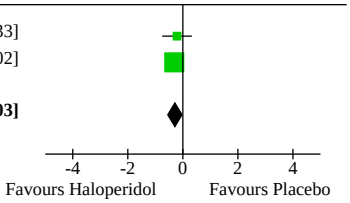
Heterogeneity: Chi² = 1.41, df = 2 (P = 0.49); I² = 0%
Test for overall effect: Z = 2.60 (P = 0.009)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Haloperidol versus placebo, Outcome 2: Psychosis

Study or Subgroup	[Not identical] Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Devanand 1998	-1.43	2.96	40	-0.85	2.08	20	23.0%	-0.21 [-0.75 , 0.33]
Tariot 2006	-5.93	5.58	86	-4.11	5.99	94	77.0%	-0.31 [-0.61 , -0.02]
Total (95% CI)			**126**			**114**	**100.0%**	**-0.29 [-0.55 , -0.03]**

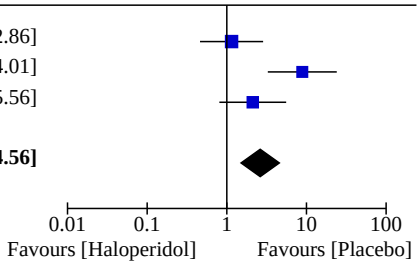
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 2.20 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Haloperidol versus placebo, Outcome 3: Somnolence

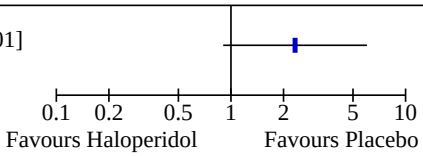
Study or Subgroup	[Not identical] Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Allain 2000	9	101	8	103	36.6%	1.15 [0.46 , 2.86]
Tariot 2006	34	94	4	98	30.7%	8.86 [3.27 , 24.01]
Teri 2000	10	34	5	36	32.7%	2.12 [0.81 , 5.56]
Total (95% CI)		**229**		**237**	**100.0%**	**2.62 [1.51 , 4.56]**
Total events:	53		17			

Heterogeneity: Chi² = 9.08, df = 2 (P = 0.01); I² = 78%
Test for overall effect: Z = 3.43 (P = 0.0006)
Test for subgroup differences: Not applicable



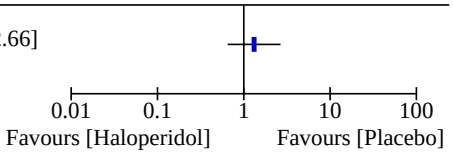
Analysis 2.4. Comparison 2: Haloperidol versus placebo, Outcome 4: Extrapyramidal symptoms

Study or Subgroup	[Not identical] Events	Total	Placebo Events	Total	Risk Ratio IV, Fixed, 95% CI
Teri 2000	11	34	5	36	2.33 [0.90 , 6.01]



Analysis 2.5. Comparison 2: Haloperidol versus placebo, Outcome 5: Serious adverse events

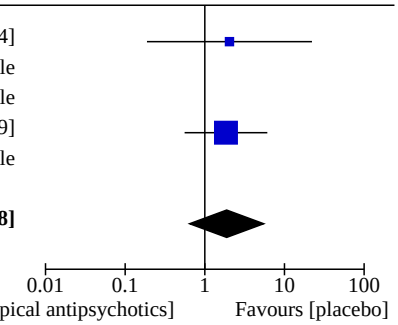
Study or Subgroup	[Not identical] Events	Total	Placebo Events	Total	Risk Ratio IV, Fixed, 95% CI
Tariot 2006	15	94	12	99	1.32 [0.65 , 2.66]



Analysis 2.6. Comparison 2: Haloperidol versus placebo, Outcome 6: Death

Study or Subgroup	[Not identical] Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Allain 2000	2	101	1	103	20.1%	2.04 [0.19 , 22.14]
Auchus 1997	0	6	0	6		Not estimable
Devanand 1998	0	42	0	24		Not estimable
Tariot 2006	7	94	4	99	79.9%	1.84 [0.56 , 6.09]
Teri 2000	0	34	0	36		Not estimable
Total (95% CI)		**277**		**268**	**100.0%**	**1.88 [0.65 , 5.48]**
Total events:	9		5			

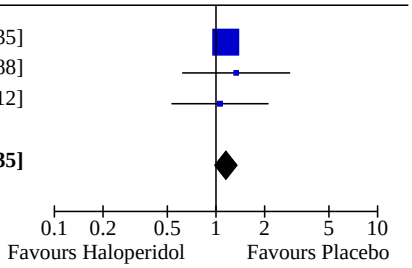
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 1.16 (P = 0.25)
Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2: Haloperidol versus placebo, Outcome 7: Number of responders for agitation

Study or Subgroup	[Not identical] Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Allain 2000	80	101	71	103	90.8%	1.15 [0.98 , 1.35]
Devanand 1998	16	40	6	20	4.1%	1.33 [0.62 , 2.88]
Teri 2000	11	34	11	36	5.1%	1.06 [0.53 , 2.12]
Total (95% CI)		**175**		**159**	**100.0%**	**1.15 [0.99 , 1.35]**
Total events:	107		88			

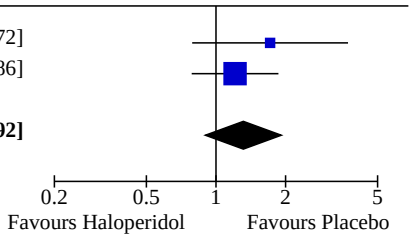
Heterogeneity: Chi² = 0.20, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 1.77 (P = 0.08)
Test for subgroup differences: Not applicable



Analysis 2.8. Comparison 2: Haloperidol versus placebo, Outcome 8: Number of responders for psychosis

Study or Subgroup	[Not identical] Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Devanand 1998	18	42	6	24	23.7%	1.71 [0.79 , 3.72]
Tariot 2006	31	94	27	99	76.3%	1.21 [0.79 , 1.86]
Total (95% CI)		**136**		**123**	**100.0%**	**1.31 [0.90 , 1.92]**
Total events:	49		33			

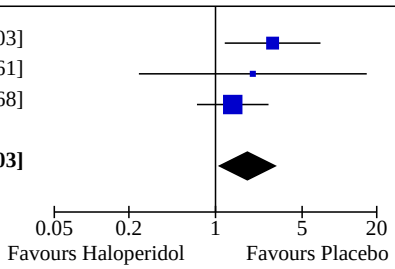
Heterogeneity: Chi² = 0.59, df = 1 (P = 0.44); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.16)
Test for subgroup differences: Not applicable



Analysis 2.9. Comparison 2: Haloperidol versus placebo, Outcome 9: Discontinuation due to adverse events

Study or Subgroup	[Not identical] Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Allain 2000	17	101	6	103	33.7%	2.89 [1.19 , 7.03]
Auchus 1997	2	6	1	6	5.9%	2.00 [0.24 , 16.61]
Tariot 2006	17	94	13	99	60.3%	1.38 [0.71 , 2.68]
Total (95% CI)		**201**		**208**	**100.0%**	**1.81 [1.08 , 3.03]**
Total events:	36		20			

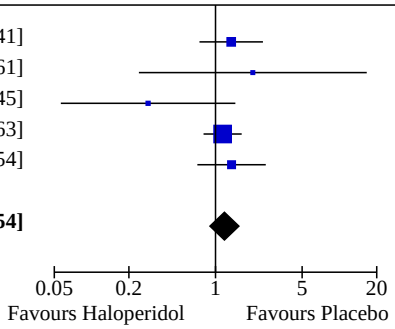
Heterogeneity: Chi² = 1.72, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 2.25 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 2.10. Comparison 2: Haloperidol versus placebo, Outcome 10: Discontinuation (any reason)

Study or Subgroup	[Not identical] Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Allain 2000	21	101	16	103	20.7%	1.34 [0.74 , 2.41]
Auchus 1997	2	6	1	6	1.6%	2.00 [0.24 , 16.61]
Devanand 1998	2	42	4	24	2.7%	0.29 [0.06 , 1.45]
Tariot 2006	39	94	36	99	57.2%	1.14 [0.80 , 1.63]
Teri 2000	14	34	11	36	17.8%	1.35 [0.71 , 2.54]
Total (95% CI)		**277**		**268**	**100.0%**	**1.18 [0.90 , 1.54]**
Total events:	78		68			

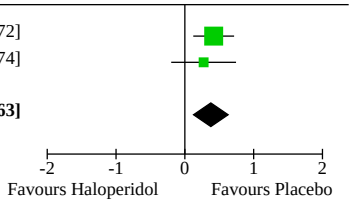
Heterogeneity: Chi² = 3.56, df = 4 (P = 0.47); I² = 0%
Test for overall effect: Z = 1.21 (P = 0.23)
Test for subgroup differences: Not applicable



Analysis 2.11. Comparison 2: Haloperidol versus placebo, Outcome 11: Functioning (ADL)

Study or Subgroup	[Not identical] Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Tariot 2006	1.59	3.06	85	0.47	2.24	94	71.6%	0.42 [0.12 , 0.72]
Teri 2000	1.79	3.2	34	0.89	3.32	36	28.4%	0.27 [-0.20 , 0.74]
Total (95% CI)			**119**			**130**	**100.0%**	**0.38 [0.13 , 0.63]**

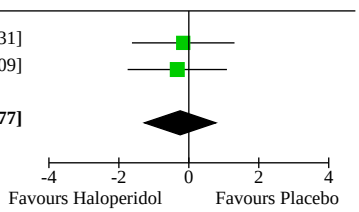
Heterogeneity: Chi² = 0.27, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 2.95 (P = 0.003)
Test for subgroup differences: Not applicable



Analysis 2.12. Comparison 2: Haloperidol versus placebo, Outcome 12: Cognitive function

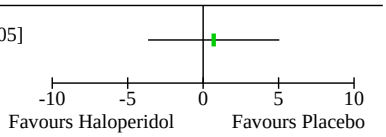
Study or Subgroup	[Not identical] Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Tariot 2006	-1.06	4.26	63	-0.9	4.42	72	48.4%	-0.16 [-1.63 , 1.31]
Teri 2000	-0.61	2.69	34	-0.28	3.35	36	51.6%	-0.33 [-1.75 , 1.09]
Total (95% CI)			**97**			**108**	**100.0%**	**-0.25 [-1.27 , 0.77]**

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable



Analysis 2.13. Comparison 2: Haloperidol versus placebo, Outcome 13: Carer burden

Study or Subgroup	[Not identical] Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Teri 2000	-1.88	8.89	34	-2.58	9.67	36	0.70 [-3.65 , 5.05]



Comparison 3. Atypical antipsychotics versus placebo

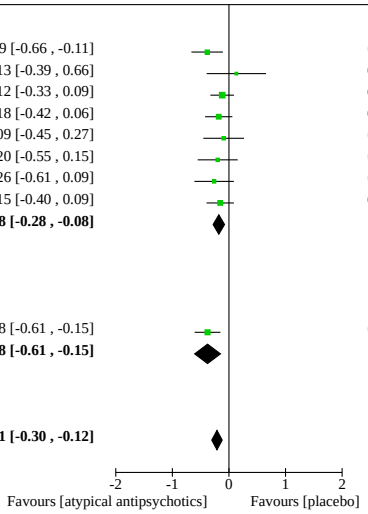
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Agitation	7	1971	Std. Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.30, -0.12]
3.1.1 *Patients with agitation*	6	1670	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.28, -0.08]
3.1.2 *Patients with aggression*	1	301	Std. Mean Difference (IV, Fixed, 95% CI)	-0.38 [-0.61, -0.15]
3.2 Psychosis	12	3364	Std. Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.18, -0.03]
3.3 Somnolence	13	3878	Risk Ratio (IV, Fixed, 95% CI)	1.93 [1.57, 2.39]
3.4 Somnolence (RD)	13	3878	Risk Difference (IV, Fixed, 95% CI)	0.07 [0.05, 0.08]
3.5 Extrapyramidal symptoms	15	4180	Risk Ratio (IV, Fixed, 95% CI)	1.39 [1.14, 1.68]
3.6 Extrapyramidal symptoms (RD)	15	4180	Risk Difference (IV, Fixed, 95% CI)	0.03 [0.02, 0.05]
3.7 Any adverse event	11	2785	Risk Ratio (IV, Fixed, 95% CI)	1.05 [1.02, 1.09]
3.8 Any adverse event (RD)	11	2785	Risk Difference (IV, Fixed, 95% CI)	0.05 [0.02, 0.07]
3.9 Any serious adverse event	15	4316	Risk Ratio (IV, Fixed, 95% CI)	1.32 [1.09, 1.61]

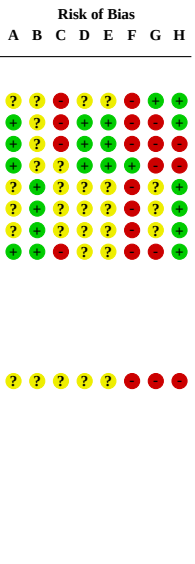
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.10 Any serious adverse event (RD)	15	4316	Risk Difference (IV, Fixed, 95% CI)	0.04 [0.02, 0.05]
3.11 Death	17	5032	Risk Ratio (IV, Fixed, 95% CI)	1.36 [0.90, 2.05]
3.12 Death (RD)	17	5032	Risk Difference (IV, Fixed, 95% CI)	0.01 [-0.00, 0.02]
3.13 Number of responders for agitation	4	1304	Risk Ratio (IV, Fixed, 95% CI)	1.31 [1.16, 1.48]
3.13.1 Assessments not including physical aggression	3	959	Risk Ratio (IV, Fixed, 95% CI)	1.22 [1.07, 1.40]
3.13.2 Assessments including physical aggression	1	345	Risk Ratio (IV, Fixed, 95% CI)	1.69 [1.31, 2.17]
3.14 Number of responders for agitation (RD)	4	1304	Risk Difference (IV, Fixed, 95% CI)	0.13 [0.08, 0.18]
3.14.1 Assessments not including physical aggression	3	959	Risk Difference (IV, Fixed, 95% CI)	0.10 [0.04, 0.16]
3.14.2 Assessments including physical aggression	1	345	Risk Difference (IV, Fixed, 95% CI)	0.22 [0.12, 0.33]
3.15 Number of responders for psychosis	7	1958	Risk Ratio (IV, Fixed, 95% CI)	1.13 [1.03, 1.23]
3.16 Number of responders for psychosis (RD)	7	1958	Risk Difference (IV, Fixed, 95% CI)	0.08 [0.04, 0.13]
3.17 Discontinuation due to adverse events	17	5058	Risk Ratio (IV, Fixed, 95% CI)	1.41 [1.15, 1.72]
3.18 Discontinuation due to adverse events (RD)	17	5058	Risk Difference (IV, Fixed, 95% CI)	0.04 [0.02, 0.06]
3.19 Discontinuation (any reason)	18	5095	Risk Ratio (IV, Fixed, 95% CI)	0.95 [0.89, 1.01]
3.20 Discontinuation (any reason) (RD)	18	5095	Risk Difference (IV, Fixed, 95% CI)	-0.00 [-0.02, 0.02]
3.21 Functioning (ADL)	3	514	Std. Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.39, -0.03]
3.22 Cognitive function	11	2698	Std. Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.19, -0.02]
3.23 Cognitive function (single study)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.24 Health-related quality of life	1	151	Mean Difference (IV, Fixed, 95% CI)	0.95 [-4.14, 6.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.25 Time spend providing care (caregiver)	1	151	Mean Difference (IV, Fixed, 95% CI)	0.08 [-1.39, 1.55]

Analysis 3.1. Comparison 3: Atypical antipsychotics versus placebo, Outcome 1: Agitation

Study or Subgroup	Atypical antipsychotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
3.1.1 *Patients with agitation*								
Allain 2000	-6.57	4.6	102	-4.71	5.01	101	11.1%	-0.39 [-0.66 , -0.11]
Ballard 2005	-4	15.4	27	-6.2	17.6	29	3.1%	0.13 [-0.39 , 0.66]
Grossberg 2020a	-19.6	15.1	272	-17.8	14.9	131	19.6%	-0.12 [-0.33 , 0.09]
Grossberg 2020b	-18.9	13.7	131	-16.5	12.8	135	14.7%	-0.18 [-0.42 , 0.06]
Schneider 2006 CATIE-AD	-0.2	1.1	84	-0.1	1	46	6.6%	-0.09 [-0.45 , 0.27]
Schneider 2006 CATIE-AD	-0.3	1	94	-0.1	1	46	6.8%	-0.20 [-0.55 , 0.15]
Schneider 2006 CATIE-AD	-0.4	1.2	99	-0.1	1	47	7.0%	-0.26 [-0.61 , 0.09]
Zhong 2007	-5.3	9.2	234	-3.9	8.6	92	14.6%	-0.15 [-0.40 , 0.09]
Subtotal (95% CI)			**1043**			**627**	**83.6%**	**-0.18 [-0.28 , -0.08]**
Heterogeneity: Chi² = 4.26, df = 7 (P = 0.75); I² = 0%								
Test for overall effect: Z = 3.47 (P = 0.0005)								
3.1.2 *Patients with aggression*								
Brodaty 2003 RIS-AUS-05	-7.5	12.2	149	-3.1	11	152	16.4%	-0.38 [-0.61 , -0.15]
Subtotal (95% CI)			**149**			**152**	**16.4%**	**-0.38 [-0.61 , -0.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.25 (P = 0.001)								
Total (95% CI)			**1192**			**779**	**100.0%**	**-0.21 [-0.30 , -0.12]**
Heterogeneity: Chi² = 6.71, df = 8 (P = 0.57); I² = 0%								
Test for overall effect: Z = 4.49 (P < 0.00001)								
Test for subgroup differences: Chi² = 2.45, df = 1 (P = 0.12), I² = 59.3%								

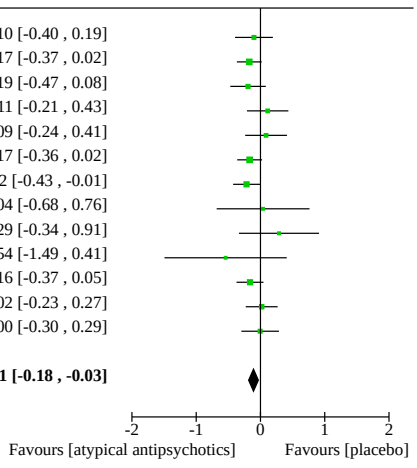




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 3.2. Comparison 3: Atypical antipsychotics versus placebo, Outcome 2: Psychosis

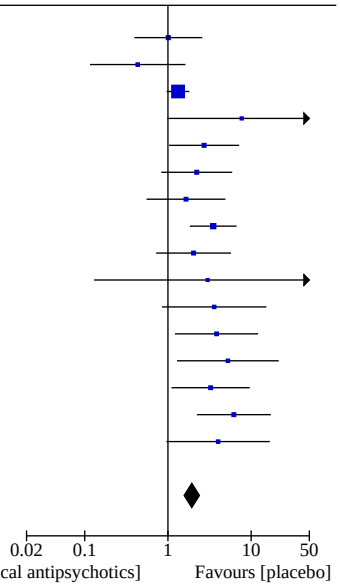
Study or Subgroup	Atypical antipsychotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Ballard 2018	-4.1	6	87	-3.5	5.8	91	6.6%	-0.10 [-0.40 , 0.19]
De Deyn 2004 F1D MC HGIV	-5.9	4.9	513	-5	6.1	129	15.2%	-0.17 [-0.37 , 0.02]
De Deyn 2005	-6.55	5.3	103	-5.52	5.3	100	7.5%	-0.19 [-0.47 , 0.08]
Deberdt 2005 F1D MC HGGU	-4	6.4	193	-4.7	5.3	46	5.5%	0.11 [-0.21 , 0.43]
Deberdt 2005 F1D MC HGGU	-4.2	5.8	190	-4.7	5.3	45	5.4%	0.09 [-0.24 , 0.41]
Mintzer 2006 RIS USA 232	-2.9	3.55	201	-2.3	3.55	212	15.2%	-0.17 [-0.36 , 0.02]
Mintzer 2007	-6.2	5.1	357	-5.1	5	117	12.9%	-0.22 [-0.43 , -0.01]
NCT00287742 2006	-1.3	2.2	13	-1.4	2.5	17	1.1%	0.04 [-0.68 , 0.76]
Paleacu 2008	-3.4	6.74	20	-5.15	5.04	20	1.5%	0.29 [-0.34 , 0.91]
RIS-INT-83 2003	-2.4	5.58	10	0.6	4.84	8	0.6%	-0.54 [-1.49 , 0.41]
Schneider 2003 RIS USA 63	-1.3	2.3	346	-0.95	1.6	117	12.9%	-0.16 [-0.37 , 0.05]
Streim 2008	-4.53	4.62	128	-4.62	4.78	121	9.2%	0.02 [-0.23 , 0.27]
Tariot 2006	-4.14	6.04	86	-4.11	5.99	94	6.6%	-0.00 [-0.30 , 0.29]
Total (95% CI)			**2247**			**1117**	**100.0%**	**-0.11 [-0.18 , -0.03]**
Heterogeneity: Chi² = 9.68, df = 12 (P = 0.64); I² = 0%								
Test for overall effect: Z = 2.83 (P = 0.005)								
Test for subgroup differences: Not applicable								



Analysis 3.3. Comparison 3: Atypical antipsychotics versus placebo, Outcome 3: Somnolence

Study or Subgroup	Atypical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Allain 2000	8	102	8	103	5.0%	1.01 [0.39 , 2.59]
Ballard 2018	3	90	7	91	2.6%	0.43 [0.12 , 1.62]
Brodaty 2003 RIS-AUS-05	61	167	47	170	45.0%	1.32 [0.96 , 1.81]
De Deyn 2005	8	106	1	102	1.0%	7.70 [0.98 , 60.46]
Deberdt 2005 F1D MC HGGU	47	203	4	47	4.7%	2.72 [1.03 , 7.18]
Deberdt 2005 F1D MC HGGU	37	196	4	47	4.6%	2.22 [0.83 , 5.92]
Grossberg 2020b	8	133	5	137	3.7%	1.65 [0.55 , 4.91]
Mintzer 2006 RIS USA 232	38	235	11	238	10.7%	3.50 [1.83 , 6.68]
Mintzer 2007	25	360	4	117	4.2%	2.03 [0.72 , 5.72]
Paleacu 2008	1	20	0	20	0.5%	3.00 [0.13 , 69.52]
Schneider 2006 CATIE-AD	13	85	2	47	2.1%	3.59 [0.85 , 15.25]
Schneider 2006 CATIE-AD	24	100	3	48	3.4%	3.84 [1.22 , 12.13]
Schneider 2006 CATIE-AD	21	94	2	47	2.3%	5.25 [1.28 , 21.45]
Streim 2008	14	130	4	121	3.8%	3.26 [1.10 , 9.62]
Tariot 2006	23	91	4	98	4.3%	6.19 [2.23 , 17.22]
Zhong 2007	21	241	2	92	2.2%	4.01 [0.96 , 16.76]
Total (95% CI)		**2353**		**1525**	**100.0%**	**1.93 [1.57 , 2.39]**
Total events:	352		108			

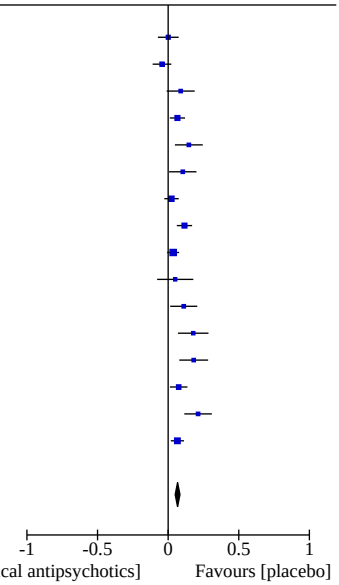
Heterogeneity: Chi² = 28.93, df = 15 (P = 0.02); I² = 48%
Test for overall effect: Z = 6.12 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: Atypical antipsychotics versus placebo, Outcome 4: Somnolence (RD)

Study or Subgroup	Atypical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
Allain 2000	8	102	8	103	5.2%	0.00 [-0.07 , 0.07]
Ballard 2018	3	90	7	91	6.5%	-0.04 [-0.11 , 0.02]
Brodaty 2003 RIS-AUS-05	61	167	47	170	2.9%	0.09 [-0.01 , 0.19]
De Deyn 2005	8	106	1	102	9.8%	0.07 [0.01 , 0.12]
Deberdt 2005 F1D MC HGGU	47	203	4	47	2.9%	0.15 [0.05 , 0.25]
Deberdt 2005 F1D MC HGGU	37	196	4	47	3.0%	0.10 [0.01 , 0.20]
Grossberg 2020b	8	133	5	137	10.8%	0.02 [-0.03 , 0.07]
Mintzer 2006 RIS USA 232	38	235	11	238	9.7%	0.12 [0.06 , 0.17]
Mintzer 2007	25	360	4	117	15.9%	0.04 [-0.01 , 0.08]
Paleacu 2008	1	20	0	20	1.7%	0.05 [-0.08 , 0.18]
Schneider 2006 CATIE-AD	13	85	2	47	3.1%	0.11 [0.01 , 0.21]
Schneider 2006 CATIE-AD	24	100	3	48	2.4%	0.18 [0.07 , 0.29]
Schneider 2006 CATIE-AD	21	94	2	47	2.7%	0.18 [0.08 , 0.28]
Streim 2008	14	130	4	121	7.3%	0.07 [0.01 , 0.14]
Tariot 2006	23	91	4	98	3.0%	0.21 [0.11 , 0.31]
Zhong 2007	21	241	2	92	13.1%	0.07 [0.02 , 0.11]
Total (95% CI)		**2353**		**1525**	**100.0%**	**0.07 [0.05 , 0.08]**
Total events:	352		108			

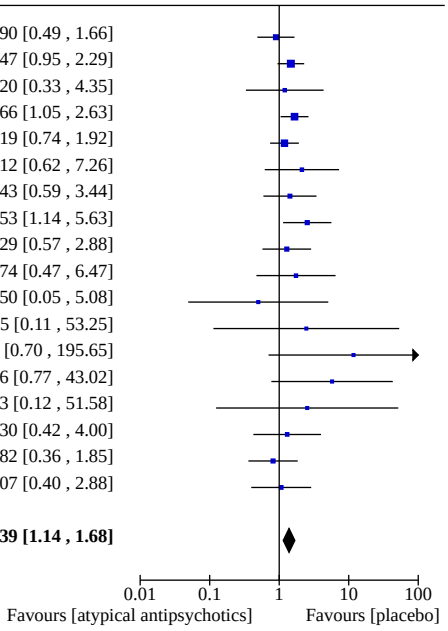
Heterogeneity: Chi² = 43.31, df = 15 (P = 0.0001); I² = 65%
Test for overall effect: Z = 7.77 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: Atypical antipsychotics versus placebo, Outcome 5: Extrapyramidal symptoms

Study or Subgroup	Atypical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Allain 2000	16	102	18	103	9.7%	0.90 [0.49 , 1.66]
Brodaty 2003 RIS-AUS-05	39	167	27	170	18.8%	1.47 [0.95 , 2.29]
De Deyn 2005	5	106	4	102	2.2%	1.20 [0.33 , 4.35]
Deberdt 2005 F1D MC HGGU	97	196	14	47	17.3%	1.66 [1.05 , 2.63]
Deberdt 2005 F1D MC HGGU	72	203	14	47	16.2%	1.19 [0.74 , 1.92]
Grossberg 2020a	14	297	3	135	2.4%	2.12 [0.62 , 7.26]
Grossberg 2020b	11	132	8	137	4.8%	1.43 [0.59 , 3.44]
Mintzer 2006 RIS USA 232	20	235	8	238	5.7%	2.53 [1.14 , 5.63]
Mintzer 2007	27	360	7	120	5.7%	1.29 [0.57 , 2.88]
NCT00287742 2006	4	13	3	17	2.1%	1.74 [0.47 , 6.47]
Paleacu 2008	1	20	2	20	0.7%	0.50 [0.05 , 5.08]
RIS-INT-83 2003	1	10	0	8	0.4%	2.45 [0.11 , 53.25]
Schneider 2006 CATIE-AD	10	85	0	47	0.5%	11.72 [0.70 , 195.65]
Schneider 2006 CATIE-AD	12	100	1	48	0.9%	5.76 [0.77 , 43.02]
Schneider 2006 CATIE-AD	2	94	0	47	0.4%	2.53 [0.12 , 51.58]
Streim 2008	7	130	5	121	2.9%	1.30 [0.42 , 4.00]
Tariot 2006	9	91	12	99	5.5%	0.82 [0.36 , 1.85]
Zhong 2007	14	241	5	92	3.7%	1.07 [0.40 , 2.88]
Total (95% CI)		**2582**		**1598**	**100.0%**	**1.39 [1.14 , 1.68]**
Total events:	361		131			

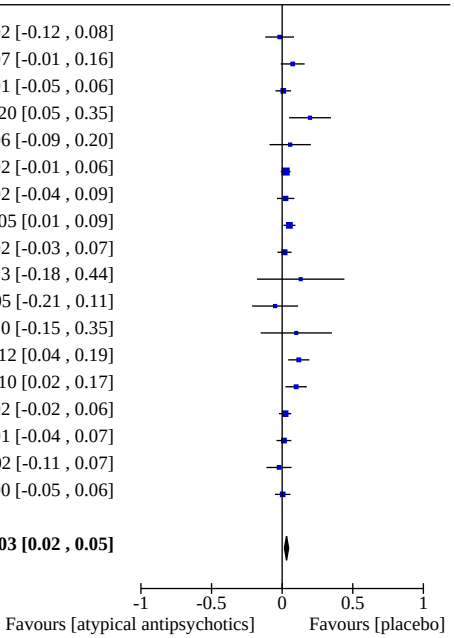
Heterogeneity: Chi² = 12.87, df = 17 (P = 0.74); I² = 0%
Test for overall effect: Z = 3.33 (P = 0.0009)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: Atypical antipsychotics versus placebo, Outcome 6: Extrapyramidal symptoms (RD)

Study or Subgroup	Atypical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
Allain 2000	16	102	18	103	2.2%	-0.02 [-0.12 , 0.08]
Brodaty 2003 RIS-AUS-05	39	167	27	170	3.1%	0.07 [-0.01 , 0.16]
De Deyn 2005	5	106	4	102	7.3%	0.01 [-0.05 , 0.06]
Deberdt 2005 F1D MC HGGU	97	196	14	47	1.0%	0.20 [0.05 , 0.35]
Deberdt 2005 F1D MC HGGU	72	203	14	47	1.0%	0.06 [-0.09 , 0.20]
Grossberg 2020a	14	297	3	135	18.6%	0.02 [-0.01 , 0.06]
Grossberg 2020b	11	132	8	137	5.9%	0.02 [-0.04 , 0.09]
Mintzer 2006 RIS USA 232	20	235	8	238	12.4%	0.05 [0.01 , 0.09]
Mintzer 2007	27	360	7	120	8.9%	0.02 [-0.03 , 0.07]
NCT00287742 2006	4	13	3	17	0.2%	0.13 [-0.18 , 0.44]
Paleacu 2008	1	20	2	20	0.8%	-0.05 [-0.21 , 0.11]
RIS-INT-83 2003	1	10	0	8	0.4%	0.10 [-0.15 , 0.35]
Schneider 2006 CATIE-AD	10	85	0	47	4.0%	0.12 [0.04 , 0.19]
Schneider 2006 CATIE-AD	12	100	1	48	3.9%	0.10 [0.02 , 0.17]
Schneider 2006 CATIE-AD	2	94	0	47	12.0%	0.02 [-0.02 , 0.06]
Streim 2008	7	130	5	121	8.1%	0.01 [-0.04 , 0.07]
Tariot 2006	9	91	12	99	2.8%	-0.02 [-0.11 , 0.07]
Zhong 2007	14	241	5	92	7.4%	0.00 [-0.05 , 0.06]
Total (95% CI)		**2582**		**1598**	**100.0%**	**0.03 [0.02 , 0.05]**
Total events:	361		131			

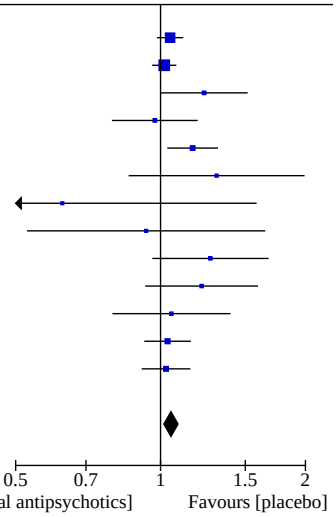
Heterogeneity: Chi² = 21.81, df = 17 (P = 0.19); I² = 22%
Test for overall effect: Z = 4.08 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 3.7. Comparison 3: Atypical antipsychotics versus placebo, Outcome 7: Any adverse event

Study or Subgroup	Atypical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Ballard 2018	88	90	85	91	29.1%	1.05 [0.98 , 1.11]
Brodaty 2003 RIS-AUS-05	157	167	157	170	34.4%	1.02 [0.96 , 1.08]
Grossberg 2020a	168	297	62	135	2.6%	1.23 [1.00 , 1.52]
Grossberg 2020b	75	132	80	137	2.7%	0.97 [0.79 , 1.19]
Mintzer 2006 RIS USA 232	175	235	152	238	7.8%	1.17 [1.03 , 1.32]
NCT00287742 2006	11	13	11	17	0.6%	1.31 [0.86 , 1.99]
Paleacu 2008	5	20	8	20	0.1%	0.63 [0.25 , 1.58]
RIS-INT-83 2003	7	10	6	8	0.4%	0.93 [0.53 , 1.65]
Schneider 2006 CATIE-AD	62	85	27	47	1.5%	1.27 [0.96 , 1.68]
Schneider 2006 CATIE-AD	71	100	28	48	1.6%	1.22 [0.93 , 1.59]
Schneider 2006 CATIE-AD	59	94	28	47	1.4%	1.05 [0.79 , 1.40]
Streim 2008	110	130	99	121	9.2%	1.03 [0.93 , 1.16]
Zhong 2007	199	241	74	92	8.5%	1.03 [0.91 , 1.15]
Total (95% CI)		**1614**		**1171**	**100.0%**	**1.05 [1.02 , 1.09]**
Total events:	1187		817			

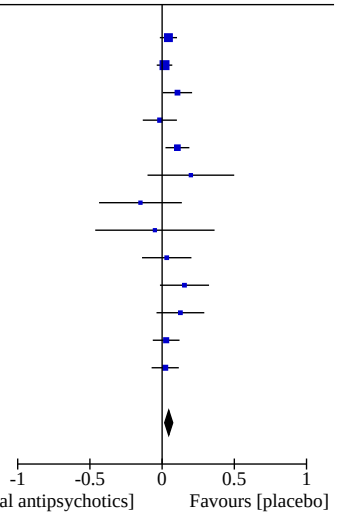
Heterogeneity: Chi² = 12.32, df = 12 (P = 0.42); I² = 3%
Test for overall effect: Z = 2.88 (P = 0.004)
Test for subgroup differences: Not applicable



Analysis 3.8. Comparison 3: Atypical antipsychotics versus placebo, Outcome 8: Any adverse event (RD)

Study or Subgroup	Atypical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
Ballard 2018	88	90	85	91	21.7%	0.04 [-0.02 , 0.10]
Brodaty 2003 RIS-AUS-05	157	167	157	170	26.4%	0.02 [-0.04 , 0.07]
Grossberg 2020a	168	297	62	135	7.5%	0.11 [0.01 , 0.21]
Grossberg 2020b	75	132	80	137	5.5%	-0.02 [-0.13 , 0.10]
Mintzer 2006 RIS USA 232	175	235	152	238	11.2%	0.11 [0.02 , 0.19]
NCT00287742 2006	11	13	11	17	0.8%	0.20 [-0.10 , 0.50]
Paleacu 2008	5	20	8	20	0.9%	-0.15 [-0.44 , 0.14]
RIS-INT-83 2003	7	10	6	8	0.4%	-0.05 [-0.46 , 0.36]
Schneider 2006 CATIE-AD	59	94	28	47	2.6%	0.03 [-0.14 , 0.20]
Schneider 2006 CATIE-AD	62	85	27	47	2.6%	0.15 [-0.02 , 0.32]
Schneider 2006 CATIE-AD	71	100	28	48	2.8%	0.13 [-0.04 , 0.29]
Streim 2008	110	130	99	121	8.9%	0.03 [-0.06 , 0.12]
Zhong 2007	199	241	74	92	8.6%	0.02 [-0.07 , 0.12]
Total (95% CI)		**1614**		**1171**	**100.0%**	**0.05 [0.02 , 0.07]**
Total events:	1187		817			

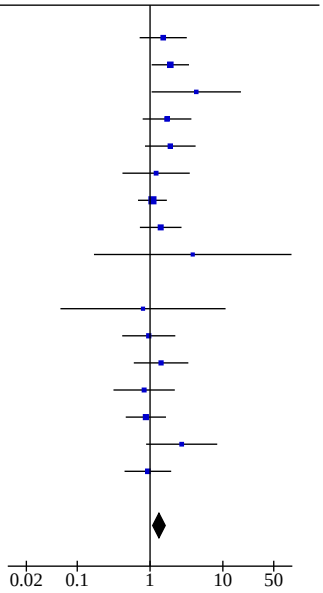
Heterogeneity: Chi² = 11.53, df = 12 (P = 0.48); I² = 0%
Test for overall effect: Z = 3.24 (P = 0.001)
Test for subgroup differences: Not applicable



Analysis 3.9. Comparison 3: Atypical antipsychotics versus placebo, Outcome 9: Any serious adverse event

Study or Subgroup	Atypical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Ballard 2018	15	90	10	91	7.0%	1.52 [0.72 , 3.20]
Brodaty 2003 RIS-AUS-05	28	167	15	170	11.2%	1.90 [1.05 , 3.43]
De Deyn 2004 F1D MC HGIV	35	523	2	129	2.0%	4.32 [1.05 , 17.71]
De Deyn 2005	16	106	9	102	6.6%	1.71 [0.79 , 3.69]
Grossberg 2020a	29	297	7	136	6.1%	1.90 [0.85 , 4.22]
Grossberg 2020b	7	132	6	137	3.4%	1.21 [0.42 , 3.51]
Mintzer 2006 RIS USA 232	33	235	31	238	18.8%	1.08 [0.68 , 1.70]
Mintzer 2007	42	360	10	120	9.0%	1.40 [0.73 , 2.70]
NCT00287742 2006	1	13	0	17	0.4%	3.86 [0.17 , 87.65]
Paleacu 2008	0	20	0	20		Not estimable
RIS-INT-83 2003	1	10	1	8	0.6%	0.80 [0.06 , 10.89]
Schneider 2006 CATIE-AD	14	100	7	48	5.5%	0.96 [0.41 , 2.22]
Schneider 2006 CATIE-AD	17	94	6	47	5.3%	1.42 [0.60 , 3.36]
Schneider 2006 CATIE-AD	9	85	6	47	4.2%	0.83 [0.31 , 2.19]
Streim 2008	16	130	17	121	9.6%	0.88 [0.46 , 1.66]
Tariot 2006	10	91	4	99	3.1%	2.72 [0.88 , 8.37]
Zhong 2007	22	241	9	92	7.2%	0.93 [0.45 , 1.95]
Total (95% CI)		**2694**		**1622**	**100.0%**	**1.32 [1.09 , 1.61]**
Total events:	295		140			

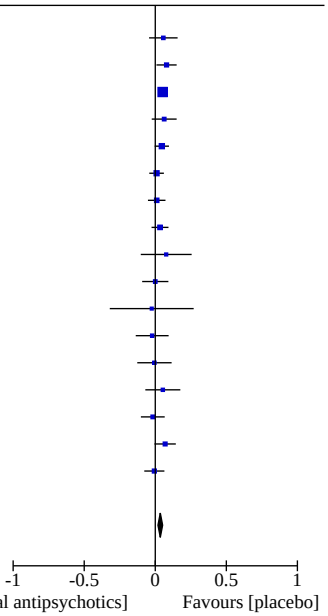
Heterogeneity: Chi² = 12.43, df = 15 (P = 0.65); I² = 0%
Test for overall effect: Z = 2.79 (P = 0.005)
Test for subgroup differences: Not applicable



Analysis 3.10. Comparison 3: Atypical antipsychotics versus placebo, Outcome 10: Any serious adverse event (RD)

Study or Subgroup	Atypical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
Ballard 2018	15	90	10	91	2.7%	0.06 [-0.04 , 0.16]
Brodaty 2003 RIS-AUS-05	28	167	15	170	5.3%	0.08 [0.01 , 0.15]
De Deyn 2004 F1D MC HGIV	35	523	2	129	29.3%	0.05 [0.02 , 0.08]
De Deyn 2005	16	106	9	102	3.5%	0.06 [-0.02 , 0.15]
Grossberg 2020a	29	297	7	136	10.6%	0.05 [-0.00 , 0.10]
Grossberg 2020b	7	132	6	137	10.2%	0.01 [-0.04 , 0.06]
Mintzer 2006 RIS USA 232	33	235	31	238	7.0%	0.01 [-0.05 , 0.07]
Mintzer 2007	42	360	10	120	7.6%	0.03 [-0.03 , 0.09]
NCT00287742 2006	1	13	0	17	0.8%	0.08 [-0.10 , 0.26]
Paleacu 2008	0	20	0	20	3.1%	0.00 [-0.09 , 0.09]
RIS-INT-83 2003	1	10	1	8	0.3%	-0.02 [-0.32 , 0.27]
Schneider 2006 CATIE-AD	9	85	6	47	2.0%	-0.02 [-0.14 , 0.09]
Schneider 2006 CATIE-AD	14	100	7	48	1.8%	-0.01 [-0.13 , 0.11]
Schneider 2006 CATIE-AD	17	94	6	47	1.8%	0.05 [-0.07 , 0.18]
Streim 2008	16	130	17	121	3.8%	-0.02 [-0.10 , 0.07]
Tariot 2006	10	91	4	99	4.8%	0.07 [-0.01 , 0.14]
Zhong 2007	22	241	9	92	5.3%	-0.01 [-0.08 , 0.06]
Total (95% CI)		**2694**		**1622**	**100.0%**	**0.04 [0.02 , 0.05]**
Total events:	295		140			

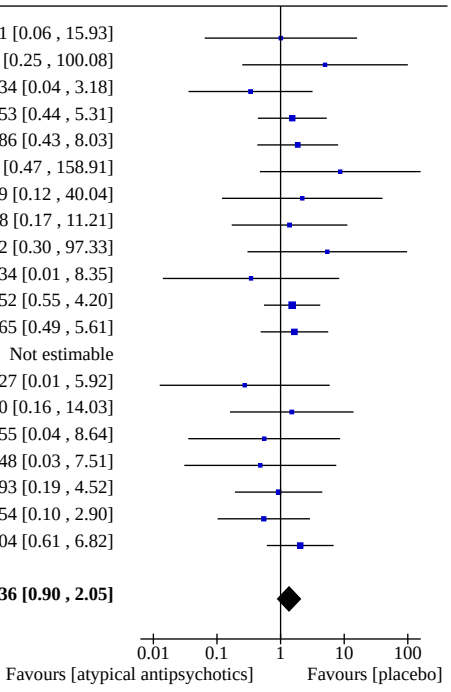
Heterogeneity: Chi² = 11.00, df = 16 (P = 0.81); I² = 0%
Test for overall effect: Z = 4.23 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 3.11. Comparison 3: Atypical antipsychotics versus placebo, Outcome 11: Death

Study or Subgroup	Atypical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Allain 2000	1	102	1	103	2.2%	1.01 [0.06 , 15.93]
Ballard 2005	2	31	0	31	1.9%	5.00 [0.25 , 100.08]
Ballard 2018	1	90	3	91	3.4%	0.34 [0.04 , 3.18]
Brodaty 2003 RIS-AUS-05	6	167	4	170	10.9%	1.53 [0.44 , 5.31]
De Deyn 2004 F1D MC HGIV	15	520	2	129	7.9%	1.86 [0.43 , 8.03]
De Deyn 2005	4	106	0	102	2.0%	8.66 [0.47 , 158.91]
Deberdt 2005 F1D MC HGGU	4	196	0	47	2.0%	2.19 [0.12 , 40.04]
Deberdt 2005 F1D MC HGGU	6	204	1	47	3.9%	1.38 [0.17 , 11.21]
Grossberg 2020a	5	277	0	136	2.0%	5.42 [0.30 , 97.33]
Grossberg 2020b	0	133	1	137	1.7%	0.34 [0.01 , 8.35]
Mintzer 2006 RIS USA 232	9	235	6	238	16.4%	1.52 [0.55 , 4.20]
Mintzer 2007	15	366	3	121	11.4%	1.65 [0.49 , 5.61]
Paleacu 2008	0	20	0	20		Not estimable
RIS-INT-83 2003	0	10	1	8	1.8%	0.27 [0.01 , 5.92]
Schneider 2006 CATIE-AD	3	94	1	47	3.4%	1.50 [0.16 , 14.03]
Schneider 2006 CATIE-AD	1	85	1	47	2.3%	0.55 [0.04 , 8.64]
Schneider 2006 CATIE-AD	1	100	1	48	2.2%	0.48 [0.03 , 7.51]
Streim 2008	3	130	3	121	6.8%	0.93 [0.19 , 4.52]
Tariot 2006	2	91	4	99	6.1%	0.54 [0.10 , 2.90]
Zhong 2007	16	241	3	92	11.6%	2.04 [0.61 , 6.82]
Total (95% CI)		**3198**		**1834**	**100.0%**	**1.36 [0.90 , 2.05]**
Total events:	94		35			

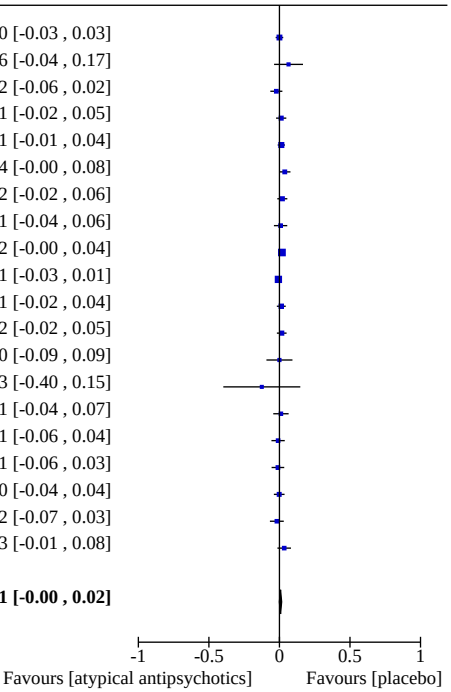
Heterogeneity: Chi² = 9.68, df = 18 (P = 0.94); I² = 0%
Test for overall effect: Z = 1.45 (P = 0.15)
Test for subgroup differences: Not applicable



Analysis 3.12. Comparison 3: Atypical antipsychotics versus placebo, Outcome 12: Death (RD)

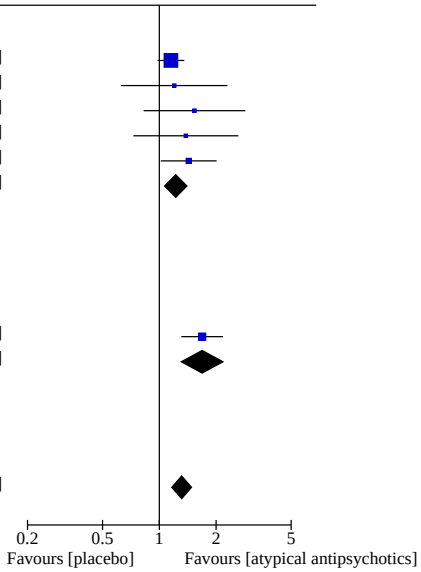
Study or Subgroup	Atypical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
Allain 2000	1	102	1	103	8.6%	0.00 [-0.03 , 0.03]
Ballard 2005	2	31	0	31	0.6%	0.06 [-0.04 , 0.17]
Ballard 2018	1	90	3	91	3.4%	-0.02 [-0.06 , 0.02]
Brodaty 2003 RIS-AUS-05	6	167	4	170	4.7%	0.01 [-0.02 , 0.05]
De Deyn 2004 F1D MC HGIV	15	520	2	129	9.4%	0.01 [-0.01 , 0.04]
De Deyn 2005	4	106	0	102	3.8%	0.04 [-0.00 , 0.08]
Deberdt 2005 F1D MC HGGU	4	196	0	47	4.9%	0.02 [-0.02 , 0.06]
Deberdt 2005 F1D MC HGGU	6	204	1	47	2.8%	0.01 [-0.04 , 0.06]
Grossberg 2020a	5	277	0	136	16.8%	0.02 [-0.00 , 0.04]
Grossberg 2020b	0	133	1	137	15.3%	-0.01 [-0.03 , 0.01]
Mintzer 2006 RIS USA 232	9	235	6	238	6.2%	0.01 [-0.02 , 0.04]
Mintzer 2007	15	366	3	121	5.3%	0.02 [-0.02 , 0.05]
Paleacu 2008	0	20	0	20	0.7%	0.00 [-0.09 , 0.09]
RIS-INT-83 2003	0	10	1	8	0.1%	-0.13 [-0.40 , 0.15]
Schneider 2006 CATIE-AD	3	94	1	47	2.1%	0.01 [-0.04 , 0.07]
Schneider 2006 CATIE-AD	1	85	1	47	2.8%	-0.01 [-0.06 , 0.04]
Schneider 2006 CATIE-AD	1	100	1	48	3.1%	-0.01 [-0.06 , 0.03]
Streim 2008	3	130	3	121	4.3%	-0.00 [-0.04 , 0.04]
Tariot 2006	2	91	4	99	2.6%	-0.02 [-0.07 , 0.03]
Zhong 2007	16	241	3	92	2.7%	0.03 [-0.01 , 0.08]
Total (95% CI)		**3198**		**1834**	**100.0%**	**0.01 [-0.00 , 0.02]**
Total events:	94		35			

Heterogeneity: Chi² = 14.37, df = 19 (P = 0.76); I² = 0%
Test for overall effect: Z = 1.89 (P = 0.06)
Test for subgroup differences: Not applicable



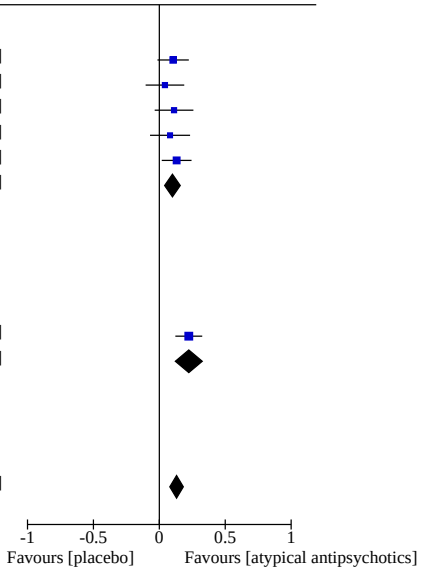
Analysis 3.13. Comparison 3: Atypical antipsychotics versus placebo, Outcome 13: Number of responders for agitation

Study or Subgroup	Atypical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
3.13.1 Assessments not including physical aggression						
Allain 2000	81	102	71	103	54.4%	1.15 [0.98 , 1.36]
Schneider 2006 CATIE-AD	24	94	10	47	3.4%	1.20 [0.63 , 2.30]
Schneider 2006 CATIE-AD	32	100	10	48	3.7%	1.54 [0.83 , 2.86]
Schneider 2006 CATIE-AD	25	85	10	47	3.5%	1.38 [0.73 , 2.62]
Zhong 2007	105	241	28	92	12.5%	1.43 [1.02 , 2.01]
Subtotal (95% CI)		**622**		**337**	**77.6%**	**1.22 [1.07 , 1.40]**
Total events:	267		129			
Heterogeneity: Chi² = 2.00, df = 4 (P = 0.74); I² = 0%						
Test for overall effect: Z = 2.88 (P = 0.004)						
3.13.2 Assessments including physical aggression						
Brodaty 2003 RIS-AUS-05	95	173	56	172	22.4%	1.69 [1.31 , 2.17]
Subtotal (95% CI)		**173**		**172**	**22.4%**	**1.69 [1.31 , 2.17]**
Total events:	95		56			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.03 (P < 0.0001)						
Total (95% CI)		**795**		**509**	**100.0%**	**1.31 [1.16 , 1.48]**
Total events:	362		185			
Heterogeneity: Chi² = 6.80, df = 5 (P = 0.24); I² = 26%						
Test for overall effect: Z = 4.44 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.80, df = 1 (P = 0.03), I² = 79.2%						



Analysis 3.14. Comparison 3: Atypical antipsychotics versus placebo, Outcome 14: Number of responders for agitation (RD)

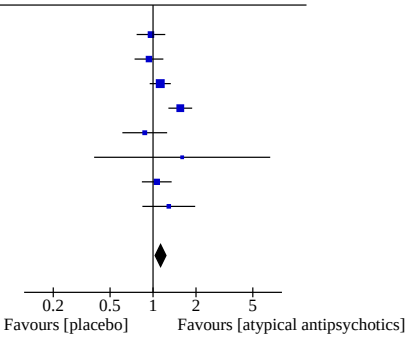
Study or Subgroup	Atypical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
3.14.1 Assessments not including physical aggression						
Allain 2000	81	102	71	103	18.5%	0.10 [-0.01 , 0.22]
Schneider 2006 CATIE-AD	24	94	10	47	12.2%	0.04 [-0.10 , 0.19]
Schneider 2006 CATIE-AD	32	100	10	48	12.2%	0.11 [-0.04 , 0.26]
Schneider 2006 CATIE-AD	25	85	10	47	11.4%	0.08 [-0.07 , 0.23]
Zhong 2007	105	241	28	92	20.5%	0.13 [0.02 , 0.24]
Subtotal (95% CI)		**622**		**337**	**74.8%**	**0.10 [0.04 , 0.16]**
Total events:	267		129			
Heterogeneity: Chi² = 0.97, df = 4 (P = 0.91); I² = 0%						
Test for overall effect: Z = 3.29 (P = 0.0010)						
3.14.2 Assessments including physical aggression						
Brodaty 2003 RIS-AUS-05	95	173	56	172	25.2%	0.22 [0.12 , 0.33]
Subtotal (95% CI)		**173**		**172**	**25.2%**	**0.22 [0.12 , 0.33]**
Total events:	95		56			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.30 (P < 0.0001)						
Total (95% CI)		**795**		**509**	**100.0%**	**0.13 [0.08 , 0.18]**
Total events:	362		185			
Heterogeneity: Chi² = 5.23, df = 5 (P = 0.39); I² = 4%						
Test for overall effect: Z = 5.01 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.25, df = 1 (P = 0.04), I² = 76.5%						



Analysis 3.15. Comparison 3: Atypical antipsychotics versus placebo, Outcome 15: Number of responders for psychosis

Study or Subgroup	Atypical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Deberdt 2005 F1D MC HGGU	125	196	31	47	14.4%	0.97 [0.77 , 1.22]
Deberdt 2005 F1D MC HGGU	126	204	31	47	14.3%	0.94 [0.74 , 1.18]
Mintzer 2006 RIS USA 232	132	235	119	238	26.6%	1.12 [0.95 , 1.33]
Mintzer 2007	277	366	59	121	20.9%	1.55 [1.28 , 1.88]
Paleacu 2008	14	20	16	20	5.9%	0.88 [0.61 , 1.26]
RIS-INT-83 2003	4	10	2	8	0.4%	1.60 [0.39 , 6.62]
Streim 2008	69	131	62	125	13.3%	1.06 [0.84 , 1.35]
Tariot 2006	32	91	27	99	4.2%	1.29 [0.84 , 1.97]
Total (95% CI)		**1253**		**705**	**100.0%**	**1.13 [1.03 , 1.23]**
Total events:	779		347			

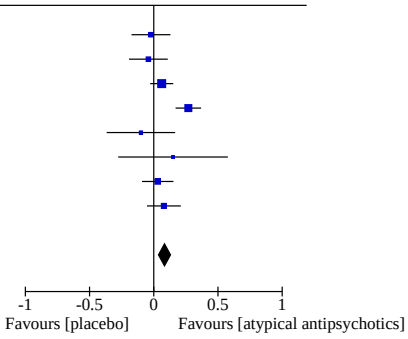
Heterogeneity: Chi² = 17.59, df = 7 (P = 0.01); I² = 60%
Test for overall effect: Z = 2.71 (P = 0.007)
Test for subgroup differences: Not applicable



Analysis 3.16. Comparison 3: Atypical antipsychotics versus placebo, Outcome 16: Number of responders for psychosis (RD)

Study or Subgroup	Atypical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
Deberdt 2005 F1D MC HGGU	125	196	31	47	9.6%	-0.02 [-0.17 , 0.13]
Deberdt 2005 F1D MC HGGU	126	204	31	47	9.6%	-0.04 [-0.19 , 0.11]
Mintzer 2006 RIS USA 232	132	235	119	238	27.1%	0.06 [-0.03 , 0.15]
Mintzer 2007	277	366	59	121	22.2%	0.27 [0.17 , 0.37]
Paleacu 2008	14	20	16	20	3.1%	-0.10 [-0.37 , 0.17]
RIS-INT-83 2003	4	10	2	8	1.2%	0.15 [-0.28 , 0.58]
Streim 2008	69	131	62	125	14.6%	0.03 [-0.09 , 0.15]
Tariot 2006	32	91	27	99	12.6%	0.08 [-0.05 , 0.21]
Total (95% CI)		**1253**		**705**	**100.0%**	**0.08 [0.04 , 0.13]**
Total events:	779		347			

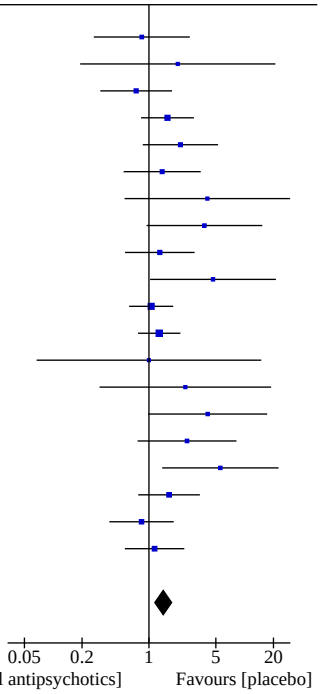
Heterogeneity: Chi² = 20.81, df = 7 (P = 0.004); I² = 66%
Test for overall effect: Z = 3.50 (P = 0.0005)
Test for subgroup differences: Not applicable



Analysis 3.17. Comparison 3: Atypical antipsychotics versus placebo, Outcome 17: Discontinuation due to adverse events

Study or Subgroup	Atypical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Allain 2000	5	102	6	103	3.0%	0.84 [0.27 , 2.67]
Ballard 2005	2	31	1	31	0.7%	2.00 [0.19 , 20.93]
Ballard 2018	8	90	11	91	5.4%	0.74 [0.31 , 1.74]
Brodaty 2003 RIS-AUS-05	22	173	14	172	10.0%	1.56 [0.83 , 2.95]
De Deyn 2004 F1D MC HGIV	43	520	5	129	4.9%	2.13 [0.86 , 5.28]
De Deyn 2005	10	106	7	102	4.7%	1.37 [0.54 , 3.47]
Deberdt 2005 F1D MC HGGU	17	196	1	47	1.0%	4.08 [0.56 , 29.87]
Deberdt 2005 F1D MC HGGU	33	204	2	47	2.1%	3.80 [0.95 , 15.29]
Grossberg 2020a	20	297	7	135	5.8%	1.30 [0.56 , 3.00]
Grossberg 2020b	9	132	2	137	1.8%	4.67 [1.03 , 21.21]
Mintzer 2006 RIS USA 232	25	235	24	238	14.4%	1.05 [0.62 , 1.79]
Mintzer 2007	62	366	16	121	15.6%	1.28 [0.77 , 2.13]
Paleacu 2008	1	20	1	20	0.6%	1.00 [0.07 , 14.90]
RIS-INT-83 2003	3	10	1	8	1.0%	2.40 [0.30 , 18.89]
Schneider 2006 CATIE-AD	15	84	2	46	2.0%	4.11 [0.98 , 17.18]
Schneider 2006 CATIE-AD	15	94	3	47	2.9%	2.50 [0.76 , 8.21]
Schneider 2006 CATIE-AD	24	99	2	46	2.1%	5.58 [1.38 , 22.60]
Streim 2008	17	131	10	125	7.4%	1.62 [0.77 , 3.41]
Tariot 2006	10	91	13	99	6.8%	0.84 [0.39 , 1.81]
Zhong 2007	27	241	9	92	7.9%	1.15 [0.56 , 2.34]
Total (95% CI)		**3222**		**1836**	**100.0%**	**1.41 [1.15 , 1.72]**
Total events:	368		137			

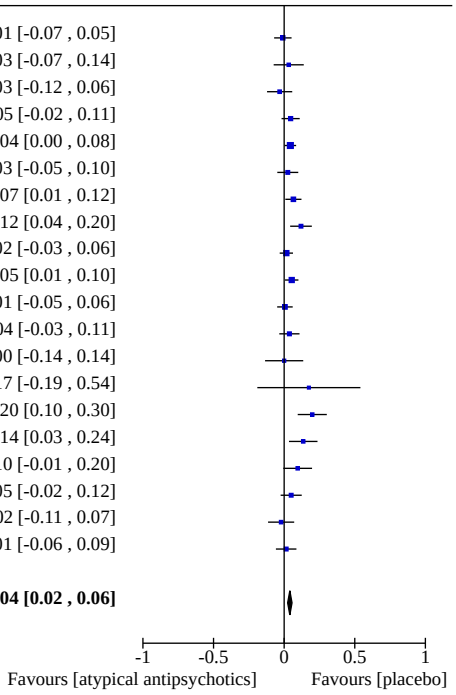
Heterogeneity: Chi² = 19.99, df = 19 (P = 0.40); I² = 5%
Test for overall effect: Z = 3.35 (P = 0.0008)
Test for subgroup differences: Not applicable



Analysis 3.18. Comparison 3: Atypical antipsychotics versus placebo, Outcome 18: Discontinuation due to adverse events (RD)

Study or Subgroup	Atypical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
Allain 2000	5	102	6	103	6.2%	-0.01 [-0.07 , 0.05]
Ballard 2005	2	31	1	31	2.1%	0.03 [-0.07 , 0.14]
Ballard 2018	8	90	11	91	3.0%	-0.03 [-0.12 , 0.06]
Brodaty 2003 RIS-AUS-05	22	173	14	172	5.7%	0.05 [-0.02 , 0.11]
De Deyn 2004 F1D MC HGIV	43	520	5	129	14.1%	0.04 [0.00 , 0.08]
De Deyn 2005	10	106	7	102	4.3%	0.03 [-0.05 , 0.10]
Deberdt 2005 F1D MC HGGU	17	196	1	47	7.3%	0.07 [0.01 , 0.12]
Deberdt 2005 F1D MC HGGU	33	204	2	47	4.0%	0.12 [0.04 , 0.20]
Grossberg 2020a	20	297	7	135	10.7%	0.02 [-0.03 , 0.06]
Grossberg 2020b	9	132	2	137	10.5%	0.05 [0.01 , 0.10]
Mintzer 2006 RIS USA 232	25	235	24	238	7.8%	0.01 [-0.05 , 0.06]
Mintzer 2007	62	366	16	121	4.6%	0.04 [-0.03 , 0.11]
Paleacu 2008	1	20	1	20	1.3%	0.00 [-0.14 , 0.14]
RIS-INT-83 2003	3	10	1	8	0.2%	0.17 [-0.19 , 0.54]
Schneider 2006 CATIE-AD	24	99	2	46	2.2%	0.20 [0.10 , 0.30]
Schneider 2006 CATIE-AD	15	84	2	46	2.3%	0.14 [0.03 , 0.24]
Schneider 2006 CATIE-AD	15	94	3	47	2.3%	0.10 [-0.01 , 0.20]
Streim 2008	17	131	10	125	4.2%	0.05 [-0.02 , 0.12]
Tariot 2006	10	91	13	99	2.8%	-0.02 [-0.11 , 0.07]
Zhong 2007	27	241	9	92	4.5%	0.01 [-0.06 , 0.09]
Total (95% CI)		**3222**		**1836**	**100.0%**	**0.04 [0.02 , 0.06]**
Total events:	368		137			

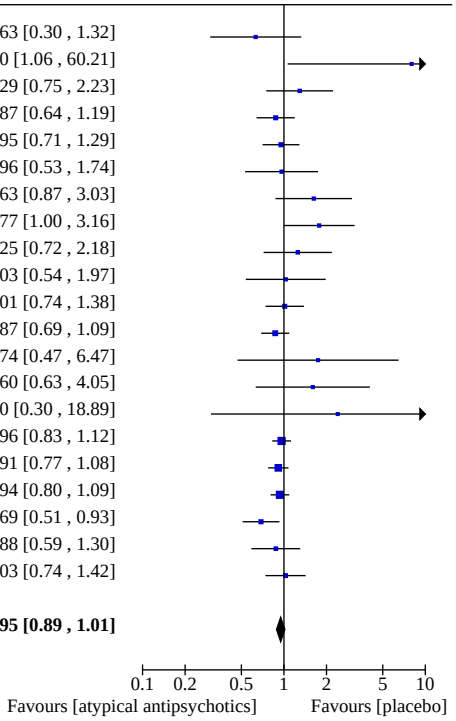
Heterogeneity: Chi² = 29.75, df = 19 (P = 0.06); I² = 36%
Test for overall effect: Z = 5.13 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.19. Comparison 3: Atypical antipsychotics versus placebo, Outcome 19: Discontinuation (any reason)

Study or Subgroup	Atypical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Allain 2000	10	102	16	103	0.8%	0.63 [0.30 , 1.32]
Ballard 2005	8	31	1	31	0.1%	8.00 [1.06 , 60.21]
Ballard 2018	23	90	18	91	1.5%	1.29 [0.75 , 2.23]
Brodaty 2003 RIS-AUS-05	51	173	58	172	4.7%	0.87 [0.64 , 1.19]
De Deyn 2004 F1D MC HGIV	146	520	38	129	5.0%	0.95 [0.71 , 1.29]
De Deyn 2005	18	106	18	102	1.3%	0.96 [0.53 , 1.74]
Deberdt 2005 F1D MC HGGU	61	196	9	47	1.2%	1.63 [0.87 , 3.03]
Deberdt 2005 F1D MC HGGU	77	204	10	47	1.4%	1.77 [1.00 , 3.16]
Grossberg 2020a	41	297	15	136	1.5%	1.25 [0.72 , 2.18]
Grossberg 2020b	16	133	16	137	1.1%	1.03 [0.54 , 1.97]
Mintzer 2006 RIS USA 232	59	235	59	238	4.6%	1.01 [0.74 , 1.38]
Mintzer 2007	147	366	56	121	8.6%	0.87 [0.69 , 1.09]
NCT00287742 2006	4	13	3	17	0.3%	1.74 [0.47 , 6.47]
Paleacu 2008	8	20	5	20	0.5%	1.60 [0.63 , 4.05]
RIS-INT-83 2003	3	10	1	8	0.1%	2.40 [0.30 , 18.89]
Schneider 2006 CATIE-AD	77	94	40	47	19.4%	0.96 [0.83 , 1.12]
Schneider 2006 CATIE-AD	66	85	40	47	16.5%	0.91 [0.77 , 1.08]
Schneider 2006 CATIE-AD	80	100	41	48	19.4%	0.94 [0.80 , 1.09]
Streim 2008	44	131	61	125	5.0%	0.69 [0.51 , 0.93]
Tariot 2006	29	91	36	99	2.9%	0.88 [0.59 , 1.30]
Zhong 2007	86	241	32	92	4.2%	1.03 [0.74 , 1.42]
Total (95% CI)		**3238**		**1857**	**100.0%**	**0.95 [0.89 , 1.01]**
Total events:	1054		573			

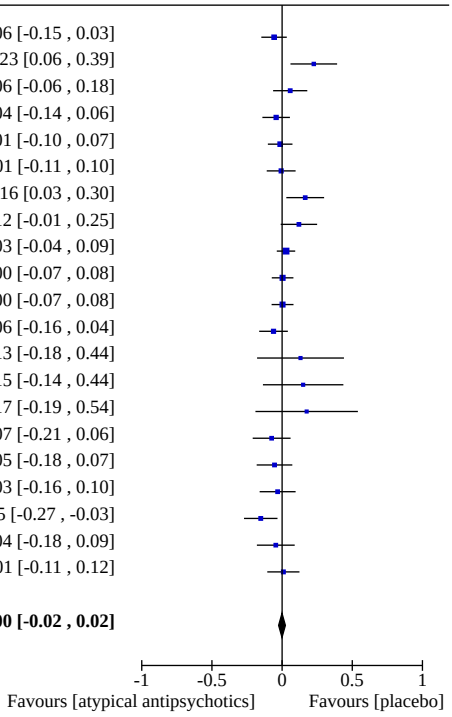
Heterogeneity: Chi² = 23.95, df = 20 (P = 0.24); I² = 17%
Test for overall effect: Z = 1.55 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 3.20. Comparison 3: Atypical antipsychotics versus placebo, Outcome 20: Discontinuation (any reason) (RD)

Study or Subgroup	Atypical antipsychotics Events	Total	Placebo Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
Allain 2000	10	102	16	103	7.0%	-0.06 [-0.15 , 0.03]
Ballard 2005	8	31	1	31	2.1%	0.23 [0.06 , 0.39]
Ballard 2018	23	90	18	91	3.9%	0.06 [-0.06 , 0.18]
Brodaty 2003 RIS-AUS-05	51	173	58	172	6.0%	-0.04 [-0.14 , 0.06]
De Deyn 2004 F1D MC HGIV	146	520	38	129	7.5%	-0.01 [-0.10 , 0.07]
De Deyn 2005	18	106	18	102	5.4%	-0.01 [-0.11 , 0.10]
Deberdt 2005 F1D MC HGGU	77	204	10	47	3.2%	0.16 [0.03 , 0.30]
Deberdt 2005 F1D MC HGGU	61	196	9	47	3.4%	0.12 [-0.01 , 0.25]
Grossberg 2020a	41	297	15	136	13.3%	0.03 [-0.04 , 0.09]
Grossberg 2020b	16	133	16	137	9.7%	0.00 [-0.07 , 0.08]
Mintzer 2006 RIS USA 232	59	235	59	238	9.5%	0.00 [-0.07 , 0.08]
Mintzer 2007	147	366	56	121	5.5%	-0.06 [-0.16 , 0.04]
NCT00287742 2006	4	13	3	17	0.6%	0.13 [-0.18 , 0.44]
Paleacu 2008	8	20	5	20	0.7%	0.15 [-0.14 , 0.44]
RIS-INT-83 2003	3	10	1	8	0.4%	0.17 [-0.19 , 0.54]
Schneider 2006 CATIE-AD	66	85	40	47	3.2%	-0.07 [-0.21 , 0.06]
Schneider 2006 CATIE-AD	80	100	41	48	3.6%	-0.05 [-0.18 , 0.07]
Schneider 2006 CATIE-AD	77	94	40	47	3.5%	-0.03 [-0.16 , 0.10]
Streim 2008	44	131	61	125	4.0%	-0.15 [-0.27 , -0.03]
Tariot 2006	29	91	36	99	3.2%	-0.04 [-0.18 , 0.09]
Zhong 2007	86	241	32	92	4.4%	0.01 [-0.11 , 0.12]
Total (95% CI)		**3238**		**1857**	**100.0%**	**-0.00 [-0.02 , 0.02]**
Total events:	1054		573			

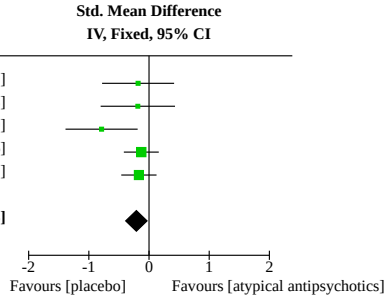
Heterogeneity: Chi² = 32.86, df = 20 (P = 0.03); I² = 39%
Test for overall effect: Z = 0.06 (P = 0.95)
Test for subgroup differences: Not applicable



Analysis 3.21. Comparison 3: Atypical antipsychotics versus placebo, Outcome 21: Functioning (ADL)

Study or Subgroup	Atypical antipsychotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Schneider 2006 CATIE-AD	-1.1	8.8	33	0.5	8.4	16	8.8%	-0.18 [-0.78 , 0.42]
Schneider 2006 CATIE-AD	-1	7.7	31	0.5	8.4	15	8.3%	-0.19 [-0.80 , 0.43]
Schneider 2006 CATIE-AD	-6.1	8.2	40	0.5	8.4	16	8.8%	-0.79 [-1.39 , -0.19]
Streim 2008	-0.83	4.94	93	-0.22	4.52	90	37.4%	-0.13 [-0.42 , 0.16]
Tariot 2006	-0.01	3.38	86	0.47	2.24	94	36.7%	-0.17 [-0.46 , 0.12]
Total (95% CI)			**283**			**231**	**100.0%**	**-0.21 [-0.39 , -0.03]**

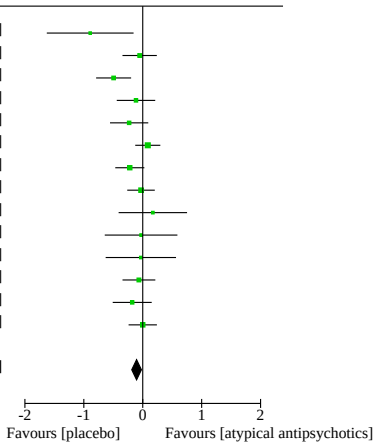
Heterogeneity: Chi² = 3.98, df = 4 (P = 0.41); I² = 0%
Test for overall effect: Z = 2.32 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 3.22. Comparison 3: Atypical antipsychotics versus placebo, Outcome 22: Cognitive function

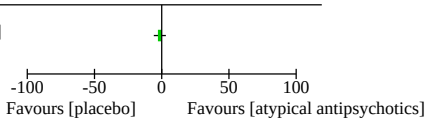
Study or Subgroup	Atypical antipsychotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Ballard 2005	-10.5	14.8	14	3.2	15.1	18	1.2%	-0.89 [-1.63 , -0.16]
Ballard 2018	-0.1	5.7	90	0.2	5.7	91	7.9%	-0.05 [-0.34 , 0.24]
De Deyn 2005	-0.81	2.7	94	0.53	2.7	86	7.6%	-0.49 [-0.79 , -0.20]
Deberdt 2005 F1D MC HGGU	-0.8	3.5	182	-0.4	3.4	45	6.3%	-0.11 [-0.44 , 0.21]
Deberdt 2005 F1D MC HGGU	-1.3	4	180	-0.4	3.4	46	6.4%	-0.23 [-0.56 , 0.09]
Grossberg 2020a	0.11	2.1	256	-0.07	2.1	127	14.9%	0.09 [-0.13 , 0.30]
Grossberg 2020b	-0.36	2	124	0.08	2	130	11.1%	-0.22 [-0.47 , 0.03]
Mintzer 2007	-1	3.5	299	-0.9	3.1	92	12.3%	-0.03 [-0.26 , 0.20]
Schneider 2006 CATIE-AD	-0.1	3.7	40	-0.7	2.7	16	2.0%	0.17 [-0.41 , 0.75]
Schneider 2006 CATIE-AD	-0.8	3.8	31	-0.7	2.7	15	1.8%	-0.03 [-0.64 , 0.59]
Schneider 2006 CATIE-AD	-0.8	3.2	33	-0.7	2.7	16	1.9%	-0.03 [-0.63 , 0.56]
Streim 2008	-0.77	2.99	106	-0.57	3.17	93	8.7%	-0.06 [-0.34 , 0.21]
Tariot 2006	-1.58	2.98	69	-0.9	4.42	72	6.2%	-0.18 [-0.51 , 0.15]
Zhong 2007	0	2.7	241	0	2	92	11.7%	0.00 [-0.24 , 0.24]
Total (95% CI)			**1759**			**939**	**100.0%**	**-0.10 [-0.19 , -0.02]**

Heterogeneity: Chi² = 17.99, df = 13 (P = 0.16); I² = 28%
Test for overall effect: Z = 2.49 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 3.23. Comparison 3: Atypical antipsychotics versus placebo, Outcome 23: Cognitive function (single study)

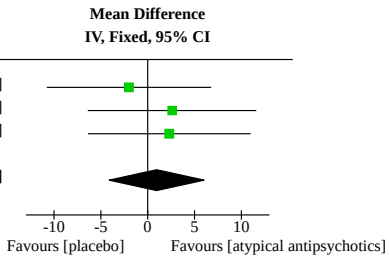
Study or Subgroup	Atypical antipsychotics Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Paleacu 2008	13.5	6.8	19	14.9	7.3	19	-1.40 [-5.89 , 3.09]



Analysis 3.24. Comparison 3: Atypical antipsychotics versus placebo, Outcome 24: Health-related quality of life

Study or Subgroup	Atypical antipsychotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Schneider 2006 CATIE-AD	2.1	12.1	33	4.1	15.8	16	33.6%	-2.00 [-10.77 , 6.77]
Schneider 2006 CATIE-AD	6.7	11.7	31	4.1	15.8	15	32.0%	2.60 [-6.39 , 11.59]
Schneider 2006 CATIE-AD	6.4	12.6	40	4.1	15.8	16	34.4%	2.30 [-6.37 , 10.97]
Total (95% CI)			**104**			**47**	**100.0%**	**0.95 [-4.14 , 6.04]**

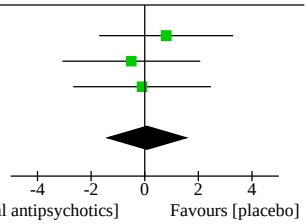
Heterogeneity: Chi² = 0.66, df = 2 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)
Test for subgroup differences: Not applicable



Analysis 3.25. Comparison 3: Atypical antipsychotics versus placebo, Outcome 25: Time spend providing care (caregiver)

Study or Subgroup	Atypical antipsychotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Schneider 2006 CATIE-AD	0.2	4.8	40	-0.6	4.1	16	34.6%	0.80 [-1.70 , 3.30]
Schneider 2006 CATIE-AD	-1.1	4.7	33	-0.6	4.1	16	32.7%	-0.50 [-3.07 , 2.07]
Schneider 2006 CATIE-AD	-0.7	4.3	31	-0.6	4.1	15	32.7%	-0.10 [-2.67 , 2.47]
Total (95% CI)			**104**			**47**	**100.0%**	**0.08 [-1.39 , 1.55]**

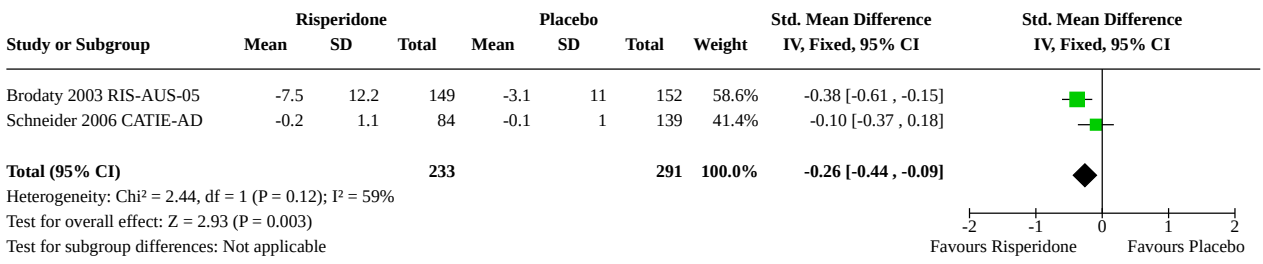
Heterogeneity: Chi² = 0.53, df = 2 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.11 (P = 0.91)
Test for subgroup differences: Not applicable



Comparison 4. Risperidone versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Agitation	2	524	Std. Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.44, -0.09]
4.2 Psychosis	5	1205	Std. Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.23, 0.01]
4.3 Somnolence	2	700	Risk Ratio (IV, Fixed, 95% CI)	3.35 [1.99, 5.65]
4.4 Extrapyramidal symptoms	6	1328	Risk Ratio (IV, Fixed, 95% CI)	1.75 [1.32, 2.33]
4.5 Any adverse event	2	700	Risk Ratio (IV, Fixed, 95% CI)	1.19 [1.07, 1.32]
4.6 Any serious adverse event	5	1085	Risk Ratio (IV, Fixed, 95% CI)	1.21 [0.88, 1.67]
4.7 Death	5	1298	Risk Ratio (IV, Fixed, 95% CI)	1.29 [0.64, 2.60]
4.8 Number of responders for agitation	2	572	Risk Ratio (IV, Fixed, 95% CI)	1.61 [1.29, 2.01]
4.9 Number of responders for psychosis	3	781	Risk Ratio (IV, Fixed, 95% CI)	1.05 [0.93, 1.19]
4.10 Discontinuation due to adverse events	5	1349	Risk Ratio (IV, Fixed, 95% CI)	1.60 [1.13, 2.27]
4.11 Discontinuation (any reason)	6	1383	Risk Ratio (IV, Fixed, 95% CI)	0.95 [0.85, 1.07]
4.12 Cognitive function	2	353	Mean Difference (IV, Fixed, 95% CI)	-0.31 [-1.04, 0.41]
4.13 Functioning (ADL)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.14 Health-related quality of life	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.15 Time spend providing care (caregiver)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

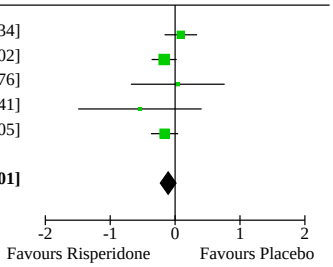
Analysis 4.1. Comparison 4: Risperidone versus placebo, Outcome 1: Agitation



Analysis 4.2. Comparison 4: Risperidone versus placebo, Outcome 2: Psychosis

Study or Subgroup	Risperidone Mean	Risperidone SD	Risperidone Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Deberdt 2005 F1D MC HGGU	-4.2	5.8	190	-4.7	5.3	91	23.4%	0.09 [-0.16 , 0.34]
Mintzer 2006 RIS USA 232	-2.9	3.55	201	-2.3	3.55	212	39.1%	-0.17 [-0.36 , 0.02]
NCT00287742 2006	-1.3	2.2	13	-1.4	2.5	17	2.8%	0.04 [-0.68 , 0.76]
RIS-INT-83 2003	-2.4	5.58	10	0.6	4.84	8	1.6%	-0.54 [-1.49 , 0.41]
Schneider 2003 RIS USA 63	-1.3	2.3	346	-0.95	1.6	117	33.1%	-0.16 [-0.37 , 0.05]
Total (95% CI)			**760**			**445**	**100.0%**	**-0.11 [-0.23 , 0.01]**

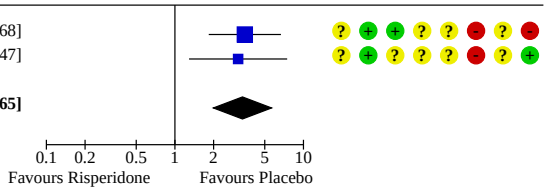
Heterogeneity: Chi² = 3.98, df = 4 (P = 0.41); I² = 0%
Test for overall effect: Z = 1.73 (P = 0.08)
Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4: Risperidone versus placebo, Outcome 3: Somnolence

Study or Subgroup	Risperidone Events	Risperidone Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Mintzer 2006 RIS USA 232	38	235	11	238	64.9%	3.50 [1.83 , 6.68]
Schneider 2006 CATIE-AD	13	85	7	142	35.1%	3.10 [1.29 , 7.47]
Total (95% CI)		**320**		**380**	**100.0%**	**3.35 [1.99 , 5.65]**
Total events:	51		18			

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 4.56 (P < 0.00001)
Test for subgroup differences: Not applicable

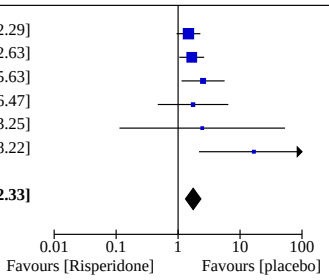


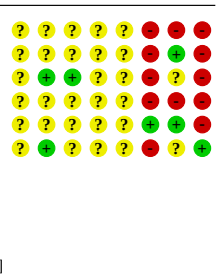
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 4.4. Comparison 4: Risperidone versus placebo, Outcome 4: Extrapyramidal symptoms

Study or Subgroup	Risperidone Events	Risperidone Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Brodaty 2003 RIS-AUS-05	39	167	27	170	41.6%	1.47 [0.95 , 2.29]
Deberdt 2005 F1D MC HGGU	97	196	14	47	38.2%	1.66 [1.05 , 2.63]
Mintzer 2006 RIS USA 232	20	235	8	238	12.7%	2.53 [1.14 , 5.63]
NCT00287742 2006	4	13	3	17	4.7%	1.74 [0.47 , 6.47]
RIS-INT-83 2003	1	10	0	8	0.9%	2.45 [0.11 , 53.25]
Schneider 2006 CATIE-AD	10	85	1	142	2.0%	16.71 [2.18 , 128.22]
Total (95% CI)		**706**		**622**	**100.0%**	**1.75 [1.32 , 2.33]**
Total events:	171		53			

Heterogeneity: Chi² = 6.22, df = 5 (P = 0.29); I² = 20%
Test for overall effect: Z = 3.86 (P = 0.0001)
Test for subgroup differences: Not applicable



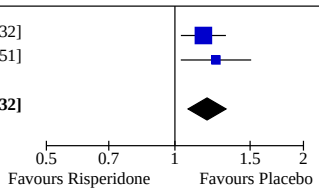


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 4.5. Comparison 4: Risperidone versus placebo, Outcome 5: Any adverse event

Study or Subgroup	Risperidone Events	Risperidone Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Mintzer 2006 RIS USA 232	175	235	152	238	71.0%	1.17 [1.03 , 1.32]
Schneider 2006 CATIE-AD	62	85	83	142	29.0%	1.25 [1.03 , 1.51]
Total (95% CI)		**320**		**380**	**100.0%**	**1.19 [1.07 , 1.32]**
Total events:	237		235			

Heterogeneity: Chi² = 0.35, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 3.32 (P = 0.0009)
Test for subgroup differences: Not applicable

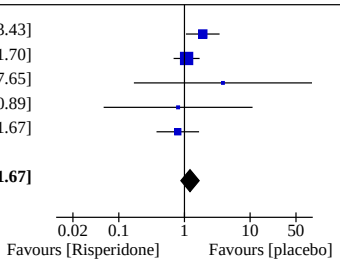


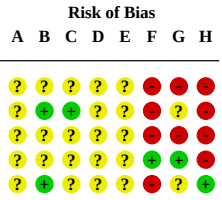
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 4.6. Comparison 4: Risperidone versus placebo, Outcome 6: Any serious adverse event

Study or Subgroup	Risperidone Events	Risperidone Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Brodaty 2003 RIS-AUS-05	28	167	15	170	29.6%	1.90 [1.05 , 3.43]
Mintzer 2006 RIS USA 232	33	235	31	238	49.4%	1.08 [0.68 , 1.70]
NCT00287742 2006	1	13	0	17	1.1%	3.86 [0.17 , 87.65]
RIS-INT-83 2003	1	10	1	8	1.5%	0.80 [0.06 , 10.89]
Schneider 2006 CATIE-AD	9	85	19	142	18.5%	0.79 [0.38 , 1.67]
Total (95% CI)		**510**		**575**	**100.0%**	**1.21 [0.88 , 1.67]**
Total events:	72		66			

Heterogeneity: Chi² = 4.37, df = 4 (P = 0.36); I² = 8%
Test for overall effect: Z = 1.19 (P = 0.23)
Test for subgroup differences: Not applicable



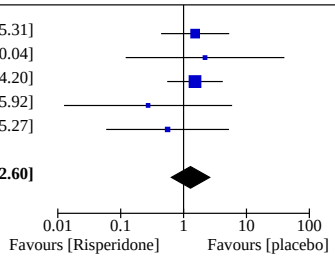


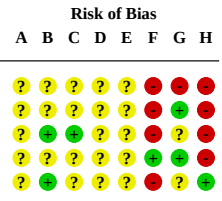
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 4.7. Comparison 4: Risperidone versus placebo, Outcome 7: Death

Study or Subgroup	Risperidone Events	Risperidone Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Brodaty 2003 RIS-AUS-05	6	167	4	170	31.7%	1.53 [0.44 , 5.31]
Deberdt 2005 F1D MC HGGU	4	196	0	47	5.8%	2.19 [0.12 , 40.04]
Mintzer 2006 RIS USA 232	9	235	6	238	47.6%	1.52 [0.55 , 4.20]
RIS-INT-83 2003	0	10	1	8	5.2%	0.27 [0.01 , 5.92]
Schneider 2006 CATIE-AD	1	85	3	142	9.7%	0.56 [0.06 , 5.27]
Total (95% CI)		**693**		**605**	**100.0%**	**1.29 [0.64 , 2.60]**
Total events:	20		14			

Heterogeneity: Chi² = 1.81, df = 4 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.71 (P = 0.48)
Test for subgroup differences: Not applicable



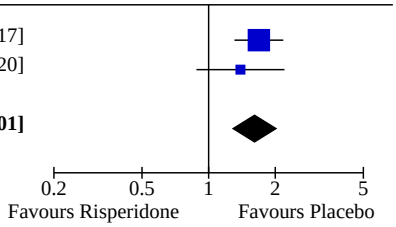


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 4.8. Comparison 4: Risperidone versus placebo, Outcome 8: Number of responders for agitation

Study or Subgroup	Risperidone Events	Risperidone Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Brodaty 2003 RIS-AUS-05	95	173	56	172	76.5%	1.69 [1.31 , 2.17]
Schneider 2006 CATIE-AD	25	85	30	142	23.5%	1.39 [0.88 , 2.20]
Total (95% CI)		**258**		**314**	**100.0%**	**1.61 [1.29 , 2.01]**
Total events:	120		86			

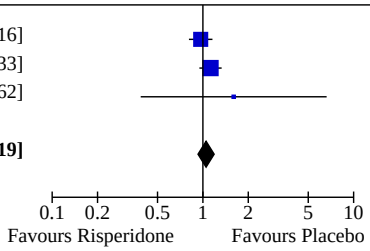
Heterogeneity: Chi² = 0.52, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 4.22 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 4.9. Comparison 4: Risperidone versus placebo, Outcome 9: Number of responders for psychosis

Study or Subgroup	Risperidone Events	Risperidone Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Deberdt 2005 F1D MC HGGU	125	196	62	94	46.9%	0.97 [0.81 , 1.16]
Mintzer 2006 RIS USA 232	132	235	119	238	52.3%	1.12 [0.95 , 1.33]
RIS-INT-83 2003	4	10	2	8	0.7%	1.60 [0.39 , 6.62]
Total (95% CI)		**441**		**340**	**100.0%**	**1.05 [0.93 , 1.19]**
Total events:	261		183			

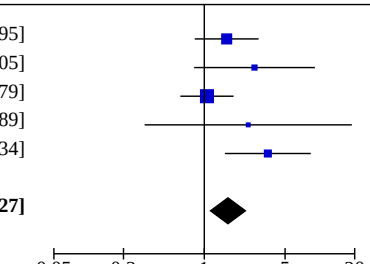
Heterogeneity: Chi² = 1.75, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.78 (P = 0.44)
Test for subgroup differences: Not applicable



Analysis 4.10. Comparison 4: Risperidone versus placebo, Outcome 10: Discontinuation due to adverse events

Study or Subgroup	Risperidone Events	Risperidone Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Brodaty 2003 RIS-AUS-05	22	173	14	172	29.7%	1.56 [0.83 , 2.95]
Deberdt 2005 F1D MC HGGU	17	196	3	94	8.3%	2.72 [0.82 , 9.05]
Mintzer 2006 RIS USA 232	25	235	24	238	42.7%	1.05 [0.62 , 1.79]
RIS-INT-83 2003	3	10	1	8	2.8%	2.40 [0.30 , 18.89]
Schneider 2006 CATIE-AD	15	84	7	139	16.4%	3.55 [1.51 , 8.34]
Total (95% CI)		**698**		**651**	**100.0%**	**1.60 [1.13 , 2.27]**
Total events:	82		49			

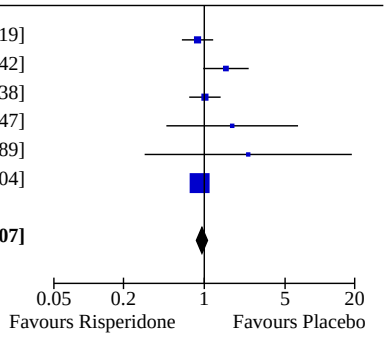
Heterogeneity: Chi² = 6.59, df = 4 (P = 0.16); I² = 39%
Test for overall effect: Z = 2.66 (P = 0.008)
Test for subgroup differences: Not applicable



Analysis 4.11. Comparison 4: Risperidone versus placebo, Outcome 11: Discontinuation (any reason)

Study or Subgroup	Risperidone Events	Risperidone Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Brodaty 2003 RIS-AUS-05	51	173	58	172	12.5%	0.87 [0.64 , 1.19]
Deberdt 2005 F1D MC HGGU	61	196	19	94	5.9%	1.54 [0.98 , 2.42]
Mintzer 2006 RIS USA 232	59	235	59	238	12.4%	1.01 [0.74 , 1.38]
NCT00287742 2006	4	13	3	17	0.7%	1.74 [0.47 , 6.47]
RIS-INT-83 2003	3	10	1	8	0.3%	2.40 [0.30 , 18.89]
Schneider 2006 CATIE-AD	66	85	121	142	68.3%	0.91 [0.80 , 1.04]
Total (95% CI)		**712**		**671**	**100.0%**	**0.95 [0.85 , 1.07]**
Total events:	244		261			

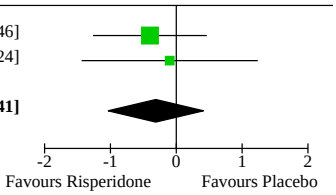
Heterogeneity: Chi² = 6.78, df = 5 (P = 0.24); I² = 26%
Test for overall effect: Z = 0.83 (P = 0.40)
Test for subgroup differences: Not applicable



Analysis 4.12. Comparison 4: Risperidone versus placebo, Outcome 12: Cognitive function

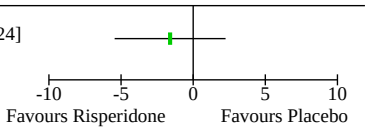
Study or Subgroup	Risperidone Mean	Risperidone SD	Risperidone Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Deberdt 2005 F1D MC HGGU	-0.8	3.5	182	-0.4	3.4	91	70.5%	-0.40 [-1.26 , 0.46]
Schneider 2006 CATIE-AD	-0.8	3.2	33	-0.7	2.7	47	29.5%	-0.10 [-1.44 , 1.24]
Total (95% CI)			**215**			**138**	**100.0%**	**-0.31 [-1.04 , 0.41]**

Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.40)
Test for subgroup differences: Not applicable



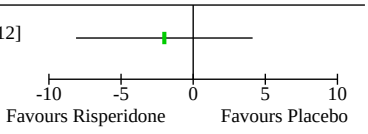
Analysis 4.13. Comparison 4: Risperidone versus placebo, Outcome 13: Functioning (ADL)

Study or Subgroup	Risperidone Mean	Risperidone SD	Risperidone Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
Schneider 2006 CATIE-AD	-1.1	8.8	33	0.5	8.4	47	-1.60 [-5.44 , 2.24]



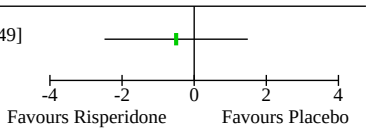
Analysis 4.14. Comparison 4: Risperidone versus placebo, Outcome 14: Health-related quality of life

Study or Subgroup	Risperidone Mean	Risperidone SD	Risperidone Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
Schneider 2006 CATIE-AD	2.1	12.1	33	4.1	15.8	47	-2.00 [-8.12 , 4.12]



Analysis 4.15. Comparison 4: Risperidone versus placebo, Outcome 15: Time spend providing care (caregiver)

Study or Subgroup	Risperidone Mean	Risperidone SD	Risperidone Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
Schneider 2006 CATIE-AD	-1.1	4.7	33	-0.6	4.1	47	-0.50 [-2.49 , 1.49]



Comparison 5. Quetiapine versus placebo

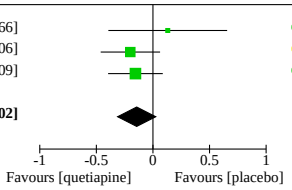
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Agitation	3	615	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.31, 0.02]
5.2 Psychosis	2	220	Std. Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.22, 0.31]
5.3 Somnolence	4	798	Risk Ratio (IV, Fixed, 95% CI)	4.83 [2.73, 8.57]
5.4 Extrapyramidal symptoms	4	799	Risk Ratio (IV, Fixed, 95% CI)	0.94 [0.52, 1.70]
5.5 Any adverse event	3	609	Risk Ratio (IV, Fixed, 95% CI)	1.03 [0.93, 1.14]
5.6 Any serious adverse event	4	799	Risk Ratio (IV, Fixed, 95% CI)	1.32 [0.86, 2.03]
5.7 Death	5	861	Risk Ratio (IV, Fixed, 95% CI)	1.48 [0.67, 3.31]
5.8 Number of responders for agitation	2	569	Risk Ratio (IV, Fixed, 95% CI)	1.35 [1.02, 1.78]
5.9 Number of responders for psychosis	2	230	Risk Ratio (IV, Fixed, 95% CI)	1.03 [0.78, 1.36]
5.10 Discontinuation due to adverse events	5	858	Risk Ratio (IV, Fixed, 95% CI)	1.37 [0.89, 2.11]
5.11 Discontinuation (any reason)	5	861	Risk Ratio (IV, Fixed, 95% CI)	0.97 [0.88, 1.08]
5.12 Functioning (ADL)	2	258	Std. Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.42, 0.07]
5.13 Cognitive function	4	584	Std. Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.28, 0.07]
5.14 Cognitive function (single study)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.15 Health-related quality of life	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.16 Time spend providing care (caregiver)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5: Quetiapine versus placebo, Outcome 1: Agitation

Study or Subgroup	[Not identical] Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Ballard 2005	-4	15.4	27	-6.2	17.6	29	10.3%	0.13 [-0.39 , 0.66]
Schneider 2006 CATIE-AD	-0.3	1	94	-0.1	1	139	41.1%	-0.20 [-0.46 , 0.06]
Zhong 2007	-5.3	9.2	234	-3.9	8.6	92	48.6%	-0.15 [-0.40 , 0.09]
Total (95% CI)			**355**			**260**	**100.0%**	**-0.14 [-0.31 , 0.02]**

Heterogeneity: Chi² = 1.23, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.67 (P = 0.09)
Test for subgroup differences: Not applicable

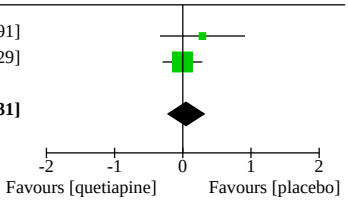


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 5.2. Comparison 5: Quetiapine versus placebo, Outcome 2: Psychosis

Study or Subgroup	[Not identical] Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Paleacu 2008	-3.4	6.74	20	-5.15	5.04	20	18.0%	0.29 [-0.34 , 0.91]
Tariot 2006	-4.14	6.04	86	-4.11	5.99	94	82.0%	-0.00 [-0.30 , 0.29]
Total (95% CI)			**106**			**114**	**100.0%**	**0.05 [-0.22 , 0.31]**

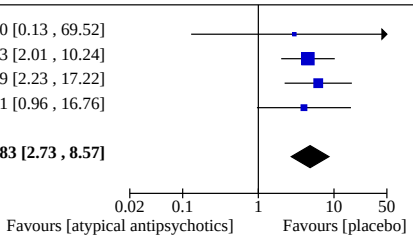
Heterogeneity: Chi² = 0.70, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.72)
Test for subgroup differences: Not applicable

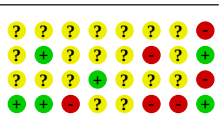


Analysis 5.3. Comparison 5: Quetiapine versus placebo, Outcome 3: Somnolence

Study or Subgroup	[Not identical] Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Paleacu 2008	1	20	0	20	3.3%	3.00 [0.13 , 69.52]
Schneider 2006 CATIE-AD	21	94	7	142	49.4%	4.53 [2.01 , 10.24]
Tariot 2006	23	91	4	98	31.3%	6.19 [2.23 , 17.22]
Zhong 2007	21	241	2	92	16.0%	4.01 [0.96 , 16.76]
Total (95% CI)		**446**		**352**	**100.0%**	**4.83 [2.73 , 8.57]**
Total events:	66		13			

Heterogeneity: Chi² = 0.40, df = 3 (P = 0.94); I² = 0%
Test for overall effect: Z = 5.40 (P < 0.00001)
Test for subgroup differences: Not applicable



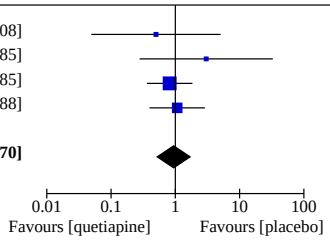


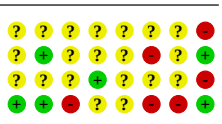
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 5.4. Comparison 5: Quetiapine versus placebo, Outcome 4: Extrapyramidal symptoms

Study or Subgroup	[Not identical] Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Paleacu 2008	1	20	2	20	6.5%	0.50 [0.05 , 5.08]
Schneider 2006 CATIE-AD	2	94	1	142	6.1%	3.02 [0.28 , 32.85]
Tariot 2006	9	91	12	99	52.2%	0.82 [0.36 , 1.85]
Zhong 2007	14	241	5	92	35.3%	1.07 [0.40 , 2.88]
Total (95% CI)		**446**		**353**	**100.0%**	**0.94 [0.52 , 1.70]**
Total events:	26		20			

Heterogeneity: Chi² = 1.38, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)
Test for subgroup differences: Not applicable



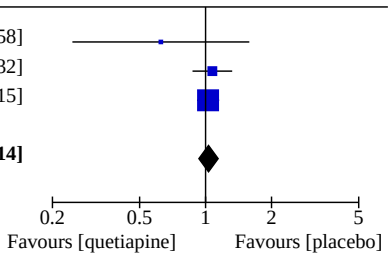


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 5.5. Comparison 5: Quetiapine versus placebo, Outcome 5: Any adverse event

Study or Subgroup	[Not identical] Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Paleacu 2008	5	20	8	20	1.2%	0.63 [0.25 , 1.58]
Schneider 2006 CATIE-AD	59	94	83	142	23.4%	1.07 [0.87 , 1.32]
Zhong 2007	199	241	74	92	75.4%	1.03 [0.91 , 1.15]
Total (95% CI)		**355**		**254**	**100.0%**	**1.03 [0.93 , 1.14]**
Total events:	263		165			

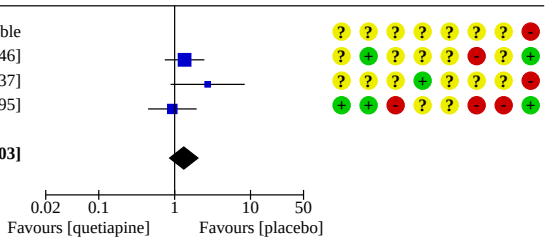
Heterogeneity: Chi² = 1.27, df = 2 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Not applicable



Analysis 5.6. Comparison 5: Quetiapine versus placebo, Outcome 6: Any serious adverse event

Study or Subgroup	[Not identical] Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Paleacu 2008	0	20	0	20		Not estimable
Schneider 2006 CATIE-AD	17	94	19	142	51.3%	1.35 [0.74 , 2.46]
Tariot 2006	10	91	4	99	14.6%	2.72 [0.88 , 8.37]
Zhong 2007	22	241	9	92	34.0%	0.93 [0.45 , 1.95]
Total (95% CI)		**446**		**353**	**100.0%**	**1.32 [0.86 , 2.03]**
Total events:	49		32			

Heterogeneity: Chi² = 2.44, df = 2 (P = 0.29); I² = 18%
Test for overall effect: Z = 1.27 (P = 0.21)
Test for subgroup differences: Not applicable

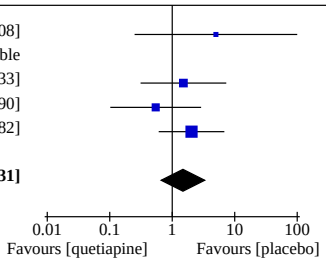


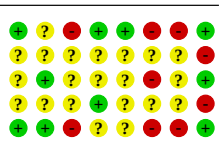
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 5.7. Comparison 5: Quetiapine versus placebo, Outcome 7: Death

Study or Subgroup	[Not identical] Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Ballard 2005	2	31	0	31	7.2%	5.00 [0.25 , 100.08]
Paleacu 2008	0	20	0	20		Not estimable
Schneider 2006 CATIE-AD	3	94	3	142	25.8%	1.51 [0.31 , 7.33]
Tariot 2006	2	91	4	99	23.0%	0.54 [0.10 , 2.90]
Zhong 2007	16	241	3	92	44.0%	2.04 [0.61 , 6.82]
Total (95% CI)		**477**		**384**	**100.0%**	**1.48 [0.67 , 3.31]**
Total events:	23		10			

Heterogeneity: Chi² = 2.28, df = 3 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.96 (P = 0.33)
Test for subgroup differences: Not applicable



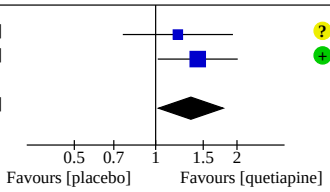


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 5.8. Comparison 5: Quetiapine versus placebo, Outcome 8: Number of responders for agitation

Study or Subgroup	[Not identical] Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Schneider 2006 CATIE-AD	24	94	30	142	34.5%	1.21 [0.76 , 1.93]
Zhong 2007	105	241	28	92	65.5%	1.43 [1.02 , 2.01]
Total (95% CI)		**335**		**234**	**100.0%**	**1.35 [1.02 , 1.78]**
Total events:	129		58			

Heterogeneity: Chi² = 0.33, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 2.13 (P = 0.03)
Test for subgroup differences: Not applicable

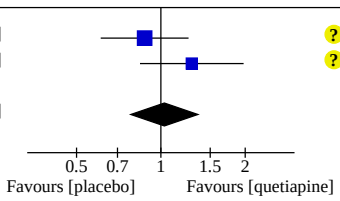


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 5.9. Comparison 5: Quetiapine versus placebo, Outcome 9: Number of responders for psychosis

Study or Subgroup	[Not identical] Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Paleacu 2008	14	20	16	20	58.2%	0.88 [0.61 , 1.26]
Tariot 2006	32	91	27	99	41.8%	1.29 [0.84 , 1.97]
Total (95% CI)		**111**		**119**	**100.0%**	**1.03 [0.78 , 1.36]**
Total events:	46		43			

Heterogeneity: Chi² = 1.85, df = 1 (P = 0.17); I² = 46%
Test for overall effect: Z = 0.20 (P = 0.84)
Test for subgroup differences: Not applicable

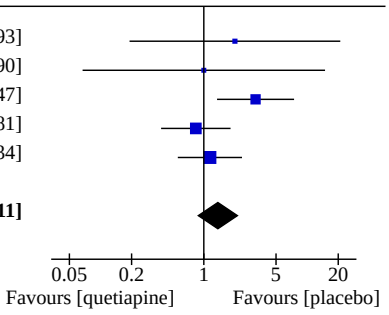


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 5.10. Comparison 5: Quetiapine versus placebo, Outcome 10: Discontinuation due to adverse events

Study or Subgroup	[Not identical] Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Ballard 2005	2	31	1	31	3.4%	2.00 [0.19 , 20.93]
Paleacu 2008	1	20	1	20	2.6%	1.00 [0.07 , 14.90]
Schneider 2006 CATIE-AD	15	94	7	139	25.6%	3.17 [1.34 , 7.47]
Tariot 2006	10	91	13	99	31.5%	0.84 [0.39 , 1.81]
Zhong 2007	27	241	9	92	36.9%	1.15 [0.56 , 2.34]
Total (95% CI)		**477**		**381**	**100.0%**	**1.37 [0.89 , 2.11]**
Total events:	55		31			

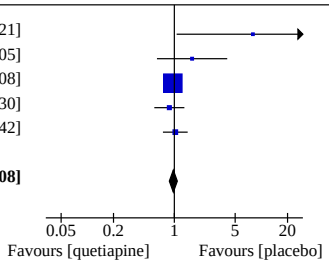
Heterogeneity: Chi² = 5.62, df = 4 (P = 0.23); I² = 29%
Test for overall effect: Z = 1.41 (P = 0.16)
Test for subgroup differences: Not applicable

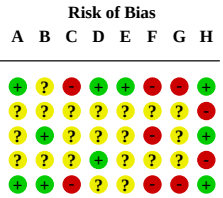


Analysis 5.11. Comparison 5: Quetiapine versus placebo, Outcome 11: Discontinuation (any reason)

Study or Subgroup	[Not identical] Events	Total	Placebo Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Ballard 2005	8	31	1	31	0.3%	8.00 [1.06 , 60.21]
Paleacu 2008	8	20	5	20	1.3%	1.60 [0.63 , 4.05]
Schneider 2006 CATIE-AD	77	94	121	142	81.0%	0.96 [0.86 , 1.08]
Tariot 2006	29	91	36	99	7.0%	0.88 [0.59 , 1.30]
Zhong 2007	86	241	32	92	10.4%	1.03 [0.74 , 1.42]
Total (95% CI)		**477**		**384**	**100.0%**	**0.97 [0.88 , 1.08]**
Total events:	208		195			

Heterogeneity: Chi² = 5.69, df = 4 (P = 0.22); I² = 30%
Test for overall effect: Z = 0.50 (P = 0.62)
Test for subgroup differences: Not applicable



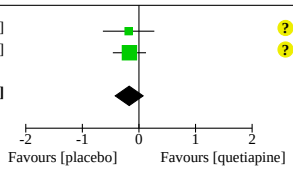


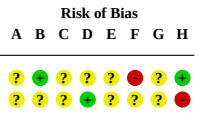
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 5.12. Comparison 5: Quetiapine versus placebo, Outcome 12: Functioning (ADL)

Study or Subgroup	[Not identical] Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Schneider 2006 CATIE-AD	-1	7.7	31	0.5	8.4	47	29.4%	-0.18 [-0.64 , 0.27]
Tariot 2006	-0.01	3.38	86	0.47	2.24	94	70.6%	-0.17 [-0.46 , 0.12]
Total (95% CI)			**117**			**141**	**100.0%**	**-0.17 [-0.42 , 0.07]**

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%
Test for overall effect: Z = 1.37 (P = 0.17)
Test for subgroup differences: Not applicable



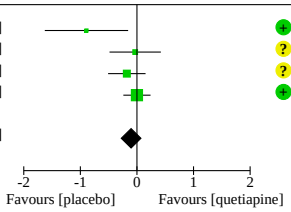


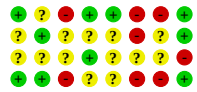
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 5.13. Comparison 5: Quetiapine versus placebo, Outcome 13: Cognitive function

Study or Subgroup	[Not identical] Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Ballard 2005	-10.5	14.8	14	3.2	15.1	18	5.6%	-0.89 [-1.63 , -0.16]
Schneider 2006 CATIE-AD	-0.8	3.8	31	-0.7	2.7	47	14.7%	-0.03 [-0.48 , 0.42]
Tariot 2006	-1.58	2.98	69	-0.9	4.42	72	27.5%	-0.18 [-0.51 , 0.15]
Zhong 2007	0	2.7	241	0	2	92	52.2%	0.00 [-0.24 , 0.24]
Total (95% CI)			**355**			**229**	**100.0%**	**-0.10 [-0.28 , 0.07]**

Heterogeneity: Chi² = 5.41, df = 3 (P = 0.14); I² = 45%
Test for overall effect: Z = 1.17 (P = 0.24)
Test for subgroup differences: Not applicable

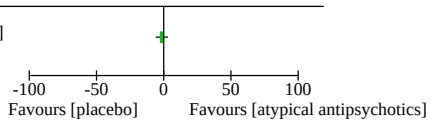




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Comparability of groups (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

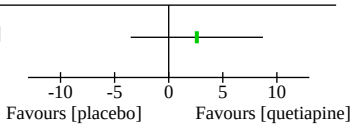
Analysis 5.14. Comparison 5: Quetiapine versus placebo, Outcome 14: Cognitive function (single study)

Study or Subgroup	[Not identical] Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Paleacu 2008	13.5	6.8	19	14.9	7.3	19	-1.40 [-5.89 , 3.09]



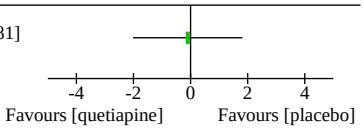
Analysis 5.15. Comparison 5: Quetiapine versus placebo, Outcome 15: Health-related quality of life

Study or Subgroup	[Not identical] Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Schneider 2006 CATIE-AD	6.7	11.7	31	4.1	15.8	47	2.60 [-3.51 , 8.71]



Analysis 5.16. Comparison 5: Quetiapine versus placebo, Outcome 16: Time spend providing care (caregiver)

Study or Subgroup	[Not identical] Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Schneider 2006 CATIE-AD	-0.7	4.3	31	-0.6	4.1	47	-0.10 [-2.01 , 1.81]



APPENDICES

Appendix 1. Sources searched and search strategies

Source	Search strategy	Hits retrieved
1. CENTRAL (the Cochrane Library) http://cr-so.cochrane.org/SearchSim-ple.php [most recent search date: 7 January 2021]	#1 MESH DESCRIPTOR Dementia EXPLODE ALL TREES 5139	Oct 2018: 396
	#2 MESH DESCRIPTOR Delirium 519	Oct 2019: 453
	#3 MESH DESCRIPTOR Wernicke Encephalopathy 4	March 2020: 83
	#4 MESH DESCRIPTOR Neurocognitive Disorders 151	Jan 2021: 37
	#5 dement*:TI,AB,KY 11330	
	#6 alzheimer*:TI,AB,KY 10070	
	#7 (lewy* adj2 bod*):TI,AB,KY 388	
	#8 (chronic adj2 cerebrovascular):TI,AB,KY 107	
	#9 ("organic brain disease" or "organic brain syndrome"):TI,AB,KY 133	
	#10 ("benign senescent forgetfulness"):TI,AB,KY 2	
	#11 (cerebr* adj2 deteriorat*):TI,AB,KY 10	
	#12 (cerebral* adj2 insufficient*):TI,AB,KY 1	
	#13 ("major neurocognitive disorder"):TI,AB,KY 18	
	#14 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 18343	
	#15 MESH DESCRIPTOR Antipsychotic Agents 4224	
	#16 (antipsychotic* or neuroleptic*):TI,AB,KY 10065	
	#17 (neurolept* or antipsychotic* or Amisulpride* or Chormethiazole* or Clomethiazole* or Distraneurin* or Chlorpromazin* or Aminazine* or Chlorazine* or Chlordelazine* or Contomin* or Fenactil* or Largactil* or Propaphenin* or Thorazine* or Flupenthixol decanoate* or Emergil* or Fluanxol* or Flupentixol* or alphaFlupenthixol* or cisFlupenthixol* or Fluphenazin* or Fluphenazine decanoate* or Flufenazin* or Fluphenazine Hydrochloride* or Lyogen* or Prolixin* or Haloperidol* or Haldol* or Levomepromazin* or Levomeprazin* or Levopromazine* or Tisercin* or Tizercine* or Tizertsin* or Methotrimeprazine* or Loxapine* or Loxapinsuccinate* or Oxilapine* or Cloxazepine* or Loxapine Monohydrochloride* or Loxipine Maleate* or Loxipine Succinate* or Loxitane* or Asendin* or Desmethylloxapine* or Amoxapine* or Olanzapine* or Perphenazine* or Chlorpiprazine* or Perfenazine* or Trilafonor* or Pimozide* or Prothipendyl* or Quetiapine* or Fumarate* or Risperidone* or Risperidal* or Sulpiride* or Dogmatil* or Eglonyl* or Sulperide* or Thioridazine* or Meleril* or Mellaril* or Melleril* or Melleryl* or Sonapax* or Thioridazine Hydrochloride* or Tiaprid* or Tiapridal* or Trifluoperazine Hydrochloride* or Trifluoroperazine* or Triftazin* or Stelazine* or "Trifluperazine*or Tripfluoperazine Hydrochloride* or Cisordinol*" or Zuclopenthixol* or Clopenthixol* or Clozapine*or Melperone hydrochloride* or Ziprasidone* or Zotemine*):TI,AB,KY 20326	
	#18 MESH DESCRIPTOR PIMOZIDE 103	
	#19 MESH DESCRIPTOR PERPHENAZINE 189	
	#20 MESH DESCRIPTOR LOXAPINE 60	
	#21 MESH DESCRIPTOR METHOTRIMEPRAZINE 33	

(Continued)

#22 MESH DESCRIPTOR HALOPERIDOL 1312

#23 MESH DESCRIPTOR FLUPHENAZINE 278

#24 MESH DESCRIPTOR FLUPENTHIXOL 105

#25 MESH DESCRIPTOR CHLORPROMAZINE 577

#26 MESH DESCRIPTOR CHLORMETHIAZOLE 58

#27 MESH DESCRIPTOR CLOPENTHIXOL 53

#28 MESH DESCRIPTOR TRIFLUOPERAZINE 110

#29 MESH DESCRIPTOR THIORIDAZINE 187

#30 MESH DESCRIPTOR SULPIRIDE 309

#31 MESH DESCRIPTOR RISPERIDONE 1245

#32 MESH DESCRIPTOR FUMARATES 235

#33 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 20431

#34 MESH DESCRIPTOR Psychotic Disorders EXPLODE ALL TREES 2574

#35 Psychoses:TI,AB,KY 558

#36 Psychosis:TI,AB,KY 5361

#37 MESH DESCRIPTOR VIOLENCE EXPLODE ALL TREES 1492

#38 MESH DESCRIPTOR HOSTILITY EXPLODE ALL TREES 265

#39 MESH DESCRIPTOR Irritable Mood EXPLODE ALL TREES 135

#40 MESH DESCRIPTOR Impulsive Behavior EXPLODE ALL TREES 1040

#41 Paranoid Behavior 7

#42 Agitat*:TI,AB,KY 4112

#43 aggress*:TI,AB,KY 9491

#44 violen*:TI,AB,KY 2668

#45 impuls*:TI,AB,KY 3638

#46 irritabl*:TI,AB,KY 3680

#47 hostil*:TI,AB,KY 1225

#48 anger:TI,AB,KY 1992

#49 angry:TI,AB,KY 418

#50 anti-social:TI,AB,KY 26

#51 impuls*:TI,AB,KY 3638

#52 Restless*:TI,AB,KY 2146

#53 #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 33621

#54 #14 AND #33 AND #53 453

(Continued)

2. MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (Ovid SP) [most recent search date: 7 January 2021]	1 exp Dementia/	Oct 2018: 1382
	2 Delirium/	Oct 2019: 100
	3 Wernicke Encephalopathy/	March 2020: 69
	4 Neurocognitive Disorders/	Jan 2021:Jan 2021: 50
	5 dement*.mp.	
	6 alzheimer*.mp.	
	7 (lewy* adj2 bod*).mp.	
	8 (chronic adj2 cerebrovascular).mp.	
	9 ("organic brain disease" or "organic brain syndrome").mp.	
	10 "benign senescent forgetfulness".mp.	
	11 (cerebr* adj2 deteriorat*).mp.	
	12 (cerebral* adj2 insufficient*).mp.	
	13 "major neurocognitive disorder".mp.	
	14 or/1-13	
	15 Antipsychotic Agents/	
	16 (antipsychotic* or neuroleptic*).ti,ab.	
	17 (neurolept* or antipsychotic* or alphaFlupenthixol* or Aminazine* or Amisulpride* or Amoxapine* or Aripiprazole or Asenapine maleate or Asendin* or Benperidol or Benzamides or Brexpiprazole or Butyrophenones or Chlorazine* or Chlordelazine* or Chlorpiprazine* or Chlorpromazin* or Chormethiazole* or cisFlupenthixol* or Cisordinol* or Clomethiazole* or Clopenthixol* or Cloxazepine* or Clozapine*OR Contomin* or Desmethylloxapine* or Diphenylbutylpiperidines or Distraneurin* or Dogmatil* or Eglonyl* or Emergil* or Fenactil* or Fluanxol* or Flufenazin* or Flupenthixol decanoate* or Flupentixol decanoate or Flupentixol* or Fluphenazin* or Fluphenazine decanoate* or Fluphenazine Hydrochloride* or Fumarate* or Haldol* or Haloperidol* or Iloperidone or Largactil* or Levomeprazin* or Levomepromazin* or Levopromazine* or Loxapine Monohydrochloride* or Loxapine* or Loxapinsuccinate* or Loxipine Maleate* or Loxipine Succinate* or Loxitane* or Lurasidone or Lyogen* or Meleril* or Mellaril* or Melleril* or Melleryl* or Melperone hydrochloride* or Methotrimeprazine* or Nalotenserin or Norquetiapine or Olanzapine embonate or Olanzapine* or Oxilapine* or Paliperidone or Perfenazine* or Pericyazine or Perphenazine* or Phenothiazine or Pimavanserin or Pimozide* or Prochlorperazine or Prolixin* or Promazine hydrochloride or Propaphenin* or Prothipendyl* or Quetiapine* or Risperidal* or Risperidone* or Sertindole or Sonapax* or Stelazine* or Sulperide* or Sulpiride* or Thioridazine Hydrochloride* or Thioridazine* or Thiothixene or Thioxanthenes or Thorazine* or Tiaprid* or Tiapridal* or Tisercin* or Tizercine* or Tizertsin* or Trifluoperazine or Trifluoroperazine* or Trifluperazine*OR Triftazin* or Trilafonor* or Tripfluoperazine Hydrochloride* or Ziprasidone* or Zotemine* or Zotepine or Zuclopenthixol or Zuclopenthixol*).ti,ab.	
	18 PIMOZIDE/	
	19 PERPHENAZINE/	
	20 LOXAPINE/	

(Continued)

21 METHOTRIMEPRAZINE/

22 HALOPERIDOL/

23 FLUPHENAZINE/

24 FLUPENTHIXOL/

25 CHLORPROMAZINE/

26 CHLORMETHIAZOLE/

27 CLOPENTHIXOL/

28 TRIFLUOPERAZINE/

29 THIORIDAZINE/

30 SULPIRIDE/

31 RISPERIDONE/

32 FUMARATES/

33 or/15-32

34 14 and 33

35 exp Psychotic Disorders/

36 Psychoses.ti,ab.

37 Psychosis.ti,ab.

38 exp VIOLENCE/

39 exp HOSTILITY/

40 exp Irritable Mood/

41 exp Impulsive Behavior/

42 exp Paranoid Behavior/

43 Agitat*.ti,ab.

44 aggress*.ti,ab.

45 violen*.ti,ab.

46 impuls*.ti,ab.

47 irritabl*.ti,ab.

48 hostil*.ti,ab.

49 anger.ti,ab.

50 angry.ti,ab.

51 anti-social.ti,ab.

52 impuls*.ti,ab.

53 Restless*.ti,ab.

54 or/35-53

(Continued)

	55 34 and 54 56 randomized controlled trial.pt. 57 controlled clinical trial.pt. 58 randomized.ab. 59 placebo.ab. 60 drug therapy.fs. 61 randomly.ab. 62 trial.ab. 63 groups.ab. 64 or/56-63 65 exp animals/ not humans.sh. 66 64 not 65 67 55 and 66	
3. Embase 1974 to present [most recent search date: 7 January 2021]	1 Dementia/ 2 Delirium/ 3 Wernicke Encephalopathy/ 4 Delirium, Dementia, Amnestic, Cognitive Disorders/ 5 ("benign senescent forgetfulness" or ("normal pressure hydrocephalus" and "shunt*") or ("organic brain disease" or "organic brain syndrome") or ((cerebral* or cerebrovascular or cerebro-vascular) adj2 insufficien*) or (cerebr* adj2 deteriorat*) or (chronic adj2 (cerebrovascular or cerebro-vascular)) or (creutzfeldt or jcd or cjd) or (lewy* adj2 bod*) or (pick* adj2 disease) or alzheimer* or binswanger* or deliri* or dement* or huntington* or korsako*).tw. 6 "major neurocognitive disorder".ti,ab. 7 or/1-6 8 neuroleptic agent/ 9 (antipsychotic* or neuroleptic*).ti,ab. 10 (neurolept* or antipsychotic* or alphaFlupenthixol* or Aminazine* or Amisulpride* or Amoxapine* or Aripiprazole or Asenapine maleate or Asendin* or Benperidol or Benzamides or Brexpiprazole or Butyrophenones or Chlorazine* or Chlordelazine* or Chlorpiprazine* or Chlorpromazin* or Chormethiazole* or cisFlupenthixol* or Cisordinol* or Clomethiazole* or Clopenthixol* or Cloxazepine* or Clozapine*OR Contomin* or Desmethylloxapine* or Diphenylbutylpiperidines or Distraneurin* or Dogmatil* or Eglonyl* or Emergil* or Fenactil* or Fluanxol* or Flufenazin* or Flupenthixol decanoate* or Flupentixol decanoate or Flupentixol* or Fluphenazin* or Fluphenazine decanoate* or Fluphenazine Hydrochloride* or Fumarate* or Haldol* or Haloperidol* or Iloperidone or Largactil* or Levomeprazin* or Levomepromazin* or Levopromazine* or Loxapine Monohydrochloride* or Loxapine* or Loxapinsuccinate* or Loxipine Maleate* or Loxipine Succinate* or Loxitane* or Lurasidone or Lyogen* or Meleril* or Mellaril* or Melleril* or Melleryl* or Melperone hydrochloride* or Methotrimeprazine* or Nalotenserin or Norquetiapine or	Oct 2018: 2303 Oct 2019: 337 March 2020: 199 Jan 2021: 165

(Continued)

Olanzapine embonate or Olanzapine* or Oxilapine* or Paliperidone or Perfenazine* or Pericyazine or Perphenazine* or Phenothiazine or Pimavanserin or Pimozide* or Prochlorperazine or Prolixin* or Promazine hydrochloride or Propaphenin* or Prothipendyl* or Quetiapine* or Risperidal* or Risperidone* or Sertindole or Sonapax* or Stelazine* or Sulperide* or Sulpiride* or Thioridazine Hydrochloride* or Thioridazine* or Thiothixene or Thioxanthenes or Thorazine* or Tiaprid* or Tiapridal* or Tisercin* or Tizercine* or Tizertsin* or Trifluoperazine or Trifluoroperazine* or Trifluperazine*OR Triftazin* or Trilafonor* or Tripfluoperazine Hydrochloride* or Ziprasidone* or Zotemine* or Zotepine or Zuclopenthixol or Zuclopenthixol*).ti,ab.

11 pimozide/

12 perphenazine/

13 loxapine/

14 levomepromazine/

15 haloperidol/

16 fluphenazine/

17 flupentixol/

18 chlorpromazine/

19 clomethiazole/

20 clopenthixol/

21 trifluoperazine/

22 thioridazine/

23 sulpiride/

24 risperidone/

25 fumaric acid derivative/

26 or/8-25

27 7 and 26

28 exp psychosis/

29 Psychoses.ti,ab.

30 Psychosis.ti,ab.

31 exp violence/

32 exp hostility/

33 exp irritability/

34 exp impulsiveness/

35 exp paranoia/

36 Agitat*.ti,ab.

37 aggress*.ti,ab.

38 violen*.ti,ab.

(Continued)

	39 impuls*.ti,ab.	
	40 irritabl*.ti,ab.	
	41 hostil*.ti,ab.	
	42 anger.ti,ab.	
	43 angry.ti,ab.	
	44 anti-social.ti,ab.	
	45 impuls*.ti,ab.	
	46 Restless*.ti,ab.	
	47 or/28-46	
	48 27 and 47	
	49 randomized controlled trial/	
	50 controlled clinical trial/	
	51 random$.ti,ab.	
	52 randomization/	
	53 intermethod comparison/	
	54 placebo.ti,ab.	
	55 (compare or compared or comparison).ti.	
	56 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.	
	57 (open adj label).ti,ab.	
	58 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.	
	59 double blind procedure/	
	60 parallel group$1.ti,ab.	
	61 (crossover or cross over).ti,ab.	
	62 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.	
	63 (assigned or allocated).ti,ab.	
	64 (controlled adj7 (study or design or trial)).ti,ab.	
	65 (volunteer or volunteers).ti,ab.	
	66 trial.ti.	
	67 or/49-66	
	68 48 and 67	
4. PSYCINFO [most recent search date: 7 January 2021]	1 exp Dementia/ 2 exp Delirium/ 3 exp Wernickes Syndrome/	Oct 2018: 447 Oct 2019: 27 March 2020: 19

(Continued)

4 exp Cognitive Impairment/	Jan 2021: 16
5 dement*.mp.	
6 alzheimer*.mp.	
7 (chronic adj2 cerebrovascular).mp.	
8 ("organic brain disease" or "organic brain syndrome").mp.	
9 "benign senescent forgetfulness".mp.	
10 (cerebr* adj2 deteriorat*).mp.	
11 "major neurocognitive disorder".mp.	
12 (lewy* adj2 bod*).mp.	
13 (cerebral* adj2 insufficient*).mp.	
14 or/1-13	
15 exp Neuroleptic Drugs/	
16 (antipsychotic* or neuroleptic*).ti,ab.	
17 (neurolept* or antipsychotic* or alphaFlupenthixol* or Aminazine* or Amisulpride* or Amoxapine* or Aripiprazole or Asenapine maleate or Asendin* or Benperidol or Benzamides or Brexpiprazole or Butyrophenones or Chlorazine* or Chlordelazine* or Chlorpiprazine* or Chlorpromazin* or Chormethiazole* or cisFlupenthixol* or Cisordinol* or Clomethiazole* or Clopenthixol* or Cloxazepine* or Clozapine*OR Contomin* or Desmethylloxapine* or Diphenylbutylpiperidines or Distraneurin* or Dogmatil* or Eglonyl* or Emergil* or Fenactil* or Fluanxol* or Flufenazin* or Flupenthixol decanoate* or Flupentixol decanoate or Flupentixol* or Fluphenazin* or Fluphenazine decanoate* or Fluphenazine Hydrochloride* or Fumarate* or Haldol* or Haloperidol* or Iloperidone or Largactil* or Levomeprazin* or Levomepromazin* or Levopromazine* or Loxapine Monohydrochloride* or Loxapine* or Loxapinsuccinate* or Loxipine Maleate* or Loxipine Succinate* or Loxitane* or Lurasidone or Lyogen* or Meleril* or Mellaril* or Melleril* or Melleryl* or Melperone hydrochloride* or Methotrimeprazine* or Nalotenserin or Norquetiapine or Olanzapine embonate or Olanzapine* or Oxilapine* or Paliperidone or Perfenazine* or Pericyazine or Perphenazine* or Phenothiazine or Pimavanserin or Pimozide* or Prochlorperazine or Prolixin* or Promazine hydrochloride or Propaphenin* or Prothipendyl* or Quetiapine* or Risperidal* or Risperidone* or Sertindole or Sonapax* or Stelazine* or Sulperide* or Sulpiride* or Thioridazine Hydrochloride* or Thioridazine* or Thiothixene or Thioxanthenes or Thorazine* or Tiaprid* or Tiapridal* or Tisercin* or Tizercine* or Tizertsin* or Trifluoperazine or Trifluoroperazine* or Trifluperazine*OR Triftazin* or Trilafonor* or Tripfluoperazine Hydrochloride* or Ziprasidone* or Zotemine* or Zotepine or Zuclopenthixol or Zuclopenthixol*).ti,ab.	
18 exp PIMOZIDE/	
19 exp PERPHENAZINE/	
20 exp LOXAPINE/	
21 exp HALOPERIDOL/	
22 exp FLUPHENAZINE/	
23 exp CHLORPROMAZINE/	
24 exp TRIFLUOPERAZINE/	

(Continued)

25 exp THIORIDAZINE/

26 exp SULPIRIDE/

27 exp RISPERIDONE/

28 or/15-27

29 14 and 28

30 exp Psychosis/

31 Psychoses.ti,ab.

32 Psychosis.ti,ab.

33 exp VIOLENCE/

34 exp HOSTILITY/

35 exp Impulsiveness/

36 exp Paranoia/

37 Agitat*.ti,ab.

38 aggress*.ti,ab.

39 violen*.ti,ab.

40 impuls*.ti,ab.

41 irritabl*.ti,ab.

42 hostil*.ti,ab.

43 anger.ti,ab.

44 angry.ti,ab.

45 anti-social.ti,ab.

46 impuls*.ti,ab.

47 Restless*.ti,ab.

48 or/30-47

49 29 and 48

50 exp Clinical Trials/

51 randomly.ab.

52 randomi?ed.ti,ab.

53 placebo.ti,ab.

54 groups.ab.

55 "double-blind*".ti,ab.

56 "single-blind*".ti,ab.

57 RCT.ti,ab.

58 or/50-57

(Continued)

	59 49 and 58	
5. CINAHL (EBSCOhost) [most recent search date: 7 January 2021]	S59 S45 AND S58 S58 S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 S57 TX random* S56 MH "Random Assignment" S55 MH "Single-Blind Studies" or MH "Double-Blind Studies" or MH "Triple-Blind Studies" S54 MH "Crossover Design" S53 MH "Factorial Design" S52 MH "Placebos" S51 MH "Clinical Trials" S50 TX "multi-centre study" OR "multi-center study" OR "multicentre study" OR "multicenter study" OR "multi-site study" S49 TX crossover OR "cross-over" S48 AB placebo* S47 TX trial* S46 TX "latin square" S45 S26 AND S44 S44 S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 S43 TX Restless* S42 TX impuls* S41 TX anti-social S40 TX angry S39 TX anger S38 TX hostil* S37 TX irritabl* S36 TX impuls* S35 TX violen* S34 TX aggress* S33 TX Agitat* S32 MH "Disruptive Behavior" S31 MH "Aggression+" S30 MH "Violence+" S29 TX Psychosis	Oct 2018: 425 Oct 2019: 575 March 2020: 36 Jan 2021: 40

(Continued)

S28 TX Psychoses

S27 MH "Psychotic Disorders+"

S26 S13 AND S25

S25 S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24

S24 MH "Risperidone"

S23 MH "Thioridazine"

S22 MH "Trifluoperazine Hydrochloride"

S21 MH "Chlorpromazine"

S20 MH "Fluphenazine"

S19 MH "Haloperidol"

S18 MH "Loxapine"

S17 MH "Perphenazine Hydrochloride"

S16
TX neurolept* or antipsychotic* or alphaFlupenthixol* OR Aminazine* OR Amisulpride* OR Amoxapine* OR Aripiprazole OR Asenapine maleate OR Asendin* OR Benperidol OR Benzamides OR Brexpiprazole OR Butyrophenones OR Chlorazine* OR Chlordelazine* OR Chlorpiprazine* OR Chlorpromazin* OR Chormethiazole* OR cisFlupenthixol* OR Cisordinol* OR Clomethiazole* OR Clopenthixol* OR Cloxazepine* OR Clozapine*OR Contomin* OR Desmethylloxapine* OR Diphenylbutylpiperidines OR Distraneurin* OR Dogmatil* OR Eglonyl* OR Emergil* OR Fenactil* OR Fluanxol* OR Flufenazin* OR Flupenthixol decanoate* OR Flupentixol decanoate OR Flupentixol* OR Fluphenazin* OR Fluphenazine decanoate* OR Fluphenazine Hydrochloride* OR Fumarate* OR Haldol* OR Haloperidol* OR Iloperidone OR Largactil* OR Levomeprazin* OR Levomepromazin* OR Levopromazine* OR Loxapine Monohydrochloride* OR Loxapine* OR Loxapinsuccinate* OR Loxipine Maleate* OR Loxipine Succinate* OR Loxitane* OR Lurasidone OR Lyogen* OR Melleril* OR Mellaril* OR Melleril* OR Melleryl* OR Melperone hydrochloride* OR Methotrimeprazine* OR Nalotenserin OR Norquetiapine OR Olanzapine embonate OR Olanzapine* OR Oxilapine* OR Paliperidone OR Perfenazine* OR Pericyazine OR Perphenazine* OR Phenothiazine OR Pimavanserin OR Pimozide* OR Prochlorperazine OR Prolixin* OR Promazine hydrochloride OR Propaphenin* OR Prothipendyl* OR Quetiapine* OR Risperidal* OR Risperidone* OR Sertindole OR Sonapax* OR Stelazine* OR Sulperide* OR Sulpiride* OR Thioridazine Hydrochloride* OR Thioridazine* OR Thiothixene OR Thioxanthenes OR Thorazine* OR Tiaprid* OR Tiapridal* OR Tisercin* OR Tizercine* OR Tizertsin* OR Trifluoperazine OR Trifluoroperazine* OR Trifluperazine*OR Triftazin* OR Trilafonor* OR Tripfluoperazine Hydrochloride* OR Ziprasidone* OR Zotemine* OR Zotepine OR Zuclopenthixol OR Zuclopenthixol*

S15 TX antipsychotic* or neuroleptic*

S14 MH "Antipsychotic Agents"

S13 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12

S12 TX "organic brain disease" or "organic brain syndrome"

S11 TX "major neurocognitive disorder"

S10 TX cerebral* n2 insufficient*

(Continued)

	S9 TX cerebr* n2 deteriorat* S8 TX "benign senescent forgetfulness" S7 TX chronic n2 cerebrovascular S6 TX lewy* n2 bod* S5 TX alzheimer* S4 TX dement* S3 MH "Wernicke's Encephalopathy" S2 MH "Delirium" S1 MH "Dementia+"	
6. ISI Web of Science – core collection [most recent search date: 7 January 2021]	TOPIC: (dement* OR alzheimer* OR "vascular cognitive impairment" OR "lew* bod*" OR CADASIL OR "cognit* impair*" OR FTD OR FTLD OR "cerebrovascular insufficienc*" OR AD OR VCI "major neurocognitive disorder") AND TOPIC: (Antipsychotic* OR neurolept* OR HALOPERIDOL OR RISPERIDONE) AND TOPIC: (Psychotic OR Psychoses OR Psychosis OR VIOLENCE OR HOSTILITY) AND TOPIC: (randomly OR randomised OR randomized OR "random allocat*" OR RCT OR CCT OR "double blind*" OR "single blind*" OR "double blind*" OR "single blind*" OR trial)	Oct 2018: 738 Oct 2019: 66 March 2020: 33 Jan 2021: 33
7. LILACS (BIREME) [most recent search date: 7 January 2021]	alzheimer OR alzheimers OR alzheimer's OR dementia OR demenc$ [Words]and Psychotic OR Psychoses OR Psychosis OR VIOLENCE OR HOSTILITY [Words]and randomly OR randomised OR randomized OR RCT OR "controlled trial" OR "double blind$" OR placebo [Words]	Oct 2018: 20 Oct 2019: 0 March 2020: 0 Jan 2021: 22
8. ClinicalTrials.gov (www.clinicaltrials.gov) [most recent search date: 7 January 2021]	Psychotic OR Psychoses OR Psychosis OR VIOLENCE OR HOSTILITY | dementia OR alzheimers OR cognition OR cognitive | Antipsychotic* OR neurolept* OR HALOPERIDOL OR RISPERIDONE OR Brexipiprazole OR Nalotenserin OR Pimavanserine	Oct 2018: 65 Oct 2019: 69 March 2020: 2 Jan 2021: 2
9. ICTRP [most recent search date: 7 January 2021]	Psychotic OR Psychoses OR Psychosis OR VIOLENCE OR HOSTILITY | dementia OR alzheimers OR cognition OR cognitive | Antipsychotic* OR neurolept* OR HALOPERIDOL OR RISPERIDONE OR Brexipiprazole OR Nalotenserin OR Pimavanserine	Oct 2018: 10 Oct 2019: 11 March 2020: 2 Jan 2021: 1
TOTAL before deduplication		Oct 2018: 5786 Oct 2019: 1638 March 2020: 443 Jan 2021: 366 **TOTAL 8233**
TOTAL after de-duplication		Oct 2018: 4911 Oct 2019: 1432

(Continued)

	March 2020: 378
	Jan 2021: 316
	TOTAL 7037

Appendix 2. Other resources searches

Source	Search strategy	Hits retrieved
1. GlaxoSmithKline register https://www.gsk-studyregister.com/en/ [Date of most recent search: 17 February 2021]	alphaflupenthixol amisulpride amoxapine asendin chlorazine chlordelazine chlormethiazole chlorpiprazine chlorpromazin chlorpromazine chormethiazole cisflupenthixol cisordinol clomethiazole clopenthixol cloxazepine clozapine contomin desmethylloxapine distraneurin dogmatil eglonyl emergil fenactil fluanxol flufenazin	Feb 2021: 4

(Continued)

flupenthixol decanoate

flupentixol

fluphenazin

fluphenazine decanoate

fluphenazine hydrochloride

fumarate

fumarates

haldol

haloperidol

largactil

levomeprazin

levomepromazin

levopromazine

loxapine monohydrochloride

loxapine

loxapinsuccinate

loxipine maleate

loxipine succinate

loxitane

lyogen

meleril

mellaril

melleril

melleryl

melperone hydrochloride

methotrimeprazine

olanzapine

oxilapine

perfenazine

perphenazine

pimozide

prolixin

propaphenin

prothipendyl

(Continued)

	quetiapine	
	risperidal	
	risperidone	
	sonapax	
	stelazine	
	sulperide	
	sulpiride	
	thioridazine hydrochloride	
	thioridazine	
	thorazine	
	tiaprid	
	tiapridal	
	tisercin	
	tizercine	
	tizertsin	
	trifluoperazine hydrochloride	
	trifluoroperazine	
	trifluperazine	
	triftazin	
	trilafonor	
	tripfluoperazine hydrochloride	
	ziprasidone	
	zotemine	
	zuclopenthixol	
2. European Medicines Agency (EMA) https://www.clinical-trialsregister.eu/ctr-search/search [Date of most recent search: 17 February 2021]	alphaflupenthixol	Feb 2021: 0
	amisulpride	
	amoxapine	
	asendin	
	chlorazine	
	chlordelazine	
	chlormethiazole	
	chlorpiprazine	
	chlorpromazin	
	chlorpromazine	

(Continued)

chormethiazole

cisflupenthixol

cisordinol

clomethiazole

clopenthixol

cloxazepine

clozapine

contomin

desmethylloxapine

distraneurin

dogmatil

eglonyl

emergil

fenactil

fluanxol

flufenazin

flupenthixol decanoate

flupentixol

fluphenazin

fluphenazine decanoate

fluphenazine hydrochloride

fumarate

fumarates

haldol

haloperidol

largactil

levomeprazin

levomepromazin

levopromazine

loxapine monohydrochloride

loxapine

loxapinsuccinate

loxipine maleate

loxipine succinate

(Continued)

loxitane

lyogen

meleril

mellaril

melleril

melleryl

melperone hydrochloride

methotrimeprazine

olanzapine

oxilapine

perfenazine

perphenazine

pimozide

prolixin

propaphenin

prothipendyl

quetiapine

risperidal

risperidone

sonapax

stelazine

sulperide

sulpiride

thioridazine hydrochloride

thioridazine

thorazine

tiaprid

tiapridal

tisercin

tizercine

tizertsin

trifluoperazine hydrochloride

trifluoroperazine

trifluperazine

(Continued)

	triftazin	
	trilafonor	
	tripfluoperazine hydrochloride	
	ziprasidone	
	zotemine	
	zuclopenthixol	
3. Food and Drug administration (FDA) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/Erleada_210951_toc.cfm [Date of most recent search: 17 February 2021]	alphaflupenthixol	Feb 2021: 0
	amisulpride	
	amoxapine	
	asendin	
	chlorazine	
	chlordelazine	
	chlormethiazole	
	chlorpiprazine	
	chlorpromazin	
	chlorpromazine	
	chormethiazole	
	cisflupenthixol	
	cisordinol	
	clomethiazole	
	clopenthixol	
	cloxazepine	
	clozapine	
	contomin	
	desmethylloxapine	
	distraneurin	
	dogmatil	
	eglonyl	
	emergil	
	fenactil	
	fluanxol	
	flufenazin	
	flupenthixol decanoate	
	flupentixol	

(Continued)

fluphenazin

fluphenazine decanoate

fluphenazine hydrochloride

fumarate

fumarates

haldol

haloperidol

largactil

levomeprazin

levomepromazin

levopromazine

loxapine monohydrochloride

loxapine

loxapinsuccinate

loxipine maleate

loxipine succinate

loxitane

lyogen

meleril

mellaril

melleril

melleryl

melperone hydrochloride

methotrimeprazine

olanzapine

oxilapine

perfenazine

perphenazine

pimozide

prolixin

propaphenin

prothipendyl

quetiapine

risperidal

(Continued)

risperidone
sonapax
stelazine
sulperide
sulpiride
thioridazine hydrochloride
thioridazine
thorazine
tiaprid
tiapridal
tisercin
tizercine
tizertsin
trifluoperazine hydrochloride
trifluoroperazine
trifluperazine
triftazin
trilafonor
tripfluoperazine hydrochloride
ziprasidone
zotemine
zuclopenthixol

WHAT'S NEW

Date	Event	Description
4 January 2022	Amended	Funnel plots added

HISTORY

Protocol first published: Issue 4, 2019
Review first published: Issue 12, 2021

CONTRIBUTIONS OF AUTHORS

VM: developing the protocol, screening relevant literature, extracting data, performing the data-analyses and drafting the review.

RM: screening relevant literature, extracting data, performing the data-analysis, and drafting the review.

MND: screening relevant literature and drafting the review.

SUZ: developing the protocol and drafting the review.

SK: developing the protocol, screening relevant literature, data-extraction, and drafting the review.

HJL: developing the protocol, screening relevant literature, data-extraction, and drafting the review.

DECLARATIONS OF INTEREST

VM: none known

RM: none known

MND: none known

SUZ: none known

SK: none known

HJL: none known

SOURCES OF SUPPORT

Internal sources

- New Source of support, Other

  None

External sources

- NIHR, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We replaced two secondary outcomes to be displayed in the SoF tables. We presented the number of responders for agitation and the number of responders for psychosis instead of risk of adverse event and serious adverse events since we judged the number of responders to be more important than the unspecific adverse events and serious adverse events - we still display specific adverse events in the SoF tables (i.e. extrapyramidal symptoms, somnolence and death).

There were eight trials that tested an atypical antipsychotic for agitation in dementia. One of those trials focussed specifically on aggression, which is a subtype of agitation. We pooled the trials as planned, but also decided to show the pooled effect of the other trials without this trial in the meta-analysis.

We did not perform the pre-planned sensitivity analyses excluding trials with at least one rating of high risk of bias because all studies had a high risk of bias rating in at least one domain. In addition, we did not perform the pre-planned sensitivity analysis excluding trials that only reported per-protocol analysis due to the lack of such studies.

We did not find any unpublished studies for which we needed to contact the pharmaceutical company.

INDEX TERMS

Medical Subject Headings (MeSH)

*Alzheimer Disease [complications] [drug therapy]; *Antipsychotic Agents [adverse effects]; *Dementia, Vascular [drug therapy]; *Psychotic Disorders [complications] [drug therapy]; Randomized Controlled Trials as Topic; Risperidone [adverse effects]

MeSH check words

Humans