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[Intervention Review]

Mirtazapine adjunct for people with schizophrenia

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ABSTRACT

Background

Many individuals who have a diagnosis of schizophrenia experience a range of distressing and debilitating symptoms. These can include positive symptoms (such as delusions, hallucinations, disorganised speech), cognitive symptoms (such as trouble focusing or paying attention or using information to make decisions), and negative symptoms (such as diminished emotional expression, avolition, alogia, and anhedonia). Antipsychotic drugs are often only partially effective, particularly in treating negative symptoms, indicating the need for additional treatment. Mirtazapine is an antidepressant drug that when taken in addition to an antipsychotic may offer some benefit for negative symptoms.

Objectives

To systematically assess the effects of mirtazapine as adjunct treatment for people with schizophrenia.

Search methods

The Information Specialist of Cochrane Schizophrenia searched the Cochrane Schizophrenia Group's Study-Based Register of Trials (including registries of clinical trials) up to May 2018.

Selection criteria

All randomised-controlled trials (RCTs) with useable data focusing on mirtazapine adjunct for people with schizophrenia.

Data collection and analysis

We extracted data independently. For binary outcomes, we calculated risk ratio (RR) and its 95% confidence interval (CI), on an intention-to-treat (ITT) basis. For continuous data, we estimated the mean difference (MD) between groups and its 95% CI. We employed a fixed-effect model for analyses. For included studies we assessed risk of bias and created 'Summary of findings' table using GRADE.

Main results

We included nine RCTs with a total of 310 participants. All studies compared mirtazapine adjunct with placebo adjunct and were of short-term duration. We considered five studies to have a high risk of bias for either incomplete outcome data, selective reporting, or other bias.

Our main outcomes of interest were clinically important change in mental state (negative and positive symptoms), leaving the study early for any reason, clinically important change in global state, clinically important change in quality of life, number of days in hospital and incidence of serious adverse events.

One trial defined a reduction in the Scale for the Assessment of Negative Symptoms (SANS) overall score from baseline of at least 20% as no important response for negative symptoms. There was no evidence of a clear difference between the two treatments with similar

numbers of participants from each group showing no important response to treatment (RR 0.81, 95% CI 0.57 to 1.14, 1 RCT, n = 20, very low-quality evidence).

Clinically important change in positive symptoms was not reported, however, clinically important change in overall mental state was reported by two trials and data for this outcome showed a favourable effect for mirtazapine (RR 0.69, 95% CI 0.51 to 0.92; I^2 = 75%, 2 RCTs, n = 77, very low-quality evidence). There was no evidence of a clear difference for numbers of participants leaving the study early (RR 1.03, 95% CI 0.64 to 1.66, 9 RCTs, n = 310, moderate-quality evidence), and no evidence of a clear difference in global state Clinical Global Impressions Scale (CGI) severity scores (MD -0.10, 95% CI -0.68 to 0.48, 1 RCT, n = 39, very low-quality evidence). A favourable effect for mirtazapine adjunct was found for the outcome clinically important change in akathisia (RR 0.33, 95% CI 0.20 to 0.52, 2 RCTs, n = 86, low-quality evidence; I^2 = 61%I). No data were reported for quality life or number of days in hospital.

In addition to the main outcomes of interest, there was evidence relating to adverse events that the mirtazapine adjunct groups were associated with an increased risk of weight gain (RR 3.19, 95% CI 1.17 to 8.65, 4 RCTs, n = 127) and sedation/drowsiness (RR 1.64, 95% CI 1.01 to 2.68, 7 RCTs, n = 223).

Authors' conclusions

The available evidence is primarily of very low quality and indicates that mirtazapine adjunct is not clearly associated with an effect for negative symptoms, but there is some indication of a positive effect on overall mental state and akathisia. No effect was found for global state or leaving the study early and data were not available for quality of life or service use. Due to limitations of the quality and applicability of the evidence it is not possible to make any firm conclusions, the role of mirtazapine adjunct in routine clinical practice remains unclear. This underscores the need for new high-quality evidence to further evaluate mirtazapine adjunct for schizophrenia.

PLAIN LANGUAGE SUMMARY

Mirtazapine as an add-on treatment for schizophrenia

Review question

Is adding mirtazapine, an antidepressant medication, to standard care an effective and safe treatment for people with schizophrenia?

Background

Schizophrenia is a severe mental illness. Those affected typically exhibit abnormal social behaviour and an inability to judge what is real. There are three main types of symptoms. Positive symptoms are where patients hear voices or see things that are not there and can also have fixed false beliefs (delusions). Examples of negative symptoms are lack of motivation and withdrawal from social activities. Cognitive symptoms include a reduced ability to concentrate or difficulty in using information to make decisions. Schizophrena can be extremely debilitating, greatly affecting a person's social functioning and their ability to live independently.

Antipsychotic medications are the main treatment for schizophrenia and are effective in treating the positive symptoms of schizophrenia but often do not fully treat the negative symptoms. Additional treatments (adjuncts) are often used alongside antipsychotics to help treat the negative symptoms. Antidepressant medications, such as mirtazapine, can be used as adjunct treatment. Mirtazapine may have the potential to improve the negative symptoms of schizophrenia, but also has the potential to cause unpleasant side effects. Evidence summarising mirtazapine's benefits and harms for people with schizophrenia is needed.

Searching

The Information Specialist of Cochrane Schizophrenia searched their specialised register for clinical trials that randomly allocated people with schizophrenia to receive either mirtazapine or another treatment in addition their standard care. The latest search was in May 2018 and we found a total of 35 references to potential trials. We carefully inspected the full-text articles of these references for inclusion or exclusion from this review.

Results

Nine randomised controlled trials met the review requirements and provided useable data. The participants in the studies received either mirtazapine plus their standard care or their standard care plus a placebo.

Results showed adding mirtazapine to standard treatment may slightly improve overall mental state but does not appear to specifically have a clinically important effect on negative symptoms. Adding mirtazapine to standard care may slightly improve the symptoms akathisia, a side effect of antipsychotics where a person is very restless and unable to keep still. No effect was found for global state or leaving the study early and data were not available for quality of life or hospital admission. In addition, some results showed mirtazapine was associated with a higher risk of weight gain and sedation. However, these results are based on evidence that is mainly very -ow quality.

Conclusions

Mirtazapine may have some positive effects for people with schizophrenia. However, these results are mainly based on very low-quality evidence and we are uncertain about these effects. Firm conclusions regarding the effectiveness and safety of mirtazapine as an add on treatment for people with schizophrenia can not be made without more high-quality research.

Summary of findings for the main comparison. Mirtazapine adjunct versus placebo adjunct

Mirtazapine versus placebo

Patient or population: schizophrenia
Setting: inpatient
Intervention: mirtazapine plus standard care
Comparison: placebo plus standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with mirtazapine				
Mental state: specific negative symptoms - clinically important change (no important response)	Study population 1000 per 1000	810 per 1000 (570 to 1000)	RR 0.81 (0.57 to 1.14)	20 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1,2,3]	Clinically important change was defined as a reduction of 20% or greater on SANS.
Mental state: overall mental state - clinically important change*	Study population 816 per 1000	563 per 1000 (416 to 751	RR 0.69 (0.51 to 0.92)	77 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [6,8,9]	* Mental state: clinically important change positive symptoms data not available. Improvement in overall mental state was defined by Abbasi 2010 as improvement in PANSS total of >50%. Terevnikov 2013: defined as improvement of PANSS total by > 20%.
Leaving the study early for any reason	Study population 162 per 1000	167 per 1000 (104 to 269)	RR 1.03 (0.64 to 1.66)	310 (9 RCTs)	⊕⊕⊕⊖ MODERATE [4]	
Global state: average endpoint score (CGI severity, high = poor)*	The mean global state: average score at endpoint	MD 0.10 lower (0.68 lower to 0.48 higher)	-	39 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1,3,5]	Data for clinically important change not reported.

	(CGI severity) was 4					
Quality of life: clinically important change	-	-	-	-	-	No study reported data for this important outcome
Service utilisation: number of days in hospital	-	-	-	-	-	No study reported data for this important outcome
Adverse effects: extrapyramidal - clinically important change akathisia	Study population		RR 0.33 (0.20 to 0.52)	86 (2 RCTs)	⊕⊕⊖⊖ LOW [6,7]	Both studies defined important change as reduction of BAS by at least 2 Adverse events - incidence of serious adverse events: data on variability was not available, preventing meta-analysis of these count data.
	930 per 1000	307 per 1000 (186 to 484)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

BAS: Barnes Akathisa Scale; **BPRS:** Brief Psychiatric Rating Scale; **CGI:** Clinical Global Impression; **CI:** Confidence interval; **HAM-D:** Hamilton Depression Rating Scale; **MD:** Mean difference; **RR:** Risk ratio; **RCT:** Randomised controlled trial; **SANS:** Scale for the Assessment of Negative Symptoms.

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

[1] Risk of bias: serious (downgraded by 1). This study did not describe blinding of outcome assessors, only analysed data from study completers (per protocol analysis)
[2] Risk of bias: serious (downgraded by 1).This study recorded depressive symptoms with HAM-D at baseline, and used the depressive subscale of BPRS at follow-up.
[3] Imprecision (downgraded by 1). Although the CI around the estimate of effect is relatively tight, the sample size was smaller than the optimal information size (one small study only N < 200).
[4] Risk of bias: serious (downgraded by 1). Several studies have unclear risk of bias, particularly regarding random sequence generation and blinding, as well as failure to describe allocation concealment. This bias is likely to lower confidence in the estimate of the effect.
[5] Indirectness: serious (downgraded by 1). Not clinically meaningful binary data
[6] Imprecision: serious (downgraded by 1). Although the CI around the estimate of effect is relatively tight, the sample size was smaller than the optimal information size (two small studies N < 200)
[7]Risk of bias: serious (downgraded by 1). One of the included studies did not report intention-to-treat data and had a high risk of bias.
[8] There was a moderate-high degree of heterogeneity for this outcome I^2 = 75%
[9] The two studies had different cutoffs for clinical significance. Abbasi 2010: defined as improvement in PANSS total of >50%. Terevnikov 2013: defined as improvement of PANSS total by > 20%.

BACKGROUND

Description of the condition

Schizophrenia is a chronic mental illness that is characterised by positive symptoms (e.g. delusions, hallucinations, disorganised speech, and abnormal motor behaviour), negative symptoms (e.g. diminished emotional expression, avolition, alogia, and anhedonia), and cognitive symptoms (e.g. trouble focusing or paying attention or using information to make decisions). Diagnosis is made on the basis of the co-occurrence of at least one positive symptom with one or more other symptoms for a significant portion of a one-month period, with associated problems over a period of six months or greater (American Psychiatric Association 2013).

While people with schizophrenia are not typically diagnosed with depression, many of the negative and cognitive symptoms of schizophrenia are very similar to those of depression as identified in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association 2013). These include loss of interest or pleasure in almost all activities, fatigue or loss of energy and trouble thinking, concentrating or making decisions.

Over 21 million people worldwide are affected by schizophrenia (WHO 2015). Estimated lifetime prevalence ranges between 1.4 and 4.6 per 1000, and the yearly incidence is between 0.16 and 0.42 per 1000, with these numbers remaining consistent for more than 25 years (Jablensky 1992; Jablensky 2000; McGrath 2008). Schizophrenia has a multi-factorial and complex aetiology, wherein biological and environmental stress diatheses and genetic risk factors are implicated (Hough 2006; Walker 1997). The incidence and prevalence of schizophrenia show prominent variation between locations. Males are more likely to develop schizophrenia than females (1.4:1). Migrant status, urban birth or residence, advanced paternal age, prenatal infection, and malnutrition are also associated with an increased risk of schizophrenia (McGrath 2009).

Approximately 80% to 90% of people diagnosed with schizophrenia are unable to maintain consistent gainful employment (Marwaha 2004). Individuals with schizophrenia have a two- to three-fold increased mortality risk compared with the general population. Additionally, it is estimated that up to 50% of individuals with schizophrenia will attempt suicide (Meltzer 2001), and 5% will die by an act of suicide (Englisch 2012). These figures underscore the devastating consequences schizophrenia can have for affected individuals.

The management of schizophrenia commonly includes the use of antipsychotic drugs, which can compound the negative symptoms that are already present (Moller 1998).

Description of the intervention

Antipsychotic medications, such as chlorpromazine (since the 1950s), and olanzapine (since the 1990s), are the mainstay treatment for schizophrenia (APA 2010; CADTH 2012). One reason for the increased use of newer antipsychotic medications in recent years is that they were thought to assist in ameliorating the negative symptoms of schizophrenia; however, study results are mixed (Leo 2000; Phan 2011). These mixed results are evidenced in the National Institute of Mental Health (United States) issuing a consensus statement describing the treatment of these negative symptoms as an unmet therapeutic need (Kirkpatrick 2006). Further evidence of the problem comes from studies indicating that negative symptoms are more closely aligned with poor functional outcomes than are positive symptoms (delusions and hallucinations), and caregivers report negative symptoms as causing significant strain (Fervaha 2014; Kirkpatrick 2006; Murphy 2006). Thus, exploring effective options for those experiencing these negative symptoms continues to be the focus of much research.

Antidepressant medications have long been the central focus and most established treatment for depression (APA 2010; Fournier 2010), and are one strategy being studied to help improve the persistent negative symptoms of schizophrenia (Phan 2011; Vidal 2015). There are many types of antidepressants, with each classification affecting different neurotransmitters in particular ways. Due to its unique pharmacologic properties, mirtazapine, a second-generation antidepressant, may be more effective than other antidepressants in decreasing negative symptoms. The usual starting dose is 15 mg once per day and it may be increased to 45 mg per day, with peak plasma concentrations occurring approximately two hours after oral administration. Seventy-five per cent of elimination occurs through the urine and mirtazapine has a half-life of approximately 20 to 40 hours, thus making it appropriate for once a day administration. It has a modest adverse effect profile, with some of the most common side effects being sedation, weight gain, constipation, dizziness, increased appetite, and dry mouth and these tend to decrease over time (Hartmann 1999; Mayo Clinic 2015).

How the intervention might work

Though falling into the overall classification of antidepressant medications, mirtazapine is unique in its chemical make-up. First introduced in 1996, mirtazapine is of the class of noradrenergic and selective serotoninergic antidepressants (NaSSA). Though the precise mechanism of antidepressant activity is unknown, mirtazapine exhibits antagonism of the central presynaptic alpha 2 noradrenergic receptor, resulting in enhanced serotonin and norepinephrine neurotransmission at the 5-HT1A receptor (de Boer 1995), suspected of being responsible for the therapeutic effects of antidepressant medications. It is also functionally antagonistic toward 5-HT2A receptors, thought to increase dopaminergic neurotransmission (de Boer 1995). While exhibiting antagonism at postsynaptic 5-HT2A, 5-HT2C, 5-HT3, and histamine H1 receptors, mirtazapine blocks serotonin receptors 5-HT2 and 5-HT3, resulting in fewer adverse effects (such as sexual dysfunction) than other antidepressant classifications, including selective serotonin and serotonin-norepinephrine reuptake inhibitors, while enhancing sleep and decreasing anxiety (de Boer 1996).

Why it is important to do this review

Approximately one-half to three-quarters of those diagnosed with schizophrenia will have identifiable negative symptoms (Selten 2000), and negative symptoms tend to persist longer than positive symptoms, as well as being more resistant to treatment. Negative symptoms are associated with a higher number of pharmacological treatments and co-morbid conditions - including obesity, dyslipidaemia and hypertension - with resultant higher healthcare costs (Sicras-Mainar 2014). Improvement in negative symptoms is frequently associated with an array of improved functional outcomes, including independent living skills, role and

social functioning (Velligan 2009), and successful ageing (Ibrahim 2010). In addition, improvements in negative symptoms are often followed by improvements in global functioning outcomes (Velligan 2009), thus addressing these negative symptoms in a meaningful, evidenced-based manner may affect the quality of life of many people with schizophrenia.

Mirtazapine may have the potential to alleviate harmful negative symptoms, but carries associated risks. There are the risks of adverse effects, increased burdens of cost and inconvenience to the user, and reduced adherence. Therefore, it is in the public interest that this important decision is backed by the highest quality evidence. The evidence base for this treatment dilemma has yet to be investigated in a Cochrane systematic review.

OBJECTIVES

To systematically assess the effects of mirtazapine as an adjunct treatment for people with schizophrenia.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all randomised controlled trials that met our inclusion criteria. If a trial had been described as 'double-blind' but implied randomisation, we would have included it in a sensitivity analysis (see Sensitivity analysis). We excluded all trials that were not randomised and those that did not report any useable data. Where individuals were given additional treatments within mirtazapine and placebo, we included data only if the adjunct treatment was evenly distributed between groups and only if the mirtazapine and placebo were randomised.

Types of participants

We included adults, however defined, with schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder, and delusional disorder, again, by any means of diagnosis . We only included trials where the majority (> 50%) of participants had schizophrenia.

We are interested in making sure that information was as relevant to the current care of people with schizophrenia as possible so, where information was available, we clearly highlighted the current clinical state (acute, early post-acute, partial remission, remission) as well as the stage (prodromal, first episode, early illness, persistent) and whether the studies primarily focused on people with particular problems (for example, negative symptoms, treatment-resistant illnesses).

Types of interventions

1. Mirtazapine (adjunct)

1.1 Mirtazapine: any dose or route of administration

2. Comparator (adjunct)

2.1 Placebo: (active or inactive) or no treatment

3. Standard care

3.1 The treatment a participant would normally receive had they not been involved in the trial

Types of outcome measures

We intended to categorise outcomes into either short term (less than six months), medium term (seven to 12 months), or long term (over one year).

Primary outcomes

1. Mental state

1.1 Specific - negative symptoms

1.1.1 Clinically important change in negative symptoms - as defined by each of the studies
1.1.2 Average endpoint/change score on negative symptoms scale

Secondary outcomes

1. Mental state

1.1 Specific - positive symptoms

1.1.1 Clinically important change in positive symptoms - as defined by each of the studies
1.1.2 Average endpoint/change score positive symptoms scale

1.2 Overall

1.2.1 Clinically important change in overall mental state - as defined by each of the studies
1.2.2 Average endpoint/change score overall mental state scale

1.3 Specific - depressive symptoms

1.3.1 Clinically important change in depressive symptoms - as defined by each of the studies
1.3.2 Average endpoint/change score depressive symptoms scale

2. Leaving the study early

2.1 for any reason
2.2 due to adverse effect

3. Global state

3.1 Clinically important change in global state - as defined by each of the studies
3.2 Average endpoint/change score global state scale

4. Cognitive function

4.1 Clinically important change in cognitive function - as defined by each of the studies
4.2 Average endpoint/change score cognitive function tests

5. Quality of life

5.1 Clinically important change in quality of life for recipients of care - as defined by each of the studies
5.2 Average endpoint/change score quality of life scale (recipients of care)
5.3 Clinically important change in quality of life for carers - as defined by each of the studies
5.4 Average endpoint/change score quality of life scale (carers)

6. Service utilisation

6.1 Days in the hospital
6.2 Requires new admission or readmission to hospital (binary)

7. Adverse events/effects

7.1 General and specific adverse events (including death by suicide or natural causes, allergic reactions, and additional drug use)

7.2 Extrapyramidal

7.2.1 Clinically important change extrapyramidal side effects - as defined by each of the studies
7.2.2 Average endpoint/change score extrapyramidal side effects scale
7.2.3 Specific extrapyramidal side effects - as defined by each of the studies
7.2.4 Use of medication for extrapyramidal side effects

8. Economic outcomes

We planned to describe/note any economic outcomes reported in included studies in Description of studies.

'Summary of findings' table

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

1. Mental state: specific - negative symptoms: clinically important change in negative symptoms - as defined by each study
2. Mental state: specific - positive symptoms: clinically important change in positive symptoms - as defined by each study
3. Leaving the study early - for any reason
4. Global state - clinically important change in global state - as defined by each study
5. Quality of life/satisfaction - clinically important change in quality of life - as defined by each study
6. Service utilisation - number of days in hospital
7. Adverse events - incidence of serious adverse events - as defined by each study

If data were not available for these outcomes but were available for ones that were similar, we presented the closest outcome to the one in the list above, but took this into account when grading the finding (see Differences between protocol and review).

Search methods for identification of studies

Electronic searches

Cochrane Schizophrenia Group's Study-Based Register of Trials

On 3 November 2015, 4 February 2016 and 3 May 2018, the Information Specialist searched the Register using the following search strategy:

(*Mirtazapine* AND *Placebo*) in Intervention of STUDY.

In such study-based register, searching the major concept retrieves all the synonyms and relevant studies because all the studies have already been organised based on their interventions and linked to the relevant topics (Shokraneh 2017).

This register is compiled by systematic searches of major resources (AMED, BIOSIS, CENTRAL, CINAHL, ClinicalTrials.Gov, Embase, MEDLINE, PsycINFO, PubMed, WHO ICTRP) and their monthly updates, ProQuest Dissertations and Theses A&I and its quarterly update, Chinese databases (CBM, CNKI, and Wanfang) and their annual updates, handsearches, grey literature, and conference proceedings (see Group's website). There is no language, date, document type, or publication status limitations for inclusion of records into the register.

Searching other resources

1. Reference searching

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

2. Personal contact

We contacted the first author of each included study for information regarding unpublished trials. We noted the outcome of this contact in the included or awaiting assessment studies tables.

Data collection and analysis

Selection of studies

Review authors SMS and DMR independently inspected citations from the searches and identified relevant abstracts. LAP independently re-inspected a random 20% sample to ensure reliability. Where disputes arose, we acquired the full-text report for more detailed scrutiny. Review author SMS obtained full-text reports of the abstracts meeting the review criteria. LAP independently inspected a random 20% of these full reports in order to ensure reliable selection. If it had not been possible to resolve disagreement by discussion, we planned to contact the authors of the study for clarification.

Data extraction and management

1. Extraction

Review authors SMS and DMR extracted data from all included studies. In addition, to ensure reliability, LAP independently extracted data from a random sample of these studies, comprising more than 10% of the total. Again, we discussed any disagreements and documented decisions. LAP helped clarify issues and we documented those final decisions. We extracted data presented only in graphs and figures whenever possible, but included the data only if two review authors independently had the same result. If studies had been multicentre, where possible, we planned to extract data relevant to each component centre separately.

2. Management

2.1 Forms

We extracted data onto standard, pre-designed, simple forms.

2.2 Scale-derived data

We included continuous data from rating scales only if:

a) the psychometric properties of the measuring instrument had been described in a peer-reviewed journal (Marshall 2000);
b) the measuring instrument has not been written or modified by one of the trialists for that particular trial;

c) the instrument should be a global assessment of an area of functioning and not sub-scores which are not, in themselves, validated or shown to be reliable. However there are exceptions, we included sub-scores from mental state scales measuring positive and negative symptoms of schizophrenia.

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

2.3 Endpoint versus change data

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

2.4 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we applied the following standards to relevant data before inclusion.

Please note, we planned to enter data from studies of at least 200 participants in the analysis, because skewed data pose less of a problem in large studies. We also planned to enter all relevant change data as when continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not.

For endpoint data from studies < 200 participants:

(a) when a scale starts from the finite number zero, we subtracted the lowest possible value from the mean, and divided this by the standard deviation. If this value was lower than 1, it strongly suggests a skew and we excluded these data. If this ratio was higher than one but below 2, there is suggestion of skew. We entered these data and tested whether its inclusion or exclusion change the results substantially. Finally, if the ratio was larger than 2 we included these data, because skew is less likely (Altman 1996; Higgins 2011a).

(b) if a scale starts from a positive value (such as the Positive and Negative Syndrome Scale (PANSS), (Kay 1986)) which can have values from 30 to 210), we modified the calculation described above to take the scale starting point into account. In these cases skew is present if 2 SD > (S-S min), where S is the mean score and 'S min' is the minimum score.

2.5 Common measure

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

2.6 Conversion of continuous to binary

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

2.7 Direction of graphs

Where possible, we entered data in such a way that the area to the left of the line of no effect indicates a favourable outcome for mirtazapine adjunct. Where keeping to this made it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'Not un-improved') we reported data where the left of the line indicates an unfavourable outcome. We noted this in the relevant graphs.

Assessment of risk of bias in included studies

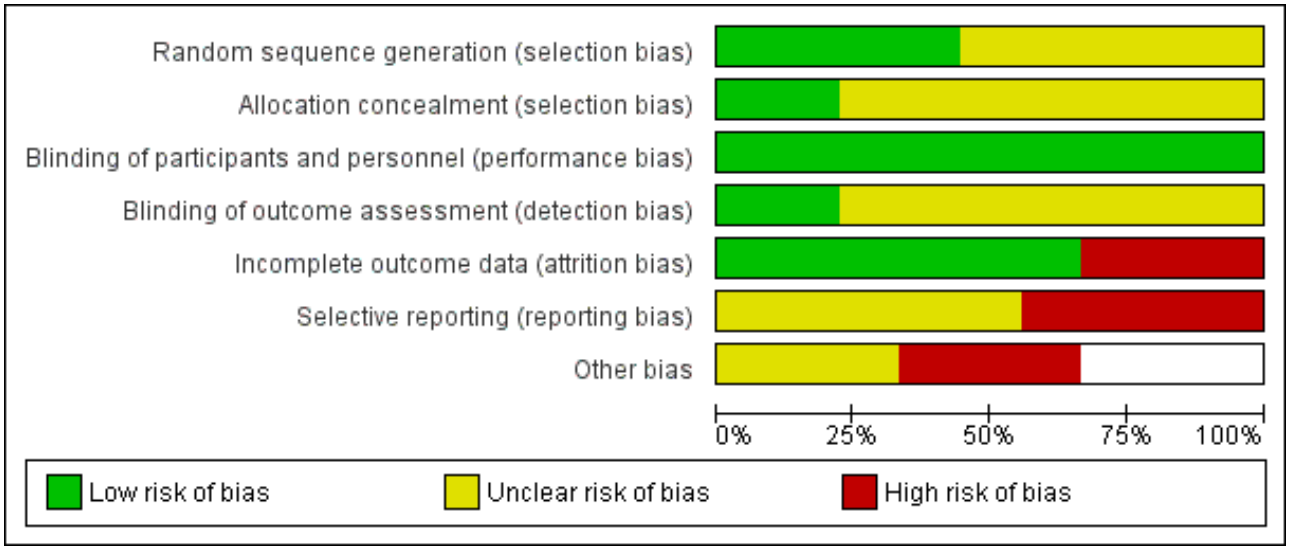
Review authors SMS, LAP, and DMR independently assessed risk of bias within the included studies by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess trial quality (Higgins 2011b). This set of criteria is based on evidence of associations between overestimate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

If the raters disagreed, we made the final rating by consensus with all review authors. Where inadequate details of randomisation and other characteristics of trials were provided, we contacted authors of the studies in order to obtain further information. If non-concurrence occurred, we reported this.

We noted the level of risk of bias in the text of the review and in Figure 1 , Figure 2 and Summary of findings for the main comparison.

Figure 1. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Measures of treatment effect

1. Binary data

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

2. Continuous data

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

Unit of analysis issues

1. Cluster trials

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

If cluster-randomised trials had been included and clustering had not been accounted for in primary studies, we planned to present the data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. If clustering had been incorporated into the analysis of primary studies, we planned to present these data as if from a non-cluster randomised study, adjusting the data for the clustering effect. In subsequent versions of this review we will seek to contact first authors of studies to obtain intraclass correlation coefficients (ICCs) of their clustered data and to adjust for this using accepted methods (Gulliford 1999).

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

If cluster studies had been appropriately analysed taking into account ICCs and relevant data documented in the report, synthesis with other studies would have been possible using the generic inverse variance technique.

2. Cross-over trials

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

3. Studies with multiple treatment groups

If included and relevant, where a study involved more than two treatment arms, we would have presented the additional treatment arms in comparisons. If data were binary, we would have simply added and combined them within the two-by-two table. If data were continuous, we planned to combine data following the formula in Chapter 7 of the *Cochrane Handbook for Systematic*

*Reviews of Interventions (*Higgins 2011a). We would not have used data where the additional treatment arms were not relevant. We would not have double counted the data.

Dealing with missing data

1. Overall loss of credibility

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

2. Binary

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

3. Continuous

3.1 Attrition

In the case where attrition for a continuous outcome was between 0% and 50%, and data only from people who completed the study to that point were reported, we reproduced these.

3.2 Standard deviations

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

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

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

Assessment of heterogeneity

1. Clinical heterogeneity

We considered all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We inspected all studies for clearly outlying people or situations that we had not predicted would arise. We planned that where clear unforeseen issues were noted that could add obvious clinical heterogeneity, we would note these unforeseen issues and consider them in analyses, undertaking sensitivity analyses for our primary outcome.

2. Methodological heterogeneity

We considered all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We inspected all studies for clearly outlying methods that we had not predicted would arise.

3. Statistical heterogeneity

3.1 Visual inspection

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

3.2 Employing the I^2 statistic

We investigated heterogeneity between studies by considering the I^2 method alongside the Chi^2 P value. The I^2 provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 depends on i. magnitude and direction of effects and ii. strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a confidence interval for I^2). An I^2 estimate greater than or equal to around 50% accompanied by a statistically significant Chi^2 statistic, can be interpreted as evidence of substantial levels of heterogeneity (Chapter 9. *Cochrane Handbook for Systematic Reviews of Interventions* Deeks 2011). We explored and discussed in the text potential reasons for substantial levels of heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

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

1. Protocol versus full study

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

2. Funnel plot

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

Data synthesis

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

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary outcomes

We did not anticipate any subgroup analyses.

1.2 Clinical state, stage or problem

We undertook this review to provide an overview of the effects of mirtazapine adjunct for individuals with schizophrenia in general. We planned to attempt to report data on subgroups of individuals in the same clinical state, stage, and with similar problems, but this was not possible.

2. Investigation of heterogeneity

If data appeared clearly heterogeneous, we investigated if it had been entered correctly. If data were correct, we inspected the graph visually and we removed studies outside of the company of the rest to see if homogeneity was restored. For this review we planned that should this occur with data contributing to the summary finding of no more than around 10% of the total weighting, we would present these data. If not, we would not pool these data and we would discuss the issues. We know of no supporting research for this 10% cut-off but are investigating use of prediction intervals as an alternative to this unsatisfactory state.

We planned that when unanticipated clinical or methodological heterogeneity were obvious we would simply state hypotheses regarding these for future reviews or versions of this review. We did not anticipate undertaking analyses relating to these.

Sensitivity analysis

1. Implication of randomisation

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

2. Assumptions for lost binary data

If assumptions had to be made regarding missing SD data (see Dealing with missing data), we would have compared the findings of the primary outcomes when we used our assumption/s and when we used data only from people who completed the study to that point. We would have undertaken a sensitivity analysis to test how prone the results were to change when completer-only data were compared to the imputed data using the above assumption. We planned that if there was a substantial difference we would report the results and discuss them, but would continue to employ our assumption.

3. Risk of bias

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

4. Imputed values

We also planned to undertake a sensitivity analysis to assess the effects of including data from trials where we used imputed values for ICC in calculating the design effect in cluster-randomised trials.

If substantial differences had been noted in the direction or precision of effect estimates in any of the sensitivity analyses listed above, we would not pool data from the excluded trials with the other trials contributing to the outcome, but would have present them separately.

5. Fixed-effect and random-effects

We synthesised all data using a fixed-effect model and we synthesised data for the primary outcome using a random-effects model to evaluate whether this altered the significance of the results. Any differences were noted.

RESULTS

Description of studies

We included nine studies involving a total of 310 participants studies which are described below in Included studies. For more detailed descriptions of each individual study, please refer to Characteristics of included studies.

Results of the search

Details of the search results are also illustrated in the study flow diagram (Figure 3).

Figure 3. Study flow diagram.

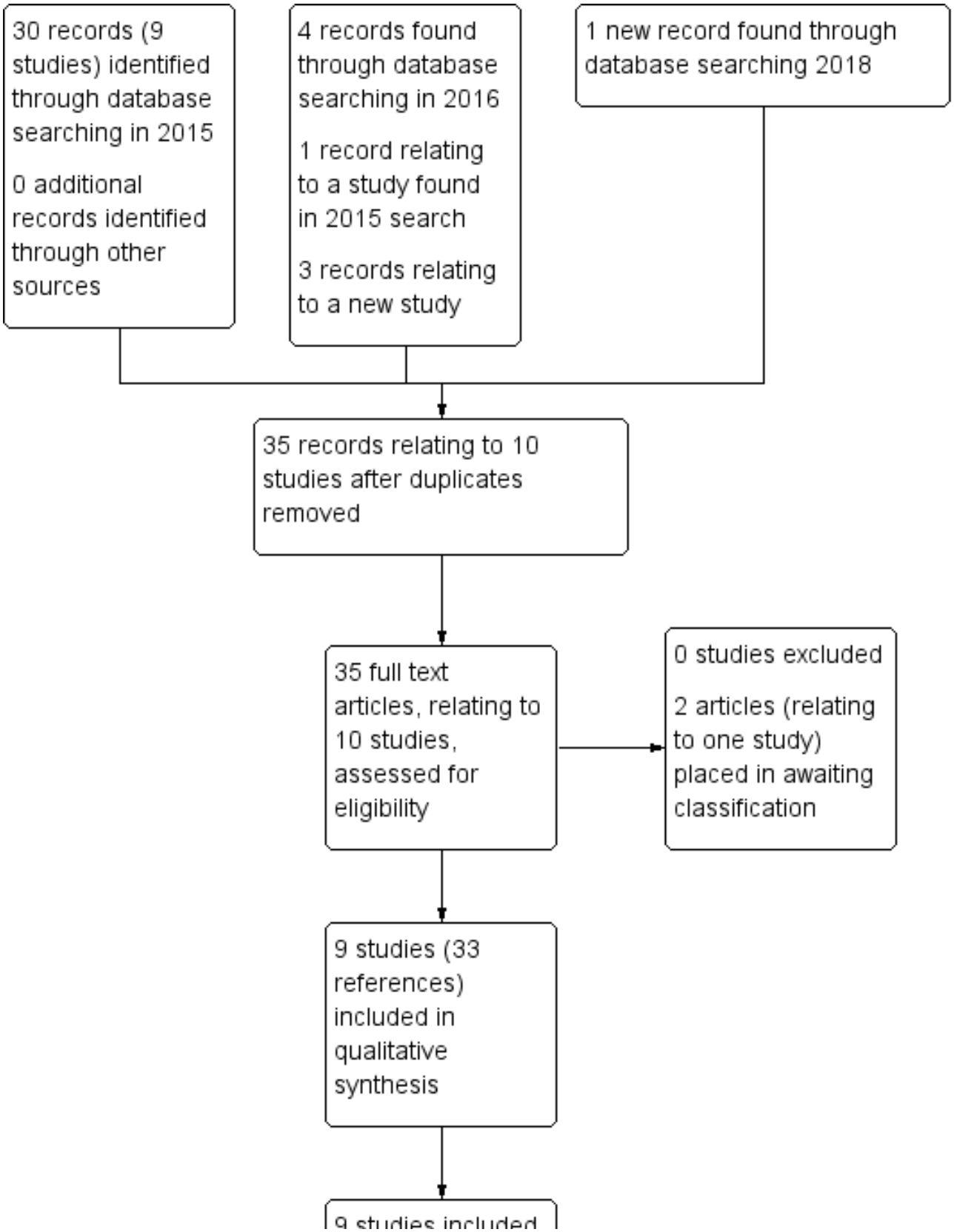
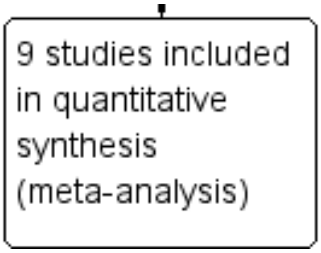


Figure 3. (Continued)



In the original 2015 search, we found 30 reports that were potentially relevant. These reports related to nine studies. An additional search in 2016 found four more records. Three of these related to one potential new study and one related to a study already awaiting assessment. In total we assessed 10 studies for inclusion or exclusion. We did not exclude any of these studies, one study is awaiting assessment and nine studies are included in the analyses. A further search in 2018 did not find any new studies but did find a record relating to the study awaiting assessment.

Included studies

1. Length of trials

All nine included studies provided short-term outcome data only. Four studies were of eight-week duration (Abbasi 2010; Caforio 2013; Cho 2011; Zoccali 2004). Three studies were of six-week duration (Berk 2001; Berk 2009; Terevnikov 2013). Two studies were of one-week or less duration (Poyurovsky 2003; Poyurovsky 2006).

2. Participants

2.1 Diagnosis

Five studies included participants with a sole diagnosis of schizophrenia based on the DSM-IV diagnostic model (Abbasi 2010; Berk 2001; Cho 2011; Terevnikov 2013; Zoccali 2004). Two studies included participants with a sole diagnosis of schizophrenia but did not specify the diagnostic model (Berk 2009; Caforio 2013). One study included participants with a diagnosis of schizophrenia and neuroleptic-induced akathisia based on the DSM-IV diagnostic model (Poyurovsky 2003). One study included mixed participants with schizophrenia (70), delusional disorder (7), or major depressive disorder with psychotic features (3), each also having neuroleptic-induced akathisia based on the DSM-IV diagnostic model (Poyurovsky 2006).

All studies included a combination of male and female participants, each with a male preponderance. Studies included participants of a variety of ages, with mean ages ranging between 28 and 48 years.

2.2 Excluded

One study did not reported specific exclusion criteria. (Poyurovsky 2003). Of the eight studies with explicit exclusion criteria, six excluded either patients with a current depressive episode or patients on antidepressant drugs (Abbasi 2010; Berk 2001; Berk 2009; Cho 2011; Terevnikov 2013; Zoccali 2004). Other common exclusion criteria were concomitant major medical or psychiatric illness other than schizophrenia, and current use of psychotropic medication other than an antipsychotic agent.

2.3 History

Several studies reported data on the stage of illness of participants, which were typically presented as an average of months from diagnosis to recruitment. These figures ranged from about 33 months to 300 months, reflecting that the studies' populations were typically first diagnosed several years prior to recruitment.

3. Setting

Five studies were set in inpatient units (Abbasi 2010; Berk 2001; Caforio 2013; Poyurovsky 2003; Poyurovsky 2006). Two studies were set in outpatient units (Cho 2011; Zoccali 2004). One study was set in both inpatient and outpatient units (Terevnikov 2013). One study did not describe the type of setting (Berk 2009).

4. Study size

The largest study had 60 participants in the mirtazapine and placebo groups combined (Poyurovsky 2006). The rest of the studies had participant sizes ranging from 20 to 40.

5. Interventions

5.1 Mirtazapine adjunct

All included studies used an adjunct dose of mirtazapine of 30 mg/day except for two, in which both used doses of 15 mg/day (Poyurovsky 2003; Poyurovsky 2006).

5.2 Placebo adjunct

Included studies compared mirtazapine plus usual antipsychotic medication versus placebo plus usual antipsychotic medication. The usual antipsychotics were typical antipsychotics in four studies and atypical antipsychotics in five studies. All participants in one study also received an anticholinergic medication (Poyurovsky 2006).

6. Outcomes

Our primary outcomes were mental state: clinically important change negative symptoms as defined by each of the studies and clinically important change in positive symptoms. Only one study reported clinically important change in negative symptoms (Zoccali 2004), whereas seven studies reported on average endpoint scores on negative symptom scales (Abbasi 2010; Berk 2001; Berk 2009; Caforio 2013; Cho 2011; Terevnikov 2013; Zoccali 2004). For Berk 2001 and Caforio 2013, these data were skewed.

Several scales and subscales were utilised by included studies to assess the effectiveness and safety of mirtazapine adjunct across the other outcomes assessed in this review. Descriptions of these are found below.

All nine studies yielded at least some usable data on adverse events or effects. Reporting of specific adverse effects was generally good. Unfortunately, none of the included studies reported on quality of life/satisfaction, service utilisation, or economic outcomes.

6.1 Mental state scales

6.1.1 Positive and Negative Syndrome Scale (PANSS) (Kay 1986)

This is one of the most commonly used scales for measuring symptom severity in persons with schizophrenia. The PANSS includes 30 items, divided into three subscales; a composite score is also provided. The general psychopathology subscale is comprised of 14 items including anxiety and disorientation. The positive symptoms subscale (PANSS-P) contains seven items incorporating delusions and hallucinations, with the negative symptoms subscale (PANSS-N) made up of seven items inclusive of blunted affect and emotional withdrawal. All subscales use a seven-point scoring system ranging from one (absent) to seven (extreme). A higher score indicates higher symptom severity.

6.1.2 Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1981)

This scale is purposed to provide a global assessment of inappropriate affect by addressing five negative symptom complexes: affective blunting (decreased or lack of facial expression), alogia (responses to questions are short, lacking detail and/or individual does not initiate conversation), avolition/apathy (lack of interest in areas such as grooming), anhedonia/asociality (lack of interest in socialising) and attention issues. All items use a six-point scoring system ranging from zero (not at all) to six (severe). A higher score indicates higher symptom severity.

6.1.3 Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984)

This scale was developed as a companion to the SANS. It addresses four positive symptom areas: hallucinations, delusions, bizarre behavior and positive formal thought disorder (disconnected thinking). All items use a six-point scoring system ranging from zero (none) to five (severe), providing a global assessment of inappropriate affect. A higher score indicates higher symptom severity.

6.1.4 Brief Psychiatric Rating Scale (BPRS) (Overall 1962)

This scale is widely used to assess the severity of positive, negative and affective symptoms of schizophrenia. The original version contained 16 items and the current version includes 18 items, inclusive of anxiety, hostility and unusual thought content. All items use a seven-point scoring system ranging from one (not present) to seven (extremely severe). A higher score indicates higher symptom severity.

6.2 Global scales

6.2.1 Clinical Global Impressions Scale (CGI) (Guy 1976)

This scale was developed for use in NIMH-sponsored clinical trials. It is purposed as a brief global pre/post medication assessment that can stand-alone and be administered by individual practitioners. This scale is used to assess illness severity (CGI-S) and clinical improvement (CGI-I). The practitioner asks themselves one question for the CGI-S regarding how mentally ill the individual is at the current time. This question is answered using a seven-point scoring system with one (not at all ill) and seven (among the most extremely ill patients). The practitioner also asks themselves one question for the CGI-I in which they are comparing the individual's current condition to their condition prior to medication initiation. The question is then answered using a seven-point scoring system with one (very much improved since the initiation of treatment) and seven (very much worse since the initiation of treatment). A higher score indicates higher symptom severity.

6.2.2 Patient Global Impression of Improvement (PGI-I) (Guy 1976)

This scale was developed as a companion to the CGI-I. A question similar to that asked of the clinician in the CGI-I, is asked of the patient in the PGI-I, to determine the patient's perception of their condition following intervention (usually medication initiation). The same seven-point scoring system is used with one (very much better) and seven (very much worse). A higher score indicates higher symptom severity. This scale has been found reliable and valid for a variety of patient groups.

6.3 Depression scales

6.3.1 Calgary Depression Severity Scale (CDSS) (Addington 1993)

This nine-item scale assesses depression in individuals with schizophrenia. A four-point scoring system is used for all items with zero (absent) and three (severe). A score of seven or above is useful for predicting the presence of a major depressive episode for someone with schizophrenia (82% specificity and 85% sensitivity). A higher score indicates higher severity of symptoms.

6.3.2 Hamilton Depression Rating Scale (HDRS abbreviated to HAM-D) (Hamilton 1980)

This is one of the most commonly used scales for determining the severity of an individual's depression prior to, during, and following treatment. The HAM-D includes 21 items with 17 items used in scoring. Eight items, including insomnia and anxiety, are scored on a five-point scale from zero (not present) to four (severe). The remaining nine items, including weight loss and insight, use a three-point scoring system ranging from zero (absent), one (mild) and two (severe). Items assessed but not used in scoring include paranoia and obsessive/compulsive symptoms. A score of eight or above is indicative of depression, with a higher score indicating a higher severity of symptoms.

6.4 Cognitive function scales

6.4.1 Wechsler Adult Intelligence Scale – Revised (WAIS-R) (Wechsler 1981)

This is one of the most commonly used instruments for assessing overall cognitive ability. The WAIS-R includes 11 subscales divided into two parts, verbal (VIQ with six subscales) and performance (PIQ with five subscales); a full scale IQ (FSIQ) is also provided. The verbal portion assesses areas such as information and similarities, with the performance portion assessing block design and digit symbols. The VIQ and PIQ are frequently reported separately, along with the FSIQ that is reported as a standard score with a mean of 100 and a standard deviation of 15.

6.4.2 Wechsler Memory Scale (WMS) (Wechsler 1945; Wechsler 2009)

This is the most commonly used instruments for measuring memory. It has been revised over time and is now in its fourth version (WMS-IV). The WMS-IV includes seven subscales. All subscales used in the studies included in this systematic review (verbal memory addressed through logical memory and verbal paired associations, with visual memory addressed through visual reproduction) were included in the tool prior to the latest revision (WMS-III) and in the latest revision. A sum of the scaled scores is provided, as is an index score, percentile rank and qualitative description (ranging from extremely low to very superior). Higher scores indicate a lower severity of symptoms.

6.4.3 Trail Making Test (TMT) (US Army 1944; Reitan 1985)

This instrument was originally used by the United States Army for testing executive function (a set of cognitive processes needed for cognitive control of behaviour) and was eventually incorporated into the Halstead-Reitan Battery. The TMT includes two parts, A (connecting circles numbered 1-25 in correct order), and B (connecting numbered and lettered circles in correct order) and is to be completed by the individual as quickly as possible. Areas addressed by the TMT include speed of attention, eye-hand co-ordination, and information processing. The score for each part represents the time needed to complete the task; therefore, a higher score indicates higher symptom severity.

6.4.4 Stroop Color-Word Test (Stroop 1935; Jensen 1966)

This instrument is used to measure executive functions including speed of processing and the cognitive ability to “sift through interference,” The test includes three parts, all timed: a) identifying the colour of dots, b) reading colour words, and c) identifying the colour of the font of the word shown, rather than the actual word shown. An example of part “C” is that the word “yellow” may be written in green and the correct answer would be green. Accuracy of answers and speed are included in scoring. Higher accuracy with lower speed is indicative of lower symptom severity.

6.4.5 Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph 1998)

This scale assesses abnormal cognitive decline. It is frequently used as it is brief, taking less than 30 minutes, and found effective in identifying and characterising cognitive decline of differing aetiologies. The RBANS includes five indexes (immediate memory, delayed memory, attention, language, and visuospatial/ constructional abilities), and index scores have a mean of 100, with a SD of 15. Its 12 subtests have a mean of 10 and a SD of 3. Lower scores are indicative of higher symptom severity.

6.5 Scales for the assessment of extrapyramidal side effects

6.5.1 Simpson-Angus Scale (SAS) (Simpson 1970)

This scale measures symptoms of pseudoparkinsonism. The SAS includes 10 items and uses a five-point rating system ranging from zero (normal) to five (severe degree of movement disorder). A higher score indicates higher severity of symptoms.

6.5.2 Barnes Akathisa Scale (BAS) (Barnes 1989)

This scale measures symptoms of akathisia, a drug-related movement disorder. Three items are rated from zero (normal) to three (severe). These are observable restless movements, subjective feelings of restlessness, and distress. Additionally, a global severity score ranging from zero (normal) to five (severe) is available.

6.5.3 Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard 1993).

This scale measures extrapyramidal symptoms by assessing parkinsonism through a nine-item questionnaire, an eight-item physical examination, and a clinical global impression of the presence and severity of tardive dyskinesia. Lower scores are indicative of milder symptom severity.

Studies awaiting assessment Suggest this could be a Heading 3

There is one study awaiting assessment (see Characteristics of studies awaiting classification).

Excluded studies

There are no excluded studies, studies awaiting classification or ongoing studies in this review.

Risk of bias in included studies

Risk of bias was assessed for all nine included studies. Please refer to Figure 1 and Figure 2 for visual representations of the 'Risk of bias' assessment of included studies.

Allocation

All included studies were reported to be randomised. Abbasi 2010 randomised participants using a computer-generated code, whereas Poyurovsky 2003, Poyurovsky 2006, and Terevnikov 2013 randomised participants according to a table of random numbers. These four studies were deemed to be of low risk in the random sequence generation component of the selection bias appraisal. The remaining five studies did not report the specific method of randomisation, and were therefore deemed to be of unclear risk for random sequence generation.

Only two studies reported allocation concealment. These were Abbasi 2010 and Terevnikov 2013, both of which utilised opaque envelopes to ensure allocation concealment and were given a low risk of bias in the allocation concealment component of the selection bias appraisal. The remaining seven studies did not describe allocation concealment and were therefore unclear risk.

Blinding

All studies were stated to be double-blind, and we considered it likely that though blinding of participants and personnel was not always fully described it is likely that all participants and personnel were blinded. Therefore, all nine trials were placed at low risk of performance bias.

Only two studies, Abbasi 2010 and Poyurovsky 2006, described blinding of outcome assessors and were placed at low risk for detection bias. The remaining seven trials were therefore unclear risk for this domain.

Incomplete outcome data

All studies reported how many participants were lost to follow-up, and the reasons for attrition were, for the most part, clearly stated. Attrition rates did not exceed 50% of the sample size in any trial.

Abbasi 2010, Berk 2001, Poyurovsky 2003, and Poyurovsky 2006 used ITT analysis with last observation carried forward (LOCF). Terevnikov 2013 used a modified ITT with LOCF whereby the study included a participant only when they had at least one on-treatment measurement. Caforio 2013 used mixed modelling for repeated measures analysis. Each of these six studies were placed at a low risk of attrition bias because the method of dealing with missing data was described, attrition rates did not exceed 50%, and the reasons for attrition were generally balanced between the mirtazapine and placebo groups. Three studies, Berk 2009, Cho 2011, and Zoccali 2004, only considered completers of the trials in their analyses and were placed at high risk for attrition bias.

Selective reporting

Five of the included studies reported all their pre-specified outcomes, which seemed to encompass most of the expected outcomes of interest (Abbasi 2010; Berk 2001; Caforio 2013; Poyurovsky 2006; Terevnikov 2013). Protocols were not available for any of these five studies, so it was unclear whether there were additional pre-specified outcomes. We therefore placed these studies at unclear risk of reporting bias.

Four studies were determined to have high risk of reporting bias (Berk 2009; Cho 2011; Poyurovsky 2003; Zoccali 2004). Berk 2009 did not report the full global impression scale it pre-specified in the methods. Cho 2011 did not report outcomes of cognitive function in their entirety as described in the methods. Poyurovsky 2003 included both an ITT and a non ITT analysis, but neglected to report most of the data from the ITT analysis. Zoccali 2004 measured depressive symptoms at baseline using the HAM-D scale, but only reported the depressive subscale of the BPRS scale at endpoint.

Other potential sources of bias

Three trials were identified to have either received funding from the pharmaceutical industry or have been co-authored by researchers who report financial conflicts of interest (Berk 2009; Caforio 2013; Terevnikov 2013). The other six trials were not clearly free from bias and were therefore attributed an unclear risk of bias from other potential sources.

Effects of interventions

See: **Summary of findings for the main comparison** Mirtazapine adjunct versus placebo adjunct

1. COMPARISON 1: Mirtazapine adjunct versus placebo adjunct - short term

Studies relevant to this review fall into a single comparison. We identified nine randomised trials from which it was possible to extract numerical data. The trails reported useable data for 15 outcomes and unusable data for nine outcomes.

1.1 Mental state: specific - 1a. Negative symptoms: clinically important change

1.1.1 No important response (reduction in SANS overall score from baseline of at least 20%)

One trial (n = 20) defined a reduction in SANS overall score from baseline of at least 20% as no important response for negative symptoms. There was no evidence of a clear difference between the two treatments with similar numbers of participants from each group showing no important response to treatment (risk ratio (RR) 0.81, 95% confidence interval (CI) 0.57 to 1.14, very low-quality evidence; Analysis 1.1).

1.2 Mental state: specific. 1b. Negative symptoms: average endpoint score (various scales)

1.2.1 PANSS negative (high = poor)

Four trials (total n = 130) reported average endpoint PANSS negative scores. There was a clear difference in scores, favouring the mirtazapine adjunct group (mean difference (MD) -2.65, 95% CI -4.45 to -0.84; Analysis 1.2).

1.2.2 SANS (high = poor)

Two trials, which included a total of 40 participants reported endpoint SANS scores. There was a clear difference in scores, favouring the mirtazapine adjunct group (MD -15.04, 95% CI -20.06 to -10.01; Analysis 1.2).

1.3 Mental state: specific. 1c. Negative symptoms: average endpoint score (PANSS negative, high = poor) - skewed data

Berk 2001 and Caforio 2013 also reported mental state scale data for negative symptoms. However, these continuous data were too skewed to enter into analyses and are presented as 'other data' (Analysis 1.3).

1.4. Mental state: specific. 2a. Positive symptoms: average endpoint score (PANSS positive, high = poor)

One trial, (total n = 20), reported data for positive symptoms using the PANSS positive subscale. There was no evidence of a difference between mirtazapine adjunct and placebo for this outcome (MD -2.20, 95% CI -5.29 to 0.89; Analysis 1.4)

1.5 Mental state: specific. 2b. Positive symptoms: average endpoint score (various scales) - skewed data

Six trials also reported on positive symptoms using various mental state scales. However, these continuous data were too skewed to enter into analyses and are presented as 'other data' (Analysis 1.5).

1.6 Mental state: overall. 3a. Clinically important change (at least 20 % change PANSS)

1.6.1 No important response

Two trials (n = 77) reported no important response for overall mental state. There was evidence for this outcome, that more people in the placebo group showed no real response compared to those receiving mirtazapine adjunct (RR 0.69, 95% CI 0.51 to 0.92, very low-quality evidence; Analysis 1.6). Heterogenity was high I^2 = 75%,

1.7 Mental state: overall 3b. Average endpoint score (various scales)

1.7.1 PANSS (high = poor)

Six trials (n = 170) reported overall PANSS endpoints scores. There was evidence of clear difference between mirtazapine and placebo groups, that favoured mirtazapine adjunct for this outcome (MD -3.84, 95% CI -7.89 to 0.21; Analysis 1.7). There were important levels of heterogeneity (I^2 = 62%).

1.7.2 BPRS (high = poor)

One trial (n = 20) reported BPRS endpoint scores. These data also showed a clear difference in scores, that favoured the mirtazapine adjunct group (MD -19.30, 95% CI -22.10 to -16.50; Analysis 1.7).

1.8 Mental state: overall. 3c. Average change scores (various scales) - skewed data

Two trials reported change score from various mental state scales. However these continuous data were skewed and could not be used in analyses. They are presented as Other data (Analysis 1.8).

1.9 Mental state: specific. 4a. Depressive symptoms: average endpoint score (HAM-D, high = poor)

Two trials (total n = 53) reported useable endpoint HAM-D scores. There was no evidence of a clear difference between the two treatment groups (MD 1.51, 95% CI -1.72 to 4.74; Analysis 1.9).

1.10 Mental state: specific. 4b. Depressive symptoms: average change scores (various scales) - skewed data

Five trials reported change scores from various depressive symptom scales. However these continuous data were skewed and could not be used in analyses. They are presented as Other data (Analysis 1.10).

1.11 Leaving the study early for any reason

Nine studies, involving 310 participants reported useable data for this outcome. There was no evidence of a clear difference between the two treatment groups for numbers of participants leaving the study early (RR 1.03, 95% CI 0.64 to 1.66, moderate-quality evidence; Analysis 1.11).

1.12 Global state: 1a. Average endpoint score (CGI severity, high = poor)

One study with a total of 39 people reported useable data for this outcome. There was no evidence of a clear difference in scores between mirtazapine adjunct and placebo groups (MD -0.10, 95% CI -0.68 to 0.48, very low-quality evidence; Analysis 1.12).

1.13 Global state: 1b. Average change score (PGI, high = poor)

For this outcome a single study, with a total of 39 people reported useable data. There was a clear difference in scores, favouring the mirtazapine adjunct group (MD -0.54, 95% CI -0.97 to -0.11; Analysis 1.13).

1.14 Global state: 1c. Average change score (various scales, skewed data)

Two trials reported change scores from various global state scales. However these continuous data were skewed and could not be used in analyses. They are presented as Other data (Analysis 1.14).

1.15 Cognitive functioning: other data

Three RCTs reported outcomes of cognitive function. Because these data are in heterogeneous formats and involve different scales we could not conduct a meta-analysis and therefore reported these data as Other data (Analysis 1.15).

1.16 Adverse events: 1a. General (participants with at least one adverse event)

Two relevant studies (total n = 71) reported useable data for this outcome . There was not a clear difference in number of participants experiencing at least one adverse event between the mirtazapine adjunct and placebo groups (RR 0.96, 95% CI 0.81 to 1.12; Analysis 1.16).

1.17 Adverse events: 1b. General (total number of adverse events) - count data

Count data for number of events presented and exceeded number of participants (Analysis 1.17).

1.18 Adverse effects: 2a. Extrapyramidal: clinically important change akathisia

1.18.1 No clinically important response (reduction by at least 2 on BAS)

Two trials, with a total of 86 people reported clinically important change in the extrapyramidal side effect, akathisia. There was a clear difference between the groups with more participants showing no response in the placebo group compared to mirtazapine adjunct group (RR 0.33, 95% CI 0.2 to 0.52, low-quality evidence; Analysis 1.18). This outcome had important levels of heterogeneity ($Chi^2 = 2.55$; df = 1.0; P = 0.11; $I^2 = 61\%$).

1.19 Adverse effects: 2b. Extrapyramidal - full resolution of akathisia

A single study involving 26 participants reported number of participants showing full resolution of akathisia. There was no clear difference between the treatment groups for this outcome (RR 11.00, 95% CI 0.67 to 180.65; Analysis 1.19).

1.20 Adverse effects: 2c. Extrapyramidal - specific events

1.20.1 Parkinsonism

One trial (total n = 30) reported useable data for this outcome. There was no evidence of a clear difference between the two treatments (RR 0.60, 95% CI 0.29 to 1.23; Analysis 1.20).

1.20.2 Akathisia

One trial (total n = 30) reported useable data for this outcome. There was no evidence of a clear difference between the two treatments (RR 0.14, 95% CI 0.01 to 2.55; Analysis 1.20).

1.20.3 Dystonia

One trial (total n = 30) reported useable data for this outcome. There was no evidence of a clear difference between the two treatments (RR 0.33, 95% CI 0.01 to 7.58; Analysis 1.20).

1.20.4 Additional anticholinergic drug use

One trial (total n = 30) reported useable data for this outcome. More participants in the placebo group required additional anticholinergic medication (RR 0.46, 95% CI 0.24 to 0.88; Analysis 1.20).

1.20.5 Tremor

One trial (total n = 38) reported useable data for this outcome. There was no evidence of a clear difference between the two treatments (RR 1.00, 95% CI 0.16 to 6.38; Analysis 1.20).

1.21 Adverse effects: 2d. Extrapyramidal: average change score (various scales)

1.21.1 SAS, high = poor

One trial (total n = 60) reported useable data for this outcome. There was no evidence of a clear difference between the two treatments (MD -0.27, 95% CI -1.97 to 1.43; Analysis 1.21).

1.21.2 BAS, high = poor

One trial (total n = 60) reported useable data for this outcome. There was no evidence of a clear difference between the two treatments (MD -0.03, 95% CI -0.69 to 0.63; Analysis 1.21).

1.22 Adverse effects: 2e. Extrapyramidal: average endpoint score (various scales) - skewed data

We were unable to use continuous data from four trials for this outcome. We, therefore, report these data in a Other data table (Analysis 1.22).

1.23 Adverse effects: 2f. Extrapyramidal: treatment details - skewed data

One trial reported data for this outcome. However these data were skewed and could not be used in analyses. They are presented as Other data (Analysis 1.23).

1.24 Adverse effects: 3. Other specific effects

1.24.1 Weight gain

Four trials, which included a total of 127 participants reported useable data for this outcome. We did find evidence that more people in the mirtazapine group experienced weight gain than in the placebo group (RR 3.19, 95% CI 1.17 to 8.65; Analysis 1.24).

1.24.2 Headache

Four trials (total n = 157) reported useable data for this outcome. There was no evidence of a difference between the two treatment groups (RR 1.44, 95% CI 0.54 to 3.82; Analysis 1.24).

1.24.3 Sedation/drowsiness

Seven trials reported useable data for this outcome (total n = 223). We found evidence of a clear difference, favouring placebo (RR 1.64, 95% CI 1.01 to 6.28; Analysis 1.24).

1.24.4 Increased appetite

Two trials (total n = 77) reported useable data for this outcome. There was no evidence of a clear difference between the two treatments (RR 2.57, 95% CI 0.66 to 10.07; Analysis 1.24).

1.24.5 Weakness

One trial (total n = 39) reported useable data for this outcome. There was no evidence of a clear difference between the two treatments (RR 2.86, 95% CI 0.12 to 66.11; Analysis 1.24).

1.24.6 Hypersedimentaiton

One trial (total n = 39) reported useable data for this outcome. There was no evidence of a clear difference between the two treatments (RR 2.86, 95% CI 0.12 to 66.11; Analysis 1.24).

1.24.7 Arrythmia/palpitations

One trial (total n = 60) reported useable data for this outcome. There was no evidence of a clear difference between the two treatments (RR 1.00, 95% CI 0.15 to 6.64; Analysis 1.24).

1.24.8 Uterine myoma

One trial (total n = 39) reported useable data for this outcome. There was no evidence of a clear difference between the two treatments (RR 2.86, 95% CI 0.12 to 66.11; Analysis 1.24).

1.24.9 Dizziness

Three trials (total n = 137) reported useable data for this outcome. There was no evidence of a clear difference between the two treatments (RR 2.32, 95% CI 0.83 to 6.51; Analysis 1.24).

1.24.10 Collapse

One trial (total n = 39) reported useable data for this outcome. There was no evidence of a clear difference between the two treatments (RR 0.32, 95% CI 0.01 to 7.35; Analysis 1.24).

1.24.11 Acute Respiratory Distress Syndrome

One trial (total n = 39) reported useable data for this outcome. There was no evidence of a clear difference between the two treatments (RR 0.32, 95% CI 0.01 to 7.35; Analysis 1.24).

1.24.12 Nausea

Two trials (total n = 77) reported useable data for this outcome. There was no evidence of a clear difference between the two treatments (RR 1.55, 95% CI 0.45 to 5.41; Analysis 1.24).

1.24.13 Agitation

Two trials (total n = 77) reported useable data for this outcome. There was no evidence of a clear difference between the two treatments (RR 0.70, 95% CI 0.15 to 3.32; Analysis 1.24).

1.24.14 Sleep disturbance

Two trials (total n = 77) reported useable data for this outcome. There was no evidence of a clear difference between the two treatments (RR 0.20, 95% CI 0.02 to 1.61; Analysis 1.24).

1.24.15 Dry mouth

Two trials (total n = 98) reported useable data for this outcome. There was no evidence of a clear difference between the two treatments (RR 2.25, 95% CI 0.74 to 6.81; Analysis 1.24).

1.24.16 Blurred vision

One trial (total n = 60) reported useable data for this outcome. There was no evidence of a clear difference between the two treatments (RR 1.33, 95% CI 0.33 to 5.45; Analysis 1.24).

1.24.17 Conjunctivitis

One trial (total n = 39) reported useable data for this outcome. There was no evidence of a clear difference between the two treatments (RR 0.32, 95% CI 0.01 to 7.35; Analysis 1.24).

Missing outcomes

No included study reported outcomes for quality of life, service utilisation, or economics.

DISCUSSION

Summary of main results

We noted slight improvement in overall mental state, and akathisia scores with the mirtazapine adjunct group. Mirtazapine adjunct was however not associated with improvements in the clinically important change in negative symptoms or any of the other main outcomes. For a tabulated representation of the summary of the main results, please refer to Summary of findings for the main comparison. Of note, in addition to the main outcomes of interest, an important but perhaps not a surprising finding relating to adverse events was that the mirtazapine groups were associated with an increased risk of weight gain and sedation/drowsiness. A summary of these main results and others of note are below.

1. Mental state: specific

1.1 Negative symptoms

Only one study including 20 participants defined and reported on clinically important change in negative symptoms (Zoccali 2004). Clinically important response was defined as a reduction in SANS overall score from baseline of at least 20%. This study reported that mirtazapine adjunct was associated with a lower risk of no response, but the result did not reach statistical significance (RR 0.81, 95% 95% CI 0.57 to 1.14, very-low quality evidence). Seven out of nine included studies reported negative symptom scores at endpoint. We were able to meta-analyse Positive and Negative Syndrome Scale (PANSS) negative subscale data of 130 participants from four studies (Abbasi 2010; Berk 2009; Cho 2011; Terevnikov 2013), and Scale for the Assessment of Negative Symptoms (SANS) overall score data for 40 participants from two studies (Cho 2011; Zoccali 2004; Analysis 1.2). Two studies reported data on negative symptoms, which were skewed, preventing their inclusion in meta-analysis (Berk 2001; Caforio 2013; Analysis 1.3). We found statistically significant improvement in negative symptoms in the PANSS negative subscale (N = 130, 4 RCTs, MD -2.65, 95% CI -4.45 to -0.84). We also found a statistically significant improvement in negative symptoms in the SANS overall score meta-analysis (N = 40, 2 RCTs, MD -15.04, 95% CI -20.06 to -10.01). Additionally, the skewed data from Berk 2001 and Caforio 2013 both showed improvement in PANSS negative subscale scores associated with mirtazapine adjunct. Despite being statistically significant, it is important to remember that the reduction in scores shown by our meta-analyses may not equate to clinically important benefit in participants.

1. 2 Positive symptoms

None of the included studies defined a clinically important change on positive symptoms. Seven of the included studies reported on positive symptom scores at endpoint (Abbasi 2010; Berk 2001; Berk 2009; Caforio 2013; Cho 2011; Terevnikov 2013; Zoccali 2004). One study, Cho 2011, reported a statistically significant reduction (improvement) in PANSS positive subscale score at endpoint (MD -2.20, 95% CI -5.29 to 0.89). Data from the remaining six studies were skewed with varying directions of effect size.

2. Mental state: overall

Two studies defined and reported on clinically important change on overall mental state (Abbasi 2010; Terevnikov 2013). Abbasi 2010 defined clinically important change as over 50% reduction in PANSS overall score at endpoint, and Terevnikov 2013 defined it as over 20% reduction in PANSS overall score at endpoint. Meta-analysis showed that mirtazapine adjunct was associated with a lower risk of having not improved by endpoint (RR 0.69, 95% CI 0.51 to 0.92; very low-quality evidence). The large difference in the threshold for clinical significance set by each study places limitation on the interpretation of this meta-analysis as a majority of studies in schizophrenia tend to use an improvement cut-off of 20% on PANSS overall scores (Leucht 2010). All nine included studies reported overall mental state scores at endpoint. We included six studies with 170 participants in a meta-analysis of PANSS overall score at endpoint (Abbasi 2010; Berk 2009; Caforio 2013; Cho 2011; Poyurovsky 2003; Terevnikov 2013), and one study had useable data on the Brief Psychiatric Rating Scale (BPRS) score at endpoint (Zoccali 2004; Analysis 1.7). Data from Berk 2001 and Poyurovsky 2006 were skewed and excluded from these analyses. We found an improvement on PANSS overall score at endpoint associated with mirtazapine adjunct (MD -3.84, 95% CI -7.89 to 0.21), but the result was not statistically significant. Zoccali 2004 reported an improvement of BPRS score at endpoint associated with mirtazapine group (MD -19.30, 95% CI -22.10 to -16.50).

3. Mental state: depressive symptoms

Six out of the nine included studies reported on depressive symptoms, although data from all but two studies were skewed and not included in the meta-analysis. The meta-analysis of the two eligible studies (Analysis 1.9), did not find a statistically significant difference in depressive symptom scores between groups at endpoint. We had hoped that there would be more useable data on the impact of mirtazapine adjunct on depressive symptoms to give some insight as to whether a reduction in depressive symptoms associated with mirtazapine adjunct might have meaningfully confounded the analysis of negative symptoms. However, due to this lack of useable data and majority of studies excluding participants with current depressive episode or use of another psychotropic drug, it is unlikely that the antidepressant effect of mirtazapine adjunct substantially confounded the other analyses.

4. Leaving the study early for any reason

All nine studies had useable data on leaving the study early for any reason. Participants from the mirtazapine groups (n = 156) appeared no more or less likely to leave the study early for any reason than those in the placebo group (n = 154) (RR 1.03, 95% CI 0.64 to 1.66; moderate-quality evidence).

5. Global state

There was a paucity of usable data on global state outcomes. Only data from one study with 39 participants were useable (Terevnikov 2013). Berk 2001 also reported outcomes of global state, but data were skewed.

6. Cognitive functioning

Four studies reported on outcomes of cognitive functioning (Berk 2009; Caforio 2013; Cho 2011; Terevnikov 2013). Due to selective reporting, all cognitive function data from Cho 2011 were excluded from this review, leaving three studies with useable data. Berk 2009 reported no significant differences between the mirtazapine and placebo groups for digit span, word learning, trail making, and verbal fluency tests. Caforio 2013 also reported no significant differences between groups for the series of N-back tasks they conducted. Terevnikov 2013 performed a more comprehensive battery of cognitive function tests, and reported a statistically

significant improvement in five out of 21 parameters tested in the mirtazapine group compared with one out of 21 in the placebo group. The between-group comparison in Terevnikov 2013 showed that mirtazapine adjunct outperformed placebo adjunct with statistical significance in just two out of 21 tested parameters. Due to the two neutral results, and the results of Terevnikov 2013, only demonstrating superiority of mirtazapine adjunct over placebo adjunct in just two neurocognitive parameters tested, we consider it unlikely that there is a substantial effect of mirtazapine adjunct on cognitive function based on available evidence.

7. Adverse effects/events

All nine studies reported on adverse effects/events. Studies described these outcomes in several different ways, but often did not include information on the distribution of count data of individual adverse events, making it impossible to conduct meta-analysis to derive meaningful information on number of adverse events per participant. What data we do have suggest that mirtazapine adjunct is associated with statistically significant increased risk for some adverse effects such as weight gain (RR 3.19, 95% CI 1.17 to 8.65), and sedation/drowsiness (RR 3.16, 95% CI 1.59 to 6.28).

Five studies reported on extrapyramidal side effects (Abbasi 2010; Berk 2001; Poyurovsky 2003; Poyurovsky 2006; Terevnikov 2013). Poyurovsky 2003 and Poyurovsky 2006 each defined a clinically significant response on akathisia symptoms, and when combined in a meta-analysis (Analysis 1.18), these data showed a statistically significant improvement associated with mirtazapine adjunct. Because the SAS and Extrapyramidal Symptom Rating Scale (ESRS) scores appear not to differ between groups in the other trials and much of these data are skewed, the effect of mirtazapine adjunct on extrapyramidal side effects appears limited to treating akathisia.

8. Missing outcomes

No included study reported outcomes for quality of life, service utilisation, or economics. This was somewhat disappointing, particularly regarding the lack of data on quality of life for the recipients of care, as improving quality of life is a fundamentally patient-centred end in caring for people with schizophrenia.

Overall completeness and applicability of evidence

There are several study characteristics that strengthen and several that weaken the external validity of this review. Study attributes that increase the applicability of this review are the variety of antipsychotic drugs used in combination with mirtazapine, the inclusion of participants at various stages of illness across the trials, and the diverse clinical and geographical settings. Factors that reduce the applicability of this review include the absence of both long-term and quality of life outcome data in all nine studies, the exclusion of participants with psychiatric and medical comorbidities, the substantial attrition rates within included studies, and the inherent difficulty in translating scale-derived measures of effect size into meaningful 'real-world' clinical importance. On balance, the overall completeness of the evidence is insufficient to address the objective of this review in full.

Quality of the evidence

All nine studies were randomised and likely blinded, however the details of random sequence generation, blinding, and allocation concealment were commonly not provided. Selective reporting was detected in four studies, and three studies were either sponsored by the pharmaceutical industry, or had at least one author with a financial conflict of interest. All included studies were short term. Each of these factors lowers the overall quality of the evidence, resulting in grades for pre-specified key outcomes ranging from moderate to very low (Summary of findings for the main comparison).

Potential biases in the review process

We added several outcomes of potential interest after reviewing results of the search, see Differences between protocol and review. We are not aware of any other potential biases in the review process.

Agreements and disagreements with other studies or reviews

We identified two systematic reviews on similar topics (Phan 2011; Vidal 2015). Our review includes additional trials and examined additional outcomes, and therefore contributes new and improved knowledge to this area of study. Despite this, the conclusions of these previous works are similar to those of this review: that mirtazapine as an add on treatment to antipsychotic medication may slightly improve overall mental state of people with schizophrenia, but the evidence is not yet convincing.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia

Mirtazapine added on to antipsychotic medication may improve overall mental state and help with the adverse effect akathisia, but the data are not yet convincing. The current level of evidence is therefore insufficient to recommend the routine use of mirtazapine adjunct in people with schizophrenia. It is also noteworthy that there is a lack of any evidence for several important patient-centred outcomes of interest, such as quality of life.

2. For clinicians

All studies included in this review are short term, and several have methodological shortcomings. The overall results suggest that mirtazapine adjunct is associated with a clinically important change in overall mental state, and for those with akathisia, a clinically important improvement of akathisia. Data showed no effect for clinically important improvement in negative symptoms but a difference in endpoint scores on SANS and PANSS negative subscale, favouring mirtazapine adjunct, were reported. The full clinical meaning of these findings are unclear. There is some evidence that mirtazapine adjunct is associated with an increased risk of weight gain and sedation/drowsiness. Depending on the clinical context, mirtazapine adjunct may perhaps be offered to people with schizophrenia when negative symptoms are severe and other avenues of management have been exhausted. However, the current level of evidence is not strong enough to firmly support or reject adjunct mirtazapine's place in routine clinical practice.

3. For hospital administrators and policymakers

There is no information on economic and service utilisation outcomes available on this subject that would be of potential use to

hospital administrators and policymakers. Should further studies report these outcomes, we will include these data in subsequent updates of this review.

Implications for research

1. General

Reporting of methodology in schizophrenia trials is often poor. Future trials should describe accurately and comprehensively the exact methods used to randomise, conceal allocation, blind participants and personnel, and rate outcomes in accordance with the CONSORT statement (Schulz 2010). Furthermore, the statistical method used to account for missing data should be clearly detailed such that the reader could repeat the experiment. Trials should be prospectively registered and their protocols made publicly available. It is noteworthy that initiatives such as ALLTrials are now endorsed by an ever-increasing body of key worldwide organisations including in Australia the National Health and Medical Research Council of Australia, Royal Australian and New Zealand College of Psychiatrists and Medical Journal of Australia. Hopefully, ongoing support for this initiative will encourage prospective researchers to ensure that contributions made by altruistic participants in research are not made in vain.

2. Specific

This review showed evidence that mirtazapine adjunct may be effective in treating the negative symptoms of schizophrenia, but the results were not conclusive. Key limitations of the design of included studies included the absence of pragmatic and holistic outcomes such as quality of life and service utilisation as well as their universally short-term duration. See Table 1 for a suggested design of future studies.

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

We have also used and adapted standardised wording for results in the Abstract and Plain Language sections of the review (Glenton 2010).

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The search term was developed by the Information Specialist of the Cochrane Schizophrenia Group and the contact author of this protocol.

Parts of this review were generated using RevMan HAL v 4.3. You can find more information about RevMan here.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abbasi 2010

Methods	Allocation: randomised Blinding: double Duration: 8 weeks Design: parallel Setting: three psychiatric inpatient hospitals in Iran.
Participants	Diagnosis: schizophrenia, DSM-IV N = 40 Age: mean ˜ 33 years (6.42) (mirtazapine group), mean ˜ 34 years (7.51) (placebo group). Sex: 25 M, 15 F History: active phase of illness, duration of illness (months, mean (SD)): 94.10 (40.86) (mirtazapine group), 89.00 (38.51) (placebo group), minimum score of 60 on PANSS and greater than 15 on the negative subscale. Exclusion criteria: participants with depressive episode, clinically significant neurological or organic disorder, serious psychotic disorders other than schizophrenia, use of medications contraindicated with mirtazapine, treatment with antidepressant within one month of screening, or a current diagnosis of major mood or substance abuse disorder. Pregnant or lactating women and those of reproductive age without adequate contraception.
Interventions	1. Mirtazapine adjunct: risperidone 6 mg/day plus mirtazapine 30 mg/day, (N = 20). 2. Placebo adjunct: risperidone 6 mg/day plus placebo, (N = 20). Starting dosage of risperidone was 2 mg/day and was increased in 2 mg increments daily to 6 mg/day. Patients started with mirtazapine 15 mg/day and the dosage of mirtazapine were increased to 30 mg/day at the end of the first week.
Outcomes	Mental state: negative symptoms (PANSS), clinically important overall change (> 50% PANSS), overall endpoint score PANSS. Leaving the study early for any reason Adverse effects/events: general and specific (including death by suicide or natural causes, allergic reactions, and additional drug use). Unable to use: Mental state: positive symptoms endpoint PANSS (skewed data).
Conflicts of interest of authors	None declared
Notes	Funding: Tehran University of Medical Sciences grant no. 4543

Risk of bias

Bias	Authors' judgement	Support for judgement

Abbasi 2010 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised to receive mirtazapine or placebo in a 1:1 ratio using a computer-generated code."
Allocation concealment (selection bias)	Low risk	Quote: "The assignments were kept in sealed, opaque envelopes until data analysis."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:"Throughout the study, the person who administered the medications, the rater and the patients were blind to assignments."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote:"Throughout the study, the person who administered the medications, the rater and the patients were blind to assignments."
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient withdrew from each group due to withdrawn consent. The specific reasons for withdrawing consent were not reported. Due to the low number of data and that missing data are balanced across both groups there is a low risk of attrition bias. Intention-to-treat analysis with last observation carried forward principle was used.
Selective reporting (reporting bias)	Unclear risk	The protocol for this study was not available, however all pre-specified outcomes were reported and most expected outcomes of interest were reported.
Other bias	Unclear risk	Funding: grant from Tehran University of Medical Sciences (grant no. 4543). Study not clearly free from other bias.

Berk 2001

Methods	Allocation: randomised (no further details) Blinding: double (no further details) Duration: 6 weeks Design: parallel Setting: inpatient unit in South Africa
Participants	Diagnosis: schizophrenia, DSM-IV N = 30 Age: mean ˜ 29.5 (9.3) years Sex: 25 M, 5 F History: first episode or recurrently ill, treated with haloperidol 5 mg daily. Excluded: participants on other psychotropic medications (except benzodiazepines), other significant medical illnesses.
Interventions	1. Mirtazapine adjunct: haloperidol 5 mg/day plus mirtazapine 30 mg/day, (N = 15). 2. Placebo adjunct: haloperidol 5 mg/day plus placebo, (N = 15).
Outcomes	Leaving the study early: for any reason Adverse effects/events: total number of events, specific extrapyramidal effects, other specific.

Berk 2001 *(Continued)*

	Unable to use: Mental state: negative symptoms positive symptoms, overall (PANSS) depressive symptoms (HAM-D) - skewed data. Global state: CGI severity - skewed data.
Conflicts of interest of authors	None declared
Notes	The source of funding for this study was not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote:"...patients were randomised to placebo or mirtazapine 30 mg daily." The method of randomisation was not further described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:"This trial was a...double blind, randomised, placebo-controlled trial..." Blinding of participants and personnel was not further described. It is likely that participants and personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment was not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three patients, all from the mirtazapine group, withdrew from the study early. The reasons were leaving the country (1) and adverse events (2 - insomnia and dry mouth). The data were analysed on an intention-to-treat or last observation carried forward basis. The point in the study at which the three patients withdrew was not reported. While two of three missing patients withdrew for reasons related to treatment effect, this small proportion is unlikely to have clinically relevant effect.
Selective reporting (reporting bias)	Unclear risk	The protocol for this study was not available, however all pre-specified outcomes were reported and most expected outcomes of interest for consumers were reported.
Other bias	Unclear risk	Study not clearly free from other bias.

Berk 2009

Methods	Allocation: randomised (no further details) Blinding: double (no further details) Duration: 6 weeks Design: parallel Setting: Australia (no further details)
Participants	Diagnosis: schizophrenia

Berk 2009 *(Continued)*

	N = 40 Age: mean ~ (37.80 +/- 10.86) years (mirtazapine), (35.90 +/- 9.20) years (placebo). Sex: 27 M, 13 F History: diagnosis of schizophrenia requiring treatment with an atypical antipsychotic. Excluded: requiring a psychotropic medication other than a benzodiazepine.
Interventions	1. Mirtazapine adjunct: atypical antipsychotic (treatment as usual) plus mirtazapine 30 mg/day, (N = 18). 2. Placebo adjunct: atypical antipsychotic (treatment as usual) plus placebo, (N = 20). Primary antipsychotic medications were clozapine (15), quetiapine (7), risperidone (6), olanzapine (3), and aripiprazole (2). The mean (SD) daily dose atypical antipsychotic was 7.10 (3.29) mg in the mirtazapine group and 6.33 (3.54) mg in the placebo group.
Outcomes	Mental state: negative symptoms, positive symptoms, overall (PANSS), depressive symptoms (HAM-D). Leaving the study early for any reason Adverse effects/events: at least one event Unable to use: Mental state: depressive symptoms (CDSS) - skewed data. Cognitive functioning: various cognitive function tests - other data.
Conflicts of interest of authors	Four of the 14 authors declare conflict of interest and have received grants or honoraria from industry.
Notes	Registered with Australian Clinical Trials Registry (ACTR012605000577617). Funding: Organon Australia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote:"randomised trial'."Further details not provided.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:"double-blind...trial of mirtazapine". Blinding of participants and personnel was not further described. It is likely that participants and personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment was not described.
Incomplete outcome data (attrition bias) All outcomes	High risk	Two participants withdrew from the mirtazapine group at baseline and were excluded from analysis. There is inconsistency in the results section regarding how many participants withdrew after baseline: three participants were withdrawn (one from the mirtazapine group and two from the placebo group), however reasons for withdrawal were only described for two of these three. It is not clear which reason for withdrawal corresponded to participants from

Berk 2009 *(Continued)*

		which group. Intention-to-treat analysis was not described. Data from participants who withdrew early were not considered.
Selective reporting (reporting bias)	High risk	The methods pre-specifies CGI as an outcome but only the severity subscale is mentioned in the results.
Other bias	High risk	Four of the 14 authors declare conflict of interest and have received grants or honoraria from industry. The study was also funded by Organon Ausralia, who markets mirtazapine.

Caforio 2013

Methods	Allocation: randomised (no further details) Blinding: double (no further details). Duration: 16 weeks (mirtazapine was added 8 weeks in) Design: parallel Setting: inpatient unit in Italy
Participants	Diagnosis: schizophrenia N = 28 Age: mean ˜ 30.7 (7.7) years (mirtazapine group), 27.8 (7.0) years (placebo group). Sex: 7 F, 21 M Elligibility criteria: diagnosis of schizophrenia with a recent exacerbation of psychotic symptoms requiring hospitalisation, duration of illness (months, mean (SD)): 90.07 (94.9) (mirtazapine group), 79.3 (68.27) (placebo group). Nine out of 14 participants in each group were drug-free and five were drug-naive at the time of admission. Average drug-free period in months was 15.1 (27.94) (mirtazapine) and 26.5 (38.6) (placebo). Excluded: history of alcohol or drug abuse, any diagnosable systemic or neurological condition.
Interventions	1. Mirtazapine adjunct: 8 weeks of olanzapine monotherapy followed by 8 weeks of olanzapine plus mirtazapine 30 mg/day, (N = 14). 2. Placebo adjunct: 8 weeks of olanzapine monotherapy followed by 8 weeks of either olanzapine monotherapy or placebo, (N = 14). The average dose of olanzapine was 16.5 (SD 7) mg/day.
Outcomes	Mental state: overall (PANSS) Leaving the study early: for any reason Adverse events/effects: total number of events, sedation/drowsiness Unable to use: Mental state: negative symptoms, positive symptoms (PANSS) - skewed data depressive symptoms (CDSS) - skewed data. Cognitive functioning: other data

Caforio 2013 *(Continued)*

Conflicts of interest of authors	The study was partially funded by a grant from Organon Italy, a manufacturer of mirtazapine. One author is an employee and stock owner of Eli Lilly, a company that produces olanzapine.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote:"After 8 weeks, patients were randomised...". The method of randomisation was not further described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:"Randomized into two groups... in a double-blind fashion". Blinding of participants and personnel was not further described. It is likely that participants and personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 28 patients enrolled into the study, 18 completed the study with outcome data available at 16 weeks. Endpoint data was calculated using mixed modelling for repeated measures, and attrition was balanced between groups.
Selective reporting (reporting bias)	Unclear risk	The protocol for this study was not available, however all pre-specified outcomes were reported and most expected outcomes of interest were reported.
Other bias	High risk	The study was partially funded by a grant from Organon Italy, a manufacturer of mirtazapine. One author is an employee and stock owner of Eli Lilly, a company that produces olanzapine.

Cho 2011

Methods	Allocation: randomised (no further details) Blinding: double (no further details) Duration: 8 weeks Design: parallel Setting: outpatient unit in South Korea
Participants	Diagnosis: schizophrenia, DSM-IV N = 21 Age: 21 - 70 years; mean ˜ 35.08 (13.58) years (mirtazapine group), 36.44 years (9.57) (placebo group). Sex: 55.6% female (mirtazapine group), 44.4% female (placebo group). History: score of at least 4 on the CGI scale, and stable illness. Duration of illness (months, mean (SD)): 83.33 (97.90) (mirtazapine group), 71.56 (89.81) (placebo group).

Cho 2011 *(Continued)*

	Excluded: participants with a depressive episode.
Interventions	1. Mirtazapine adjunct: risperidone plus mirtazapine (30 mg/day), (N = 11)*. 2. Placebo adjunct: risperidone plus placebo, (N = 9). Participants all maintained their regular dose of risperidone with a mean (SD) dosage in mg of 3.00 (1.94) (mirtazapine group) and 4.22 (1.83) (placebo group). Started with mirtazapine 15 mg/day and the dosage of mirtazapine was increased to 30 mg/day after two weeks.
Outcomes	Mental state: negative symptoms (PANSS, SANS), positive symptoms (PANSS), overall (PANSS) Leaving the study early for any reason Adverse effects/events: total number, various specific effects
Conflicts of interest of authors	None declared
Notes	* One participant left the study early from mirtazapine group. Funded by the Bundang CHA Hospital (South Korea).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote:"This study was an eight-week, double-blind, randomised controlled trial (RCT)." The specific method of random sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:"Double-blind". Blinding of participants and personnel was not further described. It is likely that participants and personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not described.
Incomplete outcome data (attrition bias) All outcomes	High risk	One person from the 12 allocated to the mirtazapine group withdrew from the study. The reason and time of withdrawal was not described. No measure was taken to include data from this participant.
Selective reporting (reporting bias)	High risk	Cognitive function was not reported in full as described in the study methods.

Poyurovsky 2003

Methods	Allocation: randomised (using a table of random numbers) Blinding: double Duration: 5 days

Poyurovsky 2003 *(Continued)*

	Design: parallel Setting: single inpatient unit in Israel
Participants	Diagnosis: schizophrenia with antipsychotic induced akathisia, DSM-IV N = 26 Age: mean ˜ 32.5 years (11.3) (mirtazapine), mean ˜ 28.5 years (9.2) (placebo). Sex: 13 F, 13 M History: people with schizophrenia and neuroleptic induced akathisia (at least two points on the BAS global subscale) and on haloperidol for at least three weeks prior to the commencement of the study. Duration of illness (months, mean (SD)): 82.8 (91.2) (mirtazapine) and 33.6 (44.4) (placebo). Excluded: none described
Interventions	1. Mirtazapine adjunct: mirtazapine 15 mg/day plus haloperidol 5 mg/day -15 mg/day or perphenazine 8 mg/day - 24 mg/day, (N = 13). 2. Placebo adjunct: placebo plus haloperidol 5 mg/day - 15 mg/day or perphenazine 8 mg/day - 24 mg/day, (N = 13).
Outcomes	Mental state: overall (PANSS), depressive symptoms (HAM-D) Leaving the study early for any reason Adverse effects/events: total number of events, extrapyramidal (full resolution), clinically important change (defined as reduction of BAS by at least 2), specific effects. Unable to use: Adverse effects/events: extrapyramidal endpoint score (BAS) - skewed data.
Conflicts of interest of authors	None reported
Notes	Funded by grant number 01T-069 from the Stanley Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote:"According to entries on a table of random numbers, the participants were allocated..."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The method of blinding was not described, however it is likely that blinding occurred.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not described.

Poyurovsky 2003 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	There were three participants who left early from each group of 13. The reason for all six was 'intolerance' and was not further described. The study conducted analysis of completers only as well as an intention-to-treat analysis.
Selective reporting (reporting bias)	High risk	An intention-to-treat analysis was performed, but most data from this analysis were not reported, instead the study reported most of its data for completers only.
Other bias	Unclear risk	Funded by grant number 01T-069 from the Stanley Foundation.

Poyurovsky 2006

Methods	Allocation: randomised (no further details) Blinding: double Duration: 7 days Design: parallel Setting: single inpatient unit in Israel
Participants	Diagnosis: schizophrenic disorder (80), delusional disorder (7), and major depressive disorder with psychotic features (3), DSM-IV N = 90 Age mean (SD)): mirtazapine 34.9 (11.5) years, propanolol 33.4 (10.1) years, placebo 34.4 (11.1) years. Sex: 33 F, 57 M History: score of greater than or equal to 2 on the BAS. All participants had been receiving FGAs (haloperidol, 5 mg/day –20 mg/day; perphenazine, 8 mg/day – 24 mg/day; or clotiapine,40 mg/day – 120 mg/day). A small proportion of patients in each group also received mood stabilisers (carbamazepine, 600 mg/day –1200 mg/day; valproic acid, 600 mg/day –100 mg/day; 2/30 in mirtazapine and 7/30 in placebo) and antidepressants (paroxetine, 20 mg/day; escitalopram, 20 mg/ day; fluvoxamine, 200 mg/day; sertraline, 150 mg/day (one participant in each group). Anticholinergic agents(trihexyphenidyl, 5 mg/day – 10 mg/day; biperiden, 2 mg/day – 6 mg/day) for neuroleptic-induced Parkinsonism or benzodiazepines (lorazepam, 1 mg/day – 2 mg/day; diazepam, 5 mg/day – 10 mg/day; or nitrazepam, 10 mg/day) for insomnia were allowed, only if they were initiated prior to the beginning of the study. Excluded: treatment with a beta blocker, anticholinergics, benzodiazepines; diagnoses of non-acute akathisia; change in antipsychotic regimen within three days prior to agents; or contraindications to beta blockers.
Interventions	1. Mirtazapine adjunct: mirtazapine 15 mg/day plus regular first-generation antipsychotic and anticholinergic, (N = 30). 2. Propranolol adjunct: propranolol 40 mg/day for one day then 80 mg/day thereafter plus regular first-generation antipsychotic and anticholinergic, (N = 30). 3. Placebo adjunct: placebo plus regular first-generation antipsychotic and anticholinergic, (N = 30).
Outcomes	Leaving the study early for any reason Adverse events: total number of events, extrapyramidal effects score (BAS, SAS), other various specific effects. Unable to use:

Poyurovsky 2006 *(Continued)*

	Mental state: overall BPRS change score (skewed data), depressive symptoms HAM-D change (skewed data).
Conflicts of interest of authors	None reported
Notes	The study was funded by the Stanley Medical Research Institute, which had no role in data collection, data analysis, data interpretation, writing the report, or decision to submit the article for publication.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned to treatment according to a table of random numbers.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:"...clinical and research staff and patients were unaware of and could not determine the study drug assignment by appearance or otherwise."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'...clinical and research staff and patients were unaware of and could not determine the study drug assignment by appearance or otherwise'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Six out of 30 patients from the mirtazapine group, 10 out of 30 patients from the placebo group and nine out of 30 from the propranolol group withdrew from the study early. Nineteen patients discontinued the study early due to insufficient response or worsening of akathisia, and five patients due to adverse events (all in the propranolol group).
Selective reporting (reporting bias)	Unclear risk	The protocol for this study was not available, however all pre-specified outcomes were reported and most expected outcomes of interest were reported.

Terevnikov 2013

Methods	Allocation: randomised Blinding: double Duration: 6 weeks Design: parallel Setting: inpatient/outpatient unit in a single hospital in Russia
Participants	Diagnosis: schizophrenia, DSM-IV N = 41 Sex: 20 F, 21 M Age: 18 years - 65 years,(years, mean (SD)): 43.4 (9.24) (mirtazapine), 48.21 (9.68) (placebo).

Terevnikov 2013 *(Continued)*

	History: presence of positive or negative symptoms or both resulting in the illness having at least moderate severity on the CGI scale, clinical condition remained unchanged for the 6 weeks prior to enrolment, participants had to have received more than one first-generation antipsychotic (FGA) and to have received at least 400 mg/day chlorpromazine equivalents for at least 6 weeks (8 weeks for depot FGAs). Duration of illness (months, mean (SD)): 239.4 (108.96) (mirtazapine), 299.4 (113.16) (placebo). Excluded: previous lack of response to an add-on antidepressant with affinity to 5-HT2, current second-generation antipsychotic (SGA), a history of non-response to SGA, a serious medical condition, a history of bipolar or schizoaffective disorder, substance misuse, expected poor compliance, suicidality, treatment with any antidepressant, mood stabiliser, buspirone, or tryptan, or benzodiazepines other than diazepam 30 mg/day.
Interventions	1. Mirtazapine adjunct: mirtazapine (30 mg/day) plus participants' usual FGA, (N = 20). 2. Placebo adjunct: placebo plus participants' usual FGA, (N = 21).
Outcomes	Mental state: negative symptoms (PANSS endpoint), clinically important overall change (> 20% change PANSS), overall symptoms (PANSS endpoint) Leaving the study early for any reason Global state: overall symptoms (CGI severity endpoint and change score), PGI change score Adverse events: total number of events, various specific effects Unable to use: Mental state: positive symptoms (PANSS endpoint), depressive symptoms (CDSS) - skewed data. Cognitive functioning: other data Adverse effects: extrapyramidal endpoint SAS score (skewed data)
Conflicts of interest of authors	Three of the six authors report conflicts of interest which were all consultancy and honoraria from pharmaceutical companies. Funding source: grant from Stanley Medical Research Institute.
Notes	Trial registration code ISRCTN00721331

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote:"Blocked randomisation was performed with a randomisation table"
Allocation concealment (selection bias)	Low risk	Quote:"Thick envelopes with randomisation codes were opened only when the database was closed."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study is 'double blind', and while this was not elaborated upon, it is likely that blinding of participants and personnel occurred.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not described.
Incomplete outcome data (attrition bias)	Low risk	Two patients from the placebo group withdrew from the study early (one withdrew consent and one violated protocol). Additionaly, in the study reporting

Terevnikov 2013 *(Continued)*

All outcomes		on cognitive function, one patient each from the mirtazapine and placebo group were unable to be tested. The incomplete outcome data are balanced across groups and unlikely to be an effect of the intervention.
Selective reporting (reporting bias)	Unclear risk	All pre-specified outcomes were reported and most expected outcomes of interest were reported.
Other bias	High risk	Three of the six authors report conflicts of interest which were all consultancy and honoraria from pharmaceutical companies. Funding source: grant from Stanley Medical Research Institute.

Zoccali 2004

Methods	Allocation: randomised (no further details) Blinding: double (no further details) Duration: 8 weeks Design: parallel Setting: outpatient unit in Italy Dates: details not provided
Participants	Diagnosis: schizophrenia, DSM-IV N = 24 Sex: 9 F, 15 M Age: (years, mean (SD)): 30.7 (6.5) (mirtazapine group), 33.4 (9.0) (placebo group). History: receiving clozapine monotherapy 150 mg/day - 650 mg/day for at least one year with persistent negative symptoms. Patients with a depressive episode were excluded. Duration of illness (months, mean (SD)): 115.2 (58.8) (mirtazapine group), 71.56 (89.81) (placebo group).
Interventions	1. Mirtazapine adjunct: clozapine plus mirtazapine 30 mg/day, (N = 12). 2. Placebo adjunct: clozapine plus placebo, (N = 12). Participants all maintained their regular dose of clozapine with a mean (SD) dosage in mg/day of 320 (151.2) (mirtazapine group) and 325 (131.7) (placebo group).
Outcomes	Mental state: clinically important change negative symptoms (> 20% change SANS), change negative symptoms (SANS), overall scores (BPRS). Leaving the study early for any reason Adverse events: various specific effects (weight gain, sedation/drowsiness) Unable to use: Mental state: positive symptoms (SAPS) - skewed data. Adverse events: count data only - number of events greater than number of participants.
Conflicts of interest of authors	None reported

Zoccali 2004 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote:"Patients were randomly allocated...". Method of sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote:"Patients were randomly allocated to receive, in a double-blind design...". Blinding of participants and personnel was probably done.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not described.
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was balanced between the two groups (two from each group left early) and the reasons were unrelated to treatment effect (one patient for concurrent illness, three patients did not comply with the visits). Only data from completers were analysed.
Selective reporting (reporting bias)	High risk	This study recorded depressive symptoms with HAM-D at baseline, and used the depressive subscale of BPRS at follow-up. Most other expected outcomes of interest were reported.

BAS: Barnes Akathisa Scale
BPRS: Brief Psychiatric Rating Scale
CGI: Clinical Global Impression
CDSS: Calgary Depression Severity Scale
DSM-IV: American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders - 4th edition
F: female
FGA: first-generation antipsychotic
HAM-D: Hamilton Depression Rating Scale
M: male
mg: milligram
N: number
PANSS: Positive and Negative Syndrome Scale
PGI: Patient Global Impression of Improvement
SANS: Scale for the Assessment of Negative Symptoms
SAPS: Scale for the Assessment of Positive Symptoms
SAS: Simpson-Angus Scale
SD: standard deviation
SGA: second-generation antipsychotic

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

ISRCTN32434568

Methods	Allocation: randomised
Participants	People with schizophrenia

ISRCTN32434568 *(Continued)*

Interventions	Mritazapine adjunct
Outcomes	Awaiting full publication
Notes	

DATA AND ANALYSES

Comparison 1. Mirtazapine adjunct versus placebo adjunct - short term

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental state: specific. 1a. Negative symptoms: clinically important change	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.57, 1.14]
1.1 No important response (reduction in SANS overall score from baseline of at least 20%)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.57, 1.14]
2 Mental state: specific. 1b. Negative symptoms: average endpoint score (various scales)	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 PANSS negative (high = poor)	4	130	Mean Difference (IV, Fixed, 95% CI)	-2.65 [-4.45, -0.84]
2.2 SANS (high = poor)	2	40	Mean Difference (IV, Fixed, 95% CI)	-15.04 [-20.06, -10.01]
3 Mental sate: specific. 1c. Negative symptoms: average endpoint score (PANSS negative, high = poor) -skewed data			Other data	No numeric data
4 Mental state: specific. 2a. Positive symptoms: average endpoint score (PANSS, high = poor)	1	20	Mean Difference (IV, Fixed, 95% CI)	-2.20 [-5.29, 0.89]
5 Mental state: specific. 2b. Positive symptoms: average endpoint score (various scales) - skewed data			Other data	No numeric data
6 Mental state: overall. 3a. Clinically important change (at least 20% change PANSS)	2	77	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.51, 0.92]
6.1 No response	2	77	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.51, 0.92]
7 Mental state: overall. 3b. Average endpoint score (various scales)	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 PANSS (high = poor)	6	170	Mean Difference (IV, Fixed, 95% CI)	-3.84 [-7.89, 0.21]

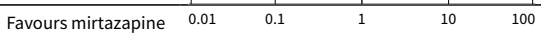
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2 BPRS (high = poor)	1	20	Mean Difference (IV, Fixed, 95% CI)	-19.30 [-22.10, -16.50]
8 Mental state: overall. 3c. Average change score (various scales) - skewed data			Other data	No numeric data
9 Mental state: specific. 4a. Depressive symptoms: average endpoint score (HAM-D, high = poor)	2	53	Mean Difference (IV, Fixed, 95% CI)	1.51 [-1.72, 4.74]
10 Mental state: specific. 4b. Depressive symptoms: average change score (various scales) - skewed data			Other data	No numeric data
11 Leaving the study early for any reason	9	310	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.64, 1.66]
12 Global state: 1. Average endpoint score (CGI severity, high = poor)	1	39	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.68, 0.48]
13 Global state: 2a. Average change score (PGI, high = poor)	1	39	Mean Difference (IV, Fixed, 95% CI)	-0.54 [-0.97, -0.11]
14 Global state: 2b. Average change date (various scales) - skewed data			Other data	No numeric data
15 Cognitive functioning: other data			Other data	No numeric data
15.1 Other data tables			Other data	No numeric data
16 Adverse events: 1a. General (participants with at least one adverse event)	2	71	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.81, 1.12]
17 Adverse events: 1b. General (total number of adverse events) - count data			Other data	No numeric data
18 Adverse effects: 2a. Extrapyramidal: clinically important change akathisia	2	86	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.20, 0.52]
18.1 No clinically important response (reduction of at least 2 on BAS)	2	86	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.20, 0.52]
19 Adverse effects: 2b. Extrapyramidal - full resolution of akathisia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20 Adverse effects: 2c. Extrapyramidal - specific effects	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 Parkinsonism	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.29, 1.23]
20.2 Akathisia	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.55]
20.3 Dystonia	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.58]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.4 Additional anticholinergic drug use	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.24, 0.88]
20.5 Tremor	1	38	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.16, 6.38]
21 Adverse effects: 2d. Extrapyramidal: average change score (various scales)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
21.1 SAS, high = poor	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.27 [-1.97, 1.43]
21.2 BAS , high = poor	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.69, 0.63]
22 Adverse effects: 2e. Extrapyramidal: average endpoint score (various scales) - skewed or unusable data			Other data	No numeric data
23 Adverse effects: 2f. Extrapyramidal: treatment details - skewed data			Other data	No numeric data
24 Adverse events: 3. Other specific effects	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
24.1 Weight gain	4	127	Risk Ratio (M-H, Fixed, 95% CI)	3.19 [1.17, 8.65]
24.2 Headache	4	157	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.54, 3.82]
24.3 Sedation/drowsiness	7	223	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.01, 2.68]
24.4 Increased appetite	2	77	Risk Ratio (M-H, Fixed, 95% CI)	2.57 [0.66, 10.07]
24.5 Weakness	1	39	Risk Ratio (M-H, Fixed, 95% CI)	2.86 [0.12, 66.11]
24.6 Hypersedimentaiton	1	39	Risk Ratio (M-H, Fixed, 95% CI)	2.86 [0.12, 66.11]
24.7 Arrythmia/palpitations	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.15, 6.64]
24.8 Uterine myoma	1	39	Risk Ratio (M-H, Fixed, 95% CI)	2.86 [0.12, 66.11]
24.9 Dizziness	3	137	Risk Ratio (M-H, Fixed, 95% CI)	2.32 [0.83, 6.51]
24.10 Collapse	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.35]
24.11 Acute Respiratory Distress Syndrome	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.35]
24.12 Nausea	2	77	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.45, 5.41]
24.13 Agitation	2	77	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.15, 3.32]
24.14 Sleep disturbance	2	77	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.02, 1.61]
24.15 Dry mouth	2	98	Risk Ratio (M-H, Fixed, 95% CI)	2.25 [0.74, 6.81]
24.16 Blurred vision	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.33, 5.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.17 Conjunctivitis	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.35]

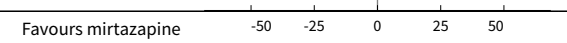
Analysis 1.1. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 1 Mental state: specific. 1a. Negative symptoms: clinically important change.

Study or subgroup	Mirtazapine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 No important response (reduction in SANS overall score from baseline of at least 20%)					
Zoccali 2004	8/10	10/10		100%	0.81[0.57,1.14]
Subtotal (95% CI)	**10**	**10**		**100%**	**0.81[0.57,1.14]**
Total events: 8 (Mirtazapine), 10 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.2(P=0.23)					
Total (95% CI)	**10**	**10**		**100%**	**0.81[0.57,1.14]**
Total events: 8 (Mirtazapine), 10 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.2(P=0.23)					



Analysis 1.2. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 2 Mental state: specific. 1b. Negative symptoms: average endpoint score (various scales).

Study or subgroup	Mirtazapine N	Mirtazapine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.2.1 PANSS negative (high = poor)							
Abbasi 2010	19	14.3 (3.1)	19	19.3 (6.3)		32.95%	-5.05[-8.19,-1.91]
Berk 2009	16	22.1 (5.1)	17	22.2 (6.2)		22.06%	-0.11[-3.95,3.73]
Cho 2011	11	18.7 (4.5)	9	21.7 (3.7)		25.56%	-2.94[-6.51,0.63]
Terevnikov 2013	20	27.3 (7)	19	28.4 (6.1)		19.44%	-1.07[-5.16,3.02]
Subtotal ***	**66**		**64**			**100%**	**-2.65[-4.45,-0.84]**
Heterogeneity: Tau^2=0; Chi^2=4.52, df=3(P=0.21); I^2=33.64%							
Test for overall effect: Z=2.88(P=0)							
1.2.2 SANS (high = poor)							
Cho 2011	11	44.4 (16.8)	9	60.1 (11.7)		16.1%	-15.75[-28.27,-3.23]
Zoccali 2004	10	36.1 (4.7)	10	51 (7.5)		83.9%	-14.9[-20.39,-9.41]
Subtotal ***	**21**		**19**			**100%**	**-15.04[-20.06,-10.01]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.9); I^2=0%							
Test for overall effect: Z=5.87(P<0.0001)							
Test for subgroup differences: Chi^2=20.69, df=1 (P<0.0001), I^2=95.17%							



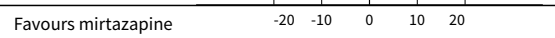
Analysis 1.3. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 3 Mental sate: specific. 1c. Negative symptoms: average endpoint score (PANSS negative, high = poor) -skewed data.

Mental sate: specific. 1c. Negative symptoms: average endpoint score (PANSS negative, high = poor) -skewed data

Study	Mirtazapine	Placebo
Berk 2001	PANSS negative at endpoint, high = poor mean = 13.9 SD = 22.076 N = 15	PANSS negative at endpoint, high = poor mean = 23.9 SD = 21.689 N = 15
Caforio 2013	PANSS negative at endpoint, high = poor mean = 15.2 SD = 5.3 N = 9	PANSS negative at endpoint, high = poor mean = 18.8 SD = 8.6 N = 11

Analysis 1.4. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 4 Mental state: specific. 2a. Positive symptoms: average endpoint score (PANSS, high = poor).

Study or subgroup	Mirtazapine N	Mirtazapine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Cho 2011	11	16.4 (1.8)	9	18.6 (4.5)		100%	-2.2[-5.29,0.89]
Total ***	**11**		**9**			**100%**	**-2.2[-5.29,0.89]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.4(P=0.16)							



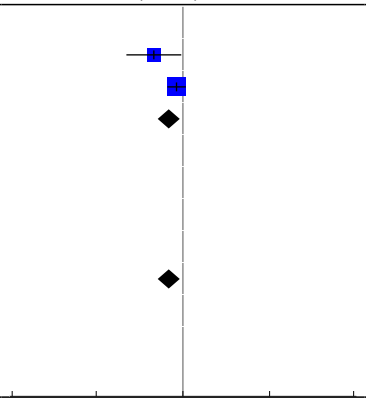
Analysis 1.5. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 5 Mental state: specific. 2b. Positive symptoms: average endpoint score (various scales) - skewed data.

Mental state: specific. 2b. Positive symptoms: average endpoint score (various scales) - skewed data

Study	Mirtazapine	Placebo
Abbasi 2010	PANSS (at endpoint) Mean = 11.875 SD = 5.625 N = 19	PANSS (at endpoint) Mean = 13.75 SD = 3.75 N = 19
Berk 2001	PANSS (at endpoint) Mean = 9.6 SD = 20.5268 N = 15	PANSS (at endpoint) Mean = 8.2 SD = 7.7459 N = 15
Berk 2009	PANSS (at endpoint) Mean = 18.47 SD = 6.44 N = 16	PANSS (at endpoint) Mean = 14.44 SD = 5.65 N = 17
Caforio 2013	PANSS (at endpoint) Mean = 10.05 SD = 1.86 N = 9	PANSS (at endpoint) Mean = 12.8 SD = 3.73 N = 11
Terevnikov 2013	PANSS (at endpoint) Mean = 18.1 SD = 7.2086 N = 20	PANSS (at endpoint) Mean = 18.42 SD = 6.0226 N = 19
Zoccali 2004	SAPS (at endpoint) Mean = 6.6 SD = 2.2 N = 10	SAPS (at endpoint) Mean = 8.5 SD = 4.3 N = 10

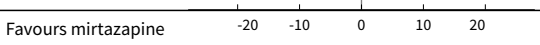
Analysis 1.6. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 6 Mental state: overall. 3a. Clinically important change (at least 20% change PANSS).

Study or subgroup	Mirtazapine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 No response					
Abbasi 2010	6/19	13/19		41.32%	0.46[0.22,0.96]
Terevnikov 2013	16/20	18/19		58.68%	0.84[0.66,1.08]
Subtotal (95% CI)	**39**	**38**		**100%**	**0.69[0.51,0.92]**
Total events: 22 (Mirtazapine), 31 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.93, df=1(P=0.05); I^2=74.54%					
Test for overall effect: Z=2.51(P=0.01)					
Total (95% CI)	**39**	**38**		**100%**	**0.69[0.51,0.92]**
Total events: 22 (Mirtazapine), 31 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.93, df=1(P=0.05); I^2=74.54%					
Test for overall effect: Z=2.51(P=0.01)					



Analysis 1.7. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 7 Mental state: overall. 3b. Average endpoint score (various scales).

Study or subgroup	Mirtazapine N	Mirtazapine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.7.1 PANSS (high = poor)							
Abbasi 2010	19	59.2 (12.2)	19	67.8 (11.1)		29.84%	-8.55[-15.97,-1.13]
Berk 2009	16	78.9 (13.1)	17	69.3 (11.7)		22.76%	9.61[1.12,18.1]
Caforio 2013	9	52 (10.1)	11	62.9 (17.6)		10.85%	-10.9[-23.2,1.4]
Cho 2011	11	73.4 (10.5)	9	82 (14.8)		12.39%	-8.64[-20.15,2.87]
Poyurovsky 2003	10	57.9 (14)	10	64 (10.3)		14.14%	-6.1[-16.87,4.67]
Terevnikov 2013	20	92.8 (20.2)	19	96.4 (20.5)		10.03%	-3.57[-16.36,9.22]
Subtotal ***	**85**		**85**			**100%**	**-3.84[-7.89,0.21]**
Heterogeneity: Tau^2=0; Chi^2=13.29, df=5(P=0.02); I^2=62.38%							
Test for overall effect: Z=1.86(P=0.06)							
1.7.2 BPRS (high = poor)							
Zoccali 2004	10	25.4 (3.2)	10	44.7 (3.2)		100%	-19.3[-22.1,-16.5]
Subtotal ***	**10**		**10**			**100%**	**-19.3[-22.1,-16.5]**
Heterogeneity: Not applicable							
Test for overall effect: Z=13.49(P<0.0001)							
Test for subgroup differences: Chi^2=37.83, df=1 (P<0.0001), I^2=97.36%							



Analysis 1.8. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 8 Mental state: overall. 3c. Average change score (various scales) - skewed data.

Mental state: overall. 3c. Average change score (various scales) - skewed data

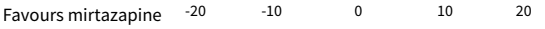
Study	Mirtazapine	Placebo
Berk 2001	PANSS (at endpoint) Mean = 46.7 SD = 67.003 N = 15	PANSS (at endpoint) Mean = 58.9 SD = 48.412 N = 15

Mental state: overall. 3c. Average change score (various scales) - skewed data

Study	Mirtazapine	Placebo
Poyurovsky 2006	BPRS (change data, positive is reduction in score and improvement in overall mental state) Mean = 0.3 SD = 6.3 N = 30	BPRS (change data, positive is reduction in score and improvement in overall mental state) Mean = 0.07 SD = 6.44 N = 30

Analysis 1.9. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 9 Mental state: specific. 4a. Depressive symptoms: average endpoint score (HAM-D, high = poor).

Study or subgroup	Mirtazapine N	Mirtazapine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Berk 2009	16	12.2 (5.9)	17	9.9 (5.8)		65.84%	2.29[-1.69,6.27]
Poyurovsky 2003	10	13.3 (6.4)	10	13.3 (6.2)		34.16%	0[-5.52,5.52]
Total ***	**26**		**27**			**100%**	**1.51[-1.72,4.74]**
Heterogeneity: Tau^2=0; Chi^2=0.43, df=1(P=0.51); I^2=0%							
Test for overall effect: Z=0.92(P=0.36)							



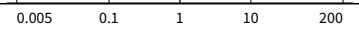
Analysis 1.10. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 10 Mental state: specific. 4b. Depressive symptoms: average change score (various scales) - skewed data.

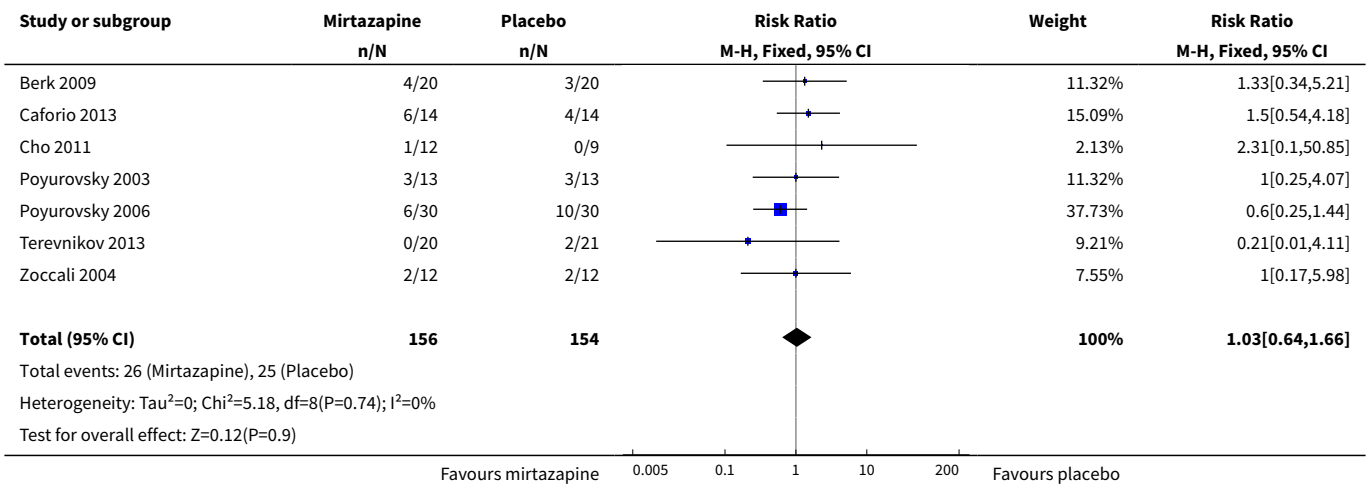
Mental state: specific. 4b. Depressive symptoms: average change score (various scales) - skewed data

Study	Mirtazapine	Placebo
Berk 2001	HAMD (at endpoint) Mean = 3.05 SD = 10.0697 N = 15	HAMD (at endpoint) Mean = 4.5 SD = 7.7459 N = 15
Berk 2009	CDSS (at endpoint) Mean = 3.94 SD = 3.73 N = 16	CDSS (at endpoint) Mean = 3.35 SD = 3.35 N = 17
Caforio 2013	CDSS (at endpoint) No significant difference detected between groups. P = 0.26	CDSS (at endpoint) No significant difference detected between groups. P = 0.26
Poyurovsky 2006	HAMD (change data, positive is reduction in HAMD and improvement in symptoms) Mean = 0.6 SD = 3.87 N = 30	HAMD (change data, positive is reduction in HAMD and improvement in symptoms) Mean = 0.4 SD = 3.5 N = 30
Terevnikov 2013	CDSS (at endpoint) Mean = 2.4 SD = 7.7607 N = 20	CDSS (at endpoint) Mean = 3.32 SD = 6.7771 N = 20

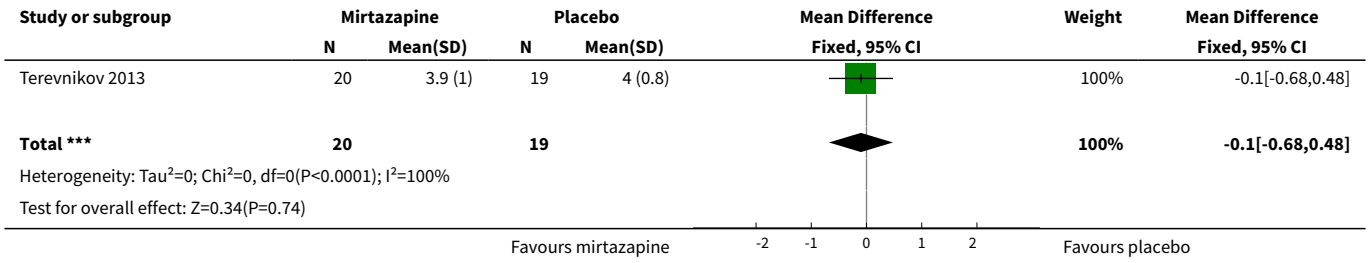
Analysis 1.11. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 11 Leaving the study early for any reason.

Study or subgroup	Mirtazapine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Abbasi 2010	1/20	1/20		3.77%	1[0.07,14.9]
Berk 2001	3/15	0/15		1.89%	7[0.39,124.83]

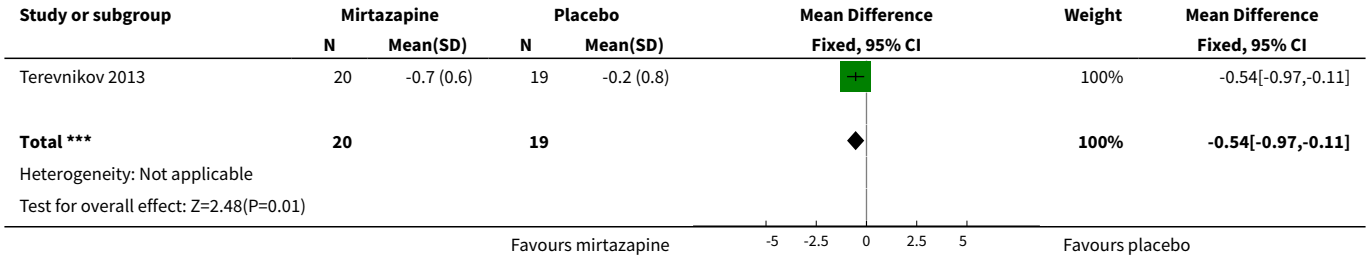




Analysis 1.12. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 12 Global state: 1. Average endpoint score (CGI severity, high = poor).



Analysis 1.13. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 13 Global state: 2a. Average change score (PGI, high = poor).



Analysis 1.14. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 14 Global state: 2b. Average change date (various scales) - skewed data.

Global state: 2b. Average change date (various scales) - skewed data

Study	Mirtazapine	Placebo
Berk 2001	CGI severity Mean = 2.31 SD = 2.09 N = 15	CGI severity Mean = 3.61 SD = 2.09 N = 15

Global state: 2b. Average change date (various scales) - skewed data

Study	Mirtazapine	Placebo
	F = 12.7, P = 0.001, df = 1	F = 12.7, P = 0.001, df = 1
Berk 2001	CGI improvement Mean = 1.41 SD = 1.81 N = 15 F = 14.62, df = 1, P < 0.001	CGI improvement Mean = 2.52 SD = 1.81 N = 15 F = 14.62, df = 1, P < 0.001
Terevnikov 2013		
Terevnikov 2013	CGI improvement (change data - positive is reduction in score and improvement in CGI) Mean change = 0.80 SD = 0.62 N = 20	CGI improvement (change data - positive is reduction in score and improvement in CGI) Mean change = 0.05 SD = 0.52 N = 19

Analysis 1.15. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 15 Cognitive functioning: other data.

Cognitive functioning: other data

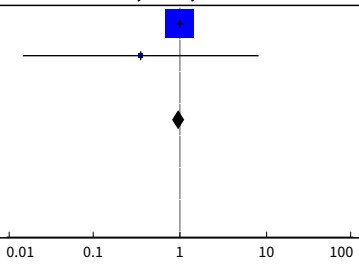
Study	Mirtazapine	Placebo
	Other data tables	
Berk 2009	Some improvement from baseline to week 6 was observed in both treatment arms for all measures of cognition. Digit span: no significant differences between groups at endpoint. Word learning: no significant differences between groups at endpoint. Trail making: significantly worse than in placebo group at endpoint. Verbal fluency: significantly worse than in placebo group at endpoint. No further details were provided.	Some improvement from baseline to week 6 was observed in both treatment arms for all measures of cognition. Digit span: no significant differences between groups at endpoint. Word learning: no significant differences between groups at endpoint. Trail making: significantly worse than in placebo group at endpoint. Verbal fluency: significantly worse than in placebo group at endpoint. No further details were provided.
Caforio 2013	No statistically significant difference was found between the two treatment groups for measures of working memory tested. **1-Back accuracy (% correct) (at endpoint)** Mean = 69 SD = 21.9 N = 14 P = 0.1 **2-Back accuracy (% correct) (at endpoint)** Mean = 53.8 SD = 14.1 N = 14 P = 0.8 **1-Back reaction time (ms) (at endpoint)** Mean = 906 SD = 144.4 N = 14 P = 0.4 **2-Back reaction time (ms) (at endpoint)** Mean = 933.6 SD = 193.5 N = 14 P = 0.1	No statistically significant difference was found between the two treatment groups for measures of working memory tested. **1-Back accuracy (% correct) (at endpoint)** Mean = 79.1 SD = 25.2 N = 14 P = 0.1 **2-Back accuracy (% correct) (at endpoint)** Mean = 57.7 SD = 24.9 N = 14 P = 0.8 **1-Back reaction time (ms) (at endpoint)** Mean = 616.8 SD = 389 N = 14 P = 0.4 **2-Back reaction time (ms) (at endpoint)** Mean = 643.2 SD = 348 N = 14 P = 0.1
Terevnikov 2013	The following data are presented as change from baseline at endpoint. Negative changes for points, and positive changes for time or for number of mistakes means improvement. **WAIS-R Block design (points)** Mean = -4.94 SD = 4.61 N = 19 P = 0.021 **Wechsler Memory Scale Digit Symbol (points)** Mean = -1.17 SD = 5.59 N = 19 P = 0.437 **Wechsler Memory Scale digit span forward (points)**	The following data are presented as change from baseline at endpoint. Negative changes for points, and positive changes for time or for number of mistakes means improvement. **WAIS-R Block design (points)** Mean = -1.18 SD = 2.90 N = 19 P = 0.313 **Wechsler Memory Scale Digit Symbol (points)** Mean = -1.53 SD = 5.62 N = 19 P = 0.347 **Wechsler Memory Scale digit span forward (points)**

Cognitive functioning: other data		
Study	**Mirtazapine**	**Placebo**
	Mean = -0.21 SD = 1.18 N = 19 P = 0.421	Mean = -0.11 SD = 0.58 N = 19 P = 0.438
	Wechsler Memory Scale digit span backward (points) Mean = -0.5 SD = 1.29 N = 19 P = 0.206	**Wechsler Memory Scale digit span backward (points)** Mean = 0.12 SD = 1.02 N = 19 P = 0.528
	Wechsler Memory Scale digit span total (points) Mean = -0.79 SD = 1.99 N = 19 P = 0.233	**Wechsler Memory Scale digit span total (points)** Mean = 0.0 SD = 0.97 N = 19 P = 0.659
	Wechsler Memory Scale logical memory (points) Mean = -1.84 (2.73) SD = 2.73 N = 19 P = 0.044	**Wechsler Memory Scale logical memory (points)** Mean = -2.28 SD = 2.40 N = 19 P = 0.039
	Wechsler Memory Scale logical memory delayed (points) Mean = -1.50 SD = 1.79 N = 19 P = 0.044	**Wechsler Memory Scale logical memory delayed (points)** Mean = -1.00 SD = 2.14 N = 19 P = 0.200
	Wechsler Memory Scale verbal paired associations (points) Mean = -1.61 SD = 2.73 N = 19 P = 0.091	**Wechsler Memory Scale verbal paired associations (points)** Mean = -1.1 SD = 3.77 N = 19 P = 0.4960
	Wechsler Memory Scale verbal paired associations delayed (points) Mean = -1.11 SD = 1.71 N = 19 P = 0.091	**Wechsler Memory Scale verbal paired associations delayed (points)** Mean = -0.55 SD = 2.17 N = 19 P = 0.437
	Wechsler Memory Scale visual reproduction (points) Mean = -0.78 SD = 1.66 N = 19 P = 0.206	**Wechsler Memory Scale visual reproduction (points)** Mean = 0.01 SD = 2.14 N = 19 P = 0.559
	Wechsler Memory Scale visual reproduction delayed (points) Mean = -1.29 SD = 2.08 N = 19 P = 0.065	**Wechsler Memory Scale visual reproduction delayed (points)** Mean = -1.50 SD = 2.96 N = 19 P = 0.0720
	Stroop dots (time) Mean = 15.17 SD = 23.47 N = 19 P = 0.044	**Stroop dots (time)** Mean = -0.22 SD = 35.93 N = 19 P = 0.525
	Stroop dots (number of mistakes) Mean = 0.28 SD = 2.11 N = 19 P = 0.421	**Stroop dots (number of mistakes)** Mean = 0.06 SD = 1.51 N = 19 P = 0.559
	Stroop coloured words (time) Mean = 16.00 SD = 34.20 N = 19 P = 0.164	**Stroop coloured words (time)** Mean = 16.18 SD = 68.05 N = 19 P = 0.421
	Stroop coloured words (number of mistakes) Mean = 0.89 SD = 1.91 N = 19 P = 0.208	**Stroop coloured words (number of mistakes)** Mean = -0.06 SD = 4.41 N = 19 P = 0.497
	Trail making test Part A (time) Mean = 17.44 SD = 15.98 N = 19 P = 0.018	**Trail making test Part A (time)** Mean = 14.29 SD = 40.41 N = 19 P = 0.421
	Trail making test Part A (number of mistakes) Mean = 0	**Trail making test Part A (number of mistakes)** Mean = -0.12

Cognitive functioning: other data		
Study	**Mirtazapine**	**Placebo**
	SD = 0.34	SD = 0.48
	N = 19	N = 19
	P = 0.659	P = 0.421
	Trail making test Part B (time)	**Trail making test Part B (time)**
	Mean = 21.76	Mean = -13.44
	SD = 37.33	SD = 75.53
	N = 19	N = 19
	P = 0.053	P = 0.659
	Trail making test Part B (number of mistakes)	**Trail making test Part B (number of mistakes)**
	Mean = 0.18	Mean = 0.07
	SD = 1.63	SD = 1.58
	N = 19	N = 19
	P = 0.421	P = 0.4210.540
	Word fluency letter words	**Word fluency letter words (points)**
	Mean = -1.16	Mean = -0.22
	SD = 2.61	SD = 2.60
	N = 19	N = 19
	P = 0.199	P = 0.659
	Word fluency semantic	**Word fluency semantic (points)**
	Mean = -0.95	Mean = -0.78
	SD = 2.97	SD = 3.04
	N = 19	N = 19
	P = 0.313	P = 0.421

Analysis 1.16. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 16 Adverse events: 1a. General (participants with at least one adverse event).

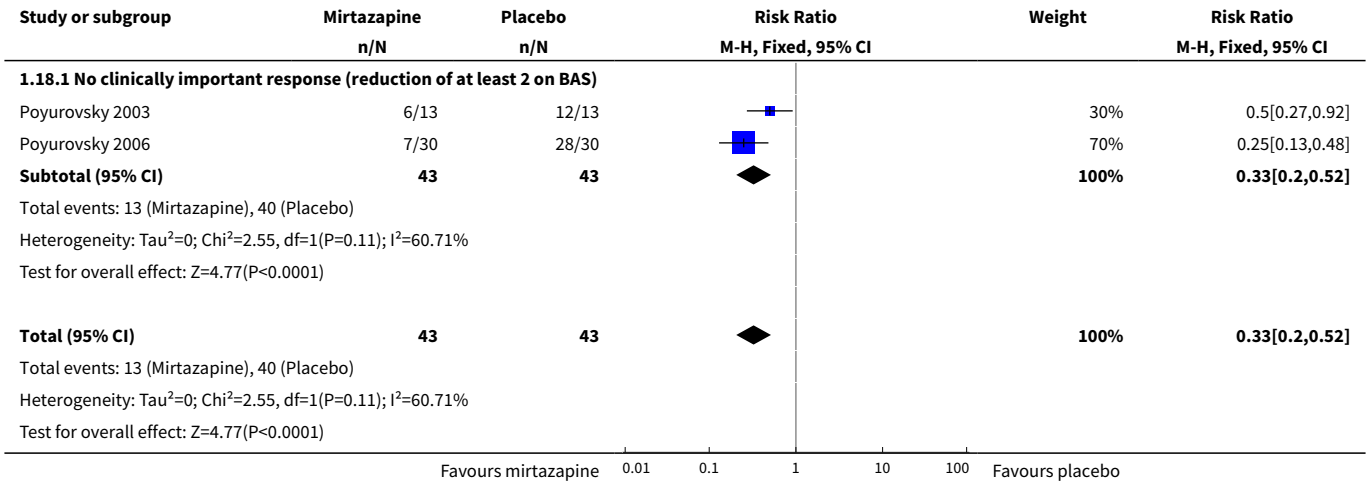
Study or subgroup	Mirtazapine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Abbasi 2010	19/19	19/19		93.05%	1[0.91,1.1]
Berk 2009	0/16	1/17		6.95%	0.35[0.02,8.08]
Total (95% CI)	**35**	**36**		**100%**	**0.96[0.81,1.12]**
Total events: 19 (Mirtazapine), 20 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.21, df=1(P=0.27); I^2=17.67%					
Test for overall effect: Z=0.55(P=0.58)					



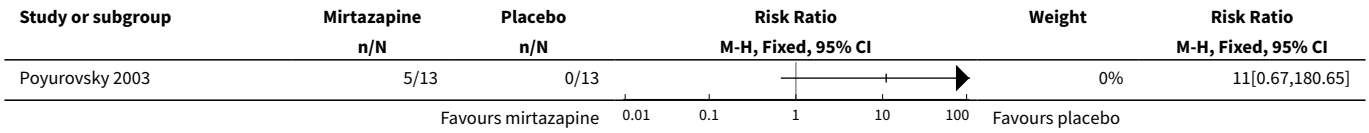
Analysis 1.17. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 17 Adverse events: 1b. General (total number of adverse events) - count data.

Adverse events: 1b. General (total number of adverse events) - count data				
Study	**Number of events (mirtazapine)**	**Number of participants (mirtazapine)**	**Number of events (placebo)**	**Number of participants (placebo)**
Abbasi 2010	33	19	20	19
Berk 2001	14	15	14	15
Berk 2009	0	16	1	17
Caforio 2013	3	14	0	14
Cho 2011	4	11	1	9
Poyurovsky 2003	5	13	1	13
Poyurovsky 2006	29	30	14	30
Terevnikov 2013	12	20	10	19
Zoccali 2004	5	10	0	

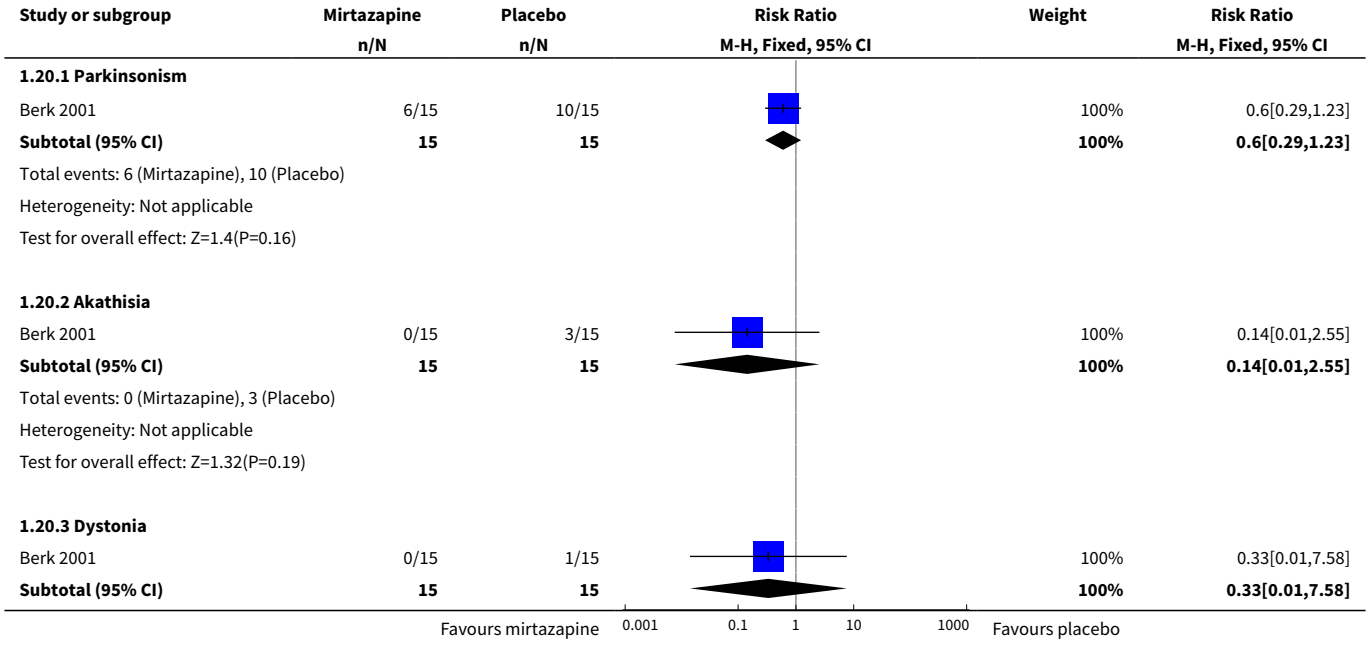
Analysis 1.18. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 18 Adverse effects: 2a. Extrapyramidal: clinically important change akathisia.

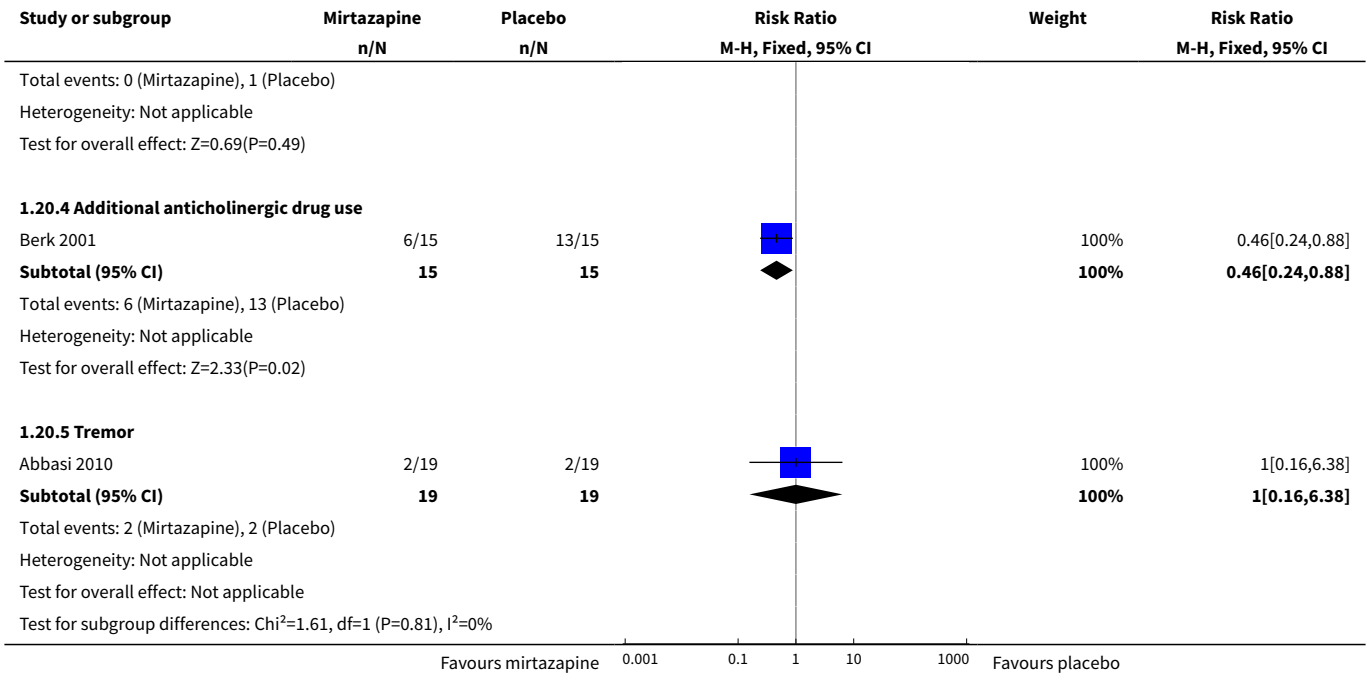


Analysis 1.19. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 19 Adverse effects: 2b. Extrapyramidal - full resolution of akathisia.

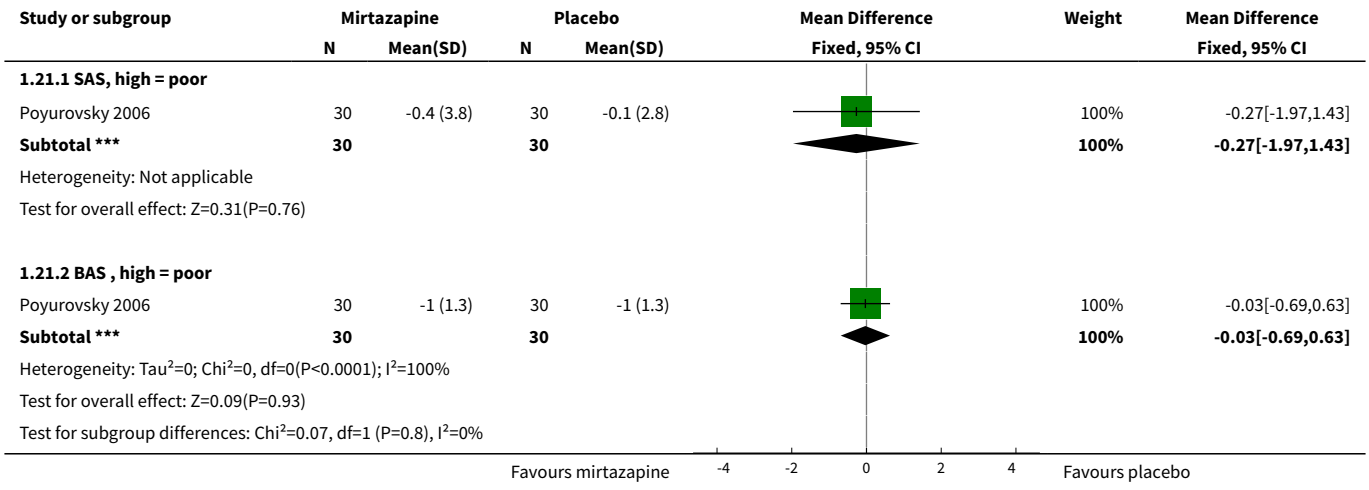


Analysis 1.20. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 20 Adverse effects: 2c. Extrapyramidal - specific effects.





Analysis 1.21. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 21 Adverse effects: 2d. Extrapyramidal: average change score (various scales).



Analysis 1.22. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 22 Adverse effects: 2e. Extrapyramidal: average endpoint score (various scales) - skewed or unusable data.

Adverse effects: 2e. Extrapyramidal: average endpoint score (various scales) - skewed or unusable data

Study	Mirtazapine	Placebo
Abbasi 2010	Mean ESRS scores for placebo group were higher throughout the trial, but the difference was not statistically significant: F = 2.05, df = 1, P = 0.16.	Mean ESRS scores for placebo group were higher throughout the trial, but the difference was not statistically significant: F = 2.05, df = 1, P = 0.16.
Berk 2001	SAS measured at endpoint with no statistical significance found between groups (specifics not reported).	SAS measured at endpoint with no statistical significance found between groups (specifics not reported).
Poyurovsky 2003	SAS (endpoint)	SAS (endpoint)

Adverse effects: 2e. Extrapyramidal: average endpoint score (various scales) - skewed or unusable data

Study	Mirtazapine	Placebo
	Mean = 4.9 SD = 2.4 N = 10 BAS (endpoint) Mean = 2.90 SD = 1.60 N = 10	Mean = 6 SD = 5.5 N = 10 BAS (endpoint) Mean = 6.5 SD = 1.55 N = 10
Terevnikov 2013	SAS (endpoint) Mean = 10.00 SD = 7.60 N = 20	SAS (endpoint) Mean = 9.58 SD = 5.77 N = 19

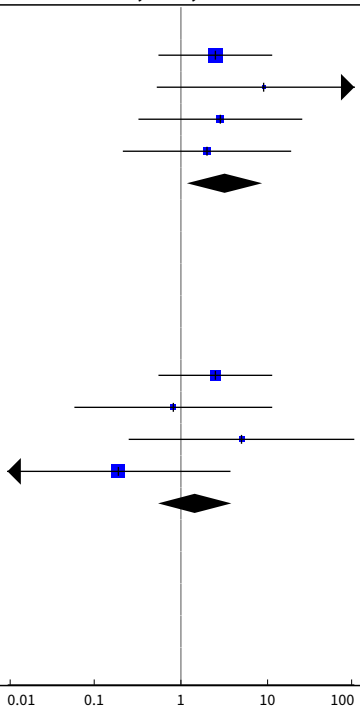
Analysis 1.23. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 23 Adverse effects: 2f. Extrapyramidal: treatment details - skewed data.

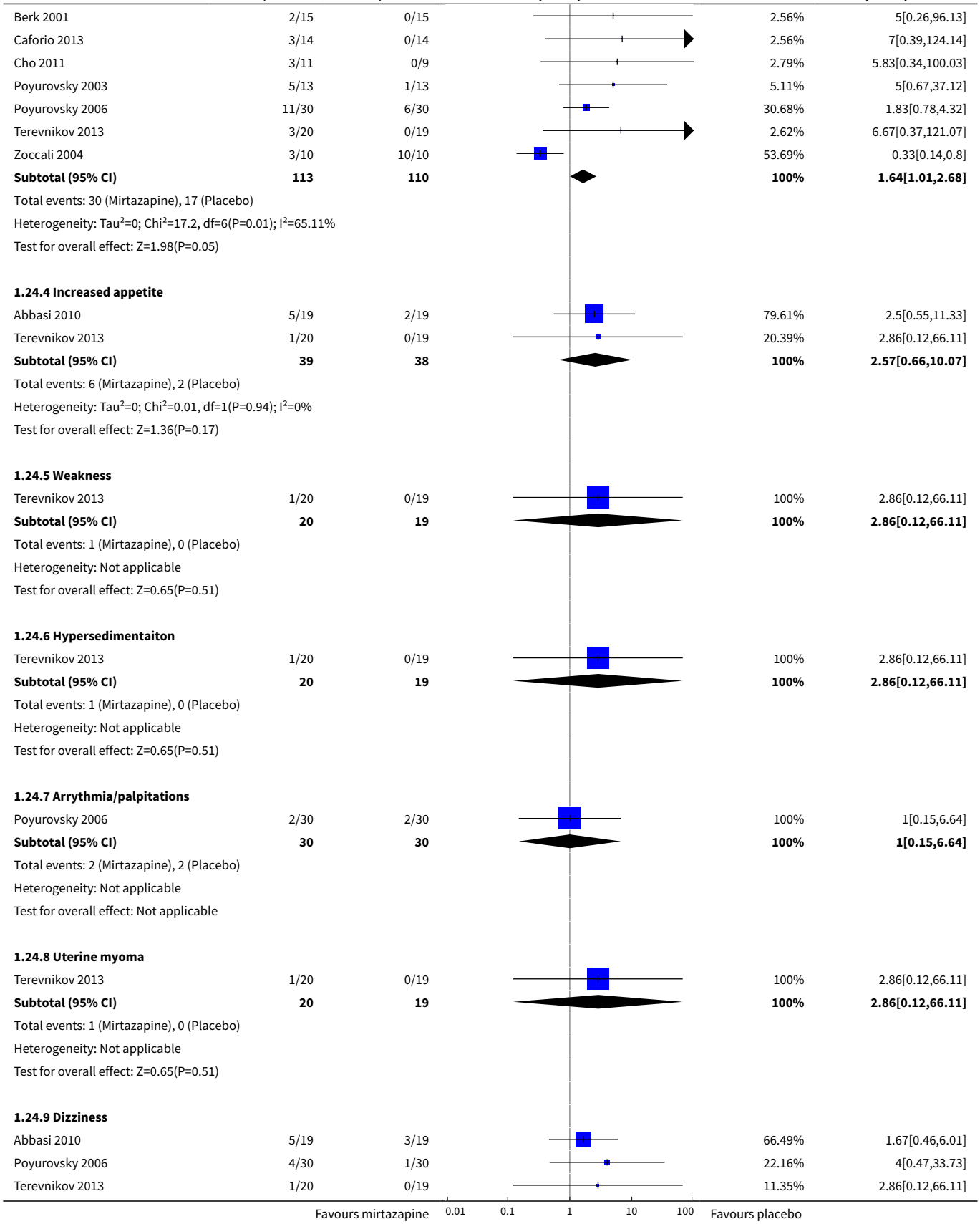
Adverse effects: 2f. Extrapyramidal: treatment details - skewed data

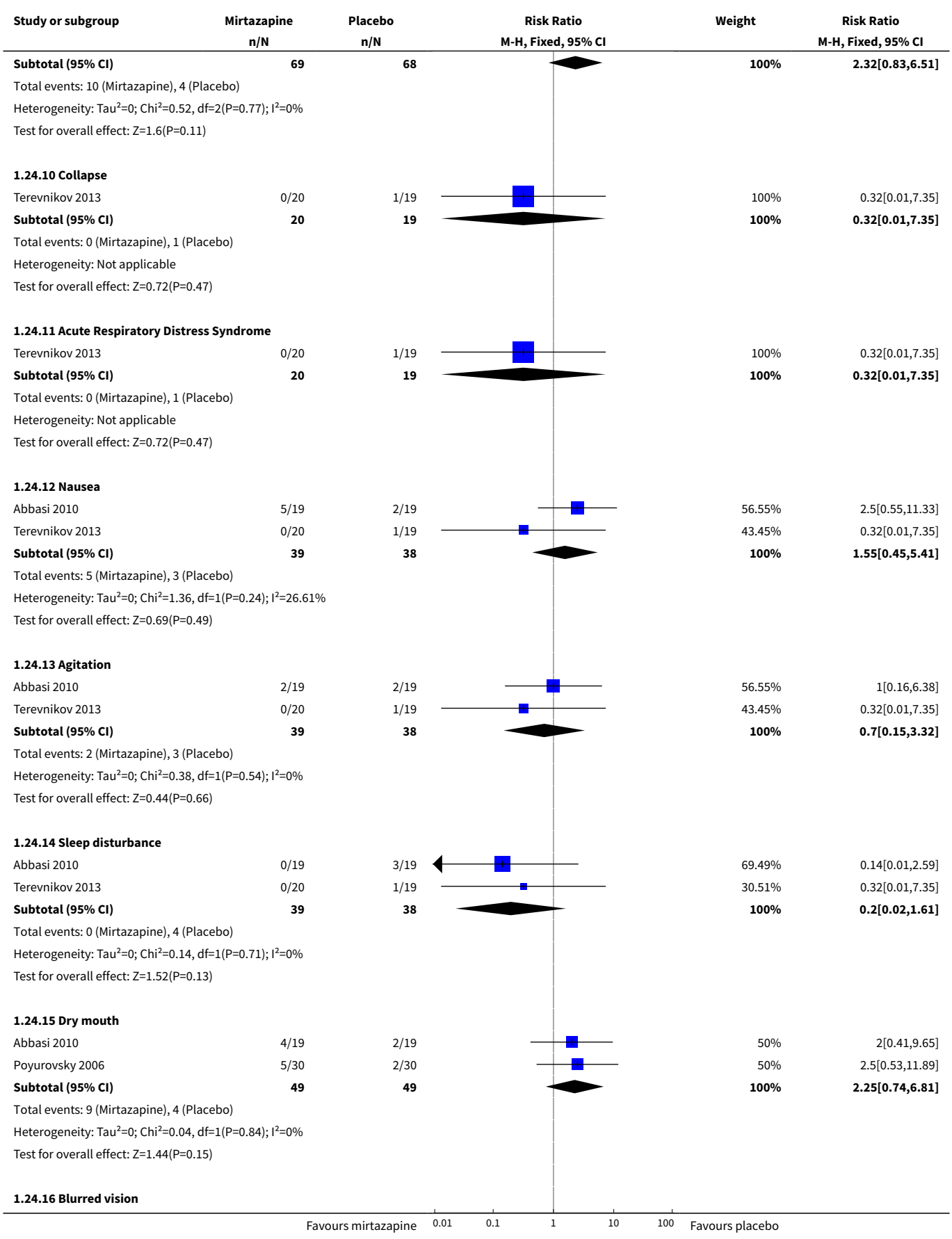
Study	Mirtazapine	Placebo
Abbasi 2010	Biperiden dose (mg) Mean = 104.04 SD = 109.215 N = 20	Biperiden dose (mg) Mean = 125.09 SD = 88.28 N = 20
Abbasi 2010	Cumulative biperiden dose (mg) = 2568 N = 20	Cumulative biperiden dose (mg) = 3108 N = 20
Abbasi 2010	Days of biperiden treatment Mean = 16.38 SD = 17.54 N = 20	Days of biperiden treatment Mean = 21.22 SD = 12.48 N = 20

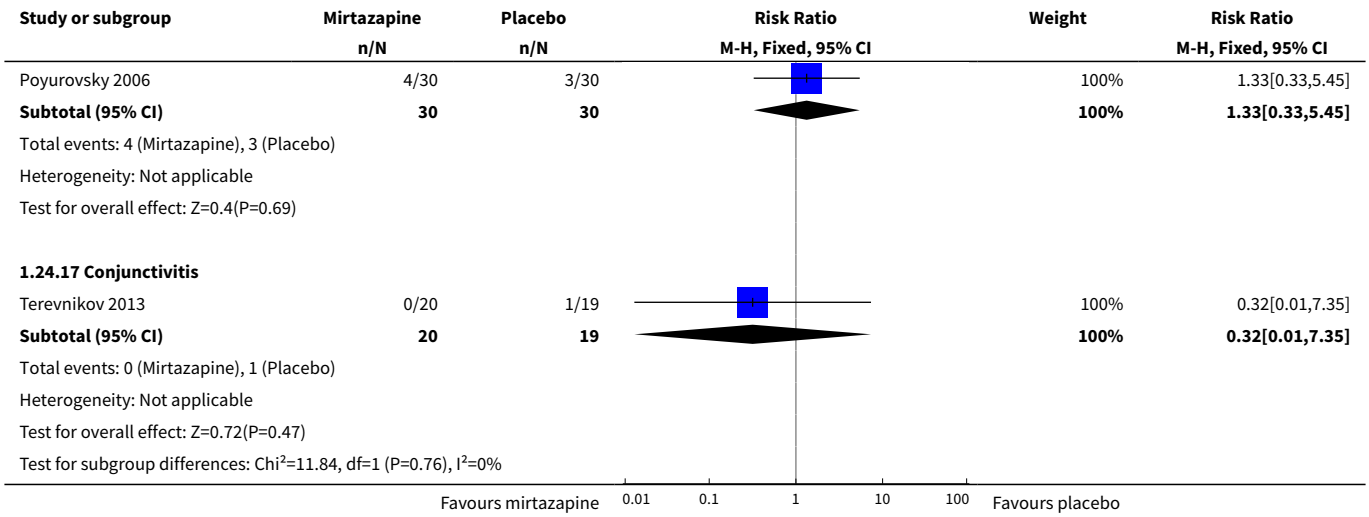
Analysis 1.24. Comparison 1 Mirtazapine adjunct versus placebo adjunct - short term, Outcome 24 Adverse events: 3. Other specific effects.

Study or subgroup	Mirtazapine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.24.1 Weight gain					
Abbasi 2010	5/19	2/19		44.19%	2.5[0.55,11.33]
Berk 2001	4/15	0/15		11.05%	9[0.53,153.79]
Terevnikov 2013	3/20	1/19		22.66%	2.85[0.32,25.07]
Zoccali 2004	2/10	1/10		22.1%	2[0.21,18.69]
Subtotal (95% CI)	**64**	**63**		**100%**	**3.19[1.17,8.65]**
Total events: 14 (Mirtazapine), 4 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.79, df=3(P=0.85); I^2=0%					
Test for overall effect: Z=2.27(P=0.02)					
1.24.2 Headache					
Abbasi 2010	5/19	2/19		32.46%	2.5[0.55,11.33]
Cho 2011	1/11	1/9		17.85%	0.82[0.06,11.33]
Poyurovsky 2006	2/30	0/30		8.12%	5[0.25,99.95]
Terevnikov 2013	0/20	2/19		41.57%	0.19[0.01,3.73]
Subtotal (95% CI)	**80**	**77**		**100%**	**1.44[0.54,3.82]**
Total events: 8 (Mirtazapine), 5 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.13, df=3(P=0.37); I^2=4.13%					
Test for overall effect: Z=0.74(P=0.46)					
1.24.3 Sedation/drowsiness					









ADDITIONAL TABLES

Table 1. Suggested design of future study

Methods	**Allocation:** random (with adequate description of sequence generation and allocation concealment)
Participants	**Blinding:** double (described and tested)
Interventions	**Duration:** 6 months
Outcomes	**Setting:** multiple centres, inpatient and outpatient units
General	**Diagnosis:** schizophrenia (DSM-V / ICD - 10)
	Age: adults
	Size: N > 300
	Sex: both
	Stage of illness: any
	Antipsychotic: any
	Exclusions: current major depressive episode or antidepressant drug use
	1. mirtazapine 30 mg plus regular antipsychotic
	2. placebo plus regular antipsychotic
	Primary outcome: quality of life
	Other outcomes: family/caretaker satisfaction, service utilisation, employment, leaving the study early, mental state (PANSS including subscales), global impression (CGI), adverse events.
	Prospectively registered and free from industry funding.

CGI: Clinical Global Impression
DSM-V: American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders - 5th edition
ICD - 10: International Statistical Classification of Diseases and Related Health Problems 10th Revision

mg: milligram
N: number
PANSS: Positive and Negative Syndrome Scale

CONTRIBUTIONS OF AUTHORS

Luke Alastair Perry - co-ordinator and guarantor of this review, contributed to designing the review, collecting and analysing data, and preparing the manuscript.

Suzanne Martin Stricklin - contributed to designing the review, collecting and analysing data, and preparing the manuscript.

Dhruvesh Manu Ramson - contributed to designing the review, collecting and analysing data, and preparing the manuscript.

DECLARATIONS OF INTEREST

Suzanne Martin Stricklin: none known.

Luke Alastair Perry: none known.

Dhruvesh Manu Ramson: none known.

SOURCES OF SUPPORT

Internal sources

- Monash University, Melbourne, Australia.

  Lead author Luke A Perry and review author Dhruvesh Ramson are students at this university.
- Miami University, Hamilton, USA.

  Employs review author Suzanne Stricklin.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In line with the latest methods for Cochrane Schizophrenia Reviews, we have reworded outcomes from 'Clinically significant response' to 'Clinically important change'. We have clarified the 'Summary of findings' outcomes to include, where possible, clinically meaningful data.

We also included several new outcomes after reviewing the search results. We believe they are of potential interest to consumers of this review and that their inclusion in our analyses would make this review more robust. The addition of these new outcomes did not result in any additional studies being included. These new outcomes are:

1.3 Mental state: specific - depressive symptoms

1.3.1 Clinically important change in depressive symptoms as defined by each of the studies
1.3.2 Average endpoint/change score depressive symptoms scale

4. Cognitive function

4.1 Clinically important change in cognitive function - as defined by each of the studies
4.2 Average endpoint/change score cognitive function tests

6. Service utilisation

6.2 Requires new admission or readmission to hospital (binary)

7. Extrapyramidal side effects

7.2 Extrapyramidal

7.2.1 Clinically important change extrapyramidal side effects - as defined by each of the studies
7.2.2 Average endpoint/change score extrapyramidal side effects scale
7.2.3 Specific extrapyramidal side effects - as defined by each of the studies
7.2.4 Use of medication for extrapyramidal side effects

We amended text within the methods to reflect the latest Cochrane schizophrenia template, these minor changes were changes in wording and layout , for example updating references, not major methodological changes.

We have changed the title from 'Mirtazapine adjunct for schizophrenia' to 'Mirtazapine adjunct for people with schizophrenia'.

INDEX TERMS

Medical Subject Headings (MeSH)

*Schizophrenic Psychology; Antidepressive Agents, Tricyclic [adverse effects] [*therapeutic use]; Antipsychotic Agents [*therapeutic use]; Chemotherapy, Adjuvant; Mianserin [adverse effects] [*analogs & derivatives] [therapeutic use]; Mirtazapine; Patient Dropouts [statistics & numerical data]; Quality of Life; Randomized Controlled Trials as Topic; Schizophrenia [*drug therapy]; Weight Gain

MeSH check words

Humans