Acetylcholinesterase inhibitors for schizophrenia (Review)

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[Intervention Review]

Acetylcholinesterase inhibitors for schizophrenia

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ABSTRACT

Background

Antipsychotic medication remains the mainstay of treatment for schizophrenia and has been in use for a long time. As evidenced by ongoing research and partial effectiveness of the antipsychotics on cognitive and negative symptoms, the search is on for drugs that may improve these domains of functioning for someone suffering from schizophrenia. Acetylcholinesterase inhibitors have long been in use for treating cognitive symptoms of dementia.

Objectives

The aim of the review was to evaluate the clinical effects, safety and cost effectiveness of acetylcholinesterase inhibitors for treating people with schizophrenia

Search methods

We searched the Cochrane Schizophrenia Group's Register (February 2009), and inspected the references of all identified studies for further trials.

Selection criteria

We included all clinical randomised trials comparing acetylcholinesterase inhibitors with antipsychotics or placebo either alone, or in combination, for schizophrenia and schizophrenia-like psychoses.

Data collection and analysis

We extracted data independently. For dichotomous data, we calculated risk ratios (RR) and their 95% confidence intervals (CI) on an intention-to-treat (ITT) basis based on a random-effects model. For continuous data, we calculated mean differences (MD), again based on a random-effects model.

Main results

The acetylcholinesterase inhibitor plus antipsychotic showed benefit over antipsychotic and placebo in the following outcomes.

1. Mental state - PANSS negative symptoms average end point score (2 RCTs, n = 31, MD -1.69 95% CI -2.80 to -0.57), PANSS General Psychopathology average end point score (2 RCTs, n = 31, MD -3.86 95% CI -5.40 to -2.32), and improvement in depressive symptoms showed at least by one short-term study as measured by CDSS scale (data skewed).

2. Cognitive domains - attention, (1 RCT, n = 73, MD 1.20 95% CI 0.14 to 2.26), visual memory (2 RCTs, n = 48 , MD 1.90 95% CI 0.52 to 3.28), verbal memory and language (3 RCTs, n = 42, MD 3.46 95% CI 0.67 to 6.26) and executive functioning (1 RCT, n = 24, MD 17.10 95% CI 0.70 to 33.50).

3. Tolerability - EPSE: AIMS, (1 RCT, n = 35, MD 1.50 95% CI 1.04 to 1.96).

No difference was noted between the two arms in other outcomes. The overall rate of participants leaving studies early was low (13.6 %) and showed no clear difference between the two groups.

Authors' conclusions

The results seem to favour the use of acetylcholinesterase inhibitors in combination with antipsychotics on a few domains of mental state and cognition, but because of the various limitations in the studies as mentioned in the main text, the evidence is weak. This review highlights the need for large, independent, well designed, conducted and reported pragmatic randomised studies.

PLAIN LANGUAGE SUMMARY

Acetylcholinesterase inhibitors versus antipsychotics for schizophrenia either alone or in combination with antipsychotics.

This review compares the effects of acetylcholinesterase inhibitors alone, or in combination with antipsychotics, compared with antipsychotics alone, or placebo plus antipsychotics. Adding acetylcholinesterase inhibitors with antipsychotics may improve the general psychopathology/negative symptomatology/depressive symptoms in people with schizophrenia. Also, the combination may be useful in improving the attention/reaction time and memory areas of cognition. The major limitation of the results was that most of the studies found were short-term studies. Considering the chronic, severe and enduring nature of schizophrenia, one cannot get a true picture unless well designed long-term studies are done. We hope that this review will highlight the need for more studies in this area.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Acetylcholinesterase inhibitors plus antipsychotic for schizophrenia

Patient or population: schizophrenia
Settings:
Intervention: Acetylcholinesterase inhibitors plus antipsychotic

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Acetylcholinesterase inhibitors plus antipsychotic				
Global effect: 1a. Medium-term - Average end point score on various outcomes - CGI-severity (low = favourable) (follow-up: mean 16 weeks)		The mean Global effect: 1a. Medium-term - Average end point score on various outcomes - CGI-severity (low = favourable) in the intervention groups was **0.46 higher** (0.15 lower to 1. 07 higher)		11 (1)	1,2,3,4	
Leaving the study early - Adverse event: Short-term	**Medium risk population**		**RR 1.91** (0.8 to 4.61)	428 (6)		
	12 per 1000	**23 per 1000** (10 to 55)				
Mental state: 1b. Average end point score on various outcomes-PANSS (medium-term) - Medium-term - PANSS negative end point score		The mean Mental state: 1b.Average end point score on various outcomes-PANSS (medium-term) - Medium-term - PANSS negative end point		31 (2)	1,4,5	

(low = favourable)		score (low = favourable) in the intervention groups was **1.69 lower** (2.8 to 0. 57 lower)		
Mental state: 1b.Average end point score on various outcomes-PANSS (medium-term) - Medium term - PANSS general psychopathology end point score (low = favourable)		The mean Mental state: 1b.Average end point score on various outcomes-PANSS (medium term) - Medium term - PANSS general psychopathology end point score (low = favourable) in the intervention groups was **3.86 lower** (5.4 to 2. 32 lower)	31 (2)	1,4
Cognitive function: 3. Short-term - Average end point score on various subscales of WAIS III (high = favourable) - Digit symbol score		The mean Cognitive function: 3. Short-term - Average end point score on various subscales of WAIS III (high = favourable) - Digit symbol score in the intervention groups was **1.2 higher** (0.14 to 2.26 higher)	73 (1)	1,2,4
Cognitive function: 4. Short-term - Average end point score on various subscales of HVLT (high = favourable) - Recognition		The mean Cognitive function: 4. Short term - Average end point score on various subscales of HVLT (high = favourable) - Recognition in the intervention groups was **1. 79 higher** (0.62 to 2.96 higher)	48 (2)	1,4

Adverse event: 11a. Short-term - Average end point score on EPSEs scale (low = favourable) - AIMS		The mean Adverse event: 11a. Short term - Average end point score on EPSEs scale (low = favourable) - AIMS in the intervention groups was **1.5 higher** (1.04 to 1.96 higher)	35 (1)	[1,2,4,6]

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

CI: Confidence interval; RR: Risk ratio;

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

[1] Randomised, but randomisation method was not described.
[2] Results were available from one study only.
[3] It was a direct comparison.
[4] Few patients were involved in the study.
[5] No explanation was provided
[6] No information available on blinding.

BACKGROUND

Description of the condition

Schizophrenia is a severe and enduring mental health problem affecting the world's population, irrespective of geographical boundaries and it has a lifetime prevalence of around one per cent (Jablensky 1992). It is characterised by symptoms that can be divided into three broad categories: 'positive' symptoms, such as hallucinations and delusions; 'negative' symptoms, such as emotional blunting and lack of motivation; and 'cognitive domain' symptoms, such as working memory, attention and information processing deficits (Mueser 2004). The severity of symptoms often causes substantial and long-lasting impairments.

Description of the intervention

The introduction of the first antipsychotic drug chlorpromazine in 1952 led to optimism that pharmaceutical treatments may hold the key for curing schizophrenia; it also paved the way to the discovery of many other psychotropic drugs, however, the concept of 'cure' still remains elusive. As evidenced by ongoing research and partial effectiveness on cognitive and negative symptoms, the search is on for drugs that may improve these domains of functioning for people suffering from schizophrenia. It has been hypothesised that a number of other neurotransmitter systems modulate the function of dopamine pathways in the central nervous system (CNS). The role of muscarinic acetylcholine receptors in modulating dopamine function is now well recognised (Yeomans 1995). Acetylcholine is a prominent neurotransmitter which acts on these receptors; it is formed in cholinergic neurons from two precursors, choline and acetyl coenzyme A, with the help of the enzyme choline acetyltransferase (Stahl 2000). An acetylcholinesterase inhibitor or anti-cholinesterase is a chemical that inhibits the cholinesterase enzyme from breaking down acetylcholine, thus increasing both the level and duration of action of the neurotransmitter acetylcholine.

How the intervention might work

The acetylcholinesterase inhibitors have been studied in cognitive deficit states such as Alzheimer's disease and others, and have been in use for sometime. Those acetylcholinesterase inhibitors which have been used for Alzheimer's disease include donepezil, rivastigmine and galantamine (Birks 2006).

Donepezil is a centrally acting reversible acetylcholinesterase inhibitor. It is known chemically as (±)-2, 3-dihydro-5, 6-dimethoxy2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-inden-1-one hydrochloride. Its main therapeutic use is to increase cortical acetylcholine in the treatment of Alzheimer's disease. It is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished through reversible inhibition of its hydrolysis by acetylcholinesterase thus increasing the concentration of acetylcholine (Wishart 2006). Rivastigmine is a reversible cholinesterase inhibitor and is known chemically as [3-[(1S)-1-dimethylaminoethyl] phenyl] N-ethyl-N-methylcarbamate. It is a cholinesterase inhibitor that inhibits both acetylcholinesterase and butyrylcholinesterase (Wishart 2006). Galantamine is a benzazepine derived from norbelladine. It is chemically known as (4aS,6R,8aS)-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol). It is found in plants such as *galanthus* and other A*maryllidaceae*. It is also a cholinesterase inhibitor and its proposed mechanism of action involves the increase of the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. It also interacts with nicotinic acetylcholine receptors (Wishart 2006). Despite the slight variations in the mode of action of the three acetylcholinesterase inhibitors, there is no evidence of any clinically important differences between them with respect to efficacy, although direct comparisons among these drugs are limited (Birks 2006).

Why it is important to do this review

All of the currently available antipsychotic drugs are effective in improving the positive symptoms of schizophrenia and are presumed to have this effect predominantly by antagonising various dopamine receptors. Antipsychotic medications have greatly improved the prospects for patients with schizophrenia and related disorders, but most individuals continue to experience symptoms throughout their lives; probably no more than one person in five recovers completely (Gelenberg 2004). Therefore, the need arises for novel therapeutic approaches, especially therapies that are effective in multiple domains of schizophrenia, particularly if they have such effects via mechanisms other than the dopamine receptor blockade. The antipsychotic-like actions of muscarinic cholinomimetics such as arecoline were first described in the literature many years ago (Shekhar 2008). Also, it has long been known that acetylcholine plays an important role in cognition and that impaired cholinergic transmission contributes to the cognitive deficits in Alzheimer's disease (Winkler 1998). Acetylcholinesterase inhibitors are a new group of compounds being tried in the treatment of schizophrenia. There are no existing systematic reviews of these groups of compounds and there is an urgent need to critically examine the available evidence to find out whether it is worth considering these medications either as a first line or second line option in the treatment of schizophrenia.

OBJECTIVES

To review the effects of acetylcholinesterase inhibitors for the treatment of schizophrenia and schizophrenia-like psychoses.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all relevant randomised controlled trials. If there was no implied randomisation in relevant trials, we tried to contact the authors to clarify the randomisation method. If there had been no randomisation, we excluded the trials. If there was no substantive difference within primary outcomes (see Types of outcome measures) when these 'implied randomisation' studies were added, then we included them in the final analysis. If there was a substantive difference, we only used clearly randomised trials and described the results of the sensitivity analysis in the text. We excluded quasi-randomised studies, such as those allocating by using alternate days of the week. Where trials were described as 'double-blind', but it was implied that the study was randomised and where the demographic details of each group's participants were similar, we included the trials and undertook a sensitivity analysis to test the presence or absence of these data. Randomised cross-over studies were eligible but only data up to the point of first cross-over because of the instability of the problem behaviours and the likely carry-over effects (Elbourne 2002).

Types of participants

People with schizophrenia or other types of schizophrenia-like psychosis (e.g. schizophreniform and schizoaffective disorders), irrespective of the diagnostic criteria used, age, ethnicity and sex. There is no clear evidence that the schizophrenia-like psychoses are caused by fundamentally different disease processes or require different treatment (Carpenter 1994). If possible, we excluded children, and people with dementing illnesses, depression and primary problems associated with substance misuse.

Where a study described the participant group as suffering from 'serious mental illnesses' and did not give a particular diagnostic grouping, we included these trials assuming that most people suffered from schizophrenia. The exception to this rule was when the majority of those randomised clearly did not have a functional non-affective psychotic illness.

Types of interventions

1. Acetylcholinesterase inhibitors given orally alone.

2. Acetylcholinesterase inhibitors in combination with other drugs.

3. Other intervention, or placebo or no intervention.

Types of outcome measures

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

Primary outcomes

1. Clinical global response

1.1 Global state: No clinically important response as defined by the individual studies - for example, global impression less than much improved or less than 50% reduction on a rating scale - long-term

Secondary outcomes

1. Clinical global response

1.1 Global state: No clinically important response as defined by the individual studies - for example, global impression less than much improved or less than 50% reduction on a rating scale - short-term, medium term
1.2 Relapse (as defined by the individual studies)
1.3 Leaving the studies early (any reason, adverse events, inefficacy of treatment)
1.4 Compliance with medication

2. Mental state (with particular reference to the positive and negative symptoms of schizophrenia)

2.1 No clinically important change in general mental state score
2.2 Average end point general mental state score
2.3 Average change in general mental state score
2.4 No clinically important change in specific symptoms (positive symptoms of schizophrenia, negative symptoms of schizophrenia)
2.5 Average end point specific symptom score
2.6 Average change in specific symptom score

3. General functioning

3.1 No clinically important change in general functioning
3.2 Average end point general functioning score
3.3 Average change in general functioning score

4. Quality of life/satisfaction with treatment

4.1 No clinically important change in general quality of life
4.2 Healthy days
4.3 Average end point general quality of life score
4.4 Average change in general quality of life score

5. Cognitive functioning (as measured by psychometric tests)

5.1 No clinically important change in overall cognitive functioning
5.2 Average end point of overall cognitive functioning score
5.3 Average change of overall cognitive functioning score

6. Service use

6.1 Number of participants hospitalised
6.2 Days in hospital

7. Adverse effect

7.1 Number of participants with at least one adverse effect
7.2 Clinically important specific adverse effects (cardiac effects, death, movement disorders, probating increase and associated effects, sedation, seizures, weight gain, effects on white blood cell count)
7.3 Average end point in specific adverse effect
7.4 Average change in specific adverse effects

8. Economic outcomes

8.1 Direct costs
8.2 Indirect costs

9. Behaviour

9.1 No clinically important change in general behaviour
9.2 Average end point general behaviour score
9.3 Average change in general behaviour scores
9.4 No clinically important change in specific aspects of behaviour
9.5 Average end point specific aspects of behaviour
9.6 Average change in specific aspects of behaviour

10. Engagement with services

Search methods for identification of studies

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

Electronic searches

We searched the Cochrane Schizophrenia Group Trials Register (February 2009) using the phrase:
[(*Acetylcholinesterase* OR *Anseculin* OR *CHF 2060* OR *Donepezil* OR *Eptastigmine* OR *Galantamine* OR *Huperzine A* OR *Icopezil* OR *Ipidacrine* OR *Itopride* OR *Metrifonate* OR *Mimopezil* OR *Phenserine* OR *Physostigmine* OR *Pramiracetam* OR *Quilostigmine* OR *Rivastigmine* OR *S 9977* OR *Tacrine* OR *Velnacrine* OR *Zanepesil* OR *Zifrosilone* in title) and (Acetylcholinesterase* OR Anseculin* OR CHF 2060* OR Donepezil* OR Eptastigmine* OR Galantamine* OR Huperzine A* OR Icopezil* OR Ipidacrine* OR Itopride* OR Metrifonate* OR Mimopezil* OR Phenserine* OR Physostigmine* OR Pramiracetam* OR Quilostigmine* OR Rivastigmine* OR S 9977* OR Tacrine* OR Velnacrine* OR Zanepesil* OR Zifrosilone* in title, abstract, index terms of REFERENCE and intervention in STUDY)]
This register is compiled by systematic searches of major databases, handsearches and conference proceedings (see group module).

Searching other resources

1. Reference lists

We examined the reference lists of all retrieved articles, previous reviews and major text books of schizophrenia for additional trials.

2. Authors of studies

We identified the authors of significant papers from authorship of trials and review articles found in the search. We contacted them, as well as other experts in the field,and asked for information of other studies, published or unpublished, relevant to the review.

3. Pharmaceutical companies

We asked relevant pharmaceutical companies to provide relevant published and unpublished data regarding any studies they may have access to.

Data collection and analysis

Selection of studies

Two review authors (JS and KK) independently inspected citations identified from the search. We identified potentially relevant reports and ordered full papers for reassessment. The same two review authors independently assessed the retrieved articles for inclusion according to the previously defined inclusion criteria. We resolved any disagreement by consensus discussions with the third member (MJ) of the review team. If it was impossible to resolve disagreements, we added these studies to Studies awaiting classification and contacted the authors of the papers for clarification. We reported non-concurrence in trial selection.

Data extraction and management

1. Extraction

Review authors JS and KK independently extracted data from included studies. Again, we discussed any disagreement, documented decisions and, if necessary, contacted the authors of studies

for clarification. With any remaining problems, MJ helped clarify issues and we documented those final decisions.

2. Management

We extracted data onto standard, simple forms.

3. 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 was not written or modified by one of the trialists; (c) the measuring instrument was either (i) a self-report or (ii) completed by an independent rater or relative (not the therapist).

Assessment of risk of bias in included studies

JS and KK worked independently by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to assess trial quality. This new set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

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

We have noted the level of risk of bias in both the text of the review and in the Summary of findings for the main comparison.

Measures of treatment effect

1. Dichotomous data

Where possible, we attempted to convert outcome measures to dichotomous data. This could be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It was generally assumed that if there had been a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (Overall 1962) or the Positive and Negative Syndrome Scale (PANSS) (Kay 1987), this could be considered as a clinically significant response (Leucht 2005). If data based on these thresholds were not available, we used the primary cut-off presented by the original authors.

We calculated the risk ratio (RR) and its 95% confidence interval (CI) based on the random-effects model, as this takes into account any differences between studies even if there is no statistically significant heterogeneity. It has been shown that RR is more intuitive (Boissel 1999) than odds ratios and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). This misinterpretation then leads to an overestimate of the impression of the effect. When the overall results were significant, we calculated the number needed to treat to provide benefit (NNTB) and the number needed to treat to induce harm (NNTH) as the inverse of the risk difference (RD).

2. Continuous data

2.1 Summary statistic

For continuous outcomes, we estimated a mean difference (MD) between groups. MDs were based on the random-effects model as this takes into account any differences between studies even if there is no statistically significant heterogeneity. We did not calculate standardised mean difference (SMD) measures.

2.2 End point versus change data

Since there is no principal statistical reason why end point and change data should measure different effects (Higgins 2011), we used scale end point data which is easier to interpret from a clinical point of view. If end point data were not available, we used change data.

2.3 Skewed data

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

2.4 Data synthesis

When standard errors (SEs) instead of SDs were presented, we converted the former to SDs. If SDs were not reported and could not be calculated from available data, we asked the authors to

supply the data. In the absence of data from authors, we used the mean SD from other studies.

2.5 Multiple doses

We considered that as a study might investigate a number of fixed doses of quetiapine, the combining of continuous data from those different groups would not be possible. In this case, we planned to use the scores from the highest dose group. None of the included studies used quetiapine as an intervention.

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 intraclass correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby P values are spuriously low, CIs unduly narrow and statistical significance overestimated. This can lead to type I error or false positive (Bland 1997; Gulliford 1999). Where clustering was not 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, but we would have adjusted 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 divided binary data as presented in a report by a 'design effect'. We calculated this using the mean number of participants per cluster (m) and the ICC [Design effect = 1+(m-1)*ICC] (Donner 2002). If the ICC was not reported, we assumed it to be 0.1 (Ukoumunne 1999). This assumption may be too high and, should this instance occur, we had planned to see if taking an ICC of 0.01 would make any substantive difference for the primary outcome. If it had not we would have used 0.01 in preference across outcomes. If cluster studies had been appropriately analysed taking into account ICCs and relevant data documented in the report, we planned to synthesise these with other studies 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 schizophrenia, we planned to use only data of the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involved more than two treatment arms, if relevant, we presented the additional treatment arms in additional relevant comparisons. We did not double count data. Where the additional treatment arms were not relevant, we did not reproduce these data.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up, data must lose credibility (Xia 2007). We are forced to make a judgment where this is for the trials likely to be included in this review. Where more than 40% of data were unaccounted for, we did not reproduce these data or use them within the analyses.

2. Binary

In the case where attrition for a binary outcome was between 0% and 40% and outcomes of these people were described, we included these data as reported. Where these data were not clearly described, we presented data on a 'once-randomised-always-analyse' basis, assuming an intention-to-treat (ITT) analysis. We assumed that those lost to follow-up to have a negative outcome, with the exception of the outcome of death. For example, for the outcome of relapse, those who were lost to follow-up all relapsed. We undertook a final sensitivity analysis to test how prone the primary outcomes were to change when 'completer' data only were compared with the ITT analysis using the negative assumption.

3. Continuous

In the case where attrition for a continuous outcome was between 0% and 40% and completer-only data were reported, we have reproduced these.

4. Intention-to-treat analysis (ITT)

We used ITT analysis when available. We anticipated that in some studies, in order to do an ITT analysis, the method of last observation carried forward (LOCF) would be employed within the study report. As with all methods of imputation to deal with missing data, LOCF introduces uncertainty about the reliability of the results. Therefore, we have indicated in the review where we used LOCF data.

Assessment of heterogeneity

1. Clinical heterogeneity

We considered all included studies hoping to use all studies together. We planned that where clear unforeseen issues became apparent that might add obvious clinical heterogeneity, we would note these issues, consider them in analyses and undertake sensitivity analyses for the primary outcome.

2. Statistical

2.1 Visual inspection

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

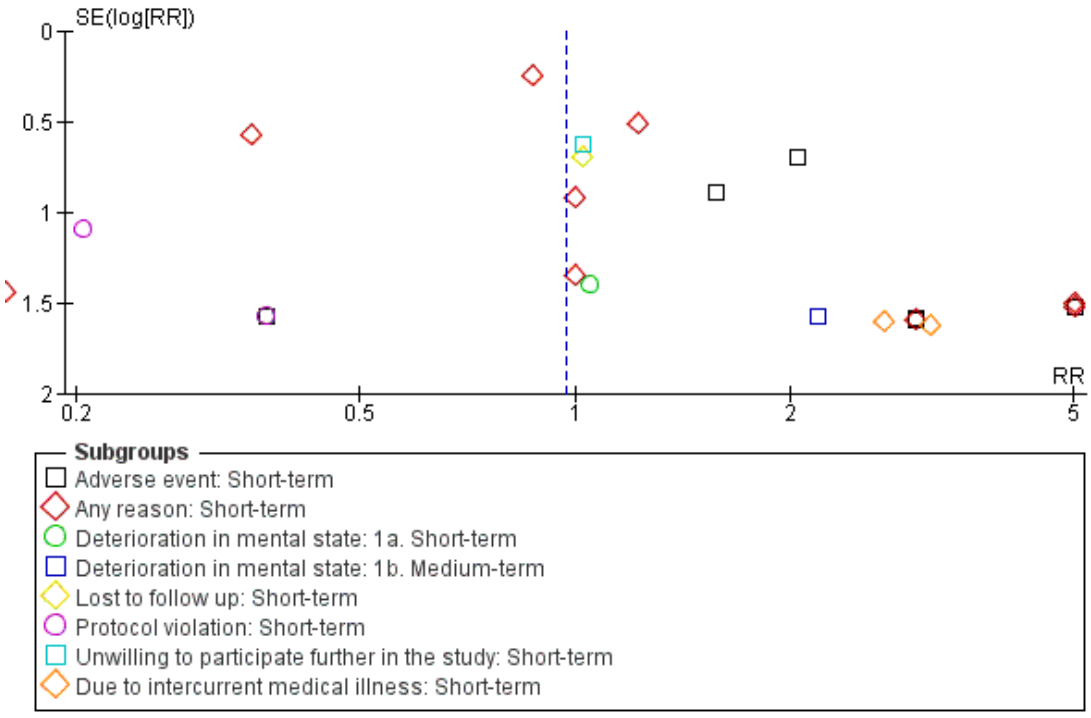
2.2 Employing the I^2 statistic

We investigated heterogeneity between studies by using the I^2 method (Higgins 2011) and the Chi^2 P value. The former provides an estimate of the percentage of variation in observed results thought unlikely to be due to chance. We considered a value equal to, or greater than, 50% indicated heterogeneity and we explored the reason for the heterogeneity. If the inconsistency was high and the clear reasons were found, we presented the data separately.

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 section 10.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) 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 use funnel plots for outcomes where there were ten or fewer studies, or where all studies were of similar sizes. In other cases, where funnel plots were possible (Figure 1) , we sought statistical advice in their interpretation.

Figure 1. Funnel plot of comparison: 1 Acetylcholinesterase inhibitors plus antipsychotics versus placebo plus antipsychotic, Outcome: 1.3 Leaving the study early



Data synthesis

Where possible for both dichotomous and continuous data, we used the random-effects model for data synthesis as this takes into account any differences between studies even if there is no statistically significant heterogeneity. 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 does seem true to us, however, random-effects does put added weight onto smaller studies - those trials that are most vulnerable to bias.

Subgroup analysis and investigation of heterogeneity

If data were clearly heterogeneous, we checked that data were correctly extracted and entered and that we had made no unit of analysis errors. If the high levels of heterogeneity remained, we did not undertake a meta-analysis at this point for if there is considerable variation in results, and particularly if there is inconsistency in the direction of effect, it may be misleading to quote an average value for the intervention effect. We planned to explore heterogeneity. We did not pre-specify any characteristics of studies that may be associated with heterogeneity except quality of trial method. If no clear association could be shown by sorting studies by quality of methods, we performed a random-effects meta-analysis. Should another characteristic of the studies have been highlighted by the investigation of heterogeneity, perhaps some clinical heterogeneity not hitherto predicted but plausible causes of heterogeneity, we planned to discuss these post-hoc reasons and analyse and present the data. However, should the heterogeneity have been substantially unaffected by the use of random-effects meta-analysis and no other reasons for the heterogeneity have been evident, we planned to present the final data without a meta-analysis.

Sensitivity analysis

We planned sensitivity analyses a priori for examining the change in the robustness of the sensitivity to including studies with implied randomisation (see Criteria for considering studies for this review - Types of studies), skewed and non-skewed data, inappropriate comparator doses of drug and different clinical groups - the latter being defined post hoc. If inclusion of studies with implied randomisation made no substantive difference to the primary outcome, we left them in the final analyses. For outcomes with both skewed data and non-skewed data, we investigated the effect of combining all data together and if no substantive difference was noted, then we left the potentially skewed data in the analyses. If necessary, we planned to analyse the effect of including studies with high attrition rates in a sensitivity analysis. We recognise that we may not have considered some clinical causes for heterogeneity that become more obvious after seeing the data. We are fully aware that these are weak investigations and only generate and do not prove hypotheses. We did not anticipate this last sensitivity analysis but wished to leave the potential for investigating any omission we may have made in consideration of studies at the stage of writing the protocol.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

For a substantial description of each of the included, excluded and ongoing studies please refer to Characteristics of included studies; Characteristics of excluded studies and Characteristics of ongoing studies. We included 17 studies which are described below in the section on included studies.

Results of the search

The initial search resulted in over 82 citations, of which we included 44 citations relating to 17 studies. We excluded 17 studies, four studies are awaiting classification and seven studies are ongoing. Two review authors (JS,KK) independently inspected all reports. We resolved any disagreement by discussion, and where there was still doubt, we acquired the full article for further inspection. Once the full articles were obtained, we independently decided whether the studies met the review criteria. If disagreement could not be resolved by discussion, we sought further information and added these trials to the list of those awaiting assessment.

Included studies

We included 17 studies in our review. All these studies were described as double blind but none of them tested for effectiveness of blinding in either the participants or the raters. Only one study (Keefe 2008a) described adequate sequence generation for the process of randomisation.

1.1 Length of trials

Of all the studies included, 14 reported data on short-term follow-up. The duration of three studies was eight weeks and 12 weeks for 11 studies.. The remaining three studies reported data on medium-term follow-up. Two studies lasted 16 weeks (Fagerlund 2007; Tuma 2003) and one study (Sharma 2006) 24 weeks. We did not identify any long-term studies.

1.2 Participants

One study included participants with no clear diagnostic criteria (Dyer 2008). Nine trials included people with a sole diagnosis of schizophrenia using DSM IV (Diagnostic Statistical Manual version 4) (Akhondzadeh 2008; Caroff 2007; Freudenreich 2005; Friedman 2002c; Kim 2005b; Lee 2005; Tugal 2003) and ICD 10 (International Statistical Classification of Diseases and Related Health Problems) (Fagerlund 2007;Tuma 2003). The remaining seven studies included participants with a diagnosis of schizophrenia or schizoaffective disorder as per DSM IV (Buchanan 2008; Chouinard 2007; Keefe 2008a; Kohler 2007; Nahas 2003; Schubert 2006; Sharma 2006). Studies included both male and female participants with the majority of participants being male; two studies included only male participants (Caroff 2007; Nahas 2003), and in another one the sex of the participants was not specified (Tuma 2003). The mean age of study participants ranged from 18 to 60 years.

Three trials did not have definitive exclusion criteria (Kohler 2007; Nahas 2003; Tugal 2003). Thirteen trials excluded people with alcohol and substance misuse, co-morbid medical conditions or patients who were using medication that might have affected their cognition. Fagerlund 2007 excluded participants with treatment-refractory illness.

1.3 Setting

Three of the 17 trials took place in inpatient settings (Chouinard 2007; Kim 2005b; Lee 2005). Six trials had outpatient settings (Dyer 2008; Keefe 2008a; Kohler 2007; Nahas 2003; Tugal 2003; Tuma 2003). Six trials had both inpatients and outpatients (Akhondzadeh 2008; Buchanan 2008; Fagerlund 2007; Freudenreich 2005; Friedman 2002c; Sharma 2006). In the remaining two trials, we could not find any explicit information on the setting (Caroff 2007; Schubert 2006).

1.4 Study size

Keefe 2008a was the largest trial with 245 participants randomised to receive either risperidone or placebo. Buchanan 2008 randomised 86 participants, Nahas 2003 randomised six participants.The rest of the studies had between 10 and 38 patients each.

1.5 Interventions

1.5.1 Acetylcholinesterase inhibitors

The most commonly used acetylcholinesterase inhibitors were donepezil, rivastigmine and galantamine. The dose of donepezil administered by the trialists varied from 5 mg a day up to 10 mg a day, rivastigmine 9 mg to 12 mg and galantamine 16 mg to 24 mg a day.

1.5.2 Comparison group

Most of the studies compared acetylcholinesterase inhibitors plus antipsychotics versus placebo and antipsychotics. Chouinard 2007 compared antipsychotic plus acetylcholinesterase inhibitor with antipsychotic alone. Both conventional and second generation antipsychotics were used along with placebo and acetylcholinesterase inhibitors.

1.6 Outcomes

Our primary outcome was Global state - no clinically important response as defined by the individual studies - long-term. Out of the 17 trials included in our meta-analysis, four of them reported the global change using the Clinical Global Impressions (CGI) scale (Buchanan 2008; Kim 2005b; Lee 2005; Schubert 2006) and Fagerlund 2007 used both CGI and Global Assessment of Functioning (GAF) scales. Buchanan 2008, Lee 2005 and Kim 2005b did not have any usable data on global functioning. For Schubert 2006, data were skewed.

Several different rating scales were used in the trials to report on the mental state. For the purpose of this review, we used the Positive and Negative Syndrome Scale (PANNS), Hamilton Depression Rating Scale (HAM-D), Calgary Depression Severity Scale (CDSS) and Brief Psychiatric Rating Scale (BPRS). Seven studies (Buchanan 2008; Caroff 2007; Freudenreich 2005; Friedman 2002c; Keefe 2008a; Kim 2005b; Kohler 2007) did not have any usable data on the mental state. The rest of the trials used either the PANSS, HAM-D, CDSS or the BPRS scale to measure their outcome. Wherever possible, we used the binary data from these measures, but the validity of dichotomising these measures, although widely accepted, is nevertheless unclear.

Adverse events are an important outcome measure from any trial. We were able to pool data on the adverse events from all the trials except four (Caroff 2007; Kohler 2007; Nahas 2003; Tugal 2003) which did not have any usable data for adverse events. There were no deaths reported in any of the studies. All but three trials (Fagerlund 2007; Nahas 2003; Tugal 2003) provided usable data on the number of participants leaving the study early. Quality of life data were not available in any of the trials.

Cognitive functioning was assessed using a battery of neuropsychological scales and subscales. We were able to pool data from the nine studies (Buchanan 2008; Dyer 2008; Friedman 2002c; Kim 2005b; Lee 2005; Nahas 2003; Schubert 2006; Tugal 2003; Tuma 2003) but the remaining studies did not have any usable data on this parameter.

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

1.6.1 Global state scales

1.6.1.1 Clinical Global Impression Scale (CGI) (Guy 1976)

This is used to assess both severity of illness and clinical improvement, by comparing the conditions of the person standardised against other people with the same diagnosis. A seven point scoring system is usually used with low scores showing decreased severity and/or overall improvement.

1.6.1.2 Global Assessment of Functioning (GAF) (DSM-IV-TR)

The GAF scale is a numeric scale (zero through 100) used by mental health clinicians and physicians to rate subjectively the social, occupational, and psychological functioning of adults. High scores mean good functioning.

1.6.2 Mental state scales

1.6.2.1 Positive and Negative Syndrome Scale (PANSS) (Kay 1986a)

This schizophrenia scale has 30 items, each of which can be defined on a seven-point scoring system varying from one (absent) to seven (extreme). It can be divided into three subscales for measuring the severity of general psychopathology, positive symptoms (PANSS-P) and negative symptoms (PANSS-N). A low score indicates lesser severity.

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

This is used to assess the severity of abnormal mental state. The original scale has 16 items, but a revised 18-item scale is commonly used. Each item is defined on a seven-point scale varying from 'not present' to 'extremely severe', scoring from zero to six or one to seven. Scores can range from zero to 126 with high scores indicating more severe symptoms.

1.6.2.3 Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1989)

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

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

This four-point scale gives a global rating of the following positive symptoms: hallucination, delusion, bizarre attitudes and positive formal thought disorder.

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

The HAM-D is a multiple choice questionnaire that clinicians may use to rate the severity of a patient's major depression. A lower score indicates less severity.

The questionnaire rates the severity of symptoms observed in depression such as low mood, insomnia, agitation, anxiety and weight loss. The questionnaire is presently one of the most commonly used scales for rating depression in medical research.

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

A nine-item scale specifically developed for assessment of depression in patients with schizophrenia.

All items are rated on a four-point scale: zero = absent; 1 = mild; 2 =moderate; 3 = severe. A lower score indicates less severity.

1.6.3 Quality of Life scales

1.6.3.1 Quality of Life Scale (QLS) (Carpenter 1994)

The QLS is a 21-item scale rated from a semi-structured interview providing information on symptoms and functioning during the preceding four weeks. It is intended to be administered by a trained clinician and requires about 45 minutes to complete. Each item is rated on a seven-point scale and , in all but two cases, requires a judgment by the clinician/interviewer. Each item is composed of three parts: (1) a brief descriptive statement to focus the interviewer on the judgment to be made; (2) a set of suggested probes; (3) the seven-point scale with descriptive anchors for every other point. The specific descriptions vary among items, but the high end of the scales (scores of five and six) reflects normal or unimpaired functioning and the low end of the scales (scores of zero and one) reflects severe impairment of the function in question. The interviewer is instructed to probe around each item until he or she has an adequate basis for making the required judgment, and is encouraged to go beyond the suggested probes with questions tailored for the individual patient. The experience of both the patient and the interviewer is thus similar to a careful clinical interview.

1.6.4 Service use

Described as the number of patients rehospitalised during the trial.

1.6.5 Adverse effects scales

1.6.5.1 Abnormal Involuntary Movement Scale (AIMS) (Guy 1976)

This has been used to assess tardive dyskinesia, a long-term, drug-induced movement disorder and short-term movement disorders such as tremor.

1.6.5.2 Barnes Akathisia Scale (BAS) (Barnes 1989)

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

1.6.5.3 Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard 1993)

This is a questionnaire relating to parkinsonian symptoms (nine items), a physician's examination for Parkinsonism and dyskinetic movements (eight items), and a clinical global impression of tardive dyskinesia. High scores indicate severe levels of movement disorder.

1.6.5.4 Simpson Angus Scale (SAS) (Simpson 1970)

This is a 10-item scale, with a scoring system of zero to four for each item, measures drug-induced Parkinsonism, a short-term drug-induced movement disorder. A low score indicates low levels of Parkinsonism.

1.6.6 Other adverse effects

Other adverse effects were reported as continuous variables for QTc prolongation (ms), cholesterol level (mg/dL), glucose level (mg/dL), prolactin level (ng/dL) and weight (kg). Other adverse events were reported in a dichotomous manner in terms of the number of people with a given effect.

1.6.7 Cognitive functions

1.6.7.1 Wisconsin Card Sorting Test Scale (WCST) (Heaton 1993)

The WCST is a neuropsychological test of executive functions. It taps a variety of executive abilities, including maintenance of task set, flexibility in response to feedback or changing circumstances, and perseverative tendencies. The test can be administered to those 6.5 years to 89 years of age and takes 20 to 30 minutes to complete. It is widely used by psychiatrists and clinical psychologists to test patients with brain injuries, neurodegenerative diseases and mental illnesses such as schizophrenia. For a 128 card trial, the typical number of perseverative errors for "well educated young adults" is 11. With reasonable executive control, scoring tends to improve as the test progresses. So for a 64 card trial, an equivalent score would be about six or seven. Categories completed can range from zero, for someone who has no idea what to do, to a maximum of six (when the test is stopped).

1.6.7.2 Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) (Wechsler 1997a)

This is a neuropsychological test in which different facets of neurological cognitive functioning are tapped by the various subtests. It contains of a total of 14 subtests. It provides two sets of summary scores. First, in addition to the global full scale, the WAIS subtests can be organised in the traditional manner into the verbal scale and performance scale. Average Score = 10 in each subtest. Scores below eight show significant deficits (Kraus 2007).

1.6.7.3 Wechsler Memory scale-Third Edition (WMS-III) (Wechsler 1997b)

This is a neuropsychological test to assess learning and memory functioning of individuals aged 16 to 89 years. It has six primary subtests and five optional subtests. It has three main scores - Immediate memory, Delayed memory and Working memory. Scores range from low to very superior. Low scores indicate poor results. When used in conjunction with the WAIS-III, meaningful comparisons between intellectual ability and memory functions can be made.

1.6.7.4 Hopkins Verbal learning Test (HVLT) (Brandt 1991)

This is a brief assessment of verbal learning and memory for individuals aged 16 years and older. The test consists of three trials of free recall of 12 items, semantically categorised list, and followed by yes/no recognition. The maximum score possible for the HVLT total score is 36 and for the HVLT recognition score is 12. A high score means good verbal learning and memory.

1.6.7.5 Verbal Fluency Test (VFT) (Miller 1984)

The VFT is a neuropsychological test to evaluate executive functions and language. In this test, participants have to say as many words as possible from a category within a given time - usually 60 seconds. This category can be semantic, such as animals or fruits or phonemic, such as words. The most common performance measure is the total number of words.

1.6.7.6 Brief Visual Memory Test (BVMT) (Benedict 1996)

The BVMT is a neuropsychological test that is designed for use as a criterion measure of visuospatial memory within a large battery of neuropsychological tests, as a screening measure within a brief neuropsychological battery, and as a repeat measure to document changes in neurocognitive skills over time. It has been standardised and is commonly used in adults between the ages of 18 and 79. It includes six equivalent alternate forms, its administration is limited to an immediate and 25-minute delayed free recall trial. This is a test to measure selective attention, cognitive flexibility and processing speed, and it is used as a tool in the evaluation of executive functions.

1.6.7.7 The Stroop test (Stroop 1935)

The Stroop effect is a demonstration of reaction time of a task. When the name of a colour (e.g., "blue," "green," or "red") is printed in a colour not denoted by the name (e.g., the word "red" printed in blue ink instead of red ink), naming the colour of the word takes longer and is more prone to errors than when the colour of the ink matches the name of the colour. An increased interference effect is found in disorders such as brain damage, dementias and other neurodegenerative diseases, attention-deficit hyperactivity disorder, or a variety of mental disorders such as schizophrenia, addictions, and depression.

1.6.7.8 Trail Making Test (TMT) (Tombaugh 2004)

The TMT is one of the most popular neuropsychological tests and is included in most test batteries. It provides information on visual search, scanning, speed of processing, mental flexibility, and executive functions. The TMT consists of two parts. TMT-A requires an individual to draw lines sequentially connecting 25 encircled numbers distributed on a sheet of paper. Task requirements are similar for TMT-B except the person must alternate between numbers and letters (e.g., 1, A, 2, B, 3, C, etc.). The score on each part represents the amount of time required to complete the task.

1.6.7.9 Continuous Performance Test (CPT) (Conners 2000)

The CPT is a psychological test which measures a person's sustained and selective attention and impulsivity. While scoring varies from test to test, there are four main scores that are used.
Correct Detection: This indicates the number of times the client responded to the target stimulus. Higher rates of correct detections indicate better attentional capacity.
Reaction time: This measures the amount of time between the presentation of the stimulus and the client's response.
Omission errors: This indicates the number of times the target was presented, but the client did not respond/click the mouse. High omission rates indicate that the person is either not paying attention to stimuli or has a sluggish response. Commission errors: This score indicates the number of times the client responded but no target was presented.
A fast reaction time and high commission error rate points to difficulties with impulsivity. A slow reaction time with high commission and omission errors, indicates inattention in general. These client's scores are compared with the normative scores for the age, group and gender of the person being tested.

1.6.7.10 Grooved Pegboard Test (Klove 1964)
The Grooved Pegboard is a manipulative dexterity test consisting of 25 holes with randomly positioned slots. This test requires more complex visual-motor coordination than most pegboards. Scores represent time in seconds required to complete the test with each hand, with high scores reflecting lower levels of performance.

1.6.7.11 Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph 1998; Wilk 2002)
The RBANS is a screening battery designed for five cognitive domains: attention and processing speed, expressive language, visual-spatial and constructional abilities, and immediate and delayed memory. The entire battery takes less than 30 minutes to administer. The score is measured as total score and five specific cognitive ability index scores.

1.6.7.12 Korean version-Mini Mental State Examination (K-MMSE) (Kang 1997)
The Mini Mental State Examination (MMSE) was developed to evaluate a person's orientation, memory, attention, calculation, and visuospatial and language abilities. Kang et al. conducted a study to examine the validity of newly constructed K-MMSE. It contains 30 questions, and the possible scores range from zero to 30.

1.6.7.13 Rey-Osterrieth Complex Figure Test (ROCFT) (Meyers 1995)
The ROCF is a neuropsychological test in which examinees are asked to reproduce a complicated line drawing, first by copying and then from memory. The test permits the evaluation of different functions, such as visuospatial abilities, memory, attention, planning, and working memory (executive functions). The RCFT provides an objective and standardized approach to scoring drawings based on the widely used 36-point scoring system. The same scoring criteria apply to all three drawing trials. Each of the 18 scoring units is scored based on accuracy and placement criteria. Unit scores range from two (accurately drawn, correctly placed) to zero (inaccurately drawn, incorrectly placed, unrecognisable, omitted). Higher scores mean better performance.

Excluded studies

We excluded 17 studies from the review. Seven trials were not randomised (Edelstein 1981; El-Yousef 1973; Ingram 1983; Janowsky 1972; Moore 1980; Risch 1981; Risch 2001). Three trials included participants who were not ill (Davis 1981; Kristiansen 2001; Pesco-Koplowitz 2000c). Two trials included participants with the main diagnosis of tardive dyskinesia (Lieberman 1988; Tamminga 1977); one trial included participants with Parkinson disease (Okereke 2002); and another had the main diagnosis as major depression or bipolar affective disorder (NCT00566735). We excluded one of the trials as it was conducted on elderly people with a possible diagnosis of dementia (Mazeh 2006) and an other trial as it was conducted on patients receiving electroconvulsive therapy (ECT) (Ophir 2004). One trial did not have any usable data (Stryjer 2004a). For further details see Characteristics of excluded studies.

Awaiting classification

Four studies are awaiting classification (Fleming 2003; Hussain 2003; Kelleher 2008; Modestin 1973). We contacted the authors for more information and the reply is awaited. For further details see Characteristics of studies awaiting classification.

Ongoing studies

Seven randomised trials (Ball 2005; Evins 2006; Gaskins 2007; George 2007; Glenthoj 2005; Johnson 2004; Nachshoni 2007) are ongoing. For further details see Characteristics of ongoing studies.

Risk of bias in included studies

Ten out of the 17 trials that were included in our review were funded by pharmaceutical companies or had some affiliation (Buchanan 2008; Caroff 2007; Chouinard 2007; Dyer 2008; Fagerlund 2007; Freudenreich 2005; Friedman 2002c; Keefe 2008a; Nahas 2003; Tugal 2003). Seven trials did not appear to have any affliation with pharmaceutical companies (Akhondzadeh 2008; Kim 2005b; Kohler 2007; Lee 2005; Schubert 2006; Sharma 2006; Tuma 2003) We collected as much information as possible and they have been enlisted in the following paragraphs.

Allocation

All included studies were said to be randomised. However, 15 of the 17 included studies did not explicitly describe the method by which this was done. Keefe 2008a used a computer-generated schedule, patients were stratified before randomisation and within each stratum, patients were randomised 1:1 to the experimental and control group. Dyer 2008 used concealed allocation with a 1:1 ratio, in blocks of four. The concealment procedure was not explained. None of the other studies reported allocation concealment. The concealment of allocation has repeatedly been shown to be of key importance in excluding selection biases (Jüni 2001).

Blinding

All 17 included studies were described as double blind however none of the studies reported any test of blinding. Three studies (Akhondzadeh 2008; Freudenreich 2005; Schubert 2006) used identical tablets/capsules to make blinding more robust. Buchanan 2008 used equal number of matched tablets. Blinding is essential for minimising observation bias and we were expecting that testing for blinding would have been a priority.

Incomplete outcome data

Friedman 2002c used ITT analysis. Four studies (Dyer 2008; Lee 2005; Schubert 2006; Sharma 2006) used the LOCF method to account for their loss to follow-up. Keefe 2008a used ITT for the efficacy data and LOCF for the safety data. Akhondzadeh 2008, Nahas 2003 and Tugal 2003 had no drop outs in the duration of their 12-week studies. There is no information about the losses to follow-up in seven studies (Buchanan 2008; Caroff 2007; Chouinard 2007; Fagerlund 2007; Kim 2005b; Kohler 2007; Tuma 2003). None of the trials made attempts to validate assumptions by following up people who did drop out early.The reasons for loss to follow-up were reasonably well reported and we have recorded these in the outcomes.

Selective reporting

Seven of the 17 included studies (Akhondzadeh 2008; Buchanan 2008; Chouinard 2007; Fagerlund 2007; Friedman 2002c; Schubert 2006; Tuma 2003) reported all of the outcomes mentioned in their methods. Of the remaining eleven studies, outcomes reported were incomplete or lacking in useable information. Of the seven studies which did report the outcomes, protocols were unavailable and hence we were unaware if the trialists reported all outcomes they intended to use. Most of the trials reported at least one measure for mental state and they all had reported adverse effects even though some of them were incomplete.

Other potential sources of bias

No study was clearly free of other potential sources of bias, with the risk of bias being unclear in eight of them. Nine studies were linked with pharmaceutical companies, either sponsored or the authors had some affiliation with the pharmaceutical companies (Buchanan 2008; Caroff 2007; Chouinard 2007; Dyer 2008; Fagerlund 2007; Freudenreich 2005; Friedman 2002c; Nahas 2003; Tugal 2003). There is evidence that industry-sponsored trials tend to be beneficial towards the intervention that they promote (Heres 2006). Poor quality reporting led to a lot of data that were not useable. Findings which were presented as graphs, percentiles or reported as inexact P values were of little use to us as reviewers. Some studies failed to provide SDs when reporting mean changes. We sought additional data from the first authors of relevant trials when required, however, none of the authors responded.

Effects of interventions

See: **Summary of findings for the main comparison**

The initial search resulted in over 82 citations. We were only able to include 17 of these studies from which usable data could be extracted. We used information obtained from drug companies that was available to the Cochrane Schizophrenia Group regarding data from unpublished trials.

Comparison 1: Acetylcholinesterase inhibitor(s) plus antipsychotics versus placebo plus antipsychotic

Sixteen studies with a total of 659 participants fell into this comparison

1.1. Global effects: various outcome

Fagerlund 2007 reported average end point, medium-term CGI - severity score which indicates global severity of the illness. There were no differences between the acetylcholinesterase plus antipsychotic and placebo plus antipsychotic groups on this measure at 16 weeks (1 RCT, n = 11, mean difference (MD) 0.46 95% confidence interval (CI) -0.15 to 1.07). The same study also reported on CGI - improvement average end point score which indicates global improvement, there were no differences on this measure (1 RCT, n = 11, MD 0.57 95% CI -0.50 to 1.64). Schubert 2006 reported average change short-term CGI score but the data were skewed. The very small differences were not stated to be significant.

1.2 Leaving the study early

The overall rate of participants leaving studies early was low (13.6 %) and showed no clear difference between groups. Nevertheless, this finding was based mainly on short-term trials and only from one medium-term trial limiting interpretation. There were no significant differences in the number of participants leaving the studies early due to - any reason (9 RCTs, n = 513, risk ratio (RR)

0.89 95% CI 0.61 to 1.28), adverse events (6 RCTs, n = 428, RR 1.94 95% CI 0.83 to 4.49), intercurrent illness (2 RCTs, n = 122, RR 2.91 95% CI 0.31 to 27.06), mental state deterioration (2 RCTs, n = 103, RR 0.65 95% CI 0.09 to 4.68), lost to follow-up (1 RCTs, n = 245, RR 1.02 95% CI 0.26 to 4.01), protocol violation (2 RCTs, n = 262, RR 0.24, 95% CI 0.04 to 1.38) and to unwillingness to participate (1 RCT, n = 245, RR 1.02, 95% CI 0.30 to 3.45). There was no significant difference in the number of participants leaving the study early in one medium-term study (Tuma 2003) due to deterioration in mental state (1 RCT, n = 17, RR 2.18 95% CI 0.10 to 46.92).

The attrition rates from all these studies were variable ranging from none in (Akhondzadeh 2008) to over 19% in (Keefe 2008a). As to why this variation occurs is hard to estimate, some of it could be due to the study design and some due to the individual drug administered.

1.3 Mental state

1.3.1 Mental state: average end point score on PANSS-short-term

1.3.1.1 PANSS Total: average total end point score

Two short-term studies (Nahas 2003; Tugal 2003) reported no significant differences (2 RCTs, n = 18, MD 3.29 95% CI -8.82 to 15.40).

1.3.1.2 PANSS Positive symptoms: average end point score

Tugal 2003 reported no significant difference (1 RCT, n = 12, MD 1.50 95% CI -4.44. to 7.44).

1.3.1.3 PANSS Negative symptoms: average end point score

Tugal 2003 reported no significant difference (1 RCT, n = 12, MD 3.50 95% CI -3.66 to 10.66).

1.3.1.4 PANSS general psychopathology: average end point score

Tugal 2003 reported no significant difference (1 RCT, n = 12, MD 1.80 95% CI -4.81 to 8.41).

1.3.2 Mental state: average end point score on PANSS-medium-term

1.3.2.1 PANSS Total: average end point score

Fagerlund 2007; Sharma 2006 reported no significant difference (2 RCTs, n = 31, MD -4.32 95% CI -11.56 to 2.92).

1.3.2.2 PANSS Positive symptoms: average end point score

Fagerlund 2007; Sharma 2006 reported no significant difference (2 RCTs, n = 31, MD 0.65 95% CI -0.12 to 1.43).

1.3.2.3 PANSS Negative symptoms: average end point score

Fagerlund 2007; Sharma 2006 favoured acetylcholinesterase inhibitor plus antipsychotic over placebo plus antipsychotic (2 RCTs, n = 31, MD -1.69 95% CI -2.80 to - 0.57).

1.3.2.4 PANSS General psychopathology: average end point score

Fagerlund 2007; Sharma 2006 favoured acetylcholinesterase inhibitor plus antipsychotic over placebo plus antipsychotic (2 RCTs, n = 31, MD -3.86 95% CI -5.40 to - 2.32).

1.3.3 Mental state: average end point score on HAM-D - short-term

Akhondzadeh 2008 reported no significant difference (1 RCT, n = 30, MD -0.60 95% CI -1.82 to 0.62).

1.3.4 Mental state: average end point score on SANS - short-term

Dyer 2008 reported no significant difference (1 RCT, n = 20, MD -5.00 95% CI -21.33 to 11.33).

1.3.5 Mental state: average change score on CDSS

1.3.5.1 CDSS: average end point score - short-term

Two studies (Dyer 2008; Tugal 2003) reported average change, short-term CDSS score. The data were skewed and are presented in tabular form. There were no significant differences as reported by one of the two studies, whereas Dyer 2008 reported benefit of acetylcholinesterase inhibitor plus antipsychotic over placebo and antipsychotic.

1.3.5.2 CDSS: average end point score

One medium-term study (Fagerlund 2007) reported benefit of acetylcholinesterase inhibitor plus antipsychotic over placebo and antipsychotic. But the baseline scores of most of the participants in the acetylcholinesterase inhibitor group were already low compared with the placebo group. Also, the number of participants in both arms were different; there were more in the intervention arm compared with the placebo group. The result therefore has to be read with caution. The data were skewed and are presented in tabular form.

1.3.6 Mental state: average change score on PANSS

One short-term study (Schubert 2006) reported data on PANSS total, positive and negative symptoms average change score but

these were skewed. The very small differences were not stated to be statistically significant.

1.4 General functioning

1.4.1 GAF: average end point score

One medium-term study (Fagerlund 2007) had data on this outcome and reported no difference (1 RCT, n = 11, MD 4.60 95% CI -5.88 to 15.08).

1.5 Quality of life

There were no data available on quality of life from any of the studies.

1.6 Cognitive functioning

1.6.1 Cognitive functioning: average end point score on K-MMSE

Two short-term studies (Kim 2005b; Lee 2005) reported an average end point KMMSE score which indicated cognitive improvement. We found no differences between acetylcholinesterase inhibitors and conventional antipsychotics versus placebo and conventional antipsychotics (2 RCTs, n = 48, MD 1.29 95% CI -0.18 to 2.77).

1.6.2 Cognitive functioning: average end point score on various subscales of WMS III which indicate learning and memory

1.6.2.1 Digit span forward

Two short-term studies (Lee 2005; Tugal 2003) reported data on digit span forward scale which indicated superiority of placebo and antipsychotics over acetylcholinesterase inhibitors and antipsychotics (2 RCTs, n = 36, MD -0.89 95% CI -1.68 to -0.10).

1.6.2.2 Digit span backward

Two short-term studies (Lee 2005; Tugal 2003) reported data on digit span backward which indicated superiority of the placebo plus antipsychotics arm compared to acetylcholinesterase inhibitors plus antipsychotic arm (2 RCTs, n = 36, MD -0.69 95% CI -1.35 to -0.02).

1.6.2.3 Figural memory test

One short-term study (Tugal 2003) reported average end point score. The study reported no difference between acetylcholinesterase inhibitors plus antipsychotics and placebo and antipsychotics (1 RCT, n = 12, MD -1.30 95% CI -0.74 to 3.34).

1.6.2.4 Visual reproduction 1

One short-term study (Tugal 2003) reported data on average end point, visual reproduction 1 score. There were no differences between acetylcholinesterase inhibitors plus antipsychotics and placebo and antipsychotics (1 RCT, n = 12, MD -1.30 95% CI -5.21 to 7.81).

1.6.2.5 Visual reproduction 2

Tugal 2003 reported data on average end point score, visual reproduction 2. There were no differences between acetylcholinesterase inhibitors plus antipsychotics and placebo and antipsychotics (1 RCT, n = 12, MD -1.50 95% CI -8.69 to 5.69).

1.6.2.6 Verbal paired associates 1

One short-term study (Tugal 2003) reported data on average end point score which found no difference between acetylcholinesterase inhibitors plus antipsychotics and placebo and antipsychotics (1 RCT, n = 12, MD 3.20 95% CI -7.28 to 0.88).

1.6.2.7 Verbal paired associates 2

One short-term study (Tugal 2003) showed no difference between acetylcholinesterase inhibitors plus antipsychotics and placebo and antipsychotics (1 RCT, n = 12, MD -0.60 95% CI -1.92 to 0.72).

1.6.2.8 Logical memory 1

(Tugal 2003) showed no difference between acetylcholinesterase inhibitors plus antipsychotics and placebo and antipsychotics (1 RCT, n = 12, MD -4.60 95% CI -12.72 to 3.52).

1.6.2.9 Logical memory 2

(Tugal 2003) showed no difference between acetylcholinesterase inhibitors plus antipsychotics and placebo and antipsychotics (1 RCT, n = 12, MD -4.60 95% CI -13.26 to 4.06).

1.6.3 Cognitive functioning: average end point score on various subscales of WAIS III which indicate different facets of cognitive functioning

1.6.3.1 Block design test

One short-term study (Tugal 2003) showed no difference between acetylcholinesterase inhibitors plus antipsychotics and placebo and antipsychotics (1 RCT, n = 12, MD 3.10 95% CI -9.71 to 15.91).

1.6.3.2 Letter number sequencing test

Buchanan 2008 reported average end point score on this test. There were no differences between acetylcholinesterase inhibitors

plus antipsychotics and placebo and antipsychotics (1 RCT, n = 73, MD 0.60 95% CI -0.48 to 1.68).

1.6.3.3 Digit symbol test

Buchanan 2008 (short-term study), reported results from the acetylcholinesterase inhibitor plus antipsychotics arm were statistically significant compared with placebo and antipsychotics group (1 RCT, n = 73, MD 1.20 95% CI 0.14 to 2.26).

1.6.3.4 Symbol search score

One short-term study, (Buchanan 2008) showed no difference between acetylcholinesterase inhibitors plus antipsychotics and placebo and antipsychotics (1 RCT, n = 73, MD 0.30 95% CI -0.92 to 1.52).

1.6.3.5 Letter number span test without reordering

One short-term study (Dyer 2008) showed no difference between acetylcholinesterase inhibitors plus antipsychotics and placebo and antipsychotics (1 RCT, n = 20, MD -1.60 95% CI -4.19 to 0.99).

1.6.3.6 Letter number span test with ordering

One short-term study (Dyer 2008) showed no difference (1 RCT, n = 20, MD 0.50 95% CI -3.27 to 2.27).

1.6.4 Cognitive functioning: average end point score on various subtests of HVLT which indicate verbal learning and memory

1.6.4.1 Immediate recall and delayed recall

One short-term study (Lee 2005) reported average end point, immediate recall and delayed recall scores. There were no differences on immediate recall score (1 RCT, n = 24, MD 3.00 95% CI -0.76 to 6.76) and delayed recall score (1 RCT, n = 24, MD 1.50 95% CI -0.20 to 3.20).

1.6.4.2 Recognition

The pooled data of two short-term studies (Lee 2005; Kim 2005b) showed superiority of acetylcholinesterase inhibitors and antipsychotic over placebo and antipsychotics (2 RCTs, n = 48 , MD 1.90 95% CI 0.52 to 3.28).

1.6.5 Cognitive functioning: average end point score on Verbal Fluency Test which evaluates verbal memory and language (High score indicates better performance)

The data from three short-term studies (Lee 2005; Nahas 2003; Tugal 2003) showed superiority of acetylcholinesterase inhibitors when combined with antipsychotic over placebo and antipsychotics in the treatment of schizophrenia (3 RCTs, n = 42, MD 3.46 95% CI 0.67 to 6.26).

1.6.6 Cognitive functioning: average end point score on BVST which evaluates visuospatial memory (High score means better performance)

One short-term study (Buchanan 2008) showed no difference between acetylcholinesterase inhibitors plus antipsychotics and placebo and antipsychotics (1 RCT, n = 73, MD -0.50 95% CI -1.42 to 0.42).

1.6.7 Cognitive functioning: average end point score on various subtests of Stroop test which evaluate executive functioning

1.6.7.1 Stroop Letter test

One short-term study (Lee 2005) reported average end point, Stroop letter test score. High score means better performance. There were no differences between acetylcholinesterase inhibitors plus antipsychotics and placebo and antipsychotics (1 RCT, n = 24, MD -1.50 95% CI -12.15 to 9.15).

1.6.7.2 Stroop Colour test

One short-term study (Lee 2005) reported average end point, Stroop colour test score. High score means better performance. The results significantly favour acetylcholinesterase inhibitors over placebo when combined with antipsychotics (1 RCT, n = 24, MD 17.10 95% CI 0.70 to 33.50).

1.6.7.3 Stroop interference test

One short-term study (Dyer 2008) reported no difference between acetylcholinesterase inhibitors and placebo when combined with antipsychotics (1 RCT, n = 20, MD -2.60 95% CI -6.68 to 1.48).

1.6.8 Cognitive functioning: average end point score on Trail making tests A & B which evaluate executive functioning (High score means better performance)

1.6.8.1 Trail making part A

Two short-term studies (Lee 2005; Tugal 2003) reported no significant difference in the average end point score (2 RCTs, n = 24, MD -8.72 95% CI -28.91 to 11.47).

1.6.8.2 Trail making part B

One short-term study (Tugal 2003) reported no significant difference (1 RCT, n = 24, MD 16.40 95% CI -32.33 to 65.13).

1.6.9 Cognitive functioning: average end point score on CPT which evaluate sustained and selective attention

1.6.9.1 Reaction time (High score = better performance)

One short-term study (Dyer 2008) reported no significant difference between acetylcholinesterase inhibitors and placebo when combined with antipsychotics. (1 RCT, n = 20, MD -5.20 95% CI -70.74 to 60.34).

1.6.9.2 Random errors (Low score = better performance)

One short-term study (Dyer 2008) reported no significant difference between acetylcholinesterase inhibitors and placebo when combined with antipsychotics (1 RCT, n=20, MD -0.20 95% CI -1.71 to 1.31).

1.6.10 Cognitive functioning: average end point score on Grooved pegboard test which evaluates motor functioning (High score means better performance)

Two short-term studies (Buchanan 2008; Dyer 2008) reported average end point, average peg score. There were no significant differences between acetylcholinesterase inhibitors and placebo when combined with antipsychotics (2 RCTs, n = 93, MD -0.29 95% CI -3.11 to 2.53).

1.6.11 Cognitive functioning: average end point score on various scales

The result from the three short-term studies (Dyer 2008; Lee 2005; Tugal 2003) showed data on various subscales: ROCFT, Letter number span with and without reordering, Wisconsin card sorting test, Visual paired associates 1 & 2, CPT, Stroop interference test. The results reported were skewed and are presented in tabular form. There did not appear to be any significant trends favouring one intervention over another.

1.6.12 Cognitive functioning: average change score on various scales

Two short-term studies (Friedman 2002c; Schubert 2006) reported mean change data on various subscales RAVLT, CPT, RBANS. The data were skewed and are presented in tabular form. There did not appear to be any significant differences between the interventions.

1.6.13 Cognitive functioning: average change score on various scales

One medium-term study (Tuma 2003) reported data on various subscales: category fluency test, trail making test, logical memory, WCST, ROCFT, verbal paired associate. The data were skewed and are presented in tabular form. There did not appear to be any significant differences between the two comparators.

1.7 Service use

No data were available for this outcome.

2.8 Adverse events

1.8.1 Central nervous system

1.8.1.1 Dizziness

Four short-term studies (Akhondzadeh 2008; Buchanan 2008; Keefe 2008a; Lee 2005) reported data on dizziness. There were no significant differences for this outcome between acetylcholinesterase inhibitors plus antipsychotics versus placebo plus antipsychotics (4 RCTs, n = 279, RR 0.77 95% CI 0.35 to 1.72).

1.8.1.2 Sialorrhea

One short-term study (Freudenreich 2005) reported data on this outcome and no significant differences were noted (1 RCT, n = 36, RR 6.30 95% CI 0.35 to 113.81).

1.8.1.3 Headache

Data from two short-term studies (Keefe 2008a; Lee 2005) reported no significant differences for this outcome (2 RCTs, n = 269, RR 0.51 95% CI 0.24 to 1.09).

1.8.1.4 Insomnia

Two short-term studies (Akhondzadeh 2008; Keefe 2008a) reported data on this event. There were no significant differences (2 RCTs, n = 269, RR 0.47 95% CI 0.18 to 1.20).

1.8.1.5 Somnolence

One short-term study (Keefe 2008a) reported data on this event. There were no differences between the comparators (1 RCT, n = 245, RR 0.44 95% CI 0.12 to 1.66).

1.8.1.6 Nonspecific central nervous system adverse event

Fagerlund 2007, a medium-term study reported data on this event, with no significant differences (1 RCT, n = 11, RR 1.88 95% CI 0.09 to 37.63).

1.8.2. Metabolic and nutritional

1.8.2.1 Weight loss - (number of participants with a significant weight loss as defined by authors).

Two short-term studies (Buchanan 2008; Lee 2005) reported data on this and found no differences between the two groups (2 RCTs, n = 102, RR 0.33 95% CI 0.10 to 1.06).

1.8.2.2 Glucose-number of participants with abnormally high fasting glucose.

Keefe 2008a, a short-term study reported data on this event and found no significant differences (1 RCT, n = 102, RR 0.46 95% CI 0.14 to 1.44).

1.8.3 Deterioration in mental state

Two short-term studies (Buchanan 2008; Schubert 2006) reported data on this event. There were no significant differences (2 RCTs, n = 102, RR 0.62 95% CI 0.09 to 4.38).

1.8.4 Biochemical - important rise in creatinine kinase levels

One short-term study (Keefe 2008a) reported data on this adverse event. There were no significant differences (1 RCT, n = 102, RR 1.17 95% CI 0.44 to 3.13).

1.8.5 Non specific

1.8.5.1 Severe adverse event and serious adverse event

One short-term study Keefe 2008a reported data on a severe adverse event (1 RCT, n = 245, RR 0.93 95% CI 0.41 to 2.11) and a serious adverse event (1 RCT, n = 245, RR 1.02 95% CI 0.37 to 2.83) and found no significant differences between acetylcholinesterase inhibitor and placebo arms when combined with antipsychotics.

1.8.5.2 Alcohol relapse: number of participants who had a relapse of alcohol.

One short-term study (Buchanan 2008) find no difference (1 RCT, n = 86, RR 3.14 95% CI 0.13 to 74.98).

1.8.5.3 Muscle cramp: number of participants who developed muscle cramps.

Two short-term studies (Akhondzadeh 2008; Dyer 2008) reported no significant differences (2 RCTs, n = 44, RR 3.00 95% CI 0.52 to 17.21).

1.8.5.4 Agitation and uncooperativeness: participants who showed agitation and uncooperativeness.

One short-term study (Friedman 2002c) found no significant difference (1RCT, n = 36, RR 5.00 95% CI 0.26 to 97.37).

1.8.6 Cardiovascular: number of participants who had a cardiovascular event

One short-term study (Keefe 2008a) reported data and found no significant differences (1 RCT, n = 245, RR 0.51 95% CI 0.23 to 1.15).

1.8.7 Gastrointestinal-short-term

1.8.7.1 Vomiting: number of participants who reported this adverse event.

Four short-term studies (Akhondzadeh 2008; Buchanan 2008; Keefe 2008a; Lee 2005) reported data on this event and found significant differences (4 RCTs, n = 371, RR 0.80 95% CI 0.38 to 1.69).

1.8.7.2 Abdominal pain and diarrhoea: number of participants who reported this adverse event.

One short-term study (Kim 2005b) reported data on this adverse event. There were no significant differences (1 RCT, n = 24, RR 3.00 95% CI 0.13 to 67.06).

1.8.7.3 Diarrhoea: number of participants who reported this adverse event.

Four short-term studies (Akhondzadeh 2008; Keefe 2008a; Lee 2005; Schubert 2006) reported data on this event. There were no significant differences (4 RCTs, n = 371, RR 1.21 95% CI 0.55 to 2.62).

1.8.7.4 Nausea: number of participants who reported this adverse event.

Three short-term studies (Akhondzadeh 2008; Keefe 2008a; Lee 2005) reported data on nausea. There were no significant differences (3 RCTs, n = 293, RR 1.14 95% CI 0.46 to 2.80).

1.8.7.5 Any gastrointestinal event

One short-term study (Keefe 2008a) reported data on any gastrointestinal adverse event. There were no significant differences (1 RCT, n = 245, RR 0.92 95% CI 0.58 to 1.46).

1.8.8 Respiratory system: number of participants who developed respiratory adverse event as pneumonia

One short-term study (Buchanan 2008) reported data on this adverse event. There were no significant differences (1 RCT, n = 86, RR 3.14 95% CI 0.13 to 74.98).

1.8.9 Extrapyramidal effects

1.8.9.1 EPSE: number of participants who developed this adverse event.

One medium-term study (Fagerlund 2007) reported data on this event. There were no significant differences (1 RCT, n = 11, RR 4.38 95% CI 0.28 to 68.06).

1.8.9.2 EPSE: average end point score on AIMS.

One short-term study (Caroff 2007) reported data on EPSE as measured on AIMS. Low score is favourable. This study favoured acetylcholinesterase inhibitor plus antipsychotic over placebo and antipsychotic (1 RCT, n = 35, MD 1.50 95% CI 1.04 to 1.96).

1.8.9.3 EPSE: average end point score on SAS.

One medium-term study (Sharma 2006) reported data on this event as measured on SAS. Low score is favourable. There were no significant differences (1 RCT, n = 21, MD -0.16 95% CI -0.38 to 0.06).

1.8.9.4 EPSE: average end point score on various scales.

There were no significant differences on various scales SARS, AIMS and ESRS in two short-term studies (Akhondzadeh 2008; Buchanan 2008). The data were skewed and are presented in tabular form.

1.8.9.5 EPSE: average end point score on various scales.

There were no significant differences in one medium-term study (Sharma 2006) on AIMS and BARS. The data were skewed and are reported in tabular form.

1.8.9.6 EPSE: average change score on EPSE scales

One short-term study (Schubert 2006) reported mean change score on AIMS and SAS scales which is presented in tabular form as the data were skewed.

1.8.9.7 ECG: average change interval on ECG-short-term.

One short-term study (Buchanan 2008) reported change interval score - PR, QRS, and QTc. The data were skewed and are presented in tabular form. There did not appear to be any significant difference.

1.9 Economic outcomes

There are no data available on economic outcomes.

1.10 Behaviour

1.10.1 Smoking expired CO measures.

One short-term study (Buchanan 2008) reported data on this behaviour. There were no significant differences (1 RCT, n = 41, MD 0.10 95% CI -6.25 to 6.45).

1.10.2 Smoking - FTND interview score.

One short-term study (Buchanan 2008) reported data on average end point score. There was a significant superiority of placebo over acetylcholinesterase inhibitors when combined with antipsychotics (1 RCT, n = 41, MD 1.50 95% CI 0.09 to 2.91).

1.11 Engagement with services

There were no data available on this outcome.

2. Comparison 2: Acetylcholinesterase inhibitors plus antipsychotic versus antipsychotic alone

Only one study (Chouinard 2007) met the inclusion criteria for this comparison. The data were available for only two outcomes.

2.1 Leaving the study early

There were no significant differences in the number of participants leaving the study early due to any reason (1 RCT, n = 24, RR 7.71 95% CI 0.46 to 129.18), due to deterioration in mental state (1 RCT, n = 24, RR 2.57 95% CI 0.12 to 57.44) or due to suicidal ideas (1 RCT, n = 24 RR 2.57 95% CI 0.12 to 57.44).

2.2. Mental state: average end point score on PANSS

2.2.1 Negative symptoms

The study reported data on the above outcome but there were no significant differences (1 RCT, n = 24, MD -0.60 95% CI -4-14 to 2.94).

2.2.2 Positive symptoms

There were no significant differences on this outcome (1 RCT, n = 24, MD 1.10 95% CI -2.59 to 4.79).

2.2.3 Disorganisation/cognitive

The data on this outcome reported no difference (1 RCT, n = 24, MD 0.50 95% CI -2.04 to 3.04).

2.2.4 Hostility/excitement: average end point score on PANSS dimensional scores

There were no significant differences (1 RCT, n = 24, MD 0.20 95% CI -1.56 to 1.96).

2.2.5 Anxiety/depressive: average end point score on PANSS dimensional scores

There were no significant differences (1 RCT, n = 24, MD 0.00 95% CI -0.93 to 0.93).

2.2.6 PANSS total

The study reported no significant difference (1 RCT, n = 24, MD 1.80 95% CI -4.47 to 8.07).

3. Publication bias

We assessed for publication bias using the studies that were included for the outcome of leaving the study early (Figure 1) which showed no evidence of possible biases.

4. Investigation of heterogeneity and sensitivity analysis

The reasons for the pre-planned sensitivity analysis did not apply and were therefore not performed

DISCUSSION

The results of the pooled data seem to favour acetylcholinesterase inhibitors over placebo when combined with antipsychotics in some of the outcome measures. Two medium-term studies suggested an improvement in negative symptoms and general psychopathology as measured on PANSS. One short-term study showed improvement in depressive symptoms as measured by CDSS. On cognitive functioning, acetylcholinesterase inhibitors showed benefit over placebo when combined with antipsychotics in various areas of cognition including: memory, recognition, attention, executive functioning, psychomotor speed and reaction time as measured by different standardised tests. Concerning tolerability, there were no significant differences in terms of different adverse effects but acetylcholinesterase inhibitors had a comparably better profile on EPSE as measured on AIMS end point score. Nevertheless, the validity of all results is challenged by the quality of the study design; especially, the small duration of studies with small number of participants.

Summary of main results

General

We were able to include 17 studies; however, data reporting in most of these studies was poor. Our primary outcome of interest was reported in only five studies. The two secondary outcomes (negative symptoms and cognition) which we expected to show improvement did show some positive results but the quality of the studies was poor. The studies were of short-term duration and the number of the participants were low. Cognitive impairment is usually a slow process of decline often progressing over months and sometimes years. To evaluate change in these parameters requires studies to be of longer-term duration. Unfortunately, we did not find any long-term studies. Fourteen of the studies were short-term and three were medium-term. In a chronic disease such as schizophrenia with possible progressive deterioration, treatment efficacy may decline as the disease worsens. A recent study (Chen 2010) has emphasised the need for trials of longer duration in assessing the efficacy of compound in question (Craig 2010). Lack of studies in the long-term, therefore, limits our generalisability of findings.

This analysis of the effects of acetylcholinesterase inhibitors in combination with an antipsychotic, or alone, compared with placebo and antipsychotics drugs in the treatment of schizophrenia currently includes 17 studies, reporting data on only six of ten possible secondary outcomes. In addition, 16 of the 17 included studies randomised less than 100 people. The duration of the trials was usually short and we identified only three medium-term studies and no long-term studies. Short-term trials are not ideal to judge efficacy and tolerability of treatments for a chronic disease. Evidence is clear that industry sponsorship leads to results being biased towards the compound that the company promotes (Smith 2003). Nine of the 17 studies were totally grant funded by the pharmaceutical industry and one of the studies (Sharma 2006) was partly funded by a pharmaceutical company. This is likely to be a further problem.

1. Comparison 1: Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

1.1 Global effect

Global effect remains an important outcome for estimating the overall improvement. In an age where rating scales seem to be predominate outcome assessments, this is perhaps one of very few scales that indicate a more pragmatic outcome. Although widely used in trials, the quality of reporting tends to vary. Of the 17 included studies, only two studies (Fagerlund 2007; Schubert 2006) reported data on this important outcome and the results of one study were skewed (Schubert 2006). There was no difference between the two comparators for this outcome.

1.2 Leaving the study early

Losses to follow-up are often significant in schizophrenia trials. Some reviews have reported studies that have lost more than half the participants (Komossa 2010), however, the number of participants leaving the study early was comparatively low in this review (13.6 %) and showed no significant difference between groups. It may be possible that participants in the included studies were inherently different from other schizophrenia trials; however, we were not able to hypothesise as to why this difference in attrition rates could have occurred. The included trials were predominantly short-term in nature, which could account to some extent

for the reduced attrition rates. Medium-term data were only available from one study (Tuma 2003) and the study reported no significant difference in participants leaving the study early between acetylcholinesterase inhibitors and placebo when combined with antipsychotics. Lack of any meaningful long-term data and no significant findings in the short-term, would indicate that there is not much to choose between acetylcholinesterase inhibitors and placebo.

1.3 Mental state

In this review, PANSS appears to have been the commonly used measuring tool as it is with most other schizophrenia trials. Three short-term studies that looked at efficacy, as measured on PANSS end point, did not show any differences between acetylcholinesterase inhibitors plus antipsychotics versus placebo plus antipsychotics, or versus antipsychotic alone. Two medium-term studies, however, showed superiority of acetylcholinesterase inhibitors over placebo when combined with antipsychotics in negative symptoms and general psychopathology as measured on PANSS end point data. These results require caution in their interpretation. The Fagerlund 2007 study had only 11 participants, who were distributed rather unevenly (seven in the donepezil group and four in the placebo group) with no mention of why this was the case. The study also had low baseline scores of participants on negative symptoms and general psychopathology scales compared with placebo. This can lead to a possibility of overestimating the treatment effects of the experimental intervention compared with the control, which in this case happens to be the compound, the manufacturers of which, funded the study. Data for participants who left the study early were not reported, which again raises the possibility of whether the participants who left the trial early were in any way different compared with those who stayed in the trial. We were unable to ascertain if more than 40% of participants left the study early or not. In the other study (Sharma 2006), the number of participants who left the study was quite high, nearly 40%. It was not clear from the data how participants were accounted for if they were lost to follow-up. As a result of these limitations, these results should be interpreted with significant caution.

1.4 Cognitive functioning

Cognitive functioning was tested using a set of neuropsychometric tests. The data were taken from both the main tests and subtests; all were checked for validity and reliability. The results gave a mixed picture, few studies favoured placebo over acetylcholinesterase inhibitors and vice versa. Of the various subtests, acetylcholinesterase inhibitors showed superiority in different areas of cognition such as: memory, executive functioning, attention and reaction time; whereas, placebo showed superiority on attention aspect as measured by digit span forward/backward tests.

The results favouring acetylcholinesterase inhibitors cannot be considered robust as the findings were from short-term studies and they did not appear to be of high quality. Tugal 2003 had affiliation with the pharmaceutical company. The study had a cross-over design and we used the data before the first cross-over (i.e. up to six weeks). The sample size was small - six in each arm. Lee 2005, we also did not have quality information about the randomisation process and the blinding was not tested. Nahas 2003 had similar issues; it was a cross-over design so we used results up to the first cross-over (six weeks).The number of participants in each arm was only three. The above findings can affect the robustness of a study especially when the condition in question is a chronic and enduring one, and there is no report on long-term effects. Buchanan 2008 seemed to be the only study with a good number of participants (n = 86) and a low attrition rate (16%). It showed superiority of acetylcholinesterase inhibitor over placebo in areas of attention and psychomotor speed as assessed by the digit symbol test.

1.5 General functioning and quality of life

Very limited data on these important outcomes were available. Only one study Fagerlund 2007 reported data on global functioning and there were no differences between acetylcholinesterase inhibitors and placebo when combined with antipsychotics.
There were no data indicating a difference in measures of quality of life.

1.6 Adverse effects

Adverse effects were available for cardiac effects, extrapyramidal symptoms, central nervous system symptoms, gastrointestinal system symptoms, respiratory system, biochemical abnormalities, non-specific and deterioration in mental state. There were no significant differences between acetylcholinesterase inhibitors and placebo when combined with antipsychotics on all the available adverse effect outcomes. Results on at least one adverse effect, extrapyramidal symptom - AIMS end point score, indicated an advantage for acetylcholinesterase over placebo (Caroff 2007). The quality of the study is in question; blinding was not specified, selective reporting was noted and the authors had affiliation with the pharmaceutical company.

1.6 Behaviour

The only behaviour for which data were collected was for smoking. One study, Buchanan 2008 showed superiority of placebo over acetylcholinesterase inhibitors on FTND interview score.

1.7 Missing outcomes

Unfortunately, only little is known from evaluation studies about service outcomes, engagement with services, economic outcomes

and satisfaction with treatment. Exactly how much patient care gains from these compounds remains unclear.

2. Comparison 2: Acetylcholinesterase inhibitors plus antipsychotic versus antipsychotic alone

Data were available for two outcomes; leaving the study early and mental state. There were no significant differences in either arms of the study in the above two outcomes.

Overall completeness and applicability of evidence

Of the 17 included studies 14 were short-term. We did not identify a single high quality study which could have compared most of the possible comparisons of acetylcholinesterase inhibitors plus antipsychotic with placebo and antipsychotic, or acetylcholinesterase inhibitors with placebo and antipsychotic drugs, or acetylcholinesterase alone with placebo.

Evidence, therefore, is incomplete. None of the studies were long-term thus limiting applicability of the evidence, for; after all, schizophrenia is often a chronic, often life-long, disorder. Furthermore, most of the included studies were efficacy studies, therefore, external validity is limited and further more pragmatic effectiveness studies are needed.

Quality of the evidence

All studies were randomised and at least single-blind, but details were rarely presented. Therefore, it is unclear in almost all studies whether randomisation and blinding were really appropriately done. Furthermore, the majority of the studies were short-term, only three were medium-term and none long-term; leading to questions about the validity of the findings. None of the studies compared acetylcholinesterase inhibitors alone with placebo; it was mostly add-on therapy with antipsychotics. This also limits the evidence because the antipsychotics used were from different classes which would have led to difference in results. Selective reporting was evident in half of the studies and half of the studies were industry sponsored or had affiliation with pharmaceutical companies. All these factors limit the quality of the evidence.

Potential biases in the review process

We are not aware of obvious flaws in our review process.

Agreements and disagreements with other studies or reviews

None known.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia

Current available evidence is not good enough for recommending acetylcholinesterase inhibitors routinely as an add-on intervention along with antipsychotics to improve efficacy or cognitive symptoms in those suffering from schizophrenia.

2. For clinicians

The majority of the studies were short-term with only three medium-term studies, of which two were of poor methodological quality. The overall results do not suggest that the intervention is better than placebo. It could perhaps be tried when all other interventions have failed, but its effects need to be assessed and treatment withdrawn if there is no evidence of any clinical benefit. This combination may be useful in improving the different aspects of cognition such as attention, reaction time and psychomotor speed, again the evidence base for which is quite limited.

3. For managers/policy makers

Little information on service use (such as time in hospital), and economic outcomes is available. There may be higher overall costs in some settings. Only one study had data on general functioning and it did not favour the drug in question.

Implications for research

1. General

Reporting of trials continues to remain poor. There needs to be better description of the randomisation process and better accountability of patients leaving the trial. As highlighted in other Cochrane reviews, authors must give consideration to better adherence to the CONSORT statement (Schulz 2010).

2. Specific

Most of the studies were short-term studies. Most of the data reported within existing comparisons are almost without value because of the assumptions and biases within them. It is therefore essential that longer-term, better reported more pragmatic trials are needed before the evidence could be assessed objectively to conclude whether or not this intervention would be of benefit to patients.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Akhondzadeh 2008

Methods	Allocation*:* randomised in 1:1 pattern. Blindness: double blind. Duration: 12 weeks. Design: not specified.
Participants	Diagnosis: schizophrenia (DSM-IV). N = 30. Age: 22 to 44 years. Duration of illness: intervention group 85.6 ± 46.6 months, placebo 89.2 ± 50.2 months. Sex: 11 F,19 M. Setting: inpatient and outpatient. Inclusion criteria: treated with a stable dose of risperidone - 8 weeks, minimum period of 4 weeks stability, total performance score at least 20 on MMSE. Exclusion criteria: any medical diagnosis, on any medication that may have affected cognitive performance, abusing substances within 6 months of entry into study, pregnant or lactating women
Interventions	1. Donepezil: dose up to 10 mg/day plus risperidone 4 to 6 mg/day.N = 15. 2. Placebo plus risperidone 4 to 6 mg/day. N = 15.
Outcomes	Leaving the study early. Mental state: PANSS, HAM-D. Cognitive functioning. Adverse events. Unable to use: PANSS
Notes	Donepezil and placebo were prepared in identical appearing tablets

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information available.
Allocation concealment (selection bias)	High risk	Not done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Both the participants and investigators were blinded to the intervention. Identical appearing tablets were used, effectiveness of this method was not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.

Akhondzadeh 2008 (*Continued*)

Selective reporting (reporting bias)	Low risk	All of the study's pre-specified outcomes are reported.
Other bias	Unclear risk	No information available.

Buchanan 2008

Methods	Allocation*:* randomised. Blindness: double blind. Duration: 12 weeks. Design: not specified.
Participants	Diagnosis: schizophrenia or schizoaffective disorder (DSM-IV). N= 86. Age: 18 to 60 years. Duration of illness: mean age - 24.9 years, intervention group; mean age - 25.9 years, placebo group. Sex: 74 M, 12 F. Setting: inpatients and outpatients. Inclusion criteria: clinically stable and in a non acute (chronic) phase of their illness, to have at least a minimal level of cognitive impairment, on antipsychotics other then clozapine, absence of concomitant anticholinergic treatment and significant extrapyramidal symptoms. Exclusion criteria: Patients who met the criteria for a DSM-IV diagnosis of alcohol or substance abuse within the last 6 months, with second-degree A-V block, CNS disorder (e.g., seizure disorder, stroke), or mental retardation
Interventions	1. Galantamine: dose up to 24 mg/day plus antipsychotic. N = 42 2. Placebo and antipsychotic.N = 44.
Outcomes	Mental state: BPRS, SANS. Global functioning: CGI. Leaving the study early. Adverse events: Simpson & Angus Neurological Rating Scale for Extrapyramidal Effects, Abnormal Involuntary Movement Scale (AIMS), weight loss, vomiting, ECG and QTc prolongation, biochemical values. Cognitive functioning: Neuropsychological tests. Expired CO measures. Unable to use: CGI-S. BPRS, SANS.
Notes	Seven participants left the study early in the galantamine group and six in the placebo group for various reasons. Both the participants and trialists were blinded to the intervention

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Buchanan 2008 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	No information available.
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding (performance bias and detection bias) All outcomes	Low risk	Both the participants and investigators were blinded to the intervention. Effectiveness of this method was not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information available.
Selective reporting (reporting bias)	Low risk	All outcomes measured and reported.
Other bias	Unclear risk	Funded by independent bodies, but authors reported affiliation to various drug companies

Caroff 2007

Methods	Allocation: randomised. Blinding: not specified. Duration: 12 weeks. Design: uni-centre, cross-over.
Participants	Diagnosis: schizophrenia (DSM-IV). N = 38. Age: 56.4 ± 9.9 years. Duration of illness: 29.6 ± 8.0 years. Sex: male. Setting: not clear. Inclusion criteria: patients with schizophrenia with tardive dyskinesia. Exclusion criteria: patients with acute medical illness, could not be withdrawn from anticholinergic medication or vitamin E supplements
Interventions	1. Galantamine up to 24 mg /day plus antipsychotic medication. N = 20. 2. Placebo plus antipsychotic medication. N = 18.
Outcomes	Mental state: BPRS. Cognition: MMSE. Adverse events: AIMS, SAS, BAS. Leaving the study early. Unable to use: BPRS, SAS, MMSE, BAS.
Notes	

Risk of bias

Caroff 2007 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available.
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information available.
Selective reporting (reporting bias)	Low risk	Not enough information available.
Other bias	High risk	Mention of support from drug company Pfizer.

Chouinard 2007

Methods	Allocation: randomised. Blindness: double blind. Duration: 12 weeks. Design: uni-centre, cross-over.
Participants	Diagnosis: Schizophrenia and schizoaffective disorder (DSM-IV). Duration of illness: mean age - 8.77 (7.99), intervention group; mean age - 4.25 (5.28) , control group. N = 24. Age: 28.85 ± 7.92 years. Sex: M and F. Settings: inpatients. Inclusion criteria: patients with schizophrenia who scored less than 75 on the immediate or delayed memory indices. Exclusion criteria: patients with history of substance use, axis 1 and III diagnosis, pronounced suicidal tendencies
Interventions	1. Rivastigmine: dose up to max 4.5 mg bd plus antipsychotic. N=9. 2. Antipsychotic alone. N=11.
Outcomes	Mental state: PANSS Cognitive functioning: CANTAB. Adverse events. Leaving the study early. Unable to use: CANTAB.

Chouinard 2007 (*Continued*)

Notes	Twenty four patients were recruited but only twenty completed the study. Both the participants and trialists were blinded to the intervention

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available.
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding (performance bias and detection bias) All outcomes	Low risk	Both the participants and investigators were blinded to the intervention. Effectiveness of this method was not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information available.
Selective reporting (reporting bias)	Low risk	All outcomes measured and reported.
Other bias	High risk	Novartis Canada, a pharmaceutical company name was mentioned in the grant section

Dyer 2008

Methods	Allocation: randomised, concealed allocation with a 1:1 ratio, in blocks of 4. Blinding: not clear. Duration: 8 weeks. Design: single centre, parallel group.
Participants	Diagnosis*:* schizophrenia or schizoaffective disorder of depressed type. Duration of illness: not mentioned. N=20. Age: mean age - 44.3 (11.9) years, in galantamine group; mean age - 50.5 (4.7) years, in placebo. Sex: M and F. Setting: outpatients. Inclusion criteria: stable, adult outpatients with schizophrenia or schizoaffective disorder depressed type, had been on stable dose of antipsychotic medication for at least 8 weeks. Exclusion Criteria: participants who were taking an anticholinergic medication or who reported use of an illicit drug or nicotine containing product in the past 3 months or who had expired carbon monoxide > 9ppm
Interventions	1. Galantamine plus antipsychotic: dose up to 16 mg twice daily, N = 10 2. Placebo plus antipsychotic: N = 10.

Dyer 2008 (*Continued*)

Outcomes	Mental state: PANSS, SANS, CDSS. Leaving the study early. Cognitive functioning: Neuropsychological tests. Adverse events. Unable to use: AIMS, SAS, Barnes Akathisia Scales.
Notes	Two participants left the study; data of these two candidates were included in the LOCF analysis. Both the participants and trialists were blind to the intervention

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information available.
Allocation concealment (selection bias)	Unclear risk	Both the participants and investigators were blinded to the intervention. Effectiveness of this method was not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	LOCF analysis was performed.
Selective reporting (reporting bias)	High risk	Not all outcomes were reported.
Other bias	Unclear risk	There is a mention of drug company affiliation.

Fagerlund 2007

Methods	Allocation: randomised. Blindness: double blind. Duration: 16 weeks. Design: multi-centre parallel group.
Participants	Diagnosis: schizophrenia using SCAN 2.1 interview, (ICD-10). Duration of illness: 1 to 17 years. N = 11. Age: 23 to 43 years. Sex: M and F. Setting: inpatients and outpatients. Inclusion criteria: schizophrenic patients, patients on ziprasidone. Exclusion criteria: treatment refractory patients.

Fagerlund 2007 (*Continued*)

Interventions	1. Donepezil: dose up to 10 mg/day plus ziprasidone. N = 7. 2. Placebo plus ziprasidone. N = 4.
Outcomes	Mental state - PANSS, CDS. Global functioning - CGI, GAF. Cognitive functioning. Leaving the study early. Adverse events. Unable to use: Cognitive functioning.
Notes	SSRIs and BZD were allowed through out the study. Patients were treated with ziprasidone for a minimum duration of eight weeks and were thereafter randomised to four-month double blind adjunctive treatment with donepezil or placebo. The total number of participants at the start of the trial were 21, 10 had to be excluded but it was not clear how many were excluded from each group. Both the participants and trialists were blinded to the intervention

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	No information available.
Allocation concealment (selection bias)	High risk	No information available.
Blinding (performance bias and detection bias) All outcomes	Low risk	Both the participants and investigators were blinded to the intervention. Effectiveness of this method was not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No mention about the data for the patients who left the study early for various reasons
Selective reporting (reporting bias)	Low risk	All outcomes were measured and reported.
Other bias	Unclear risk	Supported by Pfizzer Denmark.

Freudenreich 2005

Methods	Allocation: randomised. Blindness: double blind. Duration: 8 weeks. Design: multi-site parallel group.
Participants	Diagnosis: schizophrenia (DSM-IV). Duration of illness: average 25 years (range 13 to 4113-41 years). N = 36. Age: average - 48.7 years (range 24 to 64 years).

	Sex: M and F. Setting: Inpatient and outpatient. Inclusion criteria: patients with schizophrenia, stable on an antipsychotic medication. Exclusion criteria: patients with active substance use disorder, any cognitive disorder, on antipsychotics that are strongly anticholinergic, e.g. clozapine
Interventions	1. Donepezil:dose up to 10 mg/day plus antipscyhotic.N = 19. 2. Placebo plus antipsychotic.N = 17.
Outcomes	Adverse events: SARS, BARS, AIMS. Leaving the study early. Cognitive functioning:cognitive battery of tests. Mental state: PANSS,SANS,CDSS. Unable to use: Mental state: PANSS, SANS, CDSS. Adverse events: SARS, BARS, AIMS.
Notes	Four participants did not finish the 8-week trial, leaving 32 study completers. Not clear which group they left from. One participant left the study from the intervention group. Donepezil and placebo were prepared in identical appearing tablets.The most commonly used antipsychotic was olanzapine followed by risperidone

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information available.
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding (performance bias and detection bias) All outcomes	Low risk	Both the participants and investigators were blinded to the intervention. Identical appearing tablets were used, effectiveness of this method was not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	LOCF analysis was performed.
Selective reporting (reporting bias)	High risk	Not all the outcomes were reported.
Other bias	High risk	Sponsored by Pfizer.

Friedman 2002c

Methods	Allocation: randomised in 1:1 fashion. Duration: 12 weeks. Blinding: double blind. Design: multi-centre, parallel group study.
Participants	Diagnosis: schizophrenia (DSM-IV). N = 36. Age: mean age - 48.8 (11.1) years, intervention group; mean age - 50.3 (10.1) years, placebo. Duration of illness: donepezil group = 25.9 (13.9), placebo = 26.9 (9.6). Gender: M and F. Setting: inpatient and outpatient. Inclusion criteria: on stable dose of risperidone, 4-week symptom stability, minimum level of cognition impairment as performance on learning trials 1 to 5 on the CVLT. Exclusion criteria: if they had any medical diagnoses or were receiving medications that may have affected cognitive performance or if they were abusing substances within 6 months of entry into the study
Interventions	1. Donepezil: dose up to 10 mg/day plus risperidone = 18. 2. Placebo plus risperidone = 18.
Outcomes	Leaving the study early. Mental state: PANSS. Cognitive functioning: battery of tests. Adverse events: ESRS. Unable to use: PANSS, ESRS, battery of neuropsychological tests
Notes	Mean daily dose of risperidone was 6.4 mg and 5.9 mg. Ten participants were randomised to receive 5 mg/day of donepezil for the entire 12 weeks, while 8 patients had their dose of donepezil increased to 10 mg per day for the last 8 weeks of the study. Thirty-four participants completed the entire protocol. Two participants in the donepezil 10 mg group terminated early from the study shortly after the dose increase due to increased agitation and uncooperativeness with study procedures, but both were able to complete midpoint (week 4) cognitive assessments. ITT was done. Both the participants and trialists were blinded to the intervention

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available.
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Both the participants and investigators were blinded to the intervention. Effectiveness of this method was not mentioned

Friedman 2002c (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis was performed.
Selective reporting (reporting bias)	High risk	Not all outcomes were reported.
Other bias	High risk	Funding was provided by Janssen Research Foundation.

Keefe 2008a

Methods	Allocation: randomised with 1:1 ratio, computer generated. Blinding: double. Duration: 12 weeks. Design: placebo controlled, multi-centre study with two parallel groups
Participants	Diagnosis: schizophrenia or schizoaffective disorder (DSM-IV). Duration of illness:mean age -18.0 years, donepezil; mean age - 14.8 years, placebo. Age: 18 to 55 years. Gender: M and F. N: 245 Setting: outpatients. Inclusion criteria: clinically stable for at least 6 months, on a second generation antipsychotic medication, have a minimal cognitive impairment as performed on BACS, have minimum of 6th grade reading level. Exclusion criteria: no history of DSM-IV defined substance abuse or dependence, any diagnosis on DSM-IV of axis I psychiatric disorder, risk of suicide, violent behaviour, history of seizure, previous use of cholinesterase inhibitors, on anticholinergics, antiparkinsonian medication or on typical antipsychotics
Interventions	1.Donepezil: dose up to 10 mg/day plus second generation antipsychotic.N = 121. 2.Placebo plus second generation antipsychotic.N = 124.
Outcomes	Mental state: PANSS, MADRS. Adverse events: AIMS, BAS, SAS. Leaving the study early. Cognitive functioning. Unable to use: Cognitive functioning, Mental state, Adverse events
Notes	All results shown were derived from the ITT sample. For LOCF analysis there were no significant difference between the treatment group. Film-coated tablets were used. Use of adjunctive anticholinergic medications for emergent EPSE's was not permitted. Both the participants and trialists were blinded to the intervention

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Keefe 2008a (*Continued*)

Random sequence generation (selection bias)	Low risk	Stratified randomisation with 1:1 ratio, computer generated.
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Both the participants and investigators were blinded to the intervention. Effectiveness of this method was not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT and LOCF data analysis was performed.
Selective reporting (reporting bias)	Low risk	All outcomes measured and reported.
Other bias	High risk	It was supported and funded by Eisai Inc and Pfizer Inc.

Kim 2005b

Methods	Allocation: randomised in a 1:1 pattern. Blinding: double blind. Duration: 12 week. Design: single centre, parallel group study.
Participants	Diagnosis: schizophrenia (DSM-IV). Duration of illness: mean age (13.1) years, donepezil group; mean age - (15.9) years, placebo. Age: mean age - 44.2 years. N = 24. Gender: M and F. Setting: inpatients. Inclusion criteria: participants to be stabilised on current dose of haloperidol for a minimum period of 3 months. The level of cognitive impairment required for participation was defined as a total performance score between 15 and 24 on the K-MMSE. Exclusion criteria: who had history of CNS-stimulating drug misuse, clinically significant physical abnormalities
Interventions	1. Donepezil: dose up to 5 mg/day plus haloperidol = 12. 2. Placebo plus haloperidol = 12.
Outcomes	Adverse events. Mental state: BPRS. Leaving the study early. Global functioning: CGI-I. Cognitive functioning: Neuropsychological tests. Unable to use: BPRS, CGI-I, neuropsychological tests.

Kim 2005b (*Continued*)

Notes	Antiparkinsonian, anticholinergics and benzodiazepines were allowed if their dose did not change during the previous 12 weeks. One patient dropped out from intervention group after week 8. No serious adverse reported that would have led to participant withdrawal. Both the participants and trialists were blinded to the intervention

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised in 1:1 pattern.
Allocation concealment (selection bias)	Unclear risk	Randomised in 1:1 pattern.
Blinding (performance bias and detection bias) All outcomes	Low risk	Both the participants and investigators were blinded to the intervention. Effectiveness of this method was not mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	No mention of ITT or LOCF.
Selective reporting (reporting bias)	Unclear risk	Not enough information available.
Other bias	Unclear risk	Was funded in part by Inje university, Busan, South Korea.

Kohler 2007

Methods	Allocation: randomised Blindness: double blind Duration: 12 weeks Design: not specified.
Participants	Diagnosis: schizophrenia or schizoaffective disorder (DSM-IV). Duration of illness: less than 10 years. Age: 18 to 40 years. N = 26. Setting: outpatients. Gender: 18 M and 8 F. Inclusion criteria: clinically stable during the last 3 months, Brief Psychiatric Rating Scale score of?35.All treated with second generation antipsychotics at standard daily dosages. Participants were not treated with clozapine, antidepressants, mood stabilisers, benzodiazepines or anticholinergics. Exclusion criteria: not clearly specified.
Interventions	1. Donepezil: dose up to 10mg/day plus second generation=11. 2. Placebo plus second generation antipsychotic. N=11.

Kohler 2007 (*Continued*)

Outcomes	Cognitive functioning: neurocognitive, social cognition. Leaving the study early. Mental state: PANSS, HAM-D. Adverse events Unable to use: PANSS, HAM-D. Adverse events.
Notes	Four participants, two on donepezil and two on placebo dropped out of the trial. Reasons included stopping the medication for unspecific reasons (n=2), agitation and dizziness. Both the participants and trialists were blind to the intervention

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information available.
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding (performance bias and detection bias) All outcomes	Low risk	Both the participants and investigators were blinded to the intervention. Effectiveness of this method was not mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	No ITT or LOCF analyses were performed.
Selective reporting (reporting bias)	Unclear risk	Not enough information available.
Other bias	Unclear risk	No information available.

Lee 2005

Methods	Allocation: randomised. Blindness: double blind. Duration: 12 weeks. Design: uni-centre.
Participants	Diagnosis: schizophrenia (DSM-IV). Duration of illness: mean - 15.8 (5.7) years, intervention group; mean - 18.8 (7.2) years, placebo. N = 24. Age: mean age - 39.5 (3.2) years, intervention group; mean age - 41.5 (3.2) years, placebo group. Sex: M and F. Setting: inpatients. Inclusion criteria: patients stabilised on antipsychotics, total performance score between 18 and 24 on KMMSE.

Lee 2005 (*Continued*)

	Exclusion criteria: patients with any acute medical conditions or taking medications that would have affected their cognition
Interventions	1. Galantamine: dose up to 16 mg/day plus antipsychotic = 12. 2. Placebo plus antipsychotic = 12.
Outcomes	Mental state: BPRS, HAM-D. Global functioning: CGI-Severity and improvement scale. Adverse events. Cognitive functioning. Unable to use: Mental state, Global functioning.
Notes	Antiparkinsonian anticholinergics and benzodiazepine drugs were permitted if the dose did not change during the previous 12 weeks Two patients dropped out from the galantamine group. LOCF analysis was performed. Both the participants and trialists were blinded to the intervention

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information available.
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding (performance bias and detection bias) All outcomes	Low risk	Both the participants and investigators were blinded to the intervention. Effectiveness of this method was not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	LOCF analysis was performed.
Selective reporting (reporting bias)	Unclear risk	Not enough information available.
Other bias	Unclear risk	No information available.

Nahas 2003

Methods	Allocation: randomised. Blindness: double blind Duration: 12 weeks. Design: uni-centre, cross-over.
Participants	Diagnosis: schizophrenia or schizoaffective disorder (DSM-IV). Duration of illness: not mentioned. Age: 22 to 53 years. N = 6.

Nahas 2003 (*Continued*)

	Sex: Male. Settings: outpatients. Include: patients stable on antipsychotic medication.
Interventions	1.Donepezil: dose up to 10 mg/day plus antipsychotic.N = 3. 2.Placebo plus antipsychotic.N = 3.
Outcomes	Mental state: PANSS. Cognitive functioning: VFT. Leaving the study early.
Notes	Both the participants and trialists were blinded to the intervention

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information available.
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding (performance bias and detection bias) All outcomes	Low risk	Both the participants and investigators were blinded to the intervention. Effectiveness of this method was not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study.
Selective reporting (reporting bias)	Unclear risk	Not enough information available.
Other bias	High risk	Mention of the name of few pharmaceutical companies.

Schubert 2006

Methods	Allocation: randomised. Blinding: double. Duration: 8 weeks. Design: not specified.
Participants	Diagnosis: schizophrenia or schizoaffective disorder (DSM-IV). Duration of illness: not specified. N = 16. Age: 26 to 55 years. Sex = 16 M and 1 F. Setting = not specified. Exclusion criteria = participants with history of intolerance to cholinesterase inhibitors/

Schubert 2006 (*Continued*)

	substance dependence, use of anticholinergic medication
Interventions	1. Galanatmine: dose 8 to 24 mg/day plus risperidone: dose 4 to 6 mg/day. N = 8. 2. Placebo plus risperidone: dose 4 to 6 mg/day. N = 8.
Outcomes	Cognitive functioning: RBANS. Mental state: PANSS Side effects. Adverse events: AIMS, SAS. CGI.
Notes	Three patients from the placebo wing left the study earlier. LOCF was performed. Both the participants and trialists were blinded to the intervention

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available.
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding (performance bias and detection bias) All outcomes	Low risk	Both the participants and investigators were blinded to the intervention. Effectiveness of this method was not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	LOCF analysis was performed.
Selective reporting (reporting bias)	Low risk	All outcomes measured were reported.
Other bias	Unclear risk	No information available.

Sharma 2006

Methods	Allocation*:* randomised. Blindness: double blind. Duration: 24 weeks.
Participants	Diagnosis*:* schizophrenia or schizoaffective disorder (DSM-IV). Duration of illness: 17.45(8.58), rivastigmine;16.50 (12.57), placebo. N = 20. Age: 18 to 60 years. Sex: M and F. Setting: inpatients and outpatients. Inclusion criteria: receiving stable treatment with an atypical antipsychotic and have stable psychotic symptoms, no adjunctive anticholinergic treatment required since initiation of the antipsychotic, negative urine screening for illicit drugs and negative preg-

Sharma 2006 (*Continued*)

	nancy test for female patients, cooperative, able to ingest oral medication and willing to undertake repeated cognitive testing, able to provide written informed consent, reading ability of not more than 40 errors on National Adult Reading Test, between 1 and 2 SD below expected performance on the basis of age and education level on the California Vernal Learning Test
Interventions	1. Rivastigmine: dose up to 12 mg/day plus other second generation antipsychotic = 11. 2. Placebo plus other second generation antipsychotic = 10.
Outcomes	Mental state: PANSS Cognitive functioning: neuropsychological tests. Leaving the study early. Adverse events: AIMS, SAS, BARS. Unable to use: Cognition.
Notes	Both groups received identical appearing capsules.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information available.
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding (performance bias and detection bias) All outcomes	Low risk	Both the participants and investigators were blinded to the intervention. Effectiveness of this method was not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	LOCF analysis was performed.
Selective reporting (reporting bias)	Unclear risk	Insufficient information..
Other bias	Unclear risk	Not much information available.

Tugal 2003

Methods	Allocation: randomised. Blindness: double blind. Duration: 12 weeks. Design: uni-centre, cross-over.
Participants	Diagnosis: schizophrenia (DSM-IV). Duration of illness: 16 ± 9.0 years. N = 12.

Tugal 2003 (*Continued*)

	Age: 18 to 45 years. Sex: M and F. Setting: outpatients. Inclusion criteria: patients on high potency typical antipsychotics. Stable for 3 months, minimum education of high school graduation
Interventions	1.Donepezil:dose up to 5 mg/day plus antipsychotic.N = 6. 2.Antipsychotic plus placebo. N = 6.
Outcomes	Mental state: PANSS,CDS Cognitive functioning.
Notes	All participants completed the study.Treatment was well tolerated. Both the participants and trialists were blinded to the intervention

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information available.
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding (performance bias and detection bias) All outcomes	Low risk	Both the participants and investigators were blinded to the intervention. Effectiveness of this method was not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	All outcomes were measured and reported.
Other bias	Unclear risk	Linked with pharmaceutical company-Pfizer.

Tuma 2003

Methods	Allocation: randomised. Blinding: double blind. Duration: 16 weeks. Design: not specified.
Participants	Diagnosis: schizophrenia (ICD-10). Duration of illness: not specified. Age: average - 32 years ± 8.6 years. N: 16. Sex: not specified.

Tuma 2003 (*Continued*)

	Setting: outpatients. Inclusion criteria: patients stabilized on risperidone monotherapy, cognitive deficit in at least one domain of cognitive functioning Exclusion criteria: psychiatric or somatic co-morbidity, history of alcohol or drug abuse, ECT during previous 6 months, administration of depot neuroleptics during previous 3 months
Interventions	1. Donepezil: dose up to 10 mg/day plus risperidone = 9. 2. Placebo and risperidone = 7.
Outcomes	Mental state: PANSS. Adverse events: BARS, SARS. Cognitive functioning: Neuropsychological tests.
Notes	Both the participants and trialists were blinded to the intervention

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	No information available.
Allocation concealment (selection bias)	High risk	No information available.
Blinding (performance bias and detection bias) All outcomes	Low risk	Both the participants and investigators were blinded to the intervention. Effectiveness of this method was not mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-outs were not included.
Selective reporting (reporting bias)	High risk	All outcome measures were not reported.
Other bias	Unclear risk	Not much information available.

Diagnostic tools:
DSM III-R and DSM-IV - Diagnostic Statistical Manual version 3 Revised and version 4.
ICD 10 - The International Statistical Classification of Diseases and Related Health Problems.
BMI - Body Mass Index.
Rating Scales:
Global rating scales:
GAF - Global Assessment of Functioning
CGI - Clinical Global Impressions.
CGI-S - Clinical Global Impression-Severity.
CGI-I - Clinical Global Impression-Improvement.
HAM-D - Hamilton Depression Rating Scale
Mental state:

BPRS - Brief Psychiatric Rating Scale.
MADRS - Montgomery-Asberg Depression Rating Scale.
MMSE - Wiing Mini Mental State Examination.
PANSS - Positive and Negative Syndrome Scale.
SANS - Scale for the Assessment of Negative Symptoms.
CDSS - Calgary Depression Severity Scale.
Cognition:RBANS - Repeatable Battery for the Assessment of Neuropsychological Status
WMS III- Welsch Memory Scale Edition III.
WAIS III - Welsch Adult Intelligence Scale
VFT - Verbal Fluency Test

Side effects:
AIMS - Abnormal Involuntary Movement Scale.
BARS - Barnes Akathisia Rating Scale.
BMI - Body mass index.
EPS- Extrapyramidal symptoms.
ESRS - Extrapyramidal Syndrome Rating Scale.
HAS - Hillside Akathisia Scale.
SAS - Simpson-Angus Index - for neurological side effects.
QoL - Quality of Life Scale.
SWN -Subjective Well-being List.
Other:
CNS - central nervous system
ECG - electrocardiogram
ECT - electroconvulsive therapy
ITT - intention-to-treat
LOCF - last observation carried forward

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

Study	Reason for exclusion
Davis 1981	Allocation: randomised. Participants: normal people.
Edelstein 1981	Allocation: non randomised.
El-Yousef 1973	Allocation: non randomised.
Ingram 1983	Allocation: non randomised.
Janowsky 1972	Allocation: non randomised.
Kristiansen 2001	Allocation: randomised. Participants: normal people.
Lieberman 1988	Allocation: randomised. Participants: people with tardive dyskinesia. No mention of schizophrenia or schizoaffective disorder

(*Continued*)

Mazeh 2006	Allocation: randomised, cross-over. Participants:elderly patients with diagnosis of schizophrenia and dementia
Moore 1980	Allocation: non randomised.
NCT00566735	Allocation: randomised. Participants: patients with diagnosis of major depression, bipolar depression, schizoaffective disorder-depressed type
Okereke 2002	Allocation: randomised,double blind, cross-over. Participants: patients with Parkinson's disease.
Ophir 2004	Allocation: randomised. Participants: patients receiving ECT.
Pesco-Koplowitz 2000c	Allocation: randomised. Participants: normal, healthy participants
Risch 1981	Allocation: non randomised.
Risch 2001	Allocation: non randomised.
Stryjer 2004a	Allocation: randomised. Participants: patients with schizophrenia. Design: cross-over design. Intervention: donepezil plus clozapine versus placebo plus clozapine. Outcome: no usable data.
Tamminga 1977	Allocation: randomised. Participants: patients with tardive dyskinesia.

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

Fleming 2003

Methods	randomised,double blind,placebo controlled.
Participants	Participants were 60 patients with diagnosis of schizophrenia,
Interventions	memantine plus donepezil
Outcomes	PANSS,CGI-S,Cognitive battery
Notes	full version not found,authors contacted.

Hussain 2003

Methods	Randomised, cross over, double blind.
Participants	Participants were 39 patients, 16 males and 23 females, aged 20-58 years (mean = 38.03), with a duration of illness of six to 30 years, (mean = 15.84) and two to 11 years of taking clozapine (mean 5.38), two to five years of taking olanzapine (mean = 3.19), or two to seven years of taking risperidone (mean = 4.73).
Interventions	double-blind, placebo-controlled trial of rivastigmine (1.5 mg bid) and galantamine (3 mg bid) as adjunctive treatment in stable schizophrenic patients with cognitive impairment receiving clozapine, risperidone, or olanzapine.
Outcomes	Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Quality of life Cognitive function Employment outcomes Educational achievement Treatment attrition Smoking abstinence
Notes	Awaiting more information from authors for clarification.

Kelleher 2008

Methods	randomised,double blind trial
Participants	patients with schizophrenia or schizoaffective disorder.
Interventions	Galantamine up to dose of 24mg/day.
Outcomes	BPRS,SCANS,Cognition.
Notes	Full paper not available,authors are not contactable.

Modestin 1973

Methods	
Participants	
Interventions	
Outcomes	
Notes	Paper in non English language, awaiting translation.

bid: twice daily

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

Ball 2005

Trial name or title	Efficacy study of Galantamine for cognitive impairment in schizophrenia
Methods	Treatment, Randomized, Double-Blind, Placebo Control,Parallel design
Participants	120 participants with a diagnosis of schizophrenia or schizoaffective disorder
Interventions	Galantamine and Placebo.
Outcomes	Cognitive functions. Mental state. Side effects.
Starting date	May 2002.
Contact information	ClinicalTrials.gov
Notes	ClinicalTrials.gov Identifier:NC00176423

Evins 2006

Trial name or title	Galantamine for Cognition in People With Schizophrenia.
Methods	Treatment, Randomized, Double-Blind, Placebo Control.
Participants	Twenty adult participants,aged 18-60.
Interventions	Galatamine and Placebo.
Outcomes	Improvement from baseline in performance on the cognitive battery: Stroop, Cornblatt CPT-IP, CDR Battery, letter number span, Grooved peg board, Tower of London, and Signal Detection Task. Improvement from baseline in negative symptoms (SANS), depressive symptoms (CDSS) and impulsivity (PANSS aggression item).
Starting date	January 2004.
Contact information	North Suffolk Mental Health Association Janssen Medical Affairs.
Notes	ClinicalTrials.gov Identifier: NCT00320736.

Gaskins 2007

Trial name or title	The Use of Galantamine and CDP-Choline to Treat Adults With Schizophrenia(STAR 1).
Methods	Randomized, Double-Blind, Placebo Control.
Participants	Adults age 18-70 years,mixed gender,meets DSM-IV criteria for schizophrenia or schizoaffective disorder
Interventions	Galantamine and CDP-choline in improving symptoms associated with schizophrenia
Outcomes	Clinical Global Impression (CGI) Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Memory Safety Urinalysis Electrocardiogram (ECG) Efficacy Negative symptoms Blood samples Processing speed Side effects Concentration Attention Nicotine use Cognitive Test
Starting date	September 2007
Contact information	ClinicalTrials.gov
Notes	ClinicalTrials.gov identifier NCT00509067

George 2007

Trial name or title	Galantamine for Cognitive Deficits in Schizophrenia
Methods	Treatment, Randomized, Double-Blind, Placebo Control, Parallel Assignment, Safety/Efficacy Study
Participants	Adults between 18 to 65 years of age,mixed gender ,schizophrenic smokers and non smokers
Interventions	Galantamine and Placebo.
Outcomes	Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Hamilton Depression Scale (HAM-D / HDRS) Extrapyramidal symptoms Cognitive function Safety Prepulse inhibition

George 2007 (*Continued*)

	VIG - sustained attention Adverse events Efficacy Neurocognitive functioning Neurocognitive tests Spatial working memory test Cognitive Test
Starting date	September 2007
Contact information	ClinicalTrials.gov
Notes	ClinicalTrials.gov identifier NCT00463879

Glenthoj 2005

Trial name or title	Cholinergic Augmentation of Cognitive Deficits in Schizophrenia
Methods	Randomized, Double-Blind, Placebo Control, Parallel Assignment, Efficacy Study
Participants	Men and women between the ages 18 to 55 who meet the ICD-10 criteria for schizophrenia and healthy men and women
Interventions	Donepezil (5-10 mg/day), Ziprasidone (flexible doses),Placebo
Outcomes	PANSS (Positive and Negative Symptom Scale) CGI (Clinical Global Impression scale) ESRS (Extrapyramidal Symptom Rating Scale) Cognitive functions: A comprehensive test battery focuses on central cognitive deficits in schizophrenia: i.e. memory functions, attention, executive functions, reaction time, as well as pre- morbid and current intelligence. Secondary Outcome Measures: • MRI • fMRI
Starting date	December 2002
Contact information	ClinicalTrials.gov Identifier,Center for Neuropsychiatric Schizophrenia Research (CNSR)
Notes	ClinicalTrials.gov Identifier: NCT00206947

Johnson 2004

Trial name or title	A study of the effectiveness and safety of Galantamine on cognitive impairment in patients with schizophrenia
Methods	Treatment, Randomized, Double-Blind, Placebo Control, Single Group Assignment, Safety/Efficacy Study
Participants	Patients with a diagnosis of schizophrenia.
Interventions	Galantamine and Placebo.
Outcomes	Cognitive functions. Mental state. Side effects.
Starting date	March 2003.
Contact information	ClinicalTrials.gov
Notes	ClinicalTrials.gov identifier NCT00077727.

Nachshoni 2007

Trial name or title	Donepezil Double Blind Trial for ECT Memory Disfunction
Methods	Randomized, Double-Blind, Placebo Control,Parallel Assignment, Efficacy Study
Participants	Age:between 18 to 60 years Gender:mixed Diagnosis:schizophrenia or schizoaffective disorder-DSM-IV
Interventions	1.Donepezil 2.Placebo
Outcomes	memory and neurocognitive measures will be examined
Starting date	May 2007
Contact information	ClinicalTrials.gov
Notes	ClinicalTrials.gov identifier NCT00465283

DATA AND ANALYSES

Comparison 1. Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global effect: 1a. Medium-term - Average end point score on various outcomes	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 CGI-severity (low = favourable)	1	11	Mean Difference (IV, Random, 95% CI)	0.46 [-0.15, 1.07]
2 Global effect: 1b. Medium-term - Average end point score on CGI improvement	1	11	Mean Difference (IV, Random, 95% CI)	0.57 [-0.50, 1.64]
2.1 CGI-improvement (high = favourable)	1	11	Mean Difference (IV, Random, 95% CI)	0.57 [-0.50, 1.64]
3 Global effect : 1c. Short-term - Average change score on CGI (high = favourable)			Other data	No numeric data
4 Leaving the study early	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Adverse event: Short-term	6	428	Risk Ratio (M-H, Random, 95% CI)	1.91 [0.80, 4.61]
4.2 Any reason: Short-term	9	513	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.59, 1.28]
4.3 Deterioration in mental state: 1a. Short-term	2	103	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.09, 5.10]
4.4 Deterioration in mental state: 1b. Medium-term	1	17	Risk Ratio (M-H, Random, 95% CI)	2.18 [0.10, 46.92]
4.5 Lost to follow up: Short-term	1	245	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.26, 4.01]
4.6 Protocol violation: Short-term	2	262	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.04, 1.43]
4.7 Unwilling to participate further in the study: Short-term	1	245	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.30, 3.45]
4.8 Due to intercurrent medical illness: Short-term	2	122	Risk Ratio (M-H, Random, 95% CI)	2.91 [0.31, 27.07]
5 Mental State: 1a. Average end point score on various outcomes - PANSS (low = favourable)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Short-term - PANSS total end point score (low = favourable)	2	18	Mean Difference (IV, Random, 95% CI)	3.29 [-8.82, 15.40]
5.2 Short-term - PANSS positive end point score (low = avourable)	1	12	Mean Difference (IV, Random, 95% CI)	1.5 [-4.44, 7.44]
5.3 Short-term - PANSS negative end point score (low = favourable)	1	12	Mean Difference (IV, Random, 95% CI)	3.50 [-3.66, 10.66]

5.4 Short-term - PANSS general psychopathology end point score (low = favourable)	1	12	Mean Difference (IV, Random, 95% CI)	1.80 [-4.81, 8.41]
6 Mental state:1b.Average end point score on various outcomes-PANSS (medium-term)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Medium-term - PANSS total end point score (low = favourable)	2	31	Mean Difference (IV, Random, 95% CI)	-4.32 [-11.56, 2.92]
6.2 Medium-term - PANSS positive end point score (low = favourable)	2	31	Mean Difference (IV, Random, 95% CI)	0.65 [-0.12, 1.43]
6.3 Medium-term - PANSS negative end point score (low = favourable)	2	31	Mean Difference (IV, Random, 95% CI)	-1.69 [-2.80, -0.57]
6.4 Medium-term - PANSS general psychopathology end point score (low = favourable)	2	31	Mean Difference (IV, Random, 95% CI)	-3.86 [-5.40, -2.32]
7 Mental State: 2. Short-term - Average end point score on HAM-D (low = favourable)	1	30	Mean Difference (IV, Random, 95% CI)	-0.60 [-1.82, 0.62]
8 Mental State: 3. Short-term - Average end point score on SANS (low = favourable)	1	20	Mean Difference (IV, Random, 95% CI)	-5.0 [-21.33, 11.33]
9 Mental state: 4a. Short-term - Average end point score on CDSS (low = favourable)			Other data	No numeric data
10 Mental State: 4b. Medium-term - Average end point score on CDSS (low = favourable)			Other data	No numeric data
11 Mental State: 5. Short-term - Average change score on PANSS (low = favourable)			Other data	No numeric data
11.1 total			Other data	No numeric data
11.2 positive			Other data	No numeric data
11.3 negative			Other data	No numeric data
12 General functioning: Medium-term - average end point score on GAF	1	11	Mean Difference (IV, Random, 95% CI)	4.60 [-5.88, 15.08]
12.1 GAF (high = favourable)	1	11	Mean Difference (IV, Random, 95% CI)	4.60 [-5.88, 15.08]
13 Cognitive function: 1. Short-term - Average end point score on KMMSE (high = favourable)	2	48	Mean Difference (IV, Random, 95% CI)	1.29 [-0.18, 2.77]
14 Cognitive function: 2. Short-term - Average end point score on various subscales of WMS-III (high = favourable)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
14.1 Digit span forward	2	36	Mean Difference (IV, Random, 95% CI)	-0.89 [-1.68, -0.10]
14.2 Digit span backward	2	36	Mean Difference (IV, Random, 95% CI)	-0.69 [-1.35, -0.02]
14.3 Figural memory test	1	12	Mean Difference (IV, Random, 95% CI)	1.30 [-0.74, 3.34]

14.4 Visual reproduction 1	1	12	Mean Difference (IV, Random, 95% CI)	1.30 [-5.21, 7.81]
14.5 Visual reproduction 2	1	12	Mean Difference (IV, Random, 95% CI)	-1.5 [-8.69, 5.69]
14.6 Verbal paired associates 1	1	12	Mean Difference (IV, Random, 95% CI)	-3.20 [-7.28, 0.88]
14.7 Verbal paired associates 2	1	12	Mean Difference (IV, Random, 95% CI)	-0.60 [-1.92, 0.72]
14.8 Logical memory 1	1	12	Mean Difference (IV, Random, 95% CI)	-4.60 [-12.72, 3.52]
14.9 Logical memory 2	1	12	Mean Difference (IV, Random, 95% CI)	-4.60 [-13.26, 4.06]
15 Cognitive function: 3. Short-term - Average end point score on various subscales of of WAIS III (high = favourable)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
15.1 Block design	1	12	Mean Difference (IV, Random, 95% CI)	3.10 [-9.71, 15.91]
15.2 Letter number sequencing	1	73	Mean Difference (IV, Random, 95% CI)	0.60 [-0.48, 1.68]
15.3 Digit symbol score	1	73	Mean Difference (IV, Random, 95% CI)	1.20 [0.14, 2.26]
15.4 Symbol search score	1	73	Mean Difference (IV, Random, 95% CI)	0.30 [-0.92, 1.52]
15.5 Letter number span without reordering	1	20	Mean Difference (IV, Random, 95% CI)	-1.60 [-4.19, 0.99]
15.6 Letter number span with ordering	1	20	Mean Difference (IV, Random, 95% CI)	-0.5 [-3.27, 2.27]
16 Cognitive function: 4. Short-term - Average end point score on various subscales of HVLT (high = favourable)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
16.1 Immediate recall	1	24	Mean Difference (IV, Random, 95% CI)	3.0 [-0.76, 6.76]
16.2 Delayed recall	1	24	Mean Difference (IV, Random, 95% CI)	1.5 [-0.20, 3.20]
16.3 Recognition	2	48	Mean Difference (IV, Random, 95% CI)	1.79 [0.62, 2.96]
17 Cognitive function: 5. Short-term - Average end point score on VFT (high = favourable)	3	42	Mean Difference (IV, Random, 95% CI)	3.46 [0.67, 6.26]
17.1 Verbal fluency	3	42	Mean Difference (IV, Random, 95% CI)	3.46 [0.67, 6.26]
18 Cognitive function: 6. Short-term - Average end point score on BVST (high = favourable)	1	73	Mean Difference (IV, Random, 95% CI)	-0.5 [-1.42, 0.42]
18.1 Brief Visuospatial Memory Test	1	73	Mean Difference (IV, Random, 95% CI)	-0.5 [-1.42, 0.42]
19 Cognitive function: 7. Short-term - Average end point score on various subscales of Stroop test	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
19.1 Stroop letter end point score (high = favourable)	1	24	Mean Difference (IV, Random, 95% CI)	-1.5 [-12.15, 9.15]
19.2 Stroop color end point score (high = favourable)	1	24	Mean Difference (IV, Random, 95% CI)	17.10 [0.70, 33.50]
19.3 Stroop Interference T end point score (low = favourable)	1	20	Mean Difference (IV, Random, 95% CI)	-2.60 [-6.68, 1.48]

20 Cognitive function: 7. Short-term - Average end point score on Trail making tests A & B (high = favourable)	2	48	Mean Difference (IV, Random, 95% CI)	-5.53 [-30.67, 19.61]
20.1 Trail making A	2	36	Mean Difference (IV, Random, 95% CI)	-11.83 [-44.14, 20.49]
20.2 Trail making B	1	12	Mean Difference (IV, Random, 95% CI)	16.40 [-32.33, 65.13]
21 Cognitive function: 8. Short-term - Average end point score on CPT	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
21.1 CPT - Reaction time (high = favourable)	1	20	Mean Difference (IV, Random, 95% CI)	-5.20 [-70.74, 60.34]
21.2 CPT - Random errors (low = favourable)	1	20	Mean Difference (IV, Random, 95% CI)	-0.20 [-1.71, 1.31]
22 Cognitive function: 9. Short-term - Average end point score on Grooved pegboard test (high = favourable)	2	93	Mean Difference (IV, Random, 95% CI)	-0.29 [-3.11, 2.53]
22.1 Grooved pegboard - Average pegs	2	93	Mean Difference (IV, Random, 95% CI)	-0.29 [-3.11, 2.53]
23 Cognitive function: 10. Short-term - Average end point score on various scales (skewed data)			Other data	No numeric data
23.1 ROCFT-Immediate recall (high = favourable)			Other data	No numeric data
23.2 ROCFT-Delayed recall (high = favourable)			Other data	No numeric data
23.3 ROCFT-Recognition (high = favourable)			Other data	No numeric data
23.4 WAIS III-Letter number span without reordering (high = favourable)			Other data	No numeric data
23.5 WAIS III-Letter number span with reordering (high = favourable)			Other data	No numeric data
23.6 WCST-Categories completed (high = favourable)			Other data	No numeric data
23.7 WCST-Perseverative errors (low = favourable)			Other data	No numeric data
23.8 Visual paired associates 1 (high = favourable)			Other data	No numeric data
23.9 CPT-random errors (low = favourable)			Other data	No numeric data
23.10 Stroop Interfernece Test (low = favourable)			Other data	No numeric data
23.11 Visual paired associates 2 (high = favourable)			Other data	No numeric data

24 Cognitive function: 11a. Short-term - Average change score on various scales (skewed data)			Other data	No numeric data
24.1 RAVLT-Delayed recall (high = favourable)			Other data	No numeric data
24.2 CPT-Omission of errors (low = favourable)			Other data	No numeric data
24.6 RAVLT-total word list learning (high = favourable)			Other data	No numeric data
24.9 CPT (high = favourable)			Other data	No numeric data
24.12 RBANS total score (high = favourable)			Other data	No numeric data
25 Cognitive function: 11b. Medium-term - Average change score on various scales (skewed data)			Other data	No numeric data
25.1 Category fluency test (high = favourable)			Other data	No numeric data
25.2 Trail making test A-time (high = favourable)			Other data	No numeric data
25.3 Stroop test-interference index (low = favourable)			Other data	No numeric data
25.4 Logical memory (high = favourable)			Other data	No numeric data
25.5 Wisconsin Card Sorting Test-perseverative errors (low = favourable)			Other data	No numeric data
25.6 Wisconsin Card Sorting-number of completed categories (high = favourable)			Other data	No numeric data
25.7 Rey Osterrieth Complex Figure Test (high = favourable)			Other data	No numeric data
25.8 Verbal pair Association-global score (high = favourable)			Other data	No numeric data
26 Adverse event: 1a. Short-term - Central nervous system	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
26.1 Dizziness	4	379	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.30, 1.94]
26.2 Sialorrhea	1	36	Risk Ratio (M-H, Random, 95% CI)	6.30 [0.35, 113.81]
26.3 Headache	2	269	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.24, 1.12]
26.4 Insomnia	2	269	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.19, 1.20]
26.5 Somnolence	1	245	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.12, 1.66]
26.6 Deterioration in mental state: 1b. Medium-term	1	17	Risk Ratio (M-H, Random, 95% CI)	2.18 [0.10, 46.92]
27 Adverse event: 1b. Medium-term - Central nervous system	1	11	Risk Ratio (M-H, Random, 95% CI)	1.88 [0.09, 37.63]
28 Adverse event: 2. Short-term - Metabolic and nutritional	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
28.1 Weight loss	2	102	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.04, 6.96]

28.2 Glucose	1	245	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.14, 1.44]
29 Adverse event: 3. Short-term - Deterioration in menal state	2	102	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.08, 4.86]
30 Adverse event: 4. Short-term - Biochemical abnormalities	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
30.1 Creatine kinase	1	245	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.44, 3.13]
31 Adverse event: 5. Short-term - Non specific	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
31.1 Severe AE	1	245	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.41, 2.11]
31.2 Serious AE	1	245	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.37, 2.83]
31.3 Relapse of alcohol	1	86	Risk Ratio (M-H, Random, 95% CI)	3.14 [0.13, 74.98]
31.4 Muscle cramp	2	44	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.52, 17.20]
31.5 Agitation and uncooperativeness	1	36	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.26, 97.37]
32 Adverse event: 6. Short-term - Cardiovascular	1	245	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.23, 1.15]
33 Adverse event: 7. Short-term - Gastrointestinal	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
33.1 Vomiting	4	371	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.25, 2.48]
33.2 Abdomial pain and diarrhoea	1	24	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 67.06]
33.3 Diarrhoea	4	309	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.56, 2.70]
33.4 Nausea	3	293	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.45, 2.78]
33.5 Any	1	245	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.58, 1.46]
34 Adverse event: 9. Short-term - Respiratory system	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
34.1 Pneumonia	1	86	Risk Ratio (M-H, Random, 95% CI)	3.14 [0.13, 74.98]
35 Adverse event: 10. Medium-term - EPSE	1	11	Risk Ratio (M-H, Random, 95% CI)	4.38 [0.28, 68.06]
36 Adverse event: 11a. Short-term - Average end point score on EPSEs scale (low = favourable)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
36.1 AIMS	1	35	Mean Difference (IV, Random, 95% CI)	1.5 [1.04, 1.96]
37 Adverse event: 11b. Medium-term - Average end point score on EPSEs scale (low = favourable)	1	21	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.38, 0.06]
37.1 SAS	1	21	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.38, 0.06]
38 Adverse event: 12a. Short-term - Average end point score on EPSEs scale (low = favourable)			Other data	No numeric data
38.1 SARS			Other data	No numeric data
38.2 AIMS			Other data	No numeric data
38.3 ESRS			Other data	No numeric data
39 Adverse event: 12b. Medium-term - Average end point score on EPSEs scales (skewed data)			Other data	No numeric data
39.1 AIMS			Other data	No numeric data
39.4 BARS			Other data	No numeric data

40 Adverse event: 13. Short-term - Average change score on EPSEs scales (skewed data)			Other data	No numeric data
40.1 AIMS			Other data	No numeric data
40.2 SAS			Other data	No numeric data
41 Adverse event: 14. Short-term - Average change interval on ECG (skewed data)			Other data	No numeric data
41.1 PR interval			Other data	No numeric data
41.2 QRS interval			Other data	No numeric data
41.3 QTc interval			Other data	No numeric data
42 Behaviour: 15. Short-term - Smoking (low = favourable)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
42.1 Expired CO measures	1	41	Mean Difference (IV, Random, 95% CI)	0.10 [-6.25, 6.45]
42.2 FTND intervew score	1	41	Mean Difference (IV, Random, 95% CI)	1.50 [0.09, 2.91]

Comparison 2. Acetylcholinesterase inhibitors plus antipsychotics versus antipsychotics alone

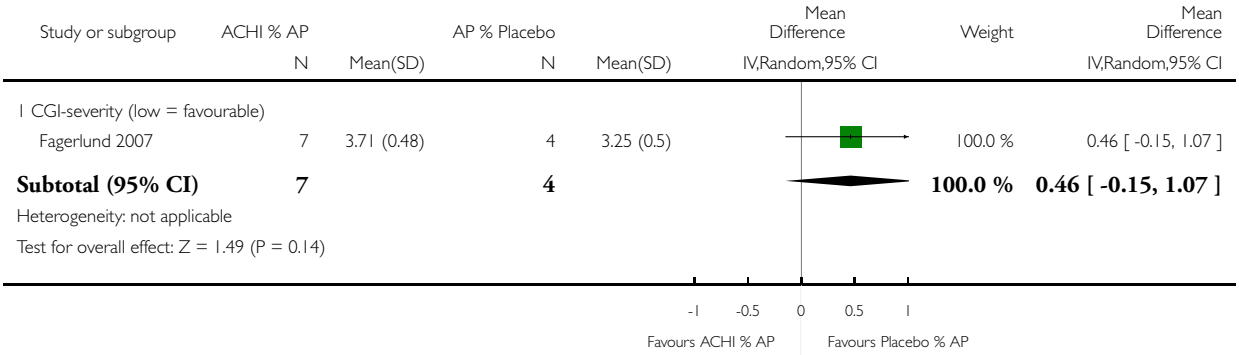
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early	1	72	Risk Ratio (M-H, Random, 95% CI)	3.89 [0.69, 22.02]
1.1 Any reason	1	24	Risk Ratio (M-H, Random, 95% CI)	7.71 [0.46, 129.18]
1.2 Deterioration in mental state	1	24	Risk Ratio (M-H, Random, 95% CI)	2.57 [0.12, 57.44]
1.3 Suicidal ideas	1	24	Risk Ratio (M-H, Random, 95% CI)	2.57 [0.12, 57.44]
2 Mental state: Short-term - Average end point score on PANSS (low = favourable)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Negative	1	18	Mean Difference (IV, Random, 95% CI)	-0.60 [-4.14, 2.94]
2.2 Positive	1	18	Mean Difference (IV, Random, 95% CI)	1.10 [-2.59, 4.79]
2.3 Disorganisation/cognitive	1	18	Mean Difference (IV, Random, 95% CI)	0.5 [-2.04, 3.04]
2.4 Hostility/excitement	1	18	Mean Difference (IV, Random, 95% CI)	0.20 [-1.56, 1.96]
2.5 Anxiety/Depressive	1	18	Mean Difference (IV, Random, 95% CI)	0.0 [-0.93, 0.93]
2.6 Total	1	18	Mean Difference (IV, Random, 95% CI)	1.80 [-4.47, 8.07]

Analysis 1.1. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 1 Global effect: 1a. Medium-term - Average end point score on various outcomes.

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 1 Global effect: 1a. Medium-term - Average end point score on various outcomes

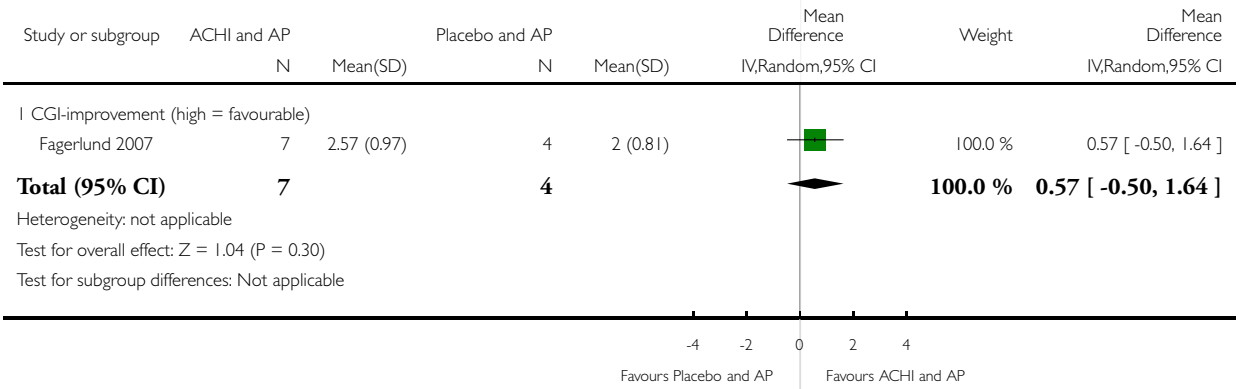


Analysis 1.2. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 2 Global effect: 1b. Medium-term - Average end point score on CGI improvement.

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 2 Global effect: 1b. Medium-term - Average end point score on CGI improvement



Analysis 1.3. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 3 Global effect : 1c. Short-term - Average change score on CGI (high = favourable).

Global effect : 1c. Short-term - Average change score on CGI (high = favourable)

Study	Intervention	Mean change	SD	N
Schubert 2006	ACHI & AP	-.57	.78	8
Schubert 2006	AP & Placebo	.0	.6	6

Analysis 1.4. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 4 Leaving the study early.

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 4 Leaving the study early

Study or subgroup	ACHI % Antipsychotic n/N	Placebo and Antipsychotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Adverse event: Short-term					
Buchanan 2008	3/42	2/44		25.5 %	1.57 [0.28, 8.94]
Dyer 2008	1/10	0/10		8.1 %	3.00 [0.14, 65.90]
Friedman 2002c	2/18	0/18		8.7 %	5.00 [0.26, 97.37]
Keefe 2008a	6/121	3/124		41.5 %	2.05 [0.52, 8.01]
Lee 2005	1/12	0/12		8.0 %	3.00 [0.13, 67.06]
Schubert 2006	0/8	1/9		8.2 %	0.37 [0.02, 7.99]
Subtotal (95% CI)	**211**	**217**		**100.0 %**	**1.91 [0.80, 4.61]**
Total events: 13 (ACHI % Antipsychotic), 6 (Placebo and Antipsychotic)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.72$, df = 5 (P = 0.89); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.45 (P = 0.15)					
2 Any reason: Short-term					
Buchanan 2008	7/42	6/44		14.7 %	1.22 [0.45, 3.34]
Caroff 2007	3/17	9/18		11.7 %	0.35 [0.11, 1.09]
Dyer 2008	1/10	1/10		2.1 %	1.00 [0.07, 13.87]
Friedman 2002c	2/18	0/18		1.7 %	5.00 [0.26, 97.37]

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Study or subgroup	ACHI % Antipsychotic n/N	Placebo and Antipsychotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Keefe 2008a	23/121	27/124		60.1 %	0.87 [0.53, 1.43]
Kim 2005b	1/12	0/12		1.5 %	3.00 [0.13, 67.06]
Kohler 2007	2/13	2/13		4.6 %	1.00 [0.16, 6.07]
Lee 2005	2/12	0/12		1.7 %	5.00 [0.27, 94.34]
Schubert 2006	0/8	3/9		1.9 %	0.16 [0.01, 2.67]
Subtotal (95% CI)	**253**	**260**		**100.0 %**	**0.87 [0.59, 1.28]**
Total events: 41 (ACHI % Antipsychotic), 48 (Placebo and Antipsychotic)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 7.65, df = 8 (P = 0.47); I^2 =0.0%					
Test for overall effect: Z = 0.70 (P = 0.49)					
3 Deterioration in mental state: 1a. Short-term					
Buchanan 2008	1/42	1/44		55.7 %	1.05 [0.07, 16.21]
Schubert 2006	0/8	1/9		44.3 %	0.37 [0.02, 7.99]
Subtotal (95% CI)	**50**	**53**		**100.0 %**	**0.66 [0.09, 5.10]**
Total events: 1 (ACHI % Antipsychotic), 2 (Placebo and Antipsychotic)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.25, df = 1 (P = 0.62); I^2 =0.0%					
Test for overall effect: Z = 0.40 (P = 0.69)					
4 Deterioration in mental state: 1b. Medium-term					
Tuma 2003	1/10	0/7		100.0 %	2.18 [0.10, 46.92]
Subtotal (95% CI)	**10**	**7**		**100.0 %**	**2.18 [0.10, 46.92]**
Total events: 1 (ACHI % Antipsychotic), 0 (Placebo and Antipsychotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.50 (P = 0.62)					
5 Lost to follow up: Short-term					
Keefe 2008a	4/121	4/124		100.0 %	1.02 [0.26, 4.01]
Subtotal (95% CI)	**121**	**124**		**100.0 %**	**1.02 [0.26, 4.01]**
Total events: 4 (ACHI % Antipsychotic), 4 (Placebo and Antipsychotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.04 (P = 0.97)					
6 Protocol violation: Short-term					
Keefe 2008a	1/121	5/124		67.5 %	0.20 [0.02, 1.73]
Schubert 2006	0/8	1/9		32.5 %	0.37 [0.02, 7.99]
Subtotal (95% CI)	**129**	**133**		**100.0 %**	**0.25 [0.04, 1.43]**
Total events: 1 (ACHI % Antipsychotic), 6 (Placebo and Antipsychotic)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.10, df = 1 (P = 0.76); I^2 =0.0%					
Test for overall effect: Z = 1.56 (P = 0.12)					
7 Unwilling to participate further in the study: Short-term					
Keefe 2008a	5/121	5/124		100.0 %	1.02 [0.30, 3.45]
Subtotal (95% CI)	**121**	**124**		**100.0 %**	**1.02 [0.30, 3.45]**

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Study or subgroup	ACHI % Antipsy-chotic n/N	Placebo and Antipsychotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 5 (ACHI % Antipsychotic), 5 (Placebo and Antipsychotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.04 (P = 0.97)					
8 Due to intercurrent medical illness: Short-term					
Buchanan 2008	1/42	0/44		49.4 %	3.14 [0.13, 74.98]
Freudenreich 2005	1/19	0/17		50.6 %	2.70 [0.12, 62.17]
Subtotal (95% CI)	**61**	**61**		**100.0 %**	**2.91 [0.31, 27.07]**
Total events: 2 (ACHI % Antipsychotic), 0 (Placebo and Antipsychotic)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%					
Test for overall effect: Z = 0.94 (P = 0.35)					

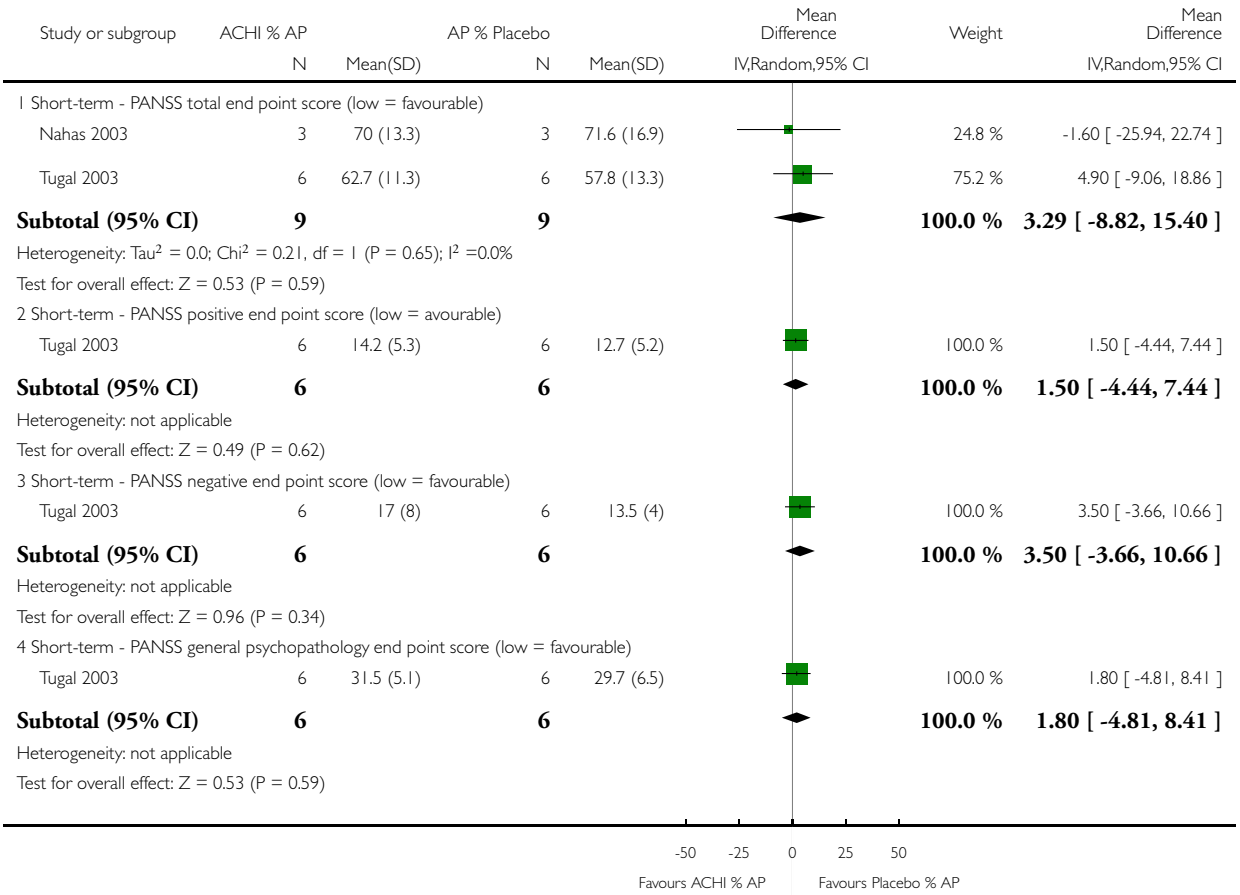
Analysis 1.5. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 5 Mental State: 1a. Average end point score on various outcomes - PANSS (low = favourable).

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 5 Mental State: 1a. Average end point score on various outcomes - PANSS (low = favourable)

Study or subgroup	ACHI % AP N	Mean(SD)	AP % Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Short-term - PANSS total end point score (low = favourable)							
Nahas 2003	3	70 (13.3)	3	71.6 (16.9)		24.8 %	-1.60 [-25.94, 22.74]
Tugal 2003	6	62.7 (11.3)	6	57.8 (13.3)		75.2 %	4.90 [-9.06, 18.86]
Subtotal (95% CI)	**9**		**9**			**100.0 %**	**3.29 [-8.82, 15.40]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.21$, df = 1 (P = 0.65); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.53 (P = 0.59)							
2 Short-term - PANSS positive end point score (low = avourable)							
Tugal 2003	6	14.2 (5.3)	6	12.7 (5.2)		100.0 %	1.50 [-4.44, 7.44]
Subtotal (95% CI)	**6**		**6**			**100.0 %**	**1.50 [-4.44, 7.44]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.49 (P = 0.62)							
3 Short-term - PANSS negative end point score (low = favourable)							
Tugal 2003	6	17 (8)	6	13.5 (4)		100.0 %	3.50 [-3.66, 10.66]
Subtotal (95% CI)	**6**		**6**			**100.0 %**	**3.50 [-3.66, 10.66]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.96 (P = 0.34)							
4 Short-term - PANSS general psychopathology end point score (low = favourable)							
Tugal 2003	6	31.5 (5.1)	6	29.7 (6.5)		100.0 %	1.80 [-4.81, 8.41]
Subtotal (95% CI)	**6**		**6**			**100.0 %**	**1.80 [-4.81, 8.41]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.53 (P = 0.59)							

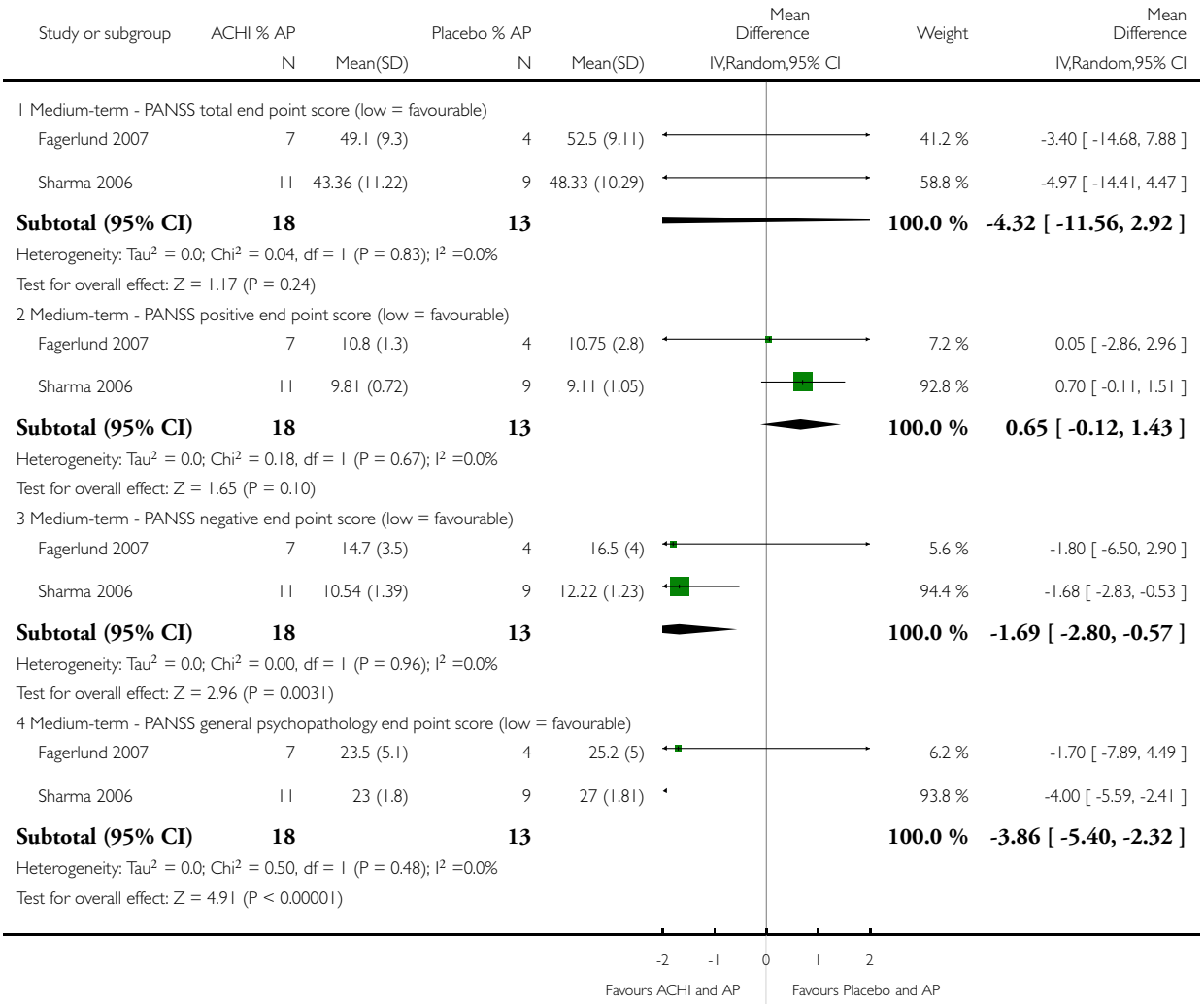


Analysis 1.6. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 6 Mental state:1b.Average end point score on various outcomes-PANSS (medium-term).

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 6 Mental state:1b.Average end point score on various outcomes-PANSS (medium-term)

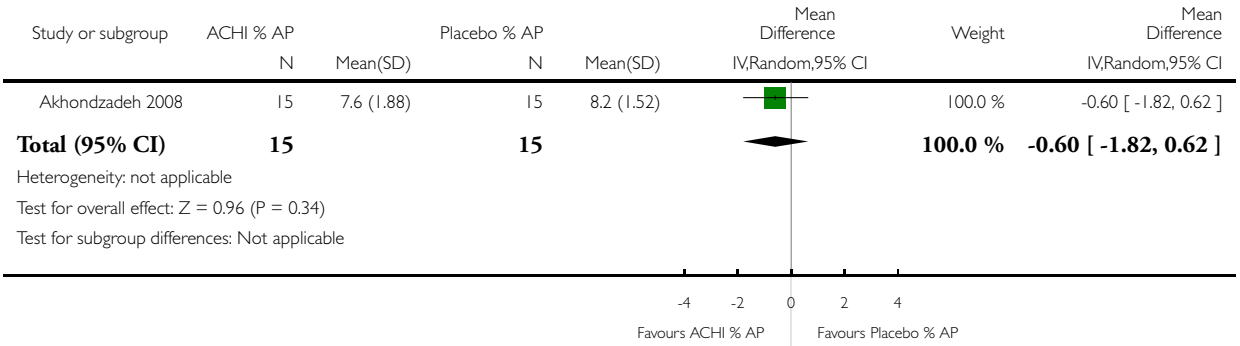


Analysis 1.7. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 7 Mental State: 2. Short-term - Average end point score on HAM-D (low = favourable).

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 7 Mental State: 2. Short-term - Average end point score on HAM-D (low = favourable)

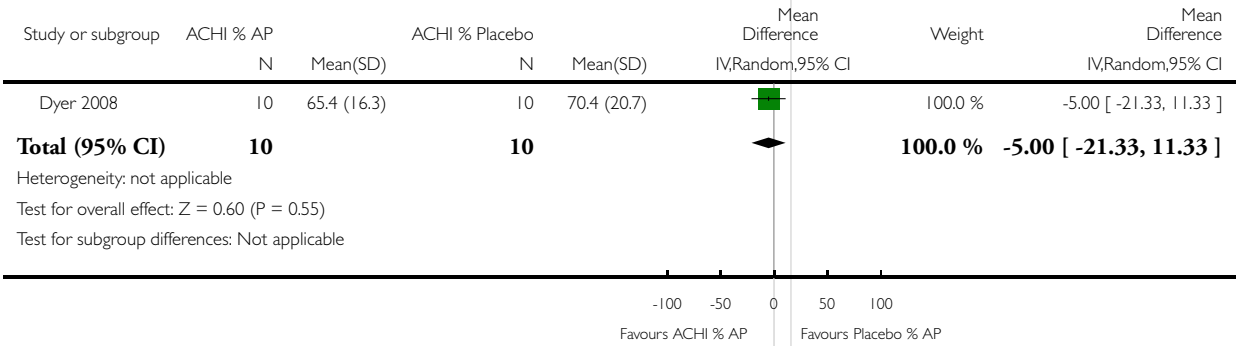


Analysis 1.8. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 8 Mental State: 3. Short-term - Average end point score on SANS (low = favourable).

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 8 Mental State: 3. Short-term - Average end point score on SANS (low = favourable)



Analysis 1.9. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 9 Mental state: 4a. Short-term - Average end point score on CDSS (low = favourable).

Mental state: 4a. Short-term - Average end point score on CDSS (low = favourable)

Study	Intervention	Mean	SD	N
Dyer 2008	ACHI & AP	3.6	3.3	10
Dyer 2008	Placebo & AP	6.9	5.2	10
Tugal 2003	ACHI & AP	2.7	1.8	6
Tugal 2003	Placebo & AP	2.7	2.4	6

Analysis 1.10. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 10 Mental State: 4b. Medium-term - Average end point score on CDSS (low = favourable).

Mental State: 4b. Medium-term - Average end point score on CDSS (low = favourable)

Study	Intervention	Mean	SD	N
Fagerlund 2007	ACHI & AP	1.71	2.13	7
Fagerlund 2007	placebo & AP	3.25	4.57	4

Analysis 1.11. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 11 Mental State: 5. Short-term - Average change score on PANSS (low = favourable).

Mental State: 5. Short-term - Average change score on PANSS (low = favourable)

Study	Intervention	Mean change	SD	N
total				
Schubert 2006	ACHI & AP	-12.2	14.4	8
Schubert 2006	AP & Placebo	-13.5	4.7	6
positive				
Schubert 2006	ACHI & AP	-4.3	6.0	8
Schubert 2006	AP & PLacebo	-4.0	4.2	6
negative				

Mental State: 5. Short-term - Average change score on PANSS (low = favourable) (*Continued*)

Schubert 2006	ACHI & AP	-3.3	4.4	8
Schubert 2006	AP & Placebo	-2.5	2.9	6

Analysis 1.12. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 12 General functioning: Medium-term - average end point score on GAF.

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

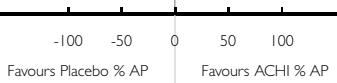
Outcome: 12 General functioning: Medium-term - average end point score on GAF

Study or subgroup	ACHI % AP N	Mean(SD)	Placebo % AP N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 GAF (high = favourable)							
Fagerlund 2007	7	64.1 (11.6)	4	59.5 (6.13)		100.0 %	4.60 [-5.88, 15.08]
Total (95% CI)	**7**		**4**			**100.0 %**	**4.60 [-5.88, 15.08]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.86 (P = 0.39)

Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 13 Cognitive function: 1. Short-term - Average end point score on KMMSE (high = favourable).

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 13 Cognitive function: 1. Short-term - Average end point score on KMMSE (high = favourable)

Study or subgroup	ACHI % AP N	Mean(SD)	Placebo and AP N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Kim 2005b	12	25.1 (3.5)	12	22.7 (3.7)		26.3 %	2.40 [-0.48, 5.28]
Lee 2005	12	25.2 (2.1)	12	24.3 (2.2)		73.7 %	0.90 [-0.82, 2.62]
Total (95% CI)	**24**		**24**			**100.0 %**	**1.29 [-0.18, 2.77]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.77$, df = 1 (P = 0.38); $I^2 = 0.0\%$

Test for overall effect: Z = 1.72 (P = 0.086)

Test for subgroup differences: Not applicable

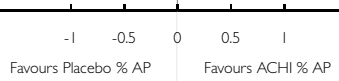
Analysis 1.14. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 14 Cognitive function: 2. Short-term - Average end point score on various subscales of WMS-III (high = favourable).

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 14 Cognitive function: 2. Short-term - Average end point score on various subscales of WMS-III (high = favourable)

Study or subgroup	ACHI and AP N	Mean(SD)	Placebo and AP N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Digit span forward							
Lee 2005	12	4.9 (0.9)	12	5.9 (1.3)		78.3 %	-1.00 [-1.89, -0.11]
Tugal 2003	6	7.3 (1.4)	6	7.8 (1.6)		21.7 %	-0.50 [-2.20, 1.20]
Subtotal (95% CI)	**18**		**18**			**100.0 %**	**-0.89 [-1.68, -0.10]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.26$, df = 1 (P = 0.61); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.21 (P = 0.027)							
2 Digit span backward							
Lee 2005	12	2.8 (0.7)	12	3.5 (1)		92.6 %	-0.70 [-1.39, -0.01]
Tugal 2003	6	5.3 (2.6)	6	5.8 (1.6)		7.4 %	-0.50 [-2.94, 1.94]
Subtotal (95% CI)	**18**		**18**			**100.0 %**	**-0.69 [-1.35, -0.02]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.02$, df = 1 (P = 0.88); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.02 (P = 0.043)							
3 Figural memory test							
Tugal 2003	6	8.3 (1.9)	6	7 (1.7)		100.0 %	1.30 [-0.74, 3.34]
Subtotal (95% CI)	**6**		**6**			**100.0 %**	**1.30 [-0.74, 3.34]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.25 (P = 0.21)							
4 Visual reproduction 1							
Tugal 2003	6	34.5 (3.8)	6	33.2 (7.2)		100.0 %	1.30 [-5.21, 7.81]
Subtotal (95% CI)	**6**		**6**			**100.0 %**	**1.30 [-5.21, 7.81]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.39 (P = 0.70)							
5 Visual reproduction 2							
Tugal 2003	6	32.2 (8.1)	6	33.7 (3.9)		100.0 %	-1.50 [-8.69, 5.69]
Subtotal (95% CI)	**6**		**6**			**100.0 %**	**-1.50 [-8.69, 5.69]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.41 (P = 0.68)							
6 Verbal paired associates 1							
Tugal 2003	6	18.8 (4.5)	6	22 (2.4)		100.0 %	-3.20 [-7.28, 0.88]
Subtotal (95% CI)	**6**		**6**			**100.0 %**	**-3.20 [-7.28, 0.88]**
Heterogeneity: not applicable							



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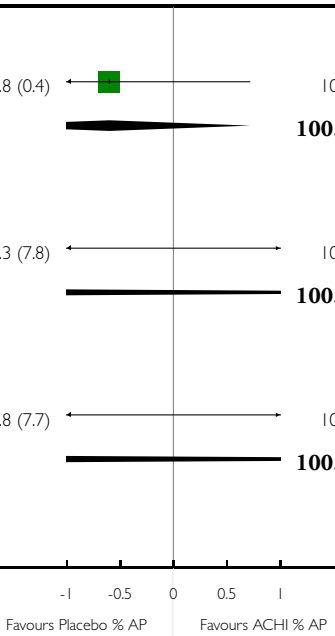
Study or subgroup	ACHI and AP N	Mean(SD)	Placebo and AP N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Test for overall effect: Z = 1.54 (P = 0.12)							
7 Verbal paired associates 2							
Tugal 2003	6	7.2 (1.6)	6	7.8 (0.4)		100.0 %	-0.60 [-1.92, 0.72]
Subtotal (95% CI)	**6**		**6**			**100.0 %**	**-0.60 [-1.92, 0.72]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.89 (P = 0.37)							
8 Logical memory 1							
Tugal 2003	6	22.7 (6.5)	6	27.3 (7.8)		100.0 %	-4.60 [-12.72, 3.52]
Subtotal (95% CI)	**6**		**6**			**100.0 %**	**-4.60 [-12.72, 3.52]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.11 (P = 0.27)							
9 Logical memory 2							
Tugal 2003	6	20.2 (7.6)	6	24.8 (7.7)		100.0 %	-4.60 [-13.26, 4.06]
Subtotal (95% CI)	**6**		**6**			**100.0 %**	**-4.60 [-13.26, 4.06]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.04 (P = 0.30)							

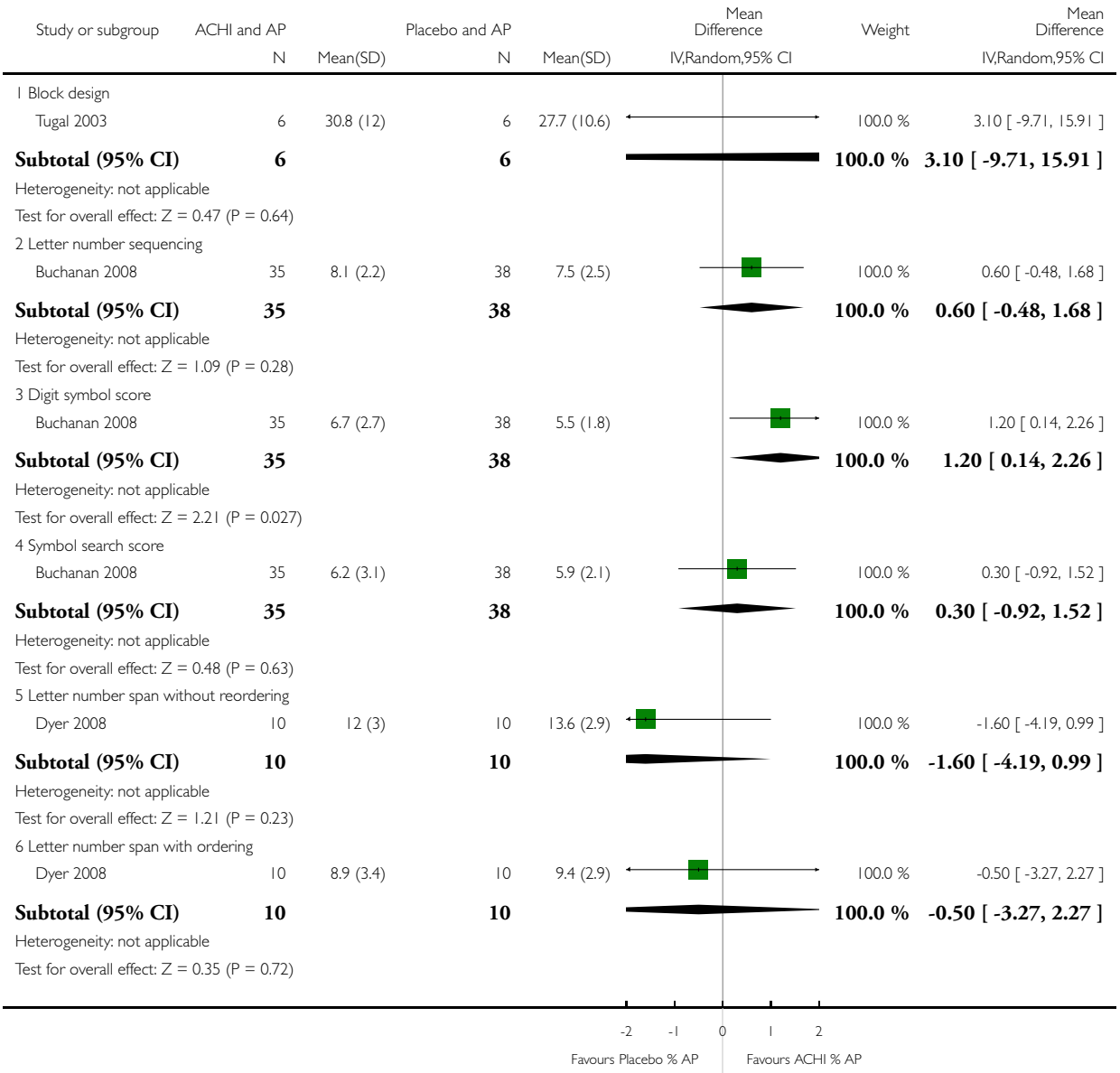


Analysis 1.15. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 15 Cognitive function: 3. Short-term - Average end point score on various subscales of of WAIS III (high = favourable).

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 15 Cognitive function: 3. Short-term - Average end point score on various subscales of of WAIS III (high = favourable)



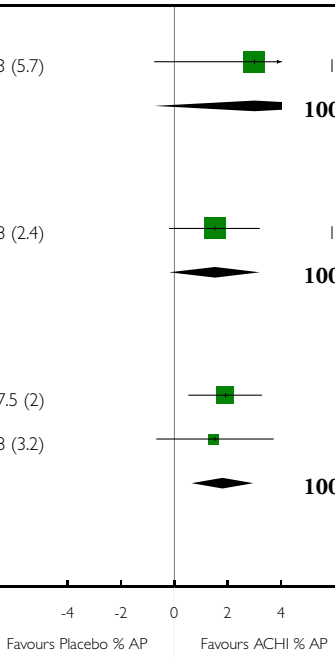
Analysis 1.16. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 16 Cognitive function: 4. Short-term - Average end point score on various subscales of HVLT (high = favourable).

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 16 Cognitive function: 4. Short-term - Average end point score on various subscales of HVLT (high = favourable)

Study or subgroup	ACHI % AP N	Mean(SD)	Placebo % AP N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Immediate recall							
Lee 2005	12	17.3 (3.4)	12	14.3 (5.7)		100.0 %	3.00 [-0.76, 6.76]
Subtotal (95% CI)	**12**		**12**			**100.0 %**	**3.00 [-0.76, 6.76]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.57 (P = 0.12)							
2 Delayed recall							
Lee 2005	12	5.3 (1.8)	12	3.8 (2.4)		100.0 %	1.50 [-0.20, 3.20]
Subtotal (95% CI)	**12**		**12**			**100.0 %**	**1.50 [-0.20, 3.20]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.73 (P = 0.083)							
3 Recognition							
Kim 2005b	12	9.4 (1.4)	12	7.5 (2)		71.7 %	1.90 [0.52, 3.28]
Lee 2005	12	7.3 (2.2)	12	5.8 (3.2)		28.3 %	1.50 [-0.70, 3.70]
Subtotal (95% CI)	**24**		**24**			**100.0 %**	**1.79 [0.62, 2.96]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.09, df = 1 (P = 0.76); I^2 =0.0%							
Test for overall effect: Z = 2.99 (P = 0.0027)							



Analysis 1.17. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 17 Cognitive function: 5. Short-term - Average end point score on VFT (high = favourable).

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 17 Cognitive function: 5. Short-term - Average end point score on VFT (high = favourable)

Study or subgroup	ACHI % AP N	Mean(SD)	Placebo and AP N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Verbal fluency							
Lee 2005	12	14.6 (4.5)	12	10.6 (2.6)		90.1 %	4.00 [1.06, 6.94]
Nahas 2003	3	29 (12)	3	29.5 (5)		3.6 %	-0.50 [-15.21, 14.21]
Tugal 2003	6	29.3 (12.6)	6	31.2 (5.8)		6.3 %	-1.90 [-13.00, 9.20]
Total (95% CI)	**21**		**21**			**100.0 %**	**3.46 [0.67, 6.26]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.30$, df = 2 (P = 0.52); $I^2 = 0.0\%$

Test for overall effect: Z = 2.43 (P = 0.015)

Test for subgroup differences: Not applicable

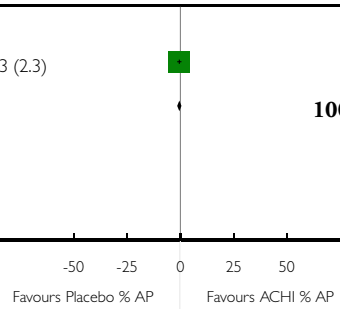
Analysis 1.18. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 18 Cognitive function: 6. Short-term - Average end point score on BVST (high = favourable).

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 18 Cognitive function: 6. Short-term - Average end point score on BVST (high = favourable)

Study or subgroup	ACHI % AP N	Mean(SD)	AP % Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Brief Visuospatial Memory Test							
Buchanan 2008	35	4.8 (1.7)	38	5.3 (2.3)		100.0 %	-0.50 [-1.42, 0.42]
Total (95% CI)	**35**		**38**			**100.0 %**	**-0.50 [-1.42, 0.42]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.06 (P = 0.29)							
Test for subgroup differences: Not applicable							

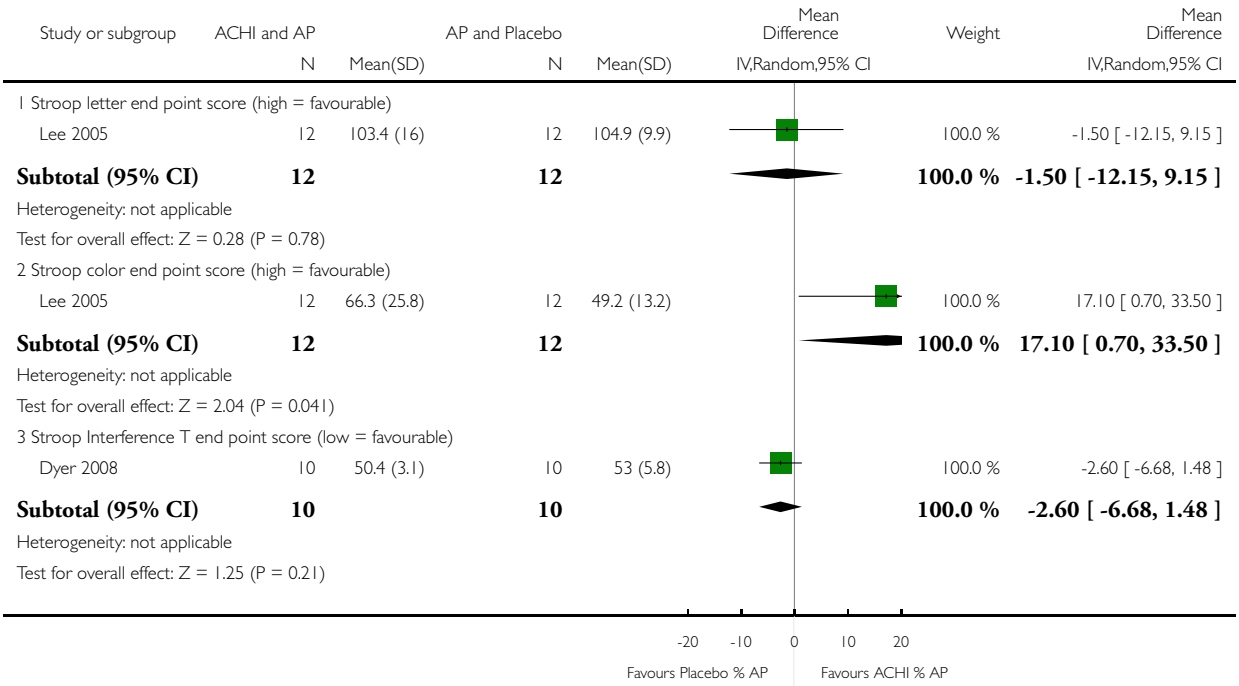


Analysis 1.19. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 19 Cognitive function: 7. Short-term - Average end point score on various subscales of Stroop test.

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 19 Cognitive function: 7. Short-term - Average end point score on various subscales of Stroop test



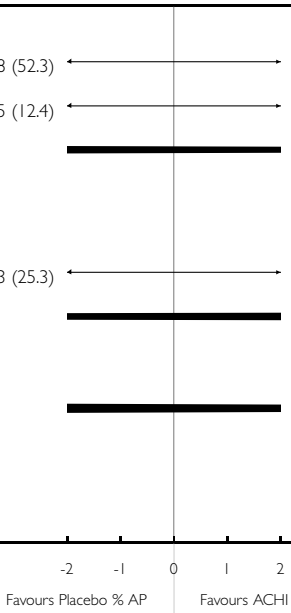
Analysis 1.20. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 20 Cognitive function: 7. Short-term - Average end point score on Trail making tests A & B (high = favourable).

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 20 Cognitive function: 7. Short-term - Average end point score on Trail making tests A % B (high = favourable)

Study or subgroup	ACHI and AP N	Mean(SD)	Placebo and AP N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Trail making A							
Lee 2005	12	82 (32.3)	12	112.8 (52.3)		32.6 %	-30.80 [-65.58, 3.98]
Tugal 2003	6	47.5 (28.4)	6	45 (12.4)		47.0 %	2.50 [-22.30, 27.30]
Subtotal (95% CI)	**18**		**18**			**79.6 %**	**-11.83 [-44.14, 20.49]**
Heterogeneity: Tau² = 316.98; Chi² = 2.33, df = 1 (P = 0.13); I² =57%							
Test for overall effect: Z = 0.72 (P = 0.47)							
2 Trail making B							
Tugal 2003	6	113.7 (55.4)	6	97.3 (25.3)		20.4 %	16.40 [-32.33, 65.13]
Subtotal (95% CI)	**6**		**6**			**20.4 %**	**16.40 [-32.33, 65.13]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.66 (P = 0.51)							
Total (95% CI)	**24**		**24**			**100.0 %**	**-5.53 [-30.67, 19.61]**
Heterogeneity: Tau² = 189.78; Chi² = 3.21, df = 2 (P = 0.20); I² =38%							
Test for overall effect: Z = 0.43 (P = 0.67)							
Test for subgroup differences: Chi² = 0.90, df = 1 (P = 0.34), I² =0.0%							

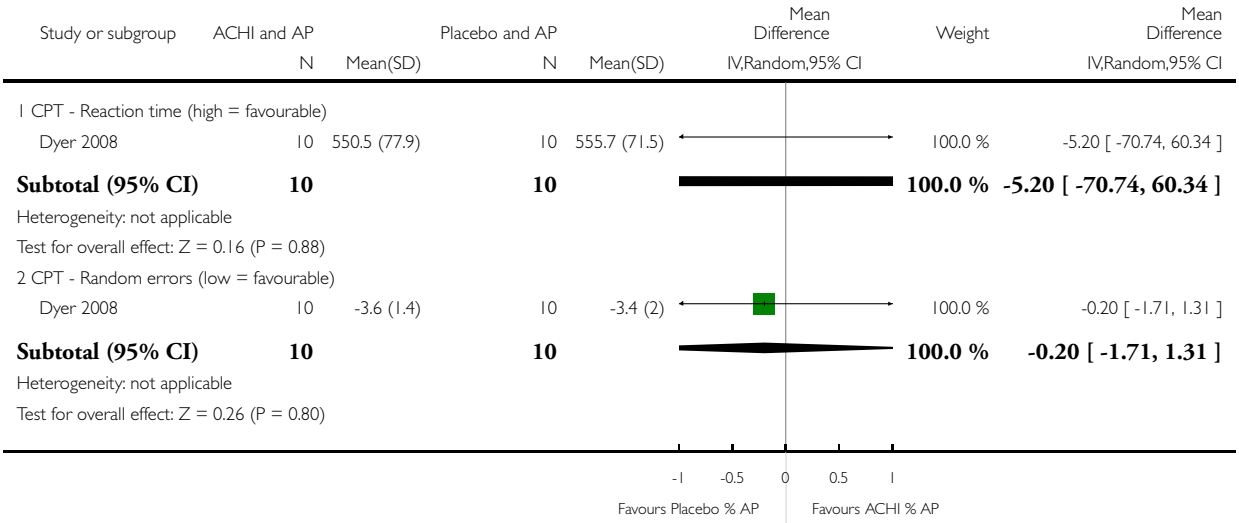


Analysis 1.21. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 21 Cognitive function: 8. Short-term - Average end point score on CPT.

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 21 Cognitive function: 8. Short-term - Average end point score on CPT

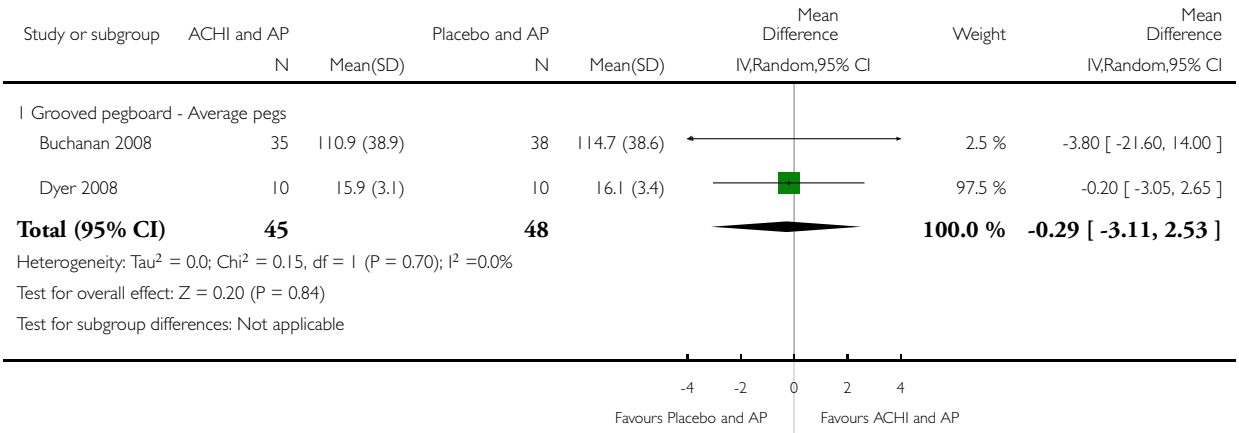


Analysis 1.22. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 22 Cognitive function: 9. Short-term - Average end point score on Grooved pegboard test (high = favourable).

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 22 Cognitive function: 9. Short-term - Average end point score on Grooved pegboard test (high = favourable)



Analysis 1.23. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 23 Cognitive function: 10. Short-term - Average end point score on various scales (skewed data).

Cognitive function: 10. Short-term - Average end point score on various scales (skewed data)

Study	Intervention	Mean	SD	N
ROCFT-Immediate recall (high = favourable)				
Lee 2005	ACHI and AP	13.4	8.4	12
Lee 2005	Placebo & AP	8.0	6.0	
ROCFT-Delayed recall (high = favourable)				
Lee 2005	ACHI and AP	13.0	8.3	12
Lee 2005	Placebo & AP	8.5	5.4	12
ROCFT-Recognition (high = favourable)				
Lee 2005	ACHI and AP	6.4	2.1	12
Lee 2005	Placebo & AP	3.9	2.3	12

Cognitive function: 10. Short-term - Average end point score on various scales (skewed data) (*Continued*)

WAIS III-Letter number span without reordering (high = favourable)				
Dyer 2008	ACHI & AP	12	3	10
Dyer 2008	Placebo & AP	13.6	2.9	10
WAIS III-Letter number span with reordering (high = favourable)				
Dyer 2008	ACHI & AP	8.9	3.4	10
Dyer 2008	Placebo & AP	8.7	2.5	10
WCST-Categories completed (high = favourable)				
Tugal 2003	ACHI & AP	2.7	1.8	6
Tugal 2003	Placebo & AP	3.3	2.9	6
WCST-Perseverative errors (low = favourable)				
Tugal 2003	ACHI & AP	21.7	9.1	6
Tugal 2003	Placebo & AP	18.3	13.3	6
Visual paired associates 1 (high = favourable)				
Tugal 2003	ACHI & AP	10.8	6.4	6
Tugal 2003	Placebo & AP	14.3	5.4	6
CPT-random errors (low = favourable)				
Dyer 2008	ACHI & Placebo	-3.6	1.4	10
Dyer 2008	Placebo & AP	-3.4	2.0	10
Stroop Interfernece Test (low = favourable)				
Dyer 2008	ACHI & AP	50.4	3.1	10
Dyer 2008	AP & Placebo	48.5	3.2	10
Visual paired associates 2 (high = favourable)				
Tugal 2003	ACHI & AP	3.8	2.4	6

Cognitive function: 10. Short-term - Average end point score on various scales (skewed data) (*Continued*)

Tugal 2003	Placebo & AP	5.7	0.8	6

Analysis 1.24. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 24 Cognitive function: 11a. Short-term - Average change score on various scales (skewed data).

Cognitive function: 11a. Short-term - Average change score on various scales (skewed data)

Study	**Intervention**	**Mean change**	**SD**	**N**
RAVLT-Delayed recall (high = favourable)				
Friedman 2002c	ACHI & AP	1.5	2.6	8
Friedman 2002c	Placebo & AP	1.6	4.4	18
CPT-Omission of errors (low = favourable)				
Schubert 2006	ACHI & AP	-3.8	5.2	8
Schubert 2006	Placebo & AP	-1.7	3.4	6
RAVLT-total word list learning (high = favourable)				
Friedman 2002c	ACHI & AP	6.5	8.8	9
Friedman 2002c	Placebo & AP	7.4	12	9
CPT (high = favourable)				
Friedman 2002c	ACHI & AP	.42	.57	8
Friedman 2002c	Placebo & AP	.03	.46	18
RBANS total score (high = favourable)				
Schubert 2006	ACHI & AP	12.1	12.8	8
Schubert 2006	Placebo & AP	-.5	7.3	6

Analysis 1.25. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 25 Cognitive function: 11b. Medium-term - Average change score on various scales (skewed data).

Cognitive function: 11b. Medium-term - Average change score on various scales (skewed data)

Study	Intervention	Mean change	SD	N
Category fluency test (high = favourable)				
Tuma 2003	ACHI & AP	-7.4	9.9	9
Tuma 2003	Placebo and AP	-3.6	10.5	7
Trail making test A-time (high = favourable)				
Tuma 2003	ACHI & AP	14.7	15.4	9
Tuma 2003	Placebo and AP	13.3	14.3	7
Stroop test-interference index (low = favourable)				
Tuma 2003	ACHI & AP	12.1	17.1	9
Tuma 2003	Placebo and AP	8.0	7.3	7
Logical memory (high = favourable)				
Tuma 2003	ACHI & AP	-10.6	5.6	9
Tuma 2003	Placebo & AP	-8.3	8.1	7
Wisconsin Card Sorting Test-perseverative errors (low = favourable)				
Tuma 2003	ACHI & AP	3.3	4.8	9
Tuma 2003	Placebo and AP	6.1	25.2	7
Wisconsin Card Sorting-number of completed categories (high = favourable)				
Tuma 2003	ACHI & AP	-0.2	1.1	9
Tuma 2003	Placebo and AP	-0.6	3.4	7
Rey Osterrieth Complex Figure Test (high = favourable)				
Tuma 2003	ACHI & AP	-2.4	2.8	9
Tuma 2003	Placebo & AP	2.8	4.0	7
Verbal pair Association-global score (high = favourable)				

Tuma 2003	ACHI & AP	-5.0	7.9	9
Tuma 2003	Placebo & AP	-8.4	10.7	7

Analysis 1.26. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 26 Adverse event: 1a. Short-term - Central nervous system.

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 26 Adverse event: 1a. Short-term - Central nervous system

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Dizziness					
Akhondzadeh 2008	3/12	1/12		17.9 %	3.00 [0.36, 24.92]
Buchanan 2008	1/42	0/44		8.3 %	3.14 [0.13, 74.98]
Keefe 2008a	3/121	7/124		40.5 %	0.44 [0.12, 1.66]
Lee 2005	2/12	4/12		33.2 %	0.50 [0.11, 2.23]
Subtotal (95% CI)	**187**	**192**		**100.0 %**	**0.76 [0.30, 1.94]**
Total events: 9 (Experimental), 12 (Control)					
Heterogeneity: Tau² = 0.10; Chi² = 3.35, df = 3 (P = 0.34); I² =10%					
Test for overall effect: Z = 0.57 (P = 0.57)					
2 Sialorrhea					
Freudenreich 2005	3/19	0/17		100.0 %	6.30 [0.35, 113.81]
Subtotal (95% CI)	**19**	**17**		**100.0 %**	**6.30 [0.35, 113.81]**
Total events: 3 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.25 (P = 0.21)					
3 Headache					
Keefe 2008a	8/121	14/124		85.7 %	0.59 [0.25, 1.35]
Lee 2005	1/12	4/12		14.3 %	0.25 [0.03, 1.92]
Subtotal (95% CI)	**133**	**136**		**100.0 %**	**0.52 [0.24, 1.12]**
Total events: 9 (Experimental), 18 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 0.58, df = 1 (P = 0.45); I² =0.0%					
Test for overall effect: Z = 1.67 (P = 0.095)					
4 Insomnia					

(*Continued* . . .)

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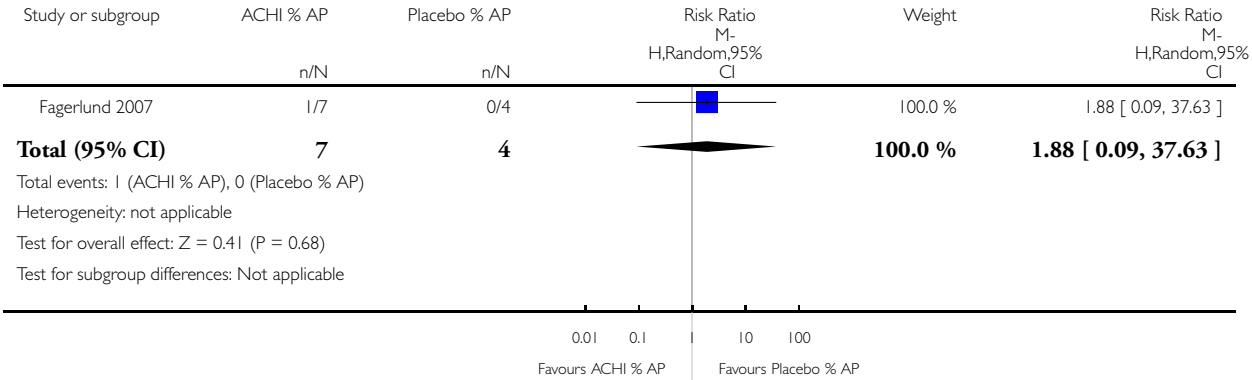
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Akhondzadeh 2008	1/12	2/12		17.1 %	0.50 [0.05, 4.81]
Keefe 2008a	5/121	11/124		82.9 %	0.47 [0.17, 1.30]
Subtotal (95% CI)	**133**	**136**		**100.0 %**	**0.47 [0.19, 1.20]**
Total events: 6 (Experimental), 13 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.96); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.58 (P = 0.12)					
5 Somnolence					
Keefe 2008a	3/121	7/124		100.0 %	0.44 [0.12, 1.66]
Subtotal (95% CI)	**121**	**124**		**100.0 %**	**0.44 [0.12, 1.66]**
Total events: 3 (Experimental), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.21 (P = 0.22)					
6 Deterioration in mental state: 1b. Medium-term					
Tuma 2003	1/10	0/7		100.0 %	2.18 [0.10, 46.92]
Subtotal (95% CI)	**10**	**7**		**100.0 %**	**2.18 [0.10, 46.92]**
Total events: 1 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.50 (P = 0.62)					

Analysis 1.27. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 27 Adverse event: 1b. Medium-term - Central nervous system.

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 27 Adverse event: 1b. Medium-term - Central nervous system

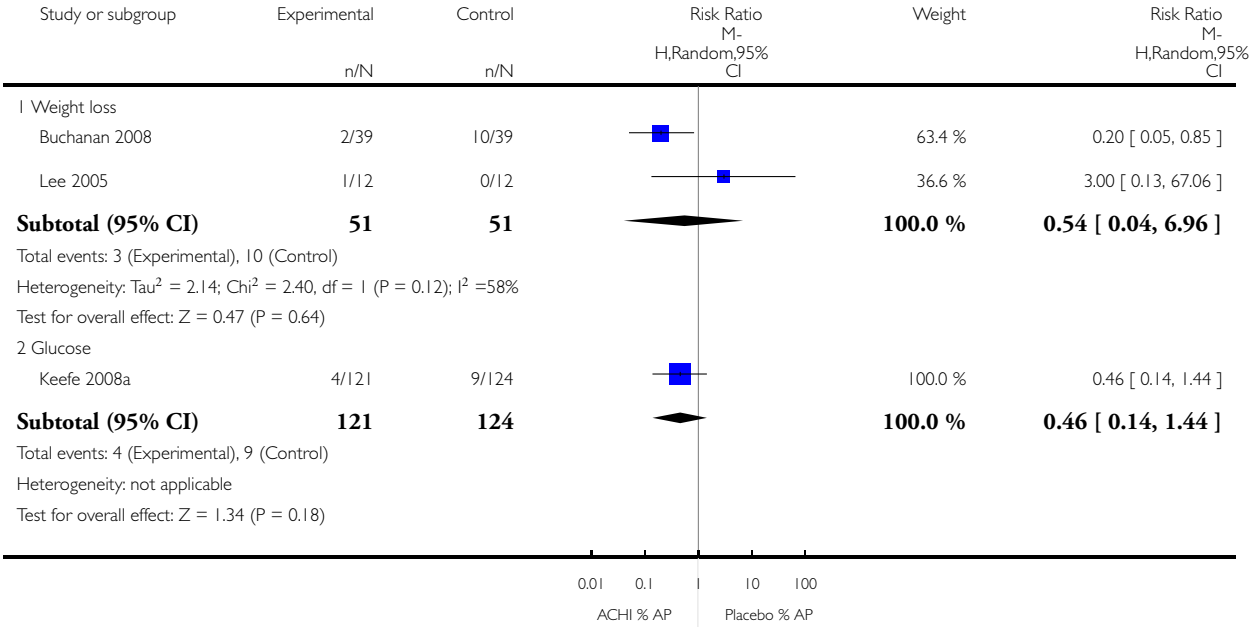


Analysis 1.28. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 28 Adverse event: 2. Short-term - Metabolic and nutritional.

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 28 Adverse event: 2. Short-term - Metabolic and nutritional

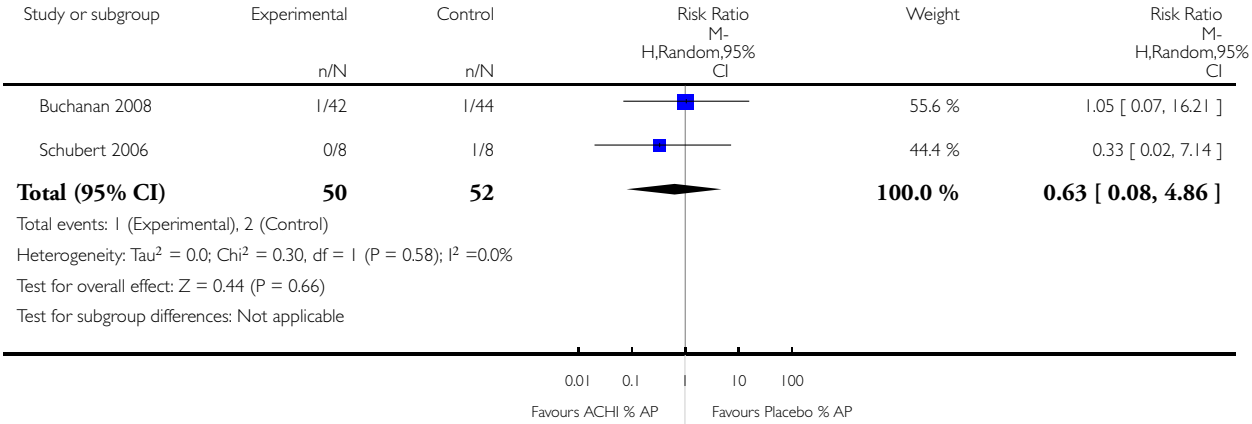


Analysis 1.29. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 29 Adverse event: 3. Short-term - Deterioration in menal state.

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 29 Adverse event: 3. Short-term - Deterioration in menal state

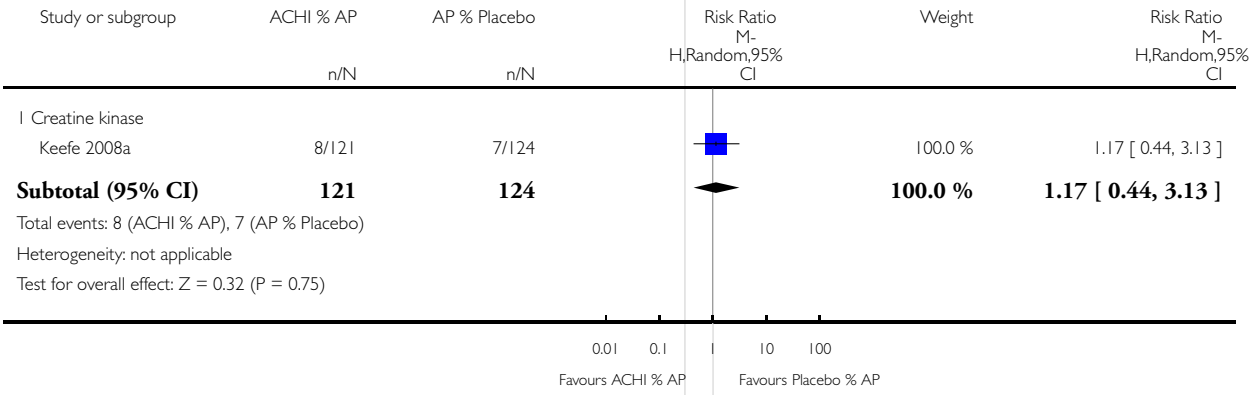


Analysis 1.30. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 30 Adverse event: 4. Short-term - Biochemical abnormalities.

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 30 Adverse event: 4. Short-term - Biochemical abnormalities

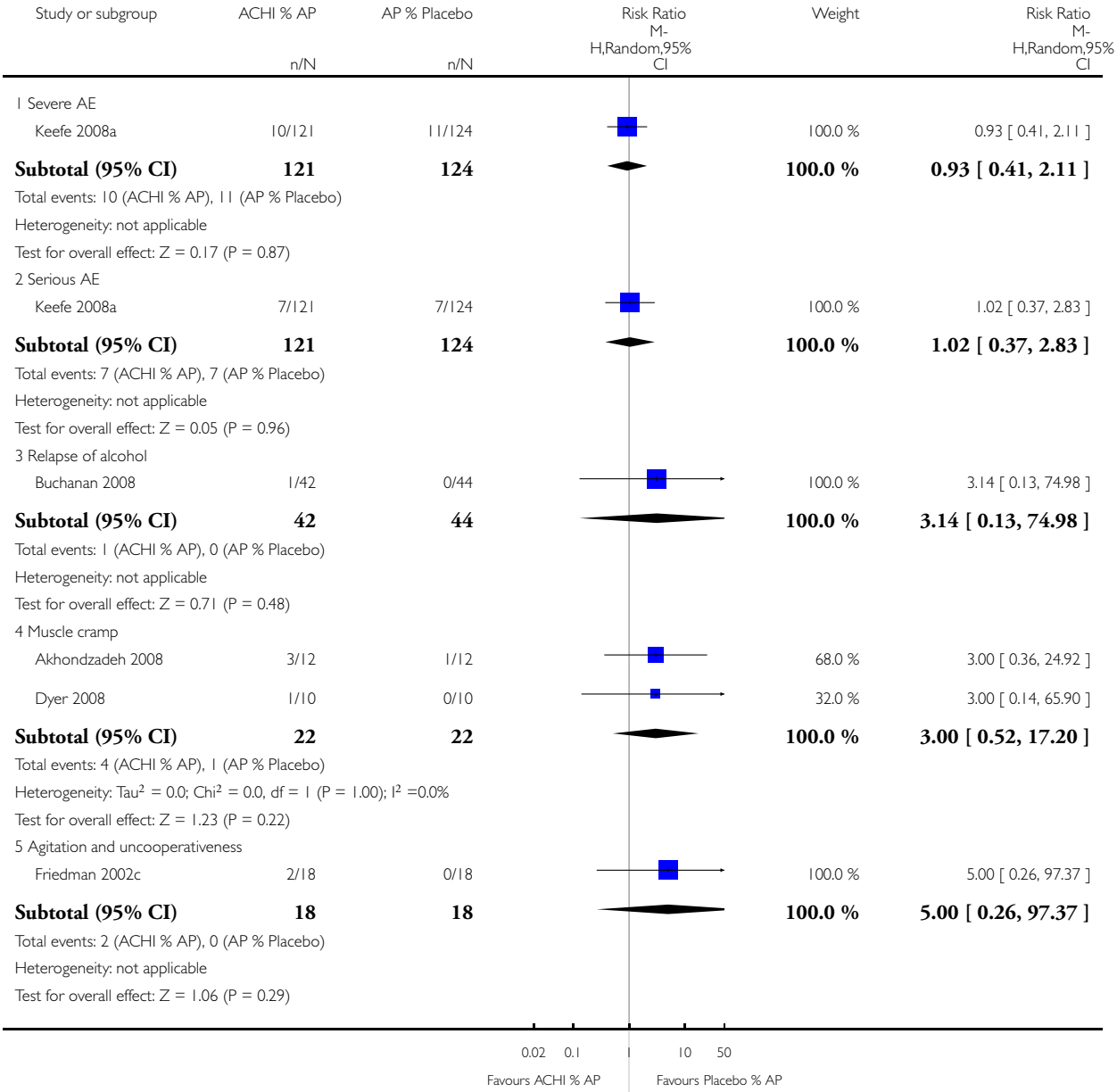


Analysis 1.31. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 31 Adverse event: 5. Short-term - Non specific.

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 31 Adverse event: 5. Short-term - Non specific

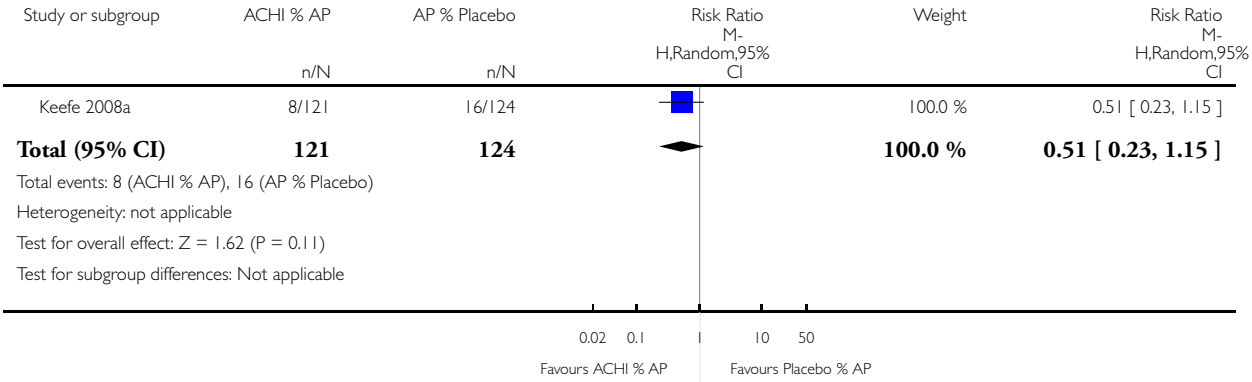


Analysis 1.32. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 32 Adverse event: 6. Short-term - Cardiovascular.

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 32 Adverse event: 6. Short-term - Cardiovascular



Analysis 1.33. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 33 Adverse event: 7. Short-term - Gastrointestinal.

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 33 Adverse event: 7. Short-term - Gastrointestinal

Study or subgroup	Ach Inhibitor + antipsych n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Vomiting					
Akhondzadeh 2008	1/12	1/12		14.6 %	1.00 [0.07, 14.21]
Buchanan 2008	7/39	3/39		36.9 %	2.33 [0.65, 8.37]
Keefe 2008a	3/121	8/124		36.2 %	0.38 [0.10, 1.41]
Lee 2005	0/12	2/12		12.4 %	0.20 [0.01, 3.77]
Subtotal (95% CI)	**184**	**187**		**100.0 %**	**0.79 [0.25, 2.48]**
Total events: 11 (Ach Inhibitor + antipsych), 14 (Placebo)					
Heterogeneity: Tau^2 = 0.50; Chi^2 = 4.79, df = 3 (P = 0.19); I^2 =37%					
Test for overall effect: Z = 0.40 (P = 0.69)					
2 Abdomial pain and diarrhoea					
Kim 2005b	1/12	0/12		100.0 %	3.00 [0.13, 67.06]
Subtotal (95% CI)	**12**	**12**		**100.0 %**	**3.00 [0.13, 67.06]**
Total events: 1 (Ach Inhibitor + antipsych), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
3 Diarrhoea					
Akhondzadeh 2008	2/12	2/12		19.4 %	1.00 [0.17, 5.98]
Keefe 2008a	7/121	5/124		49.6 %	1.43 [0.47, 4.40]
Lee 2005	3/12	2/12		24.3 %	1.50 [0.30, 7.43]
Schubert 2006	0/8	1/8		6.6 %	0.33 [0.02, 7.14]
Subtotal (95% CI)	**153**	**156**		**100.0 %**	**1.23 [0.56, 2.70]**
Total events: 12 (Ach Inhibitor + antipsych), 10 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.88, df = 3 (P = 0.83); I^2 =0.0%					
Test for overall effect: Z = 0.51 (P = 0.61)					
4 Nausea					
Akhondzadeh 2008	1/12	0/12		8.5 %	3.00 [0.13, 67.06]
Keefe 2008a	7/121	7/124		79.7 %	1.02 [0.37, 2.83]
Lee 2005	1/12	1/12		11.7 %	1.00 [0.07, 14.21]
Subtotal (95% CI)	**145**	**148**		**100.0 %**	**1.12 [0.45, 2.78]**

(*Continued . . .*)

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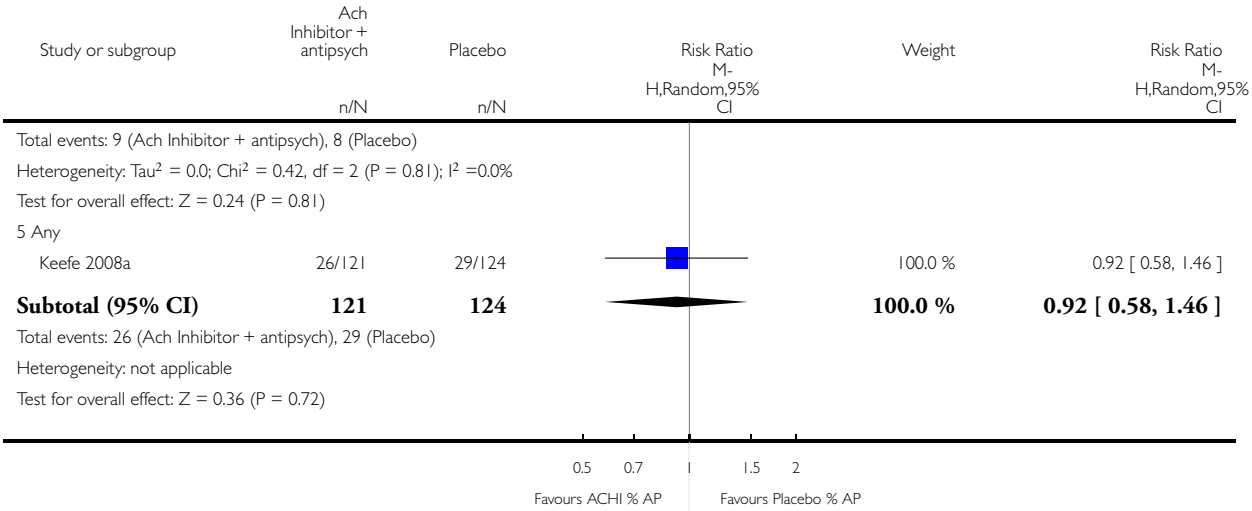
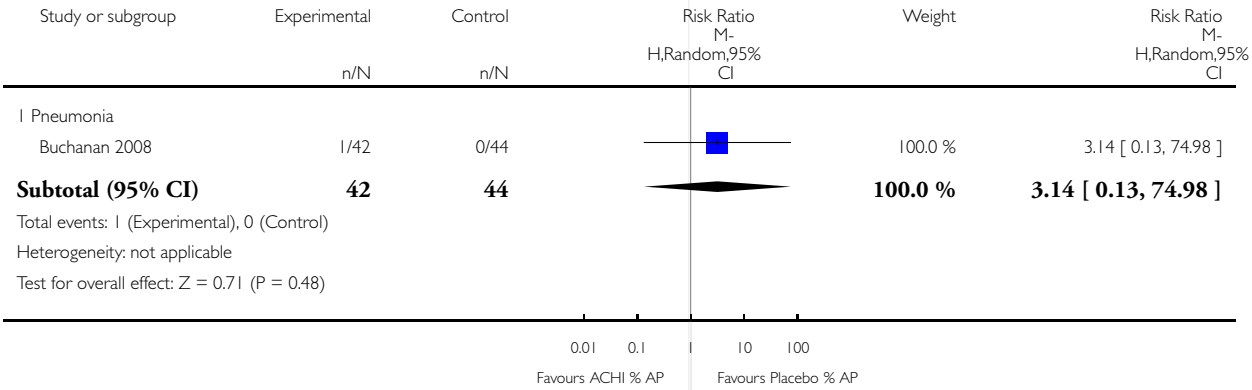


Analysis 1.34. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 34 Adverse event: 9. Short-term - Respiratory system.

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 34 Adverse event: 9. Short-term - Respiratory system

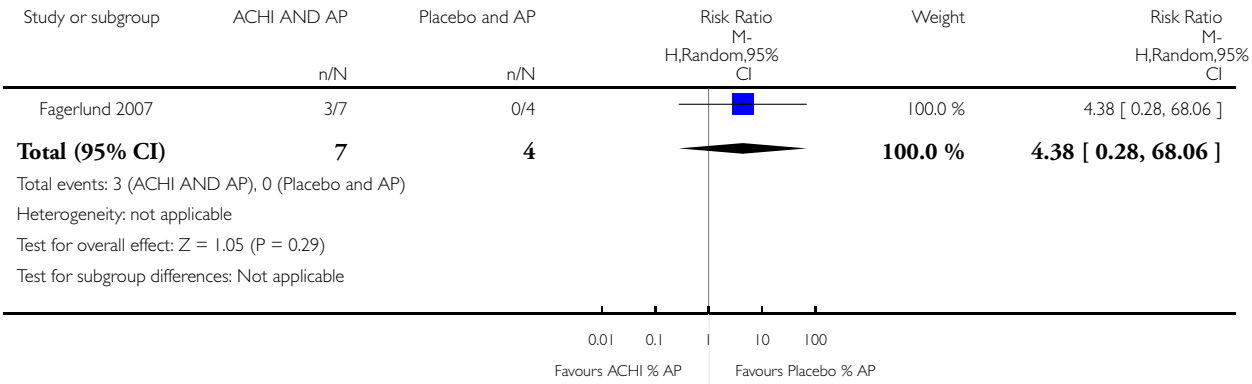


Analysis 1.35. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 35 Adverse event: 10. Medium-term - EPSE.

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 35 Adverse event: 10. Medium-term - EPSE

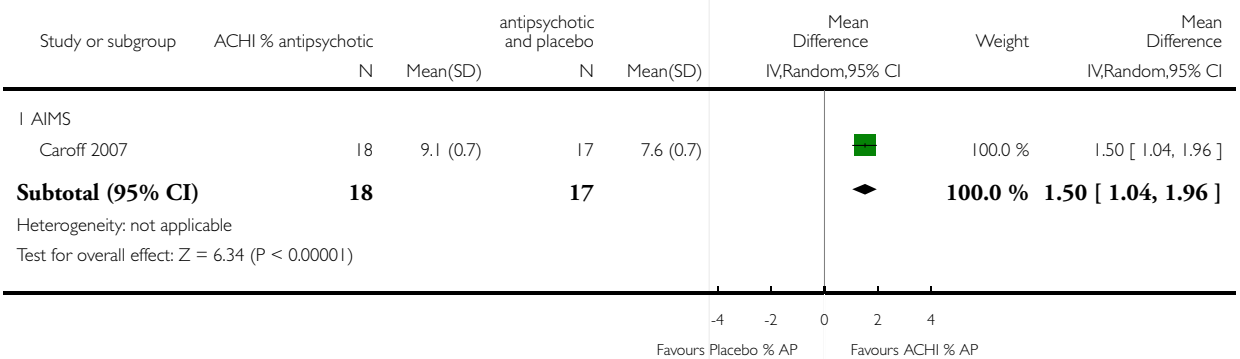


Analysis 1.36. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 36 Adverse event: 11a. Short-term - Average end point score on EPSEs scale (low = favourable).

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 36 Adverse event: 11a. Short-term - Average end point score on EPSEs scale (low = favourable)



Analysis 1.37. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 37 Adverse event: 11b. Medium-term - Average end point score on EPSEs scale (low = favourable).

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

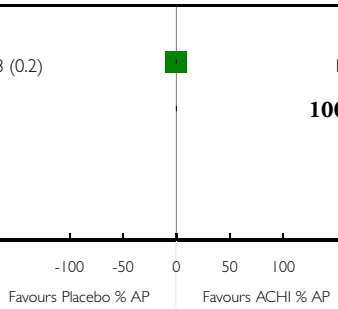
Outcome: 37 Adverse event: 11b. Medium-term - Average end point score on EPSEs scale (low = favourable)

Study or subgroup	ACHI % AP N	Mean(SD)	Placebo % AP N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 SAS							
Sharma 2006	11	0.72 (0.3)	10	0.88 (0.2)		100.0 %	-0.16 [-0.38, 0.06]
Total (95% CI)	**11**		**10**			**100.0 %**	**-0.16 [-0.38, 0.06]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.45 (P = 0.15)

Test for subgroup differences: Not applicable



Analysis 1.38. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 38 Adverse event: 12a. Short-term - Average end point score on EPSEs scale (low = favourable).

Adverse event: 12a. Short-term - Average end point score on EPSEs scale (low = favourable)

Study	Intervention	Mean	SD	N
SARS				
Buchanan 2008	ACHI & AP	1.1	1.8	42
Buchanan 2008	Placebo & AP	1.6	1.9	42
AIMS				
Buchanan 2008	ACHI & AP	2.1	3.0	42
Buchanan 2008	Placebo & AP	1.6	3.0	42
ESRS				
Akhondzadeh 2008	ACHI & AP	1.53	1.06	15
Akhondzadeh 2008	Placebo & AP	1.46	1.18	15

Analysis 1.39. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 39 Adverse event: 12b. Medium-term - Average end point score on EPSEs scales (skewed data).

Adverse event: 12b. Medium-term - Average end point score on EPSEs scales (skewed data)

Study	Intervention	Mean	SD	N
AIMS				
Sharma 2006	ACHI and AP	0.36	0.24	11
Sharma 2006	Placebo and AP	0.00	0.00	10
BARS				
Sharma 2006	ACHI & AP	0.36	0.27	11
Sharma 2006	Placebo and AP	2.11	0.27	10

Analysis 1.40. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 40 Adverse event: 13. Short-term - Average change score on EPSEs scales (skewed data).

Adverse event: 13. Short-term - Average change score on EPSEs scales (skewed data)

Study	Intervention	Mean change	SD	N
AIMS				
Schubert 2006	ACHI & AP	-2.7	1.7	8
Schubert 2006	AP & Placebo	0.2	-0.7	6
SAS				
Schubert 2006	ACHI & AP	-3.5	4.5	8
Schubert 2006	AP & Placebo	0.0	2.6	6

Analysis 1.41. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 41 Adverse event: 14. Short-term - Average change interval on ECG (skewed data).

Adverse event: 14. Short-term - Average change interval on ECG (skewed data)

Study	Intervention	Mean change	SD	N
PR interval				
Buchanan 2008	ACHI & AP	25.7	56.0	42

Adverse event: 14. Short-term - Average change interval on ECG (skewed data) (*Continued*)

Buchanan 2008	AP & Placebo	-3.0	12.0	44
QRS interval				
Buchanan 2008	ACHI & AP	11.4	25.1	42
Buchanan 2008	AP & Placebo	-1.6	11.7	44
QTc interval				
Buchanan 2008	ACHI & AP	3.03	28.83	42
Buchanan 2008	AP & Placebo	3.03	27.68	44

Analysis 1.42. Comparison 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic, Outcome 42 Behaviour: 15. Short-term - Smoking (low = favourable).

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 1 Acetylcholinesterase inhibitors plus antipsychotic versus placebo plus antipsychotic

Outcome: 42 Behaviour: 15. Short-term - Smoking (low = favourable)

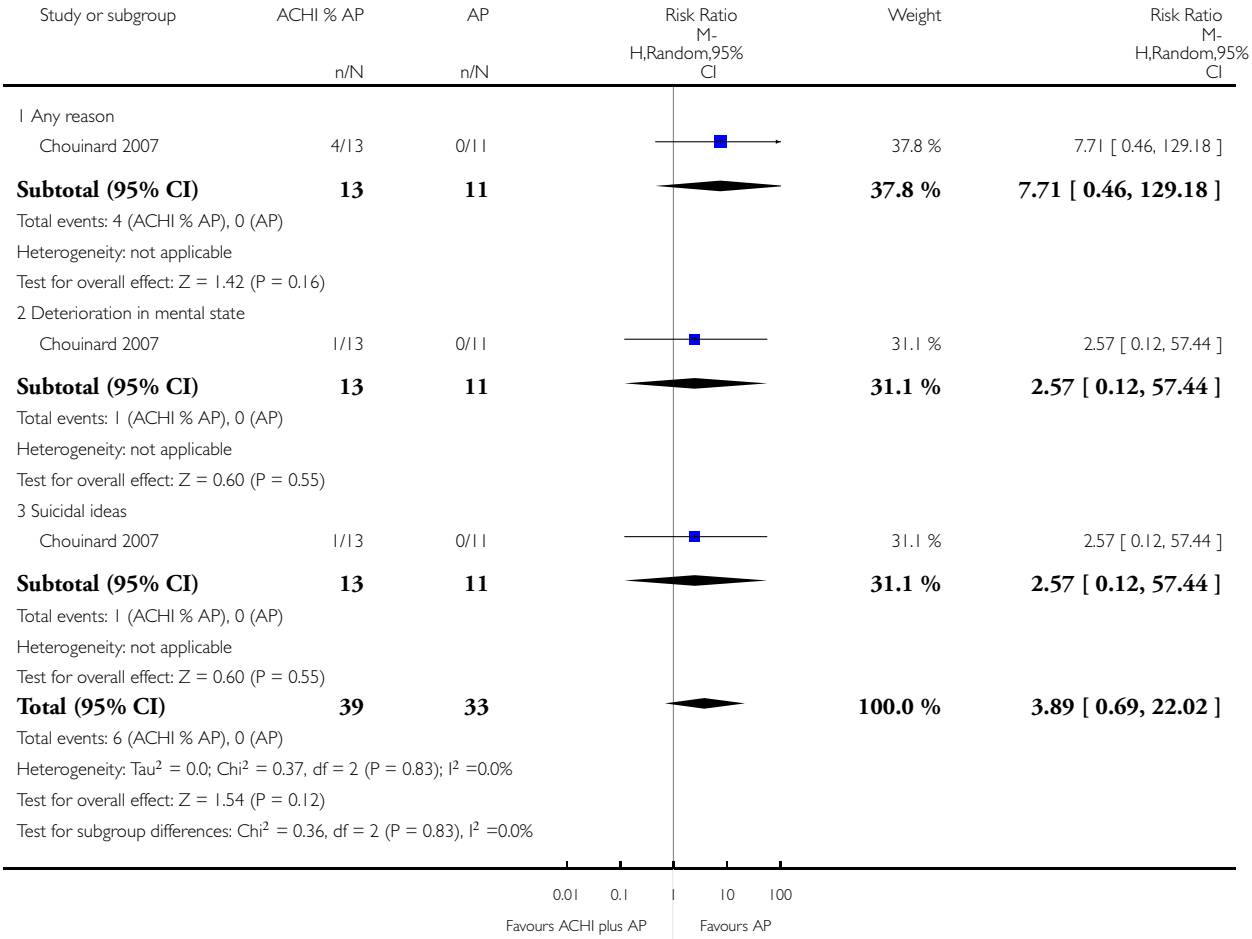
Study or subgroup	ACHI % AP N	Mean(SD)	AP % Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Expired CO measures							
Buchanan 2008	18	21.1 (10.3)	23	21 (10.3)		100.0 %	0.10 [-6.25, 6.45]
Subtotal (95% CI)	**18**		**23**			**100.0 %**	**0.10 [-6.25, 6.45]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.03 (P = 0.98)							
2 FTND intervew score							
Buchanan 2008	18	5.2 (2.2)	23	3.7 (2.4)		100.0 %	1.50 [0.09, 2.91]
Subtotal (95% CI)	**18**		**23**			**100.0 %**	**1.50 [0.09, 2.91]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.08 (P = 0.037)							

Analysis 2.1. Comparison 2 Acetylcholinesterase inhibitors plus antipsychotics versus antipsychotics alone, Outcome 1 Leaving the study early.

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 2 Acetylcholinesterase inhibitors plus antipsychotics versus antipsychotics alone

Outcome: 1 Leaving the study early



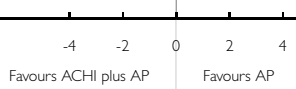
Analysis 2.2. Comparison 2 Acetylcholinesterase inhibitors plus antipsychotics versus antipsychotics alone, Outcome 2 Mental state: Short-term - Average end point score on PANSS (low = favourable).

Review: Acetylcholinesterase inhibitors for schizophrenia

Comparison: 2 Acetylcholinesterase inhibitors plus antipsychotics versus antipsychotics alone

Outcome: 2 Mental state: Short-term - Average end point score on PANSS (low = favourable)

Study or subgroup	ACHI % AP N	Mean(SD)	AP N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Negative							
Chouinard 2007	9	14.7 (2.7)	9	15.3 (4.7)		100.0 %	-0.60 [-4.14, 2.94]
Subtotal (95% CI)	**9**		**9**			**100.0 %**	**-0.60 [-4.14, 2.94]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.33 (P = 0.74)							
2 Positive							
Chouinard 2007	9	20.4 (4.9)	9	19.3 (2.8)		100.0 %	1.10 [-2.59, 4.79]
Subtotal (95% CI)	**9**		**9**			**100.0 %**	**1.10 [-2.59, 4.79]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.58 (P = 0.56)							
3 Disorganisation/cognitive							
Chouinard 2007	9	11.7 (3.2)	9	11.2 (2.2)		100.0 %	0.50 [-2.04, 3.04]
Subtotal (95% CI)	**9**		**9**			**100.0 %**	**0.50 [-2.04, 3.04]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.39 (P = 0.70)							
4 Hostility/excitement							
Chouinard 2007	9	14.2 (1.8)	9	14 (2)		100.0 %	0.20 [-1.56, 1.96]
Subtotal (95% CI)	**9**		**9**			**100.0 %**	**0.20 [-1.56, 1.96]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.22 (P = 0.82)							
5 Anxiety/Depressive							
Chouinard 2007	9	8.9 (0.9)	9	8.9 (1.1)		100.0 %	0.0 [-0.93, 0.93]
Subtotal (95% CI)	**9**		**9**			**100.0 %**	**0.0 [-0.93, 0.93]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
6 Total							
Chouinard 2007	9	73.7 (7.8)	9	71.9 (5.6)		100.0 %	1.80 [-4.47, 8.07]
Subtotal (95% CI)	**9**		**9**			**100.0 %**	**1.80 [-4.47, 8.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.56 (P = 0.57)							



WHAT'S NEW

Last assessed as up-to-date: 9 September 2011.

Date	Event	Description
17 October 2012	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 3, 2009

Review first published: Issue 1, 2012

CONTRIBUTIONS OF AUTHORS

Jasvinder Singh - protocol development, searching, study selection, data extraction, report writing.

Kamalpreet Kour - protocol development, searching, study selection, data extraction.

Mahesh B Jayaram - protocol development, study selection, report writing.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Leeds Partnership Foundation Trust, Leeds, UK.
- Bradford District Care Trust,Bradford, UK.

External sources

- Bradford District Care Trust,Bradford, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not present NNT or NNH for significant results as stated in our protocol as these have been superseeded by presentation of data in the Summary of findings for the main comparison

INDEX TERMS

Medical Subject Headings (MeSH)

Antipsychotic Agents [*therapeutic use]; Cholinesterase Inhibitors [*therapeutic use]; Galantamine [therapeutic use]; Indans [therapeutic use]; Phenylcarbamates [therapeutic use]; Piperidines [therapeutic use]; Psychotic Disorders [*drug therapy]; Randomized Controlled Trials as Topic; Schizophrenia [*drug therapy]; Schizophrenic Psychology

MeSH check words

Humans