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Antioxidant treatments for schizophrenia (Review)

Magalhães PVS, Dean O, Andreazza AC, Berk M, Kapczinski F

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[Intervention Review]

Antioxidant treatments for schizophrenia

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ABSTRACT

Background

There is accumulating evidence that progressive changes in brain structure and function take place as schizophrenia unfolds. Among many possible candidates, oxidative stress may be one of the mediators of neuroprogression, grey matter loss and subsequent cognitive and functional impairment. Antioxidants are exogenous or endogenous molecules that mitigate any form of oxidative stress or its consequences. They may act from directly scavenging free radicals to increasing anti-oxidative defences. There is evidence that current treatments impact oxidative pathways and may to some extent reverse pro-oxidative states in schizophrenia. The existing literature, however, indicates that these treatments do not fully restore the deficits in antioxidant levels or restore levels of oxidants in schizophrenia. As such, there has been interest in developing interventions aimed at restoring this oxidative balance beyond the benefits of antipsychotics in this direction. If antioxidants are to have a place in the treatment of this serious condition, the relevant and up-to-date information should be available to clinicians and investigators.

Objectives

To evaluate the effect of antioxidants as add-on treatments to standard antipsychotic medication for improving acute psychotic episodes and core symptoms, and preventing relapse in people with schizophrenia.

Search methods

We searched the Cochrane Schizophrenia Group's Study-Based Register of Trials which is based on regular searches of CINAHL, BIOSIS, AMED, Embase, PubMed, MEDLINE, PsycINFO, and registries of clinical trials. There are no language, time, document type, or publication status limitations for inclusion of records in the register. We ran this search in November 2010, and again on 8 January 2015. We also inspected references of all identified studies for further trials and contacted authors of trials for additional information.

Selection criteria

We included reports if they were randomised controlled trials (RCTs) involving people with schizophrenia who had been allocated to either a substance with antioxidant potential or to a placebo as an adjunct to standard antipsychotic treatment.

Data collection and analysis

We independently extracted data from these trials and we estimated risk ratios (RR) or mean differences (MD), with 95% confidence intervals (CI). We assessed risk of bias for included studies and created a 'Summary of findings' table using GRADE.

Main results

The review includes 22 RCTs of varying quality and sample size studying *Ginkgo biloba*, N-acetyl cysteine (NAC), allopurinol, dehydroepiandrosterone (DHEA), vitamin C, vitamin E or selegiline. Median follow-up was eight weeks. Only three studies including a minority of the participants reported our *a priori* selected primary outcome of clinically important response. Short-term data for this outcome (measured as at least 20% improvement in scores on Positive and Negative Syndrome Scale (PANSS)) were similar (3 RCTs, n = 229, RR 0.77, 95% CI 0.53 to 1.12, *low quality evidence*). Studies usually reported only endpoint psychopathology rating scale scores. Psychotic symptoms were lower in those using an adjunctive antioxidant according to the PANSS (7 RCTS, n = 584, MD -6.00, 95% CI -10.35 to -1.65, *very low quality evidence*) and the Brief Psychiatric Rating Scale (BPRS) (8 RCTS, n = 843, MD -3.20, 95% CI -5.63 to -0.78, *low quality evidence*). There was no overall short-term difference in leaving the study early (16 RCTs, n = 1584, RR 0.73, 95% CI 0.48 to 1.11, *moderate quality evidence*), or in general functioning (2 RCTs, n = 52, MD -1.11, 95% CI -8.07 to 5.86, *low quality evidence*). Adverse events were generally poorly reported. Three studies reported useable data for 'any serious adverse effect', results were equivocal (3 RCTs, n = 234, RR 0.65, 95% CI 0.19 to 2.27, *low quality evidence*). No evidence was available for relapse, quality of life or service use.

Authors' conclusions

Although 22 trials could be included in this review, the evidence provided is limited and mostly not relevant to clinicians or consumers. Overall, although there was low risk of attrition and selective data reporting bias within the trials, the trials themselves were not adequately powered and need more substantial follow-up periods. There is a need for larger trials with longer periods of follow-up to be conducted. Outcomes should be meaningful for those with schizophrenia, and include measures of improvement and relapse (not just rating scale scores), functioning and quality of life and acceptability and, importantly, safety data.

PLAIN LANGUAGE SUMMARY

Antioxidants as add-on treatment for people with schizophrenia

Antioxidants are substances that protect cells from the damage caused by unstable molecules known as free radicals (causing oxidative stress). It is well known that adding antioxidant-rich fruits and vegetables to your daily diet will strengthen your ability to fight infection and disease. There is recent evidence that progressive brain changes take place as schizophrenia unfolds. Among many possible explanations, oxidative stress may be one of the factors contributing to the deterioration of the brain and its grey matter, leading to difficulties in people's thinking and everyday functioning. The aim of this review is to evaluate the effect of antioxidants as an add-on treatment to standard antipsychotic medication. In particular, by reducing (or lessening) psychotic episodes and core symptoms, and preventing relapse

Searches for randomised trials were run in 2010 and 2012, review authors found 22 relevant trials that randomised a total of 2041 people with schizophrenia. The trials compared the effects of taking a variety of antioxidants (allopurinol, *Ginkgo biloba*, N-acetyl cysteine (NAC), selegiline, vitamins C and E) compared with placebo. Most results showed no real differences between the antioxidants and placebo although there was evidence *Ginkgo biloba* had a positive effect on psychotic symptoms in the short term. The quality of this evidence was moderate.

However, overall, the trials suffered from a lack of real-world outcomes, such as clinical response, rates of relapse, quality of life, functioning, safety and satisfaction or acceptability of treatment. Adverse effects were also poorly reported with some studies not providing any data for adverse effects.

Ginkgo biloba and NAC emerged from the trials as the most promising, so should have priority in the design of future trials that are larger, longer and better reported than the 22 studies available at the present time.

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

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Adjunctive antioxidants for schizophrenia

Patient or population: people with schizophrenia
Settings: Inpatients and outpatients
Intervention: Adjunctive antioxidants

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	Adjunctive antioxidants				
Global state: improvement, short term PANSS Follow-up: 6 to 8 weeks	**Study population**		**RR 0.77** (0.53 to 1.12)	229 (3 studies)	⊕⊕◯◯ **low**[1,2]	-
	1000 per 1000	**690 per 1000** (360 to 1000)				
	Moderate					
	1000 per 1000	**690 per 1000** (360 to 1000)				
Total PANSS scores, short term PANSS Follow-up: 6 to 12 weeks		The mean total PANSS scores in the intervention groups was **6.0 lower** (10.53 lower to 1.65 lower)		584 (7 studies)	⊕◯◯◯ **very low**[1,2,3]	-
Total BPRS scores, short term BPRS Follow-up: 6 to 16 weeks		The mean total BPRS scores in the intervention groups was **3.2 lower** (5.63 lower to 0.78		843 (8 studies)	⊕⊕◯◯ **low**[1,3,4]	-

		lower)				
General functioning - short term GAS Follow-up: 6 weeks		The mean general functioning - short term in the intervention groups was **1.11 lower** (8.07 lower to 5.86 higher)		52 (2 studies)	⊕⊕◯◯ **low**[1,5]	-
General functioning - medium term GAS Follow-up: 24 weeks		The mean general functioning - medium term in the intervention groups was **2.84 higher** (2.09 lower to 7.77 higher)		135 (1 study)	⊕⊕⊕⊕ **high**	-
Leaving the study early, short term Follow-up: 6 to 16 weeks	**Study population**		**RR 0.73** (0.48 to 1.11)	1584 (16 studies)	⊕⊕⊕◯ **moderate**[1,4]	-
	96 per 1000	**72 per 1000** (39 to 132)				
	Moderate					
	91 per 1000	**68 per 1000** (37 to 126)				
Adverse effects: 1. Serious (any time point) - any serious adverse effect Various methods	**Study population**		**RR 0.65** (0.19 to 2.27)	234 (3 studies)	⊕⊕◯◯ **low**[1]	-
	60 per 1000	**39 per 1000** (11 to 137)				
	Moderate					
	59 per 1000	**38 per 1000** (11 to 134)				

[1] Unclear process of allocation concealment in included studies
[2] High heterogeneity
[3] Difference in rating scale scores not necessarily reflects meaningful clinical change
[4] Heterogeneity high, but reduced when results are grouped by specific agent tested
[5] Very limited number of patients available

BACKGROUND

Description of the condition

Schizophrenia is a severely debilitating and progressive illness. Although not especially highly prevalent, it carries a disproportionate share of illness-related disability, partially due to its early age at onset, associated impact in functioning, and chronic course. This effect is even more devastating as the illness tends to be deteriorating, with increased disability and personal and societal burden (Berk 2009; Lieberman 2006). Furthermore, only a minority of this burden is currently averted with standard treatment (Rossler 2005).

There is accumulating evidence that progressive changes in brain structure and function take place as the disease unfolds (DeLisi 2008). Among many possible candidates, oxidative stress may be one of the mediators of neuroprogression, grey matter loss and subsequent cognitive and functional impairment (Dean 2009; Lieberman 2006; Wood 2009). Specifically, oxidative imbalance has been evidenced by the increased levels of 8-OH deoxyguanosine, (an indicator of DNA damage and potentially of apoptotic (programmed cell death) events), protein carbonylation (leading to cellular dysfunction), and lipid peroxidation (potentially leading to alterations in membrane structure and permeability) shown in individuals with schizophrenia. Oxidative defences have also been shown to be impaired, including decreased glutathione (the primary antioxidant in the brain) levels, polymorphisms in gene pathways associated with oxidative defence and changes in other antioxidants including superoxide, dismutase, catalase and glutathione peroxidase (Wood 2009).

Description of the intervention

Antioxidants are exogenous or endogenous molecules that mitigate any form of oxidative stress or its consequences. They may act from directly scavenging free radicals to increasing anti-oxidative defences (Uttara 2009). In this fashion, antioxidants with different mechanisms have been studied in different progressive illnesses (Berk 2009).

There is evidence that current treatments impact on oxidative pathways and may to some extent reverse pro-oxidative states in schizophrenia. Second generation antipsychotics have been shown to have effects in neuroprotection, the existing literature, however, indicates that these treatments do not fully restore the deficits in antioxidant levels or restore levels of oxidants in schizophrenia (Lieberman 2005; Padurariu 2010; Wang 2008).

How the intervention might work

Oxidative stress occurs when there is an overproduction of free radicals or a deficiency in antioxidant defences (Wood 2009). This has had theoretical appeal to neurodegenerative disorders, since the brain is considered particularly vulnerable to oxidative damage. This process has been implicated in many psychiatric disorders, and most robust evidence of its importance comes from studies of schizophrenia (Ng 2008). The underlying mechanisms underpinning the process of disease neuroprogression and subsequent brain changes are incompletely understood. There is, however, some evidence pointing to central and peripheral pro-oxidative changes, including lower oxidative defences and oxidative damage to proteins, lipids and DNA (Wood 2009).

As such, there has been interest in developing interventions aimed at restoring this oxidative balance beyond the benefits of antipsychotics in this direction (Dean 2009). Some work has been done investigating the modulation of antioxidants as a therapeutic target for the treatment of schizophrenia. Similarly, mechanisms of action are believed to vary between compounds. Omega-3 for example, is proposed to have some direct antioxidant properties, but works primarily by protecting against oxidative attack by reinforcing lipid membranes and lipid-associated structures (such as myelin). Alternatively, N-acetyl cysteine (NAC) is believed to act predominantly on the glutathione pathway and may also modulate glutamate function (Dean 2009).

Why it is important to do this review

The investigation on oxidative stress in schizophrenia has increased exponentially in the past decade (Ng 2008). If antioxidants are to have a place in the treatment of this serious condition, the relevant and up-to-date information should be available to clinicians and investigators.

OBJECTIVES

To evaluate the effect of antioxidants as add-on treatments to standard antipsychotic medication for improving acute psychotic episodes and core symptoms, and preventing relapse in people with schizophrenia.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised trials. We excluded quasi-randomised studies, such as those allocating by using alternate days of the week. As the level of blindness has not been definitely linked to

bias (Petiti 2000), studies with any level of blinding were eligible. Non-English language was not an obstacle to inclusion.

Types of participants

Adults (18+ years) with schizophrenia or other types of schizophrenia-like psychosis (e.g. schizophreniform and schizoaffective disorders), irrespective of diagnostic criteria used. There is no clear evidence that the schizophrenia-like psychoses are caused by fundamentally different disease processes or require different treatment approaches (Carpenter 1994).

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

Types of interventions

1. Antioxidants

Any pharmacologically active substance explicitly administered with the purpose of antioxidation.

2. Placebo

As antipsychotics are interventions with a large evidence-base of efficacy, we included only add-on studies. In these, participants already using a first line agent are randomised to an antioxidant or placebo in addition to their previous treatment. Although we required that participants were on antipsychotics, more 'naturalistic' studies including those on 'poly-therapy' could be included, provided participants are randomised to placebo or an antioxidant. Alternatively, for maintenance studies they could be randomised to stay on the antioxidant or have it substituted for a placebo.

Types of outcome measures

We grouped outcomes into immediate (four weeks or less), short-term (4-12 weeks), medium-term (13-26 weeks) and long-term (over 26 weeks).

Primary outcomes

1. Global state

1.1 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.

Secondary outcomes

1. Leaving the studies early

1.1 Any reason, adverse events, or inefficacy of treatment

2. Global state

2.1 No clinically important change in global state (as defined by individual studies)
2.2 Relapse (as defined by the individual studies)

3. Mental state

3.1 No clinically important change in general mental state score
3.2 Average endpoint general mental state score
3.3 Average change in general mental state scores
3.4 No clinically important change in specific symptoms (positive symptoms of schizophrenia, negative symptoms of schizophrenia)
3.5 Average endpoint specific symptom score
3.6 Average change in specific symptom scores

4. General functioning

4.1 No clinically important change in general functioning
4.2 Average endpoint general functioning score
4.3 Average change in general functioning scores

5. Quality of life/satisfaction with treatment

5.1 No clinically important change in general quality of life
5.2 Average endpoint general quality of life score
5.3 Average change in general quality of life scores

6. Cognitive functioning

6.1 No clinically important change in overall cognitive functioning
6.2 Average endpoint of overall cognitive functioning score
6.3 Average change of overall cognitive functioning scores

7. Service use

7.1 Number of participants hospitalised
7.2 Duration of hospitalisation

8. Adverse effects

8.1 Number of participants with at least one adverse effect
8.2 Clinically important specific adverse effects (cardiac effects, death, movement disorders and associated effects, sedation, seizures, weight gain, effects on white blood cell count)
8.3 Average endpoint in specific adverse effects
8.4 Average change in specific adverse effects

9. Laboratory data

9.1 Change in tests of oxidative stress
9.2 Change in tests of antioxidant defences / potential

'Summary of findings table

We anticipated including the following short- or medium-term outcomes in a Summary of findings for the main comparison.

1. Global state

1.1 Clinically significant response - as defined by each of the studies
1.2 Relapse

2. Mental state

2.1 Clinically significant response in mental state - as defined by each of the studies

3. Service utilisation outcome

3.1 Hospital admission
3.2 Days in hospital

4. Adverse effect

4.1 Any important adverse event

5. Quality of life

5.1 Improved to an important extent
see Differences between protocol and review

Search methods for identification of studies

Electronic searches

Cochrane Schizophrenia Group's Trials Register

On January 08, 2015, the Trials Search Co-ordinator (TSC) searched the Cochrane Schizophrenia Group's Study-Based Register of Trials using the following search strategy:
Antioxidant in Intervention Field of STUDY
In such a study-based register, searching the major concept retrieves all the synonym keywords and relevant studies because all the studies have already been organised based on their interventions and linked to the relevant topics.
The Cochrane Schizophrenia Group's Register of Trials is compiled by systematic searches of major resources (including AMED, BIOSIS, CINAHL, Embase, MEDLINE, PsycINFO, PubMed, and registries of clinical trials) and their monthly updates, handsearches, grey literature, and conference proceedings (see Group's Module). There is no language, date, document type, or publication status limitations for inclusion of records into the register. For previous searches, please see Appendix 1.

Searching other resources

1. Reference searching

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

2. Personal contact

If necessary, we contacted the authors of significant papers, as well as other experts in the field, and asked for their knowledge of further studies, published or unpublished, relevant to the review. We noted any responses in the Characteristics of included studies

Data collection and analysis

Selection of studies

Review authors PVM and OD independently inspected citations from the searches and identified relevant abstracts. MB independently re-inspected a random 20% sample of the citations and abstracts to ensure reliability. PVM and OD obtained full reports of the abstracts meeting the review criteria and inspected them. Again, MB re-inspected a random 20% of these full reports in order to ensure reliable selection. There were no disputes whether any particular study should be included.

Data extraction and management

1. Extraction

Review author PVM extracted data from all included studies. In addition, to ensure reliability, OD independently extracted data from all studies. We made attempts to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary.

2. Management

2.1 Forms

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

2.2 Scale-derived data

We included continuous data from rating scales only if:
a. the psychometric properties of the measuring instrument have been described in a peer-reviewed journal (Marshall 2000); and
b. the measuring instrument has not been written or modified by one of the trialists for that particular trial.
Ideally, the measuring instrument should either be i. a self-report or ii. completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly, in Description of studies we noted if this is the case or not.

2.3 Endpoint versus change data

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

2.4 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we aimed to apply the following standards to relevant data before inclusion.
Change data
When continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not. We would have presented and entered change data into statistical analyses.
Endpoint data
Endpoint scores on scales often have a finite start and end point and we applied the following rules:

1. standard deviations (SDs) and means are reported in the paper or obtainable from the authors;
2. when a scale starts from the finite number zero, the standard deviation (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);
3. if a scale starts from a positive value (such as the Positive and Negative Syndrome Scale (PANSS) (Kay 1986), which can have values from 30 to 210), the calculation described above would be 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.

Had we found endpoint data from studies of fewer than 200 participants we planned to present these as other data within the data and analyses section rather than entering such data into statistical analyses.
Skewed endpoint data pose less of a problem when looking at means if the sample size is large and if we found skewed endpoint data from studies of over 200 participants we entered such data from these studies into statistical analyses.

2.5 Common measure

To facilitate comparison between trials, we intended to convert variables that can be reported in different metrics, such as days in hospital (mean days per year, per week or per month) to a common metric (e.g. mean days per month), although no such occasions appeared.

2.6 Conversion of continuous data to binary data

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

2.7 Direction of graphs

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

2.8 Multiple doses

When a study investigating a number of fixed doses of an antioxidant was included, we used the method described in section 16.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to combine data from multiple groups.

Assessment of risk of bias in included studies

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

Where inadequate details of randomisation and other characteristics of trials were provided, we contacted authors of the studies in order to obtain further information. There was no disagreement in quality assessment.

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

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

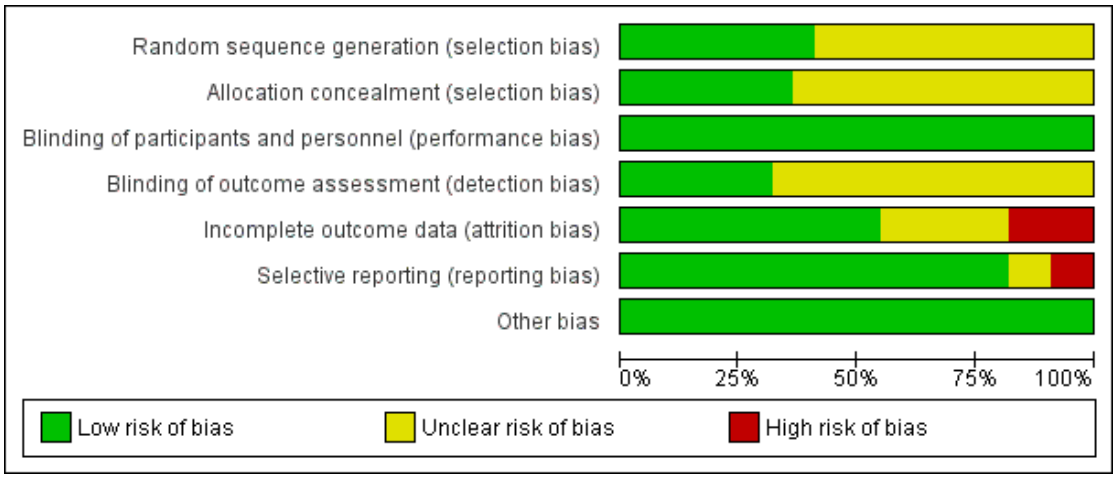
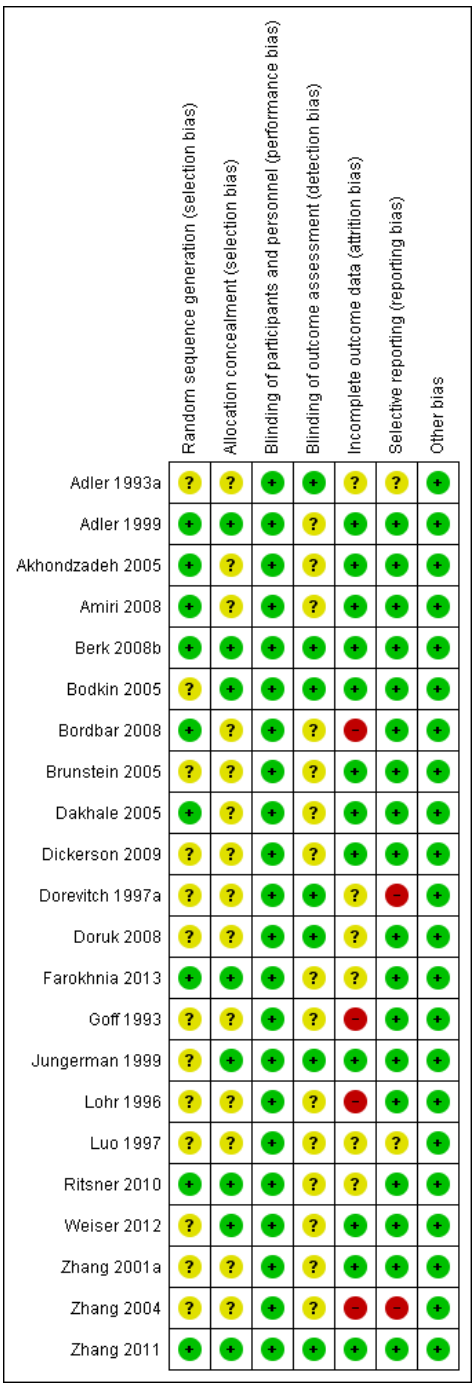


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Measures of treatment effect

1. Binary data

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

2. Continuous data

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

Unit of analysis issues

1. Cluster trials

There were no cluster-randomised trials included in the review.

2. Cross-over trials

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

3. Studies with multiple treatment groups

Where a study involved more than two treatment arms, if relevant, we presented the additional treatment arms in comparisons. If data were binary, we simply added these and combined within the two-by-two table.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up, data must lose credibility (Xia 2009). We chose that, for any particular outcome, should more than 40% of data be unaccounted for, we would not reproduce these data or use them within analyses.

2. Binary

In the case where attrition for a binary outcome is between 0% and 40% and where these data are not clearly described, data would be presented on a 'once-randomised-always-analyse' basis (an intention-to-treat (ITT) analysis). Those leaving the study early are all assumed to have the same rates of negative outcome as those who completed, with the exception of the outcome of death and adverse effects. A sensitivity analysis was planned but was not undertaken since very few studies reported on binary improvement and those that reported used ITT analysis.

3. Continuous

3.1 Attrition

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

3.2 Standard deviations

There were no instances where standard deviations were not reported.

3.3 Last observation carried forward (LOCF)

We anticipated that in some studies the method of last observation carried forward (LOCF) would be employed within study reports. As with all methods of imputation to deal with missing data, LOCF introduces uncertainty about the reliability of the results (Leucht 2007). Therefore, where LOCF data were used in the trial,

if less than 50% of the data had been assumed, we reproduced these data and indicated that they are the product of LOCF assumptions.

Assessment of heterogeneity

1. Clinical heterogeneity

We considered all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We inspected all studies for clearly outlying people or situations which we had not predicted would arise. When such situations or participant groups existed, they are discussed.

2. Methodological heterogeneity

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

3. Statistical heterogeneity

3.1 Visual inspection

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

3.2 Employing the I^2 statistic

Heterogeneity between studies was investigated by considering the I^2 method alongside the Chi^2 'P' value. The I^2 provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 depends on i. magnitude and direction of effects and ii. strength of evidence for heterogeneity (e.g. a 'P' value from Chi^2 test, or a confidence interval for I^2). an I^2 estimate greater than or equal to around 50% accompanied by a statistically significant Chi^2 statistic, was interpreted as evidence of substantial levels of heterogeneity (Section 9.5.2 - Higgins 2011). When substantial levels of heterogeneity were found, we explored reasons for heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in Section 10 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 are 10 or fewer studies, or where all studies were of similar sizes.

Data synthesis

Although the choice of model for meta-analysis remains controversial (Freemantle 1999), a random-effects model (DerSimonian 1986), which assumes that studies analysed actually comes from pool of hypothetical studies, was used in this meta-analysis. The random-effects methods does put added weight onto the smaller of the studies - those that may be most prone to bias. We nevertheless favoured using a random-effects model.

Subgroup analysis and investigation of heterogeneity

1. Subgroup

We conducted subgroup analyses regarding the specific antioxidant used.

We were interested in making sure that information is as relevant to the current care of people with schizophrenia and broad clinical groups (see Types of participants). We intended to be able to present these data according to current clinical state, stage and for people with particular problems. This was not possible, however, because none of the studies reported relevant subgroups.

2. Investigation of heterogeneity

2.1 Unanticipated heterogeneity

If inconsistency was high, we reported this.

2.2 Anticipated heterogeneity

We did not anticipate important levels of heterogeneity.

Sensitivity analysis

1. Quality

We aimed to include trials in a sensitivity analysis if they were described in some way as to imply randomisation, but there were no such instances.

2. Handling of missing observations

Where assumptions have had to be made regarding people lost to follow-up (see Dealing with missing data), we compared the findings of the primary outcomes when we used our assumption compared with completer data only.

3. Statistical model for the synthesis

For the primary outcome, if there was substantial heterogeneity, we checked if using a fixed-effect model substantively changed the final result.

RESULTS

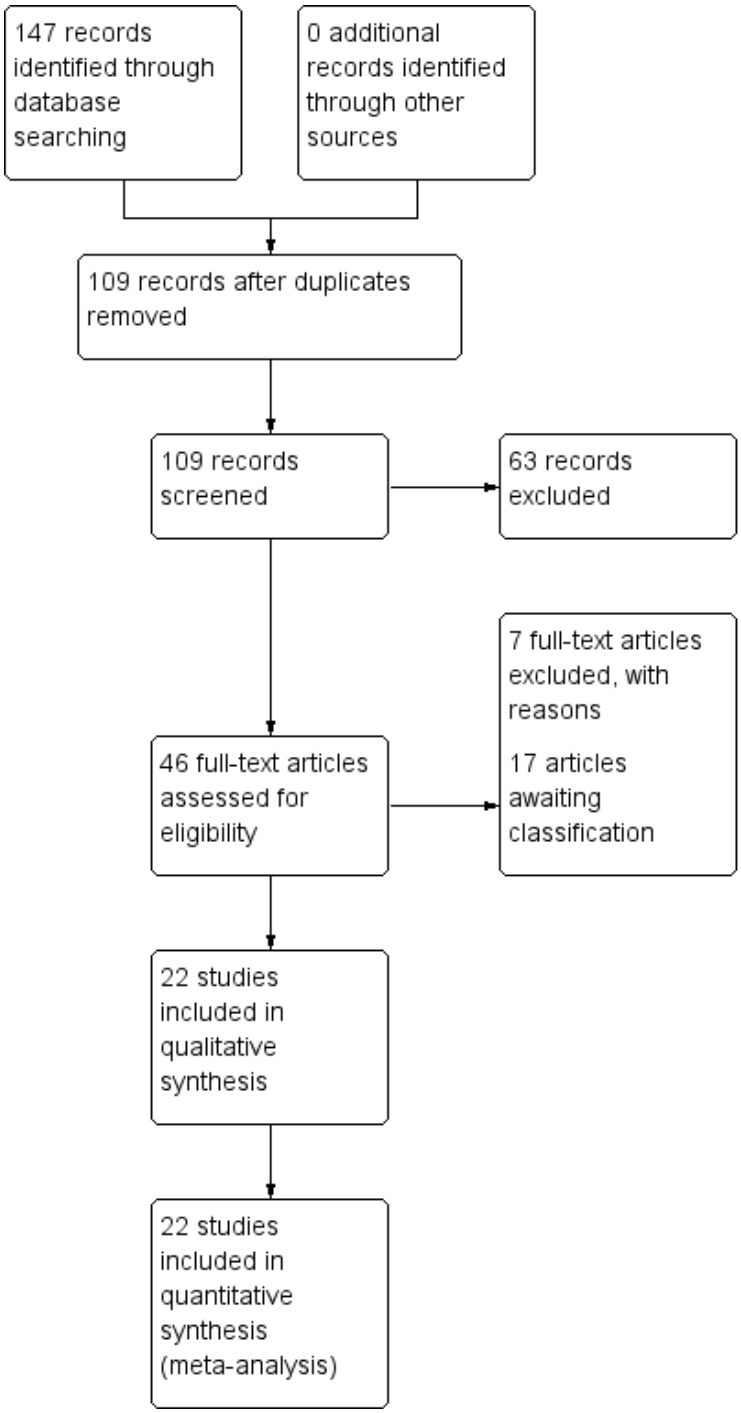
Description of studies

Please see Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

Electronic searches in 2010, 2012 and 2015 identified 147 references with no additional records identified through personal contact or inspecting references of retrieved articles. After duplicates were removed, we screened 109 records. Forty-six potentially relevant records were obtained and scrutinised and 24 of these reports either did not meet the inclusion criteria and had to be excluded (seven) or were unclear and are awaiting classification pending further information (17). Twenty-two trials are therefore included (Figure 3).

Figure 3. Study flow diagram.



Included studies

1. Allocation

All included studies were stated to be randomised and double-blinded. All were, as per protocol, add-on trials.

2. Design

All included studies had a parallel longitudinal design. Only two of 22 studies used a cross-over design with two periods and had data available from the first period (Brunstein 2005; Dorevitch 1997a).

3. Duration

All but three studies were short-term studies. Berk 2008b was a medium-term study (24 weeks) and Adler 1993a and Adler 1999 were long-term studies. We made the decision to group Luo 1997 with short-term studies, since it was the only study with a 16-week duration and it was similar to other ginkgo studies in this review in terms of diagnosis and other methodological aspects. Overall, the median follow-up was eight weeks.

4. Participants

Participants total 2041 people. The number of participants ranged from 16 to 545 (median 46). Nineteen of the 22 studies reported using Diagnostic and Statistical Manual (DSM-III, DSM-IIIR or DSM-IV) criteria to diagnose schizophrenia. Six studies also required patients to present with tardive dyskinesia for inclusion. Of the studies that reported the patients' sex, men were over-represented in most; slightly over two men to one woman.

5. Setting

Six trials were conducted in the USA, four in China, four in Iran, three in Israel and one each in Brazil, India, Romania, Australia and Turkey. Nine trials were conducted in inpatient and 11 in outpatient settings, two in mixed settings.

6. Interventions

6.1 Adjunctive antioxidants

Four studies employed adjunctive *Ginkgo biloba* extract, from 120 to 360 mg/day (Doruk 2008; Luo 1997; Zhang 2001a; Zhang 2011); five selegiline, from 5 to 15 mg/day (Amiri 2008; Bodkin 2005; Bordbar 2008; Goff 1993; Jungerman 1999); four allopurinol, from 300 to 600 mg/day (Akhondzadeh 2005; Brunstein 2005; Dickerson 2009; Weiser 2012); five, vitamin E (Adler 1993a; Adler 1999; Dorevitch 1997a; Lohr 1996; Zhang 2004), from 1200 IU to 1600 IU/day; two N-acetyl cysteine (NAC) (Berk 2008b; Farokhnia 2013); and one each dehydroepiandrosterone (DHEA) (Ritsner 2010) and vitamin C (Dakhale 2005).

6.2 Comparison group

An adjunctive placebo was used as a comparison group, with no further details given in most studies.

7. Outcomes

7.1 General

Although we intended to report on a host of clinically relevant outcomes, only a few clinical outcomes, generally derived from rating scales and quite limited oxidative stress data were reported in the included studies.

Some outcomes were presented in graphs, P values or a statement of significant or non-significant difference. This made it impossible to use data for synthesis.

Notably, very few studies (only Berk 2008b, Brunstein 2005 and Dickerson 2009) reported any clinically meaningful measure of clinical response.

7.2 Scales used to measure psychopathology, functioning and adverse effects

The two scales most employed to measure symptoms were the Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS).

7.2.1 BPRS (Overall 1962

The BPRS is a one-page, 16- or 18-item rating scale developed more than 50 years ago. It assesses a range of psychotic and affective symptoms. The original purpose was rapid evaluation of clinical change irrespective of origin in the broad range of psychiatric patients.

7.2.2 PANSS (Kay 1986).

The PANSS originated from a need to reduce the heterogeneity of schizophrenia, based on a positive-negative dichotomy for explaining and understanding variability in the aetiology of schizophrenia, treatment and prognosis.

7.2.3 SANS (Andreasen 1990)

Also often employed to determine positive and negative symptoms were Andreasen's Schedule for the Assessment of Positive Symp-

toms (SAPS) and Schedule for the Assessment of Negative Symptoms .
7.2.4 GAS (Endicott 1976) and GAF (Jones 1995).
The Global Assessment of Functioning (GAF), and its older version, the Global Assessment Scale (GAS) were used in two studies. These are general functioning scales developed to be clinically useful and easy to administer, but with the caveat that they do not separate functioning from symptoms.
7.2.5 TESS (Guy 1991)
The Treatment Emergent Symptom Scale (TESS) measures side-effects severity. It can be used as a total score or as six subscores that gather symptoms related to different body systems.

7.3 Laboratory methods used to measure oxidative stress and antioxidant defences

Three studies reported on laboratory methods. Dakhale 2005 reported serum malondialdehyde (MDA) levels, according to methods described by Satoh (Satoh 1978). MDA is an oxidative stress marker, the final product of peroxidation processes and oxidative damage in cells (Valko 2007). Zhang 2001a and Zhang 2004 reported on superoxide dysmutase (SOD, an antioxidant enzyme) serum levels with radioimmunoassay, described in Zhang 2001a.

Excluded studies

We excluded seven studies, either because they did not measure any outcome of interest (Dorevitch 1997; Elkashef 1990; Suresh 2007), were not adjunctive or randomised trials (Bhavani 1962; Kapur 1991), randomised participants to combined interventions (Rees 1951) or participants were not diagnosed with schizophrenia (Eranti 1998).

Awaiting classification

There are 17 trials awaiting classification pending provision of more information.

Ongoing studies

There are currently no ongoing studies we are aware of.

Risk of bias in included studies

Figure 1 and Figure 2 are graphical overviews of the risk of bias in the included studies.

Allocation

All 22 included studies were randomised but not all described how this was achieved, and were not generally clear about allocation concealment. Only nine (Adler 1999; Akhondzadeh 2005; Amiri 2008; Berk 2008b; Bordbar 2008; Dakhale 2005; Farokhnia 2013; Ritsner 2010; Zhang 2011) gave further details about sequence generation. Eight studies (Adler 1999; Berk 2008b; Bodkin 2005; Farokhnia 2013; Jungerman 1999; Ritsner 2010; Weiser 2012; Zhang 2011) reported a satisfactory method of concealment.

Blinding

All studies were reported as double-blind trials with participants blinded to treatment. Not all studies were clear about rater blinding. One study is in the Studies awaiting classification section because it is unclear whether it was a single-blind or open-label study (Xu 2002).

Incomplete outcome data

Several studies reported using some form of intention-to-treat analysis to account for incomplete data, usually last observation carried forward (LOCF) (Adler 1999; Akhondzadeh 2005; Amiri 2008; Berk 2008b; Bodkin 2005; Brunstein 2005; Dakhale 2005; Dickerson 2009; Weiser 2012; Zhang 2001a; Zhang 2011). One study explicitly reported all participants completed the trial (Jungerman 1999). Two studies were classified as high risk for stating using a completer analysis (Bordbar 2008; Goff 1993) or failing to report any attrition (Lohr 1996; Zhang 2004).

Selective reporting

Selective reporting was not a major issue for this review. Most studies reported primary outcomes of interest. We classified two studies as high risk primarily because of endpoint rating scale data not reported (Dorevitch 1997a; Zhang 2004).

Other potential sources of bias

We found no other obvious potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Adjunctive antioxidants for schizophrenia versus placebo

COMPARISON 1: ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

1.1 Global state: 1. No clinically important response (20% improvement PANSS)

Studies tended not to include categorical measures of response (only three out of the 20 included studies). Only two short-term studies and one medium-term study reported clinical response as

a 20% reduction in the PANSS. These results did not demonstrate an advantage for adjunctive antioxidants 3 RCTS, n = 229, risk ratio (RR) 0.77, 95% confidence interval (CI) 0.53 to 1.12 Analysis 1.1),

1.1.1 Allopurinol: PANSS improvement: short term

In this subgroup we found two relevant trials (n = 94). There was no significant difference between adjunctive allopurinol and placebo (RR 0.69 95% CI 0.36 to 1.32). This subgroup had important levels of heterogeneity (Chi^2 = 7.36; df = 1; P = 0.007; I^2 = 86%).

1.1.2 N-acetyl cysteine (NAC): PANSS improvement: medium term

In this subgroup we only found one relevant trial (n = 135). There was no significant difference between adjunctive NAC and placebo (RR 1.01 95% CI 0.53 to 1.92).

1.2 Leaving the study early:

1.2.1 Short term (all antioxidants)

Use of any adjunctive antioxidant did not change the risk of leaving the study early in the short term (16 RCTs, 1584 people, RR 0.73, 95% CI 0.48 to 1.11 Analysis 1.2). There was also no significant difference in retention in the medium term (1 RCT, n = 140, RR 0.99, 95% CI 0.67 to 1.48 Analysis 1.3), or in two long-term studies (2 RCTS, n = 195, RR 0.90 95% CI 0.59 to 1.35 Analysis 1.4).
Data could be subgrouped into individual antioxidant treatments (Figure 1).

1.2.1.1 Allopurinol

In this subgroup we found four relevant trials (n = 388). There was no significant difference between adjunctive allopurinol and placebo (RR 0.83 95% CI 0.55 to 1.24).

1.2.1.2 Ginkgo biloba

In this subgroup we found four relevant trials (n = 857). There was no significant difference between adjunctive ginkgo and placebo (RR 0.42 95% CI 0.17 to 1.03).

1.2.1.3 Selegiline

In this subgroup we found three relevant trials (n = 153). There was no significant difference between adjunctive selegiline and placebo (RR 5.22 95% CI 0.90 to 30.31).

1.2.1.4 Vitamin C

In this subgroup we only found one relevant trial (n = 40) (Dakhale 2005). There was no significant difference between adjunctive vitamin C and placebo (RR 0.25 95% CI 0.03 to 2.05).

1.2.1.5 Vitamin E

In this subgroup we found two relevant trials (n = 68). There was no significant difference between adjunctive vitamin E and placebo (RR 0.97 95% CI 0.06 to 14.48) This subgroup had moderate levels of heterogeneity (Chi^2 = 1.67; df = 1; P = 0.197; I^2 = 40%).

1.2.1.6 NAC

In this subgroup we only found one relevant trial (n = 46) (Farokhnia 2013). There was no significant difference between adjunctive NAC and placebo (RR 1.00 95% CI 0.15 to 6.51).

1.2.1.7 DHEA

In this subgroup we only found one relevant trial (n = 32) (Ritsner 2010). There was no significant difference between adjunctive DHEA and placebo (RR 0.60 95% CI 0.17 to 2.10).

1.2.2 Medium term (NAC)

Medium-term data for leaving the study early were provided by only one relevant trial (n = 140) (Berk 2008b). There was no significant difference between adjunctive NAC and placebo (RR 0.99 95% CI 0.67 to 1.48, Analysis 1.3).

1.2.3 Long term (Vitamin E)

Two trials (n = 195) provided long-term data for leaving the study early. There was no significant difference between adjunctive vitamin E and placebo (RR 0.9 95% CI 0.59 to 1.35, Analysis 1.4).

1.3 Mental state

Thirteen studies measured mental state using the BPRS or PANSS. Pooling individual antioxidant short-term data favoured antioxidants, however there were substantial levels of heterogeneity. Results varied for individual antioxidants. Medium-term data were

presented by one trial only, as were long-term data; both studies found no significant advantage of antioxidant over placebo at these time points.

1.3.1 Mental state : 1a. General - short-term BPRS total endpoint

Eight studies provided short-term BPRS endpoint data; a favourable effect for antioxidants was found (n = 843, mean difference (MD) -3.20,95% CI -5.63 to -0.78) I^2 = 74%). There was substantial heterogeneity for this outcome.(Chi^2 = 27.41, df = 7 (P = 0.0003); I^2 = 74%). Analysis 1.5

Overall, data were favourable, however, when data were subgrouped into individual antioxidant treatments, the results varied.

1.3.1.1 Ginkgo biloba

Data from three short-term studies showed a favourable effect for *Ginkgo biloba* (3 RCTS, n = 663, MD -2.74, 95% CI -5.29 to -0.20). This subgroup had important levels of heterogeneity (Chi^2 = 8.73; df = 2; P = 0.013; I^2 = 77%)

1.3.1.2 Selegiline

No effect was found for selegiline (3 RCTS, n = 111, MD -0.31, 95% CI -4.03 to 3.41)

1.3.1.3 Vitamin C

One small study showed a favourable effect for vitamin C (n = 40, MD -9.66, 95% CI - 13.27 to -6.05)

1.3.1.4 Vitamin E

A favourable effect was not found for vitamin E (n = 29, MD -7.92, 95% CI -17.20 to 1.36)

1.3.2 Mental state: 1b. General - short-term PANSS

Overall, there was substantial heterogeneity regarding differences of any antioxidant and placebo in mental state scores for the PANSS (Chi^2 = 16.96, df = 5 (P = 0.005); I^2 = 71%). Data showed a favourable effect for antioxidants (7 RCTS, n = 584, MD -6.00, 95% CI -10.35 to -1.65) (Analysis 1.6).

Data could be subgrouped into individual antioxidants.

1.3.2.1 Allopurinol

In this subgroup we found three relevant trials (n = 329). There was no significant difference between adjunctive antioxidants and placebo (MD -6.91 95% CI -15.86 to 2.04). This subgroup had important levels of heterogeneity (Chi^2 = 12.76; df = 2; P = 0.002; I^2 = 84%).

1.3.2.2 Ginkgo biloba

In this subgroup we only found one relevant trial (n = 157). There was a statistically significant difference between adjunctive antioxidants and placebo (MD -3.30 95% CI -6.51 to -0.09).

1.3.2.3 Selegiline

In this subgroup we found two relevant trials (n = 56). There was no significant difference between adjunctive antioxidants and placebo (MD -2.97 95% CI -15.68 to 9.74, Analysis 1.6). This subgroup had important levels of heterogeneity (Chi^2 = 4.06; df = 1; P = 0.044; I^2 = 75%).

1.3.2.4 NAC

In this subgroup we only found one relevant trial (n = 42). There was a statistically significant difference between adjunctive antioxidants and placebo (MD -12.86 95% CI -19.82 to -5.90).

1.3.3 Mental state: 1c. General - medium-term PANSS

Only one relevant trial (randomising NAC) presented medium-term mental state data (n = 135). There was no significant difference between adjunctive antioxidants and placebo (MD -1.71 95% CI -7.55 to 4.13, Analysis 1.7).

1.3.4 Mental state: 1d. General - long-term BPRS

Again, only one trial (randomising vitamin E) presented long-term mental state data. There was no significant difference between adjunctive antioxidants and placebo (n = 104, MD 1.20 95% CI -2.47 to 4.87, Analysis 1.8).

1.3.5 Mental state: 2a. Specific - short-term PANSS negative symptoms

Nine studies presented specific short-term scores for negative symptoms using the PANSS. Overall, results showed no effect for antioxidants over placebo (9 RCTs, n = 653, MD -0.38, 95% CI -0.77 to 0.00) (Analysis 1.9). Significant levels of heterogeneity were found (i^2 = 79%)

Data could be subgrouped into individual antioxidants.

1.3.5.1 Selegiline

In this subgroup we found three relevant trials (n = 111). There was a statistically significant difference between adjunctive antioxidants and placebo (standardised mean difference (SMD) -0.54 95% CI -1.76 to 0.68). This subgroup had important levels of heterogeneity (Chi^2 = 16.73; df = 2; P = 0.0; I^2 = 88%).

1.3.5.2 Allopurinol

In this subgroup we found three relevant trials (n = 317). There was a statistically significant difference between adjunctive antioxidants and placebo (SMD -0.37 95% CI -0.98 to 0.23). This subgroup had important levels of heterogeneity (Chi^2 = 7.4; df = 2; P = 0.025; I^2 = 73%).

1.3.5.3 Ginkgo biloba

In this subgroup we only found one relevant trial (n = 157) (Zhang 2011). There was a statistically significant difference between adjunctive antioxidants and placebo (SMD -0.17 95% CI -0.49 to 0.14).

1.3.5.4 NAC

In this subgroup we only found one relevant trial (n = 44) (Farokhnia 2013). There was a statistically significant difference between adjunctive antioxidants and placebo (SMD -1.10 95% CI -1.74 to -0.47).

1.3.5.5 DHEA

In this subgroup we only found one relevant trial (n = 24) (Ritsner 2010). There was no significant difference between adjunctive antioxidants and placebo (SMD 0.63 95% CI - 0.20 to 1.45, Analysis 1.9).

1.3.6. Mental state: 2b. Specific - short-term SANS negative

Three studies presented short-term data for negative symptoms using the SANS scale. All three studies were assessing *Ginkgo biloba* compared with placebo. There was a statistically significant difference between the antioxidant *Ginkgo biloba* and placebo (3 RCTs, n = 667, MD -7.46 95% CI -12.46 to -2.46, Analysis 1.10). This subgroup had important levels of heterogeneity (Chi^2 = 8.32, df = 2 (P = 0.02); I^2 = 76%).

1.3.7 Mental state: 2c. Specific - medium-term PANSS negative

1.11.1 NAC

Only one NAC trial (n = 135) presented medium-term data for negative symptoms. There was a statistically significant difference between adjunctive antioxidants and placebo (MD -2.33 95% CI -4.24 to -0.42, Analysis 1.11).

1.3.8 Mental state: 2d. Specific - short-term PANSS positive

Eight trials presented short-term data for positive symptoms using the PANSS scale. No effect was found (8 RCTs, n = 611, MD -0.96 95% CI -2.50 to 0.58). Substantial levels of heterogeneity were found (I^2 = 83 %)(Analysis 1.12).
Data could be subgrouped into individual antioxidants

1.3.8.1 Selegiline

In this subgroup we found two relevant trials (n = 71). There was no significant difference between adjunctive antioxidants and placebo (MD 0.57 95% CI -2.30 to 3.45). This subgroup had important levels of heterogeneity (Chi^2 = 9.23; df = 1; P = 0.002; I^2 = 89%).

1.3.8.2 Allopurinol

In this subgroup we found three relevant trials (n = 317). There was no significant difference between adjunctive antioxidants and placebo (MD -3.55 95% CI -8.24 to 1.13). This subgroup had important levels of heterogeneity (Chi^2 = 18.02; df = 2; P = 0.0; I^2 = 89%).

1.3.8.3 Ginkgo biloba

In this subgroup we only found one relevant trial (n = 157) (Zhang 2011). There was a statistically significant difference between adjunctive antioxidants and placebo (MD -1.20 95% CI -2.31 to -0.09).

1.3.8.4 NAC

In this subgroup we only found one relevant trial (n = 42) (Farokhnia 2013). There was no significant difference between adjunctive antioxidants and placebo (MD -1.14 95% CI - 3.57 to 1.29).

1.3.8.5 DHEA

In this subgroup we only found one relevant trial (n = 24) (Ritsner 2010). There was no significant difference between adjunctive antioxidants and placebo (MD 3.60 95% CI - 1.30 to 8.50).

1.3.9 Mental state: 2e. Specific - short-term SAPS positive

Two *Ginkgo biloba* trials (n = 151) presented short-term data using the SAPS positive. There was a statistically significant difference between adjunctive antioxidants and placebo (MD -5.06 95% CI -7.52 to -2.59, Analysis 1.13).

1.3.10 Mental state: 2f. Specific - medium-term PANSS positive

1.3.10.1 NAC

Only one NAC trial (n = 135) presented medium-term positive mental state data (Berk 2008b). There was no significant difference between adjunctive antioxidants and placebo (MD 0.47 95% CI -1.43 to 2.37, Analysis 1.14).

1.4 General functioning

1.4.1 General functioning: 1a. General - short-term GAS total endpoint

Two small studies presented equivocal short-term data for general functioning (2 RCTs, n = 52, MD -1.11 95% CI -8.07 to 5.86) (Analysis 1.15).
Data could be subgrouped into individual antioxidants.

1.4.1.1 Selegiline

In this subgroup we only found one relevant trial (n = 28) (Goff 1993). There was no significant difference between the antioxidant selegiline and placebo (MD 0.90 95% CI -3.25 to 5.05).
1.4.1.2 DHEA
Again, equivocal data were found for the antioxidant DHEA in one trial (n = 24, MD -7.40 95% CI -19.80 to 5.00)

1.4.2 General functioning: 1b. General - medium-term GAS total endpoint

One trial comparing NAC with placebo presented medium-term general functioning data(Berk 2008b). There was no significant difference between adjunctive NAC and placebo (n = 135, MD 2.84 95% CI -2.09 to 7.77) (Analysis 1.16).

1.4.3 General functioning; 1c. General - long-term GAS total endpoint

In this subgroup we only found one relevant trial (n = 104) (Adler 1999). There was no significant difference between adjunctive vitamin E and placebo (MD 0.10 95% CI -5.60 to 5.80) (Analysis 1.17).

1.5 Adverse effects:

Adverse effects were usually not reported in a usable way in most trials, with the exceptions of Akhondzadeh 2005; Amiri 2008; Berk 2008b; Brunstein 2005; Dickerson 2009; and Zhang 2001a. These trials reported different measures of adverse effects, including specific adverse effects, serious adverse effects and scale data. See Analysis 1.18; Analysis 1.19; Analysis 1.20.

1.5.1 Serious adverse effects (any time point)

1.5.1.1 Any 'serious' adverse effect

Three relevant trials recorded 'any serious adverse effect) (n = 234). There was no significant difference between adjunctive antioxidants and placebo (3 RCTS, n = 234, RR 0.65 95% CI 0.19 to 2.27).

1.5.1.2 Myocardial infarction

In this subgroup we only found one relevant trial (n = 59) (Dickerson 2009). There was no significant difference between adjunctive antioxidants and placebo (RR 2.72 95% CI 0.12 to 64.14).

1.5.1.3 Neutropenia

In this subgroup we only found one relevant trial (n = 59) (Dickerson 2009). There was no significant difference between adjunctive antioxidants and placebo (RR 0.30 95% CI 0.01 to 7.13).

1.5.1.4 Pneumonia

In this subgroup we found two relevant trials (n = 94). There was no significant difference between adjunctive antioxidants and placebo (RR 2.78 95% CI 0.30 to 25.75)

1.5.1.5 Seizure

In this subgroup we only found one relevant trial (n = 35) (Brunstein 2005). There was no significant difference between adjunctive antioxidants and placebo (RR 0.32 95% CI 0.01 to 7.26, Analysis 1.18).

1.5.2 Adverse effects 2. Various - less 'serious'

1.5.2.1 Allergy - rash or other dermatological problems

In this subgroup we found four relevant trials (n = 280). There was no significant difference between adjunctive antioxidants and placebo (RR 1.06 95% CI 0.61 to 1.84).

1.5.2.2 Cardiovascular - dizziness

In this subgroup we found two relevant trials (n = 82) (Amiri 2008; Farokhnia 2013). There was no significant difference between adjunctive antioxidants and placebo (RR 1.17 95% CI 0.46 to 2.96).

1.5.2.3 Cardiovascular - systemic hypertension

IIn this subgroup we found two relevant trials (n = 82) (Amiri 2008; Farokhnia 2013). There was no significant difference between adjunctive antioxidants and placebo (RR 3.30 95% CI 0.99 to 11.04)

1.5.2.4 Central nervous system - agitation

In this subgroup we only found one relevant trial (n = 40) (Amiri 2008). There was no significant difference between adjunctive antioxidants and placebo (RR 2.50 95% CI 0.55 to 11.41, Analysis 1.19).

1.5.2.5 Central nervous system - appetite increase

In this subgroup we found three relevant trials (n = 128). There was no significant difference between adjunctive antioxidants and placebo (RR 1.00 95% CI 0.54 to 1.87, Analysis 1.19).

1.5.2.6 Central nervous system - headache

In this subgroup we found four relevant trials (n = 281). There was no significant difference between adjunctive antioxidants and placebo (RR 0.99 95% CI 0.60 to 1.64, Analysis 1.19).

1.5.2.7 Central nervous system - insomnia

In this subgroup we only found one relevant trial (n = 40) (Amiri 2008). There was no significant difference between adjunctive antioxidants and placebo (RR 2.50 95% CI 0.55 to 11.41, Analysis 1.19).

1.5.2.8 Central nervous system - sedation

In this subgroup we only found two relevant trials (n = 88) (Akhondzadeh 2005; Farokhnia 2013). There was no significant difference between adjunctive antioxidants and placebo (RR 1.34 95% CI 0.70 to 2.59, Analysis 1.19).

1.5.2.9 Central nervous system - tremor

In this subgroup we found two relevant trials (n = 86). There was no significant difference between adjunctive antioxidants and placebo (RR 0.70 95% CI 0.32 to 1.54, Analysis 1.19).

1.5.2.10 Gastrointestinal - abdominal pain

In this subgroup we only found one relevant trial (n = 40) (Amiri 2008). There was no significant difference between adjunctive antioxidants and placebo (RR 2.00 95% CI 0.41 to 9.71).

1.5.2.11 Gastrointestinal - nausea

In this subgroup we found four relevant trials (n = 281). There was no significant difference between adjunctive antioxidants and placebo (RR 1.04 95% CI 0.67 to 1.62).

1.5.3 Adverse effects: 3. Average scores - endpoint total TESS

For this outcome, we only found one relevant trial (n = 109) (Zhang 2001a). There was a statistically significant difference between adjunctive antioxidants and placebo (MD -0.90 95% CI -2.34 to 0.54, Analysis 1.20).

1.6 Laboratory data (serum tests)

1.6.1 MDA levels

In this subgroup we only found one relevant trial (n = 40) (Dakhale 2005). There was a statistically significant difference between adjunctive antioxidants and placebo (SMD -2.18 95% CI -2.98 to -1.38, Analysis 1.21).

1.6.2 SOD levels

In this subgroup we found two relevant trials (n = 123). There was no significant difference between adjunctive antioxidants and placebo (SMD 0.27 95% CI -0.56 to 1.10, Analysis 1.21). This subgroup had important levels of heterogeneity (Chi^2 = 4.66; df = 1; P = 0.031; I^2 = 79%).

DISCUSSION

Summary of main results

With 22 trials, including over 2000 participants, studies testing adjunctive drugs with antioxidant potential are mostly preliminary. They are characterised by a short follow-up period, mostly underpowered, do not offer data on the most clinically meaningful outcomes and are of a relatively low quality. Efficacy data on psychopathology scale scores is highly heterogenous, which can be explained by the use of drugs with a different pharmacological profile. Safety appeared not to be a concern for the studies, with most studies not reporting relevant adverse events at all. All these issues make it difficult to interpret the effect of adding an antioxidant to the standard treatment of schizophrenia.

Regarding particular drugs, *Ginkgo biloba* is the most studied agent, overwhelmingly in Chinese participants, who were all inpatients. In these studies, ginkgo significantly reduced rating scale scores in the short term, mostly for positive symptoms. In the Chinese trials, there was also a lower rate of patients leaving the study early when compared with placebo.

A very recent independently run, high quality and adequately powered trial comparing allopurinol with placebo (Weiser 2012) changed an initial impression of benefit given by three previous small trials (Akhondzadeh 2005; Brunstein 2005; Dickerson 2009). Although allopurinol was as tolerable as placebo, at present there is no evidence for benefit in terms of improvement, total scale scores or positive or negative symptoms of schizophrenia.

For selegiline, data from four fairly small trials and of low quality do not suggest any benefit in terms of scale scores. One study suggested worsening of positive symptoms (Jungerman 1999), and pooled data showed a trend towards lower tolerability for adjunctive selegiline.

We identified two studies comparing adjunctive N-acetyl cysteine (NAC) with placebo, one short term (Farokhnia 2013) and one medium term (Berk 2008b). The data indicate a benefit in terms of negative symptoms, with no difference in positive symptoms, functioning or tolerability. One small short-term trial and two long-term trials investigated vitamin E effects, albeit they were mostly interested in tardive dyskinesia outcomes (Adler 1993a; Adler 1999; Dorevitch 1997a). They were not able to establish meaningful differences between adjunctive vitamin E and placebo in terms of symptoms of tolerability. One small trial showed a very large benefit for adjunctive vitamin C over placebo in terms of total psychopathology scores (Dakhale 2005).

Overall completeness and applicability of evidence

1. Completeness

Albeit we were able to identify a number of trials, with two trials being appreciably larger than the rest (Luo 1997; Weiser 2012), we were not able to identify our primary outcomes of interest. Most data pertained to rating scale scores, with hardly any measure of clinical improvement, functioning or quality of life.

2. Applicability

Trials recruited both inpatients and outpatients who would be recognisable in everyday care. All trials in China using adjunctive ginkgo, however, were conducted exclusively in inpatients. The interventions are accessible. Outcomes, nonetheless, were wanting in clinical applicability.

Quality of the evidence

Most trials included were very small and underpowered, with an overall poor quality of reporting. Some data were highly heterogenous. There was a recent trend, however, for better standards of reporting (for instance, see Berk 2008b; Zhang 2004; Zhang 2011). The largest trial by far (Luo 1997), however, did not report allocation concealment. Grading of the quality of evidence can be seen in the Summary of findings for the main comparison.

Potential biases in the review process

1. Missing studies

We made a significant effort to identify relevant trials. However, these are small studies generally and it is likely that we have failed to identify other studies of limited power. A few studies were reported only in abstract form and we were not able to obtain data from the authors. We were able to obtain unpublished data for two studies (Berk 2008b; Bordbar 2008), and for two Chinese papers (Luo 1997; Xu 2002); we were also able to obtain help from a native speaker.

Agreements and disagreements with other studies or reviews

There is a published Cochrane review on vitamin E for tardive dyskinesia (TD) (Soares-Weiser 2011). This was mostly interested in TD, not schizophrenia, and only on vitamin E, so there is no particular disagreement or overlap between the two reviews.
One recent systematic review investigated the use of *Ginkgo biloba* for schizophrenia (Singh 2010). This review had a more liberal approach to inclusion (it included one trial that did not use a placebo comparison and an open-label trial). The direction of results are generally the same and the authors conclude more data are needed to disentangle ginkgo's pharmacological properties.

AUTHORS' CONCLUSIONS

Implications for practice

1. For clinicians

The many difficulties with included studies, amongst them low quality and sample size and a lack of clinically meaningful outcomes, preclude us from giving general suggestions regarding the use of adjunctive substances with antioxidant potential in people with schizophrenia. Another concern was the poor reporting of adverse events throughout the trials.

Specifically, however, the data indicate the adjunctive use of allopurinol should not be encouraged at this point, since an adequately powered trial failed to show any benefit

2. For people with schizophrenia

Although there is preliminary data that suggests substances with antioxidant potential may be of use, definitive studies are lacking. This means there is substantial uncertainty on the potential benefit and risks these different compounds carry.

3. For policy makers

Currently,there is not enough good-quality evidence to suggest the use of allopurinol for schizophrenia is appropriate.

Implications for research

As different substances have different pharmacological properties and clinical effects, it is more useful to think about these medications not as antioxidants, but as distinct drugs with antioxidant potential. As such, it is preferable to discuss implications for each drug, and not for antioxidants in general. There is medium-quality evidence for the adjunctive efficacy of *Ginkgo biloba*, with relatively large numbers of people randomised to receive it, mostly in China. These studies are also short-term ones and lack measures that are most useful to patients and clinicians. The only trial we located on adjunctive N-acetyl cysteine (NAC), on the other hand, was of high quality and measured outcomes over a longer period of time and suggested benefit for negative symptoms of schizophrenia.

Overall, available data suggest that real-world studies, adequately powered with more substantial follow-up periods need to be conducted if clinicians and people with schizophrenia are to adopt adjunctive antioxidants in everyday practice. Table 1 suggests a design for such a study. Outcomes should be meaningful for those with schizophrenia, and include measures of improvement and relapse (not just rating scale scores), functioning and quality of life and acceptability and, importantly, safety data. Because of the various features discussed, ginkgo and NAC emerged from the trials located as the most promising interventions, and should have priority in the design of further trials.

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

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Adler 1993a

Methods	Allocation: randomised. Blindess: double blind: no further details. Duration: 12 weeks (36 week extension). Setting: outpatients, USA. Design: parallel.
Participants	Diagnosis: schizophrenia (36 of 37 at 36 weeks) (Diagnostic Criteria, Schooler and Kane) . N = 28 (12 weeks), 40 (36 weeks). Sex: 2 female, 27 male. Age: average ~ 60 yrs (SD ~ 9.5).
Interventions	1. Vitamin E: dose increasing over 3 weeks to 1600 IU/day. N = 22.* 2. Placebo. N = 15.* Stable neuroleptic medication: dose average (CPE) vitamin E = 536 mg/day (SD 642); placebo = 921 mg/day (SD 1026). Compliance assessed by pill counts
Outcomes	Leaving the study early (at 12 weeks and at 36 weeks) Unable to use: adverse effects (safety data - not reported)
Notes	No usable safety outcomes * 37 participants by 36 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation, no further detail provided.
Allocation concealment (selection bias)	Unclear risk	Random allocation, no further detail provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Both rater and participants were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	One participant left early and is not accounted for.

Adler 1993a (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Unclear since focuses on TD.
Other bias	Low risk	None obvious.

Adler 1999

Methods	Allocation: randomised, co-ordinated centrally, allocation with "biased coin" method, stratified by site, age, and baseline TD. Blindness: double-blind, no further details. Duration: 1 year. Setting: outpatients, USA. Design: parallel.
Participants	Diagnosis: schizophrenia, schizoaffective (DSM-IV), and neuroleptic-induced TD (Research Diagnostic Criteria). N = 158. Sex: 5F, 153M. Age: average ~ 50 years (SD ~ 10).
Interventions	1. Vitamin E: 1600 IU/day. N = 73. 2. Placebo. N = 85. Neuroleptic medication: not stable dose, average (CPE) vitamin E 380 mg/day (SD ~110); placebo 458 mg/day (SD ~433)
Outcomes	Leaving the study early. Mental state: BPRS endpoint score. General functioning: GAF endpoint score. Unable to use: safety data (not reported).
Notes	Not all patients leaving study early accounted for.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central randomisation.
Allocation concealment (selection bias)	Low risk	"Biased coin" method, stratified.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, no further details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.

Adler 1999 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis reported.
Selective reporting (reporting bias)	Low risk	Main outcomes reported.
Other bias	Low risk	None obvious.

Akhondzadeh 2005

Methods	Allocation: randomised. Blindness: double-blind. Duration: 8 weeks. Setting: hospital, Iran. Design: parallel groups.
Participants	Diagnosis: schizophrenia (DSM-IV) and PANSS > 59 criteria). N = 46. Sex: 13 female, 33 male. Age: average 33.8 (selegiline), 35.0 (placebo)
Interventions	1. Allopurinol: 300mg. N = 23. 2. Placebo. N = 23. Stable neuroleptic medication: haloperidol 15 mg.
Outcomes	Leaving the study early. Mental state: PANSS change score. Adverse events: various specific effects.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Unclear risk	No further details.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No further details.

Akhondzadeh 2005 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	LOCF analysis reported.
Selective reporting (reporting bias)	Low risk	Main outcomes reported.
Other bias	Low risk	None obvious.

Amiri 2008

Methods	Allocation: randomised. Blindness: double-blind. Duration: 8 weeks. Setting: in hospital, Iran. Design: parallel groups.
Participants	Diagnosis: schizophrenia (DSM-IV) and PANSS > 59, PANSS negative >14 criteria). N = 40. Sex: 11F, 29M. Age: average 32.7 years (selegiline), 33.7 years (placebo).
Interventions	1. Selegiline: 10 mg/day. N = 20. 2. Placebo. N = 20. Stable risperidone dose: 6 mg/day.
Outcomes	Leaving the study early. Mental state: change scores in PANSS and PANSS negative subscale Adverse events: various specific events.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated code.
Allocation concealment (selection bias)	Unclear risk	No further details.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical tablets.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No further details.

Amiri 2008 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	"ITT performed".
Selective reporting (reporting bias)	Low risk	Main outcomes reported.
Other bias	Low risk	None obvious.

Berk 2008b

Methods	Allocation: randomised. Blindness: double-blind: no further details. Duration: 24 weeks. Setting: mixed, but 95% were outpatients. Design: parallel.
Participants	Diagnosis: schizophrenia (DSM-IV) plus PANSS > 54. N = 140 Sex: 42F, 98M. Age: average ~ 37 years.
Interventions	1. NAC (2 g/day). N = 69. 2. Placebo. N = 71. Stable neuroleptic medication: "usual antipsychotics medication"
Outcomes	Leaving the study early Mental state: PANSS (total, positive, negative, general endpoint score) Functioning: GAF endpoint score. Adverse events: various specific events.
Notes	Unpublished data obtained from authors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Simple randomisation.
Allocation concealment (selection bias)	Low risk	Independent co-ordinator generated sequence.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Raters blinded.

Berk 2008b (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	135 of 140 patients available for LOCF analysis.
Selective reporting (reporting bias)	Low risk	Main outcomes reported.
Other bias	Low risk	None obvious.

Bodkin 2005

Methods	Allocation: randomised. Blindness: double-blind. Duration: 12 weeks. Setting: outpatients, USA. Design: parallel groups.
Participants	Diagnosis: schizophrenia (DSM-III-R and SANS >11 criteria). N = 67. Sex: 11F, 56M. Age: average 38.0 years (selegiline), 39.9 years (placebo).
Interventions	1. Selegiline (deprenyl): 10.mg/day. N = 33. 2. Placebo. N = 34. Stable neuroleptic medication: dose average (CPE) 727 (selegiline), 570 (placebo)
Outcomes	Leaving the study early. Mental state: SANS and BPRS endpoint scores. Unable to use: Adverse events: no usable data (not reported).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised no further details.
Allocation concealment (selection bias)	Low risk	"centrally based".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"drug and placebo in matched capsules".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Investigators as well as subjects were completely blind".

Bodkin 2005 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Authors used random regression for main analysis.
Selective reporting (reporting bias)	Low risk	Main outcomes reported.
Other bias	Low risk	None obvious.

Bordbar 2008

Methods	Allocation: randomised, no further details Blindness: no further details. Duration: six weeks Setting: inpatients, Iran Design: parallel, three groups
Participants	Diagnosis: schizophrenia (DSM-IV) + PANSS negative >14. N = 80 (10 excluded). Sex: 45M, 45 F. Age: average ~ 48 yrs
Interventions	1. Selegiline: 5 mg / day. N = 25 2. Selegiline: 10 mg/day. N = 25. 3. Placebo. N = 30. Stable neuroleptic medication:
Outcomes	Leaving the study early. Mental state: PANSS (negative and positive endpoint scores). Unable to use: safety (not reported).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Table of random numbers".
Allocation concealment (selection bias)	Unclear risk	No further information.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Identical placebo".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No further information.

Bordbar 2008 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis, 10 patients excluded.
Selective reporting (reporting bias)	Low risk	Main outcomes reported.
Other bias	Low risk	None obvious.

Brunstein 2005

Methods	Allocation: randomised, no further details. Blindness: double-blind. Duration: six weeks. Setting: Brazil (mixed inpatients and outpatients) Design: cross-over (but able to use data from first arm).
Participants	Diagnosis: schizophrenia (DSM-IV) and "moderately refractory". N = 35 (N = 23 for completer analysis). Sex: 9F, 14M (12 unclear because of completer analysis). Age: average 35.3 years (allopurinol), 42.3 years (placebo).
Interventions	1. Allopurinol: 600mg/day. N = 18. 2. Placebo. N = 17. Stable neuroleptic medication: dose average (CPE) 550 (allopurinol), 545(placebo)
Outcomes	Global state: response (20% improvement in the PANSS). Leaving the study early. Mental state: PANSS change score. Adverse events: various and serious events.
Notes	Able to use LOCF analysis for total PANSS scores and response

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised, no further details.
Allocation concealment (selection bias)	Unclear risk	No further details.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No further details.

Brunstein 2005 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	LOCF analysis reported.
Selective reporting (reporting bias)	Low risk	Main outcomes reported.
Other bias	Low risk	None obvious.

Dakhale 2005

Methods	Allocation: randomised. Blindness: double-blind: no further details. Duration: 8 weeks Setting: outpatients, India. Design: parallel.
Participants	Diagnosis: schizophrenia (DSM-IV). N = 40. Sex: not reported. Age: average ~ 38 yrs.
Interventions	1. Vitamin C (500 mg/day), N = 20. 2. Placebo. N = 20 Stable neuroleptic medication: atypical antipsychotics.
Outcomes	Leaving the study early. Mental state: BPRS endpoint score. Laboratory data: serum MDA. Unable to use: adverse events (not reported).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Unclear risk	No further details.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Medicines identical in formulation.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No further details.

Dakhale 2005 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis reported.
Selective reporting (reporting bias)	Low risk	Main outcomes reported.
Other bias	Low risk	None obvious.

Dickerson 2009

Methods	Allocation: randomised. Blindness: double-blind. Duration: 8 weeks. Setting: outpatients, USA. Design: parallel groups.
Participants	Diagnosis: schizophrenia (DSM-IV) and at least "moderate symptoms" criteria). N = 59. Sex: 20F, 39M. Age: average 43.1 years.
Interventions	1. Allopurinol: 600mg/day. N = 31. 2. Placebo. N = 28. Stable neuroleptic medication: antipsychotics as prescribed.
Outcomes	Global state: response (at least 20% reduction in total PANSS score) Leaving the study early. Adverse events: serious and various events.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised, no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No further details.

Dickerson 2009 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	LOCF used as imputation method.
Selective reporting (reporting bias)	Low risk	Main outcomes reported.
Other bias	Low risk	None obvious.

Dorevitch 1997a

Methods	Allocation: randomised. Blindness: double-blind. Duration: 20 weeks total with cross-over. Parallel period of 8 weeks. Setting: inpatients, Israel. Design: cross-over study.
Participants	Diagnosis: schizophrenia or schizoaffective (10%) (DSM-IIR) and TD criteria). N = 40. Sex: 17F 23M. Age: average 64.4 years.
Interventions	1. Vitamin E: 1600 IU. N = 18. 2. Placebo. N = 22. Stable neuroleptic medication: antipsychotics as prescribed.
Outcomes	Leaving the study early. Unable to use: adverse effects (not reported).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No further details.
Allocation concealment (selection bias)	Unclear risk	No further details.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Raters blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Two patients did not complete the study and no further details are given

Dorevitch 1997a (*Continued*)

Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Low risk	None obvious.

Doruk 2008

Methods	Allocation: randomised. Blindness: double-blind Duration: 12 weeks. Setting: outpatients, Turkey. Design: parallel.
Participants	Diagnosis: schizophrenia (SCID), treatment-resistant. N = 46. Sex: 17F, 29M. Age: average 30 years (Ginko EGb), 32 years (placebo).
Interventions	1. Ginkgo EGb, 120 mg/day. N = 23. 2. Placebo. N = 23. Stable neuroleptic medication: clozapine.
Outcomes	Leaving the study early. Mental state: BRPS, SAPS, SANS change scores. Unable to use: adverse effects (not reported).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Random allocation, no details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded rater.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Four people who left early were excluded from analysis.
Selective reporting (reporting bias)	Low risk	Main outcomes reported.

Doruk 2008 (*Continued*)

Other bias	Low risk	None obvious.

Farokhnia 2013

Methods	Allocation: randomised. Blindness: double-blind Duration: 8 weeks. Setting: inpatients, Iran. Design: parallel.
Participants	Diagnosis: schizophrenia (SCID), PANSS >=60 and PANSS negative >=20. N = 46. Sex: 22F, 20M (4 unknown). Age: average 32 years (NAC), 33 years (placebo).
Interventions	1. NAC (2 g/day). N = 23. 2. Placebo. N = 23 Stable neuroleptic medication: risperidone (2-6 mg/day).
Outcomes	Leaving the study early. Mental state: PANSS (total, negative, positive). Adverse events: various events.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Excel generated"
Allocation concealment (selection bias)	Low risk	"sealed envelope"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identical containers"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Four people who left early were excluded from analysis.
Selective reporting (reporting bias)	Low risk	Main outcomes reported.

Farokhnia 2013 (*Continued*)

Other bias	Low risk	None obvious.

Goff 1993

Methods	Allocation: random, no further details. Blindess: double-blind. Duration: six weeks. Setting: outpatients, USA. Design: parallel.
Participants	Diagnosis: schizophrenia (31/33), TD (Schooler & Kane). N = 33. Sex: 8F, 20M (5 unclear because of completer analysis). Age: average 48.7 (selegiline), 47.1 (placebo).
Interventions	1. Selegiline (deprenyl): 10 mg/day. N = 17. 2. Placebo. N = 16. Stable neuroleptic medication: dose average (CPE) 549 (selegiline), 683 (placebo)
Outcomes	Leaving the study early. Mental state: BPRS endpoint score. General functioning: GAS endpoint score. Unable to use: adverse effects (not reported).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised, no further details.
Allocation concealment (selection bias)	Unclear risk	No further details.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical capsules given.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis used.
Selective reporting (reporting bias)	Low risk	Main outcomes reported.

Goff 1993 (*Continued*)

Other bias	Low risk	None obvious.

Jungerman 1999

Methods	Allocation: randomised, no further details Blindness: double-blind Duration: eight weeks. Setting: outpatients, Israel. Design: parallel.
Participants	Diagnosis: schizophrenia (DSM-IV). N = 16. Sex: 8F, 8M. Age: average 36 years (SD 6 years). History: moderate residual symptoms.
Interventions	1. Selegiline (deprenyl): 15 mg/day. N = 8. 2. Placebo. N = 8. Stable neuroleptic medication: dose average (CPE) 360 (SD 180)
Outcomes	Mental state: PANSS total endpoint score, PANSS positive endpoint score, PANSS negative endpoint score, BPRS total endpoint score Unable to use: adverse effects (not reported).
Notes	Information on allocation concealment and sequence generation obtained from authors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"A randomization list prepared by a person who was not involvement in patient treatment or assessment"
Allocation concealment (selection bias)	Low risk	Identical drug containers.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Identical appearance".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Rater had no contact with medication preparation and allocation process"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants left the study early.
Selective reporting (reporting bias)	Low risk	Main outcomes reported.

Jungerman 1999 (*Continued*)

Other bias	Low risk	None obvious.

Lohr 1996

Methods	Allocation: randomised, no further details. Double blind: no further details. Duration: eight weeks. Setting: outpatients, USA. Design: parallel.
Participants	Diagnosis: schizophrenia (29/35), bipolar disorder, unipolar depression (no specified criteria) and neuroleptic-induced TD (Schooler and Kane criteria). N = 55 (20 patients left early, no data informed). Sex: 2F, 33M, 20 not informed. Age: average ~ 50 years (SD ~ 12).
Interventions	1. Vitamin E: 1600 IU/day. N = 27. 2. Placebo. N = 28. Stable neuroleptic medication for 2 weeks: dose average (CPE) vitamin E = 706 mg/day. (SD 680); placebo = 376 mg/day (SD 242).
Outcomes	Mental state: BPRS endpoint score. Unable to use: leaving the study early (no group information reported)
Notes	Subgroup data for schizophrenia available for the BPRS.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised, no further details.
Allocation concealment (selection bias)	Unclear risk	No further details.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis.
Selective reporting (reporting bias)	Low risk	Main outcomes reported.

Lohr 1996 (*Continued*)

Other bias	Low risk	None obvious.

Luo 1997

Methods	Allocation: randomised. Blindness: double-blind, no further details. Duration: 16 weeks (36 week extension). Setting: inpatients, China. Design: parallel.
Participants	Diagnosis: schizophrenia (ICD-10) plus SANS > 50 plus BPRS > 30. N = 545. Sex: 98F, 447M. Age: average ~ 37 years.
Interventions	1. Ginkgo (EGb 360 mg/day), N = 315 2. Placebo. N = 230. Stable neuroleptic medication: mixed antipsychotics
Outcomes	Leaving the study early. Mental state: BPRS endpoint score, SANS endpoint score. Unable to use: adverse effects (not reported).
Notes	Translation obtained from Prof. Yiming Wang

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised, no further details.
Allocation concealment (selection bias)	Unclear risk	No further details.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No further details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Those who left early (33/545) were from excluded from analysis
Selective reporting (reporting bias)	Unclear risk	No further details.

Luo 1997 (*Continued*)

Other bias	Low risk	None obvious.

Ritsner 2010

Methods	Allocation: randomised. Blindness: double-blind. Duration: 8 weeks. Setting: outpatients, Israel Design: parallel.
Participants	Diagnosis: schizophrenia (n = 19) or schizoaffective disorder (n = 5) (DSM-IV). N = 32. Sex: 6F, 18M (8 excluded not reported). Age: average ~ 36 years.
Interventions	1. DHEA (400 mg/day), N =13 2. Placebo. N =11 . Stable neuroleptic medication: mixed antipsychotics.
Outcomes	Leaving the study early. Mental state: PANSS. General functioning: GAF endpoint score. Unable to use: adverse effects (not reported).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"random number generation"
Allocation concealment (selection bias)	Low risk	"allocation details coded and kept confidential"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identical capsules"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No further information.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Eight patients who discontinued the protocol followed up, but excluded from efficacy analysis

Ritsner 2010 (*Continued*)

Selective reporting (reporting bias)	Low risk	Main outcomes reported.
Other bias	Low risk	None obvious.

Weiser 2012

Methods	Allocation: randomised. Blindess: double-blind. Duration: 8 weeks. Setting: outpatients or inpatients, Romania. Design: parallel groups.
Participants	Diagnosis: schizophrenia or schizoaffective disorder (SCID). N = 248. Sex: 120 female, 128 male. Age: average 42.5 years. History: three psychotic episodes or continuously ill.
Interventions	1. Allopurinol: 600 mg/day. N = 123. 2. Placebo. N = 125. Stable neuroleptic medication: antipsychotics as prescribed.
Outcomes	Leaving the study early. Mental state: PANSS endpoint score, PANSS positive endpoint, PANSS negative endpoint score Unable to use: global state, adverse effects (not reported).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised, no further details.
Allocation concealment (selection bias)	Low risk	Central randomisation, individual bottles.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No further details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT and LOCF used.

Weiser 2012 (*Continued*)

Selective reporting (reporting bias)	Low risk	Expected outcomes reported.
Other bias	Low risk	None obvious.

Zhang 2001a

Methods	Allocation: randomised, no further details. Blindess: double-blind. Duration: 12 weeks. Setting: inpatients, China. Design: parallel.
Participants	Diagnosis: schizophrenia (SCID) and treatment resistant. N = 109 (82 for SOD analysis). Sex: 43F, 66M. Age: average 45 years.
Interventions	1. Ginkgo EGb, 360 mg/day. N = 56. 2. Placebo. N = 53. Stable neuroleptic medication: haloperidol, 16.8 mg/day (EGb), 16.5 mg/day (placebo)
Outcomes	Leaving the study early. Mental state: BPRS endpoint score, SAPS endpoint score, SANS endpoint score Adverse effects: TESS endpoint score. Laboratory data: SOD levels.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised, no further details.
Allocation concealment (selection bias)	Unclear risk	No further details.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No further details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis reported.

Zhang 2001a (*Continued*)

Selective reporting (reporting bias)	Low risk	Main outcomes reported.
Other bias	Low risk	None obvious.

Zhang 2004

Methods	Allocation: randomised, no further details. Blindness: double-blind, no further details. Duration: 12 weeks. Setting: inpatients, China. Design: parallel.
Participants	Diagnosis: schizophrenia (SCID) and neuroleptic-induced TD (Schooler and Kane criteria). N = 41. Sex: 18F, 23M. Age: average ~ 54 years (SD ~ 10).
Interventions	1. Vitamin E: 1200 IU/day. N = 22. 2. Placebo. N = 19. Stable neuroleptic medication: dose average (CPE) vitamin E = 409.1 mg/day; placebo = 386.4 mg/day
Outcomes	Laboratory data: endpoint SOD. Unable to use: leaving the study early (not reported).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised, no further details.
Allocation concealment (selection bias)	Unclear risk	No further details.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No further details.
Incomplete outcome data (attrition bias) All outcomes	High risk	No information on completion rate.

Zhang 2004 (*Continued*)

Selective reporting (reporting bias)	High risk	Not all expected outcomes reported.
Other bias	Low risk	None obvious.

Zhang 2011

Methods	Allocation: randomised. Blindness: double-blind. Duration: 12 weeks. Setting: inpatients, China. Design: parallel.
Participants	Diagnosis: schizophrenia (SCID) and TD. N = 157. Sex: not reported. Age: average 45 years.
Interventions	1. Ginkgo EGb, 240 mg/day. N = 78. 2. Placebo. N = 79. Stable neuroleptic medication: most participants on clozapine, almost all on atypical antipsychotics (dose unclear)
Outcomes	Leaving the study early. Mental state: PANSS (total, positive, negative) endpoint score Unable to use: adverse effects (not reported).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Computer - generated sequence".
Allocation concealment (selection bias)	Low risk	"Third - party conducted allocation".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Identically appearing placebo".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Raters blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"ITT analysis".

Zhang 2011 (*Continued*)

Selective reporting (reporting bias)	Low risk	Main outcomes reported.
Other bias	Low risk	None obvious.

BPRS - Brief Psychiatric Assessment Scale; CPE - ;DHEA - dehydroepiandrosterone; DSM - Diagnostic and Statistical Manual; EGb - extract of *Ginkgo biloba*; GAF - Global Assessment of Function; ICD - International Classification of Diseases; ITT - intention-to-treat; IU - international units; LOCF - last observation carried forward; MDA - malondialdehyde; NAC - N-acetyl cysteine; PANSS - Positive and Negative Symptoms Scale; SANS - Scale for the Assessment of Negative Symptoms; SCID - structured clinical interview for DSM disorders; SD - standard deviation; SOD - superoxide dysmutase; TD - tardive dyskinesia.
*

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

Study	Reason for exclusion
Bhavani 1962	Allocation: randomised. Participants: inpatients, with schizophrenia. Intervention: vitamin C as monotherapy, not adjuvant.
Dorevitch 1997	Allocation: randomised. Participants: people with schizophrenia and tardive dyskinesia Intervention: vitamin E (1200 IU) or placebo. Outcomes: no outcomes of interest (only tardive dyskinesia reported, which is not part of this review)
Elkashef 1990	Allocation: randomised. Participants: tardive dyskinesia. Intervention: vitamin E (1200 IU) or placebo. Outcomes: no outcomes of interest (only tardive dyskinesia reported)
Eranti 1998	Allocation: randomised. Participants: not diagnosed with schizophrenia, but with an “acute transient psychosis”
Kapur 1991	Allocation: randomised. Participants: chronic schizophrenia. Intervention: no parallel placebo group, riboflavin cross-over trial
Rees 1951	Allocation: not randomised, matched pairs design.
Suresh 2007	Allocation: randomised. Participants: schizophrenia (DSM-IV) plus initial insomnia. Intervention: adjunctive melatonin (3-12 mg) or placebo. Outcomes: no outcomes of interest evaluated (only effect on sleep outcomes reported)

DSM - Diagnostic and Statistical Manual

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

Akhtar 1993

Methods	Allocation: randomised. Blindness: double-blind. Duration: Four weeks. Setting: inpatients, India. Design: parallel groups.
Participants	Diagnosis: unclear, awaiting more information. N = 32. Sex: 14F, 18M. Age: average 53 (vitamin E), 57 (placebo)
Interventions	1. Vitamin E. N = 17. 2. Placebo. N = 15.
Outcomes	Leaving the study early.
Notes	

Altman 1973

Methods	Allocation: randomised. Blindness: double-blind. Duration: 4 weeks. Setting: inpatients, USA. Design: parallel groups.
Participants	Diagnosis: unclear, awaiting more information. N = 151. Sex: unclear, awaiting more information. Age: unclear, awaiting more information.
Interventions	1. Vitamin E. N = 75. 2. Placebo. N = 76.
Outcomes	Leaving the study early.
Notes	

Atmaca 2005

Methods	Allocation: randomised. Blindness: single-blind. Duration: Eight weeks. Setting: outpatients, Turkey Design: parallel groups.
Participants	Diagnosis: schizophrenia (DSM-IV). N = 29. Sex: unclear, awaiting more information. Age: unclear, awaiting more information.
Interventions	1. *Ginkgo biloba*. N = 15. 2. No Ginkgo (placebo?) : N = 14, awaiting more information. Antipsychotic medication: olanzapine ~15 mg/day.
Outcomes	Leaving the study early.
Notes	

Ben-Dor 1998

Methods	Allocation: randomised. Blindness: double-blind. Duration: Six weeks. Setting: inpatients. Design: parallel groups.
Participants	Diagnosis: schizophrenia. N = 30. Sex: 14 female, 16 male. Age: average 53 years. History: chronic illness.
Interventions	1. Vitamin E (2000 IU/day). N = unclear, awaiting more information. 2. Placebo. N = unclear, awaiting more information. Stable antipsychotic: haloperidol.
Outcomes	Leaving the study early.
Notes	

Egan 1992

Methods	Allocation: randomised. Blindess: double-blind. Duration: Six weeks. Setting: mixed, USA. Design: cross-over.
Participants	Diagnosis: schizophrenia, other psychoses. N = 21. Sex: unclear, awaiting more information. Age: average 54 years.
Interventions	1. Vitamin E (1600 IU/day). N = 10 2. Placebo. N = 11.
Outcomes	Leaving the study early. Psychiatric Symptom Assessment Scale. Negative Symptom Rating Scale.
Notes	

Junker 1992

Methods	Allocation: randomised. Blindness; double-blind. Duration: Four weeks. Setting: unclear, Germany. Design: parallel groups.
Participants	Diagnosis: unclear. N = 16. Sex: 6 M, 10 F. Age: average ~ 52. History: tardive dyskinesia.
Interventions	1. Vitamin E (1200 IU/day). N = unclear. 2. Placebo. N = unclear.
Outcomes	
Notes	

Kodesh 2003

Methods	Allocation: randomised. Blindess: double-blind. Duration: three weeks. Setting: outpatients, Israel Design: cross-over
Participants	Diagnosis: schizophrenia. N = 10. Sex: 10M. Age: unclear. History: sexual dysfunction.
Interventions	1. Selegiline (15 mg/day). N = unclear. 2. Placebo. N = unclear. Stable antipsychotic: “typical neuroleptic agents”.
Outcomes	Leaving the study early. PANSS.
Notes	

Lam 1994

Methods	Allocation: randomised. Blindness: double-blind. Duration: six weeks. Setting: inpatients, Hong Kong. Design: cross-over.
Participants	Diagnosis: schizophrenia. N = 16. Sex: unclear. Age: unclear.
Interventions	1. Vitamin E (1200 mg/day). N = unclear. 2. Placebo. N = unclear. Stable antipsychotic: “typical neuroleptic agents”.
Outcomes	Leaving the study early. BPRS.
Notes	

Meng 1996

Methods	Allocation: randomised. Blindness: double - blind. Duration: eight weeks. Setting: inpatients, China. Design: parallel groups.
Participants	Diagnosis: schizophrenia. N = 40. Sex: unclear. Age: unclear.
Interventions	1. *Ginkgo biloba* (240 mg/day). N = 21. 2. Placebo. N = 19. Stable antipsychotic: antipsychotics, no further description
Outcomes	Leaving the study early. BPRS. SANS.
Notes	Very probably a subsample of Luo 1997

Milner 1963

Methods	Allocation: randomised. Blindness: double-blind. Duration: three weeks. Setting: inpatients, UK. Design: parallel groups.
Participants	Diagnosis: “chronic psychiatric patients”. N = 40. Sex: unclear. Age: unclear.
Interventions	1. Vitamin C (1000 mg/day). N = 20. 2. Placebo. N = 20. Stable antipsychotic: unclear
Outcomes	Leaving the study early. Self-rated symptoms.
Notes	

Salmasi 2009

Methods	Allocation: randomised. Blindness: double-blind. Duration: eight weeks. Setting: unclear, Iran. Design: parallel groups.
Participants	Diagnosis: schizophrenia. N = 32. Sex: unclear. Age: unclear.
Interventions	1. Vitamin E (800 IU/day). N = unclear. 2. Placebo. N = unclear. Stable antipsychotic: olanzapine.
Outcomes	No outcomes of interest reported.
Notes	

Schmidt 1991

Methods	Allocation: randomised. Blindess: double-blind. Duration: two weeks. Setting: inpatients, Switzerland. Design: cross--over.
Participants	Diagnosis: schizophrenia, major depression, schizoaffective disorder. N = 23. Sex: 9 F, 10 M (4 unclear) Age: average 45 years. History: tardive dyskinesia
Interventions	1. Vitamin E (1600 IU /day). N = 13. 2. Placebo. N = 10. Stable antipsychotic: typical antipsychotics.
Outcomes	Leaving the study early.
Notes	

Shamir 2000

Methods	Allocation: randomised. Blindness: double-blind. Duration: four weeks. Setting: inpatients, Israel. Design: cross-over.
Participants	Diagnosis: schizophrenia. N = 19. Sex: 11 F, 18 M. Age: average 74 years. History: tardive dyskinesia
Interventions	1. Melatonin (2 mg/day). N = 9. 2. Placebo. N = 10. Stable antipsychotic: “regular regimen”.
Outcomes	Unable to use any data (only cross-over reported)
Notes	

Shamir 2001a

Methods	Allocation: randomised. Blindness: double-blind. Duration: six weeks. Setting: inpatients, Israel. Design: cross-over.
Participants	Diagnosis: schizophrenia. N = 22. Sex: 11 F, 11 M. Age: average 64 years. History: tardive dyskinesia.
Interventions	1. Melatonin (10 mg/day). N = 10. 2. Placebo. N = 12. Stable antipsychotic: “regular regimen”.
Outcomes	Unable to use any data (only cross-over reported)
Notes	

Shriqui 1992

Methods	Allocation: randomised. Blindness: double-blind. Duration: four weeks. Setting: outpatients, Canada. Design: cross-over.
Participants	Diagnosis: schizophrenia, bipolar disorder. N = 27. Sex: unclear. Age: unclear. History: tardive dyskinesia.
Interventions	1. Vitamin E (1200 IU/day). N = unclear. 2. Placebo. N = unclear. Stable antipsychotic: “psychotropic medication”.
Outcomes	Leaving the study early.
Notes	

Stearns 1996

Methods	Allocation: randomised. Blindness: double-blind. Duration: 16 weeks. Setting: unclear Design: cross-over
Participants	Diagnosis: schizophrenia. N = 14. Sex: 3F, 11M. Age: unclear. History: tardive dyskinesia.
Interventions	1. Selegiline (unclear dose). N = unclear. 2. Placebo. N = unclear. Stable antipsychotic: unclear.
Outcomes	Unable to use any data (only cross-over reported)
Notes	

Xu 2002

Methods	Allocation: randomised. Blindess: unclear if single-blind or open-label. Duration: eight weeks Setting: inpatients, China Design: parallel
Participants	Diagnosis: schizophrenia (CCMD-2-R). N = 100. Sex: 21% female.. Age: average ~ 46 years.
Interventions	1. Ginkgo (EGb 49.6 mg three times daily), n = 50 2. Placebo. N = 50 Stable neuroleptic medication: chlorpromazine
Outcomes	SAPS. SANS.
Notes	Translation obtained from Prof. Yiming Wang.

BPRS - Brief Psychiatric Assessment Scale; CCMD-2-R - Chinese Classification of Mental Disorders; DSM - Diagnostic and Statistical Manual; IU - international units; PANSS - Positive and Negative Symptoms Scale; SANS - Scale for the Assessment of Negative Symptoms; SAPS - Schedule for the Assessment of Positive Symptoms

DATA AND ANALYSES

Comparison 1. ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global state: No clinically important response (20% improvement PANSS)	3	229	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.53, 1.12]
1.1 allopurinol - short term	2	94	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.36, 1.32]
1.2 n-acetyl cysteine - medium term	1	135	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.53, 1.92]
2 Leaving the study early: 1a. Short term	16	1584	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.48, 1.11]
2.1 allopurinol	4	388	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.55, 1.24]
2.2 DHEA	1	32	Risk Ratio (M-H, Random, 95% CI)	0.6 [0.17, 2.10]
2.3 ginkgo biloba	4	857	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.17, 1.03]
2.4 n-acetyl cysteine	1	46	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.15, 6.51]
2.5 selegiline	3	153	Risk Ratio (M-H, Random, 95% CI)	5.22 [0.90, 30.31]
2.6 vitamin C	1	40	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.03, 2.05]
2.7 vitamin E	2	68	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.06, 14.48]
3 Leaving the study early: 1b. Medium term	1	140	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.67, 1.48]
3.1 n-acetyl cysteine	1	140	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.67, 1.48]
4 Leaving the study early: 1c. Long term	2	195	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.59, 1.35]
4.1 vitamin E	2	195	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.59, 1.35]
5 Mental state: 1a. General - average overall endpoint score - short term (BPRS total, high = worse)	8	843	Mean Difference (IV, Random, 95% CI)	-3.20 [-5.63, -0.78]
5.1 ginkgo biloba	3	663	Mean Difference (IV, Random, 95% CI)	-2.74 [-5.29, -0.20]
5.2 selegiline	3	111	Mean Difference (IV, Random, 95% CI)	-0.31 [-4.03, 3.41]
5.3 vitamin C	1	40	Mean Difference (IV, Random, 95% CI)	-9.66 [-13.27, -6.05]
5.4 vitamin E	1	29	Mean Difference (IV, Random, 95% CI)	-7.92 [-17.20, 1.36]
6 Mental state: 1b. General - average overall endpoint score - short term (PANSS total, high = worse)	7	584	Mean Difference (IV, Random, 95% CI)	-6.00 [-10.35, -1.65]
6.1 allopurinol	3	329	Mean Difference (IV, Random, 95% CI)	-6.91 [-15.86, 2.04]
6.2 ginkgo biloba	1	157	Mean Difference (IV, Random, 95% CI)	-3.30 [-6.51, -0.09]
6.3 selegiline	2	56	Mean Difference (IV, Random, 95% CI)	-2.97 [-15.68, 9.74]
6.4 n-acetyl cysteine	1	42	Mean Difference (IV, Random, 95% CI)	-12.86 [-19.82, -5.90]
7 Mental state: 1c. General - average overall endpoint score - medium term (PANSS total, high = worse)	1	135	Mean Difference (IV, Random, 95% CI)	-1.71 [-7.55, 4.13]
7.1 n-acetyl cysteine	1	135	Mean Difference (IV, Random, 95% CI)	-1.71 [-7.55, 4.13]

8 Mental state: 1d. General - average overall endpoint score - long term (BPRS total, high = worse)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 vitamin E	1	104	Mean Difference (IV, Random, 95% CI)	1.20 [-2.47, 4.87]
9 Mental state: 2a. Specific - average negative symptom endpoint score - short term (PANSS negative, high = worse)	9	653	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-0.77, 0.00]
9.1 selegiline	3	111	Std. Mean Difference (IV, Random, 95% CI)	-0.54 [-1.76, 0.68]
9.2 allopurinol	3	317	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-0.98, 0.23]
9.3 ginkgo biloba	1	157	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.49, 0.14]
9.4 n-acetyl cysteine	1	44	Std. Mean Difference (IV, Random, 95% CI)	-1.10 [-1.74, -0.47]
9.5 DHEA	1	24	Std. Mean Difference (IV, Random, 95% CI)	0.63 [-0.20, 1.45]
10 Mental state: 2b. Specific - average negative symptom endpoint score - short term (SANS, high = worse)	3	667	Mean Difference (IV, Random, 95% CI)	-7.46 [-12.46, -2.46]
10.1 ginkgo biloba	3	667	Mean Difference (IV, Random, 95% CI)	-7.46 [-12.46, -2.46]
11 Mental state: 2c. Specific - average negative symptom endpoint score - medium term (PANSS negative, high = worse)	1	135	Mean Difference (IV, Random, 95% CI)	-2.33 [-4.24, -0.42]
11.1 n-acetyl cysteine	1	135	Mean Difference (IV, Random, 95% CI)	-2.33 [-4.24, -0.42]
12 Mental state: 2d. Specific - average positive symptom endpoint score - short term (PANSS positive, high = worse)	8	611	Mean Difference (IV, Random, 95% CI)	-0.96 [-2.50, 0.58]
12.1 allopurinol	3	317	Mean Difference (IV, Random, 95% CI)	-3.55 [-8.24, 1.13]
12.2 DHEA	1	24	Mean Difference (IV, Random, 95% CI)	3.60 [-1.30, 8.50]
12.3 ginkgo biloba	1	157	Mean Difference (IV, Random, 95% CI)	-1.20 [-2.31, -0.09]
12.4 n-acetyl cysteine	1	42	Mean Difference (IV, Random, 95% CI)	-1.14 [-3.57, 1.29]
12.5 selegiline	2	71	Mean Difference (IV, Random, 95% CI)	0.57 [-2.30, 3.45]
13 Mental state: 2e. Specific - average positive symptom endpoint score - short term (SAPS, high = worse)	2	151	Mean Difference (IV, Random, 95% CI)	-5.06 [-7.52, -2.59]
13.1 ginkgo biloba	2	151	Mean Difference (IV, Random, 95% CI)	-5.06 [-7.52, -2.59]
14 Mental state: 2f. Secific - average positive symptom endpoint score - medium term (PANSS positive, high = worse)	1	135	Mean Difference (IV, Random, 95% CI)	0.47 [-1.43, 2.37]
14.1 n-acetyl cysteine	1	135	Mean Difference (IV, Random, 95% CI)	0.47 [-1.43, 2.37]
15 General functioning: 1a. General - average overall endpoint score - short term (GAS total, high = worse)	2	52	Mean Difference (IV, Random, 95% CI)	-1.11 [-8.07, 5.86]
15.1 DHEA	1	24	Mean Difference (IV, Random, 95% CI)	-7.40 [-19.80, 5.00]
15.2 selegiline	1	28	Mean Difference (IV, Random, 95% CI)	0.90 [-3.25, 5.05]

16 General functioning: 1b. General - average overall endpoint score - medium term (GAS total, high = worse)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
16.1 n-acetyl cysteine	1	135	Mean Difference (IV, Random, 95% CI)	2.84 [-2.09, 7.77]
17 General functioning: 1c. General - average overall endpoint score - long term (GAS total, high = worse)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
17.1 vitamin E	1	104	Mean Difference (IV, Random, 95% CI)	0.10 [-5.60, 5.80]
18 Adverse effects: 1. Serious (any time point)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
18.1 any serious adverse effect	3	234	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.19, 2.27]
18.2 myocardial infarction	1	59	Risk Ratio (M-H, Random, 95% CI)	2.72 [0.12, 64.14]
18.3 neutropenia	1	59	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.01, 7.13]
18.4 pneumonia	2	94	Risk Ratio (M-H, Random, 95% CI)	2.78 [0.30, 25.75]
18.5 seizure	1	35	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.26]
19 Adverse effects: 2. Various - less serious	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
19.1 allergy - rash or other dermatological problems	4	280	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.61, 1.84]
19.2 cardiovascular - dizziness	2	82	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.46, 2.96]
19.3 cardiovascular - systemic hypertension	2	82	Risk Ratio (M-H, Random, 95% CI)	3.30 [0.99, 11.04]
19.4 central nervous system - agitation	1	40	Risk Ratio (M-H, Random, 95% CI)	2.5 [0.55, 11.41]
19.5 central nervous system - appetite increase	3	128	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.54, 1.87]
19.6 central nervous system - headache	4	281	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.60, 1.64]
19.7 central nervous system - insomnia	1	40	Risk Ratio (M-H, Random, 95% CI)	2.5 [0.55, 11.41]
19.8 central nervous system - sedation	2	88	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.70, 2.59]
19.9 central nervous system - tremor	2	86	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.32, 1.54]
19.10 gastrointestinal - abdominal pain	1	40	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.41, 9.71]
19.11 gastrointestinal - nausea	4	281	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.67, 1.62]
20 Adverse effects: 3. Average score (TESS endpoint, high = worse)	1	109	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-2.34, 0.54]
21 Laboratory data (serum tests) - short term	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
21.1 MDA levels	1	40	Std. Mean Difference (IV, Random, 95% CI)	-2.18 [-2.98, -1.38]
21.2 SOD levels	2	123	Std. Mean Difference (IV, Random, 95% CI)	0.27 [-0.56, 1.10]

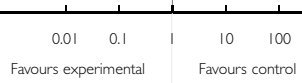
Analysis 1.1. Comparison 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO, Outcome 1 Global state: No clinically important response (20% improvement PANSS).

Review: Antioxidant treatments for schizophrenia

Comparison: 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

Outcome: 1 Global state: No clinically important response (20% improvement PANSS)

Study or subgroup	Adjunctive antioxidant n/N	Adjunctive placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 allopurinol - short term					
Brunstein 2005	9/18	17/17		29.9 %	0.51 [0.33, 0.81]
Dickerson 2009	27/31	28/28		49.2 %	0.87 [0.75, 1.01]
Subtotal (95% CI)	**49**	**45**		**79.2 %**	**0.69 [0.36, 1.32]**
Total events: 36 (Adjunctive antioxidant), 45 (Adjunctive placebo)					
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 7.36$, df = 1 (P = 0.01); $I^2 = 86\%$					
Test for overall effect: Z = 1.12 (P = 0.26)					
2 n-acetyl cysteine - medium term					
Berk 2008b	14/65	15/70		20.8 %	1.01 [0.53, 1.92]
Subtotal (95% CI)	**65**	**70**		**20.8 %**	**1.01 [0.53, 1.92]**
Total events: 14 (Adjunctive antioxidant), 15 (Adjunctive placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.02 (P = 0.99)					
Total (95% CI)	**114**	**115**		**100.0 %**	**0.77 [0.53, 1.12]**
Total events: 50 (Adjunctive antioxidant), 60 (Adjunctive placebo)					
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 5.45$, df = 2 (P = 0.07); $I^2 = 63\%$					
Test for overall effect: Z = 1.37 (P = 0.17)					
Test for subgroup differences: $Chi^2 = 0.65$, df = 1 (P = 0.42), $I^2 = 0.0\%$					



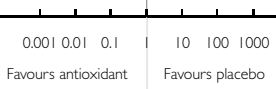
Analysis 1.2. Comparison 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO, Outcome 2 Leaving the study early: 1a. Short term.

Review: Antioxidant treatments for schizophrenia

Comparison: 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

Outcome: 2 Leaving the study early: 1a. Short term

Study or subgroup	Adjunctive antioxidant n/N	Adjunctive placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 allopurinol					
Akhondzadeh 2005	3/23	6/23		8.0 %	0.50 [0.14, 1.76]
Brunstein 2005	6/18	6/17		12.2 %	0.94 [0.38, 2.36]
Dickerson 2009	4/31	4/28		7.8 %	0.90 [0.25, 3.28]
Weiser 2012	21/123	25/125		20.0 %	0.85 [0.51, 1.44]
Subtotal (95% CI)	**195**	**193**		**47.9 %**	**0.83 [0.55, 1.24]**
Total events: 34 (Adjunctive antioxidant), 41 (Adjunctive placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.73$, df = 3 (P = 0.87); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.91 (P = 0.36)					
2 DHEA					
Ritsner 2010	3/16	5/16		8.1 %	0.60 [0.17, 2.10]
Subtotal (95% CI)	**16**	**16**		**8.1 %**	**0.60 [0.17, 2.10]**
Total events: 3 (Adjunctive antioxidant), 5 (Adjunctive placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
3 ginkgo biloba					
Doruk 2008	3/23	1/23		3.3 %	3.00 [0.34, 26.76]
Luo 1997	11/315	22/230		16.0 %	0.37 [0.18, 0.74]
Zhang 2001a	1/56	5/53		3.5 %	0.19 [0.02, 1.57]
Zhang 2011	1/78	4/79		3.3 %	0.25 [0.03, 2.22]
Subtotal (95% CI)	**472**	**385**		**26.0 %**	**0.42 [0.17, 1.03]**
Total events: 16 (Adjunctive antioxidant), 32 (Adjunctive placebo)					
Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 3.97$, df = 3 (P = 0.26); $I^2 = 25\%$					
Test for overall effect: Z = 1.89 (P = 0.058)					
4 n-acetyl cysteine					
Farokhnia 2013	2/23	2/23		4.3 %	1.00 [0.15, 6.51]
Subtotal (95% CI)	**23**	**23**		**4.3 %**	**1.00 [0.15, 6.51]**
Total events: 2 (Adjunctive antioxidant), 2 (Adjunctive placebo)					
Heterogeneity: not applicable					



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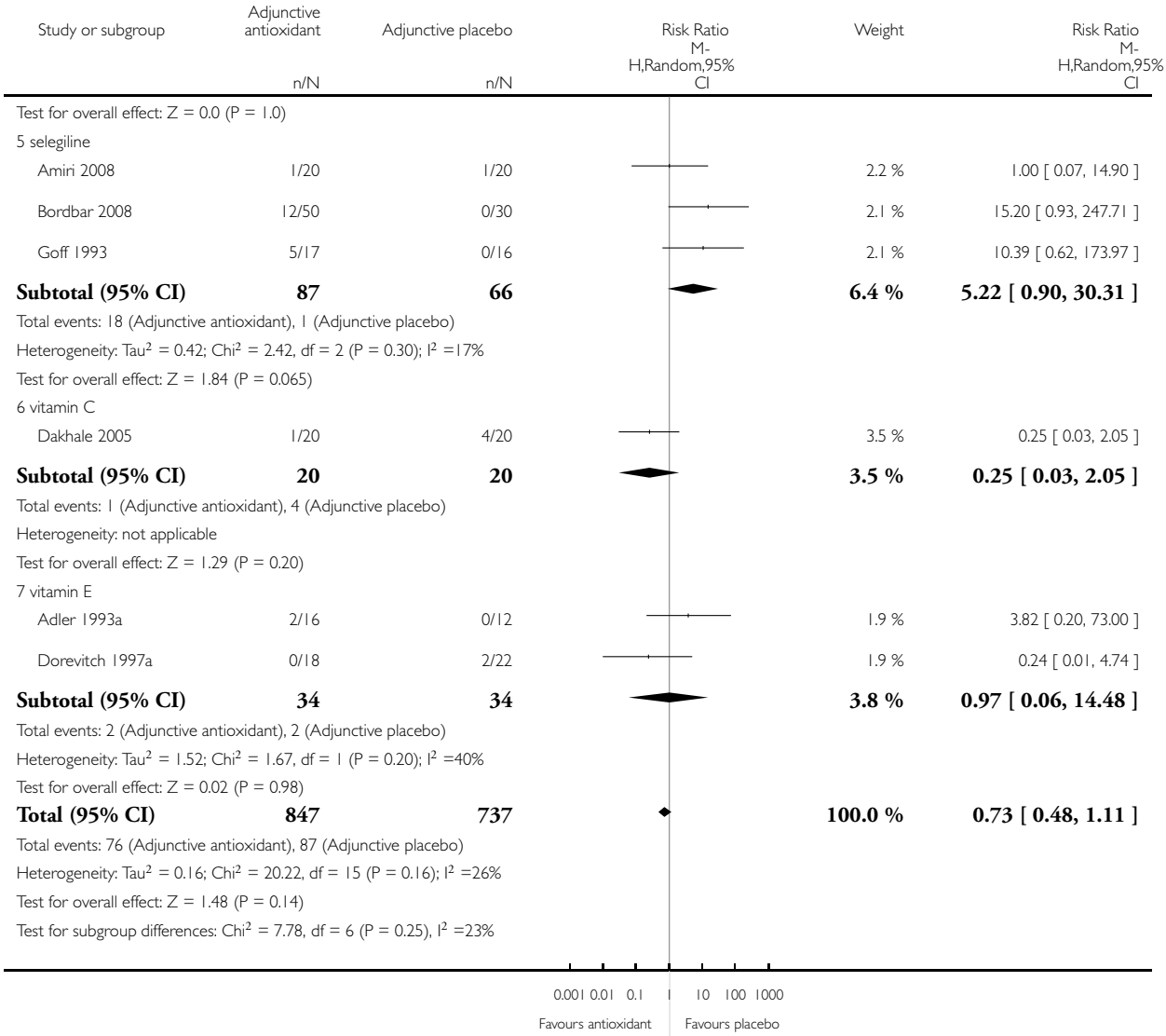


Analysis 1.3. Comparison 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO, Outcome 3 Leaving the study early: 1b. Medium term.

Review: Antioxidant treatments for schizophrenia

Comparison: 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

Outcome: 3 Leaving the study early: 1b. Medium term

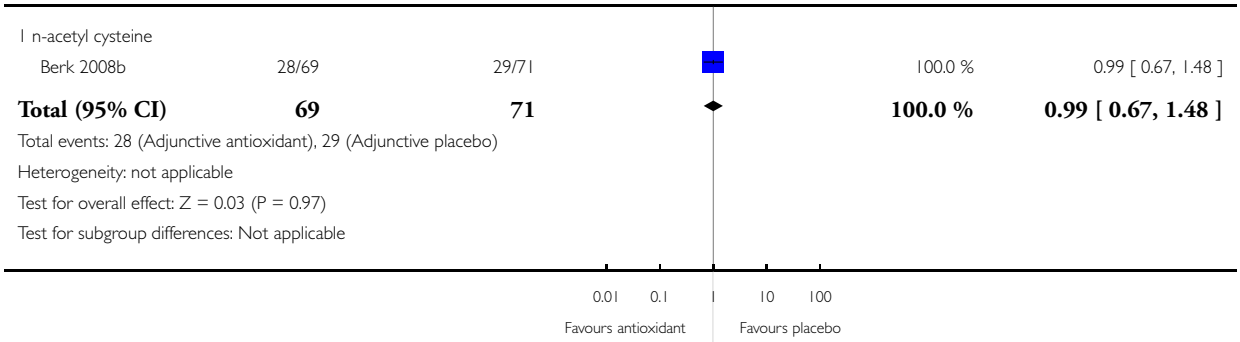
Study or subgroup	Adjunctive antioxidant n/N	Adjunctive placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 n-acetyl cysteine					
Berk 2008b	28/69	29/71		100.0 %	0.99 [0.67, 1.48]
Total (95% CI)	**69**	**71**		**100.0 %**	**0.99 [0.67, 1.48]**

Total events: 28 (Adjunctive antioxidant), 29 (Adjunctive placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.03 (P = 0.97)

Test for subgroup differences: Not applicable

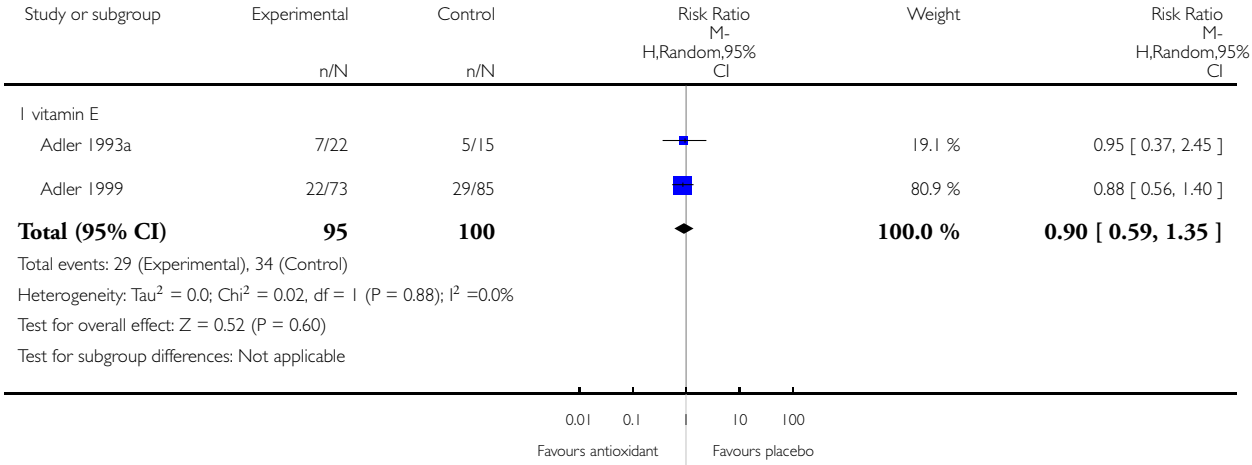


Analysis 1.4. Comparison 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO, Outcome 4 Leaving the study early: 1c. Long term.

Review: Antioxidant treatments for schizophrenia

Comparison: 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

Outcome: 4 Leaving the study early: 1c. Long term



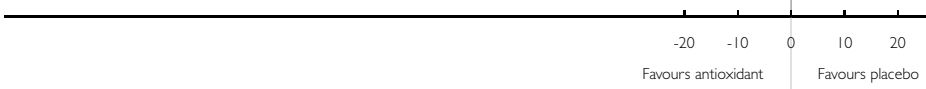
Analysis 1.5. Comparison 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO, Outcome 5 Mental state: 1a. General - average overall endpoint score - short term (BPRS total, high = worse).

Review: Antioxidant treatments for schizophrenia

Comparison: 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

Outcome: 5 Mental state: 1a. General - average overall endpoint score - short term (BPRS total, high = worse)

Study or subgroup	Adjunctive antioxidant N	Mean(SD)	Adjunctive placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 ginkgo biloba							
Doruk 2008	20	-3.8 (3.1)	22	-3.1 (3.5)		17.7 %	-0.70 [-2.70, 1.30]
Luo 1997	304	28.4 (9.1)	208	32.9 (8.5)		18.7 %	-4.50 [-6.04, -2.96]
Zhang 2001a	56	28.7 (7.2)	53	31.6 (8.7)		15.4 %	-2.90 [-5.91, 0.11]
Subtotal (95% CI)	**380**		**283**			**51.8 %**	**-2.74 [-5.29, -0.20]**
Heterogeneity: $Tau^2 = 3.81$; $Chi^2 = 8.73$, df = 2 (P = 0.01); $I^2 = 77\%$							
Test for overall effect: Z = 2.12 (P = 0.034)							
2 selegiline							
Bodkin 2005	33	37.2 (8.8)	34	40.4 (10.4)		11.7 %	-3.20 [-7.81, 1.41]
Goff 1993	12	33.7 (8.6)	16	32.8 (7.1)		9.1 %	0.90 [-5.08, 6.88]
Jungerman 1999	8	18 (8.3)	8	15 (4)		8.4 %	3.00 [-3.38, 9.38]
Subtotal (95% CI)	**53**		**58**			**29.1 %**	**-0.31 [-4.03, 3.41]**
Heterogeneity: $Tau^2 = 2.81$; $Chi^2 = 2.68$, df = 2 (P = 0.26); $I^2 = 25\%$							
Test for overall effect: Z = 0.16 (P = 0.87)							
3 vitamin C							
Dakhale 2005	20	19.3 (5.46)	20	28.96 (6.16)		13.9 %	-9.66 [-13.27, -6.05]
Subtotal (95% CI)	**20**		**20**			**13.9 %**	**-9.66 [-13.27, -6.05]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.25 (P < 0.00001)							
4 vitamin E							
Lohr 1996	14	-6 (11.26)	15	1.92 (14.16)		5.1 %	-7.92 [-17.20, 1.36]
Subtotal (95% CI)	**14**		**15**			**5.1 %**	**-7.92 [-17.20, 1.36]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.67 (P = 0.094)							
Total (95% CI)	**467**		**376**			**100.0 %**	**-3.20 [-5.63, -0.78]**
Heterogeneity: $Tau^2 = 7.59$; $Chi^2 = 27.41$, df = 7 (P = 0.00028); $I^2 = 74\%$							
Test for overall effect: Z = 2.59 (P = 0.0097)							
Test for subgroup differences: $Chi^2 = 14.84$, df = 3 (P = 0.00), $I^2 = 80\%$							



Analysis 1.6. Comparison 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO, Outcome 6 Mental state: 1b. General - average overall endpoint score - short term (PANSS total, high = worse).

Review: Antioxidant treatments for schizophrenia

Comparison: 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

Outcome: 6 Mental state: 1b. General - average overall endpoint score - short term (PANSS total, high = worse)

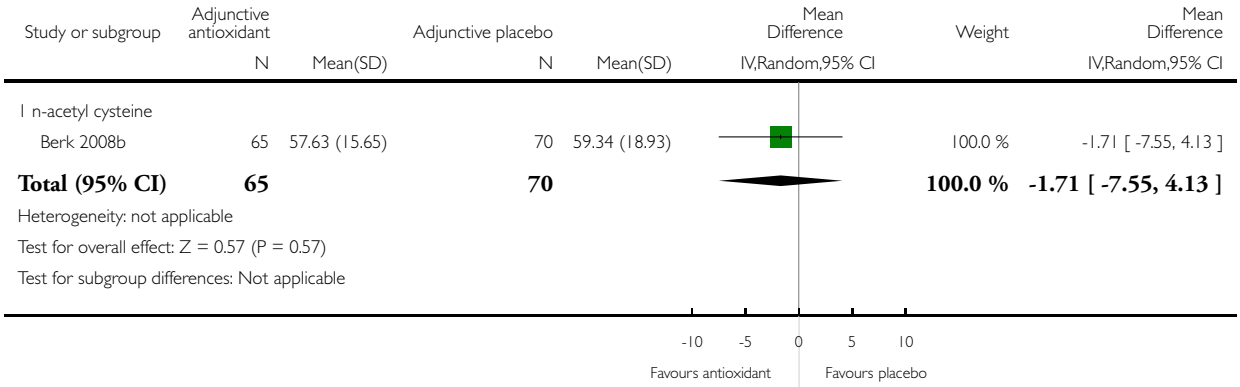
Study or subgroup	Adjunctive antioxidant N	Mean(SD)	Adjunctive placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 allopurinol							
Akhondzadeh 2005	23	-38.69 (19.35)	23	-27.13 (15.69)		9.9 %	-11.56 [-21.74, -1.38]
Brunstein 2005	18	-11 (10.3)	17	0.2 (8.3)		15.0 %	-11.20 [-17.38, -5.02]
Weiser 2012	123	77.5 (13.4)	125	77.4 (13.5)		19.1 %	0.10 [-3.25, 3.45]
Subtotal (95% CI)	**164**		**165**			**43.9 %**	**-6.91 [-15.86, 2.04]**
Heterogeneity: Tau^2 = 50.77; Chi^2 = 12.76, df = 2 (P = 0.002); I^2 =84%							
Test for overall effect: Z = 1.51 (P = 0.13)							
2 ginkgo biloba							
Zhang 2011	78	51.1 (9.7)	79	54.4 (10.8)		19.2 %	-3.30 [-6.51, -0.09]
Subtotal (95% CI)	**78**		**79**			**19.2 %**	**-3.30 [-6.51, -0.09]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.01 (P = 0.044)							
3 selegiline							
Amiri 2008	20	-55 (12.72)	20	-46 (11.48)		13.1 %	-9.00 [-16.51, -1.49]
Jungerman 1999	8	61 (13)	8	57 (6.8)		9.9 %	4.00 [-6.17, 14.17]
Subtotal (95% CI)	**28**		**28**			**23.0 %**	**-2.97 [-15.68, 9.74]**
Heterogeneity: Tau^2 = 63.71; Chi^2 = 4.06, df = 1 (P = 0.04); I^2 =75%							
Test for overall effect: Z = 0.46 (P = 0.65)							
4 n-acetyl cysteine							
Farokhnia 2013	21	57.33 (10.45)	21	70.19 (12.46)		13.9 %	-12.86 [-19.82, -5.90]
Subtotal (95% CI)	**21**		**21**			**13.9 %**	**-12.86 [-19.82, -5.90]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.62 (P = 0.00029)							
Total (95% CI)	**291**		**293**			**100.0 %**	**-6.00 [-10.35, -1.65]**
Heterogeneity: Tau^2 = 22.90; Chi^2 = 23.58, df = 6 (P = 0.00062); I^2 =75%							
Test for overall effect: Z = 2.71 (P = 0.0068)							
Test for subgroup differences: Chi^2 = 6.25, df = 3 (P = 0.10), I^2 =52%							

Analysis 1.7. Comparison 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO, Outcome 7 Mental state: 1c. General - average overall endpoint score - medium term (PANSS total, high = worse).

Review: Antioxidant treatments for schizophrenia

Comparison: 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

Outcome: 7 Mental state: 1c. General - average overall endpoint score - medium term (PANSS total, high = worse)

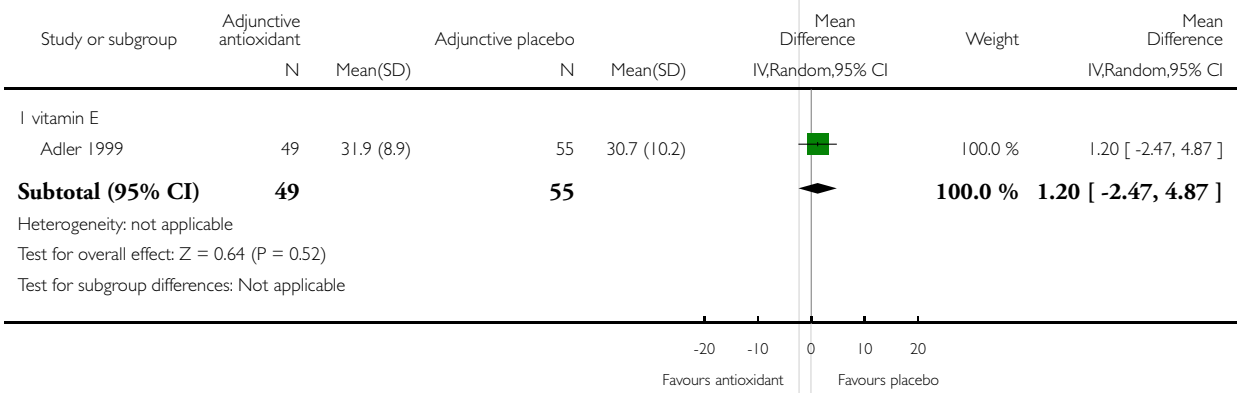


Analysis 1.8. Comparison 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO, Outcome 8 Mental state: 1d. General - average overall endpoint score - long term (BPRS total, high = worse).

Review: Antioxidant treatments for schizophrenia

Comparison: 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

Outcome: 8 Mental state: 1d. General - average overall endpoint score - long term (BPRS total, high = worse)



Analysis 1.9. Comparison 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO, Outcome 9 Mental state: 2a. Specific - average negative symptom endpoint score - short term (PANSS negative, high = worse).

Review: Antioxidant treatments for schizophrenia

Comparison: 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

Outcome: 9 Mental state: 2a. Specific - average negative symptom endpoint score - short term (PANSS negative, high = worse)

Study or subgroup	Adjunctive antioxidant N	Mean(SD)	Adjunctive placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 selegiline							
Amiri 2008	20	-13.65 (3.96)	20	-7.85 (2.7)		10.1 %	-1.68 [-2.41, -0.95]
Bordbar 2008	25	24.81 (5.71)	30	23.61 (6.56)		12.2 %	0.19 [-0.34, 0.72]
Jungerman 1999	8	20 (6.7)	8	21 (6.1)		7.9 %	-0.15 [-1.13, 0.83]
Subtotal (95% CI)	**53**		**58**			**30.2 %**	**-0.54 [-1.76, 0.68]**
Heterogeneity: Tau² = 1.01; Chi² = 16.73, df = 2 (P = 0.00023); I² =88%							
Test for overall effect: Z = 0.87 (P = 0.38)							
2 allopurinol							
Akhondzadeh 2005	23	-7.69 (5.28)	23	-5.6 (4.83)		11.7 %	-0.41 [-0.99, 0.18]
Brunstein 2005	12	-1.8 (2.9)	11	1.5 (2.8)		8.6 %	-1.11 [-2.01, -0.22]
Weiser 2012	123	20.4 (4)	125	20.2 (4.1)		14.8 %	0.05 [-0.20, 0.30]
Subtotal (95% CI)	**158**		**159**			**35.1 %**	**-0.37 [-0.98, 0.23]**
Heterogeneity: Tau² = 0.20; Chi² = 7.40, df = 2 (P = 0.02); I² =73%							
Test for overall effect: Z = 1.21 (P = 0.23)							
3 ginkgo biloba							
Zhang 2011	78	21.4 (6.3)	79	22.5 (6.3)		14.3 %	-0.17 [-0.49, 0.14]
Subtotal (95% CI)	**78**		**79**			**14.3 %**	**-0.17 [-0.49, 0.14]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.09 (P = 0.28)							
4 n-acetyl cysteine							
Farokhnia 2013	23	14.04 (2.51)	21	20.57 (7.99)		11.1 %	-1.10 [-1.74, -0.47]
Subtotal (95% CI)	**23**		**21**			**11.1 %**	**-1.10 [-1.74, -0.47]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.39 (P = 0.00070)							
5 DHEA							

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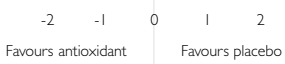
Study or subgroup	Adjunctive antioxidant N	Mean(SD)	Adjunctive placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Ritsner 2010	13	24.3 (7.1)	11	20 (6)		9.2 %	0.63 [-0.20, 1.45]
Subtotal (95% CI)	**13**		**11**			**9.2 %**	**0.63 [-0.20, 1.45]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.49 (P = 0.14)							
Total (95% CI)	**325**		**328**			**100.0 %**	**-0.38 [-0.77, 0.00]**
Heterogeneity: Tau^2 = 0.25; Chi^2 = 37.73, df = 8 (P<0.00001); I^2 =79%							
Test for overall effect: Z = 1.94 (P = 0.053)							
Test for subgroup differences: Chi^2 = 11.73, df = 4 (P = 0.02), I^2 =66%							



Analysis 1.10. Comparison 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO, Outcome 10 Mental state: 2b. Specific - average negative symptom endpoint score - short term (SANS, high = worse).

Review: Antioxidant treatments for schizophrenia

Comparison: 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

Outcome: 10 Mental state: 2b. Specific - average negative symptom endpoint score - short term (SANS, high = worse)

Study or subgroup	Adjunctive antioxidant N	Mean(SD)	Adjunctive placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 ginkgo biloba							
Doruk 2008	23	-7.9 (7)	23	-1.8 (3.5)		37.6 %	-6.10 [-9.30, -2.90]
Luo 1997	304	48.7 (23.9)	208	61.2 (23.9)		33.8 %	-12.50 [-16.72, -8.28]
Zhang 2001a	56	42.3 (15.6)	53	45.6 (14.1)		28.6 %	-3.30 [-8.88, 2.28]
Total (95% CI)	**383**		**284**			**100.0 %**	**-7.46 [-12.46, -2.46]**
Heterogeneity: Tau^2 = 14.65; Chi^2 = 8.32, df = 2 (P = 0.02); I^2 =76%							
Test for overall effect: Z = 2.92 (P = 0.0035)							
Test for subgroup differences: Not applicable							

Analysis 1.11. Comparison 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO, Outcome 11 Mental state: 2c. Specific - average negative symptom endpoint score - medium term (PANSS negative, high = worse).

Review: Antioxidant treatments for schizophrenia

Comparison: 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

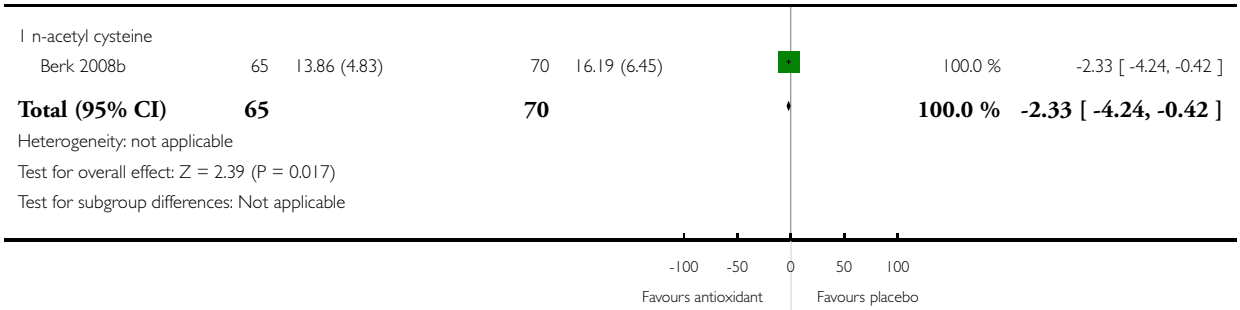
Outcome: 11 Mental state: 2c. Specific - average negative symptom endpoint score - medium term (PANSS negative, high = worse)

Study or subgroup	Adjunctive antioxidant N	Mean(SD)	Adjunctive placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 n-acetyl cysteine							
Berk 2008b	65	13.86 (4.83)	70	16.19 (6.45)		100.0 %	-2.33 [-4.24, -0.42]
Total (95% CI)	**65**		**70**			**100.0 %**	**-2.33 [-4.24, -0.42]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.39 (P = 0.017)

Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO, Outcome 12 Mental state: 2d. Specific - average positive symptom endpoint score - short term (PANSS positive, high = worse).

Review: Antioxidant treatments for schizophrenia

Comparison: 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

Outcome: 12 Mental state: 2d. Specific - average positive symptom endpoint score - short term (PANSS positive, high = worse)

Study or subgroup	Adjunctive antioxidant N	Mean(SD)	Adjunctive placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 allopurinol							
Akhondzadeh 2005	23	-14.21 (7.51)	23	-9.6 (5.74)		8.3 %	-4.61 [-8.47, -0.75]
Brunstein 2005	12	-6.2 (5.1)	11	0.5 (2.7)		9.7 %	-6.70 [-10.00, -3.40]
Weiser 2012	123	18.4 (4.2)	125	18.4 (4.6)		16.2 %	0.0 [-1.10, 1.10]
Subtotal (95% CI)	**158**		**159**			**34.2 %**	**-3.55 [-8.24, 1.13]**
Heterogeneity: Tau² = 14.92; Chi² = 18.02, df = 2 (P = 0.00012); I² =89%							
Test for overall effect: Z = 1.49 (P = 0.14)							
2 DHEA							
Ritsner 2010	13	17.3 (7.2)	11	13.7 (5)		6.3 %	3.60 [-1.30, 8.50]
Subtotal (95% CI)	**13**		**11**			**6.3 %**	**3.60 [-1.30, 8.50]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.44 (P = 0.15)							
3 ginkgo biloba							
Zhang 2011	78	8.6 (2.2)	79	9.8 (4.5)		16.1 %	-1.20 [-2.31, -0.09]
Subtotal (95% CI)	**78**		**79**			**16.1 %**	**-1.20 [-2.31, -0.09]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.13 (P = 0.033)							
4 n-acetyl cysteine							
Farokhnia 2013	21	12.19 (3.37)	21	13.33 (4.56)		12.2 %	-1.14 [-3.57, 1.29]
Subtotal (95% CI)	**21**		**21**			**12.2 %**	**-1.14 [-3.57, 1.29]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.92 (P = 0.36)							
5 selegiline							
Bordbar 2008	25	13.31 (1.81)	30	14.25 (3.75)		15.0 %	-0.94 [-2.46, 0.58]
Jungerman 1999	8	11 (1.3)	8	9 (1)		16.1 %	2.00 [0.86, 3.14]
Subtotal (95% CI)	**33**		**38**			**31.1 %**	**0.57 [-2.30, 3.45]**
Heterogeneity: Tau² = 3.85; Chi² = 9.23, df = 1 (P = 0.002); I² =89%							
Test for overall effect: Z = 0.39 (P = 0.70)							
Total (95% CI)	**303**		**308**			**100.0 %**	**-0.96 [-2.50, 0.58]**
Heterogeneity: Tau² = 3.51; Chi² = 41.36, df = 7 (P<0.00001); I² =83%							
Test for overall effect: Z = 1.23 (P = 0.22)							
Test for subgroup differences: Chi² = 5.79, df = 4 (P = 0.22), I² =31%							

Analysis 1.13. Comparison 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO, Outcome 13 Mental state: 2e. Specific - average positive symptom endpoint score - short term (SAPS, high = worse).

Review: Antioxidant treatments for schizophrenia

Comparison: 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

Outcome: 13 Mental state: 2e. Specific - average positive symptom endpoint score - short term (SAPS, high = worse)

Study or subgroup	Adjunctive antioxidant N	Mean(SD)	Adjunctive placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 ginkgo biloba							
Doruk 2008	20	-7.9 (7)	22	-1.8 (3.5)		52.6 %	-6.10 [-9.50, -2.70]
Zhang 2001a	56	7.1 (8.4)	53	11 (10.5)		47.4 %	-3.90 [-7.48, -0.32]
Total (95% CI)	**76**		**75**			**100.0 %**	**-5.06 [-7.52, -2.59]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.76$, df = 1 (P = 0.38); $I^2 = 0.0\%$

Test for overall effect: Z = 4.02 (P = 0.000058)

Test for subgroup differences: Not applicable

Analysis 1.14. Comparison 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO, Outcome 14 Mental state: 2f. Secific - average positive symptom endpoint score - medium term (PANSS positive, high = worse).

Review: Antioxidant treatments for schizophrenia

Comparison: 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

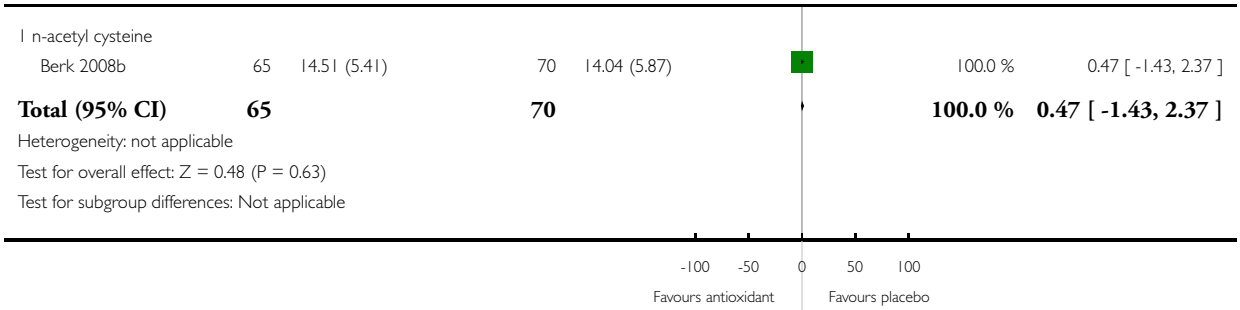
Outcome: 14 Mental state: 2f. Secific - average positive symptom endpoint score - medium term (PANSS positive, high = worse)

Study or subgroup	Adjunctive antioxidant N	Mean(SD)	Adjunctive placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 n-acetyl cysteine							
Berk 2008b	65	14.51 (5.41)	70	14.04 (5.87)		100.0 %	0.47 [-1.43, 2.37]
Total (95% CI)	**65**		**70**			**100.0 %**	**0.47 [-1.43, 2.37]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.48 (P = 0.63)

Test for subgroup differences: Not applicable



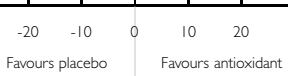
Analysis 1.15. Comparison 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO, Outcome 15 General functioning: 1a. General - average overall endpoint score - short term (GAS total, high = worse).

Review: Antioxidant treatments for schizophrenia

Comparison: 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

Outcome: 15 General functioning: 1a. General - average overall endpoint score - short term (GAS total, high = worse)

Study or subgroup	Adjunctive antioxidant N	Mean(SD)	Adjunctive placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 DHEA							
Ritsner 2010	13	55.8 (16.9)	11	63.2 (14.1)		24.2 %	-7.40 [-19.80, 5.00]
Subtotal (95% CI)	**13**		**11**			**24.2 %**	**-7.40 [-19.80, 5.00]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.17 (P = 0.24)							
2 selegiline							
Goff 1993	12	49.3 (6.1)	16	48.4 (4.7)		75.8 %	0.90 [-3.25, 5.05]
Subtotal (95% CI)	**12**		**16**			**75.8 %**	**0.90 [-3.25, 5.05]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.43 (P = 0.67)							
Total (95% CI)	**25**		**27**			**100.0 %**	**-1.11 [-8.07, 5.86]**
Heterogeneity: Tau^2 = 12.18; Chi^2 = 1.55, df = 1 (P = 0.21); I^2 =35%							
Test for overall effect: Z = 0.31 (P = 0.76)							
Test for subgroup differences: Chi^2 = 1.55, df = 1 (P = 0.21), I^2 =35%							

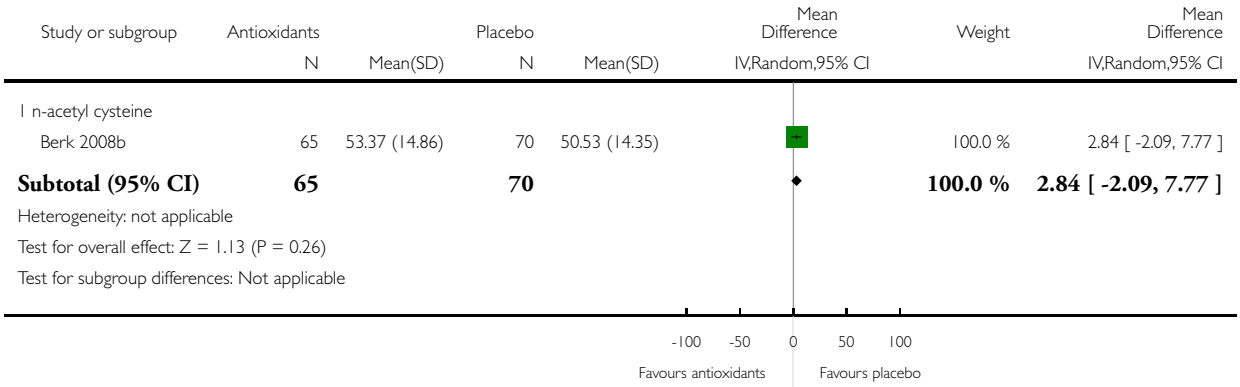


Analysis 1.16. Comparison 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO, Outcome 16 General functioning: 1b. General - average overall endpoint score - medium term (GAS total, high = worse).

Review: Antioxidant treatments for schizophrenia

Comparison: 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

Outcome: 16 General functioning: 1b. General - average overall endpoint score - medium term (GAS total, high = worse)

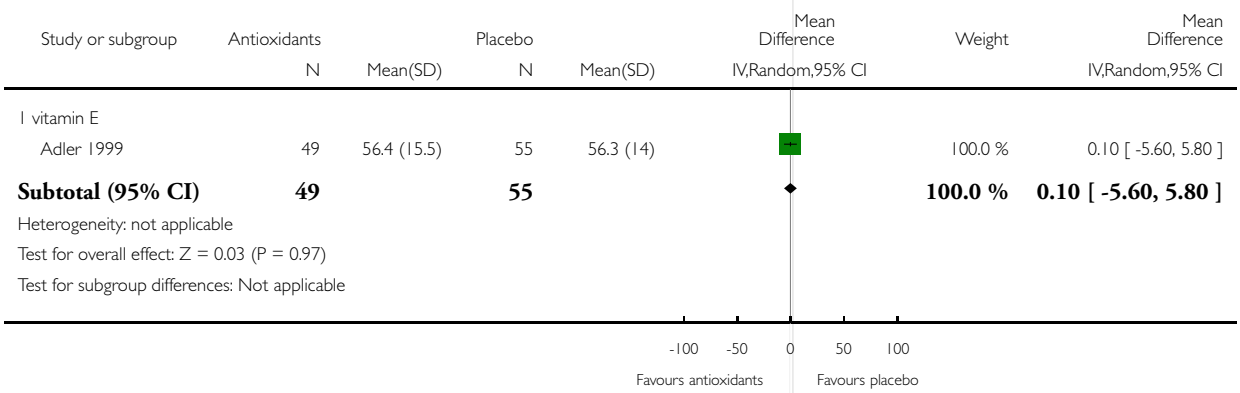


Analysis 1.17. Comparison 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO, Outcome 17 General functioning: 1c. General - average overall endpoint score - long term (GAS total, high = worse).

Review: Antioxidant treatments for schizophrenia

Comparison: 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

Outcome: 17 General functioning: 1c. General - average overall endpoint score - long term (GAS total, high = worse)

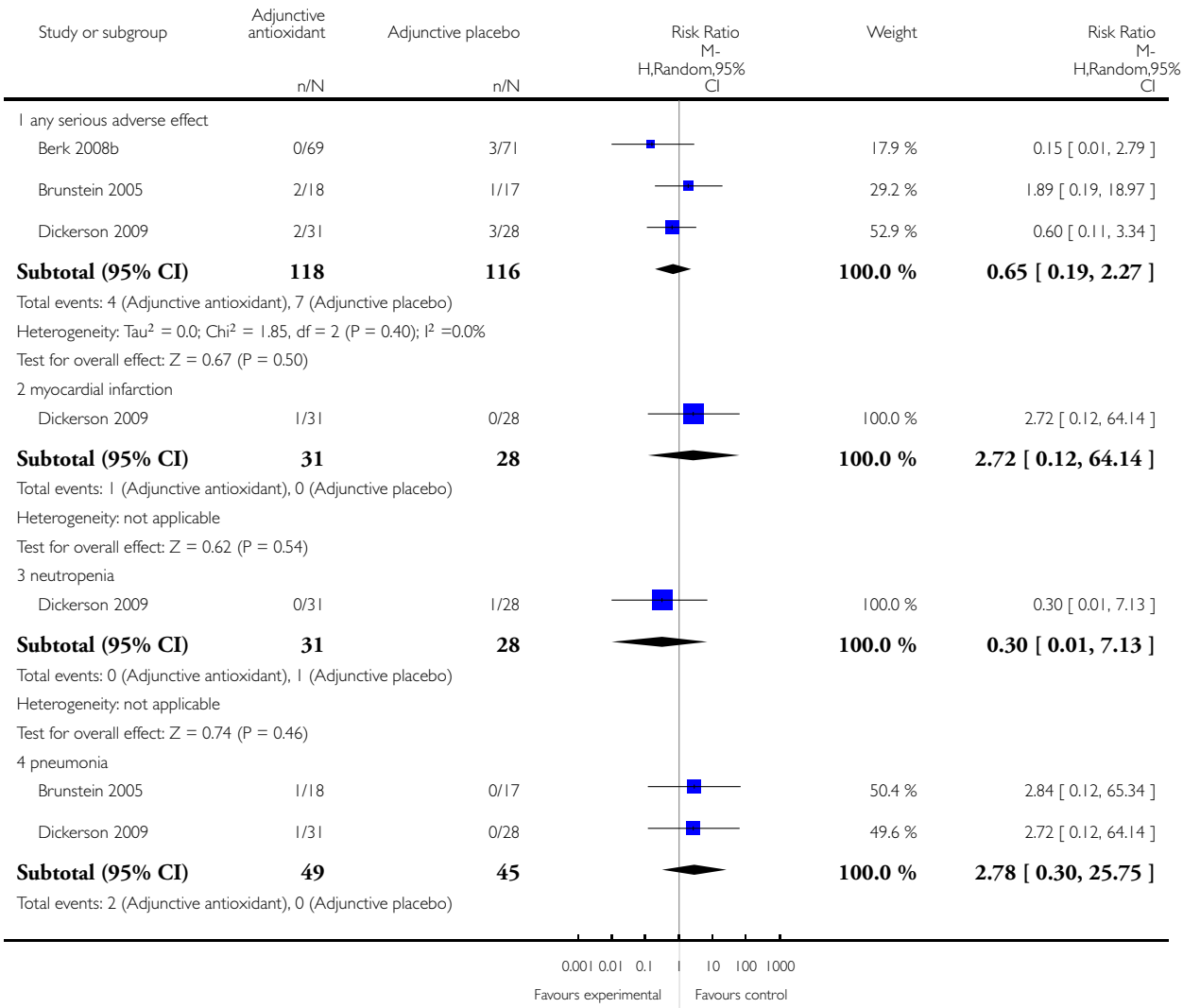


Analysis 1.18. Comparison 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO, Outcome 18 Adverse effects: 1. Serious (any time point).

Review: Antioxidant treatments for schizophrenia

Comparison: 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

Outcome: 18 Adverse effects: 1. Serious (any time point)



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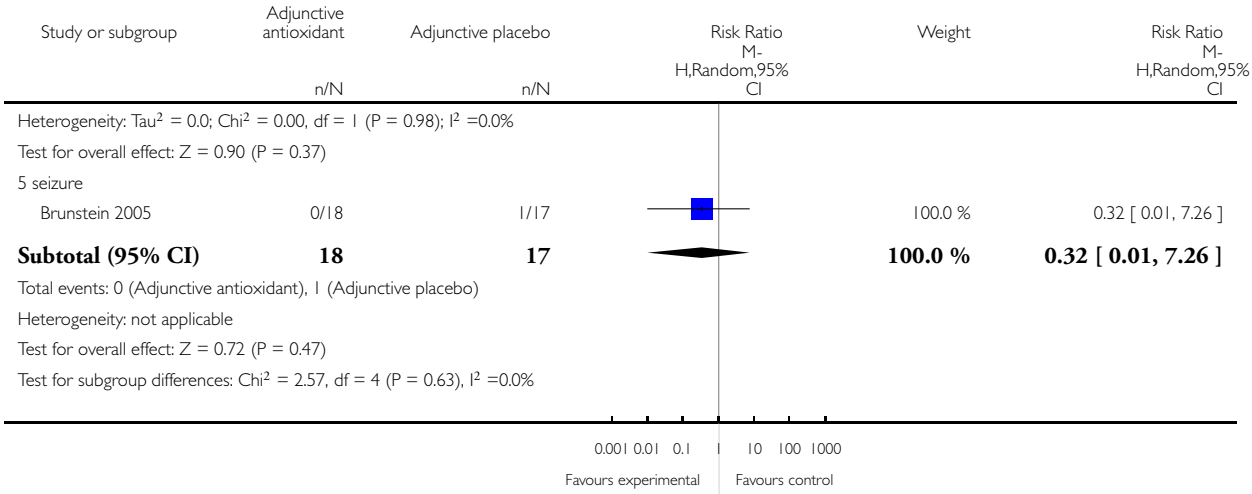
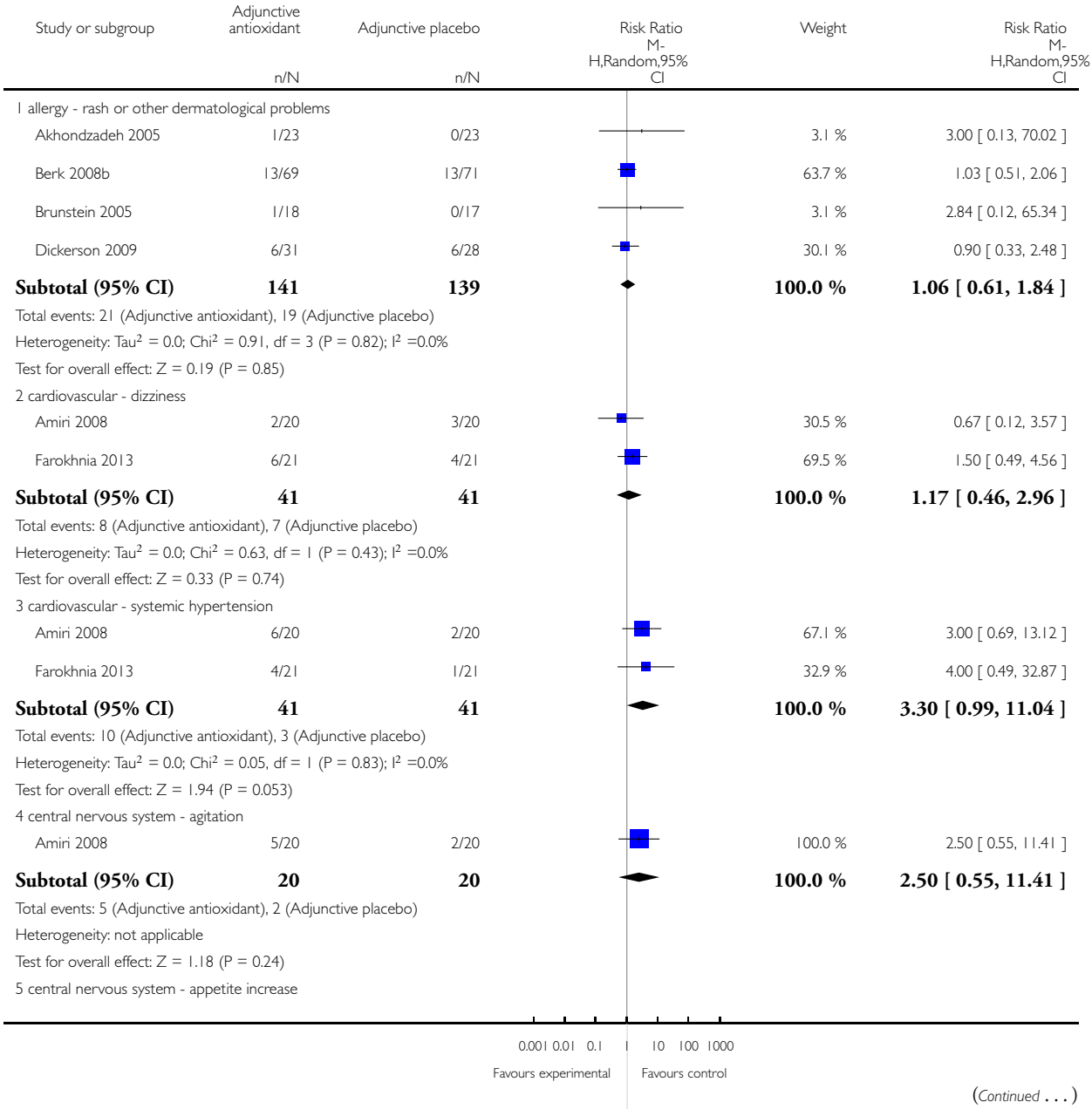


Analysis 1.19. Comparison 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO, Outcome 19 Adverse effects: 2. Various - less serious.

Review: Antioxidant treatments for schizophrenia

Comparison: 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

Outcome: 19 Adverse effects: 2. Various - less serious



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Study or subgroup	Adjunctive antioxidant n/N	Adjunctive placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Akhondzadeh 2005	6/23	6/23		41.2 %	1.00 [0.38, 2.65]
Amiri 2008	5/20	5/20		33.8 %	1.00 [0.34, 2.93]
Farokhnia 2013	4/21	4/21		25.0 %	1.00 [0.29, 3.48]
Subtotal (95% CI)	**64**	**64**		**100.0 %**	**1.00 [0.54, 1.87]**
Total events: 15 (Adjunctive antioxidant), 15 (Adjunctive placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.0, df = 2 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.0 (P = 1.0)					
6 central nervous system - headache					
Amiri 2008	5/20	3/20		15.0 %	1.67 [0.46, 6.06]
Berk 2008b	12/69	16/71		55.3 %	0.77 [0.39, 1.51]
Dickerson 2009	4/31	4/28		15.0 %	0.90 [0.25, 3.28]
Farokhnia 2013	5/21	3/21		14.8 %	1.67 [0.46, 6.10]
Subtotal (95% CI)	**141**	**140**		**100.0 %**	**0.99 [0.60, 1.64]**
Total events: 26 (Adjunctive antioxidant), 26 (Adjunctive placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.79, df = 3 (P = 0.62); I^2 =0.0%					
Test for overall effect: Z = 0.03 (P = 0.98)					
7 central nervous system - insomnia					
Amiri 2008	5/20	2/20		100.0 %	2.50 [0.55, 11.41]
Subtotal (95% CI)	**20**	**20**		**100.0 %**	**2.50 [0.55, 11.41]**
Total events: 5 (Adjunctive antioxidant), 2 (Adjunctive placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.18 (P = 0.24)					
8 central nervous system - sedation					
Akhondzadeh 2005	8/23	7/23		62.2 %	1.14 [0.50, 2.63]
Farokhnia 2013	7/21	4/21		37.8 %	1.75 [0.60, 5.10]
Subtotal (95% CI)	**44**	**44**		**100.0 %**	**1.34 [0.70, 2.59]**
Total events: 15 (Adjunctive antioxidant), 11 (Adjunctive placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.38, df = 1 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 0.88 (P = 0.38)					
9 central nervous system - tremor					
Akhondzadeh 2005	6/23	7/23		72.9 %	0.86 [0.34, 2.16]
Amiri 2008	2/20	5/20		27.1 %	0.40 [0.09, 1.83]
Subtotal (95% CI)	**43**	**43**		**100.0 %**	**0.70 [0.32, 1.54]**
Total events: 8 (Adjunctive antioxidant), 12 (Adjunctive placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.72, df = 1 (P = 0.40); I^2 =0.0%					
Test for overall effect: Z = 0.89 (P = 0.37)					
10 gastrointestinal - abdominal pain					
Amiri 2008	4/20	2/20		100.0 %	2.00 [0.41, 9.71]

(*Continued* . . .)

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Study or subgroup	Adjunctive antioxidant n/N	Adjunctive placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**20**	**20**		**100.0 %**	**2.00 [0.41, 9.71]**
Total events: 4 (Adjunctive antioxidant), 2 (Adjunctive placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.86 (P = 0.39)					
11 gastrointestinal - nausea					
Amiri 2008	6/20	3/20		12.6 %	2.00 [0.58, 6.91]
Berk 2008b	16/69	19/71		58.1 %	0.87 [0.49, 1.54]
Dickerson 2009	5/31	6/28		16.8 %	0.75 [0.26, 2.20]
Farokhnia 2013	6/21	3/21		12.4 %	2.00 [0.57, 6.96]
Subtotal (95% CI)	**141**	**140**		**100.0 %**	**1.04 [0.67, 1.62]**
Total events: 33 (Adjunctive antioxidant), 31 (Adjunctive placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.87, df = 3 (P = 0.41); I^2 =0.0%					
Test for overall effect: Z = 0.19 (P = 0.85)					
Test for subgroup differences: Chi^2 = 7.91, df = 10 (P = 0.64), I^2 =0.0%					

Analysis 1.20. Comparison 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO, Outcome 20 Adverse effects: 3. Average score (TESS endpoint, high = worse).

Review: Antioxidant treatments for schizophrenia

Comparison: 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

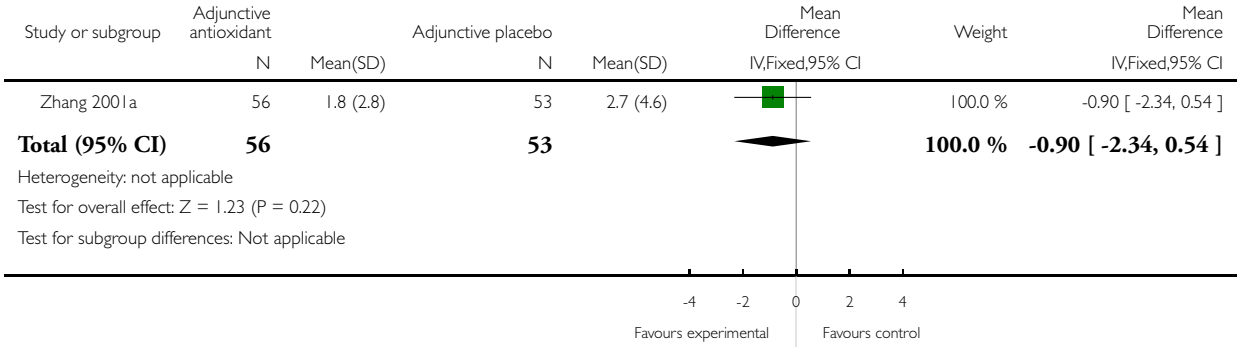
Outcome: 20 Adverse effects: 3. Average score (TESS endpoint, high = worse)

Study or subgroup	Adjunctive antioxidant N	Mean(SD)	Adjunctive placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Zhang 2001a	56	1.8 (2.8)	53	2.7 (4.6)		100.0 %	-0.90 [-2.34, 0.54]
Total (95% CI)	**56**		**53**			**100.0 %**	**-0.90 [-2.34, 0.54]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.23 (P = 0.22)

Test for subgroup differences: Not applicable

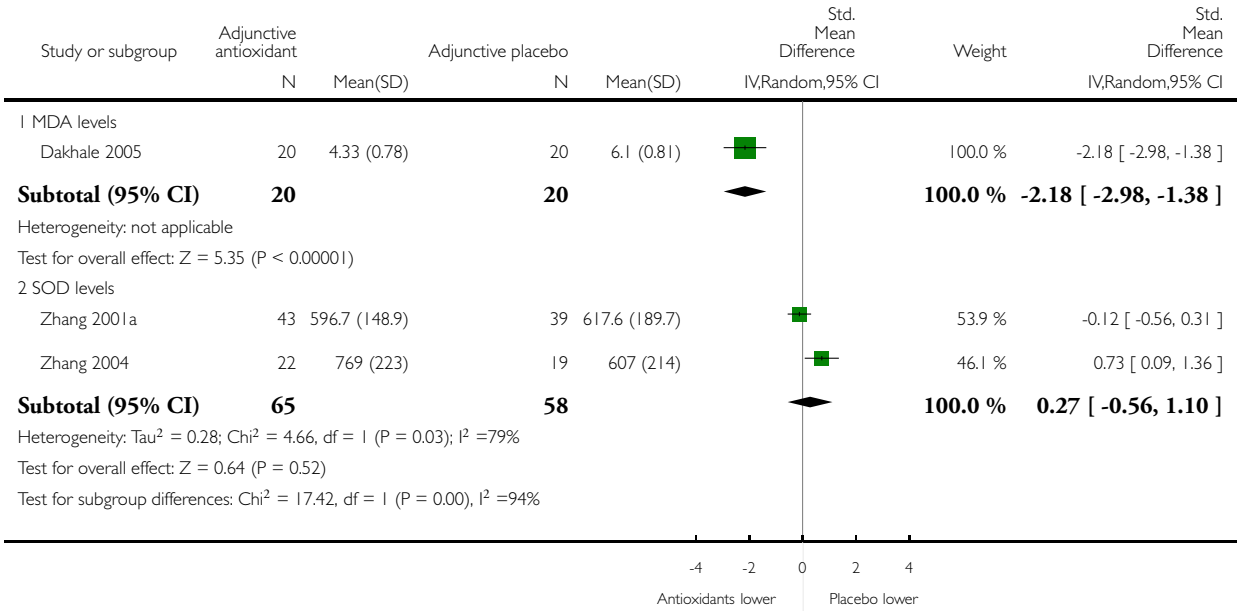


Analysis 1.21. Comparison 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO, Outcome 21 Laboratory data (serum tests) - short term.

Review: Antioxidant treatments for schizophrenia

Comparison: 1 ADJUNCTIVE ANTIOXIDANTS versus PLACEBO

Outcome: 21 Laboratory data (serum tests) - short term



ADDITIONAL TABLES

Table 1. Suggested design of future trial

Methods	Allocation: centralised sequence generation with table of random numbers or computer-generated code, stratified by severity of illness, sequence concealed till interventions assigned. Blinding: those recruiting and assigning participants, those assessing outcomes, all blind to allocated group, blinding could be tested. Duration: minimum of 24 weeks
Participants	Diagnosis: schizophrenia, if operational criteria used these should be in the context of routine care. N = 450*. Age: adults. Sex: men and women. Setting: anywhere.
Interventions	1. Adjunctive placebo 2. Adjunctive antioxidant (preferably *Ginkgo biloba* EGb or NAC)

Table 1. Suggested design of future trial (*Continued*)

Outcomes	Quality of life: healthy days,** SF-36***. Service outcomes: days in hospital, time attending psychiatric outpatient clinic. Satisfaction with care: patients/carers. Global state: CGI.*** Mental state: CGI. Social functioning: to include occupational status. Adverse effects: including mortality. Economic data.
Notes	* size of study to detect a 10% difference in improvement with 80% certainty. ** Primary outcome. *** If scales are used to measure outcome then there should be binary cut off points, defined before study starts, of clinically important improvement

CGI - Clinical Global Impression; NAC - N-acetyl cysteine; SF 36 - Short form 36

APPENDICES

Appendix 1. Previous searches

1.1 Search in 2012

1.1.1 Electronic searches

1.1.1.1 Cochrane Schizophrenia Group Trials Register (November 2010)

The register was searched by the Trial Search co-ordinator of the Cochrane Schizophrenia Group using the phrase [(*vitamin C* OR *ascorbic acid* OR *vitamin E* OR *alpha-tocopherol* OR *selegiline* OR *deprenyl* OR *n-acetyl cysteine* OR *n-acetyl-l-cysteine* OR *n-acetylcysteine* OR *acetylcysteine* OR *superoxide dismutase* OR *SOD * OR *dehydroepiandrosterone* OR *antioxidant*) in title, abstract and index terms of REFERENCE and Intervention of STUDY]
The Cochrane Schizophrenia Group's Registry of Trials is compiled by systematic searches of major resources (including AMED, BIOSIS, CINAHL, EMBASE, MEDLINE, PsycINFO, PubMed, and registries of Clinical Trials) and their monthly updates, handsearches, grey literature, and conference proceedings. The searches do not have language limitation (for details of databases searched by the Schizophreia Group please see their Group Module).

1.1.2 Searching other resources

1.1.2.1 Reference searching

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

1.1.2.2 Personal contact

If necessary we contacted the authors of significant papers, as well as other experts in the field, and asked for their knowledge of further studies, published or unpublished, relevant to the review. We noted any responses in the Characteristics of included studies

1.2 Search in 2012

1.2.1 CENTRAL 2012

Review authors ran an additional search through the CENTRAL database in November 2012 using the above search term.

CONTRIBUTIONS OF AUTHORS

Pedro Magalhães and Flávio Kapczinski drafted the original idea. Pedro Magalhães and Michael Berk were responsible for trial selection. Olivia Dean and Pedro Magalhães were responsible for data extraction and data management. All authors were responsible for the final drafting of the protocol.

DECLARATIONS OF INTEREST

Pedro Magalhães has no conflicts of interest.

Olivia Dean has received grant support from the Brain and Behavior Foundation, Simons Autism Foundation, Stanley Medical Research Institute, Lilly, NHMRC and an ASBD/Servier grant.

Anna Andreazza has no conflicts of interest.

Michael Berk was the lead investigator for one potentially relevant study for the review (Berk 2008; Berk 2008a) , but did not extract data from these trials for this review. He has received grant/research support from the Stanley Medical Research Foundation, MBF, NHMRC, beyondblue, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Organon, Novartis, Mayne Pharma, Servier; has been a consultant/speaker for: Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Pfizer, Sanofi Synthelabo, Servier, Solvay, Wyeth. Professor Berk is co-inventor on two provisional patents regarding the use of NAC and related compounds for psychiatric indications, which, whilst assigned to the Mental Health Research Institute, could lead to personal remuneration upon a commercialisation event.

Flávio Kapczinski has received grant/research support from Astra-Zeneca, Eli Lilly, the Janssen-Cilag, Servier, CNPq, CAPES, NARSAD and the Stanley Medical Research Institute; has been a member of the speakers' boards for Astra-Zeneca, Eli Lilly, Janssen and Servier; and has served as a consultant for Servier.

SOURCES OF SUPPORT

Internal sources

- Universidade Federal do Rio Grande do Sul, Brazil.

Employs Profs. Magalhaes and Kapczinski

- Deakin University, Australia.

Employs Prof. Berk

- University of Toronto, Canada.

Employs Prof. Andreazza

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

As stated in the "Duration" section, we planned to divide the studies into immediate (four weeks or less), short term (4-12 weeks), medium term (13-26 weeks) and long term (over 26 weeks) However, Luo 1997 had a follow-up period of 16 weeks and was analysed in the short-term subgroup as it was designed as an acute study and much more similar to the other *Ginkgo biloba* studies, four weeks or less), short term (4-12 weeks), medium term (13-26 weeks) and long term (over 26 weeks).

We prestated that we would include the following outcomes in a 'Summary of findings' table.

Global state: clinical response and relapse, mental state: clinical response, service use: hospital admission and days in hospital, adverse effects and quality of life.

This has not been possible. Relapse data service use and quality of life were not available. We thus opted to include, alongside improvement, endpoint psychopathology and risk of leaving the study before termination, as proxies of improvement and treatment acceptability. We noted the lack of available data for our prestated outcomes of interest in the abstract and main text.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetylcysteine [therapeutic use]; Allopurinol [therapeutic use]; Antioxidants [*therapeutic use]; Antipsychotic Agents [*therapeutic use]; Ascorbic Acid [therapeutic use]; Dehydroepiandrosterone [therapeutic use]; Drug Therapy, Combination [methods]; Free Radical Scavengers [*therapeutic use]; Ginkgo biloba; Oxidative Stress [*drug effects]; Randomized Controlled Trials as Topic; Schizophrenia [*drug therapy; metabolism]; Selegiline [therapeutic use]; Vitamin E [therapeutic use]; Vitamins [therapeutic use]

MeSH check words

Humans