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Soares-Weiser K, Maayan N, McGrath J

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[Intervention Review]

Vitamin E for neuroleptic-induced tardive dyskinesia

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ABSTRACT

Background

Antipsychotic (neuroleptic) medication is used extensively to treat people with chronic mental illnesses. Its use, however, is associated with adverse effects, including movement disorders such as tardive dyskinesia (TD) - a problem often seen as repetitive involuntary movements around the mouth and face. Vitamin E has been proposed as a treatment to prevent or decrease TD.

Objectives

To determine the effects of vitamin E for people with schizophrenia or other chronic mental illnesses who also developed neuroleptic-induced TD.

Search methods

We searched the Cochrane Schizophrenia Group Trials Register (March 2010), 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 controlled trials dealing with people with neuroleptic-induced TD and schizophrenia who had been randomly allocated to either vitamin E or to a placebo or no intervention.

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 assumed that people who dropped out had no improvement.

Main results

The review now includes 11 poorly reported randomised trials (total 427 people). There was no clear difference between vitamin E and placebo for the outcome of 'clinically relevant improvement in TD' (6 trials, 256 people, RR 0.95 CI 0.89 to 1.02). For the outcome of 'any improvement in TD symptoms', again, we found no clear difference between groups (7 trials, 311 people, RR 0.86 CI 0.75 to 1.00). However, people allocated to placebo showed more deterioration of their symptoms compared with those given vitamin E (5 trials, 98 people, RR 0.38 CI 0.16 to 0.9). There was no difference in the incidence of adverse effects (9 trials, 203 people, RR 1.29 CI 0.51 to 3.24) or leaving the study early (medium term 6 trials, 173 people, RR 1.29 CI 0.72 to 2.3). There is no trial-based information regarding the effect of vitamin E for those with early onset of TD.

Authors' conclusions

Small trials of limited quality suggest that vitamin E may protect against deterioration of TD. There is no evidence that vitamin E improves symptoms of this problematic and disfiguring condition once established. New and better trials are indicated in this under-researched area, and, of the many adjunctive treatments that have been given for TD, vitamin E would be a good choice for further evaluation.

PLAIN LANGUAGE SUMMARY

Vitamin E for neuroleptic-induced tardive dyskinesia

Having to take antipsychotic drugs for long periods of time can cause repetitive movements - often of the face and mouth. These are disfiguring and do not necessarily cease once medication is reduced or changed. Vitamin E has been evaluated for treating these movement disorders, but, so far, the benefit of this medication seems small and restricted to avoidance of deterioration.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

VITAMIN E compared with PLACEBO for neuroleptic-induced tardive dyskinesia

Patient or population: patients with neuroleptic-induced tardive dyskinesia
Settings: in hospital
Intervention: VITAMIN E
Comparison: PLACEBO

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	PLACEBO	VITAMIN E				
Tardive dyskinesia: 1. Not improved to a clinically important extent Follow-up: 1 years	**Low risk population**		**RR 0.96** (0.9 to 1.02)	256 (6 studies)	⊕◯◯◯ **very low**[1,2,3]	
	500 per 1000	**480 per 1000** (450 to 510)				
	High risk population					
	1000 per 1000	**960 per 1000** (900 to 1000)				
Tardive dyskinesia: 2. Not any improvement Follow-up: 1 years	**Low risk population**		**RR 0.86** (0.75 to 1)	311 (7 studies)	⊕◯◯◯ **very low**[3,4,5]	
	500 per 1000	**430 per 1000** (375 to 500)				
	Medium risk population					
	700 per 1000	**602 per 1000** (525 to 700)				
	High risk population					

	1000 per 1000	**860 per 1000** (750 to 1000)			
Tardive dyskinesia: 3. Deterioration of symptoms Follow-up: 1 years	**Low risk population**		**RR 0.38** (0.16 to 0.9)	98 (5 studies)	⊕○○○ **very low**[3,6,7]
	100 per 1000	**38 per 1000** (16 to 90)			
	Medium risk population				
	300 per 1000	**114 per 1000** (48 to 270)			
	High risk population				
	500 per 1000	**190 per 1000** (80 to 450)			
Adverse effect: any	**Low risk population**		**RR 1.29** (0.51 to 3.24)	203 (9 studies)	⊕○○○ **very low**[1,3,8,9,10]
	10 per 1000	**13 per 1000** (5 to 32)			
	Medium risk population				
	50 per 1000	**64 per 1000** (25 to 162)			
	High risk population				
	100 per 1000	**129 per 1000** (51 to 324)			

Adverse effect: specific	See comment	See comment	Not estimable	0 (0)	See comment	This outcome was designated to be of importance at update of protocol 2010. We found no studies rating this outcome
Quality of life	See comment	See comment	Not estimable	0 (0)	See comment	This outcome was designated to be of importance at update of protocol 2010. We found no studies rating this outcome

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

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

[1] Limitations in design - rated 'serious': two studies had adequate sequence generation, four studies were unclear as details were not given.
[2] Imprecision - rated 'serious': all studies had small or very small sample sizes.
[3] Publication bias - rated 'likely': there were few included studies and these had small sample sizes, poor reporting and were not free of other biases.
[4] Limitations in design - rated 'serious': two studies had adequate sequence generation, the other five were unclear as details were not given. Only one had adequate allocation concealment and six other studies were unclear. Two studies were adequately blinded, four were unclear, and one did not have adequate blinding. Two studies addressed incomplete data adequately, while the others were unclear. No study was free from selective reporting as key outcomes were not addressed.
[5] Imprecision - rated 'serious': all studies had small or very small sample sizes. The confidence intervals were wide for five of the studies.
[6] Limitations in design - rated 'serious': one study had adequate sequence generation, the other four studies stated there was "random allocation" - details not given. All studies had unclear allocation concealment. Two studies were adequately blinded,

two were unclear and one study did not have adequate blinding. One trial addressed incomplete data adequately, while others were unclear. No study was free from selective reporting as key outcomes were not addressed.

[7] Imprecision - rated 'serious': all studies had small or very small sample sizes. The confidence intervals were wide for all of the studies.

[8] Limitations in design - rated 'serious': one study had adequate sequence generation, the other eight stated there was "random allocation" - details not given. One study had adequate allocation concealment, eight were unclear. Five studies were adequately blinded, three were unclear stated they were "blinded" and gave no further details, one did not have adequate blinding. Two trials addressed incomplete data adequately while others studies did not report enough details about losses to follow-up. No study was free from selective reporting as key outcomes were not addressed.

[9] Inconsistency - rated 'very serious': two studies showed a benefit for vitamin E, one showed no difference and the rest showed some harm.

[10] Imprecision - rated 'serious': all studies had small or very small sample sizes. The confidence intervals were wide for all studies.

BACKGROUND

Description of the condition

Since the 1950s antipsychotic (neuroleptic) medication has been used extensively to treat people with chronic mental illnesses such as schizophrenia. These drugs can effectively control symptoms such as abnormal perceptions (hallucinations), disordered thinking and fixed false beliefs (delusions). In addition, maintenance therapy with antipsychotics is associated with a reduced risk of relapse (Schooler 1993). However, antipsychotic medication has been also associated with a wide range of adverse effects, including movement disorders. The appearance of these movement disorders can contribute to poor compliance with antipsychotic treatment (Barnes 1993).

Tardive dyskinesia (TD) is one such movement disorder and is characterised by abnormal, repetitive and involuntary movements. TD is a chronic condition of insidious onset, the severity of which spontaneously fluctuates (APA 1992). It occurs in more than 20% of those using neuroleptic medication continually for longer than three months. Every year 4%-5% of those who continually use these drugs begin to show signs of TD (APA 1992). This disorder can result in considerable social and physical disability (Barnes 1993).

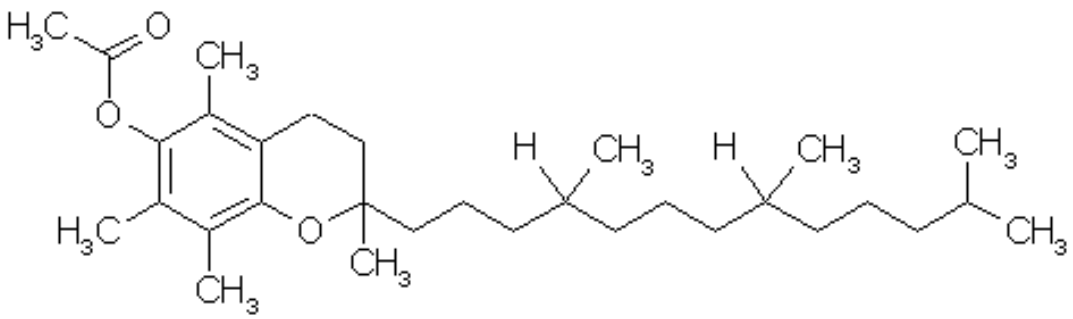
Although the most frequent cause of TD is the use of neuroleptic medication, it is striking that dose reduction can lead to a temporary exacerbation in symptoms. Conversely, increasing the dose is often associated with a temporary remission. Antipsychotic drugs block certain chemical receptor sites in the brain - one of these is specific for dopamine (Casey 1994). One hypothesis explaining the cause of neuroleptic-induced TD is that chronic blockade of dopamine receptors in specific cells of the brain (neurones from the nigrostriatum) causes an overgrowth of these receptors (Casey 1994). However, there is some suggestion that the chronic use of neuroleptics may also cause an abnormal production of highly active atoms and chemical groups (cytotoxic free radicals), which may damage specific cells in the brain. This, in turn, could be responsible for the appearance of TD (Cadet 1989).

This work updates one in a series of reviews relevant to the management of antipsychotic-induced tardive dyskinesia (Table 1).

Description of the intervention

Vitamin E (tocopherol) is a lipid-soluble antioxidant, illustrated in Figure 1, that acts as a free radical scavenger and has been proposed as a treatment for neuroleptic-induced TD (Rotrosen 1996).

Figure 1. Vitamin E



How the intervention might work

Vitamin E may assist in minimising damage caused by cytotoxic free radical over production, and may prevent or decrease the severity of TD, particularly for people who have had the onset of the problem in the preceding five years (Feltner 1993; Jeste 1993).

Why it is important to do this review

Several atypical antipsychotic drugs have been produced in the last decades that claim to cause less or no TD (Lieberman 1996). These claims may or may not be true, and certainly evidence does point to the fact that thoughtful use of older generation drugs is not associated with any more problems of TD than with newer

treatments (Chouinard 2008). However, in a global context, it is likely that the less expensive and more familiar drugs - such as chlorpromazine or haloperidol - will continue to be the mainstay of treatment of people with schizophrenia (WHO Essential List 2010). Use of drugs such as these is associated with emergence of TD and, therefore, this condition will remain a problem for years to come.

Cessation or reduction of the dose of antipsychotic medication is the ideal management for TD. In clinical practice this is not always possible, not least because in many individuals such a reduction would lead to relapse. This review focuses on whether the addition of vitamin E to those already receiving antipsychotic medication is likely to help TD.

OBJECTIVES

The primary objective was to determine the clinical effects of vitamin E in people with schizophrenia or other chronic mental illness who had developed neuroleptic-induced TD.

The secondary objectives were:

1. to examine whether the effect of vitamin E was maintained as duration of follow up increased;

2. to test the hypothesis that the use of vitamin E is most effective for those with early onset TD (less than five years) (see Subgroup analysis and investigation of heterogeneity).

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials. Where a trial was described as 'double-blind' but it was implied that the study was randomised and the demographic details of each group were similar, we have included it. We have excluded quasi-randomised studies, such as those allocated by using alternate days of the week.

Types of participants

People with schizophrenia or other chronic mental illness, diagnosed by any criteria, irrespective of gender, age or nationality who:

- required the use of antipsychotics for more than three months;
- developed TD (diagnosed by any criteria at baseline and at least one other occasion) during antipsychotic treatment; and
- for whom the dose of antipsychotic medication had been stable for one month or more (the same applies for those free of antipsychotics).

Types of interventions

1. Vitamin E: any dose or means of administration

2. Placebo or no intervention

Types of outcome measures

We have defined clinical efficacy as an improvement in the symptoms of TD of more than 50%, on any scale. We grouped outcomes into short term (less than six weeks), medium term (between six weeks and six months) and long term (more than six months).

Primary outcomes

1. Tardive dyskinesia

Any improvement in the symptoms of individuals of more than 50% on any tardive dyskinesia scale - any time period.

2. Adverse effects

No clinically significant extrapyramidal adverse effects - any time period.

Secondary outcomes

1. Tardive dyskinesia (TD)

1.1 Any improvement in the symptoms of individuals on any TD scale, as opposed to no improvement.
1.2 Deterioration in the symptoms of individuals, defined as any deleterious change on any TD scale.
1.3 Average change in severity of TD during the trial period.
1.4 Average difference in severity of TD at the end of the trial.

2. General mental state changes

2.1 Deterioration in general psychiatric symptoms (such as delusions and hallucinations) defined as any deleterious change on any scale.
2.2 Average difference in severity of psychiatric symptoms at the end of the trial.

3. Acceptability of the treatment

3.1 Acceptability of the intervention to the participant group as measured by numbers of people dropping out during the trial.

4. Adverse effects

4.1 Use of any anti-parkinsonism drugs.
4.2 Average score/change in extrapyramidal adverse effects.
4.3 Acute dystonia.

5. Other adverse effects, general and specific

6. Hospital and service utilisation outcomes

6.1 Hospital admission.
6.2 Average change in days in hospital.
6.3 Improvement in hospital status (for example: change from formal to informal admission status, use of seclusion, level of observation).

7. Economic outcomes

7.1 Average change in total cost of medical and mental health care.
7.2 Total indirect and direct costs.

8. Quality of life/satisfaction with care for either recipients of care or caregivers

8.1. No significant change in quality of life/satisfaction.
8.2 Average score/change in quality of life/satisfaction.

9. Behaviour

9.1 Clinically significant agitation.
9.2 Use of adjunctive medication for sedation.
9.3 Aggression to self or others.

10. Cognitive state

10.1 No clinically important change.
10.2 No change, general and specific.

Search methods for identification of studies

Electronic searches

1. Cochrane Schizophrenia Group Trials Register (March 2010)

This register was searched using the phrase:
[(*vitamins* or *vitamin E* or *tocopherol*) in interventions of STUDY field]
This register is compiled by systematic searches of major database, handsearches and conference proceedings (see Group Module).

2. Details of previous electronic search

See Appendix 1.

Searching other resources

1. Reference searching

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

2. Personal contact

We contacted the first author of each included study for information regarding unpublished trials.

Data collection and analysis

Selection of studies

Reviewer NM inspected all abstracts of studies identified as above and identified potentially relevant reports. In addition, to ensure reliability, KSW inspected a random sample of these abstracts, comprising 10% of the total. Where disagreement occurred, we resolved this by discussion, or where there was still doubt, acquired the full article for further inspection. We acquired the full articles of relevant reports for reassessment and carefully inspected for a final decision on inclusion (see Criteria for considering studies for this review). Once we obtained the full articles, in turn NM and KSW inspected all full reports and independently decided whether they met inclusion criteria. NM and KSW were not blinded to the names of the authors, institutions or journal of publication. Where difficulties or disputes arose, we asked author JM for help and if it was impossible to decide, added these studies to those awaiting assessment and contacted the authors of the papers for clarification.

Data extraction and management

1. Extraction

Reviewer NM extracted data from all included studies. In addition, to ensure reliability, KSW independently extracted data from

a random sample of these studies, comprising 10% of the total. Again, we discussed any disagreement, documented decisions and, if necessary, contacted authors of studies for clarification. With remaining problems JM helped clarify issues and we documented those final decisions. We extracted data presented only in graphs and figures whenever possible, but included these only if two reviewers independently had the same result. We attempted to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. Where possible, we extracted data relevant to each component centre of multi-centre studies separately.

2. Management

2.1 Forms

We extracted data onto standard, simple forms.

2.2 Scale-derived data

We included continuous data from rating scales only if:
a. the psychometric properties of the measuring instrument had been described in a peer-reviewed journal (Marshall 2000); and
b. the measuring instrument was not written or modified by one of the trialists for that particular trial.

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); normally both sets of data would be available to trialists but if change scores are presented, the SD of the change is often not provided. We decided to primarily use endpoint data and only use change data if the former were not available. We combined endpoint and change data in the analysis as we used mean differences rather than standardised mean differences throughout (Deeks 2009, Chapter 9.4.5.2).

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 all data before inclusion: a) standard deviations and means are reported in the paper or obtainable from the authors; b) when a scale starts from the finite number zero, the standard deviation, when multiplied by two, is less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution (Altman 1996); c) if a scale started from a positive value (such as PANSS which can have values from 30 to 210) the calculation described above was modified to take the scale starting point into account. In these cases skew is present if 2SD>(S-S min), where S is the mean score and S min is the minimum score. Endpoint scores on scales often have a finite start and end point and these rules can be applied. When continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not. We have entered skewed data from studies of less than 200 participants in additional tables rather than into an analysis. Skewed data of means pose less of a problem if the sample size is large; if this condition was met, then we entered skewed data into syntheses.

2.5 Conversion to common measures

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).

2.6 Conversion of continuous to binary outcome measures

Where possible, efforts were made to convert outcome measures to dichotomous data. This could be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It was generally assumed that if there had been a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS, Overall 1962) or the Positive and Negative Syndrome Scale (PANSS, Kay 1986), this could be considered as a clinically significant response (Leucht 2005a; Leucht 2005b). 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 for unfavourable outcomes in such a way that the area to the left of the line of no effect indicates a favourable outcome for vitamin E. Where the outcomes were favourable, the area to the right of the line of no effect indicates a favourable outcome for vitamin E. In either instance we labelled the direction of effect for the interventions at the bottom of the relevant graph.

2.8 Summary of findings table

We used the GRADE approach to interpret findings (Schünemann 2008) and used GRADE Profiler (GRADE 2004) to import data from Review Manager 5 (RevMan 2008) to create the 'Summary of findings table 1' for the following primary and secondary outcomes considered to be critically important or important to the management of tardive dyskinesia with vitamin E (Reviewer NM was not biased by being familiar with the data).
1. Tardive dyskinesia

1.1 Improved to an important extent (ideally this be stated as in the primary outcome for the review)
1.2 Deteriorated
2. Adverse effect
2.1 Any adverse event (ideally this should be the stated primary outcome: Adverse effects: no clinically significant extrapyramidal adverse effects)
2.2 Specific adverse event
3. Quality of life
3.1 No significant change in quality of life/satisfaction
This table provides information concerning the overall quality of the evidence from the trial, the magnitude of effect of the interventions examined, and the sum of available data on all primary outcomes and the selected secondary outcomes. This summary was used to guide our conclusions and recommendations.

Assessment of risk of bias in included studies

KSW and NM independently assessed included studies for the risk of bias using the Cochrane Collaboration's 'Risk of bias' assessment tool (Deeks 2009) on the following six domains: sequence generation, allocation concealment, blinding or masking, incomplete outcome data, selective outcome reporting and other biases. For each of these six domains, we assigned a judgement regarding the risk of bias as 'yes' for free of the risk of bias, 'no' for at high risk of bias, or 'unclear' when judgements could not be reliably made due to lack of information in the report or after contacting the trial authors. We used the criteria summarised in Table 8.5.c of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2009) to make judgements, and recorded these assessments in the standard 'risk of bias' tables in RevMan 5 (RevMan 2008). For the domains of blinding or masking and for incomplete outcome reporting, we assessed the risk of bias separately for subjectively reported and for objectively ascertained outcomes. We presented these evaluations in the 'risk of bias' summary figure (Figure 2), and risk of bias summary graph (Figure 3) and discussed them further in the results section under Risk of bias in included studies. We incorporated these judgements in assessing limitations in study design for critical and important outcomes in the Summary of findings for the main comparison

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

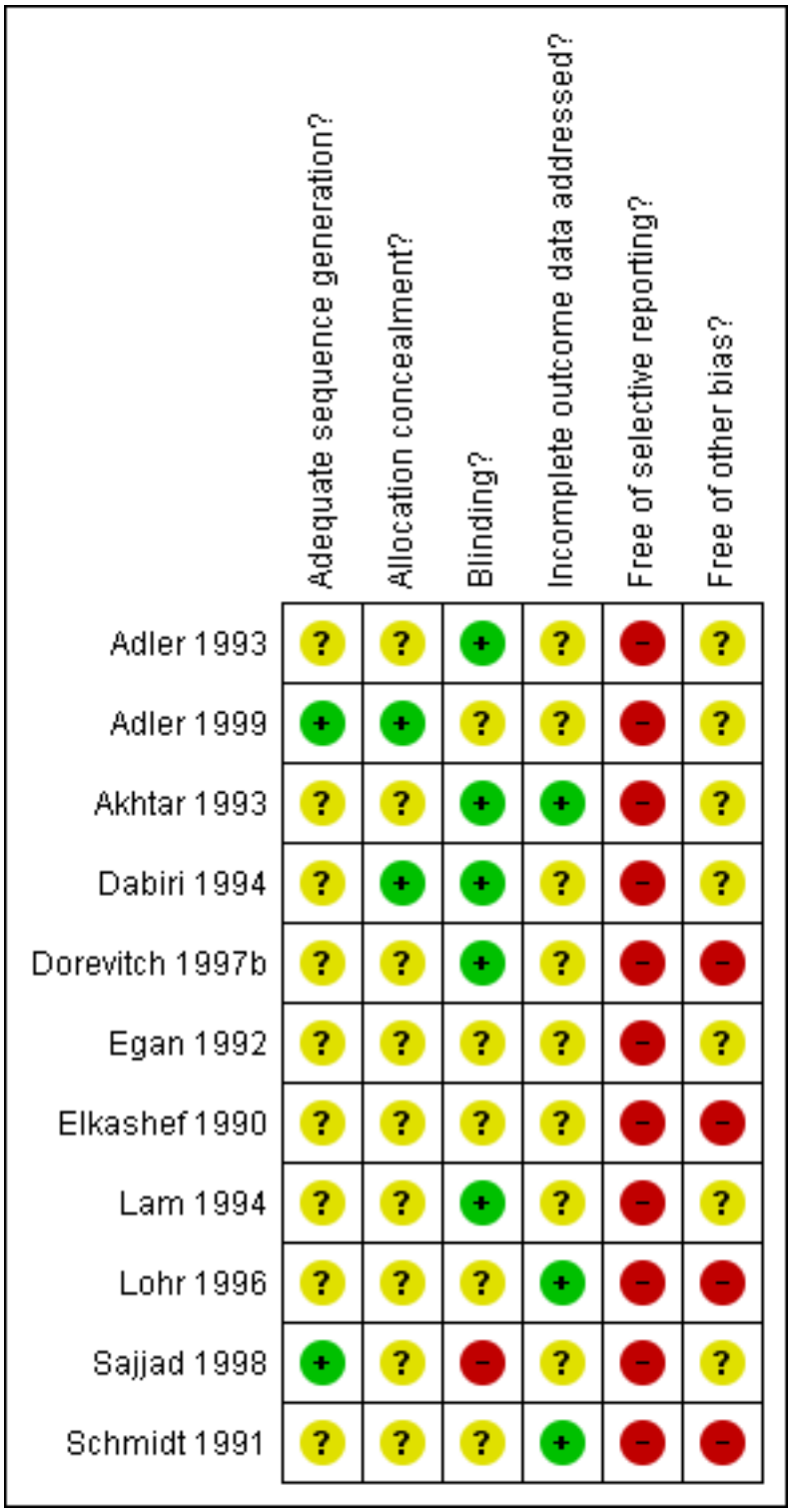
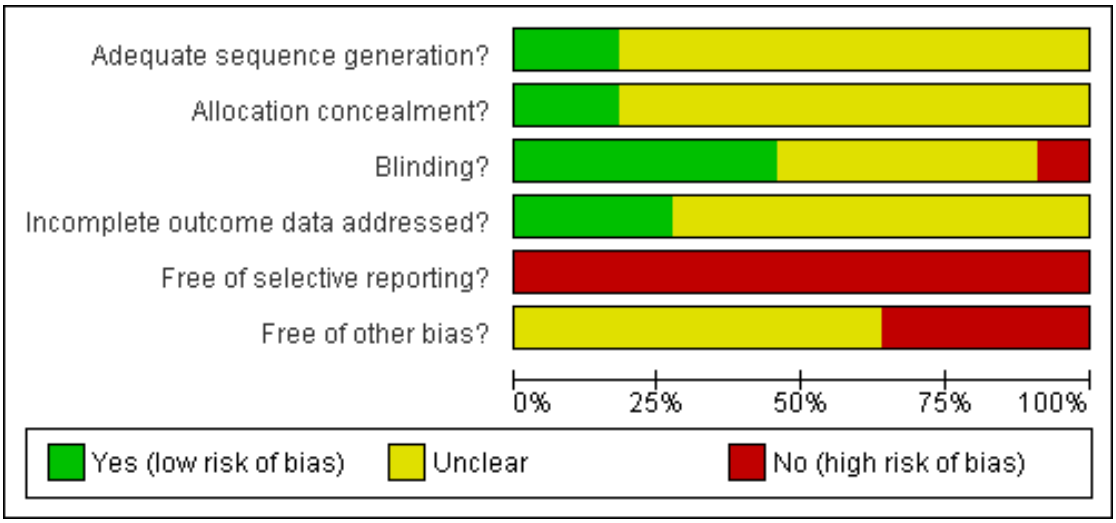


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Measures of treatment effect

1. Binary data

For binary outcomes we calculated a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI). It has been shown that RR is more intuitive (Boissel 1999) than odds ratios and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). For statistically significant results we had planned to calculate the number needed to treat to provide benefit/to induce harm statistic (NNTB/H), and its 95% confidence interval (CI) using Visual Rx (http://www.nntonline.net/) taking account of the event rate in the control group. This, however, was superseded by the Summary of findings for the main comparison and the estimates therein.

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)). However, had different scales with similar characteristics been used to measure the same outcome for comparisons, we would have calculated the SMD and transformed the weighted, pooled effect back to the units of one (or more) of the specific and familiar instruments.

Unit of analysis issues

1. Cluster trials

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

If any of the included trials had randomised participants by clusters, and if the results were adjusted for clustering, we combined the adjusted measures of effects of these cluster-randomised trials with parallel group RCTs using the generic inverse variance technique. If results had not adjusted for clustering, we would have attempted to adjust the results by multiplying the standard errors of the estimates by the square root of the design effect (where the design effect is calculated as D_{Eff} = 1 + (M - 1) ICC, where M is the average cluster size and ICC is the intra-cluster coefficient)

(Donner 2002). If the ICC was not reported nor available from the authors, we assumed it to be 0.1 (Ukoumunne 1999).

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 only use data of the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involved more than two treatment arms, if relevant, we have presented the additional treatment arms in comparisons. If data were binary we have simply added these added and combined within the two-by-two table. If data were continuous we combined data following the formula in section 7.7.3.8 (Combining groups) of the Cochrane *Handbook*. Where the additional treatment arms were not relevant, we have not reproduced these data.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up, data must lose credibility (Xia 2007). For any particular outcome should more than 20% of data be unaccounted for, we did not reproduce these data or use them within analyses. If, however, more than 20% of those in one arm of a study were lost, but the total loss was less than 20%, we marked such data with (*) to indicate that such a result may well be prone to bias.

2. Binary outcomes

We extracted data to allow an intention-to-treat analysis in which all randomised participants were analysed in the groups to which they were originally assigned. If there was a discrepancy in the number randomised and the numbers analysed in each treatment group, we calculated the percentage loss to follow-up in each group and reported this information. We sought supplementary information from trial authors such as intention to treat and per-protocol analyses data-set, or a participant flow diagram in a sufficiently detailed manner as to facilitate data retrieval. If unexplained drop-outs exceeded 20% in either group, we would have assigned the same proportion of those with the worst outcome to those lost to follow-up for dichotomous outcomes (except for mortality and adverse effects) as for those who completed the study, and assessed the impact of this in sensitivity analyses with the results of completers.

3. Continuous outcomes

For continuous outcomes, if provided and where possible, we calculated missing standard deviations from other available data such as standard errors, P, T or F values as detailed in Deeks 2009. If this was not possible, we calculated the SDs according to a validated imputation method that is based on the SDs of the other included studies (Furukawa 2006). We examined the validity of the imputations in a sensitivity analysis excluding imputed values.

3.1 Last observation carried forward

We preferred not to make any assumptions about loss to follow-up for continuous data and analysed results for those who completed the trial, since the use of methods such as the last observation carried forward (LOCF) introduce uncertainty about the reliability of the result (Leucht 2007). If LOCF data had been used in included trials, we reproduced these data and indicated that they were the result of LOCF assumptions.

Assessment of heterogeneity

1. Clinical heterogeneity

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

2. Methodological heterogeneity

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

3. Statistical heterogeneity

3.1 Visual inspection

We visually inspected the forest plots to evaluate the possibility of heterogeneity of intervention effects across trials as evidenced by outlying trials with non-overlapping confidence intervals. We also noted differences in the direction of effect estimates across trials.

3.2 Employing the I^2 statistic

We attempted to assess if significant heterogeneity was present using the Chi^2 test for homogeneity at a 10% level of significance. We used the I^2 statistic to quantify inconsistency (the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error) (Higgins 2003). The importance of the observed value of I^2 depends on i. magnitude and direction of effects and ii. strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or a CI for I^2). In general we interpreted I^2 estimates greater than or equal to 50% accompanied by a statistically significant Chi^2 statistic, as evidence of substantial levels of heterogeneity, although we acknowledge that values of I^2 ranging from 30% to 60% may also indicate substantial heterogeneity (Section 9.5.2 - Deeks 2009). When we found substantial levels of heterogeneity in the primary outcome, we explored reasons for heterogeneity (Subgroup analysis and investigation of heterogeneity). If severe heterogeneity was present (I^2 >= 75%) and could not be explained by differences across the trials in terms of clinical or methodological features or by subgroup analyses (see below), we would not have combined the trials in a meta-analysis, but presented the results in a forest plot.

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* (Deeks 2009). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We did not use funnel plots for outcomes where there were 10 or fewer studies, or where all studies were of similar sizes. In other cases, where funnel plots were possible, we sought statistical advice in their interpretation.

Data synthesis

We understand that there is no closed argument for preference for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us and the random-effects model takes into account differences between studies even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the random-effects model. It puts added weight onto small studies which often are the most biased ones. Depending on the direction of effect, these studies can either inflate or deflate the effect size. Therefore, we chose the fixed-effect model for all analyses. If the I^2 statistic indicated substantial heterogeneity (values 50% or greater), we presented the results using fixed-effect and random-effects meta-analysis and assessed the impact of both models on the direction and precision of the effect estimate.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

We anticipated one sub-group analysis to test the hypothesis that the use of vitamin E is most effective for those with early onset TD (less than five years). We had hoped to present data for this subgroup for the primary outcomes.

2. Investigation of heterogeneity

In the presence of substantial heterogeneity, we had hoped to undertake one pre-stated subgroup analysis for the primary outcomes in this review to test the hypothesis that vitamin E is more effective for those with an onset of TD within five years.

We also explored the possibility that unanticipated clinical or methodological differences contributed to significant statistical heterogeneity by removing trials with these characteristics from the meta-analysis, to assess if this reduced the I^2 estimate to below 50%. If substantial heterogeneity was reduced, we reported this but presented the forest plot with the data from these trials as well. We stated hypothesis regarding these in the discussion and hoped to evaluate them more fully in future versions of the review.

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

Sensitivity analysis

1. Implication of randomisation

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

2. Assumptions for lost binary data

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

Where assumptions had to be made regarding missing SDs data (see Dealing with missing data), we compared the findings on primary outcomes when we used our assumption compared with complete data only. We undertook a sensitivity analysis testing

how prone results were to change when 'complete' data only were compared to the imputed data using the above assumption. If there was a substantial difference, we have reported results and discussed them, but continue to employ our assumption.

RESULTS

Description of studies

Please see Characteristics of included studies, Characteristics of excluded studies, and Characteristics of studies awaiting classification.

Results of the search

The 2010 update search identified 69 studies. Agreement about which reports may have been randomised was 100% and we selected and ordered 36 of the original reports. Two of these reports are new studies to this review (Adler 1999; Sajjad 1998) and we have added one to those awaiting assessment (Kar-Ahmadi 2002). Eleven studies are now included in this review (Adler 1993; Adler 1999; Akhtar 1993; Dabiri 1994; Dorevitch 1997b; Egan 1992; Elkashef 1990; Lam 1994; Lohr 1996; Sajjad 1998; Schmidt 1991).

Included studies

Overall the review now includes 11 studies published between 1990 and 1999.

1. Methods

All studies were stated to be randomised and double blind. For further details please see sections below on allocation and blinding.

2. Design

All included studies presented a parallel longitudinal design. Five of the 11 studies used a cross-over design with two periods (Dorevitch 1997b; Egan 1992; Elkashef 1990; Lam 1994; Schmidt 1991). We had considered this as likely when embarking on the review and have used only the data from before the first cross-over for the reasons outlined above (Unit of analysis issues).

3. Duration

Most studies were of short duration (less than 13 weeks) but four had a follow-up period longer than five months (Adler 1993; Adler 1999; Dorevitch 1997b; Sajjad 1998). All the other included studies were randomised, double blind, controlled trials of short duration. Four trials employed washout periods of two weeks.

4. Participants

Participants, now totaling 427 people, were mostly men in their 50s, with diagnoses of various chronic psychiatric disorders, but mainly schizophrenia. All had neuroleptic-induced tardive dyskinesia (TD) diagnosed using Schooler and Kanes research diagnostic criteria, except Schmidt 1991, who did not report any criteria for the diagnosis of TD. The number of participants ranged from 10 to 158 (median 23).

5. Setting

Most trials were conducted in hospital. The studies themselves were from around the world, with six conducted in the USA and one each in Hong Kong (Lam 1994), India (Akhtar 1993), Israel (Dorevitch 1997b), Switzerland (Schmidt 1991) and the UK (Sajjad 1998).

6. Interventions

6.1 Vitamin E

The vitamin E dose ranged from 1200 IU/day to 1600 IU/day, with the exception of Sajjad 1998, in which the dose was 600 IU/day.

6.2 Comparison group

In most of the studies a placebo was used as a comparison group, with no further details given. In one study the comparison group was given nothing (Sajjad 1998), and in another trial the placebo was a sesame oil placebo gelcap (Lohr 1996).

7. Outcomes

7.1 General

Some outcomes were presented in graphs, inexact P values of differences, or a statement of significant or non-significant difference. This made it impossible to acquire raw data for synthesis. Some continuous outcomes could not be extracted due to missing number of participants or missing means, standard deviations, or standard errors. All included studies used the LOCF strategy for the intention-to-treat analysis of dichotomous data.

7.2 Scales used to measure the TD symptoms

We have shown details of the only scale that provided usable data below. We have provided reasons for exclusions of data under 'Outcomes' in the Characteristics of included studies table.

7.2.1 Abnormal Involuntary Movement Scale

The AIMS (Guy 1976) is a 12-item scale consisting of a standardised examination followed by questions rating the orofacial, extremity and trunk movements, as well as three global measurements. Each of these 10 items can be scored from 0 (none) to 4 (severe). Two additional items assess the dental status. The AIMS ranges from 0-40, with higher scores indicating greater severity.

7.2.2 Tardive Dyskinesia Rating Scale

The TDRS (Simpson 1970) is a 34-item scale consisting of measurement of the movements around the orofacial region, neck, trunk and extremities. Each of these items can be scored from 0 (absent) to 5 (severe). This scale ranges from 10 to 102, with higher scores indicating greater severity.

Excluded studies

Peet 1993 and Spivak 1992 were not randomised and we have therefore excluded them. We excluded Dorevitch 1997a, a randomised study, because it was not a clinical trial. We have excluded Ricketts 1995 because it is a cross-over design that does not present data from the first period. After two years of unfruitful attempts to contact authors for further details, we have had to exclude a further three randomised studies which reported no usable data (Junker 1992; Lohr 1987; Shriqui 1992).

Awaiting assessment

We have not, as yet, obtained the report of Kar-Ahmadi 2002; it may also be in Farsi. We hope to include it in the next update of this review.

Risk of bias in included studies

Please refer to Figure 2 and Figure 3 for graphical overviews of the risk of bias in the included studies.

Allocation

Only Adler 1999 was really clear about the means of allocation, although we also rated the other new study to this review (Sajjad 1998) as being of higher quality reporting. Most other studies were not explicit about how allocation was achieved other than using the word "randomized". Adler 1993 allocated people into vitamin E and placebo groups in a ratio of 3:2.

Blinding

Although all studies were conducted on a double-blind basis, none explicitly described how this was undertaken and tested the blindness of raters, clinicians and trial participants. We have, however, rated Adler 1993, Akhtar 1993, Dabiri 1994, Dorevitch 1997b and Lam 1994 as being of higher quality because they stated that the trial was double blind and specifically that either the raters or the raters and the participants were blinded. All the other studies gave no further details other than stating that they were double blinded. In Sajjad 1998 the blind was broken after one month.

Incomplete outcome data

The trialists excluded three people from Adler 1993 and four from Lam 1994 because of lack of post-baseline data. Three studies had a greater than 30% loss to follow-up (Adler 1993; Lohr 1996; Sajjad 1998). In all cases, however, we tried to ensure that every person randomised was analysed.

Selective reporting

The majority of data in this review originates from published reports. We have had no opportunity to see protocols of these trials to compare the outcomes reported in the full publications with what was measured during the conduct of the trial. As a result, we feel that there may be an element of selective reporting that we could perpetuate in this review and that this bias would favour vitamin E. Attempts to contact authors of trials for additional data were unsuccessful. Furthermore, none of the trials reported on key expected outcomes: mortality and quality of life.

Other potential sources of bias

All studies had small or very small sample sizes. Five of the studies used a cross-over design (Dorevitch 1997b; Elkashef 1990; Lam 1994; Egan 1992; Schmidt 1991). Four of the studies had the drugs used in the trials provided by pharmaceutical companies (Dorevitch 1997b; Elkashef 1990; Lohr 1996; Schmidt 1991), and in five studies no details of funding were given (Akhtar 1993; Dabiri 1994; Egan 1992; Lam 1994; Sajjad 1998).

Effects of interventions

See: **Summary of findings for the main comparison** VITAMIN E compared with PLACEBO for neuroleptic-induced tardive dyskinesia

1. Comparison 1. Vitamin E versus placebo

1.1 TD symptoms

We had chosen 'any improvement in TD symptoms of more than 50% on any TD scale - any time period' as a primary outcome (Analysis 1.1). Although the data we found in trials did not fit this exactly we feel that the outcome 'not improved to a clinically important extent' fits best with what we had hoped to find.

1.1.1 Not improved to a clinically important extent

The overall results for 'clinically relevant improvement' found no benefit of vitamin E against placebo (6 trials, 256 people, RR 0.95 CI 0.89 to 1.02).

1.1.2 Not any improvement

For the outcome of 'any improvement in TD symptoms', again added across all time periods, we found no difference between vitamin E and placebo (7 trials, 311 people, RR 0.86 CI 0.75 to 1.00, Analysis 1.2).

1.1.3 Average endpoint scores

TD symptoms were also measured on the continuous AIMS and TDRS scales (see above). No consistent pattern, suggesting either beneficial or harmful effect, emerges from these data (Analysis 1.3; Analysis 1.4).

1.1.4 Deterioration of symptoms

People allocated to placebo showed more deterioration of their symptoms compared with those on vitamin E (5 trials, 98 people, RR 0.4 CI 0.2 to 0.9, Analysis 1.5).

1.2 Any adverse effect

There was no difference in the incidence of 'any adverse effect' (9 trials, 203 people, RR 1.3 CI 0.5 to 3.2, Analysis 1.6). We had pre-specified 'No clinically significant extrapyramidal adverse effects - any time period' as a primary outcome. No study reported this as a finding.

1.3 Mental state

Only two trials reported data and were combined (Adler 1999; Akhtar 1993). We found no difference between vitamin E and placebo for a measure of psychiatric symptoms (BPRS, 2 trials, 136 people, WMD 0.72 CI -2.47 to 3.90, Analysis 1.7).

1.4 Leaving the study early

Using vitamin E did not significantly increase the chances of a person leaving the study early (medium term overall ~20% loss to follow up, 6 trials, 173 people, RR 1.3 CI 0.7 to 2.3, Analysis 1.8).

1.5 Subgroup analysis

It was not possible to evaluate whether those with recent onset TD responded differently to those with more established problems, since no trial reported data for groups with different durations of TD that could be extracted for separate analyses. Any effects that vitamin E may have did not clearly change in relation to duration of follow-up.

1.6 Heterogeneity

Data were homogeneous.

1.7 Sensitivity analyses

1.7.1 Implication of randomisation

We aimed to include trials in a sensitivity analysis if they were described in some way as to imply randomisation. As all studies were stated to be randomised we have not undertaken this sensitivity analysis.

1.7.2 Assumptions for lost binary data

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

DISCUSSION

Summary of main results

1. The search

This area of research does not seem to be active. The 2010 update has identified additional data, but all trials predate the year 2000. This could be because of reasons such as less concern with TD, or less emergence of the problem in research-active communities because of more thoughtful use of antipsychotic drugs or loss of faith in vitamin E as a potential treatment.

2. Few data

Only a little over 400 people have been involved in placebo-controlled trials of vitamin E for TD. It is possible that real, and important, effects have not been highlighted because of the necessarily wide CIs of the findings. Many outcomes were not measured at all (see Overall completeness and applicability of evidence), including one of our pre-stated outcome measures. We may have been overambitious in hoping for some of these outcomes in TD trials but simple reporting of satisfaction with care or quality of life still does not seem too demanding and does remain of interest.

3. Comparison 1. Vitamin E versus placebo

3.1 TD symptoms

Results of this review do not suggest that vitamin E improves symptoms of TD. This applies to different crude binary outcomes as well as two different continuous measures. The recent addition of Adler 1999, a larger nine-centre trial, did not produce any significant changes in this review. The finding that people allocated to placebo showed more deterioration of their symptoms compared with those allocated to vitamin E is interesting (5 trials, 98 people, RR 0.4 CI 0.2 to 0.9) and generates some hope that the experimental treatment may have a preventative role. This is worthy of further investigation.

3.2 Adverse effects

There is no evidence that vitamin E has any significant adverse effects.

3.3 Mental state

Only two trials recorded outcome on mental state. Both used the BPRS scale, but this involved only asking 136 people regarding this important outcome. There was no suggestion that vitamin E had any more effect on mental state than placebo.

3.4 Leaving the study early

It is always unclear what leaving the study early means. It could be to do with the participant not accepting treatment for a series of reasons, or of participants finding the trial intolerable. It also could be a function of a trial design in which willing participants are still asked to leave because of some degree of protocol violation. In any event, between 20% and 30% of people left the study early, but this was not different for those allocated to either group.

Overall completeness and applicability of evidence

1. Completeness

No outcomes in this review involve large numbers of people. Some are general measures and more subtle findings are not recorded. For example, we identified a few data on the outcome of 'any adverse effect' but none on 'use of any anti-parkinsonism drugs' or 'no clinically significant extrapyramidal adverse effects - any time period'- the latter being one of our pre-stated primary outcomes. There were no data on hospital and service utilisation outcomes, economic outcomes, quality of life/satisfaction with care for either recipients of care or caregivers, behavior or cognitive response.

2. Applicability

All trials were hospital based but were nevertheless on people who would be recognisable in everyday care. The intervention in question - vitamin E - is readily accessible and most outcomes understandable in terms of clinical practice. Should vitamin E have had important effects the findings may well have been applicable.

Quality of the evidence

The largest trial in this area randomised only 158 people. A trial of this size is unable to detect subtle, yet important differences due to vitamin E with any confidence. In order to detect a 20% difference between groups, probably about 150 people are need in each arm of the study (alpha 0.05, beta 0.8). Overall the quality of reporting of these trials was poor (see Figure 2). Allocation concealment was not described, generation of the sequence was not explicit, studies were not clearly blinded, we are unsure if data are incomplete or selectively reported or if other biases were operating. The small trial size, along with the poor reporting of trials, would be associated with an exaggeration of effect of the experimental treatment (Jni 2001) if an effect had been detected. This is only evident for the outcome of 'deterioration' where there is indeed an effect favouring the vitamin E group. This interesting finding may be real - but could equally be a function of biases or of chance.

Potential biases in the review process

1. Missing studies

Every effort is made to identify relevant trials. However, these studies are all small and it is likely that we have failed to identify other studies of limited power. It is likely that such studies would also not be in favour of the vitamin E group. If they had been so, it is more likely that they would have been published in accessible

literature. We do not, however, think it likely that we have failed to identify large relevant studies.

2. Introducing bias

This review group has now updated this review several times. We have tried to be balanced in our appraisal of the evidence but could have inadvertently introduced bias. We welcome comments or criticisms. New methods and innovations now make it possible to report data where, in the past, we could not report data at all or had to report data in a different way. We think the Summary of findings table 1 to be a valuable innovation - but problematic to those not 'blind' to the outcome data. It is possible to 'cherry pick' significant findings for presentation in this table. We have tried to decrease the chance of doing this by asking a new reviewer (NS) to select outcomes relevant for this table before becoming familiar with the data.

Agreements and disagreements with other studies or reviews

The only other relevant quantitative review we know of is the previous Cochrane review (Soares 1999). This update expands and improves this review but does not substantially change the findings or the conclusions.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with TD

There is some suggestion that vitamin E supplementation may alter the course of TD for those with schizophrenia and these findings are in keeping with other types of studies (Hawkins 1989). These data are very weak and should be interpreted with considerable caution. If offered vitamin E supplementation to offset symptoms of TD a person taking antipsychotic medication would be justified in asking for evidence, and encouraging generation of new better evidence by volunteering to help with a well-designed evaluative study.

2. For clinicians

TD is such a disfiguring condition. This review generates a theory that vitamin E could be a preventative measure for TD. The data in this review do not justify routine use of vitamin E. It would be reasonable, however, to ask people with schizophrenia to complicate their treatment plan if the use of vitamin E was to generate data better than seen in this review. There is a real place for clinician-driven research, with prescription within the context of a randomised trial and routine data collection on outcomes of relevant to people with TD and their clinicians.

3. Policy makers or managers

This is one of the largest in the series of TD Cochrane reviews. No evidence is convincing that addition of another drug helps with the symptoms of TD. There are, however, many unanswered questions in this area. This unattractive adverse effect is caused, to a greater or lesser extent, by antipsychotic drugs. Clinicians and researchers should feel responsible enough to continue to try to help it. Those compiling guidance could encourage supportive activity and more research into this neglected area.

Implications for research

1. General

The power of this review would have been greatly enhanced by better reporting of data. For example, only one study made explicit how randomisation was undertaken (Adler 1999). We realise that much of the work for these trials predates CONSORT, which was first published in 1996 (Begg 1996), and that it is only too easy to judge studies of the past by standards of today. Future studies, however, should report to a much higher standard.

2. Specific

Well-designed randomised controlled trials, involving a large number of participants over protracted periods of time, are needed if we are to see if vitamin E could have a role in prevention and treatment of TD.

2.1. Use of cross-over design

Trialists find it difficult to identify people with both TD and schizophrenia to participate in trials (Schmidt 1991). Randomised cross-over design is used in the hope of improving the power of the study to find outcomes of interest. This design initially asks participants to be randomised to one of the experimental interventions, and then, at a pre-specified time, to be crossed over to the treatment that they did not at first receive. Conditions with a more stable time course than TD are better suited for cross-over studies (Fleiss 1984). Further difficulties are the carry-over effect. At the very least vitamin E is dissolved in fat and probably high levels from the doses given in trials may well persist in the body for long periods after discontinuation. Unless cross-over studies include a mid-study washout period (where the person is free of treatment before starting the next arm of the study), any effect of vitamin E may continue into the second half placebo arm of the trial - the 'carry-over effect'. Also, carry-over may involve the

re-growth or retreat of neuroreceptors. This slow re-balancing, if started, could continue long after all traces of intervention drugs are gone, so physiological half life of the experimental treatment may not be the only variable to consider when thinking though the issues of carry-over. Tardive dyskinesia is also an unstable condition and people with TD may not remain compliant with medication. All these factors make the arguments for not using cross-over methodology strong, despite the initial attraction (Armitage 1991; Fleiss 1984; Pocock 1983).

2.2. Sample size calculation

Only one of the studies included in this review mentioned how they calculated the sample size (Adler 1999). However, the results suggest that larger sample size should be used to provide more precise estimates of effect.

2.3. Length of study

Three studies included in this review (Adler 1993; Adler 1999; Sajjad 1998) used the intervention for more than five months. TD, however, is a chronic condition of insidious onset, the severity of which fluctuates spontaneously (APA 1992). Even if vitamin E has a swift effect, which is unlikely, it is the long-term outcomes that must be considered of most clinical value.

2.4. Outcomes

Scale-derived data do have their place. Trials most commonly used the AIMS scale. This is a very widely used tool to measure the severity of symptoms of those who have TD. The use of this scale to measure change as a result of treatment is, however, problematic (Bergen 1984). It is therefore important that a scale is validated for measuring changes secondary to treatment in those with TD. In addition, many of the outcomes we initially desired when we started this review have not been investigated. We have reconsidered these outcomes in case they were too ambitious and tried to tailor them to a real-world pragmatic trial design (see Table 2).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Adler 1993

Methods	Allocation: 'random allocation', ratio of 3 vitamin E: 2 placebo. Double blind: no further details. Duration: 36 weeks (preceded by 2 week washout). Setting: outpatients, USA. Design: parallel.
Participants	Diagnosis: schizophrenia, depression (no criteria) and neuroleptic-induced TD (Research Diagnostic Criteria, Schooler and Kane). N = 40*. 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	TD symptoms: AIMS. Leaving the study early.
Notes	* initial report at 8 weeks, N = 29. ** three people left the study in the first 2 weeks and could not be considered in the analysis - original group unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	'random allocation', ratio of 3 vitamin E: 2 placebo.
Allocation concealment?	Unclear risk	Double blind: no further details.
Blinding? All outcomes	Low risk	Both rater and patients were blinded.
Incomplete outcome data addressed? All outcomes	Unclear risk	"One patient dropped out after 2 weeks due to non-compliance" "Two patients developed significant medical illnesses ? unrelated to study treatment", "By prior design, treatment for the first 8 patients was terminated after 8 weeks." (page 869). No further details

Adler 1993 (*Continued*)

Free of selective reporting?	High risk	Not all expected outcomes reported.
Free of other bias?	Unclear risk	Small sample size.

Adler 1999

Methods	Allocation: randomisation co-ordinated centrally, allocation with "biased coin" method, stratified by site, age, and baseline TD. 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: 5 female, 153 male. Age: average ~ 50 yrs (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). Compliance assessed by pill counts
Outcomes	TD symptoms: AIMS. Mental state: BPRS. Leaving the study early.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Randomisation coordinated centrally.
Allocation concealment?	Low risk	Allocation with "biased coin" method, stratified by site, age, and baseline TD
Blinding? All outcomes	Unclear risk	Double blind: no further details.
Incomplete outcome data addressed? All outcomes	Unclear risk	"Of the 51 subjects who did not complete 1 year, most changed their minds about participating (n = 18), moved too far away from a site to continue in the study (n = 11), or were classified as "whereabouts un-

Adler 1999 (*Continued*)

		known" (n = 8)" (page 838). No further details
Free of selective reporting?	High risk	Not all expected outcomes reported.
Free of other bias?	Unclear risk	Small sample size.

Akhtar 1993

Methods	Allocation: 'random allocation', no further details. Double blind: no further details. Duration: 4 weeks (preceded by 2 weeks washout). Setting: outpatients, India. Design: parallel group.
Participants	Diagnosis: psychiatric disorder (Spitzer criteria) and neuroleptic-induced TD (Schooler and Kane criteria). N = 32. Sex: 14 female, 18 male. Age: average ~ 55 yrs (SD ~ 12).
Interventions	1. Vitamin E: dose increasing over 1 week to 1200 IU/day. N = 17. 2. Placebo. N = 15. Stable neuroleptic medication: dose average (CPE) vitamin E = 323 mg/day (SD 249); placebo = 187 mg/day (SD 189)
Outcomes	TD symptoms: TDRS. Mental state: BPRS. Adverse effects. Leaving the study early.
Notes	Authors contacted but did not reply.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	'random allocation', no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? All outcomes	Low risk	Double blind: both investigators and raters were blinded.
Incomplete outcome data addressed? All outcomes	Low risk	There were no dropouts.
Free of selective reporting?	High risk	Not all expected outcomes reported.

Akhtar 1993 (*Continued*)

Free of other bias?	Unclear risk	Small sample size, no information about funding.

Dabiri 1994

Methods	Allocation: 'random allocation', no further details. Double blind: rater blind. Duration: 12 weeks. Setting: outpatients, USA. Design: parallel group.
Participants	Diagnosis: psychiatric disorder (no criteria) and neuroleptic-induced TD (Research diagnosis, Schooler and Kane criteria). N = 12. Sex: 5 female, 6 male, 1 not specified. Age: average 51 yrs; range 35-68.
Interventions	1. Vitamin E: dose increasing over 2 weeks to 1200 IU/day. N = 6. 2. Placebo. N = 6. Stable neuroleptic medication: dose average (CPE) 444 mg/day; range 200-1000
Outcomes	TD symptoms: AIMS. Leaving study early. Adverse effects.
Notes	Authors contacted but did not reply.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	'random allocation', no further details.
Allocation concealment?	Low risk	"patients were randomly divided into treatment and placebo groups by a non-clinical staff member" (page 925)
Blinding? All outcomes	Low risk	Double blind: raters blinded.
Incomplete outcome data addressed? All outcomes	Unclear risk	"one patient on placebo group left after 2 weeks because of diarrhoea" (page 925). No details were provided about this patient
Free of selective reporting?	High risk	Not all expected outcomes reported.

Dabiri 1994 (*Continued*)

Free of other bias?	Unclear risk	No information about funding, very small sample size.

Dorevitch 1997b

Methods	Allocation: 'randomized', no further details. Double blind: raters blinded. Duration: 20 weeks. Setting: inpatients, Israel. Design: cross-over.
Participants	Diagnosis: DSM-III-R diagnosis of schizophrenia or schizoaffective disorder, research diagnostic criteria for TD (Schooler and Kane criteria). N = 40. Sex: 17 female, 23 male. Age: average 64.4 yrs (SD 8.5); range 32-80.
Interventions	1. Vitamin E: dose increasing over 4 weeks to 1600 IU/day. N = 18. 2. Placebo. N = 22. Stable neuroleptic medication: dose average (CPE) 594 mg/day; range 75-5000
Outcomes	TD symptoms: AIMS. Leaving study early. Adverse effects. Mental state: BPRS.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Randomised - no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? All outcomes	Low risk	Double blind: raters blinded.
Incomplete outcome data addressed? All outcomes	Unclear risk	Two patients did not complete the study. Both patients were from the placebo phase of the placebo-vitamin E sequence group. One died while choking on food and the second as the result of a traffic accident (page 115). Some of the patients were not measured at all times (page 115), no further details were given about these patients

Dorevitch 1997b (*Continued*)

Free of selective reporting?	High risk	Not all expected outcomes reported.
Free of other bias?	High risk	Vitamin E and placebo supplied by industry (Teva Pharmaceuticals); very small sample size; cross-over design

Egan 1992

Methods	Allocation: 'random allocation', no further details. Double blind: no further details. Duration: 6 weeks each period (no washout). Setting: outpatients, USA. Design: two period cross-over.
Participants	Diagnosis: schizophrenia, schizoaffective, bipolar disorder, depression (DSM-III-R) and neuroleptic-induced TD (Schooler and Kane criteria). N = 21. Sex: 8 female, 13 male. Age: average vitamin E 41 yrs (SD 13.4); placebo 39 yrs (SD 8.8)
Interventions	1. Vitamin E: dose increasing over 4 weeks to 1600 IU/day. N = 12. 2. Placebo. N = 9. Stable neuroleptic medication: dose average (CPE) 1946 mg/day (no SD, N = 15)
Outcomes	TD symptoms: AIMS. Mental symptoms: NSRS, PSAS. Side effects. Leaving study early.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	'random allocation', no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? All outcomes	Unclear risk	Double blind: no further details.
Incomplete outcome data addressed? All outcomes	Unclear risk	Three patients were not included in the data analysis: one dropped out and two had inconsistent vitamin E blood levels (page 775). No further details were given

Egan 1992 (*Continued*)

Free of selective reporting?	High risk	Not all expected outcomes reported.
Free of other bias?	Unclear risk	Cross-over design; very small sample size; no information about funding

Elkashef 1990

Methods	Allocation: 'random allocation', no further details. Double blind: no further details. Duration: 4 weeks each period (preceded by 2 weeks washout). Setting: outpatients, USA. Design: two period cross-over.
Participants	Diagnosis: schizophrenia or schizoaffective disorder (DSM-III-R) and neuroleptic-induced TD (Schooler and Kane criteria). N = 10. Sex:3 female, 7 male. Age: average 56.6 yrs (SD 12). History: no description of chronicity of TD.
Interventions	1. Vitamin E: dose increasing over 3 weeks to 1200 IU/day. N = 5. 2. Placebo. N = 5. Stable neuroleptic medication: dose not specified.
Outcomes	TD symptoms: AIMS. Mental state: BPRS. Side effects. Leaving study early.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	'random allocation', no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? All outcomes	Unclear risk	Double blind: no further details.
Incomplete outcome data addressed? All outcomes	Unclear risk	"Two patients did not complete the study, one because of noncompliance and the other experienced substantial side effects (nausea) while taking placebo" (page 505). No further details

Elkashef 1990 (*Continued*)

Free of selective reporting?	High risk	Not all expected outcomes reported.
Free of other bias?	High risk	Vitamin E and placebo supplied by industry (Roche); very small sample size; cross-over design

Lam 1994

Methods	Allocation: 'random allocation', no further details. Double blind: no further details. Duration: 6 weeks each period (preceded by 2 weeks washout). Setting: in hospital, Hong Kong. Design: two period cross-over.
Participants	Diagnosis: schizophrenia (DSM-III-R) and neuroleptic-induced TD (Schooler and Kane criteria). N = 16. Sex: 8 female, 8 male. Age: average 61.8 yrs (SD 12.8 yrs). History: no history of chronicity of TD.
Interventions	1. Vitamin E: dose increasing over 3 weeks to 1200IU/day. N = 8. 2. Placebo. N = 8. Stable neuroleptic medication: dose average (CPE) vitamin E = 80 mg/day (SD 74); placebo = 568 mg/day (SD 776)
Outcomes	TD symptoms: AIMS. Mental state: BPRS. Side effects. Leaving study early.
Notes	4 people left study early (no information about allocation); reasons, death, deterioration of symptoms of schizophrenia, bacillary dysentery (all stated not to be related to treatment), poor compliance. Authors contacted and replied, no more information available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	'random allocation', no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? All outcomes	Low risk	Double blind: raters blinded.

Lam 1994 (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear risk	One patient died of unrelated medical illness, one contracted bacillary dysentery and was dropped from the trial, and one had poor compliance and refused to continue medication (page 113). No further details given
Free of selective reporting?	High risk	Not all expected outcomes reported.
Free of other bias?	Unclear risk	Cross-over design; very small sample size; no information about funding

Lohr 1996

Methods	Allocation: 'random allocation' - no further details. Double blind: no further details. Duration: 8 weeks. Setting: outpatients, USA. Design: parallel.
Participants	Diagnosis: schizophrenia, bipolar disorder, unipolar depression (no specified criteria) and neuroleptic-induced TD (Schooler and Kane criteria). N = 55. Sex: 2 female, 33 male, 20 not informed. Age: average ~ 50 yrs (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	TD symptoms: mAIMS. Leaving the study early.
Notes	Authors contacted but did not reply.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	'random allocation', no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? All outcomes	Unclear risk	Double blind: no further details.

Lohr 1996 (*Continued*)

Incomplete outcome data addressed? All outcomes	Low risk	2 developed manic symptoms necessitating medical changes, and 18 were non-compliant with either the vitamin E or the psychotropic medication. These 20 patients, who did not differ significantly from the remaining 35 patients in terms of age, gender, or diagnosis, were dropped from the study (page 168)
Free of selective reporting?	High risk	Not all expected outcomes reported.
Free of other bias?	High risk	Vitamin E and placebo supplied by industry (Hoffman-La Roche); small sample size

Sajjad 1998

Methods	Allocation: 'random allocation' patients randomly divided into 2 groups using StatView, a computer statistics programme. Double blind: no further details. Duration: 7 months. Setting: inpatients, UK. Design: parallel.
Participants	Diagnosis: neuroleptic-induced TD (Schooler and Kane criteria). N = 20. Sex: 8 female, 12 male. Age: average ~ 68 yrs (SD ~ 9).
Interventions	1. Vitamin E: dose increasing over 1 week to 600 IU/day. N = 11. 2. Placebo. N = 9. Stable neuroleptic medication for 2 weeks: dose average (CPE) vitamin E 706 mg/day (SD 680); placebo 376 mg/day (SD 242)
Outcomes	TD symptoms: AIMS. Adverse effects. Leaving the study early.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'random allocation' patients randomly divided into 2 groups using StatView, a computer statistics programme

Sajjad 1998 (*Continued*)

Allocation concealment?	Unclear risk	No further details.
Blinding? All outcomes	High risk	Double blind: rater blind. However, after one month, the rater performed statistical tests and, hence, the blindness was not maintained
Incomplete outcome data addressed? All outcomes	Unclear risk	Eleven patients were assigned to the treatment group: 1 was excluded as she refused to take the medication, 1 excluded after the first month due to developing diarrhoea, 2 excluded in third month and 2 more in the fourth month. Nine patients assigned to the control group: 1 left as his phenothiazine medication was increased, 1 excluded in the third month. 12 patients completed the trial: 5 in the treatment group and seven in the control group (pages 149-51)
Free of selective reporting?	High risk	Not all expected outcomes reported.
Free of other bias?	Unclear risk	Very small sample size; no information about funding.

Schmidt 1991

Methods	Allocation: 'random allocation', no further details. Double blind: no further details. Duration: 2 weeks each period (no washout). Setting: outpatients, Switzerland. Design: two period cross-over.
Participants	Diagnosis: schizophrenia, depression, schizoaffective psychoses (no criteria) and neuroleptic-induced TD (no criteria). N = 23. Sex: 12 female, 11 male. Age: average ~47 yrs (SD ~17).
Interventions	1. Vitamin E: dose 1200 IU/ day. N = 13. 2. Placebo. N = 10. Stable neuroleptic medication: dose unspecified.
Outcomes	TD symptoms: AIMS. Adverse effects. Leaving study early.
Notes	

Schmidt 1991 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	'random allocation', no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? All outcomes	Unclear risk	Double blind: no further details.
Incomplete outcome data addressed? All outcomes	Low risk	13 patients initially randomised to vitamin E: two left before the end of the study (1 died and the other withdrew); 10 patients initially randomised to placebo: two left before the end of the study (1 died and the other had his treatment modified) (page 204)
Free of selective reporting?	High risk	Not all expected outcomes reported.
Free of other bias?	High risk	Vitamin E and placebo supplied by industry (C Muller); very small sample size; cross-over design

Scales
AIMS - Abnormal Involuntary Movement Scale
NSRS - Negative Symptom Rating Scale
PSAS - Psychiatric Symptoms Assessment Scale
SAS - Simpsom-Angus Scale for Extrapyramidal Side Effects
TDRS - Tardive Dyskinesia Rating Scale
Others
CPE - Chlorpromazine equivalents
DSM-III-R- Diagnostic Statistical Manual of Mental Disorders
TD - tardive dyskinesia
BPRS: British Psychiatric Rating Scale
mAIMS:Adverse and Involuntary Movement Scale
SD: Standard Deviation

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

Study	Reason for exclusion
Dorevitch 1997a	Allocation: randomised. Participants: people with tardive dyskinesia and schizophrenia. N = 10. Interventions: vitamin E supplementation vs placebo. Outcomes: serum creatine phosphokinase levels, no clinical data
Junker 1992	Allocation: randomised. Participants: people with both tardive dyskinesia and schizophrenia. N = 25. Interventions: vitamin E supplementation vs no vitamin E supplementation. Outcomes: movement disorders, not possible to extract any data Authors contacted twice in 1995 and failed to reply.
Lohr 1987	Allocation: randomised, cross-over design. Participants: people with both tardive dyskinesia and schizophrenia. N = 15. Interventions: vitamin E supplementation vs no vitamin E supplementation. Outcomes: movement disorders, not possible to extract data from the first period Authors contacted twice in 1995 and failed to reply.
Peet 1993	Allocation: not randomised, cohort study.
Ricketts 1995	Allocation: quasi-randomised, cross-over study. Participants: people with both tardive dyskinesia and mental retardation, not schizophrenia
Salmasi 2009	Allocation: randomised, double-blind, placebo-controlled study. Participants: people with schizophrenia, but not tardive dyskinesia. Interventions: vitamin E supplementation vs placebo. Outcomes: insulin resistance in patients treated with olanzapine
Shriqui 1992	Allocation: randomised, cross-over design. Participants: people with both tardive dyskinesia and schizophrenia. N = 27. Interventions: vitamin E supplementation vs no vitamin E supplementation. Outcomes: movement disorders, not possible to extract data from the first period Authors contacted twice in 1995 and failed to reply.
Spivak 1992	Allocation: not randomised, cohort study.

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

Kar-Ahmadi 2002

Methods	Allocation: 'randomized' no further details. Blindness: double - no further details. Duration: 6 weeks. Setting: inpatients. Design: parallel.
Participants	Diagnosis: neuroleptic-induced TD. N = 30. Sex: unknown. Age: unknown.
Interventions	1. Vitamin E: dose 600 mg/ day. N = 15. 2. Placebo. N = 15. Stable neuroleptic medication: dose unspecified.
Outcomes	TD symptoms: AIMS.
Notes	A copy of this study was not available in the British Library

AIMS: Abnormal Involuntary Movement Scale

DATA AND ANALYSES

Comparison 1. VITAMIN E versus PLACEBO

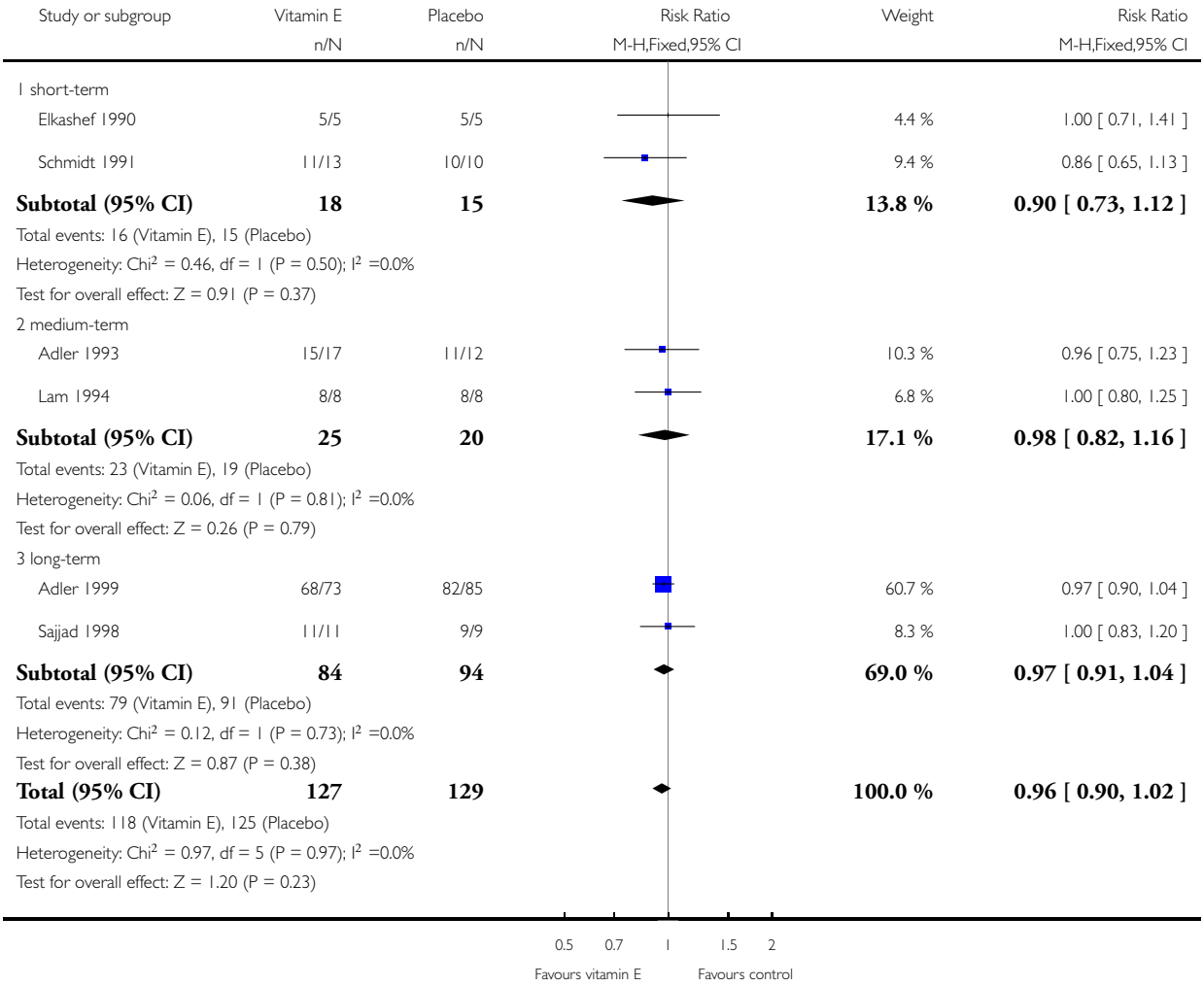
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 1. Not improved to a clinically important extent	6	256	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.90, 1.02]
1.1 short-term	2	33	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.73, 1.12]
1.2 medium-term	2	45	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.82, 1.16]
1.3 long-term	2	178	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.91, 1.04]
2 Tardive dyskinesia: 2. Not any improvement	7	311	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.75, 1.00]
2.1 short-term	2	33	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.14, 1.47]
2.2 medium-term	3	100	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.58, 0.95]
2.3 long-term	2	178	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.82, 1.15]
3 Tardive dyskinesia: 3a. Average endpoint score (AIMS, low score = best)	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 short-term	2	27	Mean Difference (IV, Fixed, 95% CI)	3.12 [0.72, 5.51]
3.2 medium-term	3	93	Mean Difference (IV, Fixed, 95% CI)	-1.02 [-2.59, 0.56]
3.3 long-term	2	129	Mean Difference (IV, Fixed, 95% CI)	-1.23 [-2.51, 0.05]
4 Tardive dyskinesia: 3b. Average endpoint score - short term (TDRS, low score = best)	1	32	Mean Difference (IV, Fixed, 95% CI)	-2.10 [-6.35, 2.15]
5 Tardive dyskinesia: 4. Deterioration of symptoms	5	98	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.16, 0.90]
5.1 short-term	2	33	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.20, 3.03]
5.2 medium-term	2	45	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.07, 1.22]
5.3 long-term	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.03, 1.52]
6 Any adverse effect	9	203	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.51, 3.24]
6.1 short-term	3	65	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.20, 3.55]
6.2 medium-term	5	118	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.40, 5.92]
6.3 long-term	1	20	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.11, 54.87]
7 Mental state: Average endpoint score (BPRS, low = best)	2	136	Mean Difference (IV, Fixed, 95% CI)	0.72 [-2.47, 3.90]
8 Leaving study early	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 short-term	3	65	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.11, 2.00]
8.2 medium-term	6	173	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.72, 2.30]
8.3 long-term	3	215	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.69, 1.54]

Analysis 1.1. Comparison 1 VITAMIN E versus PLACEBO, Outcome 1 Tardive dyskinesia: 1. Not improved to a clinically important extent.

Review: Vitamin E for neuroleptic-induced tardive dyskinesia

Comparison: 1 VITAMIN E versus PLACEBO

Outcome: 1 Tardive dyskinesia: 1. Not improved to a clinically important extent

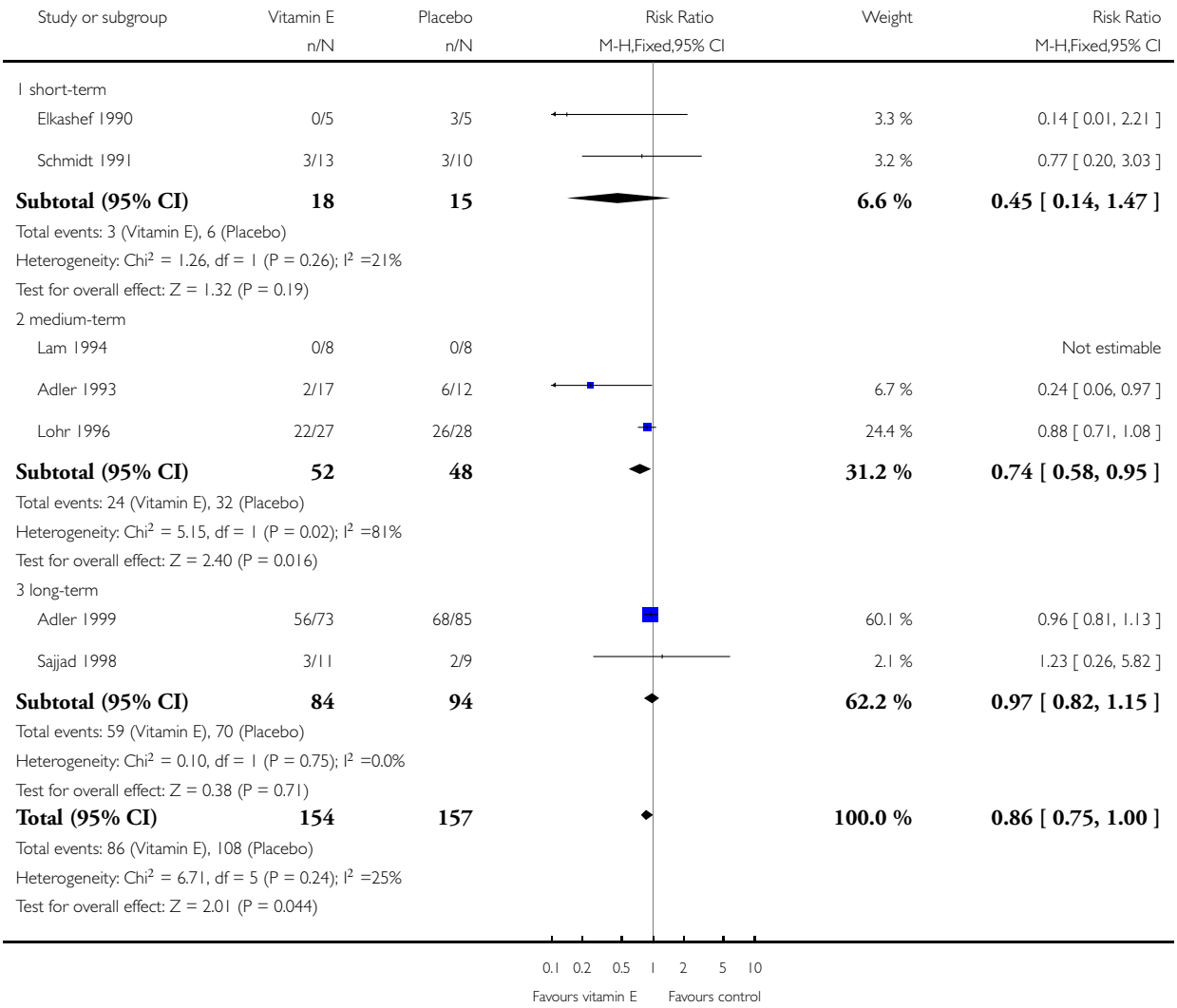


Analysis 1.2. Comparison 1 VITAMIN E versus PLACEBO, Outcome 2 Tardive dyskinesia: 2. Not any improvement.

Review: Vitamin E for neuroleptic-induced tardive dyskinesia

Comparison: 1 VITAMIN E versus PLACEBO

Outcome: 2 Tardive dyskinesia: 2. Not any improvement

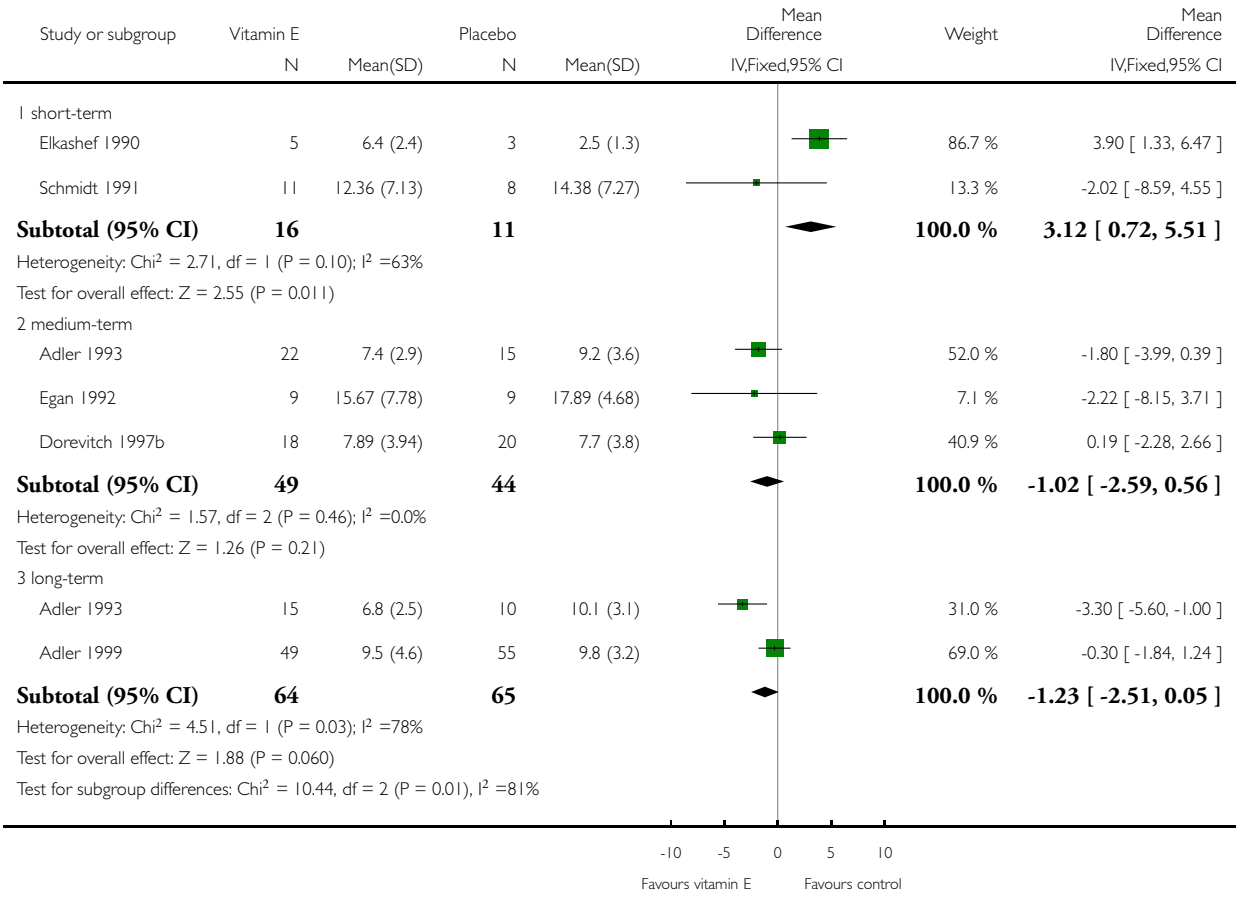


Analysis 1.3. Comparison 1 VITAMIN E versus PLACEBO, Outcome 3 Tardive dyskinesia: 3a. Average endpoint score (AIMS, low score = best).

Review: Vitamin E for neuroleptic-induced tardive dyskinesia

Comparison: 1 VITAMIN E versus PLACEBO

Outcome: 3 Tardive dyskinesia: 3a. Average endpoint score (AIMS, low score = best)



Analysis 1.4. Comparison 1 VITAMIN E versus PLACEBO, Outcome 4 Tardive dyskinesia: 3b. Average endpoint score - short term (TDRS, low score = best).

Review: Vitamin E for neuroleptic-induced tardive dyskinesia

Comparison: 1 VITAMIN E versus PLACEBO

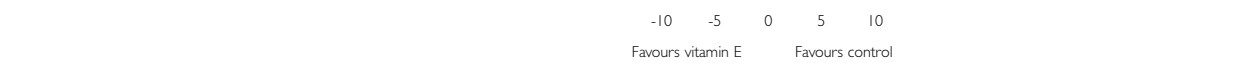
Outcome: 4 Tardive dyskinesia: 3b. Average endpoint score - short term (TDRS, low score = best)

Study or subgroup	Vitamin E N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Akhtar 1993	17	55.8 (7.1)	15	57.9 (5.1)		100.0 %	-2.10 [-6.35, 2.15]
Total (95% CI)	**17**		**15**			**100.0 %**	**-2.10 [-6.35, 2.15]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.97 (P = 0.33)

Test for subgroup differences: Not applicable



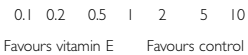
Analysis 1.5. Comparison 1 VITAMIN E versus PLACEBO, Outcome 5 Tardive dyskinesia: 4. Deterioration of symptoms.

Review: Vitamin E for neuroleptic-induced tardive dyskinesia

Comparison: 1 VITAMIN E versus PLACEBO

Outcome: 5 Tardive dyskinesia: 4. Deterioration of symptoms

Study or subgroup	Vitamin E n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 short-term					
Elkashef 1990	0/5	0/5			Not estimable
Schmidt 1991	3/13	3/10		24.8 %	0.77 [0.20, 3.03]
Subtotal (95% CI)	**18**	**15**		**24.8 %**	**0.77 [0.20, 3.03]**
Total events: 3 (Vitamin E), 3 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.37 (P = 0.71)					
2 medium-term					
Lam 1994	0/8	0/8			Not estimable
Adler 1993	2/17	5/12		42.9 %	0.28 [0.07, 1.22]
Subtotal (95% CI)	**25**	**20**		**42.9 %**	**0.28 [0.07, 1.22]**
Total events: 2 (Vitamin E), 5 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.69 (P = 0.090)					
3 long-term					
Sajjad 1998	1/11	4/9		32.2 %	0.20 [0.03, 1.52]
Subtotal (95% CI)	**11**	**9**		**32.2 %**	**0.20 [0.03, 1.52]**
Total events: 1 (Vitamin E), 4 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.55 (P = 0.12)					
Total (95% CI)	**54**	**44**		**100.0 %**	**0.38 [0.16, 0.90]**
Total events: 6 (Vitamin E), 12 (Placebo)					
Heterogeneity: Chi^2 = 1.54, df = 2 (P = 0.46); I^2 =0.0%					
Test for overall effect: Z = 2.19 (P = 0.029)					

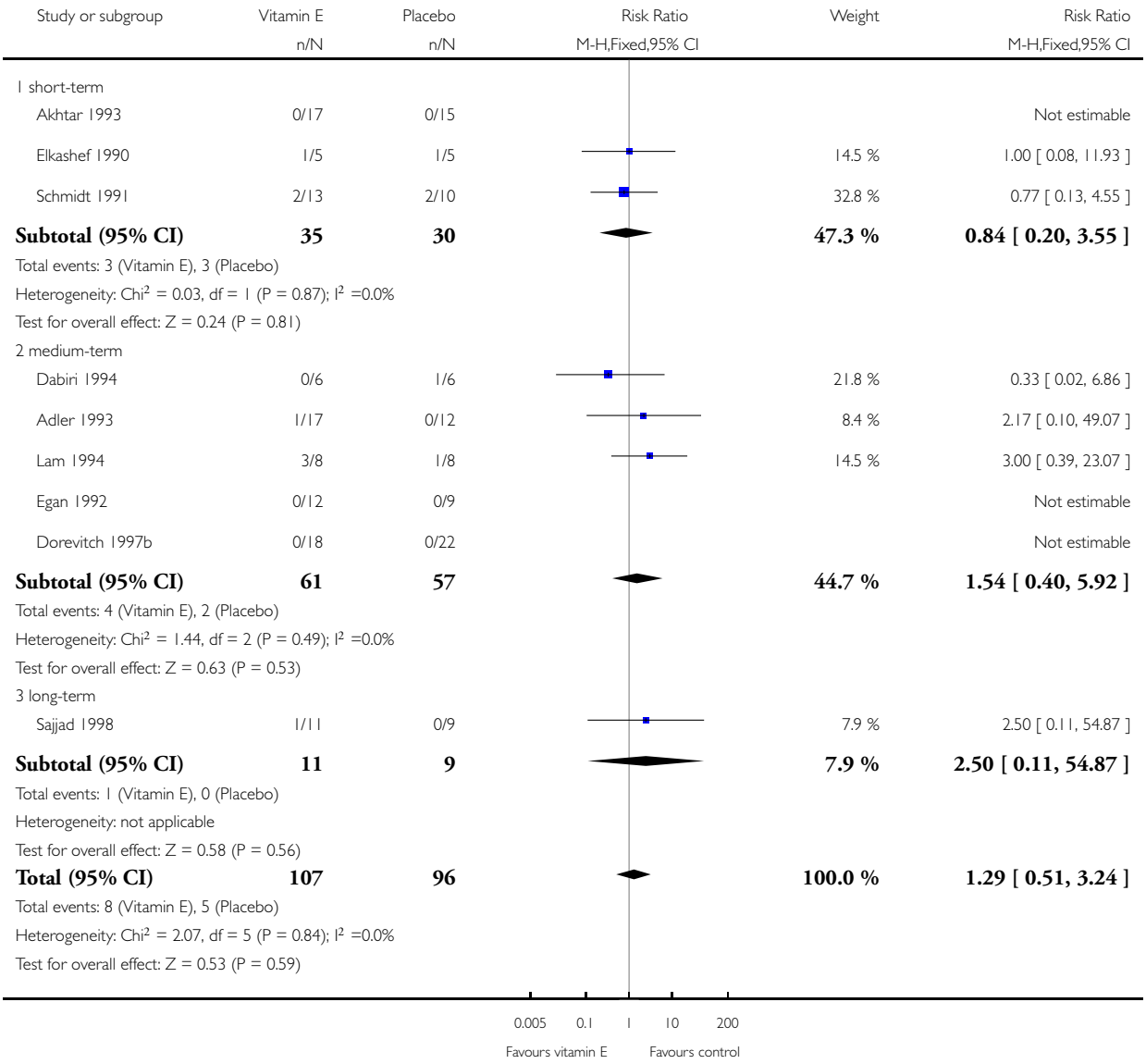


Analysis 1.6. Comparison 1 VITAMIN E versus PLACEBO, Outcome 6 Any adverse effect.

Review: Vitamin E for neuroleptic-induced tardive dyskinesia

Comparison: 1 VITAMIN E versus PLACEBO

Outcome: 6 Any adverse effect



Analysis 1.7. Comparison 1 VITAMIN E versus PLACEBO, Outcome 7 Mental state: Average endpoint score (BPRS, low = best).

Review: Vitamin E for neuroleptic-induced tardive dyskinesia

Comparison: 1 VITAMIN E versus PLACEBO

Outcome: 7 Mental state: Average endpoint score (BPRS, low = best)

Study or subgroup	Vitamin E N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Adler 1999	49	31.9 (8.9)	55	30.7 (10.2)		75.4 %	1.20 [-2.47, 4.87]
Akhtar 1993	17	33.76 (7.93)	15	34.53 (10.3)		24.6 %	-0.77 [-7.20, 5.66]
Total (95% CI)	**66**		**70**			**100.0 %**	**0.72 [-2.47, 3.90]**

Heterogeneity: Chi² = 0.27, df = 1 (P = 0.60); I² =0.0%

Test for overall effect: Z = 0.44 (P = 0.66)

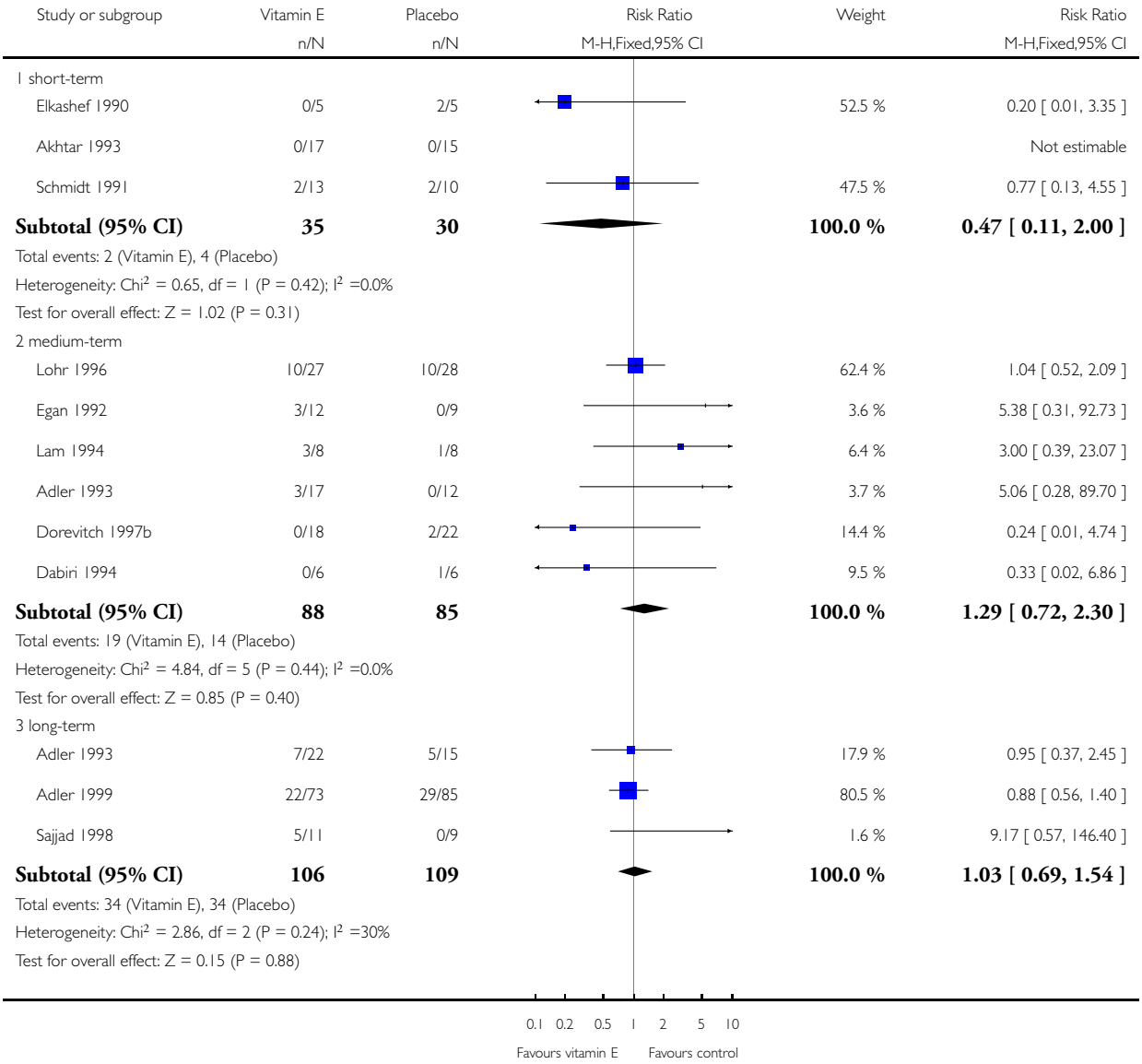
Test for subgroup differences: Not applicable

Analysis 1.8. Comparison 1 VITAMIN E versus PLACEBO, Outcome 8 Leaving study early.

Review: Vitamin E for neuroleptic-induced tardive dyskinesia

Comparison: 1 VITAMIN E versus PLACEBO

Outcome: 8 Leaving study early



ADDITIONAL TABLES

Table 1. Other reviews in the series

Interventions	Reference
Anticholinergic medication	Soares 2000c
Benzodiazepines	McGrath 2000b; Umbrich 2003
Calcium channel blockers	Soares 2000b; Soares 2001c
Cholinergic medication	McGrath 2000d; Tammenmaa 2002
Gamma-aminobutyric acid agonists	Soares 2000d; Soares 2001b
Miscellaneous treatments	McGrath 2000a; Soares-Weiser 2003
Neuroleptic reduction and/or cessation and neuroleptics	McGrath 2000c
Non-neuroleptic catecholaminergic drugs	Lyra da Silva 1997
Vitamin E	This review

Table 2. Suggestions for design of future study

Methods	Allocation: randomised, with sequence generation and concealment of allocation clearly described. Blindness: double, tested. Duration: 12 months beyond end of intervention at least. Raters: independent.
Participants	People with antipsychotic-induced tardive dyskinesia.* Age: any. Sex: both. History: any. N = 300.**
Interventions	1. Vitamin E: 1600 IU/day. N = 150. 2. Placebo: N = 150.
Outcomes	Tardive dyskinesia: any clinically important improvement in TD, any improvement, deterioration.*** Adverse effects: no clinically significant extrapyramidal adverse effects - any time period***, use of any antiparkinsonism drugs, other important adverse events. Leaving the study early. Service outcomes: admitted, number of admissions, length of hospitalisation, contacts with psychiatric services. Compliance with drugs. Economic evaluations: cost-effectiveness, cost-benefit. General state: relapse, frequency and intensity of minor and major exacerbations. Quality of life: binary measure.

Table 2. Suggestions for design of future study (*Continued*)

	Distress among relatives: binary measure. Burden on family: binary measure.
Notes	* This could be diagnosed by clinical decision. If funds were permitting all participants could be screened using operational criteria, otherwise a random sample should suffice ** Size of study with sufficient power to highlight about a 10% difference between groups for primary outcome. *** Primary outcome. The same applies to the measure of primary outcome as for diagnosis. Not everyone may need to have operational criteria applied if clinical impression is proved to be accurate

APPENDICES

Appendix 1. Search methods for identification of studies on the previous version of the review (January 2001)

1. Electronic searching
1.1 Biological Abstracts (January 1982 to January 2001) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:
[and ((tardive near (dyskine* or diskine*) or (abnormal near movement* near disorder*) or (involuntar* near movement*))]
This downloaded set of reports was handsearched for possible trials and researched, within the bibliographic package ProCite, with the phrase [vitamin or tocopherol*]
1.2 The Cochrane Schizophrenia Group's Register (January 2001) was searched using the phrase:
[vitamin or tocopherol*]
1.3 Embase (January 1980 to January 2001) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:
[and ((tardive dyskinesia in thesaurus -subheadings, prevention, drug therapy, side effect and therapy) or (neuroleptic dyskinesia in thesaurus -all subheadings) or (tardive or dyskines*) or (movement* or disorder*) or (abnormal or movement* or disorder*))]
This downloaded set of reports was handsearched for possible trials and researched, within the bibliographic package ProCite, with the phrase [vitamin or tocopherol*]
1.4 LILACS (January 1982 to January 2001) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:
[and ((tardive or (dyskinesia* or diskinesia*)) or (drug induced movement disorders in thesaurus))]
This downloaded set of reports was handsearched for possible trials and researched, within the bibliographic package ProCite, with the phrase [vitamin or tocopherol*]
1.5 Medline (January 1966 to January 2001) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:
[and ((movement-disorders in MeSH / explode all subheadings) or (anti-dyskinesia-agents in MeSH / explode all subheadings) or (dyskinesia-drug-induced in MeSH / explode all subheadings) and
(psychosis in MeSH / explode all subheadings) or (schizophrenic disorders in MeSH / explode all subheadings) or (tardive near (dyskine* or diskine*)) or (abnormal* near movement* near disorder*) or (involuntar* near movement*))]
This downloaded set of reports was hand searched for possible trials and researched, within the bibliographic package ProCite, with the phrase [vitamin or tocopherol*]
1.6 PsycLIT (January 1974 to September 1998) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:
[and ((explode movement-disorders in DE) or (explode tardive-dyskinesia in DE) or (tardive near (dyskine* or diskine*) or (abnormal* near movement* near disorder*) or (involuntar* near movement*))]

This downloaded set of reports was hand searched for possible trials and researched, within the bibliographic package ProCite, with the phrase [vitamin or tocopherol*]
1.7 SCISEARCH - Science Citation Index (1997)
Each of the included studies was sought as a citation on the SCISEARCH database. Reports of articles that had cited these studies were inspected in order to identify further trials.
2. Reference searching
The references of all identified studies were also inspected for more studies.
3. Personal contact
The first author of each included study was contacted for information regarding unpublished trials.

Appendix 2. Methods of 2001 version of this review

Criteria for considering studies for this review
Types of studies
All relevant randomised controlled trials.

Types of participants
People with schizophrenia or other chronic mental illness, diagnosed by any criteria, irrespective of gender, age or nationality who:
1. Required the use of antipsychotics for more than three months
2. Developed tardive dyskinesia (diagnosed by any criteria at baseline and at least one other occasion) during antipsychotic treatment; and
3. For whom the dose of antipsychotic medication had been stable for one month or more (the same applies for those free of antipsychotics).

Types of interventions
1. Vitamin E: any dose or means of administration.
2. Placebo or no intervention.

Types of outcome measures
Clinical efficacy was defined as an improvement in the symptoms of TD of more than 50%, on any scale, after at least six weeks of intervention.

The outcomes of interest were as follows:

1. Symptoms of tardive dyskinesia
1.1 The number of people per treatment group that did not show an improvement in the symptoms of individuals of more than 50% on any TD scale.
1.2 The number of people per treatment group that did not show any improvement in the symptoms of individuals on any TD scale, as opposed to some improvement,
1.3 Deterioration in the symptoms, defined as any deleterious change on any TD scale.
1.4 Any adverse effect, other than deterioration of symptoms of TD, as reported in the trials.
1.5 Average change in severity of TD during the trial period.
1.6 Average severity of TD at the end of the trial.

2. General mental state changes
2.1 Deterioration in general psychiatric symptoms (such as delusions and hallucinations) defined as any deleterious change on any scale.
2.2 Average severity of psychiatric symptoms at the end of the trial.

3. Acceptability of the treatment
Acceptability of the intervention to the participant group as measured by number of people dropping out during the trial.

Three time periods for reporting of outcomes were pre-stated - short term (less than 6 weeks), medium term (between 6 weeks and 6 months) and long term (over 6 months).

Search methods for identification of studies
1. Electronic searching
1.1 Biological Abstracts (January 1982 to January 2001) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:

[and ((tardive near (dyskine* or diskine*) or (abnormal near movement* near disorder*) or (involuntar* near movement*))]

This downloaded set of reports was handsearched for possible trials and researched, within the bibliographic package ProCite, with the phrase [vitamin or tocopherol*]

1.2 The Cochrane Schizophrenia Group's Register (January 2001) was searched using the phrase:

[vitamin or tocopherol*]

1.3 Embase (January 1980 to January 2001) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:

[and ((tardive dyskinesia in thesaurus -subheadings, prevention, drug therapy, side effect and therapy) or (neuroleptic dyskinesia in thesaurus -all subheadings) or (tardive or dyskines*) or (movement* or disorder*) or (abnormal or movement* or disorder*))]

This downloaded set of reports was handsearched for possible trials and researched, within the bibliographic package ProCite, with the phrase [vitamin or tocopherol*]

1.4 LILACS (January 1982 to January 2001) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:

[and ((tardive or (dyskinesia* or diskinesia*)) or (drug induced movement disorders in thesaurus))]

This downloaded set of reports was handsearched for possible trials and researched, within the bibliographic package ProCite, with the phrase [vitamin or tocopherol*]

1.5 Medline (January 1966 to January 2001) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:

[and ((movement-disorders in MeSH / explode all subheadings) or (anti-dyskinesia-agents in MeSH / explode all subheadings) or (dyskinesia-drug-induced in MeSH / explode all subheadings) and
(psychosis in MeSH / explode all subheadings) or (schizophrenic disorders in MeSH / explode all subheadings) or (tardive near (dyskine* or diskine*)) or (abnormal* near movement* near disorder*) or (involuntar* near movement*))]

This downloaded set of reports was hand searched for possible trials and researched, within the bibliographic package ProCite, with the phrase [vitamin or tocopherol*]

1.6 PsycLIT (January 1974 to September 1998) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:

[and ((explode movement-disorders in DE) or (explode tardive-dyskinesia in DE) or (tardive near (dyskine* or diskine*) or (abnormal* near movement* near disorder*) or (involuntar* near movement*))]

This downloaded set of reports was hand searched for possible trials and researched, within the bibliographic package ProCite, with the phrase [vitamin or tocopherol*]

1.7 SCISEARCH - Science Citation Index (1997)
Each of the included studies was sought as a citation on the SCISEARCH database. Reports of articles that had cited these studies were inspected in order to identify further trials.

2. Reference searching
The references of all identified studies were also inspected for more studies.

3. Personal contact
The first author of each included study was contacted for information regarding unpublished trials.

Data collection and analysis
[For definitions of terms used in this, and other sections, please refer to the Glossary.]

1. Selection of reports and studies
KSW and JM inspected every report identified by the search, independently, to see if the study was likely to be relevant. Where resolving disagreement by discussion was not possible, the full article was obtained. The reviewers then inspected these articles, independently, to assess their relevance to this review. Again, where disagreements could not be resolved by discussion the article was added to those awaiting assessment and the authors of the study were contacted for clarification for ambiguous or missing descriptions of the methodology.

2. Assessment of methodological quality
The reviewers also evaluated the quality of all included trials independently of one another. A rating was given for each trial based on the three quality categories as described in the Cochrane Collaboration Handbook (Clarke 2000). Only trials that stated to be randomised (category A or B of the Handbook) were included in this review.

3. Data extraction
Data were independently extracted by KSW and JM. When disputes arose resolution was attempted by discussion. When this was not possible and further information was necessary to resolve the dilemma, data were not entered and this outcome of the trial was added to the list of those awaiting assessment. Outcomes are assessed using continuous (for example changes on a behaviour scale), categorical (for example, one of three categories on a behaviour scale, such a 'little change', 'moderate change' or 'much change') or dichotomous measures (for example, either 'no important changes' or 'important changes' in a persons behaviour). Currently RevMan does not support categorical data so they were presented only in the text of the review.

4. Data synthesis
4.1 Intention to treat analysis
Data were excluded from studies where more than 50% of participants in any group were lost to follow up. For all events, in studies with less than 50% dropout rate, people leaving early were considered to have had the negative outcome, except for the event of death.

4.2 Binary data
For binary outcomes a standard estimation of the relative risk (RR) and its 95% confidence interval (CI) was calculated. The weighted number needed to treat or harm statistic (NNT, NNH), and its 95% confidence interval (CI), was also calculated (http://www.mango3d.cwc.net/vsx.htm). If heterogeneity was found (see section 5) a random effects model was used.

4.3 Continuous data
4.3.1 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, the following standards are applied to all data before inclusion: (i) standard deviations and means were reported in the paper or were obtainable from the authors; (ii) when a scale started from the finite number zero, the standard deviation, when multiplied by two, was less than the mean (as otherwise the mean was unlikely to be an appropriate measure of the centre of the distribution, (Altman 1996); (iii) if a scale started from a positive value (such as PANSS which can have values from 30 to 210) the calculation described above in (ii) was modified to take the scale starting point into account. In these cases skewness is present if 2SD>(S-Smin), where S is the mean score and Smin is the minimum score. Endpoint scores on scales often have a finite start and end point and these rules can be applied to them. When continuous data are presented on a scale which includes a possibility of

negative values (such as change on a scale), there is no way of telling whether data is non-normally distributed (skewed) or not. It is thus preferable to use scale end point data, which typically cannot have negative values. If end point data were not available, the reviewers used change data, but they were not subject to a meta-analysis, and were reported in the 'Additional data' tables, as were non-normally distributed end point data.

4.3.2 Summary statistic: for continuous outcomes a weighted mean difference (WMD) between groups was estimated. Again, if heterogeneity was found (see section 5) a random effects model was used.

4.3.3 Valid scales: continuous data from rating scales were included only if the measuring instrument had been described in a peer-reviewed journal (Marshall 2000) and the instrument was either a self report or completed by an independent rater or relative (not the therapist).

4.3.4 Endpoint versus change data
Where possible endpoint data were presented and if both endpoint and change data were available for the same outcomes then only the former were reported in this review.

5. Test for heterogeneity
A Mantel-Haenszel chi-square test was used, as well as visual inspection of graphs, to investigate the possibility of heterogeneity. A significance level less than 0.10 was interpreted as evidence of heterogeneity. If heterogeneity was found the data were re-analysed using a random effects model to see if this made a substantial difference. If it did, the studies responsible for heterogeneity were not added to the main body of homogeneous trials, but summated and presented separately and reasons for heterogeneity investigated.

6. Addressing publication bias
Data from all included studies were entered into a funnel graph (trial effect against trial size) in an attempt to investigate the likelihood of overt publication bias (Egger 1997).

7. Sensitivity analyses
The effect of including studies with high attrition rates was analysed in a sensitivity analysis.

8. General
Where possible, reviewers entered data in such a way that the area to the left of the line of no effect indicated a favourable outcome for vitamin E.

WHAT'S NEW

Last assessed as up-to-date: 19 July 2010.

Date	Event	Description
5 October 2011	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 2, 1995

Review first published: Issue 1, 1999

Date	Event	Description
13 April 2011	Amended	Contact details updated.
19 January 2011	New citation required but conclusions have not changed	substantial update, conclusions not substantially changed
21 July 2010	New search has been performed	New trials added (Adler 1999; Sajjad 1998), text rewritten. These weakened, but did not substantially change results
11 November 2009	Amended	Contact details updated.
26 April 2008	Amended	Converted to new review format.
13 August 2001	New citation required and conclusions have changed	Substantive amendment
9 November 2000	Amended	Reformatting
23 September 1999	Amended	Reformatted
12 July 1996	Amended	First version of review

CONTRIBUTIONS OF AUTHORS

Karla Soares-Weiser - protocol writing, searching, trial selection, data extraction and assimilation, report writing.

Nicola Maayan - data extraction, summary of findings table.

John McGrath - protocol writing, searching, trial selection, data extraction and assimilation, report writing.

DECLARATIONS OF INTEREST

None known.

KSW is a professional systematic reviewer and has received grants from Eli Lilly, USA.

JJM is a member of the following advisory boards: Janssen-Cilag Australia, Eli Lilly Australia, Lundbeck Australia. In addition JJM has been a co-investigator on studies of neuroleptic medications produced by the following companies: Astra, Janssen-Cilag, Eli Lilly, Zeneca (ICI), Sandoz and Pfizer. The same companies have provided travel and accommodation expenses for JJM to attend relevant investigator meetings and scientific symposia. No funds have been paid directly to JJM. Payments related to participation in drug trials and board attendance has been paid to a Government-audited trust account to support schizophrenia research.

SOURCES OF SUPPORT

Internal sources

- Enhance Reviews Ltd, UK.
- Queensland Health, Australia.
- Universidade Federal de Sao Paulo, Brazil.

External sources

- CAPES - Ministry of Education, Brazil.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol as published with this review has evolved over time. The 2001 version is reproduced in Appendix 2. The revisions of protocol are in line with the development of RevMan and in keeping with Cochrane guidance. We think the revision has greatly improved and enhanced this review. We do not think, however, that it has materially affected our conduct of the review or interpretation of the results.

INDEX TERMS

Medical Subject Headings (MeSH)

Antipsychotic Agents [*adverse effects]; Dyskinesia, Drug-Induced [*drug therapy; etiology]; Psychotic Disorders [drug therapy]; Randomized Controlled Trials as Topic; Schizophrenia [drug therapy]; Vitamin E [*therapeutic use]; Vitamins [*therapeutic use]

MeSH check words

Humans