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[Intervention Review]

Vitamin E for antipsychotic-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

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

Search methods

We searched the Cochrane Schizophrenia Group Trials Register (July 2015 and April 2017), 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 antipsychotic-induced TD and schizophrenia who remained on their antipsychotic medication and had been randomly allocated to either vitamin E or to a placebo, no intervention, or any other 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 left early had no improvement. We assessed risk of bias and created a 'Summary of findings' table using GRADE.

Main results

The review now includes 13 poorly reported randomised trials (total 478 people), all participants were adults with chronic psychiatric disorders, mostly schizophrenia, and antipsychotic-induced TD. There was no clear difference between vitamin E and placebo for the outcome of TD: not improved to a clinically important extent (6 RCTs, N = 264, RR 0.95, 95% CI 0.89 to 1.01, low-quality evidence). However, people allocated to placebo may show more deterioration of their symptoms compared with those given vitamin E (5 RCTs, N = 85, RR

0.23, 95% CI 0.07 to 0.76, low-quality evidence). There was no evidence of a difference in the incidence of any adverse effects (9 RCTs, N = 205, RR 1.21, 95% CI 0.35 to 4.15, very low-quality evidence), extrapyramidal adverse effects (1 RCT, N = 104, MD 1.10, 95% CI -1.02 to 3.22, very low-quality evidence), or acceptability of treatment (measured by participants leaving the study early) (medium term, 8 RCTs, N = 232, RR 1.07, 95% CI 0.64 to 1.80, very low-quality evidence). No trials reported on social confidence, social inclusion, social networks, or personalised quality of life, outcomes designated important to patients. 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 antipsychotic-induced tardive dyskinesia

Review question

Is vitamin E useful for treating an unpleasant side effect of taking antipsychotics - tardive dyskinesia - in people with schizophrenia or other similar mental illnesses?

Background

People with schizophrenia often hear voices and see things (hallucinations) and have strange beliefs (delusions). These symptoms are usually treated with antipsychotic drugs. However, these drugs can have debilitating side effects. Tardive dyskinesia is an involuntary movement that causes the face, mouth, tongue and jaw to convulse, spasm and grimace. It is caused by long-term or high-dose use of antipsychotic drugs, is difficult to treat and can be incurable. Vitamin E has been suggested as a treatment, but so far the benefit of using Vitamin E for this purpose seems small.

Study characteristics

We searched for trials, July 2015 and April 2017, using the Cochrane Schizophrenia Group's register of trials. The review includes 13 poorly reported randomised trials investigating the effects of vitamin E for people with schizophrenia or other chronic mental illnesses who also developed TD as a result of taking antipsychotics. The trials randomised a total of 478 participants who had been ill for a long time.

Key results

Vitamin E may protect against tardive dyskinesia. However, there is no clear evidence that vitamin E improves this problematic and disfiguring condition.

Quality of the evidence

Available evidence is weak, limited and poor and we are unable to make any conclusions regarding the use of Vitamin E for antipsychotic-induced tardive dyskinesia. Well-designed trials involving a large number of participants investigating the effects of vitamin E over long periods of time are needed to determine whether this vitamin provides an effective treatment option for tardive dyskinesia.

This plain language summary was adapted by the review authors from a summary originally written by Ben Gray, Senior Peer Researcher, McPin Foundation (<http://mcpin.org/>).

SUMMARY OF FINDINGS

Summary of findings for the main comparison. VITAMIN E compared with PLACEBO for antipsychotic-induced tardive dyskinesia

VITAMIN E compared with PLACEBO for antipsychotic-induced tardive dyskinesia

Patient or population: patients with various chronic psychiatric disorders, but mainly schizophrenia, and antipsychotic-induced tardive dyskinesia

Settings: in hospital and outpatients in China (1 study), Hong Kong (1), Israel (2), India (1), Switzerland (1), the UK (1), and the USA (6).

Intervention: VITAMIN E

Comparison: PLACEBO

Outcomes	Illustrative comparative risks* (CI)		Relative effect (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: up to 1 year	970 per 1000	921 per 1000 (863 to 979)	RR 0.95 (0.89 to 1.01)	264 (6 studies)	⊕⊕⊕⊕ low ^{1,2}	
Tardive dyskinesia: 3. Deterioration of symptoms Follow-up: up to 1 year	263 per 1000	61 per 1000 (18 to 200)	RR 0.23 (0.07 to 0.76)	85 (5 studies)	⊕⊕⊕⊕ low ^{1,2}	
Adverse effect: any Follow-up: up to 1 year	21 per 1000	25 per 1000 (7 to 86)	RR 1.21 (0.35 to 4.15)	205 (9 studies)	⊕⊕⊕⊕ very low ^{3,4}	
Adverse effect: extrapyramidal symptoms measured by Simpson-Angus Scale (low = better) Follow-up: up to 1 year		The mean extrapyramidal adverse events in the intervention groups was 1.10 points higher (1.02 lower to 3.22 higher)		104 (1 study)	⊕⊕⊕⊕ very low ^{1,3}	
Acceptability of treatment (measured by participants leaving the study early) Follow-up: up to 1 year	168 per 1000	180 per 1000 (108 to 303)	RR 1.07 (0.64 to 1.80)	232 (8 studies)	⊕⊕⊕⊕ very low ^{2,3,5}	This outcome was designated to be of importance at 2017 update.

Social confidence, social inclusion, social networks, or personalised quality of life	See comment	See comment	Not estimable	0 (0)	See comment	This outcome was designated to be of importance, especially to patients, at 2017 update. We found no studies rating this outcome.
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*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 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 Downgraded one step for risk of bias: most studies did not adequately describe randomisation procedure, allocation concealment or blinding, and some studies were at high risk of attrition bias.
- ² Downgraded one step for imprecision: few events (< 300) were reported.
- ³ Downgraded two steps for imprecision: small sample size, and effect estimate includes both appreciable benefit and appreciable harm for vitamin E.
- ⁴ Downgraded one step for reporting bias: only one study reported on this common, typically monitored adverse effect.
- ⁵ Downgraded one step for indirectness: leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability.

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 antipsychotic-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:

1. required the use of antipsychotics for more than three months;
2. developed tardive dyskinesia (TD) (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.a. Vitamin E

Any dose or means of administration

compared with

1.b. Placebo or no intervention

2.a. Vitamin E

Any dose or means of administration

compared with

2.b. Any other interventions

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

No clinically important improvement in the symptoms of individuals, defined as more than 50% improvement on any TD 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. Social confidence, social inclusion, social networks, or personalised quality of life measures

8.1. No significant change in social confidence, social inclusion, social networks, or personalised quality of life measures.

8.2 Average score/change in social confidence, social inclusion, social networks, or personalised quality of life measures.

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.

'Summary of findings' table

We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to interpret findings (Schünemann 2011) and used GRADEpro to export data from this review to create [Summary of findings for the main comparison](#). This table provides outcome-specific information concerning the overall quality of evidence from each included study in the comparison, the magnitude of effects of interventions examined and the sum of available data on all outcomes rated as important to patient care and decision making. We selected the following main outcomes for inclusion in the [Summary of findings for the main comparison](#). (Review author NM was not biased by being familiar with the data).

1. Tardive dyskinesia

- 1.1 Improved to a clinically important extent
- 1.2 Deteriorated

2. Adverse effect

- 2.1 Any adverse event
- 2.2 Adverse effects: no clinically significant extrapyramidal adverse effects

3. Acceptability of treatment

- 3.1 Leaving the study early

4. Social confidence, social inclusion, social networks, or personalised quality of life measures*

- 4.1 No significant change in social confidence, social inclusion, social networks, or personalised quality of life measures for either recipients of care or caregivers

This summary table was used to guide our conclusions and recommendations.

* Outcome designated important to patients. We wished to add perspectives from people's personal experience with TD to the research agenda. A consultation with service users was planned where the previously published version of this review and a lay overview of the review gave the foundation for the discussions. The session was planned to provide time to reflect on current research on TD and consider gaps in knowledge. The report is published in the Health Technology Assessment (HTA) report for the UK National Institute of Health Research (Bergman 2017). We have added one figure showing one service user's expression of frustration concerning this neglected area of research (Figure 2). Informed by the results of the consultation, for this review, we updated outcomes for the 'Summary of findings' table.

Figure 2. Message from one of the participants of the Public and patient involvement consultation of service user perspectives on tardive dyskinesia research.

Search methods for identification of studies

Electronic searches

This review update was carried out in parallel with updating eight other TD reviews, see [Table 1](#) for details. The searches covered all nine TD reviews. For details of previous electronic searches see [Appendix 1](#) and [Appendix 2](#).

1. Cochrane Schizophrenia Group's Register

We searched Cochrane Schizophrenia Group's Study-Based Register of Trials on July 16, 2015 and April 26, 2017 using the following string: **Tardive Dyskinesia* in Healthcare Condition Field of Study*. In such a study-based register, searching the major concept retrieves all the synonym keywords and relevant studies because all the studies have already been organised based on their interventions and linked to the relevant topics. The Cochrane Schizophrenia Group's Register of Trials is compiled by systematic searches of major resources (including AMED, BIOSIS, CINAHL, Embase, MEDLINE, PsycINFO, PubMed, and registries of clinical trials) and their monthly updates, handsearches, grey literature, and conference proceedings (see [Group's Module](#)). There is no language, date, document type, or publication status limitations for inclusion of records into the register.

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

Methods used for the 2017 update are presented below. For methods used in previous versions, please see [Appendix 3](#) and [Appendix 4](#).

Selection of studies

Review authors NM and HB inspected all abstracts of studies identified as above and identified potentially relevant reports. We resolved disagreement by discussion, or where there was still doubt, we acquired the full article for further inspection. We acquired the full articles of relevant reports/abstracts meeting initial criteria for reassessment and carefully inspected for a final decision on inclusion (see [Criteria for considering studies for this review](#)). NM and HB were not blinded to the names of the authors, institutions or journal of publication. Where difficulties or disputes arose, we asked author KSW for help and where it was impossible to decide or if adequate information was not available to make a decision, we added these studies to those awaiting assessment and the authors of the papers contacted for clarification.

Data extraction and management

1. Extraction

Review authors NM and HB independently extracted data from all included studies. Again, we discussed any disagreement and documented decisions. We extracted data presented only in graphs and figures whenever possible, but included only if both review

authors 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. If studies were multi-centre, where possible, we extracted data relevant to each component centre separately.

2. Management

2.1 Forms

We extracted data online in [Covidence](#).

2.2 Scale-derived data

We included continuous data from rating scales only if:

- the psychometric properties of the measuring instrument have been described in a peer-reviewed journal ([Marshall 2000](#)); and
- the measuring instrument has not been written or modified by one of the trialists for that particular trial.

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

2.3 Endpoint versus change data

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

2.4 Skewed data

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

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

For endpoint data from studies < 200 participants:

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

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

2.5 Common measure

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

2.6 Conversion of continuous to binary

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

Where possible, we 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. Where keeping to this made it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'Not unimproved'), we presented data where the left of the line indicates an unfavourable outcome and noted this in the relevant graphs.

Assessment of risk of bias in included studies

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

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

We noted the level of risk of bias in the text of the review and in Figure 3 and Figure 4 and incorporated these judgements in assessing limitations in study design for critical and important outcomes in the [Summary of findings for the main comparison](#).

Figure 3.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Adler 1993	?	?	?	?	+	?	?
Adler 1999	+	+	?	?	+	?	?
Akhtar 1993	?	?	+	+	+	?	?
Dabiri 1994	?	+	?	?	+	?	?
Dorevitch 1997a	?	?	?	?	+	-	?
Dorevitch 1997b	?	?	?	+	?	-	?
Egan 1992	?	?	?	+	-	-	?
Elkashef 1990	?	?	?	?	-	-	?
Lam 1994	?	?	?	+	-	-	?
Lohr 1996	?	?	+	?	-	-	?
Sajjad 1998	+	?	-	-	-	?	?
Schmidt 1991	?	?	?	?	+	?	?
Zhang 2004	?	?	+	+	+	-	+

Figure 4.

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 as odds ratios tend to be interpreted as RR by clinicians (Deeks 2000).

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, if scales of very considerable similarity were used, we presumed there was a small difference in measurement, and calculated effect size and transformed the effect back to the units of one or more of the specific instruments.

Unit of analysis issues

1. Cluster trials

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

If any of the included trials had randomised participants by clusters, and where clustering was not accounted for in primary studies, we would have presented such data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. In subsequent versions of this review we will seek to contact first authors of studies to obtain intra-class correlation coefficients (ICCs) for their clustered data and to adjust for this by using accepted methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we will present these data as if from a non-cluster randomised study, but adjust for the clustering effect.

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

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

2. Cross-over trials

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

3. Studies with multiple treatment groups

Had a study involved more than two treatment arms, if relevant, we would have presented the additional treatment arms in comparisons. If data were binary we simply would have added and combined within the two-by-two table. If data were continuous we would have combined data following the formula in section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We would not use data where the additional treatment arms were not relevant.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up, data must lose credibility (Xia 2009). We chose that, for any particular outcome, should more than 50% of data be unaccounted for, we would not reproduce these data or use them within analyses. If, however, more than 50% of

those in one arm of a study were lost, but the total loss was less than 50%, we would address this within the 'Summary of Findings' table by down-rating quality. We also planned to downgrade quality within the 'Summary of Findings' table should loss be 25% to 50% in total.

2. Binary

In the case where attrition for a binary outcome is between 0% and 50% and where these data were not clearly described, we presented data on a 'once-randomised-always-analyse' basis (an intention-to-treat (ITT) analysis). We assumed all those leaving the study early had no improvement in TD symptoms. We undertook a sensitivity analysis to test how prone the primary outcomes were to change by comparing data only from people who completed the study to that point to the ITT analysis using the above assumptions.

3. Continuous

3.1 Attrition

We reported and used data where attrition for a continuous outcome was between 0% and 50%, and data only from people who completed the study to that point were reported.

3.2 Standard deviations

If standard deviations were not reported, we first tried to obtain the missing values from the authors. If not available, where there were missing measures of variance for continuous data, but an exact standard error (SE) and confidence intervals available for group means, and either P value or t value available for differences in mean, we calculated them according to the rules described in the *Cochrane Handbook for Systematic reviews of Interventions* (Deeks 2011): When only the SE is reported, standard deviations (SDs) are calculated by the formula $SD = SE \times \text{square root } (n)$. Chapters 7.7.3 and 16.1.3 of the *Cochrane Handbook for Systematic reviews of Interventions* (Deeks 2011) present detailed formulae for estimating SDs from P values, t or F values, confidence intervals, ranges or other statistics. If these formulae did not apply, we calculated the SDs according to a validated imputation method which is based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome and thus to lose information. We nevertheless examined the validity of the imputations in a sensitivity analysis excluding imputed values.

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

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

ITT data were not available at all. Moreover, we addressed this issue in the item "incomplete outcome data" of the 'Risk of bias' tool.

Assessment of heterogeneity

1. Clinical heterogeneity

We considered all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We simply inspected all studies for clearly outlying people or situations which we had not predicted would arise and discussed in the text if they arose.

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 and discussed in the text if they arose.

3. Statistical heterogeneity

3.1 Visual inspection

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

3.2 Employing the I² statistic

We investigated heterogeneity between studies by considering the I² method alongside the Chi² P value. The I² provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I² depends on i. magnitude and direction of effects and ii. strength of evidence for heterogeneity (e.g. P value from Chi² test, or a confidence interval for I²). An I² estimate greater than or equal to around 50% accompanied by a statistically significant Chi² statistic, can be interpreted as evidence of substantial levels of heterogeneity (Section 9.5.2 *Cochrane Handbook for Systematic Reviews of Interventions* Deeks 2011). We explored and discussed in the text potential reasons for substantial levels of heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in Section 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We did not use funnel plots for outcomes where there are 10 or fewer studies, or where all studies were of similar sizes. In future versions of this review, if funnel plots are possible, we will seek statistical advice in their interpretation.

Data synthesis

We understand that there is no closed argument for preference for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us and the random-effects model takes into account differences between studies even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the

random-effects model. It puts added weight onto small studies, which often are the most biased ones. Depending on the direction of effect, these studies can either inflate or deflate the effect size. We chose the fixed effect model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary outcomes

We anticipated one subgroup 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.

1.2 Clinical state, stage or problem

We proposed to undertake this review and provide an overview of the effects of vitamin E for people with schizophrenia in general. In addition, however, we tried to report data on subgroups of people in the same clinical state, stage and with similar problems.

2. Investigation of heterogeneity

We reported when inconsistency was high. First, we investigated whether data were entered correctly. Second, if data were correct, we visually inspected the graph and successively removed outlying studies to see if homogeneity was restored. For this review, we decided that should this occur with data contributing to the summary finding of no more than around 10% of the total weighting, we would present data. If not, we would not pool such data but would discuss issues. We know of no supporting research for this 10% cut-off but are investigating use of prediction intervals as an alternative to this unsatisfactory state.

When unanticipated clinical or methodological heterogeneity were obvious, we simply discussed. We did not undertake sensitivity analyses relating to these.

Sensitivity analysis

1. Implication of randomisation

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

2. Assumptions for lost binary data

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

reported and discussed these results but continued to employ our assumption.

Where assumptions have 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 completer data only. We undertook a sensitivity analysis to test how prone results were to change when 'completer' data only were compared to the imputed data using the above assumption. If there was a substantial difference, we reported and discussed these results but continued to employ our assumption.

3. Risk of bias

We analysed the effects of excluding trials that we judged to be at high risk of bias across one or more of the domains of randomisation (implied as randomised with no further details available) allocation concealment, blinding and outcome reporting for the meta-analysis of the primary outcome. If the exclusion of trials at high risk of bias did not substantially alter the direction of effect or the precision of the effect estimates, we included data from these trials in the analysis.

4. Imputed values

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

If we found substantial differences in the direction or precision of effect estimates in any of the sensitivity analyses listed above, we did not pool data from the excluded trials with the other trials contributing to the outcome, but presented them separately.

5. Fixed and random effects

We synthesised data using a fixed-effect model, however, we also synthesised data for the primary outcome using a random-effects model to evaluate whether this altered the significance of the results.

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 searches up to 2017 retrieved 704 references for 344 studies, see [Figure 5](#) for study flow diagram. The 2015 and 2017 update searches were part of an update of nine Cochrane reviews, see [Table 1](#).

Figure 5. Study flow diagram for study selection from searching up to and including 2017

From the 2015 search we identified five new potentially relevant studies to add to the review and screened the full texts. Agreement about which reports may have been randomised was 100%. Two of these studies could be included. One is a new study for this review (Zhang 2004). Another study was previously excluded because all data were unusable (Dorevitch 1997a), however we could include in the update as we found some data from the first phase of this cross-over trial to extract. One of the references was a new companion paper in German to an already included study (Adler 1999) with no additional data, we also added one ongoing study (ISRCTN14688109 2015) and one excluded study (Dorfman-Etrog 1999).

The 2017 search found 8 records (5 studies). Editorial base of Cochrane Schizophrenia screened these records and no new studies were relevant to this review. They could be relevant to another reviews in this series of TD reviews (see Table 1), and have been put into awaiting assessment of Soares-Weiser 2003.

Thirteen studies are now included in this review (Adler 1993; Adler 1999; Akhtar 1993; Dabiri 1994; Dorevitch 1997a; Dorevitch 1997b; Egan 1992; Elkashef 1990; Lam 1994; Lohr 1996; Sajjad 1998; Schmidt 1991; and Zhang 2004).

Included studies

Overall the review now includes 13 studies with 478 participants published between 1990 and 2004.

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. Six of the 11 studies used a cross-over design with two periods (Dorevitch 1997a; 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 period 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 478 people, were mostly men in their 50s, with diagnoses of various chronic psychiatric disorders, but mainly schizophrenia. All had antipsychotic-induced tardive dyskinesia (TD) diagnosed using Schooler and Kaner 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 ,

two in Israel (Dorevitch 1997a; Dorevitch 1997b), and one each in China (Zhang 2004), Hong Kong (Lam 1994), India (Akhtar 1993), 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, 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). None of the included studies compared vitamin E with another active intervention.

Participants remained on schizophrenia treatment antipsychotic medication during the trials.

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 last observation carried forward (LOCF) strategy for the intention-to-treat (ITT) analysis of dichotomous data.

7.2 Scales used to measure the TD symptoms

We have shown details of the scales 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 zero (none) to four (severe). Two additional items assess the dental status. The AIMS ranges from zero to 40, with higher scores indicating greater severity.

7.2.2 Tardive Dyskinesia Rating Scale (TDRS)

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 zero (absent) to five (severe). This scale ranges from 10 to 102, with higher scores indicating greater severity.

7.3 Scales used to measure adverse events related to antipsychotic medication

7.3.1 Simpson-Angus Scale (SAS)

The SAS (Simpson 1970) is a 10-item scale, with a scoring system of zero to four for each item, measures drug-induced parkinsonism, a short-term drug-induced movement disorder. A low score indicates low levels of parkinsonism.

7.3.2 Barnes Akathisia Scale (BAS)

The BAS (Barnes 1989) 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 zero (none) to four (severe). Two additional items assess the dental status. The BAS ranges from zero to 40, with higher scores indicating greater severity.

Excluded studies

There are eight excluded studies. Peet 1993 and Spivak 1992 were not randomised and we have therefore excluded them. We excluded Dorfman-Etrog 1999 and Salmasi 2009 because participants had schizophrenia but not TD. Although participants in Ricketts 1995 had TD, we excluded this study because participants did not have schizophrenia but had mental retardation due to brain damage. After two years of unfruitful attempts to contact authors for further details, we have also had to exclude a further three randomised studies which reported no usable data (Junker 1992; Lohr 1988; 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.

Ongoing studies

We identified one ongoing study conducted in Nigeria (ISRCTN14688109 2015) investigating vitamin E compared with cannabidiol extract in participants with TD. Results of the trial are expected to be published in early 2018.

Risk of bias in included studies

Please refer to Figure 3 and Figure 4 for graphical overviews of the risk of bias in the included studies.

Allocation

Only two studies were rated at low risk of selection bias. Adler 1999 was randomised centrally and Sajjad 1998 used a computer-generated sequence although did not describe allocation concealment. 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, Lam 1994 and Zhang 2004 as being of higher quality because they stated that the trial was double-blinded 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. Expected outcomes (impact on TD symptoms) were reported for most of the trials. Six studies reported results of all outcomes listed in the methods section fully (Adler 1993; Adler 1999; Akhtar 1993; Dabiri 1994; Sajjad 1998; Schmidt 1991). We rated risk of reporting bias for these studies as unclear because 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. Seven studies did not fully report outcomes that were measured during the study and were rated at high risk of reporting bias. Attempts to contact authors of trials for additional data were unsuccessful.

Other potential sources of bias

All studies had small or very small sample sizes. Six of the studies used a cross-over design (Dorevitch 1997a; Dorevitch 1997b; Egan 1992; Elkashef 1990; Lam 1994; Schmidt 1991). Five of the studies had the drugs used in the trials provided by pharmaceutical companies (Dorevitch 1997a; 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 antipsychotic-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. Although 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 (low-quality evidence, 6 trials, 264 people, risk ratio (RR) 0.95, 95% CI 0.89 to 1.01, [Analysis 1.1](#)).

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 (low-quality evidence, 7 trials, 319 people, RR 0.87, 95% CI 0.76 to 1.00, [Analysis 1.2](#)).

1.1.3 Average endpoint scores

TD symptoms were also measured on the continuous Abnormal Involuntary Movement Scale (AIMS) and Tardive Dyskinesia Rating Scale (TDRS) scales. A beneficial effect of vitamin E was found when measured on the AIMS (medium term, 6 studies, 157 people, mean difference (MD) -1.77, 95% CI -2.59 to -0.95, [Analysis 1.3](#)), but one study found no difference as measured on the TDRS (short term, 32 people, MD -2.10 95% CI -6.35 to 2.15, [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 (low-quality evidence, 5 trials, 85 people, RR 0.23, 95% CI 0.07 to 0.76, [Analysis 1.5](#)).

1.2 Adverse effects

1.2.1 Extrapyramidal adverse effects

One study measured extrapyramidal symptoms (Simpson-Angus Scale) and found no difference between Vitamin E and placebo (very low-quality evidence, 104 people, MD 1.10, 95% CI -1.02 to 3.22, [Analysis 1.6](#)). We had pre-specified the dichotomous outcome 'No clinically significant extrapyramidal adverse effects - any time period' as a primary outcome. No study reported this as a finding.

1.2.2 Specific adverse effects

The same study measured akathisia and found no difference between Vitamin E and placebo (Barnes Akathisia Scale (BAS), 104 people, MD 0.30, 95% CI -1.03 to 1.63, [Analysis 1.7](#)).

1.2.3 Any adverse effects

There was no difference in the incidence of 'any adverse effect' (very low-quality evidence, 9 trials, 205 people, RR 1.21, 95% CI 0.35 to 4.15, [Analysis 1.8](#)).

1.2.4 Discontinuation due to adverse events

Five trials reported on this outcome with only one person in the vitamin E arm who discontinued due to adverse events (123 people, RR 2.50, 95% CI 0.11 to 54.87, [Analysis 1.9](#)).

1.3 Mental state

Two trials reported endpoint data and one trial reported change from baseline data. These were combined as described in [Data extraction and management](#) - '2.3 Endpoint versus change data'. We found no difference between vitamin E and placebo for a measure of psychiatric symptoms (British Psychiatric Rating Scale (BPRS), 3 trials, 165 people, MD -0.20, 95% CI -3.21 to 2.82, [Analysis 1.10](#)).

1.4 Leaving the study early

Using vitamin E did not significantly increase the chances of a person leaving the study early (very low-quality evidence, medium term overall ~20% loss to follow-up, 8 trials, 232 people, RR 1.07, 95% CI 0.64 to 1.80, [Analysis 1.11](#)).

We did not identify any studies that reported on hospital and service utilisation outcomes, economic outcomes, quality of life, satisfaction with care, behaviour, or cognitive state.

1.5 Subgroup analysis

1.5.1 Clinical stage: Recent onset TD

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.

1.5.2 Duration of follow-up

Any effects that vitamin E may have did not clearly change in relation to duration of follow-up.

1.6 Heterogeneity

Data were homogeneous. We did not detect clinical, methodological or statistical heterogeneity as described in [Assessment of heterogeneity](#).

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 did not undertake 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 when we used our assumption compared with completer data only. Using completer only data for no improvement in TD symptoms, we found that more people improved with vitamin E than with placebo due to a minor shift in the effect estimate and the precision of the effect estimate (RR 0.77, 95% CI 0.61 to 0.96; participants = 219; studies = 7, analysis not shown). Although there was a change in direction of effect, we continued to employ our assumption in the main results.

1.7.3 Risk of bias

When excluding three trials that we judged to be at high risk of bias across one or more of the domains, there was no substantial alteration to the direction of effect or the precision of the effect estimates (RR 0.96, 95% CI 0.90 to 1.03; participants = 218; studies = 6; analysis not shown).

1.7.4 Imputed values

We would have undertaken a sensitivity analysis to assess the effects of including data from cluster-randomised trials where we used imputed values for ICC in calculating the design effect. No cluster-randomised trials were included.

1.7.5 Fixed and random effects

We also synthesised data for the primary outcome using a random-effects model. This did not alter the significance of the results (RR 0.96, 95% CI 0.90 to 1.02; participants = 264; studies = 6).

2. Comparison 2. Vitamin E versus any other intervention

No included studies were identified that reported on this comparison.

DISCUSSION

Summary of main results

1. The search

This area of research does not seem to be active. This 2017 update has identified additional data, but most trials predate the year 2000, only one was carried out after that time (published 2004). This could be because of reasons such as less concern with tardive dyskinesia (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 under 500 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 confidence intervals 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. However, the quality of the evidence for improvement of TD symptoms is low; 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. The recent addition of [Zhang 2004](#) did not impact on the binary outcomes for improvement in TD symptoms, but changed the continuous scale results in favour of vitamin E. The finding that people allocated to placebo may show more deterioration of their symptoms compared with those allocated to vitamin E is interesting (low-quality evidence, 5 trials, 85 people, RR 0.23 95% CI 0.07 to 0.76) 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

Three trials reported on mental state. All used the BPRS scale, but this involved only asking 165 people regarding this important outcome. There was no suggestion that vitamin E had any different 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.

3.5 Social confidence, social inclusion, social networks, or personalised quality of life

This group of outcomes was selected as being of importance to patients for the 2017 review update following a service user consultation. No studies were identified that reported on any of these outcomes.

4. Comparison 2. Vitamin E versus any other intervention

We found no included study that compared the efficacy of vitamin E compared to another active intervention. There is currently one ongoing study ([ISRCTN14688109 2015](#)) comparing vitamin E to cannabidiol that is due to be published in 2018.

Overall completeness and applicability of evidence

1. Completeness

No outcomes in this review involved large numbers of people. Some are general measures and more subtle findings are not recorded. For example, we identified few data on the outcome of 'any adverse effect' but none on the binary outcomes '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 the patient-designated important outcomes quality of life and satisfaction with care for either recipients of care or caregivers, nor were there data on hospital and service utilisation outcomes, economic outcomes, behaviour 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 ([Adler 1999](#)). 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 needed in each arm of the study (alpha 0.05, beta 0.8). Overall, the quality of reporting of these trials was poor (see [Figure 3](#)). 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 ([Jüni 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 for the main comparison](#) 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 review author (NM) 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 version of this Cochrane review ([Soares-Weiser 2011](#)). 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 tardive dyskinesia (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 relevance to people with TD and their clinicians.

3. Policy makers or managers

This is one of the largest in the series of Cochrane reviews on TD. 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. Such studies are of importance to people with the problem ([Figure 2](#)) and have long been ignored.

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 through 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 Abnormal Involuntary Movement Scale (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. Finally, a service user consultation also informed the addition of outcomes of special importance to patients. We have reconsidered all 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: inpatients and outpatients of the Department of Veterans Affairs Medical Center, USA. Design: parallel group.
Participants	Diagnosis: schizophrenia, depression (no criteria) and antipsychotic-induced TD (Research Diagnostic Criteria, Schooler and Kane). N = 40*. Sex: 2 female, 27 male*. Age: average vitamin E 58.0 (SD 9.5) years; placebo 61.0 (SD 9.2) years*
Interventions	1. Vitamin E: dose increasing over 3 weeks to 1600 IU/day. N = 24.** 2. Placebo. N = 16.** Stable antipsychotic 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 assumed from 3:2 randomisation. Source of funding: Supported in part by the Department of Veterans Affairs. Declarations of interest: Not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned to treatment with Vitamin E, 400IU, or one matching placebo capsule, by mouth, b.i.d." No further details

Adler 1993 (Continued)

Allocation concealment (selection bias)	Unclear risk	"We used a randomization of 3:2 (vitamin E to placebo) to maximize the number of patients receiving active treatment while maintaining the blind". No further details
Blinding of participants and personnel (performance bias)	Unclear risk	"Both rater and patient were blind to the patient's drug assignment". No further details
Blinding of outcome assessment (detection bias)	Unclear risk	"Both rater and patient were blind to the patient's drug assignment". No further details
Incomplete outcome data (attrition bias) All outcomes	Low 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."
Selective reporting (reporting bias)	Unclear risk	All expected outcomes have been reported but there is no study protocol to confirm that all planned outcomes were reported.
Other bias	Unclear risk	Baseline AIMS scores were somewhat higher in the vitamin E group than in the placebo group, however, this difference was not statistically significant. 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 and inpatients, Department of Veterans Affairs Medical Center, USA. Design: parallel
Participants	Diagnosis: schizophrenia, schizoaffective (DSM-IV), and antipsychotic-induced TD (Research Diagnostic Criteria). N = 158 Sex: 5 female, 153 male. Age: average 50 years (SD 10).
Interventions	1. Vitamin E: 1600 IU/day. N = 73. 2. Placebo. N = 85. Antipsychotic 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. Adverse Effects: Extrapyramidal symptoms (Modified Simpson-Angus Scale); Akathisia (Barnes Akathisia Scale)
Notes	Source of funding: Cooperative Studies Program of the Department of Veterans Affairs, Veterans Affairs Headquarters, Washington, DC Declarations of interest: Not reported.

Risk of bias
Vitamin E for antipsychotic-induced tardive dyskinesia (Review)

Adler 1999 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation co-ordinated centrally
Allocation concealment (selection bias)	Low risk	Allocation with "biased coin" method, stratified by site, age, and baseline TD
Blinding of participants and personnel (performance bias)	Unclear risk	Double-blind: no further details
Blinding of outcome assessment (detection bias)	Unclear risk	Double-blind: no further details
Incomplete outcome data (attrition bias) All outcomes	Low 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 unknown" (n = 8)". "Per protocol, we analyzed the data according to the intention- to-treat principle."
Selective reporting (reporting bias)	Unclear risk	All expected outcomes have been reported but there is no study protocol to confirm that all planned outcomes were reported.
Other bias	Unclear risk	No significant differences between groups' baseline characteristics. 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: inpatients in a psychiatric hospital, India. Design: parallel group.
Participants	Diagnosis: psychiatric disorder (Spitzer criteria) and antipsychotic-induced TD (Schooler and Kane criteria). N = 32. Sex: 14 female, 18 male. Age: Vitamin E mean 53.06 years (SD 13.39); Placebo mean 56.87 years (SD11.13)..
Interventions	1. Vitamin E: initial dose 600 mg once daily, doubled in the second week 600mg twice daily (1200 mg/day). N = 17. 2. Placebo. N = 15. Stable antipsychotic medication: dose average (CPE) = 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. Source of funding: Not reported. Declarations of interest: Not reported.

Risk of bias
Vitamin E for antipsychotic-induced tardive dyskinesia (Review)

Akhtar 1993 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were then randomly assigned". Details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	Low risk	"double blind manner to receive either one capsule of 600 mg vitamin E or an identical placebo"
Blinding of outcome assessment (detection bias)	Low risk	Investigators and raters were blind to the intervention until the completion of analysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study results seem to include all participants and no one seemed to drop out from the study.
Selective reporting (reporting bias)	Unclear risk	All expected outcomes have been reported but there is no study protocol to confirm that all planned outcomes were reported.
Other bias	Unclear risk	There was no significant difference in the demographic profile of the two groups. Small sample size.

Dabiri 1994

Methods	Allocation: "random allocation", no further details. Double-blind: yes. Duration: 12 weeks. Setting: outpatients, Outpatients from San Mateo County Mental Health Services, USA. Design: parallel group.
Participants	Diagnosis: psychiatric disorder (no criteria) and antipsychotic-induced TD (Research diagnosis, Schooler and Kane criteria). N = 12. Sex: 5 female, 6 male, 1 not specified. Age: average 51 years; range 35-68.
Interventions	1. Vitamin E: 400 IU/day for the first week, 800 IU/day for the second week, and 1200 IU/day during the remaining 10 weeks. N = 7. 2. Placebo. N = 5. Stable antipsychotic medication: dose average (CPE) 444 mg/day; range 200 mg to 1000 mg/day.
Outcomes	TD symptoms: AIMS. Leaving study early. Adverse effects: any.
Notes	Authors contacted but did not reply. Source of funding: Not reported. Declarations of interest: Not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
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Vitamin E for antipsychotic-induced tardive dyskinesia (Review)

Dabiri 1994 (Continued)

Random sequence generation (selection bias)	Unclear risk	'random allocation', no further details.
Allocation concealment (selection bias)	Low risk	"patients were randomly divided into treatment and placebo groups by a non-clinical staff member"
Blinding of participants and personnel (performance bias)	Unclear risk	"double-blind study", details not reported
Blinding of outcome assessment (detection bias)	Unclear risk	"Each patient was rated blindly by one of us (L.M.D.) before and after treatment using the Abnormal Involuntary Movement Scale (AIMS)". Blinding details not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	"One patient who was taking vitamin E stopped treatment after 2 weeks because of diarrhea, leaving five patients taking placebo and six vitamin E".
Selective reporting (reporting bias)	Unclear risk	All expected outcomes have been reported but there is no study protocol to confirm that all planned outcomes were reported.
Other bias	Unclear risk	No statistically significant differences in AIMS baseline scores between groups. Very small sample size.

Dorevitch 1997a

Methods	Allocation: "randomized", no further details. Double-blind: yes. Duration: 20 weeks (4 week washout). Setting: specific setting not reported, Israel. Design: crossover.
Participants	Diagnosis: DSM-III-R diagnosis of schizophrenia. All 10 candidates had tardive dyskinesia for a minimum of 5 years and had been exposed to antipsychotic drugs for longer than 10 years N = 10. Sex: 2 female 8 male Age: average 63.1 years; range 56-70
Interventions	1. Vitamin E: dose increasing over 4 weeks to 1600 IU/day. N = 5. 2. Placebo. N = 5. At the start of the study, the patients were receiving an average dose of 652 mg/day chlorpromazine equivalents, with a range of 75 to 4000 mg/day.
Outcomes	Leaving study early. Adverse effects: parkinsonism; akathisia. Unable to use - Adverse effects: AIMS (data not reported)
Notes	Source of funding: Not reported. Teva Pharmaceuticals supplied the vitamin E and placebo for this study Declarations of interest: Not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
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Vitamin E for antipsychotic-induced tardive dyskinesia (Review)

Dorevitch 1997a (Continued)

Random sequence generation (selection bias)	Unclear risk	"randomized". Details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	Unclear risk	"double-blind". Blinding details not reported
Blinding of outcome assessment (detection bias)	Unclear risk	"double-blind". Blinding details not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study results seem to include all participants and no one seemed to drop out from the study.
Selective reporting (reporting bias)	High risk	TD symptoms (AIMS) were assessed but not reported.
Other bias	Unclear risk	Baseline characteristics not reported. Very small sample size.

Dorevitch 1997b

Methods	Allocation: "randomized", no further details. Double-blind: yes. 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 years (SD 8.5); range 32-80.
Interventions	1. Vitamin E: 400 IU/day during the first week, titrated to 800 IU/day for the second week, 1200 IU/day for the third week, and 1600 IU/day from week 4 until the end of 8 weeks. N = 18. 2. Placebo. N = 22. Stable antipsychotic medication: dose average (CPE) 594 mg/day; range 75 mg to 5000 mg/day.
Outcomes	TD symptoms: AIMS. Leaving study early. Adverse effects. Unable to use - Mental state: BPRS (data not reported).
Notes	Source of funding: Not reported. Teva Pharmaceuticals supplied the vitamin E and placebo for this study Declarations of interest: Not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
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Dorevitch 1997b (Continued)

Random sequence generation (selection bias)	Unclear risk	"Randomised" - no further details.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and personnel (performance bias)	Unclear risk	"double-blind," Blinding details were not reported
Blinding of outcome assessment (detection bias)	Low risk	"Two senior psychiatrists served as blinded raters"
Incomplete outcome data (attrition bias) 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"
Selective reporting (reporting bias)	High risk	"Addition of vitamin E or placebo did not adversely affect patient mental status as measured by brief psychiatric rating scale (BPRS).“ BPRS data not fully reported
Other bias	Unclear risk	Baseline characteristics not reported. Small sample size.

Egan 1992

Methods	Allocation: 'random allocation', no further details. Double-blind: no further details. Duration: 12 weeks (6 weeks then crossed over to another 6 weeks, no washout). Setting: inpatients and outpatients, USA. Design: cross-over.
Participants	Diagnosis: schizophrenia, schizoaffective, bipolar disorder, depression (DSM-III-R) and antipsychotic-induced TD (Schooler and Kane criteria). N = 21. Sex: 8 female, 13 male. Age: average 43.9 years (SD 2.8)
Interventions	1. Vitamin E: 400 IU/day for week 1, 800 IU/day for week 2, 1200 IU/day for week 3, and 1600 IU/day for weeks 4-6. N = 10. 2. Placebo. N = 11. Stable antipsychotic medication: dose average (CPE) 1946 mg/day (no SD, N = 15).
Outcomes	TD symptoms: AIMS. Side effects. Leaving study early. Unable to use - Mental symptoms: PSAS, NSRS (means and SDs not reported)
Notes	Three patients were not included in the data analysis: one dropped out and two had inconsistent vitamin E blood levels Source of funding: Not reported. Declarations of interest: Not reported.

Risk of bias
Vitamin E for antipsychotic-induced tardive dyskinesia (Review)

Egan 1992 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were assigned randomly" Details not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	Unclear risk	"double-blind," Details not reported.
Blinding of outcome assessment (detection bias)	Low risk	"All raters were blind to treatment with either placebo or vitamin E. "
Incomplete outcome data (attrition bias) All outcomes	High risk	Not ITT analysis: "Eighteen patients who demonstrated high blood levels of vitamin E were included in the data analysis", 3 patients were excluded from the analysis.
Selective reporting (reporting bias)	High risk	Data for mental state (PSAS and NSAS) not reported.
Other bias	Unclear risk	Baseline characteristics not reported. Very small sample size

Elkashef 1990

Methods	Allocation: 'random allocation', no further details. Double-blind: no further details. Duration: 10 weeks (4 weeks then crossed over to another four weeks; randomisation was preceded by 2 weeks washout. Setting: outpatients, USA. Design: cross-over.
Participants	Diagnosis: schizophrenia or schizoaffective disorder (DSM-III-R) and antipsychotic-induced TD (Schooler and Kane criteria). N = 10. Sex: 1 female, 7 male (among completers). Age: average 56.6 years (SD 12) (among completers). History: no description of chronicity of TD.
Interventions	1. Vitamin E: 400 IU/day for the first week. 400 IU twice daily (800 IU/day) for the second week, and 400 IU three times daily (1200 IU/day) for the final two weeks. N = 5. 2. Placebo. N = 5. Stable antipsychotic medication: dose not specified.
Outcomes	TD symptoms: AIMS. Adverse effects. Leaving study early. Unable to use - Mental state: BPRS
Notes	Source of funding: Not reported. Hollman-La Roche, Inc., supplied the drug and placebo for this study. Declarations of interest: Not reported.

Elkashef 1990 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The subjects were then assigned in a random, double-blind manner...", no further details.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Double-blind: no further details
Blinding of outcome assessment (detection bias)	Unclear risk	"The subjects were evaluated biweekly by a blind trained rater using the AIMS and the Brief Psychiatric Rating Scale (BPRS)" Details of blinding not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	2/5 participants in the placebo group while none in the vitamin E group dropped out: "Two patients did not complete the study, one because of non-compliance and the other experienced substantial side effects (nausea) while taking placebo"
Selective reporting (reporting bias)	High risk	AIMS data partially reported and BPRS evaluated but not reported
Other bias	Unclear risk	The baseline severity of tardive dyskinesia was closely matched in the two groups. Very small sample size.

Lam 1994

Methods	Allocation: 'random allocation', no further details. Double-blind: no further details. Duration: 16 weeks: 2 week placebo lead-in phase, 6 weeks intervention followed by 2 weeks wash-out then crossed over to another 6 weeks. Setting: inpatients, Hong Kong. Design: cross-over.
Participants	Diagnosis: schizophrenia (DSM-III-R) and antipsychotic-induced TD (Schooler and Kane criteria). N = 16. Sex: 7 female, 5 male*. Age: average 61.8 yrs (SD 12.8 yrs)*. History: no history of chronicity of TD.
Interventions	1. Vitamin E: 400 IU/day for the first week; 400 IU twice daily in the second week; 400 IU three times daily from week 3 to 6. N = 5*. 2. Placebo. N = 7*. Stable antipsychotic medication. For those taking antipsychotic medication the average daily dose was 365 mg CPZ equivalent.
Outcomes	TD symptoms: AIMS Leaving study early (assuming equal randomisation into the two groups). Unable to use - Mental state: BPRS (no mean or SD reported)

Lam 1994 (Continued)

Adverse effects.

Notes	<p>* Completers</p> <p>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.</p> <p>Source of funding: Not reported.</p> <p>Declarations of interest: Not reported.</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Subjects were then selected randomly". No further details.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and personnel (performance bias)	Unclear risk	"double-blind". Details not reported.
Blinding of outcome assessment (detection bias)	Low risk	"Subjects were evaluated weekly with the AIMS...and Brief Psychiatric Rating Scale..., respectively, by two independent blind raters at the initial stabilization period, and the last 2 weeks of each test period"
Incomplete outcome data (attrition bias) All outcomes	High risk	Twelve participants completed the trial. 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. It was not reported to which groups these participants were allocated.
Selective reporting (reporting bias)	High risk	TD symptoms data not reported as mean (SD); BPRS data not reported per period. Adverse effects not reported per group.
Other bias	Unclear risk	Baseline characteristics not reported. Very small sample size.

Lohr 1996

Methods	<p>Allocation: "random assigned" - no further details.</p> <p>Double-blind: participants and personnel blinded</p> <p>Duration: 8 weeks.</p> <p>Setting: outpatients, USA.</p> <p>Design: parallel.</p>
Participants	<p>Diagnosis: schizophrenia, bipolar disorder, unipolar depression (no specified criteria) and antipsychotic-induced TD (Schooler and Kane criteria).</p> <p>N = 55.</p> <p>Sex: 2 female, 33 male, 20 not informed.</p> <p>Age: average 48.9 years (SD 13.6).</p>
Interventions	<p>1. Vitamin E: 1600 IU/day. N = 17 (completers)*.</p> <p>2. Placebo. N = 18 (completers)*.</p>

Lohr 1996 (Continued)

Stable psychotropic medication for at least 1 month prior to entry into study. Antipsychotic dose average (CPE) vitamin E = 706 mg/day (SD 680); placebo = 376 mg/day (SD 242).

Outcomes	<p>TD symptoms: mAIMS.</p> <p>Mental state: BPRS (reported for subgroup with schizophrenia, n = 29)</p> <p>Leaving the study early.</p>
Notes	<p>*Total numbers randomised per group were imputed from numbers analysed per group. Authors contacted but did not reply.</p> <p>Source of funding: Partial funding by a VA Merit Review grant, and United States Public Health Service grants. Vitamin E and placebo supplied by Hoffmann-La Roche Inc.</p> <p>Declarations of interest: Not reported.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned to receive either active vitamin E or sesame oil placebo gelcaps."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment details not reported.
Blinding of participants and personnel (performance bias)	Low risk	"Patients were randomly assigned to receive either active vitamin E or sesame oil placebo gel caps, which were indistinguishable from the active gel caps."
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information to make a judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout rate of 36% (20 of 55 patients) but not reported per study group "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".
Selective reporting (reporting bias)	High risk	Adverse effects: extrapyramidal side effects (Parkinsonism) data not reported.
Other bias	Unclear risk	There were no significant differences in baseline characteristics between the two study groups. Small sample size.

Sajjad 1998

Methods	<p>Allocation: "random allocation"</p> <p>Double-blind: probably not, there was no placebo administered to the control group.</p> <p>Duration: 7 months.</p> <p>Setting: inpatients, UK.</p> <p>Design: parallel.</p>
Participants	<p>Diagnosis: antipsychotic-induced TD (Schooler and Kane criteria).</p> <p>N = 20.</p> <p>Sex: 7 female, 13 male.</p> <p>Age: average 68 yrs (SD 8.7).</p>

Sajjad 1998 (Continued)

Interventions	1. Vitamin E: first week 400 mg/day. Dose was increased to 600 mg/day in the second week, 800 mg/day in the fourth month, 1200 mg/day in the fifth month and 1600 mg/day in the sixth month. N = 11. 2. Placebo. N = 9. Stable antipsychotic medication throughout the trial.
Outcomes	TD symptoms: AIMS. Adverse effects. Leaving the study early.
Notes	Source of funding: Not reported. Declarations of interest: Not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...the patients were randomly divided into two groups using... a computer statistical programme."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	High risk	As an active group was compared to treatment as usual, the study could not be double-blinded. The only person blinded seems to have been the doctor "...the dose increased by another doctor not involved in the ratings and who, therefore, was blind as to whether or not the patient was receiving a-tocopherol for the first month of the trial"
Blinding of outcome assessment (detection bias)	High risk	Rater initially blind. However, after one month, the rater performed statistical tests and hence blindness was not maintained.
Incomplete outcome data (attrition bias) All outcomes	High risk	40% dropout (12/20 participants completed the study): 6/11 participants in the intervention and 2/9 participants in the control group did not complete the trial. By the fourth month, there were 12 patients left in the trial, five in the treatment group and seven in the control group. Patients excluded at this stage included those whose dose of antipsychotic medication was changed.
Selective reporting (reporting bias)	Unclear risk	All expected outcomes have been reported but there is no study protocol to confirm that all planned outcomes were reported.
Other bias	Unclear risk	Mean AIMS scores and age were similar between groups at baseline. Very small sample size

Schmidt 1991

Methods	Allocation: "randomized pattern", no further details. Double-blind: no further details. Duration: 4 weeks (2 weeks then crossed over to another 2 weeks, no washout). Setting: inpatients, Switzerland. Design: cross-over.
Participants	Diagnosis: schizophrenia, depression, schizoaffective psychoses (no criteria) and antipsychotic-induced TD (no criteria). N = 23.

Schmidt 1991 (Continued)

Sex: 12 female, 11 male.
Age: average 45 years; range 21-88 years.

Interventions	1. Vitamin E: dose 1200 IU/ day. N = 13. 2. Placebo. N = 10. Stable antipsychotic medication: dose unspecified.
Outcomes	TD symptoms: AIMS. Adverse effects. Leaving study early.
Notes	It was observed that 2 of the patients who benefited from the vitamin E therapy continued taking it: after stopping vitamin E medication, one of them experienced an increase in TD, while in the other the beneficial effect was still observed even 3 months later Source of funding: Not reported. Declarations of interest: Not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized pattern", no further details.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	Unclear risk	"double-blind". Details not reported
Blinding of outcome assessment (detection bias)	Unclear risk	Details not reported
Incomplete outcome data (attrition bias) 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)
Selective reporting (reporting bias)	Unclear risk	All expected outcomes have been reported but there is no study protocol to confirm that all planned outcomes were reported.
Other bias	Unclear risk	Baseline characteristics similar between study groups. Very small sample size; cross-over design.

Zhang 2004

Methods	Allocation: randomly assigned Double-blind: yes Duration: 12 weeks. Setting: inpatients, China. Design: parallel
Participants	Diagnosis: DSM-III-R criteria for schizophrenia, using the Structured Clinical Interview for DSM-III-R; TD diagnosed by Schooler and Kane criteria. N = 41. Sex: 18 female, 23 male.

Vitamin E for antipsychotic-induced tardive dyskinesia (Review)

Zhang 2004 (Continued)

Age: average vitamin E 54.5 years (SD 10.1); placebo 53.3 (SD 9.7).

Interventions	1. Vitamin E: 800 IU/day during the first week and increased up to 1200 IU/day for another 11 weeks . N = 22. 2. Placebo. N = 19. Clinically stable with duration of TD for at least 1 year; stable dose of oral antipsychotics
Outcomes	TD symptoms: AIMS. Leaving study early. Unable to use - Mental state: PANSS
Notes	Source of funding: Not reported. Declarations of interest: Not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Eligible patients were randomly assigned" no further details
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not reported
Blinding of participants and personnel (performance bias)	Low risk	"either capsulized vitamin E (N = 22) or identically capsulized placebo (N = 19) using a double-blind fashion."
Blinding of outcome assessment (detection bias)	Low risk	"TD was evaluated in all patients using the Abnormal Involuntary Movement Scale (AIMS) at baseline, 6 and 12 weeks of treatment by the same trained investigator (DCC) who was blind to the patient's medication status. The patient's psychopathology was rated at baseline and at posttreatment using the Positive and Negative Syndrome Scale (PANSS), 18 which was performed by 2 trained psychiatrists who were blinded scoring the PANSS."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Forty-one inpatients with TD completed a double- blind, placebo-controlled, parallel-group study of vitamin E. Twenty- two of the patients were randomly assigned to receive a fixed dose of 1200 IU/d vitamin E, and 19 were assigned to a placebo". "Eligible patients were randomly assigned to receive either capsulized vitamin E (N = 22) or identically capsulized placebo (N = 19)". All randomised participants seem to have completed the study.
Selective reporting (reporting bias)	High risk	Outcome data were not reported for mental symptoms (PANSS)
Other bias	Low risk	"No significant differences in demographic data were observed between vitamin E and placebo groups"

Scales

AIMS - Abnormal Involuntary Movement Scale

NSRS - Negative Symptom Rating Scale

PANSS - Positive and Negative Syndrome Scale

PSAS - Psychiatric Symptoms Assessment Scale

SAS - Simptom-Angus Scale for Extrapyrimalal Side Effects

TDRS - Tardive Dyskinesia Rating Scale

Others
Vitamin E for antipsychotic-induced tardive dyskinesia (Review)

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CPE - Chlorpromazine equivalents
 CPZ - Chlorpromazine
 DSM-III-R- Diagnostic Statistical Manual of Mental Disorders
 TD - tardive dyskinesia
 BPRS: British Psychiatric Rating Scale
 ITT - intention-to-treat
 IU - international units
 mAIMS: Adverse and Involuntary Movement Scale
 SD: Standard Deviation

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

Study	Reason for exclusion
Dorfman-Etrog 1999	Allocation: randomised. Participants: people with schizophrenia, but not tardive dyskinesia.
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 1988	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 due to brain damage, 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: antipsychotic-induced TD. N = 30. Sex: unknown. Age: unknown.
Interventions	1. Vitamin E: dose 600 mg/ day. N = 15. 2. Placebo. N = 15. Stable antipsychotic 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

TD - tardive dyskinesia

Characteristics of ongoing studies [ordered by study ID]

ISRCTN14688109 2015

Trial name or title	Investigation of the potential beneficial effects of cannabidiol in the treatment of tardive dyskinesia
Methods	Randomised, double-blind placebo-controlled study
Participants	Target number of participants: 28 per group Adults 18 years and older that currently meets the ICD-10 diagnosis of a psychotic disorder, verified with the Mini International Neuropsychiatric Interview (MINI-PLUS) questionnaire and that currently meets the clinical diagnosis of tardive dyskinesia confirmed with the Abnormal Involuntary Movement Scale (AIMS). Patients should currently be receiving treatment for a psychotic disorder and should be on either the atypical or conventional antipsychotics
Interventions	1. Group 1 has high cannabidiol extract Nabidolex® (CBD) (300 mg) administered twice a day for six weeks as an adjunctive treatment alongside their usual antipsychotic medication. CBD will be administered orally in capsules. 2. Group 2 has vitamin E (400 IU) administered daily for six weeks as an adjunctive treatment alongside their usual antipsychotic medication
Outcomes	Improvement in symptoms of tardive dyskinesia measured using the Abnormal Involuntary Movement Scale (AIMS). Assessments will be conducted at baseline, 2 weeks, 4 weeks, 6 weeks (post-treatment) and at 12 weeks follow-up. Side effects of CBD will be periodically assessed with the Glasgow check list and reported at each assessment Improvement in psychotic symptoms
Starting date	01/12/2015
Contact information	jaiyeolakajero@yahoo.com

Vitamin E for antipsychotic-induced tardive dyskinesia (Review)

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ISRCTN14688109 2015 (Continued)

Notes

Source of funding: Federal Neuropsychiatric Hospital, Nigeria. Trial is part of a Stellenbosch University PhD,

Intention to publish date: 01/01/2018.

ICD - International Classification of Diseases

IU - international units

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	264	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.89, 1.01]
1.1 short term	2	33	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.79, 1.15]
1.2 medium term	2	53	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.85, 1.14]
1.3 long term	2	178	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.87, 1.02]
2 Tardive dyskinesia: 2. Not any improvement	7	319	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.76, 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	108	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.61, 0.98]
2.3 long term	2	178	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.82, 1.13]
3 Tardive dyskinesia: 3a. Average endpoint score (AIMS, low score = best)	10		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 short term	2	27	Mean Difference (IV, Fixed, 95% CI)	-2.64 [-6.35, 1.08]
3.2 medium term	6	157	Mean Difference (IV, Fixed, 95% CI)	-1.77 [-2.59, -0.95]
3.3 long term	3	141	Mean Difference (IV, Fixed, 95% CI)	-1.92 [-3.11, -0.73]
4 Tardive dyskinesia: 3b. Average endpoint score - short term (TDRS, low score = best)	1	32	Mean Difference (IV, Random, 95% CI)	-2.10 [-6.35, 2.15]
5 Tardive dyskinesia: 4. Deterioration of symptoms	5	85	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.07, 0.76]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 short term	2	27	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.05, 9.97]
5.2 medium term	2	40	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.02, 1.12]
5.3 long term	1	18	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.03, 1.45]
6 Adverse events: Extrapyramidal adverse events - long term (Simpson-Agnus Scale, low = better)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7 Adverse events: Specific adverse events: akathisia - long term (BAS, low = better)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8 Any adverse effect	9	205	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.35, 4.15]
8.1 short term	3	65	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.07, 3.64]
8.2 medium term	5	120	Risk Ratio (M-H, Fixed, 95% CI)	2.17 [0.25, 19.11]
8.3 long term	1	20	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.11, 54.87]
9 Discontinuation due to adverse effect	5	123	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.11, 54.87]
9.1 short term	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 medium term	3	71	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 long term	1	20	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.11, 54.87]
10 Mental state: Average score (BPRS, low = best)	3	165	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-3.21, 2.82]
10.1 short term (endpoint score)	1	32	Mean Difference (IV, Fixed, 95% CI)	-0.77 [-7.20, 5.66]
10.2 medium term (change from baseline score)	1	29	Mean Difference (IV, Fixed, 95% CI)	-7.92 [-17.20, 1.36]
10.3 long term (endpoint score)	1	104	Mean Difference (IV, Fixed, 95% CI)	1.20 [-2.47, 4.87]
11 Leaving study early	13		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 short term	3	65	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.11, 2.00]
11.2 medium term	8	232	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.64, 1.80]
11.3 long term	3	215	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.67, 1.47]

Analysis 1.1. 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.

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

Study or subgroup	Vitamin E		Placebo		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI			
	N	Mean(SD)	N	Mean(SD)						
Test for overall effect: Z=3.17(P=0)										
Test for subgroup differences: Chi²=0.23, df=1 (P=0.89), I²=0%										
					-10	-5	0	5	10	
					Favours vitamin E				Favours placebo	

Analysis 1.4. 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		Placebo		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Akhtar 1993	17	55.8 (7.1)	15	57.9 (5.1)		100%	-2.1[-6.35,2.15]
Total ***	17		15			100%	-2.1[-6.35,2.15]
Heterogeneity: Not applicable							
Test for overall effect: $Z=0.97(P=0.33)$							
					-10 -5 0 5 10		Favours vitamin E Favours placebo

Analysis 1.5. 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
1.5.1 short term					
Elkashef 1990	0/5	0/3			Not estimable
Schmidt 1991	1/11	1/8		10.23%	0.73[0.05,9.97]
Subtotal (95% CI)	16	11		10.23%	0.73[0.05,9.97]
Total events: 1 (Vitamin E), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.24(P=0.81)					
1.5.2 medium term					
Adler 1993	1/16	5/12		50.49%	0.15[0.02,1.12]
Lam 1994	0/5	0/7			Not estimable
Subtotal (95% CI)	21	19		50.49%	0.15[0.02,1.12]
Total events: 1 (Vitamin E), 5 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.85(P=0.06)					
1.5.3 long term					
Sajjad 1998	1/10	4/8		39.27%	0.2[0.03,1.45]
Subtotal (95% CI)	10	8		39.27%	0.2[0.03,1.45]
Total events: 1 (Vitamin E), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.59(P=0.11)					
Total (95% CI)	47	38		100%	0.23[0.07,0.76]
Total events: 3 (Vitamin E), 10 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.94, df=2(P=0.63); I²=0%					
Favours vitamin E 0.01 0.1 1 10 100 Favours placebo					

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
Test for overall effect: $Z=2.41(P=0.02)$					
Test for subgroup differences: $\text{Chi}^2=0.93, \text{df}=1 (P=0.63), I^2=0\%$

Analysis 1.6. Comparison 1 VITAMIN E versus PLACEBO, Outcome 6 Adverse events: Extrapyramidal adverse events - long term (Simpson-Agnus Scale, low = better).

Study or subgroup	Vitamin E		Placebo		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Adler 1999	49	6 (5.4)	55	4.9 (5.6)		0%	1.1[-1.02,3.22]

Analysis 1.7. Comparison 1 VITAMIN E versus PLACEBO, Outcome 7 Adverse events: Specific adverse events: akathisia - long term (BAS, low = better).

Study or subgroup	Vitamin E		Placebo		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Adler 1999	49	2.7 (3.5)	55	2.4 (3.4)		0%	0.3[-1.03,1.63]

Analysis 1.8. Comparison 1 VITAMIN E versus PLACEBO, Outcome 8 Any adverse effect.

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
1.8.1 short term					
Akhtar 1993	0/17	0/15			Not estimable
Elkashaf 1990	0/5	1/5		34.59%	0.33[0.02,6.65]
Schmidt 1991	1/13	1/10		26.06%	0.77[0.05,10.85]
Subtotal (95% CI)	35	30		60.65%	0.52[0.07,3.64]
Total events: 1 (Vitamin E), 2 (Placebo)					
Heterogeneity: $\text{Tau}^2=0$; $\text{Chi}^2=0.17, \text{df}=1(P=0.68)$; $I^2=0\%$					
Test for overall effect: $Z=0.66(P=0.51)$					
1.8.2 medium term					
Adler 1993	1/22	0/15		13.6%	2.09[0.09,48.04]
Egan 1992	0/10	0/11			Not estimable
Dabiri 1994	1/7	0/5		13.18%	2.25[0.11,46.13]
Dorevitch 1997b	0/18	0/22			Not estimable
Dorevitch 1997a	0/5	0/5			Not estimable
Subtotal (95% CI)	62	58		26.77%	2.17[0.25,19.11]
Total events: 2 (Vitamin E), 0 (Placebo)					
Heterogeneity: $\text{Tau}^2=0$; $\text{Chi}^2=0, \text{df}=1(P=0.97)$; $I^2=0\%$					
Test for overall effect: $Z=0.7(P=0.49)$

Analysis 1.9. Comparison 1 VITAMIN E versus PLACEBO, Outcome 9 Discontinuation due to adverse effect.

Analysis 1.10. Comparison 1 VITAMIN E versus PLACEBO, Outcome 10 Mental state: Average score (BPRS, low = best).

Analysis 1.11. Comparison 1 VITAMIN E versus PLACEBO, Outcome 11 Leaving study early.

ADDITIONAL TABLES

Table 1. Other reviews in the series

Interventions	Reference
Anticholinergic medication	Soares-Weiser 1997 ; Soares 2000c
Benzodiazepines	McGrath 2000b ; Umbrich 2003 ; Bhoopathi 2006
Calcium channel blockers	Soares 2000b ; Soares 2001c ; Essali 2011
Cholinergic medication	McGrath 2000d ; Tammenmaa 2002
Gamma-aminobutyric acid agonists	Soares 2000d ; Soares 2001b ; Alabed 2011
Miscellaneous treatments	McGrath 2000a ; Soares-Weiser 2003
Neuroleptic reduction and/or cessation and neuroleptics	McGrath 2000c ; Soares-Weiser 2006
Non-neuroleptic catecholaminergic drugs	Lyra da Silva 1997 ; El-Sayeh 2006
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.

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

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. Social confidence, social inclusion, social networks, or personalised quality of life: binary measure 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 method for the 2010 update

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](#)).

Appendix 2. 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 3. 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 as '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% attrition 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 $2SD > (S - S_{min})$, 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 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.

Appendix 4. Previous methods and searches

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 2](#).

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:

- the psychometric properties of the measuring instrument had been described in a peer-reviewed journal ([Marshall 2000](#)); and
- 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 2011](#), 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 for the main comparison' 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 2011](#)) 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 2011](#)) 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 3](#)), and risk of bias summary graph ([Figure 4](#)) 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](#)

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 $D_{\text{Eff}} = 1 + (M - 1) \text{ICC}$, 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 dropouts 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 2011. 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 χ^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 χ^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 χ^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 2011](#)). 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 ($I^2 \geq 75\%$) 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 2011](#)). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We did not use funnel plots for outcomes where there were 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.

WHAT'S NEW

Date	Event	Description
24 September 2019	Amended	Correction to Summary title of Plain Language Summary (PLS). Previous text referred to the review question. Summary Title of PLS has been added to this section.

HISTORY

Protocol first published: Issue 2, 1995

Review first published: Issue 1, 1999

Date	Event	Description
18 October 2017	New citation required but conclusions have not changed	New data added do not substantially change previous conclusions.
26 April 2017	New search has been performed	Update search run 26 April, 2017. Eight records found and assessed by editorial base at Cochrane Schizophrenia, none of the records found were relevant to this review. The records were all added to Studies awaiting classification of Miscellaneous treatments for antipsychotic-induced tardive dyskinesia (see also Results of the search).
16 May 2016	Amended	Title changed from 'Vitamin E for neuroleptic-induced tardive dyskinesia'. Two new trials added from 2015 searching (Dorevitch 1997a ; Zhang 2004), text updated, conclusions not substantially changed.

Date	Event	Description
15 July 2015	Amended	Update search run July 15 2015. 704 records found and assessed by review authors.
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.

Hanna Bergman - data extraction, report writing

DECLARATIONS OF INTEREST

KSW is the Deputy Editor-in-Chief for Cochrane and Cochrane Innovations. When the NHR HTA programme grant was awarded that included to update this review, Karla was the Managing Director of Enhance Reviews Ltd.

NM worked for Enhance Reviews Ltd during the preparation of this review, a company that carries out systematic reviews mostly for the public sector, it currently does not provide services for the pharmaceutical industry.

HB worked for Enhance Reviews Ltd during the preparation of this review, a company that carries out systematic reviews mostly for the public sector, it currently does not provide services for the pharmaceutical industry.

SOURCES OF SUPPORT

Internal sources

- Enhance Reviews Ltd, UK.

Salary and logistics support for Karla Soares-Weiser and Nicola Maayan for earlier published versions of this review, and for Hanna Bergman for the 2017 update.

- Queensland Health, Australia.

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- Universidade Federal de Sao Paulo, Brazil.

Salary and logistics support for Karla Soares-Weiser for earlier published versions of this review

External sources

- CAPES - Ministry of Education, Brazil.

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- NIHR HTA Project Grant, reference number: 14/27/02, UK.

Salary support for Hanna Bergman.

Support for patient involvement.

Support for traceable data database.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol as published with this review has evolved over time. The revisions of protocol are in line with the development of RevMan and in keeping with Cochrane guidance. We think the revisions have 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.

There was a substantial update to the protocol in the 2010 review update that the 2017 update also follows, but with two additions.

1. The comparison: 'Vitamin E: any dose or means of administration compared to any other intervention'
2. The outcomes 'Acceptability of treatment' and 'Social confidence, social inclusion, social networks, or personalised quality of life' were added to the 'Summary of findings' table. These outcomes were designated to be of importance to patients.

The previous methods are reproduced in [Appendix 3](#) and [Appendix 4](#).

INDEX TERMS

Medical Subject Headings (MeSH)

Antipsychotic Agents [*adverse effects]; Disease Progression; Dyskinesia, Drug-Induced [*drug therapy] [etiology]; Patient Acceptance of Health Care [statistics & numerical data]; Psychotic Disorders [drug therapy]; Randomized Controlled Trials as Topic; Schizophrenia [drug therapy]; Vitamin E [adverse effects] [*therapeutic use]; Vitamins [adverse effects] [*therapeutic use]

MeSH check words

Adult; Humans