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Miscellaneous treatments for antipsychotic-induced tardive dyskinesia (Review)

Soares-Weiser K, Rathbone J, Ogawa Y, Shinohara K, Bergman H

Soares-Weiser K, Rathbone J, Ogawa Y, Shinohara K, Bergman H.
Miscellaneous treatments for antipsychotic-induced tardive dyskinesia.
Cochrane Database of Systematic Reviews 2018, Issue 3. Art. No.: CD000208.
DOI: [10.1002/14651858.CD000208.pub2](https://doi.org/10.1002/14651858.CD000208.pub2).

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[Intervention Review]

Miscellaneous treatments for antipsychotic-induced tardive dyskinesia

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Editorial group: Cochrane Schizophrenia Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 3, 2018.

Citation: Soares-Weiser K, Rathbone J, Ogawa Y, Shinohara K, Bergman H. Miscellaneous treatments for antipsychotic-induced tardive dyskinesia. *Cochrane Database of Systematic Reviews* 2018, Issue 3. Art. No.: CD000208. DOI: [10.1002/14651858.CD000208.pub2](https://doi.org/10.1002/14651858.CD000208.pub2).

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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. This review, one in a series examining the treatment of TD, covers miscellaneous treatments not covered elsewhere.

Objectives

To determine whether drugs, hormone-, dietary-, or herb-supplements not covered in other Cochrane reviews on TD treatments, surgical interventions, electroconvulsive therapy, and mind-body therapies were effective and safe for people with antipsychotic-induced TD.

Search methods

We searched the Cochrane Schizophrenia Group's Study-Based Register of Trials including trial registers (16 July 2015 and 26 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 randomised controlled trials (RCTs) dealing with people with antipsychotic-induced TD and schizophrenia or other chronic mental illnesses who remained on their antipsychotic medication and had been randomly allocated to the interventions listed above versus 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 (CIs). We assumed that people who left early had no improvement. We assessed risk of bias and created 'Summary of findings' tables using GRADE.

Main results

We included 31 RCTs of 24 interventions with 1278 participants; 22 of these trials were newly included in this 2017 update. Five trials are awaiting classification and seven trials are ongoing. All participants were adults with chronic psychiatric disorders, mostly schizophrenia, and antipsychotic-induced TD. Studies were primarily of short (three to six weeks) duration with small samples size (10 to

157 participants), and most (61%) were published more than 20 years ago. The overall risk of bias in these studies was unclear, mainly due to poor reporting of allocation concealment, generation of the sequence, and blinding.

Nineteen of the 31 included studies reported on the primary outcome 'No clinically important improvement in TD symptoms'. Two studies found moderate-quality evidence of a benefit of the intervention compared with placebo: valbenazine (RR 0.63, 95% CI 0.46 to 0.86, 1 RCT, $n = 92$) and extract of *Ginkgo biloba* (RR 0.88, 95% CI 0.81 to 0.96, 1 RCT, $n = 157$), respectively. However, due to small sample sizes we cannot be certain of these effects.

We consider the results for the remaining interventions to be inconclusive: Low- to very low-quality evidence of a benefit was found for buspirone (RR 0.53, 95% CI 0.33 to 0.84, 1 RCT, $n = 42$), dihydrogenated ergot alkaloids (RR 0.45, 95% CI 0.21 to 0.97, 1 RCT, $n = 28$), hypnosis or relaxation, (RR 0.45, 95% CI 0.21 to 0.94, 1 study, $n = 15$), pemoline (RR 0.48, 95% CI 0.29 to 0.77, 1 RCT, $n = 46$), promethazine (RR 0.24, 95% CI 0.11 to 0.55, 1 RCT, $n = 34$), insulin (RR 0.52, 95% CI 0.29 to 0.96, 1 RCT, $n = 20$), branched chain amino acids (RR 0.79, 95% CI 0.63 to 1.00, 1 RCT, $n = 52$), and isocarboxazid (RR 0.24, 95% CI 0.08 to 0.71, 1 RCT, $n = 20$). There was low- to very low-certainty evidence of no difference between intervention and placebo or no treatment for the following interventions: melatonin (RR 0.89, 95% CI 0.71 to 1.12, 2 RCTs, $n = 32$), lithium (RR 1.59, 95% CI 0.79 to 3.23, 1 RCT, $n = 11$), ritanserin (RR 1.00, 95% CI 0.70 to 1.43, 1 RCT, $n = 10$), selegiline (RR 1.37, 95% CI 0.96 to 1.94, 1 RCT, $n = 33$), oestrogen (RR 1.18, 95% CI 0.76 to 1.83, 1 RCT, $n = 12$), and gamma-linolenic acid (RR 1.00, 95% CI 0.69 to 1.45, 1 RCT, $n = 16$).

None of the included studies reported on the other primary outcome, 'no clinically significant extrapyramidal adverse effects'.

Authors' conclusions

This review has found that the use of valbenazine or extract of *Ginkgo biloba* may be effective in relieving the symptoms of tardive dyskinesia. However, since only one RCT has investigated each one of these compounds, we are awaiting results from ongoing trials to confirm these results. Results for the remaining interventions covered in this review must be considered inconclusive and these compounds probably should only be used within the context of a well-designed evaluative study.

PLAIN LANGUAGE SUMMARY

Miscellaneous treatments for antipsychotic-induced tardive dyskinesia

What is the aim of this review?

The aim of this Cochrane Review was to find out if drugs, supplements, surgical interventions, electroconvulsive therapy, or mind-body therapies not covered in other Cochrane reviews of tardive dyskinesia can improve tardive dyskinesia. We collected and analysed all relevant randomised controlled trials to answer this question.

Key messages

The drug valbenazine and extract of the herb *Ginkgo biloba* probably improves symptoms of tardive dyskinesia. But we still need more high-quality studies to confirm these findings that were taken from only one study per intervention.

What was studied in the review?

Antipsychotic drugs are used to treat chronic mental illnesses such as schizophrenia by controlling, for instance, abnormal perceptions (hallucinations), disordered thinking and fixed false beliefs (delusions). Tardive dyskinesia is a disfiguring and disabling disorder of abnormal, repetitive and involuntary movements, and it is often caused by antipsychotic drugs. More than 20% of people who rely on antipsychotic drugs to control their mental illness have developed tardive dyskinesia. Many different interventions have been studied for easing the symptoms of tardive dyskinesia. Several Cochrane reviews have summarised the effects of the many treatments used to manage these involuntary movements. This review focusses on 'miscellaneous', a group of other non-connected, interventions not covered in the other Cochrane reviews on tardive dyskinesia.

What are the main results of the review?

We found 31 studies that reported on 24 different interventions to improve tardive dyskinesia in 1278 people who take antipsychotic medication for their chronic mental illnesses. Unfortunately most studies followed up on participants for a short time (most were three to six weeks) and included few participants (the average number of participants was 41 per study).

- Valbenazine probably reduces symptoms of tardive dyskinesia to a clinically important extent compared with placebo (moderate-certainty evidence). However, this evidence is based on only one study in the USA with 92 participants; we are awaiting results from recently completed and ongoing trials to confirm these results.
- Extract of *Ginkgo biloba* probably reduces symptoms of tardive dyskinesia to a clinically important extent compared with placebo (moderate-certainty evidence). However, this evidence is based on only one study in China with 157 participants; we are awaiting results from recently completed and ongoing trials to confirm these results.

- Evidence for the remaining interventions was of low- to very low-certainty evidence and we consider the results for these other interventions to be inconclusive.

How up-to-date is this review?

We searched for studies that had been published up to 26 April 2017.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. ALKALOID - DIHYDROGENATED ERGOT ALKALOIDS versus PLACEBO for antipsychotic-induced tardive dyskinesia

DIHYDROGENATED ERGOT ALKALOIDS versus PLACEBO for antipsychotic-induced tardive dyskinesia

Patient or population: female and male 59-80 (mean) years old patients with antipsychotic-induced tardive dyskinesia

Settings: inpatients in Japan and the UK

Intervention: dihydrogenated ergot alkaloids (co-dergocrine mesylate) (4.5 mg/day to 6 mg/day) versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	DIHYDROGENATED ERGOT ALKALOIDS				
Tardive dyskinesia: No clinically important improvement follow-up: 6 weeks	786 per 1000	354 per 1000 (165 to 762)	RR 0.45 (0.21 to 0.97)	28 (1 RCT)	⊕⊕⊕⊕ low ^{1,2}	
Tardive dyskinesia: Deterioration of symptoms follow-up: 6 weeks	71 per 1000	24 per 1000 (1 to 539)	RR 0.33 (0.01 to 7.55)	28 (1 RCT)	⊕⊕⊕⊕ very low ^{1,3}	
Adverse effects - any adverse effect follow-up: 6 weeks	214 per 1000	499 per 1000 (161 to 1000)	RR 2.33 (0.75 to 7.23)	28 (1 RCT)	⊕⊕⊕⊕ very low ^{1,3}	
Acceptability of treatment (measured by participants leaving the study early) follow-up: 6 weeks	42 per 1000	14 per 1000 (1 to 305)	RR 0.33 (0.02 to 7.32)	48 (2 RCTs)	⊕⊕⊕⊕ very low ^{1,3,4}	
Social confidence, social inclusion, social networks, or personalised quality of life - not reported	This outcome was not reported.					

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RCT:** randomised controlled trial; **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: randomisation procedure and allocation concealment were not adequately described.

² Downgraded one step for imprecision: very small sample size and few events reported.

³ Downgraded two steps for imprecision: very small sample size and very few events reported with the 95% CI around the effect estimate indicating both appreciable benefit for dihydrogenated ergot alkaloids and no effect.

⁴ Downgraded one step for indirectness: leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability.

Summary of findings 2. ANTIEPILEPTIC - LEVETIRACETAM versus PLACEBO for antipsychotic-induced tardive dyskinesia

LEVETIRACETAM versus PLACEBO for antipsychotic-induced tardive dyskinesia

Patient or population: female and male 47-54 years old (mean) patients with various psychiatric conditions and antipsychotic-induced tardive dyskinesia

Settings: in- and outpatients in Belgium, Bulgaria, and the USA

Intervention: levetiracetam (1500 mg twice per day) versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	LEVETIRACETAM				
Tardive dyskinesia: No clinically important improvement - not reported	This outcome was not reported.					
Tardive dyskinesia: Deterioration of symptoms - not reported	This outcome was not reported.					
Adverse effects - any adverse effect follow-up: 8 weeks	457 per 1000	233 per 1000 (114 to 475)	RR 0.51 (0.25 to 1.04)	69 (1 RCT)	⊕⊕⊕⊕ low ^{1,2}	
Acceptability of treatment (measured by participants leaving the study early) follow-up: 8-12 weeks	167 per 1000	168 per 1000 (77 to 370)	RR 1.01 (0.46 to 2.22)	119 (2 RCTs)	⊕⊕⊕⊕ very low ^{1,2,3}	
Social confidence, social inclusion, social networks, or personalised quality of life - not reported	This outcome was not reported.					

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RCT:** randomised controlled trial; **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: randomisation procedure, allocation concealment and blinding were not adequately described.

² Downgraded one step for imprecision: small sample size and few events reported with the 95% CI around the effect estimate indicating both appreciable benefit for levetiracetam and no effect.

³ Downgraded one step for inconsistency: substantial heterogeneity ($I^2 = 73\%$).

Summary of findings 3. ANXIOLYTIC - BUSPIRONE versus PLACEBO for antipsychotic-induced tardive dyskinesia

BUSPIRONE versus PLACEBO for antipsychotic-induced tardive dyskinesia

Patient or population: female and male 33-year old (mean) patients with schizophrenia and antipsychotic-induced tardive dyskinesia

Setting: inpatients, China

Intervention: Buspirone versus placebo.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with buspirone				
Tardive dyskinesia: No clinically important improvement follow-up: 6 weeks	905 per 1,000	480 per 1,000 (299 to 760)	RR 0.53 (0.33 to 0.84)	42 (1 RCT)	⊕⊕⊕⊖ low ^{1,2}	
Tardive dyskinesia: Deterioration of symptoms - not reported	This outcome was not reported.					
Adverse effects - not reported	This outcome was not reported.					
Acceptability of treatment (measured by participants leaving the study early) follow-up: 6 weeks	not estimable	not estimable	RR not estimable	42 (1 RCT)	⊕⊕⊕⊖ very low ^{1,3}	No events were reported.

Social confidence, social inclusion, social networks, or personalised quality of life - not reported

This outcome was not reported.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RCT:** randomised controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ Downgraded one step for risk of bias: randomisation procedure, allocation concealment and blinding were not adequately described.

² Downgraded one step for imprecision: very small sample size and few events reported.

³ Downgraded two steps for imprecision: effect could not be estimated due to very small sample size with no events reported.

Summary of findings 4. ENZYME INHIBITOR - VMAT2-INHIBITOR (valbenazine) versus PLACEBO for antipsychotic-induced tardive dyskinesia

VMAT2-inhibitor compared to placebo for antipsychotic-induced tardive dyskinesia

Patient or population: 18 to 85 year-old patients with schizophrenia, schizoaffective disorder, mood disorder, or gastrointestinal disorder + antipsychotic-induced tardive dyskinesia

Settings: in- and outpatients in the USA

Intervention: Valbenazine (NBI-98854) (25mg to 75mg/day) versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	VMAT2-inhibitor				
Tardive dyskinesia: 1. No clinically important improvement Follow-up: 6 weeks	826 per 1000	520 per 1000 (380 to 710)	RR 0.63 (0.46 to 0.86)	92 (1 study)	⊕⊕⊕⊖ moderate ¹	
Adverse effects - any adverse effect Follow-up: 6 weeks	327 per 1000	490 per 1000 (300 to 800)	RR 1.50 (0.92 to 2.45)	100 (1 study)	⊕⊕⊖⊖ low ²	
Leaving the study early follow-up: 6 weeks	98 per 1000	98 per 1000 (30 to 319)	RR 1.00 (0.31 to 3.25)	102 (1 study)	⊕⊖⊖⊖	

very low^{2,3}

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

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Downgraded one step for imprecision: small sample size and few events reported

² Downgraded two steps for serious imprecision: small sample size and very few events reported with the 95% CI around the effect estimate indicating both appreciable benefit for valbenazine and no effect.

³ Downgraded one step for indirectness: leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability.

Summary of findings 5. FATTY ACID - ETHYL-EPA versus PLACEBO for antipsychotic-induced tardive dyskinesia

ETHYL-EPA versus PLACEBO for antipsychotic-induced tardive dyskinesia

Patient or population: female and male 42 (mean) years old patients with schizophrenia or schizoaffective disorder and antipsychotic-induced tardive dyskinesia

Settings: in- and outpatients in South Africa

Intervention: ethyl-EPA (omega-3 fatty acid eicosapentaenoic acid derivative) versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	ETHYL-EPA				
Tardive dyskinesia: No clinically important improvement - not reported	This outcome was not reported.					
Tardive dyskinesia: Deterioration of symptoms - not reported	This outcome was not reported.					
Adverse effects: EPS: parkinsonism measured by average ESRS change scores follow-up: 12 weeks	mean: -1.1 (3.3)	The mean change in ESRS: parkinsonism scale score in the ethyl-EPA group was 0.3 points higher (1.17 lower to 1.77 higher)	MD 0.30 (-1.17 to 1.77)	75 (1 RCT)	⊕⊕⊕⊖ low ^{1,2}	

Adverse effects: EPS: dystonia measured by average ESRS change scores follow-up: 12 weeks	mean: 0.4 (0.5) The mean change in ESRS: dystonia scale score in the ethyl-EPA group was 0.35 points lower (0.58 to 0.12 lower)	MD -0.35 (-0.58 to -0.12)	75 (1 RCT)	⊕⊕⊕⊕ low ^{1,2}
Adverse effects: EPS: akathisia measured by average ESRS change scores follow-up: 12 weeks	mean: -0.06 (0.7) The mean change in ESRS: akathisia scale score in the ethyl-EPA group was 0.04 points lower (0.3 lower to 0.22 higher)	MD -0.04 (-0.30 to 0.22)	75 (1 RCT)	⊕⊕⊕⊕ very low ^{1,3}
Acceptability of treatment (measured by participants leaving the study early) follow-up: 12 weeks	548 per 1000 214 per 1000 (115 to 406)	RR 0.57 (0.27 to 1.22)	84 (1 RCT)	⊕⊕⊕⊕ very low ^{1,2,4}
Social confidence, social inclusion, social networks, or personalised quality of life - not reported	This outcome was not reported.			

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **EPS:** extrapyramidal symptoms; **ESRS:** Extrapyramidal Symptom Rating Scale; **ethyl-EPA:** ethyl-eicosapentaenoic acid; **RCT:** randomised controlled trial; **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: randomisation procedure, allocation concealment and blinding were not adequately described.

² Downgraded one step for imprecision: small sample size.

³ Downgraded two steps for serious imprecision: small sample size with the 95% CI around the effect estimate indicating both appreciable benefit for ethyl-EPA and no effect.

⁴ Downgraded one step for indirectness: leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability.

Summary of findings 6. HERB - GINKGO BILOBA versus PLACEBO for antipsychotic-induced tardive dyskinesia

GINKGO BILOBA versus PLACEBO for antipsychotic-induced tardive dyskinesia

Patient or population: male 45.2 (mean) years old patients with schizophrenia and antipsychotic-induced tardive dyskinesia

Settings: inpatients in China
Intervention: *GINKGO BILOBA* (EGb-761, standardised extract of *Ginkgo biloba* leaves) versus PLACEBO

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	<i>GINKGO BILOBA</i>				
Tardive dyskinesia: No clinically important improvement follow-up: 12 weeks	987 per 1000	869 per 1000 (800 to 948)	RR 0.88 (0.81 to 0.96)	157 (1 RCT)	⊕⊕⊕⊖ moderate ¹	
Tardive dyskinesia: Deterioration of symptoms - not reported	This outcome was not reported.					
Adverse effects - not reported	This outcome was not reported.					
Acceptability of treatment (measured by participants leaving the study early) follow-up: 12 weeks	51 per 1000	13 per 1000 (2 to 112)	RR 0.25 (0.03 to 2.22)	157 (1 RCT)	⊕⊖⊖⊖ very low ^{2,3}	
Social confidence, social inclusion, social networks, or personalised quality of life - not reported	This outcome was not reported.					

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RCT:** randomised controlled trial; **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 imprecision: small sample size and few events reported.

² Downgraded two steps for serious imprecision: small sample size and very few events reported with the 95% CI around the effect estimate indicating both appreciable benefit for *Ginkgo biloba* and no effect.

³ Downgraded one step for indirectness: leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability.

Summary of findings 7. HORMONE - MELATONIN versus PLACEBO OR NO TREATMENT for antipsychotic-induced tardive dyskinesia

MELATONIN versus PLACEBO OR NO TREATMENT for antipsychotic-induced tardive dyskinesia

Patient or population: female and male 28 to 91 years old patients with antipsychotic-induced tardive dyskinesia

Settings: in- and outpatients in Israel and Venezuela

Intervention: melatonin (2-20 mg/day) versus placebo or no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo/no treatment	MELATONIN				
Tardive dyskinesia: No clinically important improvement follow-up: 3-12 weeks	1000 per 1000	890 per 1000 (710 to 1000)	RR 0.89 (0.71 to 1.12)	32 (2 RCTs)	⊕⊕⊕⊕ low ^{1,2}	
Tardive dyskinesia: Deterioration of symptoms follow-up: 3 weeks	200 per 1000	44 per 1000 (2 to 810)	RR 0.22 (0.01 to 4.05)	19 (1 RCT)	⊕⊕⊕⊕ low ³	
Adverse effects follow-up: 3-12 weeks	See comment	See comment	Not estimable	54 (3 RCTs)	⊕⊕⊕⊕ low ³	No events were reported.
Acceptability of treatment (measured by participants leaving the study early) follow-up: 3-12 weeks	See comment	See comment	Not estimable	54 (3 RCTs)	⊕⊕⊕⊕ very low ^{3,4}	No events were reported.
Social confidence, social inclusion, social networks, or personalised quality of life - not reported	This outcome was not reported.					

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RCT:** randomised controlled trial; **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 inconsistency: substantial heterogeneity ($I^2 = 46\%$).
- 2 Downgraded one step for imprecision: small sample size and few events reported with the 95% CI around the effect estimate indicating both appreciable benefit for melatonin and no effect.
- 3 Downgraded two steps for imprecision: very small sample size and no or very few events reported.
- 4 Downgraded one step for indirectness: leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability.

Summary of findings 8. POLYPEPTIDE - CERULETIDE versus PLACEBO for antipsychotic-induced tardive dyskinesia

CERULETIDE versus PLACEBO for antipsychotic-induced tardive dyskinesia

Patient or population: female and male 55-59 year old (mean) patients with various psychiatric conditions and antipsychotic-induced tardive dyskinesia

Settings: in- and outpatients in Japan

Intervention: ceruletide (0.8 microgram/kg/week) versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	CERULETIDE				
Tardive dyskinesia: No clinically important improvement - not reported	This outcome was not reported.					
Tardive dyskinesia: Deterioration of symptoms follow-up: 4-8 weeks	20 per 1000	19 per 1000 (3 to 133)	RR 0.97 (0.14 to 6.80)	103 (2 RCTs)	⊕⊕⊕⊕ low ^{1,2}	
Adverse effects - any adverse effect follow-up: 4-8 weeks	233 per 1000	308 per 1000 (173 to 551)	RR 1.32 (0.74 to 2.36)	122 (2 RCTs)	⊕⊕⊕⊕ low ^{1,2}	
Acceptability of treatment (measured by participants leaving the study early) follow-up: 8 weeks	214 per 1000	234 per 1000 (105 to 514)	RR 1.09 (0.49 to 2.40)	85 (1 RCT)	⊕⊕⊕⊕ very low ^{1,2,3}	
Social confidence, social inclusion, social networks, or personalised quality of life - not reported	This outcome was not reported.					

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RCT:** randomised controlled trial; **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: unclear methods of randomisation, blinding not assessed, and potential introduction of detection bias due to subjective nature of outcome assessments.

² Downgraded one step for imprecision: the two included studies included only 132 participants and the 95% CI around the effect estimate indicated both appreciable benefit for ceruletide and no effect.

³ Downgraded one step for indirectness: leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability.

Summary of findings 9. HYPNOSIS or RELAXATION versus TAU for antipsychotic-induced tardive dyskinesia

HYPNOSIS OR RELAXATION versus TAU for antipsychotic-induced tardive dyskinesia

Patients or population: female and male 35 (mean) years old patients with schizophrenia and tardive dyskinesia, acute extrapyramidal symptoms, and/or pseudoparkinsonism

Setting: outpatients in the USA

Interventions: hypnosis or relaxation (8 sessions) versus TAU

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with TAU	Risk with hypnosis or relaxation				
Tardive dyskinesia: No clinically important improvement follow-up: 8 weeks	1,000 per 1,000	450 per 1,000 (210 to 940)	RR 0.45 (0.21 to 0.94)	15 (1 RCT)	⊕⊕⊕⊕ very low ^{1,2}	
Tardive dyskinesia: Deterioration of symptoms follow-up: 8 weeks	200 per 1,000	36 per 1,000 (2 to 762)	RR 0.18 (0.01 to 3.81)	15 (1 RCT)	⊕⊕⊕⊕ very low ^{1,3}	
Adverse effects - not reported	This outcome was not reported.					
Acceptability of treatment (measured by participants leaving the study early) follow-up: 8 weeks	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	15 (1 RCT)	⊕⊕⊕⊕ very low ^{1,4}	No events were reported.

Social confidence, social inclusion, social networks, or personalised quality of life - not reported

This outcome was not reported.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RCT:** randomised controlled trial; **RR:** Risk ratio; **TAU:** treatment as usual

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ Downgraded two steps for risk of bias: fully randomised sequence generation and blinding was not achieved.

² Downgraded one step for imprecision: very small sample size.

³ Downgraded two steps for imprecision: 95% CI includes benefit for both intervention arms; very small sample size with few events reported.

⁴ Downgraded two steps for imprecision: effect could not be estimated due to very small sample size with no events reported.

BACKGROUND

Description of the condition

Since the 1950's antipsychotic (neuroleptic) medication has been extensively used to treat people with chronic mental illnesses such as schizophrenia. These drugs can effectively control symptoms such as abnormal perceptions (hallucinations), disordered thinking and fixed false beliefs (delusions). In addition, maintenance therapy with neuroleptics is associated with a reduced risk of relapse (Schooler 1993).

Antipsychotic medication, however, has also been associated with a wide range of adverse effects, including movement disorders. The appearance of these movement disorders can contribute to poor compliance with antipsychotic treatment (Barnes 1993), and hence relapse.

Tardive dyskinesia (TD) is one such movement disorder and is characterised by abnormal, repetitive and involuntary movements (APA 1992). The clinical features include tongue protrusion, side-to-side or rotatory movement of the jaw, lip smacking, puckering and pursing, and rapid eye blinking (Casey 1994). In some people rapid movements of the arms, legs, and trunk may also occur. TD is a chronic condition of insidious onset, the severity of which spontaneously fluctuates (APA 1992). Studies on the natural history of TD have reported widely variable remission rates (1% to 62%) depending on patient age, psychiatric diagnosis, course of the psychiatric disorder, and duration of therapy (Bergen 1989; Fernandez 2001; Glazer 1990).

Although the most frequent cause of TD is the use of antipsychotic medication, it is clinically striking that dose reduction can lead to a temporary exacerbation in symptoms. Conversely, increasing the dose is often associated with a temporary remission (Cavallaro 1993; Smith 1980). The exact mechanisms of the pathophysiology of TD are unknown. Antipsychotic drugs block certain chemical receptor sites in the brain - one of these is specific for dopamine (Casey 1994). One hypothesis explaining the cause of antipsychotic-induced TD is that chronic blockade of dopamine receptors in specific cells of the brain (neurones from the nigrostriatum) causes an overgrowth of these receptors (Casey 1994). There is also a suggestion that the chronic use of antipsychotics may also cause an abnormal production of highly active atoms and chemical groups (cytotoxic free radicals), which may damage specific cells in the brain. This, in turn, could be responsible for the appearance of TD (Cadet 1989; Sachdev 2000).

TD occurs in more than 20% of those using antipsychotic medication continually for longer than three months (Glazer 2000; Kane 1982; Tarsy 2011). Every year 4% to 5% of adults and 25% to 30% of elderly persons who continually use these drugs begin to show signs of TD (APA 1992; Correll 2004). Advancing age is a risk factor for both TD's prevalence and severity, with those who are < 60 years of age being three times more likely to spontaneously remit (Jeste 2000; Smith 1980).

The prevalence of TD is often thought to be decreasing based on the use of atypical antipsychotics in place of typical antipsychotics (Cloud 2014). A systematic review found that the incidence of TD associated with atypical antipsychotics (2% to 4%) was significantly lower than that for typical antipsychotics (5% to 8%) (Correll 2008). Despite this, the widespread use of atypical antipsychotics in

clinical settings, increased off-label use, and an ageing population may still result in an overall increase in the number of cases of TD (Cloud 2014; Glazer 2000; Maher 2012). The problem will be considerably greater for people in countries where use of newer drugs is less prevalent (Ballesteros 2000; Martins 2011).

Description of the intervention

Various types of interventions have been evaluated as potential treatments for TD. There is now a series of Cochrane reviews relevant to the care of people with TD (Table 1). This review summarises any trial-based evidence for the effects of any other treatments that were not summarised in any of the other reviews evaluating interventions for TD. Please see Included studies, 6. Interventions for the 24 interventions included in this review.

How the intervention might work

Use of treatments such as botulin, endorphin, oestrogen, essential fatty acid, EX11582A, ganglioside, lithium, naloxone, periactin, phenylalanine, piracetam, stepholidine, and tryptophan is based on their possible beneficial effects in other movement disorders. Also, interventions using neurosurgery or electroconvulsive therapy have been used for managing the distressing signs and symptoms of TD.

Why it is important to do this review

Several atypical antipsychotic drugs have been produced in the last decades that claim to cause less or no TD (Lieberman 1996). These claims may or may not be true, and certainly evidence does point to the fact that thoughtful use of older generation drugs is not associated with any more problems of TD than with newer treatments (Chouinard 2008). However, in a global context, it is likely that the less expensive and more familiar drugs - such as chlorpromazine or haloperidol - will continue to be the mainstay of treatment of people with schizophrenia (WHO Essential List 2010). Use of drugs such as these is associated with emergence of TD and, therefore, this condition will remain a problem for years to come.

TD can result in considerable social and physical disability (Barnes 1993) and symptoms are often irreversible (Bergen 1989; Fernandez 2001; Glazer 1990). Additionally, TD is frequently associated with lower quality of life (Ascher-Svanum 2008) and a greater mortality rate (Chong 2009). Given the high incidence and prevalence of TD among people taking antipsychotic medication, the need for prevention or treatment is clear. Unfortunately, there has been sparse evidence to guide clinicians (NICE 2014; Taylor 2009). Although many treatments have been tested, no one intervention has been shown clearly to be effective. Cessation or reduction of the dose of antipsychotic medication would be the ideal management for TD. In clinical practice this is not always possible, not least because in many individuals such a reduction would lead to relapse. This review focuses on whether the addition of different types of miscellaneous medications to those already receiving antipsychotic medication is likely to help TD.

This review is one in a series of nine Cochrane reviews (see Table 1) evaluating treatments for antipsychotic-induced TD, and is an update of a Cochrane review first published in 2000 (McGrath 2000).

OBJECTIVES

1. To determine the effects of any of the following drugs or supplements for antipsychotic-induced TD in people with schizophrenia or other chronic mental illnesses: botulin toxin, branched-chain amino acids, buspirone, ceruletide, cyproheptadine, dihydrogenated ergot alkaloids, dimethylaminoethanol, eicosapentaenoic acid, endorphin, oestrogen, essential fatty acid, EX 11-582A, gamma-linolenic acid, ganglioside GM1, *Ginkgo biloba*, insulin, isocarboxazid, levetiracetam, lithium, melatonin, methylphenidate, naloxone, naltrexone, papaverine, pemoline, periactin, phenylalanine, piracetam, procyclidine, promethazine, ritanserin, selegiline, stepholidine and tryptophan, VMAT-2 inhibitors.

2. To determine the effects of surgical interventions or electroconvulsive therapy (ECT) for antipsychotic-induced TD in people with schizophrenia or other chronic mental illnesses.

3. To determine the effects of body therapies such as yoga, hypnosis, or relaxation for antipsychotic-induced TD in people with schizophrenia or other chronic mental illnesses.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials. Where a trial was described as 'double-blind', but it was only implied that the study was randomised, we included these trials in a sensitivity analysis. If there was no substantive difference within primary outcomes (see [Types of outcome measures](#)) when these 'implied randomisation' studies were added, then we included these in the final analysis. If there was a substantive difference, we only used clearly randomised trials and described the results of the sensitivity analysis in the text. We excluded quasi-randomised studies, such as those allocating by using alternate days of the week.

Types of participants

We included people with schizophrenia and other types of schizophrenia-like psychosis (e.g. schizophreniform and schizoaffective disorders), irrespective of the diagnostic criteria used, who: i. required the use of antipsychotics for more than three months; ii. developed TD (diagnosed by any criteria) during antipsychotic treatment; and iii. for whom the dose of antipsychotic medication had been stable for one month or more before the trial (the same applies for those free of antipsychotics). There is no clear evidence that the schizophrenia-like psychoses are caused by fundamentally different disease processes or require different treatment approaches ([Carpenter 1994](#)).

Types of interventions

1. Compounds

Including drugs, hormone-, dietary-, or herb-supplements such as botulin toxin, buspirone, ceruletide, dihydrogenated ergot alkaloids, dimethylaminoethanol, endorphin, oestrogen, essential and omega fatty acids, EX 11-582A, *Ginkgo biloba*, ganglioside GM1, insulin, levetiracetam, lithium, melatonin, methylphenidate, naloxone, naltrexone, pemoline, periactin, phenylalanine, piracetam, stepholidine, tryptophan, VMAT-2

inhibitors. Any doses, frequencies or means of administration were acceptable.

2. Surgical intervention of any sort

3. Electroconvulsive therapy (ECT)

4. Mind-body therapies, such as relaxation techniques or hypnotherapy

Compared with:

1. Placebo, no treatment or standard care; or

2. Any other intervention for the treatment of tardive dyskinesia

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 important 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 treatment

3.1 Acceptability of the intervention to the participant group as measured by numbers of people leaving the study early.

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

10. Cognitive state

10.1 Clinically important change.
10.2 Any change, general and specific.

'Summary of findings' tables

We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to interpret findings (Schünemann 2011) and used GRADEpro GDT to export data from this review to create 'Summary of findings' tables. These tables provide 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' tables.

1. Tardive dyskinesia
 - 1.1 No clinically important improvement
 - 1.2 Deterioration of symptoms
2. Adverse effects
 - 2.1 Clinically important extrapyramidal adverse effects
 - 2.2 Any adverse effect
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 Clinically important change in social confidence, social inclusion, social networks, or personalised quality of life measures for either recipients of care or caregivers.

* 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 another review in the tardive dyskinesia series (Soares-Weiser 2011; Table 1) and a lay overview of that 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 from the report showing service user expression of frustration concerning this neglected area of research (Figure 1). Informed by the results of the consultation, for this review, we updated outcomes for the 'Summary of findings' tables.

Figure 1. Message from one of the participants of the Public and patient involvement consultation of service user perspectives on tardive dyskinesia research.

Prioritising interventions for 'Summary of findings' tables

Twenty-four different interventions were included in this review (see [Table 2](#)), and many of the studies were very small (< 60 participants) pilot studies testing out new interventions to treat TD. Due to the vast number of included interventions and to the small sample size and experimental nature of many of the studies, as a post hoc change to methods, we decided to prioritise interventions and create 'Summary of findings' tables only for those comparisons that: 1) included more than 60 participants, or 2) included more than one trial, or 3) was selected as an intervention of special interest for the UK National Health Service in the prioritisation process for the recently published HTA report ([Bergman 2017](#)).

Search methods for identification of studies

Electronic searches

The 2017 review update was carried out in parallel with updating eight other TD reviews, see [Table 1](#) for details. The search covered all nine TD reviews.

Cochrane Schizophrenia Group's Study-Based Register of Trials

On 16 July 2015 and 26 April 2017, the information specialist searched the register using the following search strategy:

Tardive Dyskinesia in Health Care Condition Field of STUDY

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

This register is compiled by systematic searches of major resources (AMED, BIOSIS, CINAHL, ClinicalTrials.Gov, Embase,

MEDLINE, PsycINFO, PubMed, WHO ICTRP) and their monthly updates, ProQuest Dissertations and Theses A&I and its quarterly update, Chinese databases (CBM, CNKI, and Wanfang) and their annual updates, handsearches, grey literature, and conference proceedings (see [Group's Module](#)). There is no language, date, document type, or publication status limitations for inclusion of records into the register.

For previous searches, please see [Appendix 1](#)

Searching other resources

1. Reference searching

We inspected 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

For previous data collection and analysis please see [Appendix 2](#)

Selection of studies

For the 2017 update, Rosie Asher (RA and Antonio Grande (AG) (see [Acknowledgements](#)) inspected all abstracts of studies identified as above and selected potentially relevant reports. We resolved disagreement by discussion, or where there was still doubt, we acquired the full-text article for further inspection. We acquired the full-text articles of relevant reports/abstracts meeting initial criteria for re-assessment and carefully inspected for a final decision on inclusion (see [Criteria for considering studies for this review](#)). RA

and AG were not blinded to the names of the authors, institutions or journal of publication. Where difficulties or disputes arose, we asked review author Hanna Bergman (HB) 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 classification and contacted the authors of the papers for clarification.

Data extraction and management

1. Extraction

For the 2017 update, RA and HB independently extracted data from all included studies. Jun Xia (JX) and Sai Zhao (SZ) (see [Acknowledgements](#)) extracted data from studies in Chinese. For any problems, review author Karla Soares-Weiser (KSW) helped clarify issues and we documented these final decisions. We extracted data presented only in graphs and figures whenever possible, but included only if two 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

For the 2017 update we extracted data online in [Covidence](#). Extracted data are available [here](#) with a link to the original source PDF for each item.

2.2 Scale-derived data

We included continuous data from rating scales only if:

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

Ideally, the measuring instrument should either be i. a self-report or ii. completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly, 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 planned to enter data from studies of at least 200 participants in the analysis, because skewed data pose less of a problem in large studies. We 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:

(a) when a scale starts from the finite number zero, we subtracted the lowest possible value from the mean, and divided this by the standard deviation (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 their 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 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

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 the active intervention. Where keeping to this made it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'Not un-improved'), 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

RA 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 2011](#)). 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 2](#), [Figure 3](#) and [Summary of findings 8](#).

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	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
Bucci 1971	?	?	-	-	+	-	?
Cai 1988	?	?	+	+	+	-	?
Castro 2011	?	?	+	?	+	?	+
Emsley 2006	?	?	+	?	+	-	?
Gardos 1979	?	?	-	+	?	?	?
Glazer 1985	?	?	?	?	+	-	-
Glover 1980	-	?	-	?	+	+	?
Goff 1993	?	?	+	+	-	-	+
Hajioff 1983	?	?	?	?	+	?	?
Kojima 1992	?	?	?	?	-	-	?
Koshino 1979	?	+	?	?	+	?	?
Koshino 1983	?	+	?	?	+	?	?
Libov 2007	?	?	?	+	-	+	+
Mackay 1980	?	?	+	+	+	-	?
Matsunaga 1988	?	?	?	?	-	?	+
Meco 1989	?	?	?	?	?	?	+
Mosnik 1997	?	?	+	?	+	?	+
Mouret 1991	?	?	?	?	?	?	?
O'Brien 2014	+	+	+	+	+	?	+
Rastogi 1982	?	?	+	?	?	?	?

Figure 2. (Continued)

Rastogi 1982	?	?	+	?	?	?	?
Richardson 2003	?	?	?	+	?	-	?
Shamir 2000	+	+	+	+	+	?	?
Shamir 2001	+	+	+	?	+	?	?
Shi 2009	?	?	-	?	+	+	?
UCB Pharma 2005	?	?	?	?	-	-	?
Wolkin 1986	?	?	?	?	+	?	+
Woods 2008	?	?	?	?	+	-	+
Yang 1999	+	+	?	+	+	+	+
Zeng 1995	?	?	+	?	+	+	+
Zeng 1996	?	?	+	?	+	+	+
Zhang 2011	+	+	+	+	+	-	+

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

Measures of treatment effect

1. Binary data

For binary outcomes we calculated a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI). It has been shown that RR is more intuitive (Boissel 1999) than odds ratios 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).

Had cluster trials been included and clustering had not been 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, if cluster-randomised trials are included, we will seek to contact first authors of studies to obtain intra-class correlation coefficients (ICCs) for their clustered data and 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 = $1 + (m - 1) \times \text{ICC}$] (Donner 2002). If the ICC is not reported it will be assumed to be 0.1 (Ukoumunne 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

Where a study involved more than two treatment arms, if relevant, we presented the additional treatment arms in comparisons. If data were binary we simply added 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 for Systematic Reviews of Interventions* (Higgins 2011). We did 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 addressed this within the 'Summary of findings' table/

s by down-rating quality. We also downgraded quality within the 'Summary of findings' table/s should loss be 25% to 50% in total.

2. Binary

In the case where attrition for a binary outcome was between 0% and 50% and where these data were not clearly described, we presented data on a 'once-randomised-always-analyse' basis (an intention-to-treat (ITT) analysis). We assumed all those leaving the study early to have no improvement. 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 (SDs) were not reported, we first tried to obtain the missing values from the authors. If not available, where there were missing measures of variance for continuous data, but an exact standard error (SE) and confidence intervals available for group means, and either the P value or t value available for differences in mean, we calculated them according to the rules described in the *Cochrane Handbook for Systematic reviews of Interventions* (Higgins 2011). When only the SE is reported, SDs are calculated by the formula $\text{SD} = \text{SE} \times \text{square root } (n)$. Chapters 7.7.3 and 16.1.3 of the *Cochrane Handbook for Systematic reviews of Interventions* (Higgins 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 the trials early or were lost to follow-up. Some trials just present the results of study completers, others use the method of last observation carried forward (LOCF), while more recently methods such as multiple imputation or mixed-effects models for repeated measurements (MMRM) have become more of a standard. While the latter methods seem to be somewhat better than LOCF (Leon 2006), we feel that the high percentage of participants leaving the studies early and differences in the reasons for leaving the studies early between groups is often the core problem in randomised schizophrenia trials. We therefore did not exclude studies based on the statistical approach used. However, we 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 these 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 these 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 I^2 statistic

We investigated heterogeneity between studies by considering the I^2 method alongside the χ^2 P value. The I^2 provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 depends on i. magnitude and direction of effects and ii. strength of evidence for heterogeneity (e.g. P value from χ^2 test, or a confidence interval for I^2). An I^2 estimate greater than or equal to around 50% accompanied by a statistically significant χ^2 statistic, can be interpreted as evidence of substantial levels of heterogeneity (Section 9.5.2 *Cochrane Handbook for Systematic Reviews of Interventions* Higgins 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* (Higgins 2011). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We did not use funnel plots for outcomes where there were 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

With this wide range of miscellaneous treatments of mainly experimental interventions, we did not expect many studies or participants per intervention that would enable us to carry out subgroup analyses. We proposed to undertake this review and provide an overview of the effects of this group of miscellaneous treatments 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 is 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 did not pool such data and discussed 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 the issues. 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 [Risk of bias in included studies](#) for the meta-analysis of the primary outcomes. 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.

5. Fixed and random effects

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

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.

RESULTS

Description of studies

Please see [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#), and [Characteristics of ongoing studies](#).

Results of the search

The updated searches carried out in 2015 and 2017 were part of an update of nine Cochrane reviews, see [Table 1](#).

The 2015 search retrieved 704 references for 344 studies, see [Figure 4](#) for study flow diagram. We also screened the full texts of 10 additional records that were identified through screening reference lists of Cochrane reviews on tardive dyskinesia (TD). From these records we identified 60 new potentially relevant records for this review and screened the full texts. Agreement about which studies may have been randomised was 100%.

Figure 4. Study flow diagram for 2015 and 2017 searches.

Twenty-six of these 60 new records are records for the 21 new included studies in this update (Bucci 1971; Castro 2011; Gardos 1979; Glover 1980; Goff 1993; Hajioff 1983; Koshino 1979; Koshino 1983; Meco 1989; O'Brien 2014; Rastogi 1982; Richardson 2003; Shamir 2000; Shamir 2001; Shi 2009; UCB Pharma 2005; Woods 2008; Yang 1999; Zeng 1995; Zeng 1996; Zhang 2011). Three of the records are new companion papers to two previously included studies (Libov 2007; Mosnik 1997). Twenty of the new records were excluded (11 new unique excluded studies: Chaplin 2002; Fann 1973; Goetz 2013; Huang 1981; Kabes 1985; Lieberman 1987; Lieberman 1994; Moore 1980; Shah 2012; Tammimga 1983; Vaddadi 2002), and three of which were companions to previously excluded studies (Casey 1981; Kabes 1982; Vaddadi 1989). Four of the 60 records are in awaiting classification under three of the studies (Fernandez 2016; Hauser 2016; NCT01393600 2011) and seven are ongoing studies (Garcia 1992; ISRCTN14688109 2015; NCT00621634 2008; NCT01391390 2011; NCT01688037 2012; NCT01804920 2013; NCT02291861 2014).

The 2017 search found eight records (five studies). The editorial base of Cochrane Schizophrenia screened these records and six records (four studies) have been put into awaiting classification (Fernandez 2016; Hauser 2016; Pattojoshi 2016; Xu 2012), see [Characteristics of studies awaiting classification](#). The two remaining records are companion papers to an included study identified in the 2015 search (O'Brien 2014).

In addition, one previously excluded study could be included (Cai 1988), two studies that were in awaiting classification in the previous version of the review could be excluded (Bockenheimer 1976; Koller 1982), and one study that was in awaiting classification in the previous review was in fact a companion to the included study Libov 2007.

Included studies

This review now includes 31 studies of 24 interventions with 1278 participants, published between 1971 and 2014. See [Table 2](#) for an overview of characteristics of the included studies.

1. Methods

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

2. Design

All included studies presented a parallel longitudinal design. Seven of the 31 studies used a cross-over design with two periods (Gardos 1979; Libov 2007; Mackay 1980; Meco 1989; Mosnik 1997; Shamir 2000; Shamir 2001). We had considered this as likely when embarking on the review and have used only the data from before the first cross-over for the reasons outlined above ([Unit of analysis issues](#)).

3. Duration

Most studies were of short duration (less than nine weeks) and only one had a follow-up period longer than three months (Bucci 1971).

4. Participants

Participants, now totalling 1278 people, were mostly men in their 50s, with diagnoses of various chronic psychiatric disorders, but mainly schizophrenia. All had antipsychotic-induced TD though

only eight trials explicitly described the use of criteria for the diagnosis of TD. The number of participants ranged from 10 to 157 (median 34).

5. Setting

Most trials were conducted in hospital, seven included both in- and outpatients (Castro 2011; Emsley 2006; Kojima 1992; Mosnik 1997; O'Brien 2014; Richardson 2003; Wolkin 1986), and five included only outpatients (Bucci 1971; Glazer 1985; Glover 1980; Goff 1993; Woods 2008). The studies themselves were from around the world, with 10 conducted in the USA (Bucci 1971; Gardos 1979; Glazer 1985; Glover 1980; Goff 1993; Mosnik 1997; O'Brien 2014; Richardson 2003; Wolkin 1986; Woods 2008), six in China (Cai 1988; Shi 2009; Yang 1999; Zeng 1995; Zeng 1996; Zhang 2011), four in Japan (Kojima 1992; Koshino 1979; Koshino 1983; Matsunaga 1988), three in Israel (Libov 2007; Shamir 2000; Shamir 2001), three in the UK (Hajioff 1983; Mackay 1980; Rastogi 1982), and one each in Italy (Meco 1989), Venezuela (Castro 2011), South Africa (Emsley 2006), Morocco (Mouret 1991), and Belgium/Bulgaria (UCB Pharma 2005).

6. Interventions

6.1 Miscellaneous drugs

6.1.1 Alkaloids

a. Co-dergocrine mesylate (Hydergine)

Co-dergocrine mesylate (Hydergine; dihydrogenated ergot alkaloids) is an ergot alkaloid used to treat patients with dementia. Hajioff 1983 and Rastogi 1982 both used co-dergocrine mesylate in a dose of 4.5 mg/day. Koshino 1983 used dihydrogenated ergot alkaloids in a dose of 6 mg/day.

b. L-stepholidine

Stepholidine is a naturally occurring chemical compound found in the herb *Stephania intermedia*. Cai 1988 used L-stepholidine in a dose of two tablets, three times per day (no exact dosage provided).

c. Papaverine

Papaverine is a vasodilating agent. Gardos 1979 used papaverine in a dose ranging from 300 mg/day to 600 mg/day.

6.1.2 Amino acids

a. Branched-chain amino acids (BCAAs)

BCAAs are essential amino acids. Richardson 2003 used branched-chain amino acids in a dose ranging from 56 mg/kg to 222 mg/kg body weight.

b. Phenylalanine

Phenylalanine is an essential amino acid. Mosnik 1997 used phenylalanine in a dose of 100 mg/kg body weight for one day.

6.1.3 Antidepressant

a. MAO-B inhibitor - Selegiline

Goff 1993 used selegiline, a drug that is mainly used to reduce symptoms of Parkinson's.

b. Monoamine oxidase inhibitor (MAOI) - Isocarboxazid

Isocarboxazid is a MAOI) [Bucci 1971](#) used isocarboxazid in a dose ranging from 20 mg/day to 100 mg/day.

c. SSRI - Risperidone

Risperidone is an experimental serotonin receptor antagonist and was used in [Meco 1989](#).

6.1.4 Antiepileptics

a. Levetiracetam

Levetiracetam is a medication used to treat epilepsy. It was used by two studies ([UCB Pharma 2005](#); [Woods 2008](#)) in a maximum dose of 3000 mg/day.

6.1.5 Antihistamines

a. Cyproheptadine

Cyproheptadine is a first-generation antihistamine with additional anticholinergic, antiserotonergic, and local anaesthetic properties. [Koshino 1979](#) used cyproheptadine in a dose ranging from 12 mg/day to 24 mg/day.

6.1.6 Antipsychotics

a. Promethazine

[Yang 1999](#) used promethazine, a drug mainly used for sedation and to treat nausea.

6.1.7 Anxiolytics

a. Buspirone

Buspirone is an anxiolytic psychotropic drug used to treat general anxiety disorder. It was used by one study ([Zeng 1995](#)) in a dose of 6 to 12 capsules per day (exact dose not provided).

6.1.8 Cognitive enhancer

a. Pemoline

Pemoline is a stimulant drug of the 4-oxazolidinone class. It was used by [Zeng 1996](#) in a dose of two capsules per day (exact dose not provided).

b. Piracetam

Piracetam is a cyclic derivative of GABA. [Libov 2007](#) used piracetam in a dose of 4800 mg/day.

6.1.9 Enzyme inhibitor

a. Valbenazine (NBI-98854)

Valbenazine is a vesicular monoamine transporter type 2 (VMAT2) inhibitor. [O'Brien 2014](#) used NBI-98854 in a dose ranging from 25 mg/day to 75 mg/day.

6.1.10 Fatty acid

a. Ethyl-EPA

Ethyl-EPA is a derivative of eicosapentaenoic acid (EPA), an omega-3 fatty acid. [Emsley 2006](#) used ethyl-EPA in a dose of 2 g/day.

b. Gamma-linolenic acid

Gamma-linolenic acid was first isolated from the seed oil of evening primrose. It was used by one study ([Volkin 1986](#)) in a dose of 600 mg/day.

6.1.11 Herb

a. EGB-761

EGB-761 is the standardised extract of *Ginkgo biloba* leaves that has antioxidant properties as a free radical scavenger. It was used by [Zhang 2011](#) in a dose of 240 mg/day.

6.1.12 Hormone

a. Oestrogen

Oestrogen is the primary female sex hormone. [Glazer 1985](#) used oestrogen in a dose of 1.25 mg/day.

b. Insulin

Insulin is a peptide hormone produced by the pancreas. [Mouret 1991](#) used insulin in a dose of 10 units per day (exact dose not provided).

c. Melatonin

Melatonin is a naturally occurring hormone. Four studies ([Castro 2011](#); [Shamir 2000](#); [Shamir 2001](#); [Shi 2009](#)) used melatonin in doses ranging from 2 mg/day to 20 mg/day.

6.1.13 Mood stabiliser

a. Lithium

Lithium is primarily used for bipolar disorder. [Mackay 1980](#) used lithium in an unspecified dose.

6.1.14 Polypeptide

a. Ceruletide

Ceruletide is a 10 amino acid oligopeptide that stimulates smooth muscle and increases digestive secretions. [Kojima 1992](#) and [Matsunaga 1988](#) both used ceruletide in a dose of 0.8 microgram/kg/week.

6.2 Other miscellaneous treatments

6.2.1 Hypnosis or relaxation

[Glover 1980](#) used eight sessions of hypnosis or relaxation.

6.3 Comparison groups

In most of the studies a placebo was used as a comparison group, with few further details given. In one study the comparison group was given procyclidine ([Bucci 1971](#)), which is an anticholinergic drug (see also [Bergman 2018a](#)). Three studies ([Gardos 1979](#); [Glover 1980](#); [Shi 2009](#)) compared active intervention against standard treatment.

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 (AIMS)

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 Abbreviated Dyskinesia Rating Scale - Simpson Rating Scale (SRS)

This 15-item scale measures the movements around the orofacial region, neck, trunk and extremities ([Simpson 1979](#)). Each of these items can be scored from one (absent) to six (severe). This scale ranges from 10 to 102 with higher scores indicating greater severity.

7.2.3 Rockland Tardive Dyskinesia Rating Scale- Rockland TD

The Rockland TD ([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.

7.2.4 Extrapyramidal symptom rating scale (ESRS)

The ESRS was developed to assess four types of drug-induced movement disorders (DIMD): parkinsonism, akathisia, dystonia, and TD ([Chouinard 2005](#)). The score for TD, ranging from zero to 42, is based on the sum of all seven items in the TD objective examination.

7.2.5 St. Hans Rating Scale (SHRS) for extrapyramidal syndromes

The SHRS is a multidimensional rating scale for the evaluation of antipsychotic-induced hyperkinesia, parkinsonism, akathisia and dystonia ([Gerlach 1993](#)). Each item is rated from zero (not present) to six (present to an extreme degree). This gives a total score from zero to 48 for hyperkinesia and parkinsonism.

7.3 Scales used to measure global- and mental state and behaviour

7.3.1 Brief Psychiatric Rating Scale (BPRS)

The BPRS is an 18-item scale measuring positive symptoms, general psychopathology and affective symptoms ([Overall 1962](#)). The original scale has 16 items, although a revised 18-item scale is commonly used. Total scores can range from zero to 126. Each item

is rated on a seven-point scale, with high scores indicating more severe symptoms.

7.3.2 Wechsler Adult Intelligence Scale (WAIS)

The WAIS is an IQ test designed to measure intelligence and cognitive ability in adults and older adolescents ([Wechsler 1958](#)).

7.3.3 Wechsler Memory Scale (WMS)

The WMS is a neuropsychological test designed to measure different memory functions in a person ([Wechsler 1945](#)).

7.3.4 Positive and Negative Syndrome Scale (PANSS)

The PANSS is a medical scale used for measuring symptom severity of patients with schizophrenia ([Kay 1987](#)). The patient is rated from one to seven on 30 different symptoms based on the interview as well as reports of family members or primary care hospital workers.

7.3.5 Continuous performance test (CPT)

The CPT is a neurophysiological test that measures a person's sustained and selective attention ([Rosvold 1956](#)).

7.3.6 Clinical Global Impression Scale (CGI)

The CGI assesses both severity of illness and clinical improvement by comparing conditions of the person standardised against other people with the same diagnosis ([Guy 1976](#)).

7.4 Scales used to measure adverse events

7.4.1 Treatment Emergent Symptom Scale (TESS)

The TESS is a checklist that assesses a variety of characteristics for each adverse event ([Guy 1976](#)).

Excluded studies

There are 39 excluded studies. Sixteen studies ([Bjorndal 1980](#); [Blum 1984](#); [Bowers 1979](#); [Casey 1981](#); [Gardos 1978](#); [Jus 1974](#); [Korsgaard 1981](#); [Moore 1980](#); [Prange 1973](#); [Reda 1974](#); [Reker 1982](#); [Simpson 1976 a](#); [Simpson 1976 b](#); [Villeneuve 1970](#); [Villeneuve 1980](#); [Volavka 1986](#)) were not randomised and we have therefore excluded them. Eight studies ([Apseloff 2000](#); [Chaplin 2002](#); [Emsley 2002](#); [Goetz 2013](#); [Lieberman 1987](#); [Lieberman 1994](#); [Shah 2012](#); [Vaddadi 2002](#)) were excluded because participants had schizophrenia or other disorders but not TD. After unfruitful attempts to contact authors for further details, we have also excluded a further 14 randomised studies which reported no usable data ([Fann 1973](#); [Fudge 1991](#); [Gerlach 1975](#); [Jus 1978](#); [Kabes 1982](#); [Kabes 1985](#); [Koller 1982](#); [Lindenmayer 1988](#); [Nasrallah 1986](#); [Peselow 1989](#); [Tamminga 1983](#); [Vaddadi 1989](#); [Wonodi 2004](#)). One study that was excluded in the previous version of this review ([Huang 1981](#)), and [Bockenheimer 1976](#) that was previously in awaiting classification, have now been included in other intervention reviews for TD and were excluded from this review.

Awaiting classification

There are currently five studies awaiting classification.

1. [Fernandez 2016](#) investigated the VMAT-2 inhibitor deutetrabenazine (SD-809) compared to placebo in participants with TD in the USA and three European countries. We could only identify a conference abstract with limited details for this study. We are awaiting more detailed data to add to the review.

2. [Hauser 2016](#) investigated the VMAT-2 inhibitor valbenazine (NBI-98854) compared to placebo in participants with TD in Canada, Puerto Rico, and the USA. We could only identify two conference abstracts, a poster, and an online trial registry record with limited details for this study. We are awaiting more detailed data to add to the review.
3. [NCT01393600 2011](#) investigated the VMAT-2 inhibitor valbenazine (NBI-98854) compared to placebo in participants with TD in the USA. This online cross-over trial record reported outcome results for combined groups only. We are awaiting separate results for the period before cross-over.
4. [Pattojoshi 2016](#) investigated right dorsolateral prefrontal cortex-repetitive transcranial magnetic stimulation (rTMS) versus sham rTMS in participants with TD. We could only identify a conference abstract with limited details for this study. We are awaiting more detailed data to add to the review.
5. [Xu 2012](#) investigated *Ginkgo biloba* extract versus standard treatment in participants with TD in China. We are awaiting translation of this article in Chinese.

Ongoing studies

We identified seven ongoing studies.

1. [Garcia 1992](#) investigates buspirone compared with placebo in participants with TD in the USA.
2. [ISRCTN14688109 2015](#) investigates cannabidiol extract compared to vitamin E in participants with TD in Nigeria.
3. [NCT00621634 2008](#) investigates omega-3 fish oil capsules (including docosahexaenoic acid) compared to placebo in participants with TD in Canada.
4. [NCT01391390 2011](#) investigates melatonin compared to placebo in participants with TD in China.
5. ([NCT01688037 2012](#)) investigates the VMAT-2 inhibitor valbenazine (NBI-98854) compared to placebo in participants with TD in the USA and Puerto Rico.
6. [NCT01804920 2013](#) investigates d-serine compared to placebo in participants with TD in Israel.
7. [NCT02291861 2014](#) investigates the VMAT-2 inhibitor deutetrabenazine (SD-809) compared to placebo in participants with TD in the USA and five European countries.

Risk of bias in included studies

Please refer to [Figure 2](#) and [Figure 3](#) for graphical overviews of the risk of bias in the included studies.

Allocation

Only four studies ([Shamir 2000](#); [Shamir 2001](#); [Yang 1999](#); [Zhang 2011](#)) were rated at low risk of selection bias. These studies were randomised centrally and described concealed allocation to groups. Most other studies were not explicit about how allocation was achieved or how a randomised sequence was generated other than using the word "randomized".

Blinding

Although most studies were stated to be conducted on a double-blind basis, only five studies ([Cai 1988](#); [Goff 1993](#); [Mackay 1980](#); [Shamir 2000](#); [Zhang 2011](#)) explicitly described how blinding of the participants, personnel, and outcome assessors was performed. No study reported testing the blindness of raters, clinicians and trial

participants. Many of the other studies gave no further details other than stating that they were double-blinded.

Incomplete outcome data

Most studies reported that either all participants completed the study, or analysed outcomes for all randomised participants. Five studies ([Goff 1993](#); [Kojima 1992](#); [Libov 2007](#); [Matsunaga 1988](#); [UCB Pharma 2005](#)) were rated as having a high risk of attrition bias, due to high rate of participants who dropped out and a lack of ITT analyses.

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. Five studies reported results of all outcomes listed in the methods section fully ([Glover 1980](#); [Libov 2007](#); [Shi 2009](#); [Yang 1999](#); [Zeng 1995](#); [Zeng 1996](#)). We rated risk of reporting bias for many of the other studies as unclear because we have had no opportunity to see protocols of these trials to compare the outcomes reported in the full-text publications with what was measured during the conduct of the trial. Eleven 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, which increases the likelihood of treatment effects going undetected. Seven of the studies used a cross-over design ([Gardos 1979](#); [Libov 2007](#); [Mackay 1980](#); [Meco 1989](#); [Mosnik 1997](#); [Shamir 2000](#); [Shamir 2001](#)). One study ([Glazer 1985](#)) was rated at high risk of bias as they described unequal groups at baseline with regard to duration of TD symptoms and medication use.

Effects of interventions

See: [Summary of findings for the main comparison ALKALOID - DIHYDROGENATED ERGOT ALKALOIDS versus PLACEBO for antipsychotic-induced tardive dyskinesia](#); [Summary of findings 2 ANTIEPILEPTIC - LEVETIRACETAM versus PLACEBO for antipsychotic-induced tardive dyskinesia](#); [Summary of findings 3 ANXIOLYTIC - BUSPIRONE versus PLACEBO for antipsychotic-induced tardive dyskinesia](#); [Summary of findings 4 ENZYME INHIBITOR - VMAT2-INHIBITOR \(valbenazine\) versus PLACEBO for antipsychotic-induced tardive dyskinesia](#); [Summary of findings 5 FATTY ACID - ETHYL-EPA versus PLACEBO for antipsychotic-induced tardive dyskinesia](#); [Summary of findings 6 HERB - GINKGO BILOBA versus PLACEBO for antipsychotic-induced tardive dyskinesia](#); [Summary of findings 7 HORMONE - MELATONIN versus PLACEBO OR NO TREATMENT for antipsychotic-induced tardive dyskinesia](#); [Summary of findings 8 POLYPEPTIDE - CERULETIDE versus PLACEBO for antipsychotic-induced tardive dyskinesia](#); [Summary of findings 9 HYPNOSIS OR RELAXATION versus TAU for antipsychotic-induced tardive dyskinesia](#)

1. Comparison 1. Alkaloid - Dihydrogenated ergot alkaloids (DEA) versus placebo

Three trials ([Hajioff 1983](#); [Koshino 1983](#); [Rastogi 1982](#)) carried out in Japan and the UK that included 88 inpatients with antipsychotic-induced TD were included for this comparison.

1.1 TD symptoms

1.1.1 No clinically important improvement

The overall results for 'clinically relevant improvement' found a benefit in favour of DEA against placebo (low-quality evidence, 1 trial, 28 people, risk ratio (RR) 0.45, 95% confidence interval (CI) 0.21 to 0.97, [Analysis 1.1](#)).

1.1.2 Not any improvement

For the outcome of 'any improvement in TD symptoms', we found no benefit of DEA against placebo (1 trial, 28 people, RR 0.50, 95% CI 0.23 to 1.09, [Analysis 1.2](#)).

1.1.3 Deterioration of symptoms

There was no difference on deterioration of symptoms between DEA and placebo (very low-quality evidence, 1 trial, 28 people, RR 0.33, 95% CI 0.01 to 7.55, [Analysis 1.3](#)).

1.1.4 Average endpoint scores

TD symptoms were also measured on the continuous Simpson scale (see above). No benefit was found when DEA is compared to placebo (1 trial, 28 people, mean difference (MD) -2.80, 95% CI -12.25 to 6.65, [Analysis 1.4](#)).

1.1.4 Average change scores

TD symptoms were also measured on the continuous Abnormal Involuntary Movement Scale (AIMS), Rockland Tardive Dyskinesia Rating Scale (RTDS), and Abbreviated Dyskinesia Scale (ADS) scales (see above). No benefit was found when pooling changes scores of these scales for DEA compared to placebo (2 trials, 59 people, standardised mean difference (SMD) -0.31, 95% CI -0.83 to 0.20, [Analysis 1.5](#)).

1.2 Mental state

For the outcome of mental state deterioration, no benefit was found for DEA when compared to placebo (1 trial, 28 people, MD 0.50, 95% CI 0.05 to 4.90, [Analysis 1.6](#)).

1.3 Adverse effects

There was no difference in the incidence of 'any adverse effect' between DEA and placebo (very low-quality evidence, 1 trial, 28 people, RR 2.33 95% CI 0.75 to 7.23, [Analysis 1.7](#)).

1.4 Leaving the study early

Using DEA did not significantly increase the chances of a person leaving the study early (very low-quality evidence, 2 trials, 48 people, RR 0.33, 95% CI 0.02 to 7.32, [Analysis 1.8](#)).

2. Comparison 2. Alkaloid - L-Stepholidine (SPD) versus placebo

One trial ([Cai 1988](#)) that included 57 patients with antipsychotic-induced TD was included for this comparison.

2.1 TD symptoms

2.1.1 No clinically important improvement

The overall results for 'clinically relevant improvement' found a benefit in favour of SPD against placebo (1 trial, 57 people, RR 0.54, 95% CI 0.35 to 0.82, [Analysis 2.1](#)).

2.2 Mental state

General mental state was measured using the continuous BPRS scale (see above). A benefit was found in favour of SPD when compared to placebo (1 trial, 20 people, MD -4.50, 95% CI -7.60 to -1.40, [Analysis 2.2](#)).

2.3 Adverse effects

No adverse effects were reported.

2.4 Leaving the study early

No participants left the included study early.

3. Comparison 3. Alkaloid - Papaverine versus placebo

One trial ([Gardos 1979](#)) carried out in the USA that included 22 inpatients with antipsychotic-induced TD was included for this comparison.

3.1 TD symptoms

TD symptoms were measured on the continuous AIMS scale (see above). No difference was found when papaverine was compared to placebo (1 trial, 22 people, MD 0.51, 95% CI -1.18 to 2.20, [Analysis 3.1](#)).

4. Comparison 4. Amino acid - Branched-chain amino acids (BCAA) versus placebo

One trial ([Richardson 2003](#)) carried out in the USA that included 52 in- and out-patients with antipsychotic-induced TD was included for this comparison.

4.1 TD symptoms

4.1.1 No clinically important improvement

The overall results for 'clinically relevant improvement' found no benefit of BCAA against placebo (1 trial, 52 people, RR 0.79, 95% CI 0.63 to 1.00, [Analysis 4.1](#)).

4.1.2 Not any improvement

For the outcome of 'any improvement in TD symptoms', we again found no benefit of BCAA against placebo (1 trial, 52 people, RR 0.64, 95% CI 0.36 to 1.11, [Analysis 4.2](#)).

4.1.3 Deterioration of symptoms

There was no difference on deterioration of symptoms between BCAA and placebo (1 trial, 36 people, RR 0.29, 95% CI 0.07 to 1.19, [Analysis 4.3](#)).

4.1.4 Average endpoint scores

TD symptoms were also measured on the continuous Simpson scale (see above). A benefit was found in favour of BCAA when compared to placebo (1 trial, 41 people, MD -92.90, 95% CI -167.57 to -18.23, [Analysis 4.4](#)).

4.2 Leaving the study early

Using BCAA did not significantly increase the chances of a person leaving the study early when compared to placebo (1 trial, 52 people, RR 0.84, 95% CI 0.37 to 1.92, [Analysis 4.5](#)).

5. Comparison 5. Amino acid - Phenylalanine versus placebo

One trial ([Mosnik 1997](#)) carried out in the USA that included 18 in- and out-patients with antipsychotic-induced TD was included for this comparison.

5.1 Leaving the study early

Using phenylalanine did not significantly increase the chances of a person leaving the study early when compared to placebo (1 trial, 18 people, RR 2.45, 95% CI 0.11 to 53.25, [Analysis 5.1](#)).

6. Comparison 6. Antidepressant (MAO-B inhibitor) - Selegiline versus placebo

One trial ([Goff 1993](#)) carried out in the USA that included 33 outpatients with antipsychotic-induced TD was included for this comparison.

6.1 TD symptoms

6.1.1 No clinically important improvement

The overall results for 'clinically relevant improvement' found no benefit of selegiline against placebo (1 trial, 33 people, RR 1.37, 95% CI 0.96 to 1.94; [Analysis 6.1](#)).

6.2 Leaving the study early

Using selegiline did not significantly increase the chances of a person leaving the study early (1 trial, 33 people, RR 10.39, 95% CI 0.62 to 173.97; [Analysis 6.2](#)).

7. Comparison 7. Antidepressant (MAOI) - Isocarboxazid versus procyclidine

One trial ([Bucci 1971](#)) carried out in the USA that included 20 outpatients with antipsychotic-induced TD was included for this comparison.

7.1 TD symptoms

7.1.1 No clinically important improvement

The overall results for 'clinically relevant improvement' found a benefit in favour of isocarboxazid against procyclidine (1 trial, 20 people, RR 0.24, 95% CI 0.08 to 0.71, [Analysis 7.1](#)).

7.1.2 Not any improvement

For the outcome of 'any improvement in TD symptoms', we again found a benefit in favour of isocarboxazid against procyclidine (1 trial, 20 people, RR 0.14, 95% CI 0.03 to 0.64, [Analysis 7.2](#)).

7.2 Adverse effects

There was no difference in the incidence of 'any adverse effect' between isocarboxazid and procyclidine (1 trial, 20 people, RR 3.00, 95% CI 0.14 to 65.90, [Analysis 7.3](#)).

7.3 Leaving the study early

Using isocarboxazid did not significantly increase the chances of a person leaving the study early compared with procyclidine (1 trial, 20 people, RR 3.00, 95% CI 0.14 to 65.90, [Analysis 7.4](#)).

8. Comparison 8. Antidepressant (SSRI) - Risperidone versus placebo

One trial ([Meco 1989](#)) carried out in Italy that included 10 inpatients with antipsychotic-induced TD was included for this comparison.

8.1 TD symptoms

8.1.1 No clinically important improvement

For the outcome of 'any improvement in TD symptoms', we found no benefit of risperidone against placebo (1 trial, 10 people, RR 1.00, 95% CI 0.70 to 1.43; [Analysis 8.1](#)).

8.1.2 Not any improvement

For the outcome of 'any improvement in TD symptoms', we again found no benefit of risperidone against placebo (1 trial, 10 people, RR 0.28, 95% CI 0.02 to 4.66; [Analysis 8.2](#)).

8.1.3 Deterioration of symptoms

There was no difference on deterioration of TD symptoms between risperidone and placebo (1 trial, 10 people, RR 0.47, 95% CI 0.02 to 9.26; [Analysis 8.3](#)).

8.1.4 Average change scores

TD symptoms were measured on the continuous AIMS scale (see above). No difference was found when risperidone was compared to placebo (1 trial, 10 people, MD -2.00, 95% CI -5.93 to 1.93; [Analysis 8.4](#)).

8.2 Mental state

8.2.1 Deterioration of symptoms

There was no difference on deterioration of mental state symptoms between risperidone and placebo (1 trial, 10 people, RR 0.47, 95% CI 0.02 to 9.26; [Analysis 8.5](#)).

8.2.2 Average change scores

General mental state was measured using the continuous BPRS scale (see above). No benefit was found for risperidone when compared to placebo (1 trial, 10 people, MD -0.80, 95% CI -3.10 to 1.50; [Analysis 8.6](#)).

9. Comparison 9. Antiepileptic - Levetiracetam versus placebo

Two trials ([UCB Pharma 2005](#); [Woods 2008](#)) carried out in Belgium, Bulgaria, and the USA that included 119 in- or out-patients with antipsychotic-induced TD were included for this comparison.

9.1 TD symptoms

9.1.1 Average endpoint scores

TD symptoms were measured on the continuous AIMS scale (see above). A benefit was found in favour of levetiracetam compared to placebo (1 trial, 50 people, MD -2.18, 95% CI -3.65 to -0.71, [Analysis 9.1](#)).

9.1.1 Average change scores

TD symptoms were also measured on the continuous St Hans rating scale (see above). There was no difference in change scores between levetiracetam and placebo (1 trial, 69 people, MD 0.13, 95% CI -0.73 to 0.99, [Analysis 9.2](#)).

9.2 Leaving the study early

Using levetiracetam did not significantly increase the chances of a person leaving the study early (very low-quality evidence, 2 trials, 119 people, RR 1.01, 95% CI 0.46 to 2.22, [Analysis 9.3](#)).

9.3 Adverse effects

There was no difference in the incidence of 'any adverse effect' between levetiracetam and placebo (low-quality evidence, 1 trial, 69 people, RR 0.51, 95% CI 0.25 to 1.04, [Analysis 9.4](#)).

9.4 Mental state

We found no difference between levetiracetam and placebo for deterioration of mental state (1 trial, 50 people, RR 0.67, 95% CI 0.12 to 3.65, [Analysis 9.5](#)).

10. Comparison 10. Antihistamine - Cyproheptadine versus placebo

One trial ([Koshino 1979](#)) carried out in Japan that included 42 inpatients with schizophrenia and TD was included for this comparison.

10.1 TD symptoms

10.1.1 Not any improvement

For the outcome of 'any improvement in TD symptoms', we found no benefit of cyproheptadine against placebo (1 trial, 42 people, RR 0.54, 95% CI 0.27 to 1.08, [Analysis 10.1](#)).

10.1.2 Deterioration of symptoms

There was no difference on deterioration of symptoms between cyproheptadine and placebo (1 trial, 42 people, RR 0.33, 95% CI 0.01 to 7.74, [Analysis 10.2](#)).

10.2 Adverse effects

There was no difference in the incidence of 'any adverse effect' between cyproheptadine and placebo (1 trial, 42 people, RR 0.33, 95% CI 0.04 to 2.95, [Analysis 10.3](#)).

10.3 Leaving the study early

Using cyproheptadine did not significantly increase the chances of a person leaving the study early (1 trial, 42 people, RR 0.33, 95% CI 0.01 to 7.74, [Analysis 10.4](#)).

11. Comparison 11. Antipsychotic - Promethazine versus placebo

One trial ([Yang 1999](#)) carried out in China that included 34 inpatients with antipsychotic-induced TD was included for this comparison.

11.1 TD symptoms

11.1.1 No clinically important improvement

The overall results for 'clinically relevant improvement' found a benefit in favour of promethazine against placebo (1 trial, 34 people, RR 0.24, 95% CI 0.11 to 0.55, [Analysis 11.1](#)).

11.1.2 Not any improvement

For the outcome of 'any improvement in TD symptoms', we again found a benefit in favour of promethazine against placebo (1 trial, 34 people, RR 0.06, 95% CI 0.01 to 0.43; [Analysis 11.2](#)).

11.1.3 Average endpoint scores

A benefit in favour of promethazine against placebo was also found for reduction of TD symptoms on the AIMS scale (1 trial, 34 people, MD -7.10, 95% CI -9.53 to -4.67; [Analysis 11.3](#)).

11.2 Mental state

11.2.1 Average endpoint scores

General mental state was measured using the continuous BPRS scale (see above). No benefit was found for promethazine when compared to placebo (1 trial, 34 people, MD 0.70, 95% CI -3.77 to 5.17; [Analysis 11.4](#)).

11.3 Adverse effects

11.3.1 Any adverse effects

No difference was found for any adverse events measured on the TESS scale (see above) between promethazine and placebo (1 trial, 34 people, MD -0.10, 95% CI -0.53 to 0.33; [Analysis 11.5](#)).

11.3.2 Parkinsonism: average endpoint scores

No difference was found for parkinsonism adverse events measured on the RSESE scale (see above) between promethazine and placebo (1 trial, 34 people, MD -0.50, 95% CI -1.36 to 0.36; [Analysis 11.6](#)).

11.4 Global state

11.4.1 Average endpoint scores

Global state was measured using the continuous Clinical Global Impression (CGI) scale (see above). A benefit in global state was found for promethazine when compared to placebo (1 trial, 34 people, MD -3.00, 95% CI -3.78 to -2.22; [Analysis 11.7](#)).

12. Comparison 12. Anxiolytic - Buspirone versus placebo

One study ([Zeng 1995](#)) carried out in China that included 42 inpatients with schizophrenia and TD was included for this comparison.

12.1 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 the data we found in trials did not fit this exactly we feel that the outcome 'clinically relevant improvement' fits best with what we had hoped to find.

12.1.1 No clinically important improvement

The overall results for 'clinically relevant improvement' found a benefit in favour of buspirone against placebo (low-quality evidence, 1 trial, 42 people, RR 0.53, 95% CI 0.33 to 0.84, [Analysis 12.1](#)).

12.1.2 Not any improvement

For the outcome of 'any improvement in TD symptoms', we found a benefit of buspirone against placebo (1 trial, 42 people, RR 0.33, 95% CI 0.15 to 0.75, [Analysis 12.2](#)).

12.1.3 Average endpoint scores

TD symptoms were also measured on the continuous AIMS scale (see above). No difference was found when buspirone was compared to placebo (1 trial, 42 people, MD 0.00, 95% CI -1.45 to 1.45, [Analysis 12.3](#)).

12.2 Leaving the study early

No participants left the included study early.

13. Comparison 13. Cognitive enhancer - Piracetam versus placebo

One trial ([Libov 2007](#)) carried out in Israel that included 40 inpatients with antipsychotic-induced TD was included for this comparison.

13.1 TD symptoms

13.1.1 Average endpoint scores

TD symptoms were measured on the continuous Extrapyramidal System Rating Scale (ESRS) scale (see above). No difference was found between piracetam and placebo (1 trial, 35 people, MD -0.70, 95% CI -4.30 to 2.90, [Analysis 13.1](#)).

13.2 Adverse effects

Symptoms of parkinsonism were also measured on the continuous ESRS scale (see above). No difference was found between piracetam and placebo (1 trial, 35 people, MD 2.50, 95% CI -4.73 to 9.73, [Analysis 13.2](#)).

13.3 Leaving the study early

Using piracetam did not significantly increase the chances of a person leaving the study early (1 trial, 40 people, RR 0.23, 95% CI 0.03 to 1.85, [Analysis 13.3](#)).

13.4 Global state

We found no difference in global state measured by the CGI (see above) between piracetam and placebo (1 trial, 35 people, MD 0.20, 95% CI -0.35 to 0.75, [Analysis 13.4](#)).

14. Comparison 14. Cognitive enhancer/stimulant - Pemoline versus placebo

One trial ([Zeng 1996](#)) carried out in China that included 46 inpatients with antipsychotic-induced TD was included for this comparison.

14.1 TD symptoms

14.1.1 No clinically important improvement

The overall results for 'clinically relevant improvement' found a benefit in favour of pemoline against placebo (1 trial, 46 people, RR 0.48, 95% CI 0.29 to 0.77, [Analysis 14.1](#)).

14.1.2 Not any improvement

For the outcome of 'any improvement in TD symptoms', we again found a benefit in favour of pemoline against placebo (1 trial, 46 people, RR 0.29, 95% CI 0.13 to 0.66, [Analysis 14.2](#)).

14.1.3 Average endpoint scores

TD symptoms were also measured on the continuous AIMS scale (see above). A difference in favour of pemoline was found when

compared to placebo (1 trial, 46 people, MD -3.90, 95% CI -5.47 to -2.33, [Analysis 14.3](#)).

14.2 Leaving the study early

No participants left the included study early.

15. Comparison 15. Enzyme inhibitor - VMAT2 inhibitors versus placebo

15.1 TD symptoms

15.1.1 No clinically important improvement

The overall results for 'clinically relevant improvement' found a benefit in favour of valbenazine (NBI-98854) against placebo (moderate-quality evidence, 1 trial, 92 people, RR 0.63, 95% CI 0.46 to 0.86, [Analysis 15.1](#)).

15.1.2 Average change scores

TD symptoms were measured on the continuous AIMS scale (see above). A benefit in favour of valbenazine was found against placebo (1 trial, 89 people, MD -2.50, 95% CI -4.00 to -1.00; [Analysis 15.2](#)).

15.2 Adverse effects

The incidence of overall adverse events such as fatigue, headache, decreased appetite, nausea and somnolence was higher in the valbenazine group compared to placebo (low-quality evidence, 1 trial, 100 people, RR 1.50, 95% CI 0.92 to 2.45; [Analysis 15.3](#)), but the difference was not significant.

15.3 Leaving the study early

Using VMAT2-I did not significantly increase the chances of a person leaving the study early (very low-quality evidence, 1 trial, 102 people, RR 1.00, 95% CI 0.31 to 3.25, [Analysis 15.4](#)).

16. Comparison 16. Fatty acid - Ethyl-eicosapentaenoic acid (ethyl-EPA) versus placebo

One trial ([Emsley 2006](#)) carried out in South Africa that included 84 in- and out-patients with antipsychotic-induced TD was included for this comparison.

16.1 TD symptoms

16.1.1 Not any improvement

For the outcome of 'any improvement in TD symptoms', there was no benefit of ethyl-EPA against placebo (1 trial, 75 people, RR 0.82, 95% CI 0.57 to 1.18, [Analysis 16.1](#)).

16.2 Mental state

There was no difference on deterioration of mental state between ethyl-EPA and placebo (1 trial, 75 people, RR 0.49, 95% CI 0.05 to 5.14, [Analysis 16.2](#)).

16.3 Adverse effects

16.3.1 Extrapyramidal symptoms: parkinsonism

Symptoms of parkinsonism were measured on the continuous ESRS scale (see above). No difference was found between ethyl-EPA and placebo (low-quality evidence, 1 trial, 75 people, MD 0.30, 95% CI -1.17 to 1.77, [Analysis 16.3](#)).

16.3.2 Extrapyramidal symptoms: dystonia

Symptoms of dystonia were measured on the continuous ESRS scale (see above). A benefit was found in favour of ethyl-EPA when compared to placebo (low-quality evidence, 1 trial, 75 people, MD -0.35, 95% CI -0.58 to -0.12, [Analysis 16.4](#)).

16.3.3 Extrapyramidal symptoms: akathisia

Symptoms of akathisia were measured on the continuous ESRS scale (see above). No difference was found between ethyl-EPA and placebo (very low-quality evidence, 1 trial, 75 people, MD -0.04 CI -0.30 to 0.22, [Analysis 16.5](#)).

16.4 Leaving the study early

Using ethyl-EPA did not significantly increase the chances of a person leaving the study early (very low-quality evidence, 1 trial, 84 people, RR 0.57, 95% CI 0.27 to 1.22, [Analysis 16.6](#)).

17. Comparison 17. Fatty acid - Gamma-linolenic acid versus placebo

One trial ([Wolkin 1986](#)) carried out in the USA that included 16 in- and out-patients with antipsychotic-induced TD was included for this comparison.

17.1 TD symptoms

17.1.1 No clinically important improvement

The overall results for 'clinically relevant improvement', added across all time points, found no benefit of gamma-linolenic acid against placebo (1 trial, 16 people, RR 1.00, 95% CI 0.69 to 1.45, [Analysis 17.1](#)).

17.1.2 Not any improvement

For the outcome of 'any improvement in TD symptoms', we again found no benefit of gamma-linolenic acid against placebo (1 trial, 16 people, RR 0.75, 95% CI 0.24 to 2.33, [Analysis 17.2](#)).

17.1.3 Deterioration of symptoms

There was no difference on deterioration of symptoms between gamma-linolenic acid and placebo (1 trial, 16 people, RR 1.50, 95% CI 0.34 to 6.70, [Analysis 17.3](#)).

17.1.4 Average change scores

TD symptoms were also measured on the continuous AIMS scale (see above). No benefit was found for gamma-linolenic acid when compared to placebo (1 trial, 16 people, MD -0.20, 95% CI -3.10 to 2.70, [Analysis 17.4](#)).

17.2 Mental state

General mental state was measured using the continuous Brief Psychiatric Rating Scale (BPRS) (see above). No benefit was found for gamma-linolenic acid when compared to placebo (1 trial, 10 people, MD -6.00, 95% CI -15.99 to 3.99, [Analysis 17.5](#)).

17.3 Leaving the study early

No participants left the included study early.

18. Comparison 18. Herb - Ginkgo biloba versus placebo

One trial ([Zhang 2011](#)) carried out in China that included 157 inpatients with antipsychotic-induced TD was included for this comparison.

18.1 TD symptoms

18.1.1 No clinically important improvement

The overall results for 'clinically relevant improvement' found a benefit in favour of *Ginkgo biloba* when compared to placebo (moderate-quality evidence, 1 trial, 157 people, RR 0.88, 95% CI 0.81 to 0.96, [Analysis 18.1](#)).

18.1.2 Not any improvement

For the outcome of 'any improvement in TD symptoms', we again found a benefit of *Ginkgo biloba* when compared to placebo (1 trial, 157 people, RR 0.51, 95% CI 0.41 to 0.65, [Analysis 18.2](#)).

18.1.3 Average endpoint scores

TD symptoms were also measured on the continuous AIMS scale (see above). A benefit was found in favour of *Ginkgo biloba* compared to placebo (1 trial, 157 people, MD -2.06, 95% CI -2.94 to -1.18, [Analysis 18.3](#)).

18.2 Leaving the study early

Using *Ginkgo biloba* did not significantly increase the chances of a person leaving the study early (very low-quality evidence, 1 trial, 157 people, RR 0.25, 95% CI 0.03 to 2.22, [Analysis 18.4](#)).

18.3 Mental state

18.3.1 Deterioration of mental state

There was no difference in deterioration of mental state between *Ginkgo biloba* and placebo (1 trial, 157 people, RR 0.34, 95% CI 0.01 to 8.16, [Analysis 18.5](#)).

18.3.2 Average endpoint scores

Mental state was also measured using the continuous Positive and Negative Syndrome Scale (PANSS) (see above). A benefit was found in favour of *Ginkgo biloba* when compared to placebo (1 trial, 157 people, MD -3.30, 95% CI -6.51 to -0.09, [Analysis 18.6](#)).

18.4 Cognitive function

Cognitive function was measured using the continuous CPT-37 scale (see above). No difference was found between *Ginkgo biloba* and placebo on this outcome (1 trial, 119 people, MD -0.02, 95% CI -0.10 to 0.06, [Analysis 18.7](#)).

19. Comparison 19. Hormone - Oestrogen versus placebo

One trial ([Glazer 1985](#)) carried out in the USA that included 12 outpatients with antipsychotic-induced TD was included for this comparison.

19.1 TD symptoms

19.1.1 No clinically important improvement

The overall results for 'clinically relevant improvement' found no benefit of oestrogen against placebo (1 trial, 12 people, RR 1.18, 95% CI 0.76 to 1.83, [Analysis 19.1](#)).

19.1.2 Not any improvement

For the outcome of 'any improvement in TD symptoms', we again found no benefit of oestrogen against placebo (1 trial, 12 people, RR 0.33, 95% CI 0.05 to 2.37, [Analysis 19.2](#)).

19.1.3 Deterioration of symptoms

There was no difference on deterioration of symptoms between oestrogen and placebo (1 trial, 10 people, RR 0.20, 95% CI 0.01 to 3.35, [Analysis 19.3](#)).

19.1.4 Average endpoint scores

TD symptoms were also measured on the continuous AIMS scale (see above). No difference was found between oestrogen and placebo (1 trial, 10 people, MD -1.20, 95% CI -4.18 to 1.78, [Analysis 19.4](#)).

19.2 Adverse effects

There was no difference in the incidence of 'any adverse effect' between oestrogen and placebo (1 trial, 12 people, RR 0.33, 95% CI 0.02 to 6.86, [Analysis 19.5](#)).

19.3 Leaving the study early

Using oestrogen did not significantly increase the chances of a person leaving the study early (1 trial, 12 people, RR 1.00, 95% CI 0.08 to 12.56, [Analysis 19.6](#)).

20. Comparison 20. Hormone - Insulin versus placebo

One trial ([Mouret 1991](#)) carried out in Morocco that included 20 inpatients with antipsychotic-induced TD was included for this comparison.

20.1 TD symptoms

20.1.1 No clinically important improvement

The overall results for 'clinically relevant improvement' found a benefit in favour of insulin against placebo (1 trial, 20 people, RR 0.52, 95% CI 0.29 to 0.96, [Analysis 20.1](#)).

20.1.2 Not any improvement

For the outcome of 'any improvement in TD symptoms', we again found a benefit in favour of insulin against placebo (1 trial, 20 people, RR 0.06, 95% CI 0.00 to 0.90, [Analysis 20.2](#)).

20.1.3 Deterioration of symptoms

There was no difference on deterioration of symptoms between insulin and placebo (1 trial, 20 people, RR 0.14, 95% CI 0.01 to 2.45, [Analysis 20.3](#)).

20.1.4 Average endpoint scores

TD symptoms were also measured on the continuous AIMS scale (see above). A benefit in favour of insulin was found when compared to placebo (1 trial, 20 people, MD -6.20, 95% CI -10.53 to -1.87, [Analysis 20.4](#)).

20.2 Leaving the study early

No participants left the included study early.

21. Comparison 21. Hormone - Melatonin versus placebo or no treatment

Four trials ([Castro 2011](#); [Shamir 2000](#); [Shamir 2001](#); [Shi 2009](#)) carried out in China, Israel, and Venezuela that included 132 in- and out-patients with antipsychotic-induced TD was included for this comparison.

21.1 TD symptoms

21.1.1 No clinically important improvement

The overall results for 'clinically relevant improvement', added across all time points, found no benefit of melatonin against placebo (low-quality evidence, 2 trials, 32 people, RR 0.89, 95% CI 0.71 to 1.12, [Analysis 21.1](#)).

21.1.2 Not any improvement

For the outcome of 'any improvement in TD symptoms', we again found no benefit of melatonin against placebo (1 trial, 19 people, RR 1.11, 95% CI 0.47 to 2.60, [Analysis 21.2](#)).

21.1.3 Deterioration of symptoms

There was no difference on deterioration of symptoms between melatonin and placebo (low-quality evidence, 1 trial, 19 people, RR 0.22, 95% CI 0.01 to 4.05, [Analysis 21.3](#)).

21.1.4 Average endpoint scores

TD symptoms were also measured on the continuous AIMS scale (see above). No benefit was found for melatonin when compared to placebo (1 trial, 13 people, MD -2.38, 95% CI -6.58 to 1.82, [Analysis 21.4](#)).

21.2 Adverse effects

No participants reported adverse effects.

21.3 Leaving the study early

No participants left the included studies early.

21.4 Cognitive function

Cognitive function was measured using the continuous Wechsler Adult Intelligence Scale (WAIS) and Wechsler Memory Scale (WMS) scales (see above). There was a benefit in favour of melatonin when compared to placebo on the WAIS (1 trial, 76 people, MD 15.83, 95% CI 4.61 to 27.05, [Analysis 13.7](#)), however this benefit was not seen on the WMS (1 trial, 76 people, MD 3.77, 95% CI -8.21 to 15.75, [Analysis 21.7](#)).

21.5 Mental state

No participants reported deterioration of mental state.

22. Comparison 22. Mood stabiliser - Lithium versus placebo

One trial ([Mackay 1980](#)) carried out in the UK that included 11 inpatients with antipsychotic-induced TD was included for this comparison.

22.1 TD symptoms

22.1.1 No clinically important improvement

The overall results for 'clinically relevant improvement' found no benefit of lithium against placebo (1 trial, 11 people, RR 1.59, 95% CI 0.79 to 3.23, [Analysis 22.1](#)).

22.1.2 Not any improvement

For the outcome of 'any improvement in TD symptoms', we found no benefit of lithium against placebo (1 trial, 11 people, RR 4.29, 95% CI 0.25 to 72.90, [Analysis 22.2](#)).

22.1.3 Deterioration of symptoms

There was no difference on deterioration of symptoms between lithium and placebo (1 trial, 11 people, RR 4.29, 95% CI 0.25 to 72.90, [Analysis 22.3](#)).

22.1.4 Average endpoint scores

TD symptoms were also measured on the continuous AIMS scale (see above). No difference was found when lithium was compared to placebo (1 trial, 11 people, MD 0.63, 95% CI -5.23 to 6.49, [Analysis 22.4](#)).

22.2 Adverse effects

There was no difference in the incidence of 'any adverse effect' between lithium and placebo (1 trial, 11 people, RR 6.00, 95% CI 0.38 to 94.35, [Analysis 22.5](#)).

22.3 Leaving the study early

Using lithium did not significantly increase the chances of a person leaving the study early (1 trial, 11 people, RR 2.57, 95% CI 0.13 to 52.12, [Analysis 22.6](#)).

23. Comparison 23. Polypeptide - Ceruletide versus placebo

Two trials ([Kojima 1992](#); [Matsunaga 1988](#)) carried out in Japan that included 85 in- and out-patients with schizophrenia and TD, or chronic psychosis and TD were included for this comparison.

23.1 TD symptoms

23.1.1 Not any improvement

For the outcome of 'any improvement in TD symptoms', we found no benefit of ceruletide against placebo (2 trials, 132 people, RR 0.83, 95% CI 0.65 to 1.07, [Analysis 23.1](#)).

23.1.2 Deterioration of symptoms

There was no difference on deterioration of symptoms between ceruletide and placebo (low-quality evidence, 2 trials, 103 people, RR 0.97 CI 0.14 to 6.80, [Analysis 23.2](#)).

23.2 Adverse effects

There was no difference in the incidence of 'any adverse effect', across all time periods, between ceruletide and placebo (low-quality evidence, 2 trials, 122 people, RR 1.32, 95% CI 0.74 to 2.36, [Analysis 23.3](#)).

23.3 Leaving the study early

Using ceruletide did not significantly increase the chances of a person leaving the study early (very low-quality evidence, 1 trial, 85 people, RR 1.09, 95% CI 0.49 to 2.40, [Analysis 23.4](#)).

24. Comparison 24. Hypnosis or relaxation versus treatment as usual (TAU)

One trial ([Glover 1980](#)) carried out in the USA that included 15 outpatients with antipsychotic-induced TD was included for this comparison.

24.1 TD symptoms

24.1.1 No clinically important improvement

The overall results for 'clinically relevant improvement' found a benefit in favour of hypnosis or relaxation when compared to TAU (very low-quality evidence, 1 trial, 15 people, RR 0.45, 95% CI 0.21 to 0.94, [Analysis 24.1](#)). There was no difference, however, when hypnosis was compared to relaxation (1 trial, 10 people, RR 0.11, 95% CI 0.01 to 1.64, analysis not shown).

24.1.2 Not any improvement

For the outcome of 'any improvement in TD symptoms', we found no benefit of hypnosis or relaxation when compared to TAU (1 trial, 15 people, RR 0.18, 95% CI 0.01 to 3.81, [Analysis 24.2](#)).

24.1.3 Deterioration of symptoms

There was no difference on deterioration of symptoms between hypnosis or relaxation and TAU (very low-quality evidence, 1 trial, 15 people, RR 0.18, 95% CI 0.01 to 3.81, [Analysis 24.3](#)).

24.2 Leaving the study early

No participants left the included study early.

25. Subgroup analyses

25.1 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.

25.2 Duration of follow-up

Any effects that the miscellaneous interventions described in this review may have did not clearly change in relation to duration of follow-up.

26. Heterogeneity

For most comparisons only one study was included, consequently, for these comparisons subgroup- and sensitivity analyses could not be undertaken and there was no heterogeneity. For the four comparisons that included more than one study (ceruletide, levetiracetam, melatonin, and dehydrogenated ergot alkaloids), pooled data for leaving the study early for levetiracetam versus placebo were statistically heterogeneous ([Analysis 9.3](#), $I^2=73\%$), but neither study ([UCB Pharma 2005](#); [Woods 2008](#), total N=119) found statistically significant results.

27. Sensitivity analyses

27.1 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.

27.2 Assumptions for lost binary data

We were unable to perform this sensitivity analysis because there were so few studies within each comparison in this review.

27.3 Risk of bias

We were unable to perform this sensitivity analysis because there were so few studies within each comparison in this review.

27.4 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 intra-class correlation coefficients (ICCs) in calculating the design effect. No cluster-randomised trials were included.

27.5 Fixed and random effects

We were unable to perform this sensitivity analysis because there were so few studies within each comparison in this review.

DISCUSSION

Summary of main results

1. Searching

This review has identified mainly old studies published before the year 2000 (65%); only six studies were published in the past 10 years. These more recent studies assessed melatonin (Castro 2011; Shi 2009), piracetam (Libov 2007), valbenazine (NBI-98854) (O'Brien 2014), levetiracetam (Woods 2008), and *Ginkgo biloba* (Zhang 2011).

2. Few data

Overall, data from 1278 people were included in this review, but few participants were included for each intervention. The number of participants per comparison ranged from 10 (experimental compound ritanserine) to 157 (Chinese herb *Ginkgo biloba*). 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 tardive dyskinesia (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. Alkaloid - dihydrogenated ergot alkaloids (DEAs) versus placebo

3.1 TD symptoms

We found low-quality evidence (downgraded due to risk of bias and small sample size) favouring DEAs compared with placebo for no clinically important improvement in TD symptoms after six weeks (RR 0.45, 95% CI 0.21 to 0.97, 1 study, 28 participants). Because the quality of evidence is low, we have limited confidence in the effect estimates and CIs; the true effects may be substantially different. We also found very low-quality evidence (downgraded due to risk of bias and small sample size) of little or no difference in deterioration of TD symptoms at six-week follow-up (RR 0.33, 95% CI 0.01 to 7.55, 1 study, 28 participants). Because the quality of evidence is very low, we are very uncertain about the estimate.

3.2 Adverse events

More participants in the DEAs group experienced adverse events compared with placebo (50% and 21%, respectively), however, the difference was not significant (very low-quality evidence, RR 2.33,

95% CI 0.75 to 7.23, 1 study, 28 participants). Because the quality of evidence is very low, we are very uncertain about the estimate.

3.3 Acceptability of treatment (measured through participants leaving the study early)

We found very low-quality evidence (downgraded due to risk of bias, indirectness of measurement, and small sample size) of little to no difference in acceptability of treatment (RR 0.33, 95% CI 0.02 to 7.32, 2 studies, 48 participants). Because the quality of evidence is very low, we are very uncertain about the estimate.

The included study did not report on 'social confidence, social inclusion, social networks, or personalised quality of life' - outcomes assessed by patients and review authors as particularly important (see [Types of outcome measures](#)). Please see [Summary of findings for the main comparison](#) for GRADE ratings.

4. Anxiolytic - buspirone versus placebo

4.1 TD symptoms

We found low-quality evidence (downgraded due to risk of bias and small sample size) favouring buspirone compared with placebo for no clinically important improvement in TD symptoms after 6 weeks (RR 0.53, 95% CI 0.33 to 0.84, 1 study, 42 participants). Because the quality of evidence is low, we have limited confidence in the effect estimates and CIs; the true effects may be substantially different.

4.2 Acceptability of treatment (measured through participants 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, all randomised participants completed the trial and there were no dropouts among 42 participants in one trial with a duration of six weeks.

The included study did not report on 'adverse events' or 'social confidence, social inclusion, social networks, or personalised quality of life' - outcomes assessed by patients and review authors as particularly important (see [Types of outcome measures](#)). Please see [Summary of findings 3](#) for GRADE ratings.

5. Antiepileptic - levetiracetam versus placebo

5.1 TD symptoms

No studies reported on the TD symptoms outcomes chosen for our 'Summary of findings' tables ('no clinically important improvement in TD symptoms' and 'deterioration of TD symptoms').

5.2 Adverse events

We found low-quality evidence (downgraded due to risk of bias and small sample size) that more participants experienced adverse events with placebo (46%) compared with levetiracetam (23.5%) at eight-week follow-up, however, the difference was not significant (RR 0.51, 95% CI 0.25 to 1.04, 69 participants, 1 study). Because the quality of evidence is low, we have limited confidence in the effect estimates and CIs; the true effects may be substantially different.

5.3 Acceptability of treatment (measured through participants leaving the study early)

We found very low-quality evidence (downgraded due to risk of bias, inconsistency ($I^2 = 73\%$), and small sample size) that 17% of participants left the study early, and there was little to no difference between levetiracetam and placebo (RR 1.01, 95% CI 0.46 to 2.22, 119 participants, 2 studies). Because the quality of evidence is very low, we are very uncertain about the estimate.

The included studies did not report on 'social confidence, social inclusion, social networks, or personalised quality of life' - outcomes assessed by patients and review authors as particularly important (see [Types of outcome measures](#)). Please see [Summary of findings 2](#) for GRADE ratings.

6. Enzyme inhibitor - VMAT2-inhibitors versus placebo

6.1 TD symptoms

We found moderate-quality evidence (downgraded due to small sample size) favouring valbenazine (NBI-98854) compared with placebo for no clinically important improvement in TD symptoms after six weeks (RR 0.63, 95% CI 0.46 to 0.86, 1 study, 92 participants). Because the quality of evidence is moderate, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

6.2 Adverse events

More participants in the valbenazine group experienced adverse events compared with placebo (49% and 33%, respectively), however, the difference was not significant (low-quality evidence, (RR 1.50, 95% CI 0.92 to 2.45, 1 study, 100 participants). Because the quality of evidence is low (downgraded due to small sample size and very few events reported), we have limited confidence in the effect estimates and CIs; the true effects may be substantially different.

6.3 Acceptability of treatment (measured through participants leaving the study early)

We found very low-quality evidence (downgraded due to small sample size and very few events reported, and indirectness of measurement) that 10% of participants left the study early, and there was little to no difference between the valbenazine group and the placebo group (RR 1.00, 95% CI 0.31 to 3.25, 102 participants, 1 study). Because the quality of evidence is very low, we are very uncertain about the estimate.

The included study did not report on 'social confidence, social inclusion, social networks, or personalised quality of life' - outcomes assessed by patients and review authors as particularly important (see [Types of outcome measures](#)). Please see [Summary of findings 4](#) for GRADE ratings.

7. Fatty acid - ethyl-EPA versus placebo

7.1 TD symptoms

No studies reported on the TD symptoms outcomes chosen for our 'Summary of findings' tables ('no clinically important improvement in TD symptoms' and 'deterioration of TD symptoms').

7.2 Adverse events

We found low-quality evidence (downgraded due to risk of bias and small sample size) of little to no difference between ethyl-EPA and placebo in parkinsonism extrapyramidal symptoms (EPSs) measured on the Extrapyramidal System Rating Scale (ESRS) (MD 0.30, 95% CI -1.17 to 1.77, 1 trial, 75 participants), and of a benefit to ethyl-EPA compared with placebo in dystonia EPSs measured on the ESRS (MD -0.35, 95% CI -0.58 to -0.12) 1 trial, 75 participants). Because the quality of evidence is low, further research is likely to have an important impact on our confidence in the estimates of effect and may change the estimates. Further, we found very low-quality evidence (downgraded due to risk of bias and small sample size with very wide CIs) of little to no difference between ethyl-EPA and placebo in akathisia EPSs measured on the ESRS (MD -0.04, 95% CI -0.30 to 0.22, 1 trial, 75 participants). Because the quality of evidence is very low, we are very uncertain about the estimate.

7.3 Acceptability of treatment (measured through participants leaving the study early)

More participants in the placebo group left the study early than in the ethyl-EPA group (33% and 19%, respectively), however, the difference was not significant (very low-quality evidence, (RR 0.57, 95% CI 0.27 to 1.22, 1 study, 84 participants). Because the quality of evidence is very low, we are very uncertain about the estimate.

The included study did not report on 'social confidence, social inclusion, social networks, or personalised quality of life' - outcomes assessed by patients and review authors as particularly important (see [Types of outcome measures](#)). Please see [Summary of findings 5](#) for GRADE ratings.

8. Herb - Ginkgo biloba versus placebo

8.1 TD symptoms

We found moderate-quality evidence (downgraded due to small sample size) favouring *Ginkgo biloba* compared with placebo for no clinically important improvement in TD symptoms after 12 weeks (RR 0.88, 95% CI 0.81 to 0.96, 1 trial, 157 participants). Because the quality of evidence is moderate, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

8.3 Acceptability of treatment (measured through participants leaving the study early)

More participants left the study early in the placebo group compared to the *Ginkgo biloba* group (5% and 1.3%, respectively), however the difference was not significant (very low-quality evidence, RR 0.25, 95% CI 0.03 to 2.22, 1 trial, 157 participants). Because the quality of evidence is very low (downgraded due to small sample size with very few events reported and indirectness of measurement), we are very uncertain about the estimate.

The included study did not report on 'adverse events' or 'social confidence, social inclusion, social networks, or personalised quality of life' - outcomes assessed by patients and review authors as particularly important (see [Types of outcome measures](#)). Please see [Summary of findings 6](#) for GRADE ratings.

9. Hormone - melatonin versus placebo

9.1 TD symptoms

We found low-quality evidence (downgraded due to inconsistency ($I^2 = 46\%$) and small sample size) of little or no difference for no clinically important improvement in TD symptoms for melatonin compared with placebo after three to 12 weeks (RR 0.89, 95% CI 0.71 to 1.12, 2 studies, 32 participants). Again, we found low-quality evidence (downgraded due to very small sample size) of little or no difference in deterioration of TD symptoms at three-week follow-up (RR 0.22, 95% CI 0.01 to 4.05, 1 study, 19 participants). Because the quality of evidence is low for these outcomes, we have limited confidence in the effect estimates and CIs; the true effects may be substantially different.

9.2 Adverse events

No events were reported for this outcome among 54 participants in three studies with a duration of three to 12 weeks.

9.3 Acceptability of treatment (measured through participants leaving the study early)

All randomised participants completed the trial and there were no dropouts among 54 participants in three studies with a duration of three to 12 weeks.

The included studies did not report on 'social confidence, social inclusion, social networks, or personalised quality of life' - outcomes assessed by patients and review authors as particularly important (see [Types of outcome measures](#)). Please see [Summary of findings 7](#) for GRADE ratings.

10. Polypeptide - ceruletide versus placebo

10.1 TD symptoms

We found low-quality evidence (downgraded due to risk of bias and small sample size) of little or no difference in deterioration of TD symptoms at four to eight weeks follow-up (RR 0.97, 95% CI 0.14 to 6.80, 2 studies, 103 participants). Because the quality of evidence is low, we have limited confidence in the effect estimates and CIs; the true effects may be substantially different.

10.2 Adverse events

We found low-quality evidence (downgraded due to risk of bias and small sample size) that more participants experienced adverse events with ceruletide (31%) compared with placebo (23%) at four to eight weeks follow-up, however, the difference was not significant (RR 1.32, 95% CI 0.74 to 2.36, 122 participants, 2 studies). Because the quality of evidence is low, we have limited confidence in the effect estimates and CIs; the true effects may be substantially different.

10.3 Acceptability of treatment (measured through participants leaving the study early)

We found very low-quality evidence (downgraded due to risk of bias, indirectness of measurement, and small sample size) that around 20% of participants left the study early, and there was little to no difference between ceruletide and placebo (RR 1.09, 95% CI 0.49 to 2.40, 85 participants, 1 study). Because the quality of evidence is very low, we are very uncertain about the estimate.

The included studies did not report on 'social confidence, social inclusion, social networks, or personalised quality of life' - outcomes assessed by patients and review authors as particularly important (see [Types of outcome measures](#)). Please see [Summary of findings 8](#) for GRADE ratings.

11. HYPNOSIS OR RELAXATION versus TAU

11.1 TD symptoms

We found very low-quality evidence favouring hypnosis or relaxation compared with placebo for 'no clinically important improvement in TD symptoms' after 8 sessions (RR 0.45, 95% CI 0.21 to 0.94, 1 study, 15 participants). We also found very low quality evidence of little or no difference in deterioration of TD symptoms between hypnosis or relaxation and placebo after 8 sessions (RR 0.18, 95% CI 0.01 to 3.81, 1 study, 15 participants). Because the quality of evidence is very low (downgraded due to serious risk of bias and very small sample size), we are very uncertain about these estimates.

11.3 Acceptability of treatment (measured through participants leaving the study early)

All randomised participants completed the study and there were no dropouts among 15 participants in one study of eight sessions (exact duration was not reported).

The included study did not report on 'adverse events' and 'social confidence, social inclusion, social networks, or personalised quality of life' - outcomes assessed by patients and review authors as particularly important (see [Types of outcome measures](#)). Please see [Summary of findings 9](#) for GRADE ratings.

12. OTHER COMPARISONS

The remaining 15 comparisons (cyproheptadine, lithium, papaverine, pemoline, piracetam, promethazine, ritanerlin, selegiline, isocarboxazid, oestrogen, insulin, gamma-linolenic acid, branched-chain amino acids, phenylalanine, and stepholidine) included less than 60 participants each (10 to 57 participants per intervention with a median of 22 participants) and were not prioritised in the selection process for the NIHR HTA systematic review ([Bergman 2017](#)). Consequently, we did not create 'Summary of findings' tables for these interventions (see [Prioritising interventions for 'Summary of findings' tables](#), [Types of outcome measures](#)). We summarise the results from these trials narratively below. We would like to point out that due to the small sample sizes per comparison, potential treatment effects could have gone undetected.

12.1 TD symptoms

A benefit for the intervention compared with placebo was found for pemoline, promethazine, insulin, and branched-chain amino acids, and for isocarboxazid compared with procyclidine (one trial per comparison, average number of participants: 38, follow-up duration: three to 40 weeks (median: 12 weeks)). However, due to the small sample sizes and risk of biases for most of these trials, we are very uncertain about these results. For lithium, ritanerlin, selegiline, oestrogen, and gamma-linolenic acid compared to placebo, results showed no significant difference between groups on 'no clinically important improvement in TD symptoms' (one trial per comparison, average number of participants: 16, follow-up duration: three to six weeks). Due to the small sample sizes,

short study duration, and risk of biases for most of these trials, we are very uncertain about these results. Studies assessing cyproheptadine, papaverine, piracetam, and phenylalanine did not report on 'no clinically important improvement in TD symptoms'.

For cyproheptadine, lithium, ritanserin, oestrogen, and gamma-linolenic acid compared to placebo, results showed no significant difference between groups on 'deterioration of TD symptoms' (one trial per comparison, average number of participants: 18, follow-up duration: three to six weeks). Due to the small sample sizes, short study duration, and risk of biases for most of these trials, we are very uncertain about these results. Studies assessing papaverine, pemoline, piracetam, promethazine, selegiline, isocarboxazid, insulin, branched-chain amino acids, phenylalanine, and stepholidine did not report on 'deterioration of TD symptoms'.

12.2 Adverse events

Only seven of the 15 other comparisons reported on adverse events. Studies evaluating cyproheptadine, lithium, piracetam, promethazine, and oestrogen found no significant difference between intervention and placebo (one trial per comparison, average number of participants: 28, follow-up duration: three to 12 weeks (median: four weeks)), the study evaluating isocarboxazid versus procyclidine also found no significant difference between groups (one trial, 20 participants, follow-up duration: 40 weeks), and the study assessing stepholidine versus placebo reported that no adverse events occurred (57 participants, follow-up duration: eight weeks). Due to the small sample sizes, short study duration, and risk of biases for most of these trials, we are very uncertain about these results. Studies assessing papaverine, pemoline, ritanserin, selegiline, insulin, gamma-linolenic acid, branched-chain amino acids, and phenylalanine did not report on adverse events.

12.3 Acceptability of treatment (measured through participants leaving the study early)

Studies assessing cyproheptadine, lithium, pemoline, piracetam, promethazine, selegiline, isocarboxazid, oestrogen, insulin, gamma-linolenic acid, branched-chain amino acids, phenylalanine, and stepholidine reported no significant differences in participants leaving the studies early compared to placebo groups (one trial per comparison, average number of participants: 31, follow-up duration: one day to 40 weeks (median: six weeks)). Again, due to the small sample sizes, short study duration, and risk of biases for most of these trials, we are very uncertain about these results. Studies assessing papaverine and ritanserin did not clearly report on number of randomised participants and were consequently not analysed for this outcome.

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

Again, none of the other included studies assessed this group of outcomes that were prioritised by patients as particularly important (see [Types of outcome measures](#)).

Overall completeness and applicability of evidence

1. Completeness

No outcomes in this review involved large numbers of people. Many of the included studies were no more than pilot studies, and due

to their small size, they cannot really be expected to fully answer any questions about the effects of this miscellaneous group of interventions for people with TD.

Some outcomes 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 of social confidence, social inclusion, social networks, or personalised quality of life for either recipients of care or caregivers, nor were there data on hospital and service utilisation outcomes, or economic outcomes.

Deutetrabenazine and valbenazine, both recently approved by the FDA for TD ([Brooks 2017](#); [FDA 2017](#)), are VMAT-2 inhibitors that were assessed in included study [O'Brien 2014](#) (valbenazine), in awaiting classification studies [Fernandez 2016](#), [Hauser 2016](#) and [NCT01393600 2011](#), and in ongoing studies [NCT01688037 2012](#) and [NCT02291861 2014](#). We look forward to including results from these new and ongoing trials in a future update of this review.

2. Applicability

Trials were a mixture of hospital-based and outpatient, and were on people who would be recognisable in everyday care, however, mostly on men in their 50s with schizophrenia in hospital and mostly in high-income countries. Overall, sample sizes in relevant studies were particularly small. In light of the lack of power available to examine the compounds of interest, the results should be interpreted as inconclusive rather than negative at this stage. The majority of studies had a duration of six weeks or less whilst only seven had a duration of at least 12 weeks. Whether the effects of the interventions were maintained at longer periods of follow-up may therefore be under-reported in short-term studies.

Quality of the evidence

Overall, the quality of the evidence is low to very low. This means that we have limited to very little confidence in the effect estimates, and the true effect may be, or is likely to be, substantially different from the estimate of the effect. The main reasons for our low confidence in the evidence include the following.

1. Poor study methodology and reporting of methods resulting in downgrading evidence for risk of bias. 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.
2. Very small sample sizes resulting in downgrading evidence for imprecision. The median sample size in this review was only 34 people. A trial of this size is unable to detect subtle, yet important differences due to an intervention 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).
3. Wide CIs (often due to low event rates) that included appreciable benefit or harm for the intervention as well as no effect, resulting in downgrading evidence for imprecision.

Please see Additional tables, 'Summary of findings' tables 1-9 for full details.

The small trial sizes, along with the poor reporting of trials, would be associated with an exaggeration of effect of the experimental treatment (Jüni 2001) when an effect was detected.

Potential biases in the review process

1. Missing studies

Every effort was 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 intervention 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. Missing data

We excluded 12 studies published between 1973 and 2004 that did not provide any usable data, see [Excluded studies](#). We contacted authors and two replied to confirm no usable data are available. Authors of eight studies did not reply, and we could not find up-to-date contact details for authors of two studies (both over 30 years old). We find it very unlikely we would receive a reply from authors regarding research conducted so many years ago; therefore, these studies were also excluded.

3. Introducing bias

This review has now been updated 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 believe the 'Summary of findings' tables are 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 (HB) to select outcomes relevant for these tables before becoming familiar with the data.

Agreements and disagreements with other studies or reviews

This review substantially updates earlier versions. The previous version of this review contained assessments of eight interventions (ceruletide, gammalinolenic acid, insulin, lithium, oestrogen, phenylalanine, piracetam, and ethyl-EPA) and the conclusions on those interventions has not changed with this update. In addition, we have updated this review with evidence from another 16 interventions. [Bergman 2017](#) reports on interventions in all nine Cochrane reviews on TD in this series (see [Table 1](#)) and is in agreement with the findings and conclusions of this review.

Other systematic reviews have covered melatonin ([Nelson 2003](#)), extract of *Ginkgo biloba* ([Zheng 2016](#)), and any treatment for TD ([Alimi 2013](#)). We are in agreement with both [Nelson 2003](#), that "There are inadequate data at the present time to support the use of melatonin in patients with TD", and with [Zheng 2016](#), that *Ginkgo biloba* appears to be safe and effective for improving TD symptoms

and that better randomised controlled trials are needed to confirm this evidence.

[Alimi 2013](#) found that three of the interventions included in this review may help to improve TD symptoms: BCAAs, *Ginkgo biloba*, and piracetam. Our review included the same studies for these three interventions and also found that BCAAs and *Ginkgo biloba* appear to reduce TD symptoms. However, for BCAAs, we also conclude that due to the small sample size ($n = 68$), short follow-up (three weeks), and risk of bias, we are very uncertain about this result, and for *Ginkgo biloba*, we also conclude that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate because evidence was of moderate quality (due to small sample size, $n = 157$). [Libov 2007](#), the study that evaluated piracetam, is a cross-over study and we extracted data only from the first phase because of risk of carry-over effect despite a wash-out period and because TD is an unstable condition (see [Implications for research](#), 2.1 *Use of cross-over design*). This may be why our results differed from [Alimi 2013](#) on piracetam; we found no benefit.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with antipsychotic induced tardive dyskinesia (TD)

Most of this group of miscellaneous treatments do not look even promising for helping symptoms of TD. There is, however, some suggestion that valbenazine and extract of *Ginkgo biloba* may alter the course of TD for those with schizophrenia. The findings on *Ginkgo biloba* are in keeping with other reviews ([Alimi 2013](#); [Zheng 2016](#)), and valbenazine has been approved by the FDA for use in TD ([FDA 2017](#)). To date, these data are still weak and should be interpreted with caution. If offered any of these treatments 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

Most of this miscellaneous group of treatments remain purely experimental and there is no place for their use in every day practice. This review generates a theory that valbenazine and extract of *Ginkgo biloba* could reduce TD symptoms to a clinically important degree. The data in this review do not justify routine use of these treatments, however, valbenazine is the only treatment included in this review that has been approved by the FDA for use in TD ([FDA 2017](#)). It would be reasonable, however, to ask people with schizophrenia to complicate their treatment plan if the use of this group of miscellaneous treatments were 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. For policy makers and managers

This is the largest in the series of Cochrane reviews on TD. We found inconclusive (low- to very low-certainty evidence) evidence on most of the interventions, however, there was moderate-certainty evidence that adding valbenazine or extract of *Ginkgo biloba* to

treatment with antipsychotic medication probably helps with the symptoms of TD. Valbenazine is the only treatment included in this review that has been approved by the FDA for use in TD (FDA 2017). More well-designed randomised controlled trials are needed to confirm these results. 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 five studies (16%) made explicit how randomisation was undertaken, and only seven (23%) described allocation concealment. Many of the studies we found were performed decades ago, before CONSORT (CONsolidated Standards of Reporting Trials; CONSORT; Moher 2001). This is intended to improve reporting of randomised controlled trials, enabling readers to understand the design, conduct, analysis and interpretation, and to assess the validity of results. CONSORT emphasises that this can only be achieved through complete transparency from authors. 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

The number of disparate compounds targeted in this review is indicative of the frustration felt by researchers. Still, after decades of research, no clearly effective treatments for TD have emerged. Presumably an even greater variety of interventions never even reached the stage of warranting examination in a randomised controlled trial. As basic science increases our understanding of the neurobiological basis of involuntary movements, psychiatric researchers should remain vigilant for new candidate compounds for the treatment of TD. TD remains a large problem and worthy of research, even with use of lower doses and newer compounds. Well-designed randomised controlled trials, involving a large number of participants over protracted periods of time, are needed if we are to see if an intervention could have a role in prevention and treatment of TD. Such studies are of importance to people with the problem (Figure 1) 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. 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 an intervention 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 the intervention 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. TD 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

The results suggest that larger sample size should be used to provide more precise estimates of effect and to help avoid false conclusions about the effects of the proposed treatment.

2.3 Length of study

One study included in this review (Bucci 1971) used the intervention for more than three months. TD, however, is a chronic condition of insidious onset, the severity of which fluctuates spontaneously (APA 1992). Even if an intervention has a swift effect, 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 3).

ACKNOWLEDGEMENTS

The authors are indebted to Geoff Davies, Kirsten Mason, Carmel Meir and Leanne Roberts for assistance with this review.

We are especially grateful to the following trialists who provided additional material; Professor Jes Gerlach, Dr Tetsuo Matsunaga, Dr Jacques Mouret, Dr Jan Sikora, Dr Krishna Viddadi and Dr Adam Wolkin. Thank you to John McGrath for protocol development, data extraction and assimilation and report writing. John authored this review from 1997-2002.

For the 2017 update, we wish to thank Rosie Asher (RA) and Antonio Grande (AG) for screening literature and helping with data extraction, Farhad Sokrane for carrying out the trial search and helping to find full-text papers, Ben Gray for writing the Plain language summary, and Nicholas Henschke and Loukia Spineli for assistance with preparing the report. We also acknowledge Dawn-Marie Walker, Ruth Sayers, Megan Lees, and Vanessa Pinfold from McPin Foundation for organising and holding the public and patient involvement consultation with TD service users that contributed to selecting outcomes for the 'Summary of findings' tables and to guide future research. Finally, we wish to thank Sai Zhao and Jun Xia for assessing and extracting data from articles in Chinese.

The Cochrane Schizophrenia Group Editorial Base in Nottingham produces and maintains standard text for use in the Methods

sections of their reviews. We have used this text as the basis of what appears here and adapted it as required.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bucci 1971

Methods	Allocation: random, further details not reported. Blindness: not reported. Duration: 40 weeks. Design: parallel. Setting: outpatients, USA (probably).
Participants	Diagnosis: chronic schizophrenia treated with phenothiazine for several years and demonstrating obvious dyskinetic manifestations. N = 20 Sex: 16 female and 4 male Age: range 45-62 years History: at least two years of TD.
Interventions	1. Procyclidine (Anticholinergic), 5 mg twice a day + chlorpromazine, 100 mg three times a day N = 10. 2. Isocarboxazid (MAOI), 10 mg twice a day + chlorpromazine, 100 mg three times a day N = 10. Continuous phenothiazine-antiparkinsonian treatment for at least 2 years. . Other concomitant medication was not reported.
Outcomes	TD symptoms (clinical evaluation, scale not reported) Leaving the study early Adverse events Unable to use - Mental state (data not reported for both groups)
Notes	Sponsorship source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were divided at random into groups of 10 each", no further details reported.

Bucci 1971 (Continued)

Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	“One male patient on chlorpromazine and isocarboxazid was discontinued after 6 weeks as he became increasingly tense, apprehensive and sleepless”
Selective reporting (reporting bias)	High risk	Adverse effects reported only as those related to treatment. Mental state data not reported for group 2. Unclear if all outcomes have been reported, a protocol is not available for verification.
Other bias	Unclear risk	Insufficient information to make a judgement

Cai 1988

Methods	Allocation: not reported. Blinding: double-blind. Duration: 8 weeks. Design: parallel Setting: not reported.
Participants	Diagnosis: antipsychotic-induced TD; N = 57 Sex: 33 male and 24 female 24 Age: mean 39.5 (SD 10.3) years old, range 28-59 History: Duration of TD on average 2.4 (SD 1.8) years. Patients assigned to the treatment group were stable to AP dose from 0.7 to 27 years, whereas patients assigned to the control group were stable to AP dose from 1 to 10 years before start of study.
Interventions	1. L-stepholidine (SPD) Group: Management: L-stepholidine was prescribed two tablets each time, three times per day for 8 weeks. N = 42 2. Placebo Group: The placebo with similar appearance to L-stepholidine was prescribed two tablets each time, three times per day for 8 weeks. N = 15 All participants received stable AP and concomitant anticholinergic drug. Other concomitant medication is not reported.
Outcomes	Clinical improvement on TD symptoms: no definition. Clinical improvement on psychosis symptoms: no definition. Mental state: BPRS Adverse event: any adverse events

Cai 1988 (Continued)

--Unable to use
TESS, (the author did not report the data)
Blood routine examination, urine routine test and liver function test, electrocardiography. (the author only stated results of these tests were normal but did not report the data)

Notes
Twenty cases from the SPD group received blood routine examination, urine routine test and liver function test; five cases received electrocardiography. Ten cases in each group received BPRS and TESS measurements.

We attempted to contact the study author for information on randomisation, but were informed he had retired.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...randomized, parallel-group..." no further details.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind" "The placebo with similar appearance", Blinding of participants and key study personnel ensured.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double blind" "The placebo with similar appearance", Blinding of participants and key study personnel ensured.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the trial.
Selective reporting (reporting bias)	High risk	The author did not report the outcome: TESS, Blood routine examination, urine routine test and liver function test, electrocardiography
Other bias	Unclear risk	No further details reported

Castro 2011

Methods
Allocation: randomised.
Blindness: "double blind".
Duration: 12 weeks.
Design: parallel.
Setting: inpatients and outpatients, Venezuela

Participants
Diagnosis: Psychiatric patients meeting DSM-IV-TR diagnostic criteria for the diagnosis of antipsychotic-induced TD.

N = 13.
Sex: 4 female and 9 male
Age: mean (SD) 59.9 (2.7) years; range 46-75 years.
History: Duration of TD not reported. Most of the patients have been receiving the same antipsychotic treatment for at least 3 years up to 10 years. Antipsychotics received were levomepromazine (9 patients), haloperidol (4), clozapine (2), aripiprazole (2), olanzapine (1), quetiapine (1) and risperidone (1).

Castro 2011 (Continued)

Interventions	<p>1. Melatonin: 20 mg/day. N = 7. Duration: 12 weeks.</p> <p>2. Placebo: N = 6. Duration: 12 weeks.</p> <p>All individuals who participated faithfully complied with antipsychotic treatment and maintained it throughout the study.</p> <p>Other concomitant medication: The treatment with anticholinergics was maintained for ethical reasons. In each of the groups two patients received biperidine. Other treatments applied were, in the melatonin group, valproic acid (1 patient), carbamazepine (1 patient), alprazolam (1 patient), indapamide (1 patient); in the placebo group: carbamazepine (2 patients), chlorimipramine (2 patients) and lithium carbonate (1 patient). During the study there were no dosage adjustments.</p>
Outcomes	<p>Tardive dyskinesia: Brief Psychiatric Rating Scale (BPRS)</p> <p>Tardive dyskinesia: symptoms: AIMS</p> <p>Adverse events: other observed effects.</p> <p>Leaving the study early</p>
Notes	This study was supported by the Instituto Venezolano de Investigaciones Científicas (IVIC), Venezuela

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The individuals selected were divided randomly into two groups"; no further details.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"A group of 6 patients received placebo capsules, identical in appearance".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double blind". Blinding of outcome assessors not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the trial.
Selective reporting (reporting bias)	Unclear risk	Unclear if all pre-defined outcomes were reported. A protocol is not available for verification.
Other bias	Low risk	The study seems to be free of other sources of bias.

Emsley 2006

Methods	<p>Allocation: randomised.</p> <p>Blindness: double-blind.</p> <p>Duration: 12 weeks.</p> <p>Design: parallel.</p> <p>Setting: inpatients and outpatients, South Africa.</p>
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Emsley 2006 (Continued)

Participants	<p>Diagnosis: schizophrenia, schizoaffective disorder with TD (DSM-IV). N = 84. Sex: 51 male and 26 female Age: mean 42 years. History: Duration of TD more than 5 years. Patients were stabilised for at least 6 months prior to trial.</p>
Interventions	<p>1. Ethyl-eicosapentaenoic acid (omega-3 fatty acid eicosapentaenoic acid derivative): dose 2 g/day + antipsychotics. N = 42. 2. Placebo + antipsychotics. N = 42.</p> <p>Patients who were stabilised on other psychotropic medications (anxiolytic, hypnotic, antidepressant, mood stabilising) before entry to the trial were allowed to continue on these medications; anticholinergic medication for treatment-emergent extrapyramidal symptoms (EPS); anxiolytic or hypnotic medication for treatment emergent insomnia or acute anxiety; any medication for physical conditions that was taken prior to the commencement of the trial could be continued; medication for other conditions that arose during the course of the trial, at the investigator's discretion. Other omega-3 fatty acid preparations, additional antipsychotics or antidepressants were not permitted.</p>
Outcomes	<p>Extrapyramidal symptoms: ESRS</p> <p>Mental state deterioration</p> <p>Leaving the study early. Unable to use - Mental state: PANSS (no usable data). Global state: CGI (no usable data)</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...randomized, parallel-group..." no further details.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"...double-blind..." "Subjects were randomly assigned to receive either an encapsulated ethyl-EPA supplement 2 g/day... or an identical capsule containing placebo (medicinal liquid paraffin BP 2 g/day)... Trial supplies were packed by an independent contract clinical trials supplies company (DHP), who prepared the placebo and active packs for the entire trial and assigned the randomization numbers to the packs. The randomization code was broken after completion of the trial".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors for efficacy outcomes (TD symptoms and Mental State) not reported. Adverse events blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall drop-out rate: 35%. 7/84 (8%) participants dropped out before the first post-randomisation visit. 7/84 (8%) participants were not included in the analysis. "Data from... 77 patients were included in the final analysis". "The number of subjects who discontinued medication prematurely in the ethyl-EPA group was 8 (19%) (consent withdrawal n=4; non-compliance n=3; protocol violation n=1), and in the placebo group 14 (33%) (consent withdrawal n=9; non-compliance n=3; adverse events n=2 (congestive cardiac failure; nose-bleed) (Chisquare=2.2, df=1, p=0.1)."

Emsley 2006 (Continued)

It seems that these participants were included in the analysis.

Selective reporting (reporting bias)	High risk	Data for some outcomes stated in the protocol have not been reported (e.g. remission, CGI severity)
Other bias	Unclear risk	"The demographic characteristics and baseline PANSS scores in the two treatment groups were similar, but baseline ESRS dystonia subscale and TD CGI scores differed significantly". Unclear if the differences (confounding variables) may be biased

Gardos 1979

Methods	Allocation: "randomised" unclear. Blindness: single-blind. Duration: 12 weeks. (6 weeks then crossed over to another 6 weeks. Washout period unknown) Design: cross-over. Setting: inpatients, USA
Participants	Diagnosis: psychogeriatric (23) and schizophrenic (18) patients with obvious TD. N = 41 Sex: 28 female and 13 male. Age: mean 64 years, range 32-84 years. History: Duration of TD not reported.
Interventions	1. Papaverine: dose 150 mg/day twice a day for the first week and 300 mg twice a day for the subsequent 5 weeks. N = 21. 2. No treatment: 6 weeks (followed by 6 weeks of papaverine). N = 20. Concomitant medication: antipsychotics, antidepressants, anxiolytics, or no medication. No changes were made in psychotropic drug administration during the study.
Outcomes	TD symptoms: AIMS (only reported for Boston sample) Unable to use (not reported for first treatment phase before cross-over) Leaving the study early Adverse effects: Parkinsonism
Notes	Sponsorship source: Supported in part by a grant from the Drug Abuse and Mental Health Administration of HEW. * Authors state that the two samples differed greatly in the incidence and severity of tardive dyskinesia prior to the study. The differences were to a large extent due to the differences in the two populations: Boston patients were older with longer duration of disability and hospitalizations and showed more extensive dyskinesia. In view of the major differences in the populations, data from the two groups were analysed separately.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"random order", further details not reported.

Gardos 1979 (Continued)

Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"single-blind". As the participants were randomised to receive papaverine or not, neither the participants nor the study personnel could have been blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"A single blind design was used with blind raters and a 6-weeks no drug control condition."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Although not clearly reported, it seems that 1/23 participants in the Boston sample and 0/18 participants in the Kentucky sample were withdrawn from the study.
Selective reporting (reporting bias)	Unclear risk	Unclear if all predefined outcomes have been reported. Also, the reason for not assessing TD symptoms using AIMS in the Kentucky sample is not reported.
Other bias	Unclear risk	The two samples were very different in their baseline characteristics. However, this was controlled by reporting data separately. Unclear if there might have been other confounding variables to affect bias.

Glazer 1985

Methods	Allocation: randomised. Blindness: double-blind. Duration: 3 weeks. Design: parallel. Setting: Outpatients, Connecticut Mental Health Center, USA
Participants	Diagnosis: psychiatric disorder (no operational criteria) and Schooler & Kane's criteria for TD N = 12. Sex: 12 females. Age: 50-65 years, mean 57 years. History: Duration of TD on average 32.3 months (range 6-60 months). Patients maintained their antipsychotic medication
Interventions	1. Oestrogen: 1.25 mg/day. N = 6.* 2. Placebo. N = 6. Nine of the 10 patients were on medications other than antipsychotics; 7 were on psychiatric medication. Further details not provided.
Outcomes	Tardive dyskinesia: AIMS improved/not improved, deterioration in symptoms, AIMS scale scores . Adverse events: other observed effects. Leaving the study early. Unable to use - Adverse events: Parkinson scores (no data). Mental state: BPRS (no data).
Notes	Sponsorship source: Supported by HD 13587 and Ayerst Pharmaceuticals

Risk of bias

Glazer 1985 (Continued)

Bias	Authors' judgement	Support for judgement
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) All outcomes	Unclear risk	"double-blind". Details not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	TD related and mental state outcomes: "double-blind". "All ratings were administered without knowledge of the study status of the individual subject. Patients were videotaped during the research nurse's rating on visits 1 and 4. These tapes were subsequently rated by a senior psychiatric resident who administered the AIMS and counted the frequency of abnormal movements of the most severely affected anatomical region as determined by the study psychiatrist during the baseline assessment". Details of blinding not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Twelve patients were admitted to the study, and 10 completed the 3-week trial. One patient in the placebo group was hospitalized for congestive heart failure. One patient in the oestrogen group required psychiatric hospitalization after taking an overdose of medications; she had been depressed at the onset of the trial and became worse at the third visit during a period of severe marital discord." Balance between groups, reasons reported.
Selective reporting (reporting bias)	High risk	TD symptoms data not reported as mean (SD) but rather as mean only (table 1). Data for Mental state (BPRS) not reported. Adverse effects reported only as adverse events leading to study discontinuation.
Other bias	High risk	"Although our study involved randomization and double-blind drug procedures to prevent bias, the small sample size resulted in some imbalances between groups at the first visit. Thus, the conjugated oestrogen group had less exposure to antipsychotic medication and a shorter duration of TD. They also had higher mean baseline AIMS scores than did the placebo group, thereby leaving more possibility for improvement in scores. The small sample size does not allow statistical analysis to adjust for these differences. Although we found a positive but non-significant association between duration of TD and decrease in AIMS score between visits 1 and 4, we doubt that TD duration is a confounding factor, since the direction of this association is the opposite of what we would have expected".

Glover 1980

Methods	Allocation: randomised. Blindness: not mentioned. Duration: 8 sessions. Design: parallel. Setting: Outpatients, USA
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Glover 1980 (Continued)

Participants	<p>Diagnosis: Diagnosis of chronic schizophrenia; diagnoses of either acute extra pyramidal symptoms, TD, and/or pseudoparkinsonism.</p> <p>N = 15.</p> <p>Sex: 12 females and 3 males.</p> <p>Age: mean 34.9 years.</p> <p>History: Duration of TD not reported. Not reported whether patients were stabilised prior to study.</p>
Interventions	<p>1. Hypnosis: 8 sessions. N = 5.</p> <p>2. Relaxation. 8 sessions. N = 5.</p> <p>3. Treatment as usual (control group). 8 sessions. N = 5.</p> <p>Psychotropic medication continued.</p>
Outcomes	Leaving the study early: number of dropouts
Notes	Sponsorship source: Sponsorship source not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"There was a total of fifteen subjects randomly selected". "I made the assumption that the order in which patients approached the clinic was not related in any way to their susceptibility or effectiveness of subsequent treatments. Based on these assumptions I assigned the first patient who came into the study to group 1, the second patient ""as assigned to group 2, and the third patient was assigned to Group 3; after every three assignments I started the assignments with group 1 again and continued until each treatment modality had a total of five"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	As participants in group 1 received hypnosis, those in group 2 received relaxation training, and those in group 3, TAU without any other treatment, blinding could not be achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no refusals, or dropouts among the referrals.
Selective reporting (reporting bias)	Low risk	It seems that all outcomes have been reported. However data are not usable.
Other bias	Unclear risk	"(Tables 1, 2 and 3). Using a non-parametric test for testing differences on demographic data between treatment groups yielded no significant difference among these groups (Table 7). With respect to the regimen of medication for each patient (Tables 4, 5, 6), there was close similarity in each group. The majority of patients in each group received either haloperidol or trifluoperazine; therefore any alternative treatment differences could not be influenced by medication. However, due to the formula which is used by physicians in dispensing medication, it was not possible to use a statistical procedure for testing the equality of the three groups in this study. The sample size, sex and mar-

Glover 1980 (Continued)

ital status variables was so small to preclude a statistical test on these two variables."

Goff 1993

Methods	Allocation: "randomly assigned" unclear. Blindness: double, (identical capsules). Duration: 6 weeks. Design: parallel. Setting: outpatients, USA Raters: "AIMS were videotaped and scored by a second rater unaware of the temporal sequence of examinations"
Participants	Diagnosis: antipsychotic-induced TD according to DSM-III-R, Schooler and Kane criteria with a score of at least 3 (moderate) on a single item or 2 (mild) on at least two items of the AIMS and have a history of at least 6 months of exposure to a antipsychotic prior to onset of dyskinetic movements. N = 33 Sex: 13 female and 20 male. Age: mean 48.8 (SD 9.8) years Duration TD: not reported.
Interventions	1. Selegiline (L-Deprenyl): dose 5 mg (one capsule daily for the first week, then one twice daily thereafter) for 6 weeks. N = 17. 2. Placebo for 6 weeks. N = 16 Doses of antipsychotics and anticholinergic agents were stable for at least 4 months before the trial. Patients receiving depot antipsychotic were included only if injections were administered on a biweekly schedule.
Outcomes	TD symptoms: not significant clinically improved (defined as an improvement of more than 50%) Leaving the study early Unable to use: Adverse effects: severity of parkinsonian symptoms and akathisia using SAS, Mental state: BPRS for positive, negative and depressive symptoms, Global assessment scale, Average change in severity of TD using AIMS
Notes	Sponsorship source: Supported by PHS grant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned", further details not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identical capsules containing either selegiline 5 mg or placebo." "double-blind"

Goff 1993 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Examinations with the AIMS were videotaped and scored by a second rater unaware of the temporal sequence of examinations."
Incomplete outcome data (attrition bias) All outcomes	High risk	"Five subjects, all receiving selegiline, dropped out prior to the completion of week 1 and so were not included in analysis of outcome." 29% drop out in the active medications group, not ITT.
Selective reporting (reporting bias)	High risk	Data not reported for mental state (BPRS total and sub scales), severity of parkinsonian symptoms (SAS)
Other bias	Low risk	The study seems to be free of other sources of bias.

Hajioff 1983

Methods	Allocation: "randomly assigned", no further details. Blindness: double-blind Duration: 14 weeks (2 week run-in, 6 week treatment, 6 week no-treatment follow-up) Design: parallel Setting: Inpatients, UK (probably)
Participants	Diagnosis: schizophrenia (9), dementia (3 with paranoid features, 3 without), depression (3), pre-senile dementia (1). and epileptic psychosis (1). N = 20. Sex: 10 female and 5 male. Age: mean 65.4 (males)-79.5 (females) years, range 60-92 years History: Duration of TD not reported. Seventeen patients were each receiving one antipsychotic drug, thioridazine (5), promazine (5), chlorpromazine (3), haloperidol (2), trifluoperazine (1) and chlomethiazole (1). Their dosage regimen had remained constant for at least 6 months. Two patients with chronic schizophrenia and one with depression were not taking any antipsychotic drugs for the same period.
Interventions	1. 4.5 mg co-dergocrine mesylate once daily for 6 weeks. N = 10. 2. Placebo once daily for 6 weeks. N = 10. Only two patients had never received anti-Parkinsonian drugs, the remainder receiving therapy for various periods of time (3 months to 8 years). Two other patients were receiving anti-Parkinsonian drugs at a constant dose during the study period. Details of medications, not reported.
Outcomes	The abbreviated dyskinesia scale of the Rockland Research Institute (ADS). Death. Leaving study early.
Notes	Sponsorship source not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned", no further details.
Allocation concealment (selection bias)	Unclear risk	Details on allocation concealment were not reported.

Miscellaneous treatments for antipsychotic-induced tardive dyskinesia (Review)

Hajioff 1983 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double blind", no further details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details on blinding of outcome assessment were not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant from the placebo group died in the second week of the study (run-in phase) and was not part of the final analyses.
Selective reporting (reporting bias)	Unclear risk	No details.
Other bias	Unclear risk	No details.

Kojima 1992

Methods	Allocation: randomised, not described. Blindness: double, not described. Duration: 8 weeks. Design: parallel. Setting: Inpatients and outpatients, Japan
Participants	Diagnosis: schizophrenia (DSM-III-R). N = 85. Sex: 34 female and 32 male. Age: 31-75 years, mean 55.2 years. History: antipsychotic-induced TD (mean duration 5 years).
Interventions	1. Ceruletine IM: dose 0.8 mcg/kg/week for 3 weeks. N = 43. 2. Placebo. N = 42. Previous background medication and treatment held constant throughout trial.
Outcomes	Tardive dyskinesia: AIMS improved/not improved, deterioration in symptoms. Adverse events: other observed effects. Leaving the study early.
Notes	Data presented for 33 matched pairs only. Sponsorship source: Sponsorship source not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...patients were randomized into matched pairs on the basis of age and sex, and of the severity and duration of TD symptoms." Details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.

Kojima 1992 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double- blind", further details not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double- blind", further details not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	"Of the 85 patients who entered the study, eight were excluded from data analysis because of protocol violations (e.g., an insufficient severity of TD symptoms during the baseline period or missing observations)." One patient was discontinued due to adverse event (table 2). Actually, 19 participants were excluded from the analysis (66/85 participants, 33 in each group, were analysed. "Analyses were performed on the 33 pairs (i.e., 33 patients in the ceruletide group vs. 33 patients in the placebo group). p. 131, 1st paragraph.
Selective reporting (reporting bias)	High risk	Judgement Comment: "Of the 85 patients who entered the study, eight were excluded from data analysis because of protocol violations (e.g., an insufficient severity of TD symptoms during the baseline period or missing observations)." "Analyses were performed on the 33 pairs (i.e. 33 patients in the ceruletine group versus 33 patients in the placebo group)"
Other bias	Unclear risk	Insufficient information. Baseline information reported for participants included in the analyses but not for the participants who were not entered to the analysis due to "protocol violations"

Koshino 1979

Methods	Allocation: "randomly allocated", Details not reported. Blindness: "double-blind," Details not reported Duration: 4 weeks Design: Parallel Setting: Inpatients in 4 psychiatric hospitals in Japan
Participants	Diagnosis: Schizophrenia (n = 35), others (n = 7), drug-induced TD N = 42 Sex: Male 13, Female 29 Age: 56.1 (SD: 8.69) History: Duration of TD not reported.
Interventions	1. Cyproheptadine (12 mg/day to 24 mg/day Flexible, 4 week). N = 21 2. Placebo. N = 21 Concomitant medication not reported.
Outcomes	Tardive dyskinesia: Assessment scale developed by the researchers Leaving the study early.

Koshino 1979 (Continued)

Adverse effects

Notes Sponsorship source: Cyproheptadine and placebo tablets supplied by Merck-Banyu Co.Ltd
Assessed and data extracted by Yusuke Ogawa.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated", Details not reported.
Allocation concealment (selection bias)	Low risk	Randomization was conducted by the third person (outside of the research group). Allocation codes were stored until the end of the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind," Details not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double-blind," Details not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Forty-two patients were admitted to the study, and 41 completed the 4-week trial. One patient in the placebo group dropped out due to side effects. Reason reported.
Selective reporting (reporting bias)	Unclear risk	Unclear if all pre-defined outcomes were reported. A protocol is not available.
Other bias	Unclear risk	Insufficient information to make a judgement.

Koshino 1983

Methods	Allocation: "randomly allocated", Details not reported. Blindness: "double-blind," Details not reported Duration: 6 weeks Design: Parallel Setting: Inpatients in a psychiatric hospital in Japan
Participants	Diagnosis: antipsychotic-induced TD, Schizophrenia N = 28 Sex: Male 16, Female 12 Age: 59.3 (SD: 8.29) History: Duration of TD not reported.
Interventions	1. Dihydrogenated Ergot Alkaloids (6 mg/day, 6 week). N = 14 2. Placebo. N = 14

Koshino 1983 (Continued)

Concomitant medication not reported.

Outcomes	Tardive dyskinesia: Not clinically improved Tardive dyskinesia: Not any improved Tardive dyskinesia: Simpson scale Tardive dyskinesia: Deterioration Mental state: Not any change in general mental state Adverse effects general Leaving the study general Leaving the study Due to side effect
Notes	Sponsorship source: Dihydrogenated Ergot Alkaloids and placebo tablets supplied by Sandoz Assessed and data extracted by Yusuke Ogawa.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated", Details not reported.
Allocation concealment (selection bias)	Low risk	Randomization was conducted by the third person (outside of the research group). Allocation codes were stored until the end of the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind," Details not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double-blind," Details not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Twenty-eight patients were admitted to the study, and all of them completed the 4-week trial.
Selective reporting (reporting bias)	Unclear risk	Unclear if all pre-defined outcomes were reported. A protocol is not available.
Other bias	Unclear risk	Insufficient information to make a judgement.

Libov 2007

Methods	Allocation: randomised, not described. Blindness: double-blind, not described. Duration: 9 weeks. Design: cross-over, 4 weeks treatment one week wash out. Setting: Inpatients, Be'er Sheva Mental Health Center, Israel.
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Libov 2007 (Continued)

Participants	<p>Diagnosis: schizophrenia, schizoaffective disorder (DSM-IV). N = 40. Sex: 27 male, 23 female. Age: 26-69 years; mean 44.9 (SD 12.4) years. History: Duration of TD at least 1 year. Patients were stabilised at least one month prior to entry. Anti-psychotic medication was not altered.</p>
Interventions	<p>1. Piracetam: dose 4800 mg/day + conventional antipsychotics. N = 21 2. Placebo. N = 19</p> <p>Twenty-four patients received various mood stabilisers (lithium, carbamazepine, or valproate) in combination with antipsychotic agents</p>
Outcomes	<p>Tardive dyskinesia: Extrapyramidal System Rating Scale (ESRS).</p> <p>TD symptoms: not any improvement Adverse events: other observed effects. Leaving the study early.</p>
Notes	<p>Sponsorship source: Supported by a Clinical Trials Grant from the Stanley Medical Research Institute, Bethesda, Md.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"subjects were randomized to receive either piracetam or placebo." Details not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Both patients and raters were blinded to group allocation." further details not reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"raters were blinded to group allocation"
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>"Of the 40 randomly assigned patients, 5 subjects (4 taking placebo and 1 taking piracetam) did not comply with the treatment regimen following the first 2 weeks of the study and were not included in the statistical analysis. Therefore, 35 patients completed phase I, and, of these, 4 patients (2 receiving placebo and 2 receiving piracetam) did not agree to continue to phase II, resulting in 31 patients completing both phases of the crossover protocol. The main reason for patient dropout was the large size and number of the capsules that they were required to take."</p> <p>In the first phase there was a 12.5% dropout while in the completed cross-over trial 22.5% dropout. Patients who dropped out were not included in the analysis</p>
Selective reporting (reporting bias)	Low risk	Outcomes defined in the Protocol have been reported. NCT00190008
Other bias	Low risk	The study seems to be free of other sources of bias.

Miscellaneous treatments for antipsychotic-induced tardive dyskinesia (Review)

Mackay 1980

Methods	Allocation: randomised, not described. Blindness: double-blind, not described. Duration: 5 weeks treatment per arm separated by 6 week washout. Design: cross-over. Setting: Chronic inpatients, UK
Participants	Diagnosis: schizophrenia (7), bipolar affective illness (3), depressive psychosis (1) (no diagnostic criteria). N = 11. Sex: not described. Age: 56-70 years, median 59 years. History: antipsychotic-induced TD for at least one year and not pre-dating antipsychotic treatment; treatment with antipsychotics for a period of at least 2 years.
Interventions	1. Lithium: dose not specified. N = 6. 2. Placebo. N = 5. Previous background medication and treatment continued throughout trial, patients were receiving a variety of antipsychotic and anxiolytic drugs: 4 patients received no antipsychotic medication.
Outcomes	Tardive dyskinesia: improved/not improved, deterioration in symptoms, Rockland TD scale score. Adverse events: other observed effects - parkinsonian and drowsiness. Leaving the study early. Unable to use - Tardive dyskinesia: SAS (no data). Mental state: BPRS (no data). Behaviour: NOSIE (no data).
Notes	Sponsorship source: Sponsorship source not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"A random Li (Camcolit QDS)/placebo cross-over design", further details not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Raters, nurses and patients were blind to treatment. Two non-blind 'coordinators'... adjusted the oral dose of Li carbonate to aim at a serum concentration between 0.8 and 1.3 mM. Adjustment of U dosage was mirrored by a similar change for the 'placebo twin'" "At completion of the study, the patients, a psychiatrist and nursing staff involved in ratings were asked to guess the nature of the treatment block. There was a choice of 3 alternative answers: inactive tablets, active drug or uncertain. "Analysis of the guesses made by staff and patients as to the sequence of treatments showed that correct guesses occurred randomly. Thus, despite inevitable cues from side-effects, it seemed that the double-blind nature of the study was preserved".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Raters, nurses and patients were blind to treatment." "At completion of the study, the patients, a psychiatrist and nursing staff involved in ratings were asked to guess the nature of the treatment block. There was a choice of 3 alternative answers: inactive tablets, active drug or uncertain. "Analysis of the guesses made by staff and patients as to the sequence of treatments showed

Mackay 1980 (Continued)

that correct guesses occurred randomly. Thus, despite inevitable cues from side-effects, it seemed that the double-blind nature of the study was preserved".		
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/11 participants (in the lithium first group) did not complete the study. Reason not reported.
Selective reporting (reporting bias)	High risk	Mental State and behaviour outcome data not reported. TD symptoms scale scores data not reported.
Other bias	Unclear risk	"Patients were divided, as far as possible into matched for age, sex, severity of TD, duration of psychiatric illness and duration of neuroleptic treatment. Matching for sex was exact and the maximum discrepancies between members for any pair for other variables were as follows: age $\pm$ 4 years, total Rockland TD scores $\pm$ 17, duration of illness $\pm$ 11years, duration of neuroleptic treatment $\pm$ 5 years" Unclear of a discrepancy of $\pm$ 17 on the total Rockland TD scores is significant.

Matsunaga 1988

Methods	Allocation: randomised, not described. Blindness: double-blind, not described. Duration: 4 weeks. Design: parallel group. Setting: inpatient, Japan
Participants	Diagnosis: chronic psychotic inpatients with TD N = 47 Sex: 22 female and 15 male Age: 59 (SD 8.8) years History: antipsychotic-induced TD from 7 months to 20 years. Patients stabilised at least 3 weeks prior to entry.
Interventions	1. Ceruletide: 0.8 mcg/kg/week. N = 19. 2. Placebo. N = 18. Background medication and treatment continued throughout trial.
Outcomes	Tardive dyskinesia: AIMS improved/ not improved, deterioration in symptom. Adverse events: other observed effects. Leaving study early.
Notes	Sponsorship source: Shionogi & Co., Ltd., Japan supplied Ceruletide

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were assigned at random". Details not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.

Matsunaga 1988 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind" Details not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double blind" Details not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	"Of the original 47 patients, one patient dropped out of the study because of fever of unknown origin. Nine patients in whom assessment of TD symptoms was unreliable either due to the erratic variation in symptomatology or to the emotional or situational effect unrelated to the drug treatment, were excluded from the final analyses before opening of the key code. Thus, 37 patients were available for analysis, 19 receiving Ceruletide and 18 receiving placebo". Data not reported for 21% of the participants.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make a judgement. A protocol is not available to verify all outcomes defined prior to study.
Other bias	Low risk	The study seems to be free of other sources of bias.

Meco 1989

Methods	Allocation: randomised. Blindness: double-blind. Design: cross-over. Setting: inpatients, Italy. Duration: 30 days (then crossed over to another 30 days).
Participants	Diagnosis: Chronic schizophrenia (DSM-III-R criteria) and suffering from antipsychotic-induced TD previously untreated with other drugs. N = 10. Age: mean 57 years, range 33-72 years. Sex: 5 Male and 5 Female History: Duration of TD ranging from 0.5 to 3 years; Eight patients received anticholinergic drugs before TD; Duration of antipsychotic therapy ranging from 4 to 15 years.
Interventions	No washout period was reported before trial entry. 1. Ritanserin: dose 10 mg three times a day for 30 days. N = 4. 2. Placebo for 30 days. N = 6. Concomitant medication: The patients continued receiving their basic treatment for the psychosis (i.e. haloperidol, lorazepam, haloperidol decanoate, chlorpromazine, clotiapine, thioridazine)
Outcomes	TD symptoms (AIMS): not clinically improved, not improved, deteriorated Mental state: BPRS
Notes	Sponsorship source: Sponsorship source not reported Results are presented for each phase

Meco 1989 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Six patients, chosen at random (patients 1-6; group A), first received the placebo and then ritanserin; the other four patients (patients 7 -10; group B) received treatment in the reverse order" Further details not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind" Details not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double-blind" Details not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Participant flow through the study is not clearly reported. However, full data for all participants have been reported for all visits including post intervention.
Selective reporting (reporting bias)	Unclear risk	All outcomes seem to have been reported. However, a protocol is not available for verification.
Other bias	Low risk	The study seems to have been free of other sources of bias.

Mosnik 1997

Methods	Allocation: randomised, not described. Blindness: double-blind, not described. Duration: 2 days (1 day/single dose crossed over to another day/single dose) Design: cross-over. Setting: Inpatients and outpatients, USA.
Participants	Diagnosis: schizophrenia (DSM-III-R). N = 18. Sex: 18 male. Age: 28-65 years, mean 44 (SD 11.8) years. History: currently receiving antipsychotics, clinically significant TD. Duration of TD nor reported. Patient stabilisation prior to study entry not reported.
Interventions	1. Phenylalanine: 100 mg/kg body weight (day 1) followed by placebo (day 2). N = 10. 2. Placebo: (day 1) followed by phenylalanine 100mg/kg body weight (day 2). N = 8. Background medication and treatment continued throughout trial.
Outcomes	Leaving the study early. Unable to use - Tardive dyskinesia: AIMS endpoint score (not reported for placebo group or not reported for the first treatment phase before crossing over to the next treatment)

Mosnik 1997 (Continued)

Cognitive ability: Rey Auditory Verbal Learning Test (AVLT) (not reported for the first treatment phase before crossing over to the next treatment)

Mental state: SANS & SAPS (modified version of scales used).
Cognitive ability: Edinburgh Inventory test (no data)

Notes Sponsorship source: Supported in part by a VA Merit Review grant to one of the authors by The National Institute of Mental Health Grants to a second author, and a NARSAD Young Investigator Award to a third author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomized..." Details not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Drinks were prepared by an assistant and administered by the first author in a double blind manner". "The fine white L-phenylalanine powder could not be tasted or detected visually when mixed with the bright orange colored powder." Thus, patients may have been blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"TD ratings were performed double-blind". No further details are reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"One subject in the group who received phenylalanine on the first day, left the hospital against medical advice after completing only 1 day of the study; however, his data were included in the analyses"
Selective reporting (reporting bias)	Unclear risk	Not all data are fully reported. Some data are reported partially. No protocol are available
Other bias	Low risk	The study seems to be free of other sources of data

Mouret 1991

Methods	Allocation: randomised, not described. Blindness: double-blind, not described. Duration: 12 weeks. Design: parallel. Setting: inpatients, Morocco
Participants	Diagnosis: schizophrenia (DSM-III). N = 20. Sex: 7 female and 13 male Age: 20-67 years, mean 38.3 years. History: chronic with antipsychotic-induced TD. Duration of TD from 1 to 9 years. The antipsychotic therapy was maintained at the same dose but it is not clear the duration of stabilisation prior to study entry.
Interventions	1. Insulin, 'standard' type: 10 units/day for 15 days administered at 10:00am; weekly for 5 weeks thereafter. N = 10. 2. Placebo. N = 10.

Miscellaneous treatments for antipsychotic-induced tardive dyskinesia (Review)

Mouret 1991 (Continued)

Background medication and treatment continued throughout trial.

Anticholinergics were withdrawn at least 2 weeks prior to the beginning of the study

Outcomes	Tardive dyskinesia: AIMS improved/not improved, deterioration in symptoms, AIMS scale scores. Leaving the study early.
Notes	Sponsorship source: Standard Insulin or placebo supplied by Novo Industry.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"They were randomly assigned..." Details not reported.
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: Allocation concealment not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"...double-blind..." "The patients and the rater were blind to treatment conditions" Details not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"...double-blind..." "The patients and the rater were blind to treatment conditions". Details not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition information has not been reported. However, as end of trial data had been individually reported for all randomised participants, it is assumed that all participants completed the trial
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make a judgement. A protocol is not available to verify all outcomes defined prior to study.
Other bias	Unclear risk	"At day 0, all 20 patients had severe orofacial dyskinesia and the two groups of patients did not differ in scores, age, duration of disease. Neuroleptic treatment was however significantly ($p=0.037$) longer in the placebo group than in the insulin group". Unclear if this could have influenced bias.

O'Brien 2014

Methods	Allocation: randomised, not described. Blindness: double-blind, not described. Duration: 6 weeks. Design: parallel. Setting: inpatients/outpatients, USA
Participants	Diagnosis: schizophrenia or schizoaffective disorder, mood disorder, or gastrointestinal disorder + antipsychotic-induced TD N = 78. Sex: not reported Age: 18-85 years

O'Brien 2014 (Continued)

History: Duration of TD at least 3 months prior to study. Patient stabilisation was minimum of 30 days before study start. Participants who were not using antipsychotic medication had stable psychiatric status.

Interventions	1. NBI-98854 (VMAT2 inhibitor): dose 25mg/d-75mg/d for 6 weeks. N = 39. 2. Placebo for 6 weeks. N = 49. Concomitant medication not reported.
Outcomes	Tardive dyskinesia: AIMS. CGI-TD and a patient-reported scale were also reported for TD symptoms but not included in the review. Adverse events. Leaving the study early
Notes	Sponsorship source: Neurocrine Biosciences

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation.
Allocation concealment (selection bias)	Low risk	Central interactive web response system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	""double-blind, "blinded physician investigator," Personnel blinded, details not reported for participants but we judge that participants were likely to be blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Movement Disorder Neurologists as blinded central AIMS raters"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Early discontinuation rates were comparable (5 subjects each, placebo and active)." Active 13% and placebo 10% dropouts. Reasons were reported.
Selective reporting (reporting bias)	Unclear risk	Results for some scales to assess safety were not fully reported.
Other bias	Low risk	Appears to be free from other sources of bias.

Rastogi 1982

Methods	Allocation: "randomly allocated" Blindness: double-blind, unclear. Duration: 12 weeks (6 weeks intervention and 6 weeks post intervention follow-up). Design: parallel Setting: Inpatients, UK
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Rastogi 1982 (Continued)

Participants	<p>Diagnosis: Schizophrenia (29), dementia (5), depressive psychosis (3), oligophrenia (2), bipolar affective psychosis (1). Presence of persistent involuntary movements predominantly in the orofacial region and unrelated to drug-induced Parkinsonian movements.</p> <p>N = 40.</p> <p>Sex: 22 female and 18 male.</p> <p>Age: mean 69.9 years.</p> <p>History: Duration of TD at least 1 year..</p>
Interventions	<p>1. Co-dergocrine (hydergine): dose 4.5 mg/day for 6 weeks. N = 19.</p> <p>2. Placebo for 6 weeks. N = 21</p> <p>Background antipsychotic and antiparkinsonian medication was held constant throughout the study.</p>
Outcomes	TD symptoms: AIMS combined with abbreviated Rockland Tardive Dyskinesia Rating Scale
Notes	Sponsorship source: Sponsorship source not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly allocated to two groups" Further details not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"[...], one of which received co-dergocrine, 4.5 mg tablets once daily for 6 weeks, and the other received an identical placebo tablet for the same period. The 2 raters, ward staff and patients were blind to the treatment procedure."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition information not reported.
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcomes have been reported.
Other bias	Unclear risk	Baseline characteristics, except for age, sex, and TD scores, not reported per intervention group.

Richardson 2003

Methods	<p>Allocation: randomised, not described.</p> <p>Blindness: double-blind, not described.</p> <p>Duration: 3 weeks.</p> <p>Design: parallel.</p> <p>Setting: Inpatients and outpatients, USA</p>
Participants	Diagnosis: Psychiatric patients with long histories of antipsychotic treatment

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Richardson 2003 (Continued)

N = 68.

Sex: 68 male

Age: mean 44.6(SD 9.9).

History: Duration of TD: "presumably long-standing tardive dyskinesia".

Patients stable for 2 weeks prior to entry. Patients who began the trial with stable doses of medication but who had changes in antipsychotic antiparkinson, antidepressant, or anticonvulsant drug doses during the trial were dropped from the study.

Interventions	<p>1. Branched-chain amino acids: low dose 56 mg/kg of body weight for 3 weeks. N = not reported</p> <p>2. Branched-chain amino acids: medium dose 167 mg/kg of body weight for 3 weeks. N = not reported</p> <p>3. Branched-chain amino acids: high dose 222 mg/kg of body weight for 3 weeks. N = 25</p> <p>4. Placebo for 3 weeks. N = 27</p> <p>Only results from the high dose and placebo groups were reported.</p> <p>Concomitant medication not reported</p>
Outcomes	Tardive dyskinesia: Simpson Abbreviated Dyskinesia Scale: improvement, deterioration, scale scores. Leaving the study early.
Notes	Sponsorship source: Supported by NIMH grant MH-44153, institutional support from the New York State Office of Mental Health, and a grant and product support from Scientific Hospital Supplies International, Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned" Details not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind," Details not reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Movement frequencies were counted from the videotapes by the first author, who was blind to the patients' treatment status and the chronological order of the videotapes."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Participants treated with low and medium dose were not entered to the analysis. ITT was conducted for 41 participants who were treated with high-dose amino acid or placebo.
Selective reporting (reporting bias)	High risk	Outcome data not reported for low- and medium-dose treatment. Patient recruitment of these two groups was stopped after interim analysis. Full details of interim analysis results not reported.
Other bias	Unclear risk	The authors state that there were no differences between participants treated with high dose and placebo. However, details of the two other groups randomised to the trial have not been reported.

Shamir 2000

Methods	Allocation: randomised. Blindness: double-blind. Duration: 3 weeks. Design: cross-over (2 week washout) Setting: Inpatients, Israel
Participants	Diagnosis: Chronic schizophrenia (DSM-IV criteria) N = 19. Sex: 13 female and 6 male Age: range 62-91 years, mean 73 years (SD 9.9). History: Duration of TD for a minimum of 5 years. Patient stabilisation duration was unclear but "all patients continued to receive antipsychotic treatment during the trial and treatment was unchanged throughout the study".
Interventions	1. Melatonin: dose 2 mg/day for 4 weeks. N = 9 2. Placebo for 4 weeks. N = 10 Concomitant medication not reported.
Outcomes	Tardive dyskinesia: AIMS improved/not improved, deterioration in symptoms, AIMS scale scores. Leaving the study early. Adverse effects
Notes	Sponsorship source: Melatonin (Circadin) and placebo tablets supplied by Neurim Pharmaceuticals, Tel Aviv, Israel.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly assigned". Although details of randomisation have not been reported. As allocation was done by the hospital pharmacy, it is assumed that random sequence generation was not biased.
Allocation concealment (selection bias)	Low risk	"Both patients and physicians were blinded to the group allocation and all medications were dispensed by the center's pharmacy and added to the patients' regular treatment regimens".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The patients were randomly assigned to receive placebo or melatonin 2mg/day, supplied in identical tablet form by Neurim Pharmaceuticals...Both patients and physicians were blinded to the group allocation and all medications were dispensed by the center's pharmacy and added to the patients' regular treatment regimens".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	TD symptoms' outcomes: "The patients were randomly assigned to receive placebo or melatonin 2mg/day, supplied in identical tablet form by Neurim Pharmaceuticals...Both patients and physicians were blinded to the group allocation and all medications were dispensed by the center's pharmacy and added to the patients' regular treatment regimens". "The same investigator...rated the individual patients throughout the trial."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All 19 patients completed the 10-week study."

Shamir 2000 (Continued)

Selective reporting (reporting bias)	Unclear risk	Unclear if all outcomes previously stated were reported. A protocol is not available for verification. Also, although stated that "Prior to separating the data into the 2 treatment groups, the data were examined according to order...No carryover effects were demonstrated and baseline values did not differ significantly", data not reported per period.
Other bias	Unclear risk	Insufficient information to make a judgement.

Shamir 2001

Methods	Allocation: randomised. Blindness: double-blind. Duration: 16 weeks. Design: cross-over (4 week washout) Setting: inpatient (probably), Israel
Participants	Diagnosis: Schizophrenia (Structured Clinical Interview for DSM-IV); antipsychotic-induced TD (DSM-IV criteria) N = 24 (2 were discharged after randomisation, but before initiation of treatment, and were not included). Sex: 6 female and 6 male Age: range 28-82 years, mean 64.2 years (SD 14.3). History: Duration of TD not reported. Patient stabilisation duration unclear but "the antipsychotic medication regimens remained unchanged throughout the study".
Interventions	1. Melatonin: dose 10 mg/day for 6 weeks. N = 12 2. Placebo for 6 weeks. N = 10 Concomitant medications: "anticholinergics 12 patients; benzodiazepines, 5 patients; antidepressants, 4 patients; and mood stabilizers, 5 patients. The regimens of these additional medications also remained unchanged throughout the study"
Outcomes	Leaving the study early. Adverse effects Unable to use - Tardive dyskinesia: AIMS improved/not improved, deterioration in symptoms, AIMS scale scores (not reported separately for the first treatment phase before cross-over to the next treatment).
Notes	Sponsorship source: Sponsorship source not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomized," Although details of randomisation have not been reported, as allocation was done by the hospital pharmacy, it is assumed that random sequence generation was not biased.
Allocation concealment (selection bias)	Low risk	"Medication and placebo were dispensed by the hospital's pharmacy and added to the patients' ongoing treatment regimen."

Shamir 2001 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"using sealed envelopes."...tablets identical in appearance..."...unblinding code following database lock..."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details are provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Two female patients were discharged from the hospital before initiation of the study and are not included in the analysis." Participants were randomised; 2/24(8%) were withdrawn before first dose of medication. It seems that the two withdrawn participants were originally randomised to the placebo group.
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcomes previously stated were reported. A protocol is not available for verification.
Other bias	Unclear risk	Insufficient information to make a judgement.

Shi 2009

Methods	Allocation: "randomly assigned" Blinding: not reported. Duration: 12 weeks. Design: parallel Setting: inpatient (probably) China
Participants	Diagnose: Antipsychotic-induced TD. N = 76 Sex: male 26, female 50. Age: mean 56.1 (SD 9.12) years old History: Duration of TD not reported. Patient were stabilised before entry to trial but the duration is not reported.
Interventions	1. Melatonin Group: dose: 9 mg melatonin, oral taken before sleep for 12 weeks. N = 39 2. Control Group: no medication control group for 12 weeks. N = 37 Concomitant medication not reported.
Outcomes	Cognitive function: Wechsler Adult Intelligence Scale (WAIS) Cognitive function: Wechsler Memory Scale (WMS) Cognitive function: Vocabulary fluency scale (VFS) Adverse events: Treatment Emergent Symptom Scale (TESS) --Unable to use (These outcomes were not predefined by this review and data were translated) WAIS subscale-score (verbal scale, verbal IQ, performance scale, performance IQ, and full scale IQ). VFT subscale-score: animal, fruits, making words.

Shi 2009 (Continued)

RBANS, subscale-score. The author did not report the total score and other subscales scores excluding the subscale-semantic fluency; because a significant difference was only observed on the latter subscale.

Notes Funding source: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“randomly assigned...” The author did not state the method of randomisation
Allocation concealment (selection bias)	Unclear risk	No information about allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	It's not possible that the participants and personnel could be blinded. As the control group did not receive intervention in addition to antipsychotics.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information about blinding outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	Low risk	The authors reported all measured outcomes.
Other bias	Unclear risk	Insufficient information to make a judgement.

UCB Pharma 2005

Methods	Allocation: randomised, not described. Blindness: double-blind, not described. Duration: 8 weeks. Design: parallel. Setting: inpatient (probably), Belgium and Bulgaria.
Participants	Diagnosis: antipsychotic-induced TD N = 70. Sex: 35 female and 35 male Age: 18-80 years, mean 53.92 (SD 10.83) years. History: Duration of TD at least one month. Patient stabilised for at least 1 month prior to entry.
Interventions	1. Levetiracetam: dose: 1500 mg twice a day (stable dose) for 8 weeks. N = 34. 2. Placebo for 8 weeks. N = 36. Concomitant medication not reported.
Outcomes	Tardive dyskinesia: mean change of symptoms (hyperkinesia subscale of the St Hans rating scale). Leaving the study early.

UCB Pharma 2005 (Continued)

Adverse events

Notes	Sponsorship source: Sponsored by UCB Pharma	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...randomized ..." Clinical Study Summary (CSS). Details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	" ...double blind..." Clinical Study Summary (CSS). Details not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	" ...double blind..." Clinical Study Summary (CSS). Details not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	"All data are presented on the intent-to-Treat population (all randomized subjects who took at least one dose of study medication). ". Clinical Study Summary (CSS) The authors actually performed modified ITT.
Selective reporting (reporting bias)	High risk	Outcome data for 2/3 secondary outcomes (antipsychotic-induced akathisia and other extrapyramidal symptoms, effect on the primary psychiatric disorder) not reported. Only summary data from Sponsor is available.
Other bias	Unclear risk	Insufficient information to make a judgement.

Wolkin 1986

Methods	Allocation: randomised, not described. Blindness: double-blind, not described. Duration: 6 weeks. Design: parallel. Setting: Inpatients and outpatients, USA.
Participants	Diagnosis: schizophrenia* (no operational criteria). N = 16. Sex: male. Age: mean 54 (SD 9) years. History: Duration of TD at least 1 year. Individual antipsychotic regimens (including no antipsychotic drugs in three patients) were kept constant from at least 1 month before the study through termination. Chronic with antipsychotic-induced TD.
Interventions	1. Gamma-Linolenic acid supplementation (oil of evening primrose) 600 mg/day for 6 weeks. N = 8. 2. Placebo for 6 weeks. N = 8. Background medication and treatment continued throughout trial. 1 patient was on lithium carbonate. Other concomitant medications not reported.
Outcomes	Tardive dyskinesia: AIMS improved/not improved, deterioration in symptoms, AIMS scale scores.

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Wolkin 1986 (Continued)

Mental state: BPRS scale scores.
Leaving the study early**.

Notes

Sponsorship source: Supported in part by Efamol, Ltd., and by the VA

* one participant might have been bipolar.

** assume loss is 0 as all AIMS scores available after 6 weeks.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Subjects were assigned on a random, double-blind basis" Details not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment details not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind". Details not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double-blind". Details not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although attrition details have not been reported, as end of trial data are reported individually for all randomised participants, it is assumed that all participants completed the trial.
Selective reporting (reporting bias)	Unclear risk	Indufficient information to make a judgement. As a protocol is not available, it is not possible to verify if all outcomes defined prior to study have been reported. (e.g. adverse events have not been reported) .
Other bias	Low risk	The study seems to be free of other sources of bias.

Woods 2008

Methods	Allocation: "assigned at random", not described. Blindness: double-blind, not described. Duration: 12 weeks. Design: parallel Setting: outpatients, USA
Participants	Diagnosis: schizophrenia/schizoaffective disorder (45), affective disorder (4), other psychiatric diagnosis (1) (DSM-IV); and TD (Glazer-Morgenstem criteria, i.e., total AIMS score ≥ 3 , with at least 1 body area rated ≥ 2). N = 50. Sex: 21 female and 29 male. Age: mean 47.4 (SD 9.6) years. History: Duration of TD in the levetiracetam group is 7.5 ± 8.4 years, whereas in the placebo group is 9.0 ± 7.3 years. "sufficiently stable psychiatrically that their CMHC clinician indicated that changes in prescribed antipsychotic medication drug or dosage were not anticipated in the next 3 months".

Woods 2008 (Continued)

"Changes in the prescribed concomitant antipsychotic medications or their doses during the randomised phase occurred in 3 levetiracetam patients (12%) versus 5 placebo patients (20%)..."

Interventions	<p>1. Levetiracetam: maximum dose 1500 mg* twice a day for 12 weeks. N = 25</p> <p>2. Placebo for 12 weeks. N = 25</p> <p>* side effects permitting and assuming lack of complete response, the dose was recommended to be escalated weekly by 500 mg/day to the maximum dose of 3000 mg/day, given in 2 divided doses.</p> <p>Concomitant medication: baseline anticholinergics (52%, levetiracetam group; 48% placebo group). Changes occurred in 2 placebo patients and none of the active patients.</p>
Outcomes	<p>Tardive dyskinesia: AIMS</p> <p>Leaving the study early.</p> <p>Adverse effects.</p> <p>Unable to use () -</p> <p>Mental State: Positive and Negative Syndrome Scale (PANSS); Young Mania Scale (YMRS); Montgomery-Asberg Depression Rating Scale (MADRS); Hamilton Rating Scale for Anxiety (HAM-A)</p>
Notes	Sponsorship source: Supported by a grant from UCB Pharma.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Eligible patients who gave written informed consent were assigned at random", further details not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double blind phase" no further details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double blind phase" no further details.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Completion rates (64% [N = 16] for the levetiracetam group and 80% [N = 20] for the placebo group, P = 0.345), reasons for discontinuation did not differ significantly between treatment groups. Data were reported for all participants randomized to the two groups (mixed-effects model).
Selective reporting (reporting bias)	High risk	Primary outcome, total AIMS scores reported. However the authors stated that: "In addition to the principal analyses of the AIMS total score, we also investigated the relative rates at which subjects achieved remission, defined a priori as no longer meeting the Glazer-Morgenstern TD entry criteria." Remission data only reported as "...Group differences did not achieve statistical significance." Also, although not stated in the Protocol, the publication reported that: "At each study visit, patients were weighed and underwent an AIMS examination and symptom ratings using the Positive and Negative Syndrome Scale (PANSS); Young Mania Rating Scale (YMRS), Montgomery Asberg Depression Rating Scale (MADRS), and the Hamilton Rating Scale for Anxiety (HAM-A) administered via a structured interview guide. Adverse events were rated using the Systematic Assessment for Treatment Emergent Events, general in-

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Woods 2008 (Continued)

quiry method. Complete blood counts were obtained at baseline and at 6, 12". Only baseline data for these outcomes have been reported.

Other bias	Low risk	"...none of the interactions with baseline were statistically significant...Further analyses revealed that the small age difference at baseline did not confound the levetiracetam treatment effect, nor did the small baseline differences in years of education, antipsychotic chlorpromazine equivalent dose, antipsychotic type at baseline (only atypical vs. any conventional), or gender."
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Yang 1999

Methods	Allocation: "randomly assigned". Blinding: double-blind, outcome assessor was blinded. Design: parallel. Setting: inpatients, China. Duration: 12 weeks.
Participants	Diagnosis: Antipsychotics-induced TD (Research Diagnosis Criteria for TD, RD-TD) N = 36 (2 participants left the study early due to discharge) Sex: male 18 , female 16 Age: mean 50.2 years old, SD 13.4 years old. History: mean ~ 8.9 years (SD ~ 7.3years) TD; mean ~ 17.7years (SD ~ 9.22 years) schizophrenia.
Interventions	1. Promethazine Group: (n = 18) Management: 50 mg promethazine was administrated by IM, twice per day for 2 weeks following with a 2-week period of IV drip (50 mg promethazine dissolved in 500 mL normal saline, once per day). This 4-week treatment regimen was conducted three circles in 12 weeks. 2. Placebo Group: (n = 16) Management: The same treatment regimen as promethazine. The placebo drug was 2 mL normal saline with same appearance as promethazine. All participants received antipsychotics as usual but were not allowed to use clozapine, anticholinergic drug, vitamin E or calcium channel blocker.
Outcomes	TD symptoms: improvement, AIMS Global state: CGI Mental state: BPRS Extrapyramidal side effects: RSESE (rating scale for extrapyramidal side effects) Adverse events: TESS (Treatment Emergent Symptom Scale)
Notes	*defined by the 4-level clinical response standard, recovery, obvious improvement, improvement, no clinical response. Funding source: not reported. Paper in Chinese, assessed and data extracted by Sai Zhao.

Risk of bias

Bias	Authors' judgement	Support for judgement
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Yang 1999 (Continued)

Random sequence generation (selection bias)	Low risk	"randomly assigned", no further details. Although the author did not state the method of randomisation, we have rated selection bias as low: because central allocation was used, it is very likely that an adequate randomisation sequence was generated.
Allocation concealment (selection bias)	Low risk	Central allocation, pharmacy-controlled randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double blind", no details of blinding of participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The outcome assessor was blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	The author reported all measured outcomes.
Other bias	Low risk	None obvious.

Zeng 1995

Methods	Allocation: "randomly assigned..." Blinding: double-blind study. Details are provided Duration: 6 weeks Design: parallel Setting: inpatients
Participants	Diagnose: Antipsychotics-induced TD Total: N = 42 Sex: male 28, female 14 Age: mean ~32.5 years old, SD ~10.3 years old. Length of illness (schizophrenia): mean ~7.5 years, SD ~3.4 years History: Duration of TD on average 5.4 ± 4.2 years in active group, whereas 5.7 ± 4.5 years in control group.
Interventions	1. Buspirone Group: (n = 21) Management: The initial dosage, one capsule each day, was titrated to 6-12 capsules each day within 10 days. 2. Placebo Group: (n = 21) Management: The initial dosage, one capsule each day, was titrated to 6-12 capsules each day within 10 days.

Zeng 1995 (Continued)

All participants received stable AP and concomitant anticholinergic drug.

Outcomes	<p>Clinical response*</p> <p>Tardive dyskinesia: AIMS (Abnormal Involuntary Movement Scale)</p> <p>Adverse events: dizziness, headache, nausea, vomiting</p> <p>--Unable to use</p> <p>Blood routine examination, urine routine test and liver function test, electrocardiography, electroencephalogram (the author only stated results of these tests were normal but did not report the data)</p>
Notes	Funding source: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned..." The author did not state the method of randomisation.
Allocation concealment (selection bias)	Unclear risk	The author did not state the method of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>"double blind study , the interventions were coded as intervention A or B by the researcher in pharmacy ". "Participants and personnel did not know the allocation result. The two drugs were contained in capsules with same appearance"</p> <p>Blinding of participants and key study personnel ensured.</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	The author reported all measured outcomes.
Other bias	Low risk	None obvious.

Zeng 1996

Methods	<p>Allocation: "randomly assigned..."</p> <p>Blinding: "double blind". Details are provided.</p> <p>Duration: 6 weeks.</p> <p>Design: parallel</p> <p>Setting: inpatients</p>
Participants	<p>Diagnosis: Antipsychotic induced TD.</p> <p>N = 46</p> <p>Sex: male 30, female 16.</p>

Zeng 1996 (Continued)

Age: mean ~33 years old, SD ~10 years old.

History: Duration of TD on average 2.2 years (SD ~1.7 years). Patients stabilised prior to study for 5 ± 4 years.

Interventions	<p>1. Pemoline Group: (n = 23)</p> <p>Management: two capsules per day for six days per week, oral taken before breakfast.</p> <p>2. Placebo Group: (n = 23)</p> <p>Management: two capsules per day for six days per week, oral taken before breakfast.</p> <p>All participants received stable AP and concomitant anticholinergic drug.</p>
Outcomes	<p>Clinical response*</p> <p>Tardive dyskinesia: AIMS (Abnormal Involuntary Movement Scale)</p> <p>Adverse events: dizziness and headache; nausea and anorexia</p> <p>--Unable to use</p> <p>Blood routine examination, urine routine test and liver function test, electrocardiography, electroencephalogram (the author only stated results of these tests were normal but did not report the data)</p>
Notes	Funding source: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned". The author did not state the method of randomisation.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study), the interventions were coded as intervention I or II by the researcher in pharmacy. "Participants and personnel did not know the allocation result. The two drugs were contained in capsules with same appearance." Blinding of participants and key study personnel ensured.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	The author reported all measured outcomes.
Other bias	Low risk	None obvious.

Zhang 2011

Methods	Allocation: "randomized", described.
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Zhang 2011 (Continued)

Blindness: double-blind, described.
Duration: 12 weeks.
Design: parallel
Setting: inpatients, China

Participants	<p>Diagnosis: DSM-IV diagnosis of schizophrenia; diagnosis of TD based on the Schooler-Kane criteria. N = 157. Sex: 157 male. Age: mean 45.2 (SD 6.7) years.</p> <p>History: Duration of TD at least 1 year. "A stable dose of antipsychotics for at least 4 weeks prior to trial entry".</p>
Interventions	<p>1. EGb-761 (standardised extract of <i>Ginkgo biloba</i> leaves that has antioxidant properties as a free radical scavenger): dose 80 mg, three times a day for 12 weeks. N = 78</p> <p>2. Placebo for 12 weeks. N = 79</p> <p>Patient regular antipsychotic medication. Antipsychotics and all other medications remained fixed throughout the double-blind period (i.e. clozapine, risperidone, aripiprazole, olanzapine, quetiapine, chlorpromazine, haloperidol, sulpiride). Their chlorpromazine-equivalent doses were 429.3 mg/day and 440.2 mg/day in the EGb-761 and placebo groups, respectively. Anticholinergics were allowed during the trial. Twenty-seven patients (12 in the EGb-761 group and 15 in the placebo group) were treated with anticholinergics for a long time prior to entering the study; however, anticholinergic treatment was stable during the clinical trial. No new use of anticholinergic drugs was allowed.</p>
Outcomes	<p>Tardive dyskinesia: AIMS improved/not improved, deterioration in symptoms, AIMS scale scores. Mental state: PANSS; Cognitive performance Continuous Performance Test-37 (CBT-37)</p> <p>Leaving the study early.</p>
Notes	<p>Sponsorship source: Supported by the National Basic Research Program of China and the National Natural Science Foundation of China. Statistical analysis was funded by Glaxo Smith Kline.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients had an equal probability of being assigned to the 2 groups. An independent third party placed them in either the active or placebo group according to a computer-generated randomization list compiled through simple randomization"
Allocation concealment (selection bias)	Low risk	"To ensure the concealment of allocation, this third party used a protected computer database for the randomization list."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"After the run-in period, patients were randomly assigned to receive either capsulized EGb-761... or an identically capsulized placebo in a double-blind manner". "All of the study personnel and participants were blinded to the treatment assignment for the duration of the double-blind period, except 1 study staff member in the pharmacy, who remained unblinded to provide the placebo and EGb-761 treatments"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All efficacy outcomes: "Each subject was assessed by the same investigator, who was blind to treatment status". Cognitive tests: computer assessments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"intention-to-treat analysis for the 2 groups of randomly assigned patients, with last-observation-carried-forward imputation."

Zhang 2011 (Continued)

Selective reporting (reporting bias)	High risk	Side effects and Adverse Events data not reported. "Systemic side effects were evaluated by means of routine physical and neurologic examinations and laboratory tests and reviewed by applying the UKU Side Effect Rating Scale. These systemic side effects were all mild and brief. For none of the subjects were the routine blood cell count, chemistry, urinalysis, or electrocardiogram parameters significantly affected by the experimental treatment (data not shown)". Also, Change in Simpson-Angus Rating Scales for EPS not reported.
Other bias	Low risk	The study seems to be free from other sources of bias.

AIMS - Abnormal Involuntary Movement Scale
 AVLT - Rey Auditory and Verbal Learning Test
 BPRS - Brief Psychiatric Rating Scale
 CGI - Clinical Global Impression
 DSM - Diagnostic and Statistical Manual of Mental Disorders
 EPS - extrapyramidal symptoms
 ESRS - Extrapyramidal System Rating Scale
 IM - intramuscular
 ITT - intention-to-treat
 IV - intravenous
 MAOI - monoamine oxidase inhibitor
 mcg - microgram
 NOSIE - Nurses Observation Scale for Inpatient Evaluation
 PANSS - Positive and Negative Syndrome Scale
 Rockland TD - Rockland Tardive Dyskinesia Rating Scale
 SANS - Scale for the Assessment of Negative Symptoms
 SAPS - Scale for the Assessment of Positive Symptoms
 SAS - Simpson Angus Scale
 SD - Standard deviation
 TAU - treatment as usual
 TD - tardive dyskinesia
 TESS - Treatment Emergent Symptoms Scale
 VMAT - vesicular monoamine transporter 2

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Apseloff 2000	Allocation: randomised. Participants: healthy, non-smoking males, not TD.
Bjorndal 1980	Allocation: not randomised.
Blum 1984	Allocation: not randomised.
Bockenheimer 1976	Allocation: randomised Participants: TD Intervention: Deanol vs placebo, not relevant for this review, included in Cholinergics review
Bowers 1979	Allocation: not randomised.
Casey 1981	Allocation: not randomised.
Chaplin 2002	Allocation: randomised. Participants: schizophrenia (40), schizoaffective disorder (11), bipolar disorder (5); not TD at baseline.

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Study	Reason for exclusion
Emsley 2002	Allocation: randomised. Participants: people with schizophrenia, but not specifically TD.
Fann 1973	Allocation: randomised. Participants: TD. Interventions: Methylphenidate vs placebo. Outcomes: No outcome data have been provided for the first phase before cross-over. Author was contacted but no information was received and this over 40 years old study was excluded.
Fudge 1991	Allocation: randomised. Participants: schizophrenia (DSM-III-R) and TD. Interventions: Electromyographic biofeedback vs noncontingent "false" feedback (placebo). Outcomes: No useable data were extractable. Study author was contacted but no information was received and this 25 years old study was excluded.
Gardos 1978	Allocation: not randomised.
Gerlach 1975	Allocation: randomised. Participants: Psychiatric inpatients with a BLM syndrome induced by antipsychotic treatment; psychiatric-neurological condition stable and pharmacological treatment unchanged for at least 2 months. Interventions: Lithium vs placebo. Outcomes: All data unusable. Unable to extract from the first phase of cross-over. We were unable to find up-to-date contact details for the study authors of this over 40 years old study; it was excluded.
Goetz 2013	Allocation: unclear if randomised. Participants: people with Parkinson's disease and not TD symptoms at baseline
Huang 1981	Allocation: randomised Participants: TD Intervention: Alpha-methyl dopa vs. reserpine vs. placebo, not relevant for this review, included in the Non-antipsychotics review.
Jus 1974	Not randomised, controlled clinical trial. Benztropine vs diazepam vs diphenylhydantoin vs DL tryptophan. No placebo control.
Jus 1978	Allocation: randomised. Participants: people with TD. N = 29. Interventions: deanol versus lithium carbonate versus placebo. Outcomes: AIMS, TD symptom rating scale, CGI, BPRS, NOSIE, vital signs, lab values. Trial used cross-over design. Impossible to extract data from segment before cross-over. One of authors contacted to confirm lack of additional data.
Kabes 1982	Allocation: randomised Population: antipsychotic-induced extrapyramidal side effects: (i) akathisia, (ii) tremor, (iii) muscle rigidity and (iv) dyskinesia. Interventions: Piracetam versus placebo administered IV in 1-hour intervals.

Study	Reason for exclusion
	Outcomes: not useable, measured 30 mins after intervention.
Kabes 1985	Allocation: randomised Population: patients suffering from TD and receiving antipsychotic treatment. Interventions: Piracetam 2.4 g/d vs Piracetam 4.8 g/d vs Piracetam 10 g/d vs placebo for 4 weeks. Outcomes: no usable data. We were unable to find up-to-date contact details for the study authors of this over 30 years old study; it was excluded.
Koller 1982	Allocation: randomised. Participants: Various dyskinesias and movement disorders, including TD. Interventions: Oestrogen vs. placebo Outcomes: No usable data since they are reported in figures with no variability measures. No reply from author. Study is over 30 years old and was excluded.
Korsgaard 1981	Allocation: not randomised.
Lieberman 1987	Allocation: randomised Population: not TD
Lieberman 1994	Allocation: randomised Participants: not TD, participants classified as TD or not TD only during measuring outcomes after intervention
Lindenmayer 1988	Allocation: randomised. Participants: DSM-III diagnoses were predominantly schizophrenia (N = 16) and included four cases of major affective disorder. All participants had TD for at least 1 year. Interventions: Nalaxone 20g vs Nalaxone 40 g vs placebo. Outcomes: No outcome data have been provided for the first period before cross-over. Author was contacted but no information was received and this over 25 years old study was excluded.
Moore 1980	Allocation: not randomised.
Nasrallah 1986	Allocation: randomised. Participants: Psychiatric patients; Schooler and Kane criteria for persistent TD. Interventions: AMPT vs L-DOPA vs Cholone chloride vs Valproic acid vs Hydroxytryptophan. Outcomes: No outcome data has been provided for the first period before cross-over. Author was contacted but no information was received and this 30 years old study was excluded.
Peselow 1989	Allocation: randomised. Participants: people with chronic schizophrenia with multiple hospitalisations and averaged 5.5 years of TD. Interventions: Monosialotetrahexosylganglioside (GM1) versus placebo. Outcomes: All data unusable. Authors were contacted and confirmed data were inaccessible.
Prange 1973	Allocation: not randomised.

Study	Reason for exclusion
Reda 1974	Allocation: not randomised.
Reker 1982	Allocation: not randomised.
Shah 2012	Allocation: randomised. Participants: Parkinson's disease, not TD.
Simpson 1976 a	Allocation: not randomised.
Simpson 1976 b	Allocation: not randomised.
Tamminga 1983	Allocation: randomised. Participants: chronic schizophrenia patients with symptoms of TD. Interventions: Muscimol vs placebo. Outcomes: No useable data were extractable. Study author was contacted but no information was received and this over 30 years old study was excluded.
Vaddadi 1989	Allocation: randomised Population: psychiatric patients (DSM-II criteria) with established movement disorders who had been exposed to antipsychotics over a long period of time; TD (Schooler and Kane criteria). Interventions: Efamol (essential fatty acid) + Vitamin E vs liquid paraffin + vitamin E. Outcomes: No outcome data have been provided for the first period before cross-over. Study author was contacted but no information was received and this over 25 years old study was excluded.
Vaddadi 2002	Allocation: randomised Population: Huntington's disease, not TD
Villeneuve 1970	Allocation: not randomised.
Villeneuve 1980	Allocation: not randomised.
Volavka 1986	Allocation: not randomised.
Wonodi 2004	Allocation: randomised Population: schizophrenia patients; treated by antipsychotics; TD (Schooler and Kane). Interventions: Naltrexone vs placebo and Naltrexone + clonazepam vs placebo + clonazepam. Outcomes: No outcome data have been provided for the first phase before cross-over. Study author was contacted but no information was received and this over 10 years old study was excluded.

AIMS: Abnormal involuntary Movement Scale

CGI - Clinical Global Impression

DSM - Diagnostic and Statistical Manual of Mental Disorders

TD = tardive dyskinesia

IV = intravenous

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

[Fernandez 2016](#)

Methods	Allocation: randomised.
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Miscellaneous treatments for antipsychotic-induced tardive dyskinesia (Review)

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Fernandez 2016 (Continued)

	<p>Blindness: double-blind</p> <p>Duration: 12 weeks</p> <p>Design: parallel.</p> <p>Setting: USA, Czech Republic, Poland, Slovakia</p>
Participants	<p>Diagnosis: History of using a dopamine receptor antagonist for at least 3 months; clinical diagnosis of tardive dyskinesia and has had symptoms for at least 3 months prior to screening; participants with underlying psychiatric diagnosis are stable and have no change in psychoactive medications</p> <p>N = 117</p> <p>Sex: male and female</p> <p>Age: 18 to 75 years old</p>
Interventions	<p>1. SD-809 (deutetrabenazine) tablets taken twice daily for 12 weeks, includes a dose titration period and maintenance period. N = 58</p> <p>2. Placebo tablets taken twice daily for 12 weeks. N = 59</p>
Outcomes	<p>Change in AIMS score from baseline to week 12.</p> <p>Quality of life; Treatment success based on Patient Global Impression of Change (PGIC) questionnaire; Percentage reduction in AIMS score; Proportion of responders based on AIMS change from baseline</p>
Notes	<p>Other study ID: SD-809-C-18</p> <p>Sponsor: Auspex Pharmaceuticals, Inc.</p> <p>From 2017 update search, conference abstract with limited details, awaiting more detailed data.</p>

Hauser 2016

Methods	<p>Allocation: randomised.</p> <p>Blindness: double-blind</p> <p>Duration: 6 weeks + 42 weeks extension</p> <p>Design: parallel</p> <p>Setting: USA, Canada, Puerto Rico</p>
Participants	<p>Diagnosis: schizophrenia, schizoaffective disorder, or mood disorder (for at least 3 months prior to screening); a clinical diagnosis of antipsychotic-induced TD for at least 3 months prior to screening; if using maintenance medication(s), be on stable doses; negative drug screen for amphetamines, barbiturates, benzodiazepines, phencyclidine, cocaine, opiates, or cannabinoids</p> <p>N = 240</p> <p>Sex: male and female</p> <p>Age: 18 to 85 years old</p>
Interventions	<p>1. NBI-98854 administered orally as one 40 mg capsule and one placebo capsule for 6 weeks. At the end of week 6, participants will enter a double-blind NBI-98854 treatment period and continue with their current dose N = 80</p> <p>2. Participants randomised to the NBI-98854 80 mg dose will receive NBI-98854 40 mg for the first week (administered orally as one 40 mg capsule and one placebo capsule), followed by NBI-98854 80 mg administered orally as two 40 mg capsules for 5 weeks. At the end of week 6, participants will enter a double-blind NBI-98854 treatment period and continue with their current dose. N = 80</p>

Hauser 2016 (Continued)

3. Placebo administered orally as two placebo capsules 6 weeks. At the end of Week 6, participants will enter a double-blind NBI-98854 treatment period and be randomised to either a 40 mg or 80 mg dose. N = 80

Outcomes	<p>Severity of TD symptoms assessed by AIMS, change from baseline</p> <p>Clinical Global Impression of Change - TD (CGI-TD);</p> <p>Tardive Dyskinesia Impact Scale (TDIS);</p> <p>Patient Global Impression of Change (PGIC);</p> <p>Percentage of participants classified as responders based on AIMS dyskinesia total score % change from baseline;</p> <p>Percentage of participants classified as responders based on CGI-TD</p>
Notes	<p>Study ID: NCT02274558</p> <p>Sponsor: Neurocrine Biosciences</p> <p>From 2017 update search, conference abstracts, poster, and online trial registration record with limited details, awaiting more detailed data.</p>

NCT01393600 2011

Methods	<p>Allocation: randomised</p> <p>Blindness: double-blind</p> <p>Duration: 1 month</p> <p>Design: cross-over</p> <p>Setting: USA</p>
Participants	<p>Diagnosis: schizophrenia or schizoaffective disorder and a clinical diagnosis of antipsychotic-induced TD (DSM-IV) for at least 3 months prior to screening; stable dose of antipsychotic medication for a minimum of 30 days before study start; participants not using antipsychotic medication must have stable psychiatric status; the doses of concurrent medications and the conditions being treated be stable for a minimum of 30 days before study start and be expected to remain stable during the study.</p> <p>N = 37</p> <p>Sex: male and female</p> <p>Age: 18 to 65 years old</p>
Interventions	<p>1. 12.5 mg NBI-98854 once daily dose for days 1-14 and placebo once daily dose for days 15-28 (participants will be randomly assigned to receive one of these treatment sequences)</p> <p>2. Placebo once daily dose for days 1-14 and 50 mg NBI-98854 once daily dose for days 15 mg to 28 mg or 50 mg NBI-98854 once-daily dose for days 1-14 and placebo once-daily dose for days 15-28 (participants will be randomly assigned to receive one of these treatment sequences)</p>
Outcomes	<p>Treatment efficacy (AIMS)</p> <p>Efficacy of 12.5 mg or 50 mg doses of NBI-98854 administered once daily for the treatment of TD symptoms using CGI-TD and PGIC questionnaire</p> <p>Safety and tolerability for adverse events</p>
Notes	<p>Other study ID: NBI-98854-1101</p> <p>Sponsor: Neurocrine Biosciences</p>

Miscellaneous treatments for antipsychotic-induced tardive dyskinesia (Review)

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NCT01393600 2011 (Continued)

Online trial registration record, results are provided for combined groups in this cross-over study, awaiting separate data.

Pattojoshi 2016

Methods	Randomised, double-blind, sham-controlled study, 22 months duration.
Participants	Diagnosis: psychosis with TD (Schooler and Kane criteria).
Interventions	10 right dorsolateral prefrontal cortex-repetitive transcranial magnetic stimulation (rTMS) sessions versus 10 sham rTMS sessions, total n = 30.
Outcomes	AIMS, MMSE, CPRS.
Notes	From 2017 update search, conference abstract with limited details, awaiting more detailed data.

Xu 2012

Methods	Randomised controlled trial, 12 weeks duration.
Participants	Diagnosis: schizophrenia (CHMD-3) with tardive dyskinesia.
Interventions	<i>Ginkgo biloba</i> extract (n = 42) versus standard treatment (n = 40).
Outcomes	AIMS, TESS.
Notes	From 2017 update search, article in Chinese, awaiting translation.

AIMS - Abnormal involuntary Movement Scale

CGI - Clinical Global Impression

CHMD-3 - Chinese Classification of Mental Disorders Version 3

CPRS - Comprehensive Psychopathological Scale

DSM IV - Diagnostic and Statistical Manual of Mental Disorders

MMSE - Mini Mental State Examination

PGIC - Patient Global Impression of Change

rTMS - right dorsolateral prefrontal cortex-repetitive transcranial magnetic stimulation

TD - tardive dyskinesia

TESS - Treatment Emergent Symptom Scale

Characteristics of ongoing studies [ordered by study ID]

Garcia 1992

Trial name or title	Double-blind placebo controlled study using buspirone in the treatment of tardive dyskinesia
Methods	Allocation: randomised. Blindness: double-blind. Duration: 12 weeks. Design: cross-over. Setting: USA.
Participants	Diagnosis: TD patients, criteria not reported. N = 20.

Miscellaneous treatments for antipsychotic-induced tardive dyskinesia (Review)

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Garcia 1992 (Continued)

	Sex: not reported. Age: not reported
Interventions	1. Buspirone: Not reported, increasing dose. N = 20. 2. Placebo. N = 20.
Outcomes	AIMS score
Starting date	
Contact information	
Notes	Abstract of a study protocol, there are no data to be extracted.

ISRCTN14688109 2015

Trial name or title	Investigation of the potential beneficial effects of cannabidiol in the treatment of tardive dyskinesia
Methods	Allocation: randomised Blindness: double-blind (no further details) Duration: 1 year Design: parallel Setting: Nigeria
Participants	Diagnosis: ICD-10 diagnosis of a psychotic disorder, verified with the MINI-PLUS questionnaire; clinical diagnosis of TD confirmed with the AIMS; currently receiving treatment for a psychotic disorder and be on either the atypical or conventional antipsychotics. N = 56 Sex: male and female Age: at least 18 years old
Interventions	1. High cannabidiol extract Nabidiolex® (CBD) (300 mg) administered orally in capsules twice a day for six weeks as an adjunctive treatment alongside their usual antipsychotic medication. N = 28 2. Vitamin E (400 IU) administered daily for six weeks as an adjunctive treatment alongside their usual antipsychotic medication N = 28
Outcomes	Primary: Improvement in symptoms of TD measured using the Abnormal Involuntary Movement Scale (AIMS). Secondary: Side effects of CBD; improvement in psychotic symptoms.
Starting date	December 2015
Contact information	Dr Jaiyeola Kajero, +234 08037140976, jaiyeolakajero@yahoo.com, Nigeria
Notes	Sponsor: South Africa Research Chair in PTSD, Stellenbosch University

NCT00621634 2008

Trial name or title	Efficacy of docosahexaenoic acid on tardive dyskinesia
Methods	Allocation: randomised. Blindness: double-blind (Participant, Investigator, Outcomes Assessor). Duration: 12 weeks. Design: parallel. Setting: Canada
Participants	Diagnosis: chronic schizophrenia; under long-term antipsychotic drug treatment, stable for at least 3 months before study entry; presence of TD following Schooler-Kane research criteria (mild intensity (2/4 points) in at least two body segments, or moderate intensity (3/4 points) for at least one body segment). N = 40 Sex: male and female Age: 30-75 years
Interventions	1. Omega-3 fish oil capsules (including docosahexaenoic acid): Fish oil capsules of 1000 mg each, including DHA 460 mg-540 mg/capsule; dose: 6 capsules per day; N = 20. 2. Placebo: Corn/Soybean placebo 1000 mg capsules; dose: 6 capsules per day; N = 20.
Outcomes	Primary: Clinical rating scales (AIMS, St.Hans) Secondary: Quantitative motor testing (kinematic parameters); Monitoring of psychopathology (Neuro-Psychiatric Inventory, Positive and Negative Syndrome Scale, Calgary Depression Scale for Schizophrenia); Erythrocyte membrane phospholipid profile (gas chromatography)
Starting date	February 2008
Contact information	Pierre J. Blanchet, MD, PhD, (514) 890-8123, Pierre.J.Blanchet@umontreal.ca
Notes	Sponsor: Université de Montréal, National Alliance for Research on Schizophrenia and Depression Study IDs: NCT00621634; HD06.067

NCT01391390 2011

Trial name or title	Melatonin treatment for tardive dyskinesia in schizophrenia.
Methods	Allocation: randomised Blindness: double-blind (Subject, Investigator) Duration: 12 weeks Design: parallel Setting: China
Participants	Diagnosis: diagnosis of both schizophrenia and TD; duration of TD symptoms longer than 1 year; on stable doses of antipsychotic drug for at least 6 months. N = 120 Sex: male and female Age: 18 to 70 years old
Interventions	1. Melatonin (other Name: APRD00742)10mg/day, 12-week treatment. N = 60.

NCT01391390 2011 (Continued)

2. Placebo 10mg/day, 12-week treatment. N = 60

Outcomes	Primary: AIMS at 12 weeks Secondary: the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS); the Positive and Negative Syndrome Scale (PANSS); the Simpson-Angus Scale for extrapyramidal side effects (SAS)
Starting date	September 2008
Contact information	Lian Y Cao, MD, Beijing Hui-Long-Guan Hospital
Notes	Sponsor: Beijing HuiLongGuan Hospital, Stanley Medical Research Institute Other study ID: BJ-7072035

NCT01688037 2012

Trial name or title	NBI-98854 for the for the treatment of tardive dyskinesia in subjects with schizophrenia or schizoaffective disorder (KINECT study)
Methods	Allocation: randomised Blindness: double-blind (Subject, Caregiver, Investigator, Outcomes Assessor) Duration: 6 weeks Design: parallel Setting: USA, Puerto Rico
Participants	Diagnosis: Clinical diagnosis of schizophrenia or schizoaffective disorder and a clinical diagnosis of antipsychotic-induced TD for at least 3 months prior to screening;receiving a stable dose of antipsychotic medication for a minimum of 30 days before study start; participants not using antipsychotic medication must have stable psychiatric status;the doses of concurrent medications and the conditions being treated be stable for a minimum of 30 days before study start and be expected to remain stable during the study. N = 109 Sex: male and female Age: 18 to 65 years old
Interventions	1. NBI-98854 50 mg administered as two 25 mg capsules by mouth, taken every morning for 6 weeks. N = NR 2. NBI-98854 100 mg and 50 mg. NBI-98854 100 mg administered as two 50 mg capsules taken every morning between for 2 weeks. After 2 weeks, NBI-98854 50 mg administered by two 25 mg capsules by mouth, taken every morning for remaining 4 weeks. N = NR 3. Placebo capsule containing no active substance, manufactured to mimic NBI-98854 25 mg and 50 mg capsules. N = NR
Outcomes	Primary: Severity of TD symptoms assessed by AIMS Secondary: CGI-TD; Number of participants with adverse events following dosing with NBI-98854; Evaluation of plasma concentrations of NBI-98854 and metabolites following repeated daily doses (50 mg and 100 mg) of NBI-98854

NCT01688037 2012 (Continued)

Starting date	September 2012
Contact information	Principal Investigator: Chris O'Brien, MD
Notes	Other study ID: NBI-98854-1201 Sponsor: Neurocrine Biosciences

NCT01804920 2013

Trial name or title	D-Serine treatment for tardive dyskinesia
Methods	Allocation: randomised Blindness: double-blind (Subject, Investigator, Outcomes Assessor) Duration: 8 weeks Design: parallel Setting: Israel
Participants	Diagnosis: Diagnosis of schizophrenia/schizoaffective disorder according to DSM-IV criteria; history of at least 3 months antipsychotic drugs treatment and present stable dose antipsychotic treatment for at least 4 weeks; fulfilment of Schooler-Kane TD research criteria on a first evaluation performed 2-12 weeks prior to study entrance and on a subsequent evaluation performed prior to allocation to experimental treatment. N = 60 Sex: male and female Age: 18 to 70 years old
Interventions	1. D-Serine (amino acid) 4 g/dN for 8 weeks. N = 30 2. Placebo adjuvant treatment for 8 weeks. N = 30
Outcomes	Primary: Change in AIMS total score
Starting date	January 2013
Contact information	Contact: Uriel Heresco-Levy, MD, +972-2-5316906, urielh@ekmd.huji.ac.il
Notes	Other Study ID Numbers: 1600

NCT02291861 2014

Trial name or title	Addressing involuntary movements in tardive dyskinesia (AIM-TD)
Methods	Allocation: randomised. Blindness: double-blind (Subject, Investigator, Outcomes Assessor). Duration: 12 weeks Design: parallel. Setting: USA, Czech Republic, Germany, Hungary, Poland, Slovakia
Participants	Diagnosis: History of using a dopamine receptor antagonist for at least 3 months; clinical diagnosis of TD and has had symptoms for at least 3 months prior to screening, participants with underlying psychiatric diagnosis are stable and have no change in psychoactive medications.

NCT02291861 2014 (Continued)

N = 288

Sex: male and female

Age: 18 to 80 years old

Interventions	1. SD-809 12 mg tablets dose titrated for 4 weeks to target randomised dose. The dose is maintained for an additional 8 weeks. N = 72 2. SD-809 24 mg tablets dose titrated for 4 weeks to target randomised dose. The dose is maintained for an additional 8 weeks. N = 72 3. SD-809 36 mg tablets dose titrated for 4 weeks to target randomised dose. The dose is maintained for an additional 8 weeks. N = 72 4. Placebo tablets taken twice daily for 12 weeks. N = 72
Outcomes	Primary: Change in AIMS score from Baseline to Week 12 Secondary: Quality of Life; treatment success based on Patient Global Impression of Change (PGIC) questionnaire; percentage reduction in AIMS score; proportion of responders based on AIMS score change from baseline.
Starting date	October 2014
Contact information	Teva US Medical Information (+1-800-896-5855)
Notes	Auspex Pharmaceuticals, Inc. Other Study ID Numbers: SD-809-C-23

AIMS - Abnormal Involuntary Movement Scale

CGI - Clinical Global Impression

DHA - docosahexaenoic acid

DSM - Diagnostic and Statistical Manual of Mental Disorders

ICD - International Classification of Diseases

PGIC - Patient Global Impression of Change

TD = tardive dyskinesia

DATA AND ANALYSES

Comparison 1. ALKALOID - DIHYDROGENATED ERGOT ALKALOIDS versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 1. No clinically important improvement - medium term	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.21, 0.97]
2 Tardive dyskinesia: 2. Not any improvement - medium term	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.23, 1.09]
3 Tardive dyskinesia: 3. Deterioration - medium term	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.55]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Tardive dyskinesia: 3. Average end-point scale score (Simpson scale, high=poor) - medium term	1	28	Mean Difference (IV, Fixed, 95% CI)	-2.80 [-12.25, 6.65]
5 Tardive dyskinesia: Average scale change scores (various scales, high=poor) - medium term	2	59	Std. Mean Difference (IV, Fixed, 95% CI)	-0.31 [-0.83, 0.20]
5.1 AIMS+RTDS	1	40	Std. Mean Difference (IV, Fixed, 95% CI)	-0.31 [-0.93, 0.32]
5.2 ADS	1	19	Std. Mean Difference (IV, Fixed, 95% CI)	-0.33 [-1.24, 0.57]
6 Mental state: Deterioration - medium term	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 4.90]
7 Adverse events - medium term	1	28	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [0.75, 7.23]
8 Leaving the study early - medium term	2	48	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 7.32]

Analysis 1.1. Comparison 1 ALKALOID - DIHYDROGENATED ERGOT ALKALOIDS versus PLACEBO, Outcome 1 Tardive dyskinesia: 1. No clinically important improvement - medium term.

Analysis 1.2. Comparison 1 ALKALOID - DIHYDROGENATED ERGOT ALKALOIDS versus PLACEBO, Outcome 2 Tardive dyskinesia: 2. Not any improvement - medium term.

Analysis 1.3. Comparison 1 ALKALOID - DIHYDROGENATED ERGOT ALKALOIDS versus PLACEBO, Outcome 3 Tardive dyskinesia: 3. Deterioration - medium term.

Analysis 1.4. Comparison 1 ALKALOID - DIHYDROGENATED ERGOT ALKALOIDS versus PLACEBO, Outcome 4 Tardive dyskinesia: 3. Average endpoint scale score (Simpson scale, high=poor) - medium term.

Analysis 1.5. Comparison 1 ALKALOID - DIHYDROGENATED ERGOT ALKALOIDS versus PLACEBO, Outcome 5 Tardive dyskinesia: Average scale change scores (various scales, high=poor) - medium term.

Analysis 1.6. Comparison 1 ALKALOID - DIHYDROGENATED ERGOT ALKALOIDS versus PLACEBO, Outcome 6 Mental state: Deterioration - medium term.

Analysis 1.7. Comparison 1 ALKALOID - DIHYDROGENATED ERGOT ALKALOIDS versus PLACEBO, Outcome 7 Adverse events - medium term.

Analysis 1.8. Comparison 1 ALKALOID - DIHYDROGENATED ERGOT ALKALOIDS versus PLACEBO, Outcome 8 Leaving the study early - medium term.

Comparison 2. ALKALOID - L-STEPHOLIDINE (SPD) versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 1. No clinically important improvement - medium term	1	57	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.35, 0.82]
2 Mental state: 1. Average endpoint scale score (BPRS, high=poor) - medium term	1	20	Mean Difference (IV, Fixed, 95% CI)	-4.5 [-7.60, -1.40]
3 Adverse events: any adverse events - medium term	1	57	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Leaving the study early - medium term	1	57	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 ALKALOID - L-STEPHOLIDINE (SPD) versus PLACEBO, Outcome 1 Tardive dyskinesia: 1. No clinically important improvement - medium term.

Analysis 2.2. Comparison 2 ALKALOID - L-STEPHOLIDINE (SPD) versus PLACEBO, Outcome 2 Mental state: 1. Average endpoint scale score (BPRS, high=poor) - medium term.

Analysis 2.3. Comparison 2 ALKALOID - L-STEPHOLIDINE (SPD) versus PLACEBO, Outcome 3 Adverse events: any adverse events - medium term.

Study or subgroup	SPD n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Cai 1988	0/42	0/15			Not estimable
Total (95% CI)	42	15			Not estimable
Total events: 0 (SPD), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable

Analysis 2.4. Comparison 2 ALKALOID - L-STEPHOLIDINE (SPD) versus PLACEBO, Outcome 4 Leaving the study early - medium term.

Study or subgroup	SPD n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Cai 1988	0/42	0/15			Not estimable
Total (95% CI)	42	15			Not estimable
Total events: 0 (SPD), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable

Comparison 3. ALKALOID - PAPAVERINE versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 3. Average scale score (AIMS, high=poor) - medium term	1	22	Mean Difference (IV, Fixed, 95% CI)	0.51 [-1.18, 2.20]

Analysis 3.1. Comparison 3 ALKALOID - PAPAVERINE versus PLACEBO, Outcome 1 Tardive dyskinesia: 3. Average scale score (AIMS, high=poor) - medium term.

Study or subgroup	Papaverine		Placebo		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Gardos 1979	11	-2.5 (1.7)	11	-3 (2.3)		100%	0.51[-1.18,2.2]
Total ***	11		11			100%	0.51[-1.18,2.2]
Heterogeneity: Not applicable							
Test for overall effect: Z=0.59(P=0.55)

Comparison 4. AMINO ACID - BRANCHED-CHAIN AMINO ACID (BCAA) versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 1. No clinically important improvement - short term	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.63, 1.00]
2 Tardive dyskinesia: 1. Not any improvement - short term	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.36, 1.11]
3 Tardive dyskinesia: 2. Deterioration - short term	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.07, 1.19]
4 Tardive dyskinesia: Average endpoint score (Simpson scale, high=poor) - short term	1	41	Mean Difference (IV, Fixed, 95% CI)	-92.9 [-167.57, -18.23]
5 Leaving the study early - short term	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.37, 1.92]

Analysis 4.1. Comparison 4 AMINO ACID - BRANCHED-CHAIN AMINO ACID (BCAA) versus PLACEBO, Outcome 1 Tardive dyskinesia: 1. No clinically important improvement - short term.

Analysis 4.2. Comparison 4 AMINO ACID - BRANCHED-CHAIN AMINO ACID (BCAA) versus PLACEBO, Outcome 2 Tardive dyskinesia: 1. Not any improvement - short term.

Analysis 4.3. Comparison 4 AMINO ACID - BRANCHED-CHAIN AMINO ACID (BCAA) versus PLACEBO, Outcome 3 Tardive dyskinesia: 2. Deterioration - short term.

Analysis 4.4. Comparison 4 AMINO ACID - BRANCHED-CHAIN AMINO ACID (BCAA) versus PLACEBO, Outcome 4 Tardive dyskinesia: Average endpoint score (Simpson scale, high=poor) - short term.

Analysis 4.5. Comparison 4 AMINO ACID - BRANCHED-CHAIN AMINO ACID (BCAA) versus PLACEBO, Outcome 5 Leaving the study early - short term.

Comparison 5. AMINO ACID - PHENYLALANINE versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early - short term	1	18	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [0.11, 53.25]

Analysis 5.1. Comparison 5 AMINO ACID - PHENYLALANINE versus PLACEBO, Outcome 1 Leaving the study early - short term.

Comparison 6. ANTIDEPRESSANT (MAO-B inhibitor) - SELEGILINE versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 1. No clinically important improvement - medium term	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.96, 1.94]
2 Leaving the study early - medium term	1	33	Risk Ratio (M-H, Fixed, 95% CI)	10.39 [0.62, 173.97]

Analysis 6.1. Comparison 6 ANTIDEPRESSANT (MAO-B inhibitor) - SELEGILINE versus PLACEBO, Outcome 1 Tardive dyskinesia: 1. No clinically important improvement - medium term.

Analysis 6.2. Comparison 6 ANTIDEPRESSANT (MAO-B inhibitor) - SELEGILINE versus PLACEBO, Outcome 2 Leaving the study early - medium term.

Comparison 7. ANTIDEPRESSANT (MAOI) ISOCARBOXAZID versus PROCYCLIDINE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 1. No clinically important improvement - long term	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.08, 0.71]
2 Tardive dyskinesia: 1. Not any improvement - long term	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.03, 0.64]
3 Adverse effects - long term	1	20	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.14, 65.90]
4 Leaving the study early - long term	1	20	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.14, 65.90]

Analysis 7.1. Comparison 7 ANTIDEPRESSANT (MAOI) ISOCARBOXAZID versus PROCYCLIDINE, Outcome 1 Tardive dyskinesia: 1. No clinically important improvement - long term.

Analysis 7.2. Comparison 7 ANTIDEPRESSANT (MAOI) ISOCARBOXAZID versus PROCYCLIDINE, Outcome 2 Tardive dyskinesia: 1. Not any improvement - long term.

Analysis 7.3. Comparison 7 ANTIDEPRESSANT (MAOI) ISOCARBOXAZID versus PROCYCLIDINE, Outcome 3 Adverse effects - long term.

Analysis 7.4. Comparison 7 ANTIDEPRESSANT (MAOI) ISOCARBOXAZID versus PROCYCLIDINE, Outcome 4 Leaving the study early - long term.

Comparison 8. ANTIDEPRESSANT (SSRI) - RITANSERIN vs PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: No clinically important improvement (short term)	1	10	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.70, 1.43]
2 Tardive dyskinesia: Not any improvement (short term)	1	10	Risk Ratio (IV, Fixed, 95% CI)	0.28 [0.02, 4.66]
3 Tardive dyskinesia: Deterioration (short term)	1	10	Risk Ratio (IV, Fixed, 95% CI)	0.47 [0.02, 9.26]
4 Tardive dyskinesia: Average change score (AIMS, high=poor) (short term)	1	10	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-5.93, 1.93]
5 General mental state: Deterioration (short term)	1	10	Risk Ratio (IV, Fixed, 95% CI)	0.47 [0.02, 9.26]
6 General mental state: Average change score (BPRS, high=poor) (short term)	1	10	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-3.10, 1.50]

Analysis 8.1. Comparison 8 ANTIDEPRESSANT (SSRI) - RITANSERIN vs PLACEBO, Outcome 1 Tardive dyskinesia: No clinically important improvement (short term).

Analysis 8.2. Comparison 8 ANTIDEPRESSANT (SSRI) - RITANSERIN vs PLACEBO, Outcome 2 Tardive dyskinesia: Not any improvement (short term).

Analysis 8.3. Comparison 8 ANTIDEPRESSANT (SSRI) - RITANSERIN vs PLACEBO, Outcome 3 Tardive dyskinesia: Deterioration (short term).

Analysis 8.4. Comparison 8 ANTIDEPRESSANT (SSRI) - RITANSERIN vs PLACEBO, Outcome 4 Tardive dyskinesia: Average change score (AIMS, high=poor) (short term).

Analysis 8.5. Comparison 8 ANTIDEPRESSANT (SSRI) - RITANSERIN vs PLACEBO, Outcome 5 General mental state: Deterioration (short term).

Analysis 8.6. Comparison 8 ANTIDEPRESSANT (SSRI) - RITANSERIN vs PLACEBO, Outcome 6 General mental state: Average change score (BPRS, high=poor) (short term).

Comparison 9. ANTIEPILEPTIC - LEVETIRACETAM versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 1. Average endpoint score (AIMS, high=poor) - medium term	1	50	Mean Difference (IV, Fixed, 95% CI)	-2.18 [-3.65, -0.71]
2 Tardive dyskinesia: 1. Average change score (hyperkinesia subscale of the SHRS, high=poor) - medium term	1	69	Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.73, 0.99]
3 Leaving the study early - medium term	2	119	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.46, 2.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Adverse effects - medium term	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.25, 1.04]
5 Mental state: deterioration - medium term	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.65]

Analysis 9.1. Comparison 9 ANTIEPILEPTIC - LEVETIRACETAM versus PLACEBO, Outcome 1 Tardive dyskinesia: 1. Average endpoint score (AIMS, high=poor) - medium term.

Analysis 9.2. Comparison 9 ANTIEPILEPTIC - LEVETIRACETAM versus PLACEBO, Outcome 2 Tardive dyskinesia: 1. Average change score (hyperkinesia subscale of the SHRS , high=poor) - medium term.

Analysis 9.3. Comparison 9 ANTIEPILEPTIC - LEVETIRACETAM versus PLACEBO, Outcome 3 Leaving the study early - medium term.

Analysis 9.4. Comparison 9 ANTIEPILEPTIC - LEVETIRACETAM versus PLACEBO, Outcome 4 Adverse effects - medium term.

Analysis 9.5. Comparison 9 ANTIEPILEPTIC - LEVETIRACETAM versus PLACEBO, Outcome 5 Mental state: deterioration - medium term.

Comparison 10. ANTIHISTAMINE - CYPROHEPTADINE versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 2. Not any improvement - short term	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.27, 1.08]
2 Tardive dyskinesia: 3. Deterioration - short term	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.74]
3 Adverse events - short term	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 2.95]
4 Leaving the study early - short term	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.74]

Analysis 10.1. Comparison 10 ANTIHISTAMINE - CYPROHEPTADINE versus PLACEBO, Outcome 1 Tardive dyskinesia: 2. Not any improvement - short term.

Analysis 10.2. Comparison 10 ANTIHISTAMINE - CYPROHEPTADINE versus PLACEBO, Outcome 2 Tardive dyskinesia: 3. Deterioration - short term.

Analysis 10.3. Comparison 10 ANTIHISTAMINE - CYPROHEPTADINE versus PLACEBO, Outcome 3 Adverse events - short term.

Analysis 10.4. Comparison 10 ANTIHISTAMINE - CYPROHEPTADINE versus PLACEBO, Outcome 4 Leaving the study early - short term.

Comparison 11. ANTIPSYCHOTIC - PROMETHAZINE vs PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: No clinically important improvement (medium term)	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.11, 0.55]
2 Tardive dyskinesia: Not any improvement (medium term)	1	34	Risk Ratio (IV, Fixed, 95% CI)	0.06 [0.01, 0.43]
3 Tardive dyskinesia: Average endpoint score (AIMS, high=poor) (medium term)	1	34	Mean Difference (IV, Fixed, 95% CI)	-7.10 [-9.53, -4.67]
4 General mental state: Average endpoint score (BPRS, high=poor) (medium term)	1	34	Mean Difference (IV, Fixed, 95% CI)	0.70 [-3.77, 5.17]
5 Adverse effects: Any adverse effects (TESS, high=poor) (medium term)	1	34	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.53, 0.33]
6 Adverse effects: Parkinsonism - Average endpoint score (RSESE) (medium term)	1	34	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-1.36, 0.36]
7 Global state: Average endpoint score (CGI, high=poor) (medium term)	1	34	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-3.78, -2.22]

Analysis 11.1. Comparison 11 ANTIPSYCHOTIC - PROMETHAZINE vs PLACEBO, Outcome 1 Tardive dyskinesia: No clinically important improvement (medium term).

Analysis 11.2. Comparison 11 ANTIPSYCHOTIC - PROMETHAZINE vs PLACEBO, Outcome 2 Tardive dyskinesia: Not any improvement (medium term).

Analysis 11.3. Comparison 11 ANTIPSYCHOTIC - PROMETHAZINE vs PLACEBO, Outcome 3 Tardive dyskinesia: Average endpoint score (AIMS, high=poor) (medium term).

Analysis 11.4. Comparison 11 ANTIPSYCHOTIC - PROMETHAZINE vs PLACEBO, Outcome 4 General mental state: Average endpoint score (BPRS, high=poor) (medium term).

Analysis 11.5. Comparison 11 ANTIPSYCHOTIC - PROMETHAZINE vs PLACEBO, Outcome 5 Adverse effects: Any adverse effects (TESS, high=poor) (medium term).

Analysis 11.6. Comparison 11 ANTIPSYCHOTIC - PROMETHAZINE vs PLACEBO, Outcome 6 Adverse effects: Parkinsonism - Average endpoint score (RSESE) (medium term).

Analysis 11.7. Comparison 11 ANTIPSYCHOTIC - PROMETHAZINE vs PLACEBO, Outcome 7 Global state: Average endpoint score (CGI, high=poor) (medium term).

Comparison 12. ANXIOLYTIC - BUSPIRONE versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 1. No clinically important improvement - medium term	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.33, 0.84]
2 Tardive dyskinesia: 2. Not any improvement - medium term	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.15, 0.75]
3 Tardive dyskinesia: 3. Average scale score (AIMS, high=poor) - medium term	1	42	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.45, 1.45]
4 Leaving the study early - medium term	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 12.1. Comparison 12 ANXIOLYTIC - BUSPIRONE versus PLACEBO, Outcome 1 Tardive dyskinesia: 1. No clinically important improvement - medium term.

Analysis 12.2. Comparison 12 ANXIOLYTIC - BUSPIRONE versus PLACEBO, Outcome 2 Tardive dyskinesia: 2. Not any improvement - medium term.

Analysis 12.3. Comparison 12 ANXIOLYTIC - BUSPIRONE versus PLACEBO, Outcome 3 Tardive dyskinesia: 3. Average scale score (AIMS, high=poor) - medium term.

Analysis 12.4. Comparison 12 ANXIOLYTIC - BUSPIRONE versus PLACEBO, Outcome 4 Leaving the study early - medium term.

Comparison 13. COGNITIVE ENHANCER - PIRACETAM versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 1. Average endpoint score (ESRS, high=poor) - short term	1	35	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-4.30, 2.90]
2 Parkinsonism: 1. Average endpoint score (ESRS, high=poor) - short term	1	35	Mean Difference (IV, Fixed, 95% CI)	2.5 [-4.73, 9.73]
3 Leaving the study early - short term	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.03, 1.85]
4 Global state: Average endpoint score (CGI, high=poor) - short term	1	35	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.35, 0.75]

Analysis 13.1. Comparison 13 COGNITIVE ENHANCER - PIRACETAM versus PLACEBO, Outcome 1 Tardive dyskinesia: 1. Average endpoint score (ESRS, high=poor) - short term.

Analysis 13.2. Comparison 13 COGNITIVE ENHANCER - PIRACETAM versus PLACEBO, Outcome 2 Parkinsonism: 1. Average endpoint score (ESRS, high=poor) - short term.

Analysis 13.3. Comparison 13 COGNITIVE ENHANCER - PIRACETAM versus PLACEBO, Outcome 3 Leaving the study early - short term.

Analysis 13.4. Comparison 13 COGNITIVE ENHANCER - PIRACETAM versus PLACEBO, Outcome 4 Global state: Average endpoint score (CGI, high=poor) - short term.

Comparison 14. COGNITIVE ENHANCER/STIMULANT - PEMOLINE versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 1. No clinically important improvement - medium term	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.29, 0.77]
2 Tardive dyskinesia: 2. Not any improvement - medium term	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.13, 0.66]
3 Tardive dyskinesia: 3. Average scale score (AIMS, high=poor) - medium term	1	46	Mean Difference (IV, Fixed, 95% CI)	-3.90 [-5.47, -2.33]
4 Leaving the study early - medium term	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 14.1. Comparison 14 COGNITIVE ENHANCER/STIMULANT - PEMOLINE versus PLACEBO, Outcome 1 Tardive dyskinesia: 1. No clinically important improvement - medium term.

Analysis 14.2. Comparison 14 COGNITIVE ENHANCER/STIMULANT - PEMOLINE versus PLACEBO, Outcome 2 Tardive dyskinesia: 2. Not any improvement - medium term.

Analysis 14.3. Comparison 14 COGNITIVE ENHANCER/STIMULANT - PEMOLINE versus PLACEBO, Outcome 3 Tardive dyskinesia: 3. Average scale score (AIMS, high=poor) - medium term.

Analysis 14.4. Comparison 14 COGNITIVE ENHANCER/STIMULANT - PEMOLINE versus PLACEBO, Outcome 4 Leaving the study early - medium term.

Comparison 15. ENZYME INHIBITOR - VMAT2 INHIBITORS versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 1. No clinically important improvement - medium term	1	92	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.46, 0.86]
2 Tardive dyskinesia: 3. Average change score (AIMS, high=poor) - medium term	1	89	Mean Difference (IV, Fixed, 95% CI)	-2.5 [-2.00, -1.00]
3 Adverse events - medium term	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.92, 2.45]
4 Leaving the study early - medium term	1	102	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.31, 3.25]

Analysis 15.1. Comparison 15 ENZYME INHIBITOR - VMAT2 INHIBITORS versus PLACEBO, Outcome 1 Tardive dyskinesia: 1. No clinically important improvement - medium term.

Analysis 15.2. Comparison 15 ENZYME INHIBITOR - VMAT2 INHIBITORS versus PLACEBO, Outcome 2 Tardive dyskinesia: 3. Average change score (AIMS, high=poor) - medium term.

Analysis 15.3. Comparison 15 ENZYME INHIBITOR - VMAT2 INHIBITORS versus PLACEBO, Outcome 3 Adverse events - medium term.

Analysis 15.4. Comparison 15 ENZYME INHIBITOR - VMAT2 INHIBITORS versus PLACEBO, Outcome 4 Leaving the study early - medium term.

Comparison 16. FATTY ACID - ETHYL EICOSAPENTAENOIC ACID versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 2. No clinically important improvement - medium term	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.57, 1.18]
2 Mental state: deterioration - medium term	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.05, 5.14]
3 Adverse events: Parkinsonism - Average change in scale score (ESRS, low=better) - medium term	1	75	Mean Difference (IV, Fixed, 95% CI)	0.30 [-1.17, 1.77]
4 Adverse events: Dystonia - Average change in scale score (ESRS, low=better) - medium term	1	75	Mean Difference (IV, Fixed, 95% CI)	-0.35 [-0.58, -0.12]
5 Adverse events: Akathisia - Average change in scale score (ESRS, low=better) - medium term	1	75	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.30, 0.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Leaving the study early - medium term	1	84	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.27, 1.22]

Analysis 16.1. Comparison 16 FATTY ACID - ETHYL EICOSAPENTAENOIC ACID versus PLACEBO, Outcome 1 Tardive dyskinesia: 2. No clinically important improvement - medium term.

Analysis 16.2. Comparison 16 FATTY ACID - ETHYL EICOSAPENTAENOIC ACID versus PLACEBO, Outcome 2 Mental state: deterioration - medium term.

Analysis 16.3. Comparison 16 FATTY ACID - ETHYL EICOSAPENTAENOIC ACID versus PLACEBO, Outcome 3 Adverse events: Parkinsonism - Average change in scale score (ESRS, low=better) - medium term.

Analysis 16.4. Comparison 16 FATTY ACID - ETHYL EICOSAPENTAENOIC ACID versus PLACEBO, Outcome 4 Adverse events: Dystonia - Average change in scale score (ESRS, low=better) - medium term.

Analysis 16.5. Comparison 16 FATTY ACID - ETHYL EICOSAPENTAENOIC ACID versus PLACEBO, Outcome 5 Adverse events: Akathisia - Average change in scale score (ESRS, low=better) - medium term.

Analysis 16.6. Comparison 16 FATTY ACID - ETHYL EICOSAPENTAENOIC ACID versus PLACEBO, Outcome 6 Leaving the study early - medium term.

Comparison 17. FATTY ACID - GAMMA-LINOLENIC ACID versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 1. No clinically important improvement - medium term	1	16	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.69, 1.45]
2 Tardive dyskinesia: 2. Not any improvement - medium term	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.24, 2.33]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Tardive dyskinesia: 3. Deterioration - medium term	1	16	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.34, 6.70]
4 Tardive dyskinesia: 1. Average change in scale score (AIMS, high=poor) - medium term	1	16	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-3.10, 2.70]
5 Mental state: 2. Average change in scale score (BPRS, high=poor) - medium term	1	10	Mean Difference (IV, Fixed, 95% CI)	-6.0 [-15.99, 3.99]
6 Leaving the study early - medium term	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 17.1. Comparison 17 FATTY ACID - GAMMA-LINOLENIC ACID versus PLACEBO, Outcome 1 Tardive dyskinesia: 1. No clinically important improvement - medium term.

Analysis 17.2. Comparison 17 FATTY ACID - GAMMA-LINOLENIC ACID versus PLACEBO, Outcome 2 Tardive dyskinesia: 2. Not any improvement - medium term.

Analysis 17.3. Comparison 17 FATTY ACID - GAMMA-LINOLENIC ACID versus PLACEBO, Outcome 3 Tardive dyskinesia: 3. Deterioration - medium term.

Analysis 17.4. Comparison 17 FATTY ACID - GAMMA-LINOLENIC ACID versus PLACEBO, Outcome 4 Tardive dyskinesia: 1. Average change in scale score (AIMS, high=poor) - medium term.

Analysis 17.5. Comparison 17 FATTY ACID - GAMMA-LINOLENIC ACID versus PLACEBO, Outcome 5 Mental state: 2. Average change in scale score (BPRS, high=poor) - medium term.

Analysis 17.6. Comparison 17 FATTY ACID - GAMMA-LINOLENIC ACID versus PLACEBO, Outcome 6 Leaving the study early - medium term.

Study or subgroup	GLA n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Not applicable					
			Favours GLA 0.1 0.2 0.5 1 2 5 10 Favours placebo		

Comparison 18. HERB - *GINKGO BILOBA* versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 1. No clinically important improvement - medium term	1	157	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.81, 0.96]
2 Tardive dyskinesia: 2. Not any improvement - medium term	1	157	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.41, 0.65]
3 Tardive dyskinesia: 3. Average scale score (AIMS, high=poor) - medium term	1	157	Mean Difference (IV, Fixed, 95% CI)	-2.06 [-2.94, -1.18]
4 Leaving the study early - medium term	1	157	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.22]
5 Mental state: deterioration - medium term	1	157	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.16]
6 Mental state: 1. Average endpoint scale score (PANSS total, high=poor) - medium term	1	157	Mean Difference (IV, Fixed, 95% CI)	-3.30 [-6.51, -0.09]
7 Cognitive function: CPT-37 - proportion correct responses (high=better) - medium term	1	119	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.10, 0.06]

Analysis 18.1. Comparison 18 HERB - *GINKGO BILOBA* versus PLACEBO, Outcome 1 Tardive dyskinesia: 1. No clinically important improvement - medium term.

Study or subgroup	Ginkgo biloba n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Zhang 2011	68/78	78/79		100%	0.88[0.81,0.96]
Total (95% CI)	78	79		100%	0.88[0.81,0.96]
Total events: 68 (Ginkgo biloba), 78 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.75(P=0.01)					
			Favours ginkgo biloba 1 Favours placebo		

Analysis 18.2. Comparison 18 HERB - GINKGO BILOBA versus PLACEBO, Outcome 2 Tardive dyskinesia: 2. Not any improvement - medium term.

Analysis 18.3. Comparison 18 HERB - GINKGO BILOBA versus PLACEBO, Outcome 3 Tardive dyskinesia: 3. Average scale score (AIMS, high=poor) - medium term.

Analysis 18.4. Comparison 18 HERB - GINKGO BILOBA versus PLACEBO, Outcome 4 Leaving the study early - medium term.

Analysis 18.5. Comparison 18 HERB - GINKGO BILOBA versus PLACEBO, Outcome 5 Mental state: deterioration - medium term.

Analysis 18.6. Comparison 18 HERB - GINKGO BILOBA versus PLACEBO, Outcome 6 Mental state: 1. Average endpoint scale score (PANSS total, high=poor) - medium term.

Analysis 18.7. Comparison 18 HERB - GINKGO BILOBA versus PLACEBO, Outcome 7 Cognitive function: CPT-37 - proportion correct responses (high=better) - medium term.

Comparison 19. HORMONE - OESTROGEN versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 1. No clinically important improvement - short term	1	12	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.76, 1.83]
2 Tardive dyskinesia: 2. Not any improvement - short term	1	12	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.05, 2.37]
3 Tardive dyskinesia: 3. Deterioration - short term	1	10	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 3.35]
4 Tardive dyskinesia: 4. Average scale score (AIMS, high=poor) - short term	1	10	Mean Difference (IV, Fixed, 95% CI)	-1.2 [-4.18, 1.78]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Adverse effects - short term	1	12	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 6.86]
6 Leaving the study early - short term	1	12	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.08, 12.56]

Analysis 19.1. Comparison 19 HORMONE - OESTROGEN versus PLACEBO, Outcome 1 Tardive dyskinesia: 1. No clinically important improvement - short term.

Analysis 19.2. Comparison 19 HORMONE - OESTROGEN versus PLACEBO, Outcome 2 Tardive dyskinesia: 2. Not any improvement - short term.

Analysis 19.3. Comparison 19 HORMONE - OESTROGEN versus PLACEBO, Outcome 3 Tardive dyskinesia: 3. Deterioration - short term.

Analysis 19.4. Comparison 19 HORMONE - OESTROGEN versus PLACEBO, Outcome 4 Tardive dyskinesia: 4. Average scale score (AIMS, high=poor) - short term.

Analysis 19.5. Comparison 19 HORMONE - OESTROGEN versus PLACEBO, Outcome 5 Adverse effects - short term.

Analysis 19.6. Comparison 19 HORMONE - OESTROGEN versus PLACEBO, Outcome 6 Leaving the study early - short term.

Comparison 20. HORMONE - INSULIN versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 1. No clinically important improvement - medium term	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.29, 0.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Tardive dyskinesia: 2. Not any improvement - medium term	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.00, 0.90]
3 Tardive dyskinesia: 3. Deterioration - medium term	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.45]
4 Tardive dyskinesia: 3. Average scale score (AIMS, high=poor) - medium term	1	20	Mean Difference (IV, Fixed, 95% CI)	-6.20 [-10.53, -1.87]
5 Leaving the study early - medium term	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 20.1. Comparison 20 HORMONE - INSULIN versus PLACEBO, Outcome 1 Tardive dyskinesia: 1. No clinically important improvement - medium term.

Analysis 20.2. Comparison 20 HORMONE - INSULIN versus PLACEBO, Outcome 2 Tardive dyskinesia: 2. Not any improvement - medium term.

Analysis 20.3. Comparison 20 HORMONE - INSULIN versus PLACEBO, Outcome 3 Tardive dyskinesia: 3. Deterioration - medium term.

Analysis 20.4. Comparison 20 HORMONE - INSULIN versus PLACEBO, Outcome 4 Tardive dyskinesia: 3. Average scale score (AIMS, high=poor) - medium term.

Analysis 20.5. Comparison 20 HORMONE - INSULIN versus PLACEBO, Outcome 5 Leaving the study early - medium term.

Comparison 21. HORMONE - MELATONIN versus PLACEBO OR NO TREATMENT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 1. No clinically important improvement	2	32	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.71, 1.12]
1.1 Short term	1	19	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.83, 1.21]
1.2 Medium term	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.44, 1.23]
2 Tardive dyskinesia: 2. Not any improvement - short term	1	19	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.47, 2.60]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Tardive dyskinesia: 3. Deterioration - short term	1	19	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.01, 4.05]
4 Tardive dyskinesia: 3. Average scale score (AIMS, high=poor) - medium term	1	13	Mean Difference (IV, Fixed, 95% CI)	-2.38 [-6.58, 1.82]
5 Adverse effects	3	54	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.1 Short term	1	19	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Medium term	2	35	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Leaving the study early	3	54	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.1 Short term	1	19	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Medium term	2	35	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Cognitive function: Average scale score - medium term	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 WAIS	1	76	Mean Difference (IV, Fixed, 95% CI)	15.83 [4.61, 27.05]
7.2 WMS	1	76	Mean Difference (IV, Fixed, 95% CI)	3.77 [-8.21, 15.75]
8 Mental state: deterioration - medium term	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 21.1. Comparison 21 HORMONE - MELATONIN versus PLACEBO OR NO TREATMENT, Outcome 1 Tardive dyskinesia: 1. No clinically important improvement.

Analysis 21.2. Comparison 21 HORMONE - MELATONIN versus PLACEBO OR NO TREATMENT, Outcome 2 Tardive dyskinesia: 2. Not any improvement - short term.

Analysis 21.3. Comparison 21 HORMONE - MELATONIN versus PLACEBO OR NO TREATMENT, Outcome 3 Tardive dyskinesia: 3. Deterioration - short term.

Analysis 21.4. Comparison 21 HORMONE - MELATONIN versus PLACEBO OR NO TREATMENT, Outcome 4 Tardive dyskinesia: 3. Average scale score (AIMS, high=poor) - medium term.

Analysis 21.5. Comparison 21 HORMONE - MELATONIN versus PLACEBO OR NO TREATMENT, Outcome 5 Adverse effects.

Analysis 21.6. Comparison 21 HORMONE - MELATONIN versus PLACEBO OR NO TREATMENT, Outcome 6 Leaving the study early.

Analysis 21.7. Comparison 21 HORMONE - MELATONIN versus PLACEBO OR NO TREATMENT, Outcome 7 Cognitive function: Average scale score - medium term.

Analysis 21.8. Comparison 21 HORMONE - MELATONIN versus PLACEBO OR NO TREATMENT, Outcome 8 Mental state: deterioration - medium term.

Study or subgroup	Melatonin	Placebo/no treatment	Risk Ratio		Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI			M-H, Fixed, 95% CI
Test for overall effect: Not applicable						
			Favours Melatonin	0.01 0.1 1 10 100		Favours Placebo/no treatment

Comparison 22. MOOD STABILISER - LITHIUM versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 1. No clinically important improvement - short term	1	11	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.79, 3.23]
2 Tardive dyskinesia: 2. Not any improvement - short term	1	11	Risk Ratio (M-H, Fixed, 95% CI)	4.29 [0.25, 72.90]
3 Tardive dyskinesia: 3. Deterioration - short term	1	11	Risk Ratio (M-H, Fixed, 95% CI)	4.29 [0.25, 72.90]
4 Tardive dyskinesia: 3. Average scale score (AIMS, high=poor) - short term	1	11	Mean Difference (IV, Fixed, 95% CI)	0.63 [-5.23, 6.49]
5 Adverse events - short term	1	11	Risk Ratio (M-H, Fixed, 95% CI)	6.0 [0.38, 94.35]
6 Leaving the study early - short term	1	11	Risk Ratio (M-H, Fixed, 95% CI)	2.57 [0.13, 52.12]

Analysis 22.1. Comparison 22 MOOD STABILISER - LITHIUM versus PLACEBO, Outcome 1 Tardive dyskinesia: 1. No clinically important improvement - short term.

Study or subgroup	Lithium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI		Weight	Risk Ratio M-H, Fixed, 95% CI
Mackay 1980	6/6	3/5			100%	1.59[0.79,3.23]
Total (95% CI)	6	5			100%	1.59[0.79,3.23]
Total events: 6 (Lithium), 3 (Placebo)						
Heterogeneity: Not applicable						
Test for overall effect: Z=1.29(P=0.2)						
			Favours Lithium	0.1 0.2 0.5 1 2 5 10		Favours Placebo

Analysis 22.2. Comparison 22 MOOD STABILISER - LITHIUM versus PLACEBO, Outcome 2 Tardive dyskinesia: 2. Not any improvement - short term.

Study or subgroup	Lithium n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI		Weight	Risk Ratio M-H, Fixed, 95% CI
Mackay 1980	2/6	0/5			100%	4.29[0.25,72.9]
			Favours Lithium	0.01 0.1 1 10 100		Favours Placebo

Analysis 22.3. Comparison 22 MOOD STABILISER - LITHIUM versus PLACEBO, Outcome 3 Tardive dyskinesia: 3. Deterioration - short term.

Analysis 22.4. Comparison 22 MOOD STABILISER - LITHIUM versus PLACEBO, Outcome 4 Tardive dyskinesia: 3. Average scale score (AIMS, high=poor) - short term.

Analysis 22.5. Comparison 22 MOOD STABILISER - LITHIUM versus PLACEBO, Outcome 5 Adverse events - short term.

Analysis 22.6. Comparison 22 MOOD STABILISER - LITHIUM versus PLACEBO, Outcome 6 Leaving the study early - short term.

Comparison 23. POLYPEPTIDE - CERULETIDE versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 1. Not any improvement	2	132	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.65, 1.07]
1.1 Short term	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.50, 1.06]
1.2 Medium term	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.64, 1.27]
2 Tardive dyskinesia: 2. Deterioration	2	103	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.14, 6.80]
2.1 Short term	1	37	Risk Ratio (M-H, Fixed, 95% CI)	2.85 [0.12, 65.74]
2.2 Medium term	1	66	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.90]
3 Adverse effects	2	122	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.74, 2.36]
3.1 Short term	1	37	Risk Ratio (M-H, Fixed, 95% CI)	3.79 [0.47, 30.77]
3.2 Medium term	1	85	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.61, 2.07]
4 Leaving the study early - medium term	1	85	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.49, 2.40]

Analysis 23.1. Comparison 23 POLYPEPTIDE - CERULETIDE versus PLACEBO, Outcome 1 Tardive dyskinesia: 1. Not any improvement.

Analysis 23.2. Comparison 23 POLYPEPTIDE - CERULETIDE versus PLACEBO, Outcome 2 Tardive dyskinesia: 2. Deterioration.

Analysis 23.3. Comparison 23 POLYPEPTIDE - CERULETIDE versus PLACEBO, Outcome 3 Adverse effects.

Analysis 23.4. Comparison 23 POLYPEPTIDE - CERULETIDE versus PLACEBO, Outcome 4 Leaving the study early - medium term.

Comparison 24. HYPNOSIS OR RELAXATION versus TREATMENT AS USUAL

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 1. No clinically important improvement - medium term	1	15	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.21, 0.94]
2 Tardive dyskinesia: 2. Not any improvement - medium term	1	15	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 3.81]
3 Tardive dyskinesia: 3. Deterioration - medium term	1	15	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 3.81]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Leaving the study early - medium term	1	15	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.1 Short term	1	15	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 24.1. Comparison 24 HYPNOSIS OR RELAXATION versus TREATMENT AS USUAL, Outcome 1 Tardive dyskinesia: 1. No clinically important improvement - medium term.

Analysis 24.2. Comparison 24 HYPNOSIS OR RELAXATION versus TREATMENT AS USUAL, Outcome 2 Tardive dyskinesia: 2. Not any improvement - medium term.

Analysis 24.3. Comparison 24 HYPNOSIS OR RELAXATION versus TREATMENT AS USUAL, Outcome 3 Tardive dyskinesia: 3. Deterioration - medium term.

Analysis 24.4. Comparison 24 HYPNOSIS OR RELAXATION versus TREATMENT AS USUAL, Outcome 4 Leaving the study early - medium term.

ADDITIONAL TABLES

Table 1. Other relevant reviews

Review	Citation
Anticholinergics	Bergman 2018a
Benzodiazepines	Bergman 2018
Calcium-channel blockers	Essali 2011
Cholinergics	Tammenmaa 2002
GABAergic compounds	Alabed 2011
Neuroleptic medications (including dose reduction and cessation)	Soares-Weiser 2006
Non-neuroleptic compounds that impact on the dopamine and noradrenaline systems (catecholaminergics)	El-Sayeh 2006
Vitamin E	Soares-Weiser 2011
This review, Miscellaneous treatments	

Table 2. Overview of study characteristics

Study	N and setting	Condition	Sex and age	Intervention and duration	Comparison	Outcomes
Bucci 1971	20 outpatients in the USA	schizophrenia + TD	F+M 45-62 years	Isocarboxazid + AP 40 weeks	Procyclidine + AP	TD symptoms, AEs
Cai 1988	57 participants, setting not reported	TD	F+M 28-59 years	L-stepholidine + AP 8 weeks	Placebo + AP	TD symptoms, AEs, mental state
Castro 2011	13 in- and outpatients in Venezuela	various psychiatric conditions + TD	F+M 46-75 years	Melatonin + AP 12 weeks	Placebo + AP	TD symptoms, AEs, mental state
Emsley 2006	84 in- and outpatients in South Africa	schizophrenia or schizoaffective disorder + TD	F+M m = 42 years	Omega-3 fatty acid + AP 12 weeks	Placebo + AP	TD symptoms, AEs, mental state
Gardos 1979	22 inpatients in the USA	schizophrenia, dementia + TD	F+M 32-84 years	Papaverine + AP 6 weeks	TAU + AP	TD symptoms
Glazer 1985	12 outpatients in the USA	various psychiatric conditions + TD	F 50-65 years	Oestrogen + AP 3 weeks	Placebo + AP	TD symptoms, AEs
Glover 1982	15 outpatients in the USA	schizophrenia + TD or EPS	F+M m = 34.9 years	Hypnosis or relaxation + AP 8 sessions	TAU + AP	TD symptoms
Goff 1993	33 outpatients in the USA	TD	F+M m = 49 years	Selengiline + AP 6 weeks	Placebo + AP	TD symptoms
Hajioff 1983	20 inpatients in the UK	various psychiatric conditions + TD	F+M 60-92 years	Ergoloid mesylates + AP 6 weeks	Placebo + AP	TD symptoms
Kojima 1992	85 in- and outpatients in Japan	schizophrenia + TD	F+M 31-75 years	Ceruletide + AP 6 weeks	Placebo + AP	TD symptoms, AEs
Koshino 1979	42 inpatients in Japan	various psychiatric conditions + TD	F+M m = 56 years	Cyproheptadine + AP 4 weeks	Placebo + AP	TD symptoms, AEs
Koshino 1983	28 inpatients in Japan	schizophrenia + TD	F+M m = 59 years	Ergoloid mesylates + AP 6 weeks	Placebo + AP	TD symptoms, AEs, mental state
Libov 2007	40 inpatients in Israel	schizophrenia or schizoaffective disorder + TD	F+M 26-69 years	Piracetam + AP 4 weeks	Placebo + AP	TD symptoms, AEs, global state
Mackay 1980	11 inpatients in the UK	various psychiatric conditions + TD	NR 56-70 years	Lithium + AP 5 weeks	Placebo + AP	TD symptoms, AEs

Table 2. Overview of study characteristics (Continued)

Matsunaga 1988	37 inpatients in Japan	various psychiatric conditions + TD	F+M m = 59 years	Ceruletide + AP 4 weeks	Placebo + AP	TD symptoms, AEs
Meco 1989	10 inpatients in Italy	schizophrenia + TD	F+M 33-72 years	Ritanserin + AP 4 weeks	Placebo + AP	TD symptoms, AEs, mental state
Mosnik 1997	18 in- and outpatients in the USA	schizophrenia + TD	M 28-65 years	Phenylalanine + AP 1 day	Placebo + AP	Leaving the study early
Mouret 1991	20 inpatients in Morocco	schizophrenia + TD	F+M 20-67 years	Insulin + AP 12 weeks	Placebo + AP	TD symptoms
O'Brien 2014	88 in- and outpatients in the USA	various psychiatric conditions + TD	NR 18-85 years	NBI-98854 (VMAT2 inhibitor valbenazine) + AP 6 weeks	Placebo + AP	TD symptoms, AEs
Rastogi 1982	40 inpatients in the UK	various psychiatric conditions + TD	F+M m = 70 years	Ergoloid mesylates + AP 6 weeks	Placebo + AP	TD symptoms
Richardson 2003	52 in- and outpatients in the USA	various psychiatric conditions + TD	M m = 45 years	Branched-chain amino acids + AP 3 weeks	Placebo + AP	TD symptoms
Shamir 2000	19 inpatients in Israel	schizophrenia + TD	F+M 62-91 years	Melatonin + AP 4 weeks	Placebo + AP	TD symptoms, AEs
Shamir 2001	22 inpatients in Israel	schizophrenia + TD	F+M 28-82 years	Melatonin + AP 6 weeks	Placebo + AP	AEs
Shi 2009	76 inpatients in China	TD	F+M m = 56 years	Melatonin + AP 12 weeks	TAU + AP	Cognitive function
UCB Pharma 2005	69 inpatients in Belgium and Bulgaria	TD	F+M 18-80 years	Levetiracetam + AP 8 weeks	Placebo + AP	TD symptoms, AEs
Wolkin 1986	16 in- and outpatients in the USA	schizophrenia + TD	M m = 54 years	Evening primrose oil + AP 6 weeks	Placebo + AP	TD symptoms, mental state
Woods 2008	50 outpatients in the USA	various psychiatric conditions + TD	F+M m = 47 years	Levetiracetam + AP 12 weeks	Placebo + AP	TD symptoms, mental state
Yang 1999	34 inpatients in China	schizophrenia + TD	F+M m = 50 years	Promethazine + AP 12 weeks	Placebo + AP	TD symptoms, AEs, mental state, global state
Zeng 1995	42 inpatients in China	schizophrenia + TD	F+M m = 32.5 years	Buspirone + AP 6 weeks	Placebo + AP	TD symptoms
Zeng 1996	46 inpatients in China	schizophrenia + TD	F+M	Pemoline + AP 6 weeks	Placebo + AP	TD symptoms

Table 2. Overview of study characteristics (Continued)

			m = 33 years			
Zhang 2011	157 inpatients in China	schizophrenia + TD	M m = 45 years	<i>Ginkgo biloba</i> + AP 12 weeks	Placebo + AP	TD symp- toms, mental state, cogni- tive function

AE = adverse effects, AP = antipsychotics, EPS = extrapyramidal symptoms, F = female, M = male, m = mean, N = number, TAU = treatment as usual, TD = tardive dyskinesia

Table 3. Suggestions for design of future study

Methods	Allocation: randomised, with sequence generation and concealment of allocation clearly described. Blindness: double, tested. Duration: 12 months beyond end of intervention at least. Raters: independent.
Participants	People with antipsychotic-induced tardive dyskinesia.* Age: any. Sex: both. History: any. N = 300.**
Interventions	1. Active intervention. 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. Earlier searches

1.1 The 2002 update search

The Cochrane Schizophrenia Group's Register (January 2002) was searched with the following phrase

dyskinesia AND (*botulin* or *endorphin* or *estrogen* or *fatty acid* or *EX ?11?582A* or *ganglioside* or *insulin* or *lithium* or *naloxone* or *periactin* or *phenylalanine* or *piracetam* or *stepholidine* or *tryptophan* or *neurosurg* or *ect*)

1.2 The search for the previous versions of this review

1.2.1 Biological Abstracts (January 1982 to May 1995) 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*)))]

The resulting set of reports was handsearched for possible trials and researched, within the bibliographic package, ProCite, with the phrase [botulin or endorphin or estrogen or (fatty and acid) or EX ?11?582A or ganglioside or lithium or naloxone or periactin or phenylalanine or piracetam or stepholidine or tryptophan or neurosurg* or ect]

1.2.2 Cochrane Schizophrenia Group's Register (January 1996) was searched using the phrase:

[(dyskinesia or (#30=60) or (#30=2)) and botulin or endorphin or estrogen or (#42=297) or (fatty and acid) or EX ?11?582A or ganglioside or lithium or (#42=16) or naloxone or (#42=8) or periactin or phenylalanine or piracetam or (#42=119) or stepholidine or tryptophan or (#42=181) or neurosurg* or ect or (#42=48)]

1.2.3 EMBASE (January 1980 to May 1995) 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*))]

The resulting set of reports was handsearched for possible trials and researched, within the bibliographic package, ProCite, with the phrase [botulin or endorphin or estrogen or (fatty and acid) or EX ?11?582A or ganglioside or lithium or naloxone or periactin or phenylalanine or piracetam or stepholidine or tryptophan or neurosurg* or ect]

1.2.4 LILACS (January 1982 to September 1996) 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))]

The resulting set of reports was handsearched for possible trials and researched, within the bibliographic package, ProCite, with the phrase [botulin or endorphin or estrogen or (fatty and acid) or EX ?11?582A or ganglioside or lithium or naloxone or periactin or phenylalanine or piracetam or stepholidine or tryptophan or neurosurg* or ect]

1.2.5 MEDLINE (January 1966 to May 1995) 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*))]

The resulting set of reports was handsearched for possible trials and researched, within the bibliographic package, ProCite, with the phrase [botulin or endorphin or estrogen or (fatty and acid) or EX ?11?582A or ganglioside or lithium or naloxone or periactin or phenylalanine or piracetam or stepholidine or tryptophan or neurosurg* or ect]

1.2.6 PsycLIT (January 1974 to May 1995) 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*))]

The resulting set of reports was handsearched for possible trials and researched, within the bibliographic package, ProCite, with the phrase [botulin or endorphin or estrogen or (fatty and acid) or EX ?11?582A or ganglioside or lithium or naloxone or periactin or phenylalanine or piracetam or stepholidine or tryptophan or neurosurg* or ect]

1.2.7 SCISEARCH - Science Citation Index

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.

Appendix 2. Previous methods

Methods

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials. Where a trial was described as 'double-blind', but it was only implied that the study was randomised, we included these trials in a sensitivity analysis. If there was no substantive difference within primary outcomes (see [Types of outcome measures](#)) when these 'implied randomisation' studies were added, then we included these in the final analysis. If there was a substantive difference, we only used clearly randomised trials and described the results of the sensitivity analysis in the text. We excluded quasi-randomised studies, such as those allocating by using alternate days of the week.

Types of participants

We included people with schizophrenia and other types of schizophrenia-like psychosis (e.g. schizophreniform and schizoaffective disorders), irrespective of the diagnostic criteria used, who: i. required the use of neuroleptics for more than three months; ii. developed tardive dyskinesia (diagnosed by any criteria) during neuroleptic treatment; and iii. for whom the dose of neuroleptic medication had been stable for one month or more before the trial. There is no clear evidence that the schizophrenia-like psychoses are caused by fundamentally different disease processes or require different treatment approaches ([Carpenter 1994](#)).

Types of interventions

1. Drugs

Botulin toxin, dimethylaminoethanol, endorphin, oestrogen, essential fatty acid, EX 11-582A, ganglioside GM1, lithium, methylphenidate, naloxone, naltrexone, periactin, phenylalanine, piracetam, stepholidine, tryptophan. Any doses, frequencies or means of administration were acceptable.

2. Surgical intervention of any sort.

3. Electroconvulsive therapy (ECT).

Compared with:

1. Standard care; or

2. Placebo or no treatment.

Types of outcome measures

Where possible, outcomes were grouped into time periods - short term (less than 6 weeks), medium term (between 6 weeks and 6 months) and long term (over 6 months).

Primary outcomes

1. Tardive dyskinesia

1.1 No clinically important change in tardive dyskinesia

2. Mental state

2.1 No clinically important change in general mental state

3. Adverse effects

3.1 Clinically important general adverse effects

4. Leaving the study early

4.1 For general reasons

Secondary outcomes

1. Tardive dyskinesia

Miscellaneous treatments for antipsychotic-induced tardive dyskinesia (Review)

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- 1.2 Not any change in tardive dyskinesia
- 1.3 Average endpoint tardive dyskinesia score
- 1.4 Average change in tardive dyskinesia score
- 2. Mental state
 - 2.1 Not any change in general mental state
 - 2.2 Average endpoint general mental state score
 - 2.3 Average change in general mental state score
 - 2.4 No clinically important change in specific symptoms
 - 2.5 Not any change in specific symptoms
 - 2.6 Average endpoint specific symptom score
 - 2.7 Average change in specific symptom score
- 3. Adverse effects
 - 3.1 Any general adverse effects
 - 3.2 Average endpoint general adverse effect score
 - 3.3 Average change in general adverse effect score
 - 3.4 Clinically important change in specific adverse effects
 - 3.5 Any change in specific adverse effects
 - 3.6 Average endpoint specific adverse effects
 - 3.7 Average change in specific adverse effects
- 4. Leaving the study early
 - 4.1 For specific reasons

Search methods for identification of studies

Electronic searches

1. Update of 2009

We searched the Cochrane Schizophrenia Group Trials Register (September 2009) using the phrase:

[*dyskinesia* in title, abstract and index fields or REFERENCE]

This register is compiled by systematic searches of major databases, hand searches and conference proceedings (see [Group Module](#)).

2. Previous searches for earlier versions of this review

Please see ([Appendix 1](#)).

Searching other resources

1. Reference searching

We also inspected the references of all studies identified in this way for more 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

Two reviewers independently inspected all study citations identified by the searches, and full reports of the studies of agreed relevance were obtained. Where disputes arose, we acquired the full report for more detailed scrutiny. These articles were then inspected, independently, by two reviewers to assess their relevance to this review. Again, where disagreement occurred attempts were made to resolve this through discussion; if doubt still remained we added these trials to the list of those awaiting assessment pending acquisition of further information.

Data extraction and management

1. Extraction

We independently extracted data. Where disagreement occurred attempts were made to resolve this by discussion, where doubt still remained we sought further information from the study authors to resolve the dilemma, and added the trial to the list of those awaiting assessment.

2. Management

2.1 Data storage

We extracted the data onto standard, simple forms. Where possible, data were entered into RevMan in such a way that the area to the left of the 'line of no effect' indicates a 'favourable' outcome for the treatment group. Where this was not possible, (e.g. scales that calculate higher scores=improvement) the graphs in RevMan analyses were labelled accordingly so that the direction of effects were clear.

2.2 Categorical or continuous into binary

Where possible, efforts were made to convert outcome measures to binary data. This can be done by identifying cut off points on rating scales and dividing participants accordingly into "clinically improved" or "not clinically improved". It is generally assumed that if there is a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS [Overall 1962](#)) or the Positive and Negative Syndrome Scale (PANSS, [Kay 1986](#), this could be considered a clinically significant response ([Leucht 2005a](#), [Leucht 2005](#)). It is recognised that for many people, especially those with chronic or severe illness, a less rigorous definition of important improvement (e.g. 25% on the BPRS) would be equally valid. If individual patient data are available, we used the 50% cut-off point for non-chronically ill people and a 25% cut-off point for those with chronic illness. If data based on these thresholds were not available, we used the primary cut-off presented by the original authors.

2.3 Continuous data and their distribution

Continuous data on outcomes in mental health trials are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data we applied the following standards to all endpoint data derived from continuous measures. The criteria were used before inclusion: (a) standard deviations and means had to be obtainable; and, for finite scores, such as endpoint measures on rating scales, (b) the standard deviation (SD), when multiplied by 2 had to be less than the mean (as otherwise the mean was unlikely to be an appropriate measure of the centre of the distribution) ([Altman 1996](#)). If a scale starts from a positive value (such as PANSS, which can have values from 30 to 210) the calculation described above in (b) should be 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.

Skewed endpoint data from studies with less than 200 participants were not shown graphically, but were added to 'Other data' tables and briefly commented on in the text. However, skewed endpoint data from larger studies (≥ 200 participants) pose less of a problem and we entered the data for analysis ([Higgins 2009](#)).

For continuous mean change data (endpoint minus baseline) the situation is even more problematic. In the absence of individual patient data it is impossible to know if change data are skewed. The RevMan meta-analyses of continuous data are based on the assumption that the data are, at least to a reasonable degree, normally distributed. We included such data, unless endpoint data were also reported from the same scale.

2.4 Final endpoint value versus change data

Where both final endpoint data and change data were available for the same outcome category, only final endpoint data were presented. We acknowledge that by doing this much of the published change data may be excluded, but argue that endpoint data is more clinically relevant and that if change data were to be presented along with endpoint data, it would be given undeserved equal prominence.

3. Scale-derived data

A wide range of instruments are available to measure outcomes in mental health studies. These instruments vary in quality and many are not validated, or are even ad hoc. It is accepted generally that measuring instruments should have the properties of reliability (the extent to which a test effectively measures anything at all) and validity (the extent to which a test measures that which it is supposed to measure) ([Rust 1989](#)). Unpublished scales are known to be subject to bias in trials of treatments for schizophrenia ([Marshall 2000](#)). Therefore continuous data from rating scales were included only if the measuring instrument had been described in a peer-reviewed journal. In addition, the following minimum standards for instruments were set: the instrument should either be (a) a self-report or (b) completed by an independent rater or relative (not the therapist) and (c) the instrument should be a global assessment of an area of functioning.

Assessment of risk of bias in included studies

We assessed risk of bias using the tool described in the Cochrane Collaboration Handbook ([Higgins 2009](#)). This tool encourages consideration of how the sequence was generated, how allocation was concealed, the integrity of blinding at outcome, the completeness of outcome data, selective reporting and other biases. We would not have included studies where sequence generation was at high risk of bias or where allocation was clearly not concealed.

The categories are defined below:

YES - low risk of bias
NO - high risk of bias
UNCLEAR - uncertain risk of bias

If disputes arose as to which category a trial has to be allocated, again, resolution was made by discussion, after working with a third reviewer.

Earlier versions of this review used a different means of categorising risk of bias (see [Appendix 3](#)).

Measures of treatment effect

1. Binary data

For binary outcomes we calculated the relative risk (RR) and its 95% confidence interval (CI) based on the fixed effects model. Relative Risk is more intuitive (Boissel 1999) than odds ratios and odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). This misinterpretation then leads to an overestimate of the impression of the effect. When the overall results were significant we calculated the number needed to treat (NNT) and the number-needed-to-harm (NNH). Where people were lost to follow up at the end of the study, we assumed that they had had a poor outcome and once they were randomised they were included in the analysis (intention-to-treat / ITT analysis).

2. Continuous data

For continuous outcomes we estimated a weighted mean difference (WMD) between groups based on a fixed effects model.

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).

Where clustering had not been accounted for in primary studies, we presented the 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 co-efficients of their clustered data and to adjust for this using accepted methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we will also present these data as if from a non-cluster randomised study, but adjusted 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 intraclass correlation co-efficient (ICC) [Design effect = $1 + (m-1) \times ICC$] (Donner 2002). If the ICC is not reported we assumed it to be 0.1 (Ukumunne 1999). If cluster studies had been appropriately analysed taking into account intra-class correlation coefficients and relevant data documented in the report, we synthesised these with other studies using the generic inverse variance technique.

2. Cross-over design

A major concern of cross-over trials is the carry-over effect. It occurs if an effect (e.g. pharmacological, physiological or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence on entry to the second phase the participants can differ systematically from their initial state despite a wash-out phase. For the same reason cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both effects are very likely in schizophrenia, we will 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, the additional treatment arms were presented in comparisons. Where the additional treatment arms were not relevant, these data were not reproduced.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss to follow-up data must lose credibility (Xia 2007). We are forced to make a judgment where this is for the trials likely to be included in this review. Should more than 50% of data be unaccounted for by 8 weeks we did not reproduce these data or use them within analyses.

2 Intention to treat analysis

We excluded data from studies where more than 50% of participants in any group were lost to follow up (this did not include the outcome of 'leaving the study early'), as such data were felt to be too prone to bias. In studies with less than 50% dropout rate, people leaving early were considered to have had the negative outcome, except for the event of death. We analysed the impact of including studies with high attrition rates (25-50%) in a sensitivity analysis. If inclusion of data from this latter group resulted in a substantive change in the estimate of effect, we did not add their data to trials with less attrition, but presented them separately.

Assessment of heterogeneity

1. Clinical heterogeneity

We preempted heterogeneity by keeping different treatment groups separate but also tried to think if there were such obvious clinical differences in studies that synthesis be inadvisable.

2. Statistical

2.1 Visual inspection

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

2.2 Employing the I-squared statistic

This provided an estimate of the percentage of inconsistency thought to be due to chance. I-squared estimate greater than or equal to 50% was interpreted as evidence of high levels of heterogeneity (Higgins 2003).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. These are described in section 10.1 of the Cochrane Handbook (Higgins 2009). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects (Egger 1997). We did not use funnel plots for outcomes where there were ten or fewer studies, or where all studies were of similar sizes. Should funnel plots have been possible, we would have sought statistical advice in their interpretation.

Data synthesis

Where possible we used a fixed effects model for analyses. We understand that there is no closed argument for preference for use of fixed or random effects models. The random effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This does seem true to us, however, random effects does put added weight onto the smaller studies - those trials that are most vulnerable to bias.

Subgroup analysis and investigation of heterogeneity

When heterogeneous results were found, we investigated the reasons for this. Where heterogeneous data substantially altered the results and the reasons for the heterogeneity were identified, these studies were not summated in the meta-analysis, but presented separately and discussed in the text.

Sensitivity analysis

Apart from the investigation of heterogeneity, the effect of including studies with high attrition rates were analysed in sensitivity analyses.

Appendix 3. Assessment of quality

Trials were allocated to three quality categories, as described in the Cochrane Collaboration Handbook (Clarke 2000) by each reviewer working independently. When disputes arose as to which category a trial was allocated to, again, resolution was attempted by discussion. When this was not possible, and further information was necessary, data were not entered into the analyses and the study was allocated to the list of those awaiting assessment. Only trials in Category A or B were included in the review.

WHAT'S NEW

Date	Event	Description
16 January 2018	New citation required but conclusions have not changed	Results of 2017 updated search have been added to the review and have not changed the overall conclusions of the review.
26 April 2017	New search has been performed	Search was updated again, five Studies (eight References) were found and assessed.
31 October 2016	Amended	Title updated, results of 2015 update search added - 22 new included studies included, outcomes list updated due to patient consultation, PRISMA study flow chart added, 'Summary of findings' tables added, text (including methods) updated, conclusions updated.

HISTORY

Protocol first published: Issue 1, 1997

Review first published: Issue 3, 1997

Date	Event	Description
5 October 2011	Amended	Contact details updated.
13 April 2011	Amended	Contact details updated.
16 October 2009	New search has been performed	Two new studies included, two awaiting assessment, one excluded. Reformatted.
23 January 2003	New citation required and conclusions have changed	Substantive amendment
2 June 1997	New citation required and conclusions have changed	First version of Cochrane review
27 November 1996	Amended	Protocol first published

CONTRIBUTIONS OF AUTHORS

Karla Soares-Weiser (KSW) - protocol development, searching, study selection, data extraction and assimilation, report writing - all versions.

John Rathbone (JR - helped update review in 2009

Hanna Bergman (HB) - updated review in 2017

DECLARATIONS OF INTEREST

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

JR - none known.

HB worked for Enhance Reviews Ltd. during preparation of this review and was paid for her contribution to this review. Enhance Reviews Ltd. is a private company that performs systematic reviews of literature. HB works for Cochrane Response, an evidence consultancy linked to Cochrane that take commissions from healthcare guideline developers and policy makers.

SOURCES OF SUPPORT

Internal sources

- CAPES - Ministry of Education, Brazil, Brazil.
- Universidade Federal de Sao Paulo, Brazil, Brazil.
- Cochrane Schizophrenia Group, UK.
- Enhance Reviews Ltd., UK.

Logistics support for Hanna Bergman for the 2016 update.

External sources

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

Salary support for Hanna Bergman.

Support for patient involvement consultation.

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 2016 review update with main changes being to:

1. change the title from 'Miscellaneous treatments for *neuroleptic*-induced tardive dyskinesia';
2. broaden the inclusion criteria by adding the comparison: 'Any intervention compared with any other intervention for the treatment of tardive dyskinesia';
3. rename and update list of important outcomes following consultation with consumers;
4. prioritise comparisons for 'Summary of findings' tables: 'Summary of findings' tables were created only for those comparisons that: 1) included more than 60 participants, or 2) included more than one trial;
5. we analysed outcomes using risk ratios (see [Methods](#)) - rather than odds ratios.

The previous methods are reproduced in [Appendix 1](#); [Appendix 2](#), and [Appendix 3](#).

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic Uptake Inhibitors [therapeutic use]; Anti-Anxiety Agents [therapeutic use]; Antipsychotic Agents [adverse effects]; Dihydroergotoxine [therapeutic use]; Dyskinesia, Drug-Induced [etiology] [*therapy]; Ginkgo biloba; Hypnosis; Plant Extracts; Randomized Controlled Trials as Topic; Relaxation Therapy; Tetrabenazine [analogs & derivatives] [therapeutic use]; Valine [analogs & derivatives] [therapeutic use]

MeSH check words

Adult; Humans