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Treatments for movement disorders

Introduction

A supplementary or adjunctive treatment is administered in conjunction with a patient's antipsychotic therapy. Adjunct medications may improve symptoms of the disorder that are not sufficiently addressed with antipsychotic medications. They may also be prescribed to treat the side effects of antipsychotic medications, which increases adherence to these medications and reduces the risk of psychotic relapse. Extrapyramidal symptoms are movement disorders that are common side effects of many antipsychotic medications. Extrapyramidal symptoms include tardive dyskinesia, a severe and chronic condition involving repetitive, involuntary movements, most commonly occurring around the mouth and face. Akathisia is another extrapyramidal symptom, and is characterised by a feeling of restlessness and movements such as shuffling of the legs, pacing, rocking from foot to foot, or the inability to sit down or stand still. These movements are typically bilateral and relatively symmetrical. This table presents the available evidence on treatments for these and other movement disorders that arise from the use of antipsychotic medications.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data were prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

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Results

We found 11 systematic reviews that met our inclusion criteria[3-13].

- For tardive dyskinesia, moderate to low quality evidence finds large benefits over placebo of the hormone insulin, the antipsychotic promethazine, and pyridoxal 5 phosphate (vitamin B6). There was a medium to large benefit of the antidepressant isocarboxazid over the anticholinergic procyclidine. There were medium-sized benefits over placebo for the anxiolytic buspirone, the cognitive enhancer/stimulant pemoline, and the alkaloids dihydrogenated ergot alkaloid and L-Stepholidine. There were small benefits over placebo for GABA-acting agents, branched-chain amino acids, enzyme VMAT2 inhibitors, ginkgo biloba, and the antiepileptic levetiracetam.
- Moderate to low quality evidence found no significant benefits for tardive dyskinesia of ceruletide, vitamin E, cholinergic medications, noradrenergic or dopaminergic medications, benzodiazepines, evening primrose oil, lithium, oestrogen, the antidepressants selegiline and ritanserin, melatonin, the antihistamine cyproheptadine, the alkaloid papaverine the cognitive enhancer piracetam, omega-3 fatty acid eicosapentaenoic acid derivative, and the antiepileptic levetiracetam.
- For akathisia, moderate quality evidence finds a large benefit of 5-HT2A antagonists over placebo, with no differences in sedation levels. There was no benefit of omega-3 fatty acid eicosapentaenoic acid derivative.
- For dystonia, moderate to low quality evidence finds a small benefit of omega-3 fatty acid eicosapentaenoic acid derivative over placebo.

Adelufosi AO, Abayomi O, Ojo TMF

Pyridoxal 5 phosphate for neuroleptic-induced tardive dyskinesia

Cochrane Database of Systematic Reviews 2015; 4: Art. No.: CD010501. DOI: 10.1002/14651858.CD010501.pub2.

View review abstract online

Comparison	**Pyridoxal 5 phosphate (Vitamin B6) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (very small samples, consistent, imprecise, direct) suggests improved tardive dyskinesia with Pyridoxal 5 phosphate (Vitamin B6).**
Tardive dyskinesia	
A large, significant effect of improved tardive dyskinesia with Pyridoxal 5 phosphate, with no differences between groups in deterioration of symptoms; Reduced ESRS scores: 2 RCTs, N = 65, RR = 19.97, 95%CI 2.87 to 139.19, *p* = 0.0025, I^2 = 0%, p = 0.80 Average ESRS endpoint scores: 2 RCTs, N = 60, MD = -4.07, 95%CI -6.36 to -1.79, *p* = 0.00048, I^2 = 39%, *p* = 0.20 Deterioration in tardive dyskinesia symptoms: 2 RCTs, N = 65, RR = 0.16, 95%CI 0.01 to 3.14, *p* = 0.23	
Discontinuation of treatment	
No significant differences between groups; 2 RCTs, N = 65, RR = 8.72, 95%CI 0.51 to 149.75, *p* = 0.14	
Risks	No significant differences in any adverse effect: 2 RCTs, N = 65, RR = 3.97, 95%CI 0.20 to 78.59, *p* = 0.37
Consistency in results‡	Consistent where reported.
Precision in results§	Imprecise
Directness of results‖	Direct

Alabed S, Latifeh Y, Mohammad HA, Rifai A

Gamma-aminobutyric acid agonists for antipsychotic-induced tardive dyskinesia

Cochrane Database of Systematic Reviews 2018; 4: CD000203.

View review abstract online

Comparison	**GABA-acting agents (varying doses of gamma-aminobutyric acid, baclofen, progabide or sodium valproate) plus antipsychotic medications vs. placebo plus antipsychotic medications.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, consistent, precise, direct) suggests a small benefit of GABA-acting agents over placebo for tardive dyskinesia. There may be more sedation and dizziness with GABA-acting agents.**
Tardive dyskinesia	
A significant, small effect of more clinically important improvement with GABA-acting agents; 6 RCTs, N = 258, RR = 0.83, 95%CI 0.74 to 0.92, p = 0.00047, I^2 = 0%, p = 0.54 Authors report the trials were of low quality.	
Risks	There was more sedation and dizziness with GABA-acting agents.
Consistency in results	Consistent
Precision in results	Precise for tardive dyskinesia only.
Directness of results	Direct

Bergman H, Bhoopathi PS, Soares-Weiser K

Benzodiazepines for antipsychotic-induced tardive dyskinesia

Cochrane Database of Systematic Reviews 2018; 1: CD000205

View review abstract online

Comparison	**Diazepam vs. placebo**

Summary of evidence	**Moderate to low quality evidence (very small samples, imprecise, consistent, direct) suggests no differences between groups.**
Tardive dyskinesia	
No significant differences between groups; Clinically meaningful improvement: 2 RCTs, N = 32, RR = 1.12, 95%CI 0.60 to 2.09, $p = 0.72$, $I^2 = 14\%$, $p = 0.28$ Deterioration: 2 RCTs, N = 30, RR = 1.48, 95%CI 0.22 to 9.82, $p = 0.69$, $I^2 = 19\%$, $p = 0.27$	
Risks	No differences in adverse effects.
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

El-Sayeh HG, da Silva LJP, Rathbone J, Soares-Weiser K

Non-neuroleptic catecholaminergic drugs for neuroleptic-induced tardive dyskinesia

Cochrane Database of Systematic Reviews 2006; 1: DOI: 10.1002/14651858. CD000458

View review abstract online

Comparison 1	**Noradrenergic medication (celiprolol, dose 200mg/day) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (very small sample, imprecise, direct) suggests no differences between groups.**
Study attrition	
No significant differences between groups; 1 RCT, N = 35, RR = 5.28, 95%CI 0.27 to 102.58, $p = 0.27$	
Consistency in results	Not applicable, 1 RCT
Precision in results	Imprecise

Directness of results	Direct
Comparison 2	**Dopaminergic medication (tiapride, dose 100mg/twice daily) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (very small sample, unable to assess precision, direct) finds no benefit of dopaminergic medication.**
Study attrition	
One RCT (N = 24) reported no significant difference between groups in risk of leaving the study early. Both groups recorded zero attrition.	
Consistency in results	Not applicable (1 RCT).
Precision in results	Imprecise
Directness of results	Direct

Laoutidis ZG, Luckhaus C

5-HT2A receptor antagonists for the treatment of neuroleptic-induced akathisia: a systematic review and meta-analysis

International Journal of Neuropsychopharmacology 2014; 17: 823-832

View review abstract online

Comparison	**5-HT2A antagonists (mianserin, mirtazapine or trazodone) vs. placebo.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, consistent, imprecise, direct) suggests a large effect of 5-HT2A antagonists for improving akathisia symptoms when compared to placebo, with no differences between groups in study attrition or sedation.**
Akathisia	
A large, significant effect of increased response to treatment in those receiving 5-HT2A antagonists; BARS score reduces by 2 points or more: 5 RCTs, N = 214, RR = 7.10, 95%CI 3.08 to 16.40, $p < 0.0001$, $I^2 = 14.07\%$	

A large, significant effect of increased remission of akathisia in those receiving 5-HT2A antagonists; 5 RCTs, N = 196, RR = 4.95, 95%CI 2.01 to 12.22, *p* = 0.0005, I^2 not reported Authors report low risk for bias in the studies
Study attrition
No difference between groups; 5 RCTs, N = 196, RR = 0.62, 95%CI 0.31 to 1.25, *p* = 0.18, I^2 not reported

Risks	There was no difference between groups in risk of sedation: 5 RCTs, N = 200, RR = 1.42, 95%CI 0.54 to 3.73, *p* = 0.55.
Consistency in results	Consistent for response, unable to assess remission or study attrition.
Precision in results	Imprecise
Directness of results	Direct

Soares-Weiser K, Maayan N, Bergman H

Vitamin E for antipsychotic-induced tardive dyskinesia

Cochrane Database of Systematic Reviews 2018; 1: CD000209

View review abstract online

Comparison	**Adjunctive vitamin E (600-1600IU/day) vs. adjunctive placebo.**
Summary of evidence	**Moderate to high quality evidence (small to medium-sized samples, consistent, precise, direct) suggests no benefit of Vitamin E.**
Tardive dyskinesia	
No significant differences in rates of improvement of tardive dyskinesia symptoms; 6 RCTs, N = 264, RR = 0.95, 95%CI 0.89 to 1.01, *p* > 0.05, I^2 = 0% Authors report this is low quality evidence from poorly randomised trials.	
Risks	*No differences between groups in any adverse effects;* 9 RCTs, N = 205, RR = 1.21, 95%CI 0.35 to 4.15, *p* > 0.05, I^2 = 0%

Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Soares-Weiser KV, Joy C

Miscellaneous treatments for neuroleptic-induced tardive dyskinesia

Cochrane Database of Systematic Reviews 2018; 2: DOI: 10.1002/14651858.CD000208

View review abstract online

Comparison 1	**Ceruletide (0.8 µg/kg/week) vs. placebo.**
Summary of evidence	**Moderate quality evidence (small samples, consistent, imprecise, direct) suggests no differences between groups for tardive dyskinesia.**
Tardive dyskinesia	
No significant differences between groups; 2 RCTs, N = 132, RR = 0.83, 95%CI 0.65 to 1.07, p = 0.15, I^2 = 0%, p = 0.41	
Study attrition	
No significant differences between groups; 1 RCT, N = 85, RR = 1.09, 95%CI 0.49 to 2.40, p = 0.84	
Risks	*No differences between groups in any adverse effects;* 2 RCTs, N = 122, RR = 1.32, 95%CI 0.74 to 2.36, p = 0.35, I^2 = 16%, p = 0.28
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct
Comparison 2	**Gamma linolenic acid supplementation (evening primrose oil; 600 mg/day) vs. placebo.**

Summary of evidence	**Moderate to low quality evidence (very small sample, imprecise, direct) finds no benefit of evening primrose oil.**
Tardive dyskinesia	
No significant differences between groups; 1 RCT, N = 16, RR = 1.00, 95%CI 0.69 to 1.45, *p* = 1.00 The finding was similar using other measures (deterioration, scales).	
Risks	No adverse effects were reported in either group.
Consistency in results	Not applicable (1 RCT).
Precision in results	Imprecise
Directness of results	Direct
Comparison 3	**Hormones insulin (10 IU/day) or melatonin (2-20mg per day for 4-12 weeks) vs. placebo or no treatment.**
Summary of evidence	**Moderate to low quality evidence (very small sample, imprecise, direct) finds a large benefit of insulin for tardive dyskinesia, with no benefit of melatonin.**
Tardive dyskinesia	
A significant, large effect of more clinically important improvement in tardive dyskinesia with insulin; 1 RCT, N = 20, RR = 0.06, 95%CI 0.00 to 0.90, *p* = 0.042 The finding was similar using AIMS but not deterioration measures. *No significant differences between melatonin and placebo or no treatment;* 2 RCTs, N = 32, RR = 0.89, 95%CI 0.71 to 1.12, *p* = 0.33, I^2 = 14%, *p* = 0.28 The finding was similar using AIMS and deterioration measures.	
Risks	Not reported
Consistency in results	Not applicable (1 RCT).
Precision in results	Imprecise
Directness of results	Direct
Comparison 4	**Lithium (dose not reported) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (very small sample, imprecise,**

	direct) finds no benefit of lithium for tardive dyskinesia.
Tardive dyskinesia	
No significant differences between groups; 1 RCT, N = 11, RR = 1.59, 95%CI 0.79 to 3.23, *p* = 0.20 The finding was similar using other measures (deterioration, AIMS).	
Study attrition	
No significant differences between groups; 1 RCT, N = 11, RR = 2.57, 95%CI 0.13 to 52.12, *p* = 0.54	
Risks	*There was no difference in risk of any adverse effect;* 1 RCT, N = 11, RR = 6.00, 95%CI 0.38 to 94.35, *p* = 0.20.
Consistency in results	Not applicable (1 RCT).
Precision in results	Imprecise
Directness of results	Direct
Comparison 5	**Phenylalanine (amino acid, 100mg/kg) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (very small sample, imprecise, direct) finds no differences in study attrition with phenylalanine.**
Study attrition	
No significant differences between groups; 1 RCT, N = 18, RR = 2.45, 95%CI 0.11 to 53.25, *p* = 0.57	
Risks	Not reported.
Consistency in results	Not applicable (1 RCT).
Precision in results	Imprecise
Directness of results	Direct
Comparison 6	**Oestrogen (1.25 mg/day) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (very small sample, imprecise, direct) finds no benefit of oestrogen.**

Tardive dyskinesia	
No significant differences between groups; 1 RCT, N = 12, RR = 1.18, 95%CI 0.76 to 1.83, *p* = 0.45 The finding was similar using other measures (deterioration, AIMS).	
Study attrition	
No significant differences between groups; 1 RCT, N = 12, RR = 1.00, 95%CI 0.08 to 12.56, *p* = 1.0	
Risks	*There was no difference in risk of any adverse effect;* RCT, N = 12, RR = 0.33, 95%CI 0.02 to 6.86, *p* = 0.48
Consistency in results	Not applicable - 1 RCT
Precision in results	Imprecise
Directness of results	Direct
Comparison 7	**Dihydrogenated ergot alkaloid (6mg/day, 6 weeks) or L-stepholidine alkaloid (two tablets three times per day for 8 weeks) or papaverine alkaloid (150 mg/day twice a day for the first week and 300 mg twice a day for the next 5 weeks) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (very small sample, imprecise, direct) finds medium-sized benefits of dihydrogenated ergot alkaloid and L-Stepholidine alkaloid for tardive dyskinesia, with no benefit of papaverine alkaloid.**
Tardive dyskinesia	
A significant, medium-sized effect of more clinically important improvement in tardive dyskinesia with L-Stepholidine alkaloid; 1 RCT, N = 57, RR = 0.54, 95%CI 0.35 to 0.82, *p* = 0.004 *A significant, medium-sized effect of more clinically important improvement in tardive dyskinesia with dihydrogenated ergot alkaloid;* 1 RCT, N = 28, RR = 0.45, 95%CI 0.21 to 0.97, *p* = 0.04 There were no significant differences using other measures (scales, deterioration). *No significant benefits of papaverine;*	

AIMS: 1 RCT, N = 22, MD = 0.51, 95%CI -1.18 to 2.20, *p* = 0.55	
Study attrition	
No significant differences between dihydrogenated ergot alkaloid and placebo; 1 RCT, N = 48, RR = 0.33, 95%CI 0.02 to 7.32, *p* = 0.49	
Risks	*There was no difference in risk of any adverse effect between dihydrogenated ergot alkaloid and placebo;* 1 RCT, N = 28, RR = 2.33, 95%CI 0.75 to 7.14, *p* = 0.14
Consistency in results	Not applicable - 1 RCT
Precision in results	Imprecise
Directness of results	Direct
Comparison 8	**Branched-chain amino acid (mixed doses for 3 weeks) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (very small sample, precise, direct) finds a small effect of more clinically important improvement in tardive dyskinesia with branched-chain amino acid.**
Tardive dyskinesia	
A significant, small effect of more clinically important improvement in tardive dyskinesia with branched-chain amino acid; 1 RCT, N = 52, RR = 0.79, 95%CI 0.63 to 1.00, *p* = 0.04 The finding was similar using other measures (deterioration, scales).	
Study attrition	
No significant differences between groups; 1 RCT, N = 52, RR = 0.84, 95%CI 0.37 to 1.92, *p* = 0.68	
Risks	Not reported.
Consistency in results	Not applicable - 1 RCT
Precision in results	Precise
Directness of results	Direct

Comparison 9	**Antidepressant selegiline (5mg for 1 week, then 10mg twice daily for 6 weeks) or ritanserin (10 mg three times a day for 30 days) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (very small sample, precise, direct) finds no effect of antidepressants selegiline or ritanserin.**
Tardive dyskinesia	
No significant differences between selegiline and placebo; 1 RCT, N = 33, RR = 1.37, 95%CI 0.96 to 1.94, *p* = 0.08 *No significant differences between ritanserin and placebo;* 1 RCT, N = 10, RR = 1.00, 95%CI 0.70 to 1.43, *p* = 1.00	
Study attrition	
No significant differences between selegiline and placebo; 1 RCT, N = 33, RR = 10.39, 95%CI 0.62 to 173.97, *p* = 0.10	
Risks	Not reported.
Consistency in results	Not applicable - 1 RCT
Precision in results	Precise
Directness of results	Direct
Comparison 10	**Antidepressant isocarboxazid (10mg per day for 40 weeks) vs. procyclidine (5mg per day for 40 weeks).**
Summary of evidence	**Moderate to low quality evidence (very small sample, precise, direct) finds a medium to large effect of a benefit for tardive dyskinesia with the antidepressant isocarboxazid over procyclidine.**
Tardive dyskinesia	
A significant, medium to large effect of more clinically important improvement in tardive dyskinesia with isocarboxazid; 1 RCT, N = 20, RR = 0.24, 95%CI 0.08 to 0.71, *p* = 0.01	
Risks	*There was no difference in risk of any adverse effect;* 1 RCT, N = 20, RR = 3.00, 95%CI 0.14 to 65.90, *p* = 0.49

Consistency in results	Not applicable - 1 RCT
Precision in results	Precise
Directness of results	Direct
Comparison 11	**Antiepileptic levetiracetam (up to 1500 mg twice a day for 12 weeks) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (very small samples, imprecise, direct) finds a benefit for tardive dyskinesia with the antiepileptic levetiracetam than placebo, with no benefit for hyperkinesia. There may be fewer adverse events with levetiracetam.**
Tardive dyskinesia	
A significant effect of more improvement in tardive dyskinesia on the AIMS with levetiracetam; 1 RCT, N = 20, MD = -2.18, 95%CI -3.65 to -0.71, *p* = 0.003 *There were no differences in hyperkinesia using the SHRS;* 1 RCT, N = 69, MD = 0.13, 95%CI -0.73 to 0.99, *p* = 0.77	
Study attrition	
No significant differences between groups; 2 RCTs, N = 119, RR = 1.01, 95%CI 0.46 to 2.22, *p* = 0.98, I^2 = 73%, *p* = 0.06	
Risks	*A trend effect of fewer adverse effects with levetiracetam;* 1 RCT, N = 69, RR = 0.59, 95%CI 0.25 to 1.04, *p* = 0.06
Consistency in results	Inconsistent for study attrition, not applicable for other outcomes.
Precision in results	Imprecise
Directness of results	Direct
Comparison 12	**Antihistamine cyproheptadine (12 mg/day to 24 mg/day for 4 weeks) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (very small sample, imprecise, direct) finds no significant benefit for tardive dyskinesia over placebo.**
Tardive dyskinesia	

A non-significant medium-sized trend effect of greater improvement in tardive dyskinesia with cyproheptadine; 1 RCT, N = 42, RR = 0.54, 95%CI 0.27 to 1.08, *p* = 0.07	
Study attrition	
No significant differences between groups; 1 RCT, N = 42, RR = 0.33, 95%CI 0.01 to 7.74, *p* = 0.49	
Risks	*No significant differences between groups;* 1 RCT, N = 42, RR = 0.33, 95%CI 0.04 to 2.95, *p* = 0.32
Consistency in results	Not applicable - 1 RCT
Precision in results	Imprecise
Directness of results	Direct
Comparison 13	**Antipsychotic promethazine (50 mg by IM twice per day for 2 weeks then 2 weeks of IV drip, repeated 3 times over 12 weeks) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (very small sample, imprecise, direct) finds a large benefit for tardive dyskinesia with the antipsychotic promethazine.**
Tardive dyskinesia	
A significant, large effect of greater clinically important improvement in tardive dyskinesia with promethazine; 1 RCT, N = 34, RR = 0.24, 95%CI 0.11 to 0.55, *p* = 0.006 Results were similar in the analysis of the AIMS scale.	
Risks	*There was no difference in risk of any adverse effect;* 1 RCT, N = 34, MD = -0.10, 95%CI -0.53 to 0.33, *p* = 0.65
Consistency in results	Not applicable - 1 RCT
Precision in results	Imprecise
Directness of results	Direct
Comparison 14	**Anxiolytic buspirone (1 capsule per day titrated to 6-12 capsules each day for 10 days) vs. placebo.**

Summary of evidence	**Moderate to low quality evidence (very small sample, precise, direct) finds a medium-sized benefit for tardive dyskinesia with the anxiolytic buspirone.**
Tardive dyskinesia	
A significant, medium-sized effect of greater clinically important improvement in tardive dyskinesia with buspirone; 1 RCT, N = 42, RR = 0.53, 95%CI 0.33 to 0.84, *p* = 0.007 Results were not significant in the analysis of the AIMS scale.	
Risks	Not reported.
Consistency in results	Not applicable - 1 RCT
Precision in results	Precise
Directness of results	Direct
Comparison 15	**Cognitive enhancer piracetam (4800mg per day for 9 weeks) or pemoline (2 capsules per day for six days every week for 6 weeks) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (very small sample, imprecise, direct) finds a medium-sized benefit of cognitive enhancer/stimulant pemoline over placebo for tardive dyskinesia, with no benefit of cognitive enhancer piracetam.**
Tardive dyskinesia	
A significant, medium-sized effect of greater clinically important improvement in tardive dyskinesia with pemoline; 1 RCT, N = 42, RR = 0.48, 95%CI 0.29 to 0.77, *p* = 0.002 Results were similar on the AIMS. *No significant differences between piracetam and placebo on the ESRS;* 1 RCT, N = 35, MD = -0.70, 95%CI -4.30 to 2.90, *p* = 0.70	
Study attrition	
No significant differences between piracetam and placebo; 1 RCT, N = 40, RR = 0.33, 95%CI 0.03 to 1.85, *p* = 0.17	
Risks	Not reported.

Consistency in results	Not applicable - 1 RCT
Precision in results	Imprecise
Directness of results	Direct
Comparison 16	**Enzyme VMAT2 inhibitors (25-75mg per day for 6 weeks) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (very small sample, some imprecision, direct) finds a small benefit of enzyme VMAT2 inhibitors for tardive dyskinesia over placebo.**
Tardive dyskinesia	
A significant, small effect of greater clinically important improvement in tardive dyskinesia with VMAT2 inhibitors; 1 RCT, N = 92, RR = 0.63, 95%CI 0.46 to 0.86, *p* = 0.003 Results were similar on the AIMS.	
Study attrition	
No significant differences between groups; 1 RCT, N = 102, RR = 1.00, 95%CI 0.31 to 3.25, *p* = 1.00	
Risks	*There was no difference in risk of any adverse effect;* 1 RCT, N = 100, RR = 1.50, 95%CI 0.92 to 2.45, *p* = 0.10
Consistency in results	Not applicable - 1 RCT
Precision in results	Precise for tardive dyskinesia only.
Directness of results	Direct
Comparison 17	**Omega-3 fatty acid eicosapentaenoic acid derivative (2g per day for 12 weeks) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (very small sample, imprecise, direct) finds a small benefit of Omega-3 fatty acid eicosapentaenoic acid derivative over placebo for dystonia, with no benefits for tardive dyskinesia, parkinsonism or akathisia.**
Movement disorders	

Significantly less dystonia with Omega-3; Dystonia: 1 RCT, N = 75, MD = -0.35, 95%CI -0.58 to -0.12, *p* = 0.002 *No significant differences between Omega-3 and placebo;* Tardive dyskinesia: 1 RCT, N = 75, RR = 0.82, 95%CI 0.57 to 1.12, *p* = 0.28 Parkinsonism: 1 RCT, N = 75, MD = 0.30, 95%CI -1.17 to 1.77, *p* = 0.69 Akathisia: 1 RCT, N = 75, MD = -0.04, 95%CI -0.30 to 0.22, *p* = 0.76	
Study attrition	
No significant differences between Omega-3 and placebo; 1 RCT, N = 84, RR = 0.57, 95%CI 0.27 to 1.22, *p* = 0.15	
Risks	Not reported.
Consistency in results	Not applicable - 1 RCT
Precision in results	Imprecise
Directness of results	Direct
Comparison 18	**Ginkgo biloba (80mg three times a day for 12 weeks) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (small sample, precise, direct) finds a small benefit of ginkgo biloba for tardive dyskinesia.**
Tardive dyskinesia	
A significant, small effect of greater clinically important improvement in tardive dyskinesia with ginkgo biloba; 1 RCT, N = 157, RR = 0.88, 95%CI 0.81 to 0.96, *p* = 0.006 The finding was similar using other measures (deterioration, scales).	
Study attrition	
No significant differences between groups; 1 RCT, N = 157, RR = 0.25, 95%CI 0.03 to 2.22, *p* = 0.21	
Risks	Not reported.
Consistency in results	Not applicable - 1 RCT

Precision in results	Precise
Directness of results	Direct

Sun C-H, Zheng W, Yang X-H, Cai D-B, Ng CH, Ungvari GS, Li H-Y, Wu Y-J, Ning Y-P, Xiang Y-T

Adjunctive melatonin for tardive dyskinesia in patients with schizophrenia: A meta-analysis

Shanghai Archives of Psychiatry 2017; 29: 129-36

View review abstract online

Comparison	**Melatonin (various doses) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (small samples, imprecise, consistent, direct) suggests no differences between groups.**
Tardive dyskinesia	
No significant differences between groups 4 RCTs, N = 130, WMD = -1.52, 95%CI -3.24 to 0.20, p = 0.08, I^2 = 0%	
Risks	Not reported.
Consistency in results	Consistent
Precision in results	Unable to assess WMDs (not standardised).
Directness of results	Direct

Tammenmaa-Aho I, Asher R, Soares-Weiser K, Bergman H

Cholinergic medication for antipsychotic-induced tardive dyskinesia

Cochrane Database of Systematic Reviews 2018; 3: CD000207

View review abstract online

Comparison	**Any cholinergic drug vs. placebo.** **This review included both cholinergic medications and acetylcholinesterase-inhibitors.**
Summary of evidence	**Moderate to low quality evidence (mostly very small samples, imprecise, consistent where applicable, direct) suggests no differences between groups for tardive dyskinesia or adverse effects.**
Tardive dyskinesia	
No significant differences between groups in a 50% improvement in tardive dyskinesia symptoms; Overall: 4 RCTs, N = 27, RR = 0.89, 95%CI 0.65 to 1.23, p = 0.49, I^2 = 0%, p = 0.86 Deanol: 2 RCTs, N = 11, RR = 0.91, 95%CI 0.51 to 1.60, p = 0.73, I^2 = 0%, p = 0.77 Lecithin: 1 RCT, N = 6, RR = 0.71, 95%CI 0.31 to 1.66, p = 0.43 Donepezil: 1 RCT, N = 10, RR = 1.00, 95%CI 0.70 to 1.43, p = 1.00 *No significant differences between groups in AIMS scores;* Overall: 7 RCTs, N = 171, MD = -0.12, 95%CI -0.44 to 0.21, p = 0.48, I^2 = 44%, p = 0.10 Lecithin: 1 RCT, N = 14, MD = -0.10, 95%CI -1.04 to 0.84, p = 0.83 Deanol: 1 RCT, N = 6, MD = 1.42, 95%CI -0.29 to 3.13, p = 0.10 Meclofenoxate: 1 RCT, N = 60, MD = -0.19, 95%CI -0.58 to 0.20, p = 0.33 Galantamine: 1 RCT, N = 35, MD = 1.50, 95%CI -0.44 to 3.44, p = 0.13 Rivastigmine: 1 RCT, N = 40, MD = 2.20, 95%CI -1.16 to 5.56, p = 0.20 Donepezil: 1 RCT, N = 10, MD = 1.10, 95%CI -4.22 to 6.42, p = 0.69	
Risks	There were no differences in any adverse event.
Consistency in results	Consistent where applicable (> 1 RCT).
Precision in results	Imprecise, unable to assess MDs.
Directness of results	Direct

Zaman H, Gibson RC, Walcott G

Benzodiazepines for catatonia in people with schizophrenia or other serious mental illnesses

Cochrane Database of Systematic Reviews 2019; 8: CD006570 View review abstract online	
Comparison	**Benzodiazepines (lorazepam or oxazepam) vs. placebo.**
Summary of evidence	**Low quality evidence (very small samples, imprecise, direct) is unable to determine the effects of lorazepam or oxazepam for catatonia.**
Catatonia	
There was no difference between groups; 1 study, N = 17, RR = 0.95, 95%CI 0.42 to 2.16, *p* > 0.05	
Risks	Not reported.
Consistency in results	Not applicable (1 study)
Precision in results	Imprecise
Directness of results	Direct

Zheng W, Li XH, Cai DB, Yang XH, Ungvari GS, Ng CH, Ning YP, Xiang YT

Adjunctive azapirone for schizophrenia: A meta-analysis of randomized, double-blind, placebo-controlled trials

European Neuropsychopharmacology 2018; 28: 149-58

View review abstract online

Comparison	**Buspirone (6-24 weeks; 21.6-60mg/d) plus antipsychotics (various) vs. antipsychotics plus placebo.**
Summary of evidence	**Moderate to low quality evidence (very small sample, consistent, imprecise, direct) finds a medium-sized effect of greater improvement in extrapyramidal symptoms with buspirone over placebo.**
Extrapyramidal symptoms	
A significant, medium-sized effect of greater improvement in extrapyramidal symptoms with	

adjunctive buspirone; 2 RCTs, N = 67, SMD = -0.51, 95%CI -0.99 to -0.02, *p* = 0.04, I^2 = 0%, *p* = 0.45	
Risks	There were no differences in adverse effects.
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Explanation of acronyms

AIMS = Abnormal Involuntary Movement Scale, AVLT = Auditory Verbal Learning Test, BARS = Barnes Akathisia Rating Scale, CGI = Clinical Global Impressions scale, CI = confidence interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences (see below for interpretation of effect size), ESRS = Extrapyramidal Symptom Rating Scale, GABA = gamma-amino butyric acid, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MD = mean difference, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic for the test of heterogeneity, RCT = randomised controlled trial, RR = relative risk, SHRS = St. Hans Rating Scale, TD = tardive dyskinesia, TDRS = Tardive Dyskinesia Rating Scale, vs. = versus, WMD = weighted mean difference

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[14].

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† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives thath are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[14].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[15]. lnOR stands for logarithmic OR where a lnOR of 0 shows no

difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[14];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[16].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. El-Sayeh HG, Lyra da Silva JP, Rathbone J, Soares-Weiser K (2006): Non-neuroleptic catecholaminergic drugs for neuroleptic-induced tardive dyskinesia. *Cochrane Database of Systematic Reviews*: CD000458.
4. Laoutidis ZG, Luckhaus C (2014): 5-HT2A receptor antagonists for the treatment of neuroleptic-induced akathisia: a systematic review and meta-analysis. *International Journal of Neuropsychopharmacology* 17: 823-32.
5. Adelufosi AO, Abayomi O, Ojo TM (2015): Pyridoxal 5 phosphate for neuroleptic-induced tardive dyskinesia. *Cochrane Database of Systematic Reviews* 4: CD010501.
6. Soares-Weiser K, Maayan N, Bergman H (2018): Vitamin E for antipsychotic-induced tardive dyskinesia. *Cochrane Database of Systematic Reviews* 1: CD000209.
7. Soares-Weiser K, Rathbone J, Ogawa Y, Shinohara K, Bergman H (2018): Miscellaneous treatments for antipsychotic-induced tardive dyskinesia. *Cochrane Database of Systematic Reviews* 3: CD000208.
8. Sun C-H, Zheng W, Yang X-H, Cai D-B, Ng CH, Ungvari GS*, et al.* (2017): Adjunctive melatonin for tardive dyskinesia in patients with schizophrenia: A meta-analysis. *Shanghai Archives of Psychiatry* 29: 129-36.
9. Bergman H, Bhoopathi PS, Soares-Weiser K (2018): Benzodiazepines for antipsychotic-induced tardive dyskinesia. *Cochrane Database of Systematic Reviews* 1: CD000205.
10. Alabed S, Latifeh Y, Mohammad HA, Bergman H (2018): Gamma-aminobutyric acid agonists for antipsychotic-induced tardive dyskinesia. *Cochrane Database of Systematic Reviews* 4: CD000203.
11. Zheng W, Li XH, Cai DB, Yang XH, Ungvari GS, Ng CH*, et al.* (2018): Adjunctive azapirone for schizophrenia: A meta-analysis of randomized, double-blind, placebo-controlled trials. *European Neuropsychopharmacology* 28: 149-58.
12. Tammenmaa-Aho I, Asher R, Soares-Weiser K, Bergman H (2018): Cholinergic medication for antipsychotic-induced tardive dyskinesia. *Cochrane Database of Systematic Reviews* 3: CD000207.
13. Zaman H, Gibson RC, Walcott G (2019): Benzodiazepines for catatonia in people with schizophrenia or other serious mental illnesses. *Cochrane Database of Systematic Reviews* 8: CD006570.
14. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
15. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
16. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*