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Glutamate modulators

Introduction

Antipsychotic medications predominantly target the dopamine neurotransmitter system, with some efficacy for alleviating the positive symptoms of schizophrenia. However, the persistence of negative and cognitive symptoms suggests that other mechanisms are also likely to be involved. The glutamate hypothesis of schizophrenia proposes that reduction of glutamatergic N-methyl-D-aspartate (NMDA) receptor function represents a primary neuropathology in schizophrenia. Therefore, glutamate receptor modulators have been suggested as an adjunctive therapy to standard antipsychotic treatments, when individuals have sub-optimal responses to treatment. The glutamate receptor modulators that have been trialed in schizophrenia are predominantly amino acids, and act on several different aspects of the glutamatergic neurotransmission system. Agents include glycine, D-serine, D-cycloserine, D-alanine, CX516, sarcosine, N-acetyl cysteine, and memantine. These agents have been studied for efficacy in improving symptom severity and cognitive function.

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 given priority for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, which describes a preferred way to present a meta-analysis[1]. Reviews reporting less than 50% of items 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 10 systematic reviews that met inclusion criteria[3-12].

- Moderate to high quality evidence shows small improvements in negative, positive, and total symptoms with adjunctive N-methyl-d-aspartate modulators. For negative symptoms, D-serine, N-acetyl-cysteine, and D-alanine were most effective. For positive symptoms, NMDA receptor modulators with non-clozapine adjuncts were most effective. For total symptoms, D-serine, glycine, N-acetyl-cysteine, sarcosine, and D-alanine were most effective.
- For memantine, moderate to high quality evidence finds medium-sized improvements in total and negative symptoms, with no significant effects on positive symptoms or general psychopathology. Lower quality evidence suggests there may also be some improvement in cognitive symptoms with adjunctive memantine.
- For minocycline, moderate to low quality evidence suggests a small benefit for overall and negative symptoms, with no benefit for positive or depressive symptoms.
- Moderate to high quality evidence suggests no overall benefit of adjunctive N-methyl-d-aspartate receptor-enhancing agents for cognition, although it may be beneficial in people aged between 30 and 39 years, and when taking N-acetyl cysteine for working memory.

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Chang C-H, Lane H-Y, Tseng P-T, Chen S-J, Liu C-Y, Lin C-H

Effect of N-methyl-D-aspartate-receptor-enhancing agents on cognition in patients with schizophrenia: A systematic review and meta-analysis of double-blind randomised controlled trials

Journal of Psychopharmacology 2019; 33: 436-48

View review abstract online

Comparison	**Adjunctive N-methyl-d-aspartate receptor-enhancing agents vs. placebo**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, precise, direct) suggests no overall benefit of adjunctive N-methyl-d-aspartate receptor-enhancing agents for cognition, although it may be beneficial in people ages between 30 and 39 years, and N-acetyl cysteine for working memory.**
Cognition	
25 RCTs, N = 1,951 *No significant difference between groups;* 15 studies, SMD = 0.068, 95%CI -0.056 to 0.193, $p = 0.283$ *Subgroup analysis of patients aged between 30 and 39 years showed a small, significant effect of improved cognition;* 8 studies, SMD: 0.163, 95%CI 0.016 to 0.310, $p = 0.030$ *Subgroup analysis showed N-acetyl cysteine had a significant effect on working memory;* 4 studies, SMD = 0.679, 95%CI 0.397 to 0.961, $p < 0.001$	
Consistency in results	Authors state the results are consistent.
Precision in results	Precise
Directness of results	Direct

Choi K, Wykes T, Kurtz M

Adjunctive pharmacotherapy for cognitive deficits in schizophrenia: meta-analytical investigation of efficacy

The British Journal of Psychiatry 2013; 203: 172-178

View review abstract online

Comparison	**Glycine, D-cycloserine, D–serine or CX516 + antipsychotics vs. placebo + antipsychotics.**
Summary of evidence	**Moderate to high quality evidence (medium or unclear sample sizes, consistent, precise, direct) suggests a medium effect of adjunctive glycine, D-cycloserine, D–serine or CX516 for improving overall and negative symptoms, with no benefit for cognitive functioning. D-serine is most effective for overall symptoms when added to non-clozapine antipsychotics, and CX516 when added to clozapine.**

Symptoms

Significant, medium-sized improvement in overall and negative symptoms, with no effect on positive symptoms;

Overall symptoms: 4 RCTs, N unclear, d = 0.41, 95%CI 0.01 to 0.81, p = 0.044, Q_W = 11.09, p = 0.01

Negative symptoms: 7 RCTs, N = 325, d = 0.62, 95%CI 0.34 to 0.90, p = 0.000, Q_W = 9.13, p = 0.17

Positive symptoms: 6 RCTs, N unclear, d = 0.08, 95%CI -0.24 to 0.39, p = 0.637, Q_W = 0.48, p = 0.99

D-serine produced a large improvement in overall symptoms when added to non-clozapine antipsychotics, while CX516 produced a large improvement in overall symptoms when added to clozapine.

Cognition

No differences between groups;

Overall function: 7 RCTs, N = 325, d = 0.06, 95%CI -0.22 to 0.35, p = 0.661 Q_W = 3.65, p = 0.72

Attention/vigilance: 3 RCTs, N unclear, d = -0.01, 95%CI -0.37 to 0.36, p = 0.970, Q_W = 0.13, p = 0.94

Verbal learning and memory: 3 RCTs, N unclear, d = 0.07, 95%CI -0.31 to 0.46, p = 0.708, Q_W = 5.93, p = 0.05

Spatial learning and memory: 3 RCTs, N unclear, d = 0.04, 95%CI -0.35 to 0.43, p = 0.841, Q_W = 2.51, p = 0.28 Reasoning/problem-solving: 6 RCTs, N unclear, d = -0.13, 95%CI -0.43 to 0.18, p = 0.411, Q_W = 3.26, p = 0.66 Speed of processing: 4 RCTs, N unclear, d = -0.03, 95%CI -0.38 to 0.32, p = 0.862, Q_W = 2.25, p = 0.52	
Consistency in results	Consistent, apart from verbal learning and memory and overall symptoms.
Precision in results	Precise
Directness of results	Direct

Fusar-Poli P, Papanastasiou E, Stahl D, Rocchetti M, Carpenter W, Shergill S, McGuire P

Treatments of Negative Symptoms in Schizophrenia: Meta-Analysis of 168 Randomized Placebo-Controlled Trials

Schizophrenia Bulletin 2015; 41(4): 892-899

View review abstract online

Comparison	**Effectiveness of adjunctive glutamatergic agents vs. placebo.**
Summary of evidence	**Moderate quality evidence (unclear sample size, inconsistent, precise, direct) suggests a small improvement in negative symptoms with adjunctive glutamatergic agents, although the effect may not be clinically significant.**
Negative symptoms	
A small effect of greater improvement in negative symptoms with glutamatergic agents; 26 studies, SMD = -0.289, 95%CI -0.478 to -0.1, p = 0.003, I^2 = 66.4%, p < 0.001 Authors state that this finding was not clinically significant as measured by the Clinical Global Impression Scale (severity and improvement). There were no effects of potential moderators (outcome scales, study attrition rates, illness duration, age, percentage of males, trial duration, year of publication, and quality of studies), and no evidence of publication bias.	
Consistency in results	Inconsistent

Precision in results	Precise
Directness of results	Direct

Kishi T, Matsuda Y, Iwata N

Memantine add-on to antipsychotic treatment for residual negative and cognitive symptoms of schizophrenia: a meta-analysis

Psychopharmacology 2017; 234: 2113-25

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Comparison	**Adjunctive memantine vs. placebo.**
Summary of evidence	**Moderate quality evidence (medium to large samples, inconsistent, imprecise, direct) finds a large improvement in negative symptoms with adjunctive memantine, with no significant effect on positive, overall and depressive symptoms and no differences in adverse effects. There may also be some improvement in cognitive symptoms.**

Symptoms

A significant, large effect of greater improvement in negative symptoms with adjunctive memantine;

7 RCTs, N = 367, SMD = -0.96, 95%CI -1.64 to -0.27, $p = 0.006$, $I^2 = 88\%$, $p < 0.00001$

Meta-regression showed younger patient age was associated with increased effect sizes.

There were no significant differences in;

Overall symptoms: 5 RCTs, N = 271, SMD = -0.75, 95%CI -1.52 to 0.03, $p = 0.06$, $I^2 = 86\%$, $p < 0.05$

Positive symptoms: 7 RCTs, N = 367, SMD = -0.46, 95%CI -0.96 to 0.05, $p = 0.07$, $I^2 = 80\%$, $p < 0.05$

Depressive symptoms: 4 RCTs, N = 201, SMD = -0.13, 95%CI -0.38 to 0.13, $p = 0.326$, $I^2 = 0\%$

Cognition

A significant effect of greater improvement in cognition (MMSE) with adjunctive memantine;

3 RCTs, N = 83, MD = -3.07, 95%CI -4.46 to -1.69, $p < 0.0001$, $I^2 = 21\%$, $p = 0.28$

Risks	There were no significant differences in any adverse event (all-cause discontinuation, fatigue, dizziness, headache, nausea, constipation)
Consistency in results	Inconsistent, apart from depressive and cognitive symptoms.
Precision in results	Imprecise
Directness of results	Direct

Oya K, Kishi T, Iwata N

Efficacy and tolerability of minocycline augmentation therapy in schizophrenia: a systematic review and meta-analysis of randomized controlled trials

Human Psychopharmacology: Clinical and Experimental 2014; 29: 483-491

View review abstract online

Comparison	**Minocycline + antipsychotics vs. placebo + antipsychotics. Mean treatment duration 25 weeks.**
Summary of evidence	**Moderate to low quality evidence (inconsistent, imprecise, direct, medium-sized samples) suggests a small benefit of adjunctive minocycline for overall and negative symptoms, but not positive or depressive symptoms.**

Symptoms

Small, significant effect of improved overall and negative symptoms with adjunctive minocycline;

PANSS total: 4 RCT, N = 267, SMD = -0.70, 95%CI -1.31 to -0.08, p = 0.03, I^2 81%, p = 0.0002

PANSS general: 4 RCT, N = 267, SMD = -0.50, 95%CI = -0.99 to -0.01, p = 0.05, I^2 72%, p = 0.007

PANSS negative: 4 RCT, N = 267, SMD = -0.86, 95%CI -1.32 to -0.41, p = 0.0002, I^2 66%, p = 0.02

SANS: 2 RCT, N = 133, SMD = -0.74, 95%CI -1.23 to -0.25, p = 0.003, I^2 44%, p not reported

CGI: 3 RCT, N = 227, SMD = -0.47, 95%CI -0.82 to -0.13, p = 0.007, I^2 34%, p not reported

No differences for positive or depressive symptoms;

PANSS positive: 4 RCT, N = 267, SMD = -0.26, 95%CI -0.55 to 0.02, p = 0.07, I^2 22%, p not reported

Depressive symptoms: 2 RCT, N = 94, SMD = -0.28, 95%CI = -0.70 to 0.14, p = 0.20, I^2 = 0%, p not

reported Authors report no evidence of publication bias	
Risks	Minocycline and placebo did not differ on discontinuation rates for inefficacy or any adverse event. Minocycline was superior to placebo in Extrapyramidal Symptom Rating Scale/Abnormal Involuntary Movement Scale scores (3 RCT, N = 189, SMD = -0.32, 95%CI -0.64 to -0.01, p = 0.04, I^2 = 0%).
Consistency in results	Inconsistent for PANSS scales only.
Precision in results	Some imprecision.
Directness	Direct

Singh SP, Singh V

Meta-Analysis of the Efficacy of Adjunctive NMDA Receptor Modulators in Chronic Schizophrenia

CNS Drugs 2011; 25 (10): 859-885

View review abstract online

Comparison	**Adjunctive NMDA receptor modulators (ampakine CX516, D-alanine, D-cycloserine, D-serine, glycine, memantine, N-acetyl-cysteine, sarcosine) + antipsychotics vs. placebo + antipsychotics. Treatment duration range 4 - 28 weeks.**
Summary of evidence	**Moderate to high quality evidence (large overall samples, some inconsistency, precise, direct) shows small improvements in negative, positive and total symptoms with adjunctive NMDA modulators.** **For negative symptoms, D-serine, N-acetyl-cysteine, and D-alanine were most effective. For positive symptoms, NMDA receptor modulators with non-clozapine adjuncts were most effective. For total symptoms, D-serine, Glycine, N-acetyl-cysteine, Sarcosine, and D-alanine were most effective.**
Symptoms	
Negative symptoms	

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Significant small improvements in negative symptoms with adjunctive NMDA modulators;

32 RCTs, N = 1,413, SMD = -0.27, 95%CI -0.49 to -0.05, *p* = 0.01, Q_W = 97.70, *p* = 0.000

A similar effect size was found after omitting seven trials using adjunctive clozapine.

Significant, medium to large improvements in negative symptoms with;

D-serine: 5 RCTs, N = 203, SMD = -0.53, 95%CI -0.81 to -0.24, *p* = 0.00, Q_W = 7.97, *p* = 0.093

N-acetyl-cysteine: 1 RCT, N = 140, SMD = -0.45, 95%CI -0.79 to -0.12, *p* = 0.01, Q_W, *p* = NA

D-alanine: 1 RCT, N = 31, SMD = -0.81, 95%CI -1.54 to -0.07, *p* = 0.03, Q_W, *p* = NA

There were no significant effects for;

Sarcosine: 4 RCTs, N = 132, SMD = -0.32, 95%CI -0.66 to 0.03, *p* = 0.07, Q_W, *p* = not reported

Removing one clozapine trial gave a significant effect in favour of sarcosine (SMD = -0.39).

CX516: 2 RCTs, N = 123, SMD = 0.09, 95%CI -0.27 to 0.45, *p* = 0.63, Q_W, *p* = not reported

D-cycloserine: 10 RCTs, N = 360, SMD = 0.12, 95%CI -0.28 to 0.53, *p* = 0.55, Q_W, *p* = not reported

Glycine: 7 RCTs, N = 268, SMD = -0.39, 95%CI -0.90 to 0.11, *p* = 0.13, Q_W, *p* = not reported

Memantine: 2 RCTs, N = 156, SMD = -1.51, 95%CI -4.48 to 1.47, *p* = 0.32, Q_W, *p* = not reported

<u>Positive symptoms</u>

Trend effect of small improvements in positive symptoms with adjunctive NMDA modulators;

28 RCTs, N = 1,101, SMD = -0.10, 95%CI -0.22 to 0.02, *p* = 0.09, Q_W = 34.26, *p* = 0.159

The effect became significant after omitting seven trials using adjunctive clozapine.

Meta-regression found greater benefit in patients with higher baseline scores on positive symptoms, or those with a high ratio of negative to positive symptoms.

There were no significant effects for;

CX516: 2 RCTs, N = 123, SMD = 0.02, 95%CI -0.34 to 0.38, *p* = 0.91, Q_W, *p* = not reported

D-alanine: 1 RCT, N = 31, SMD = -0.54, 95%CI -1.26 to 0.18, *p* = 0.14

D-cycloserine: 8 RCTs, N = 215, SMD = 0.08, 95%CI -0.35 to 0.19, *p* = 0.55, Q_W, *p* = not reported

D-serine: 4 RCTs, N = 163, SMD = -0.16, 95%CI -0.47 to 0.15, *p* = 0.31, Q_W, *p* = not reported

Glycine: 7 RCTs, N = 181, SMD = -0.06, 95%CI -0.54 to 0.42, *p* = 0.80, Q_W, *p* = not reported

After omitting 3 trials using clozapine, this result became significant in favour of glycine (SMD = -0.54)

Memantine: 2 RCTs, N = 156, SMD = -0.06, 95%CI -0.37 to 0.26, *p* = 0.71, Q_W, *p* = not reported

N-acetyl-cysteine: 1 RCT, N = 140, SMD = -0.11, 95%CI -0.44 to 0.22, *p* = 0.51

Sarcosine: 3 RCTs, N = 92, SMD = -0.13, 95%CI -0.54 to 0.28, *p* = 0.52, Q_W, *p* = not reported

<u>Total symptoms</u>

Significant small to medium improvements in total symptoms with adjunctive NMDA modulators;

29 RCTs, N = 1,159, SMD = -0.40, 95%CI -0.60 to -0.19, p = 0.00, Q_W = 68.45, p = 0.000 A similar effect size was found after omitting seven trials using adjunctive clozapine. *Significant, medium-sized improvements in total symptoms with;* D-serine: 5 RCTs, N = 203, SMD = -0.40, 95%CI -0.68 to -0.12, p = 0.01, Q_W = 4.84, p = 0.304 Glycine: 6 RCTs, N = 159, SMD = -0.66, 95%CI -1.28 to -0.04, p = 0.04, Q_W = 18.16, p = 0.003 After omitting 2 trials using clozapine, the SMD increased to -1.12 N-acetyl-cysteine: 1 RCT, N = 140, SMD = -0.64, 95%CI -0.98 to -0.30, p = 0.00 Sarcosine: 4 RCTs, N = 132, SMD = -0.41, 95%CI -0.76 to -0.06, p = 0.02, Q_W = 2.56, p = 0.464 D-alanine: 1 RCT, N = 31, SMD = -0.79, 95%CI -1.52 to -0.05, p = 0.04 *There were no significant effects for;* CX516: 2 RCTs, N = 123, SMD = -0.53, 95%CI -1.96 to 0.91, p = 0.47, Q_W, p = not reported D-cycloserine: 8 RCTs, N = 215, SMD = -0.09, 95%CI -0.36 to 0.18, p = 0.52, Q_W, p = not reported Memantine: 2 RCTs, N = 156, SMD = -1.01, 95%CI -2.97 to 0.95, p = 0.31, Q_W, p = not reported	
Consistency in results	Consistent for overall effect on positive symptoms, inconsistent for overall effect on negative and total symptoms.
Precision in results	Precise for overall effects.
Directness of results	Direct

Tiihonen J, Wahlbeck K

Glutamatergic drugs for schizophrenia

Cochrane Database of Systematic Reviews 2006; Issue 2. Art. No.: CD003730. DOI: 10.1002/14651858.CD003730.pub2.

View review abstract online

Comparison 1	**D-cycloserine (10 – 100mg/day) + antipsychotic medication vs. placebo + antipsychotic medication. Treatment duration 4 to 16 weeks.**
Summary of evidence	**Moderate to low quality evidence (small samples, inconsistent or imprecise, direct) suggest no benefit of adjunctive D-cycloserine for study retention, global effects or mental state.**

Leaving the study early
No significant differences between groups; 6 RCTs, N = 134, RR = 2.73, 95%CI 0.94 to 7.96, *p* = 0.066, Q = 3.01, *p* = 0.39, I^2 =0%
Global effects
No significant differences between groups; Relapse rates: 2 RCTs, N = 73, RR = 2.40, 95%CI 0.37 to 15.40, *p* = 0.36, Q = 0.03, *p* = 0.85, I^2 = 0.0% Hospital admissions: 1 RCT N = 47, RR = 1.04 95%CI 0.07 to 15.72, *p* = 0.98 Average improvement score (CGI): 1 RCT, N = 26, MD = 0.31 95%CI -0.33 to 0.95, *p* = 0.34
Symptoms
<u>Overall symptoms</u> *No significant differences between groups in;* Endpoint BPRS/PANSS total: 4 RCTs, N = 73, SMD = 0.08, 95%CI -0.40 to 0.56, *p* = 0.75, Q = 8.66, *p* = 0.03, I^2 = 65% Worsening of BPRS/PANSS total: 4 RCTs, N = 70, RR = 1.35, 95%CI 0.68 to 2.68, *p* = 0.38, Q = 2.13, *p* = 0.55, I^2 = 0.0% General psychopathology PANSS: 3 RCTs, N = 51, MD = 0.72 95%CI -3.31 to 4.76, *p* = 0.72, Q = 6.82, *p* = 0.03, I^2 = 71% <50% improvement on BPRS/PANSS: 4 RCTs, N = 70, RR = 0.87, 95%CI 0.61 to 1.24, *p* = 0.45, Q = 0, *p* = 1.00, I^2 = 0.0% <20% improvement on BPRS/PANSS: 4 RCTs, N = 70, RR = 1.24, 95%CI 0.92 to 1.68, *p* = 0.16, Q = 2.31, *p* = 0.51, I^2 = 0.0% <20% improvement on PANSS general: 2 RCTs, N = 35, RR = 1.12, 95%CI 0.76 to 1.64, *p* = 0.57, Q = 0.02, *p* = 0.89, I^2 = 0.0% <u>Positive symptoms</u> *No significant differences between groups in;* Endpoint BPRS/PANSS: 4 RCTs, N = 73, SMD = 0.01 95%CI -0.46 to 0.48, *p* = 0.98, Q = 4.84, *p* = 0.18, I^2 = 38% <50% improvement on BPRS/PANSS: 4 RCTs, N = 70, RR = 0.77, 95%CI 0.35 to 1.70, *p* = 0.52, Q = 5.48, *p* = 0.02, I^2 = 82% <20% improvement on BPRS/PANSS: 4 RCTs, N = 70, RR = 0.88, 95%CI 0.65 to 1.19, *p* = 0.40, Q = 3.20, *p* = 0.36, I^2 = 6%

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Negative symptoms *No significant differences between groups in;* Endpoint SANS/PANSS total: 5 RCTs, N = 119, SMD = -0.11, 95%CI -0.48 to 0.25, *p* = 0.55, Q = 6.50, *p* = 0.16, I^2 = 38% <20% improvement on SANS/PANSS: 5 RCTs, N = 117, RR 0.78, 95%CI 0.60, 1.01, *p* = 0.057, Q = 4.39, *p* = 0.36, I^2 = 9%	
Risks	No differences were reported in vague somatic discomfort (RR = 3.13 [0.13 to 73.01], *p* = 0.48).
Consistency in results	Consistent apart from: general psychopathology PANSS score and < 50% improvement on BPRS/PANSS positive symptoms.
Precision in results	Imprecise apart from: endpoint BPRS/PANSS overall symptoms scores, endpoint BPRS/PANSS positive scores and all measures of negative symptoms.
Directness of results	Direct
Comparison 2	**Glycine or D-serine + antipsychotic medication vs. placebo + antipsychotic medication.**
Summary of evidence	**Moderate to high quality evidence (small samples, consistent, precise, direct) shows some benefit of adjunctive glycine or D-serine for overall and negative symptom severity.** **Moderate quality evidence (either inconsistent or imprecise) finds no benefit of adjunctive glycine for study retention, global effects or cognition.**
Leaving the study early	
No significant differences between groups; 9 RCTs, N = 181, RR = 1.13, 95%CI 0.50, 2.53, *p* = 0.77, Q = 3.02, *p* = 0.70, I^2 = 0.0%	
Global effects	
Significant differences, favouring glycine or D-serine in; D-serine: Average improvement score (CGI): 2 RCTs, N = 49, MD = -0.87, 95%CI -1.42 to -0.32, *p* = 0.0019, Q = 3.16, *p* = 0.08, I^2 = 68% Glycine: Average endpoint score (GAS): 2 RCTs, N = 35, MD = -3.87, 95%CI -7.69 to -0.05, *p* = 0.047, Q = 0.48, *p* = 0.49, I^2 = 0% *No significant differences between groups in;*	

Relapse rates: 1 RCT, N = 22, RR = 0.39, 95%CI 0.02 to 8.73, $p = 0.56$

Hospital admissions: 1 RCT, N = 28, RR = 2.63 95%CI 0.12 to 59.40, $p = 0.54$

Clinically significant improvement (GAS/CGI): 3 RCTs, N = 58, RR = 0.60, 95%CI 0.25 to 1.44, $p = 0.25$, Q = 0.0, $p = 1.00$, $I^2 = 0\%$

Symptoms

Overall symptoms

Significant differences, favouring glycine or D-serine in;

Glycine: Endpoint BPRS/PANSS total: 3 RCTs, N = 57, SMD = -0.62, 95%CI -1.18 to -0.06, $p = 0.029$, Q = 6.85, $p = 0.03$, $I^2 = 71\%$

Glycine or D-serine: General psychopathology PANSS: 6 RCTs, N = 120, MD = -3.25, 95%CI -5.88 to -0.62, $p = 0.016$, Q = 13.74, $p = 0.02$, $I^2 = 64\%$

Glycine: <20% improvement on BPRS/PANSS: 4 RCTs, N = 80, RR = 0.63, 95%CI 0.45 to 0.88, $p = 0.0069$, Q = 6.17, $p = 0.10$, $I^2 = 51\%$

Glycine: <20% improvement on PANSS general: 3 RCTs, N = 62, RR = 0.58, 95%CI 0.38 to 0.87, $p = 0.0089$, Q = 4.56, $p = 0.10$, $I^2 = 56\%$

No significant differences between groups in;

Glycine: Worsening of BPRS/PANSS total: 3 RCTs, N = 62, RR = 0.63, 95%CI 0.31 to 1.27, $p = 0.20$, Q = 2.48, $p = 0.29$, $I^2 = 19\%$

Glycine: <50% improvement on BPRS/PANSS: 4 RCTs, N = 80, RR = 0.92, 95%CI 0.79 to 1.08, $p = 0.30$, Q = 0.08, $p = 0.78$, $I^2 = 0\%$

Glycine: <50% improvement on PANSS general: 3 RCTs, N = 62, RR = 1.03, 95%CI 0.87 to 1.23, $p = 0.70$, Q = 2.42, $p = 0.30$, $I^2 = 17\%$

Negative symptoms

Significant differences, favouring glycine or D-serine in:

Glycine or D-serine: Endpoint PANSS total scores: 7 RCTs, N = 132, SMD = -0.66, 95%CI -1.02 to -0.29, $p = 0.00037$, Q = 10.03, $p = 0.12$, $I^2 = 40\%$

No significant differences between groups in;

Glycine: <50% improvement on SANS/PANSS: 3 RCTs, N = 62, RR = 0.87, 95%CI 0.74 to 1.03, $p = 0.11$, Q = 0.85, $p = 0.65$, $I^2 = 0\%$

Glycine: <20% improvement on SANS/PANSS: 3 RCTs, N = 62, RR = 0.70, 95%CI 0.29 to 1.71, $p = 0.44$, Q = 8.01, $p = 0.02$, $I^2 = 75\%$

Positive symptoms

No significant differences between groups in;

Glycine or D-serine: Endpoint BPRS/PANSS scores: 7 RCTs, N = 142, SMD = 0.03, 95%CI -0.30 to 0.37, $p = 0.85$, Q = 9.16, $p = 0.16$, $I^2 = 34\%$

Glycine: <50% improvement on BPRS/PANSS: 3 RCTs, N = 62, RR = 1.02, 95%CI 0.77 to 1.35, *p* = 0.88, Q = 1.00, *p* = 0.32, I^2 = 0% Glycine: <20% improvement on BPRS/PANSS: 3 RCTs, N = 62, RR = 0.81, 95%CI 0.49 to 1.34, *p* = 0.41, Q = 6.38, *p* = 0.04, I^2 = 69%	
Cognition	
No significant differences between groups in; Glycine: <20% clinically significant improvement: 2 RCTs, N = 34, RR = 0.72, 95%CI 0.41 to 1.27, *p* = 0.26, Q = 0.0, *p* = 1.00, I^2 = 0.0% Glycine or D-serine: Endpoint PANSS cognitive scores: 4 RCTs, N = 80, MD = -2.79, 95%CI -6.17 to 0.60, *p* = 0.11, Q = 11.76, *p* = 0.01, I^2 = 74%	
Risks	No differences were reported in constipation (RR 0.61, [0.06 to 6.02], *p* = 0.67), diarrhoea (RR 0.61, [0.06 to 6.02], *p* = 0.67), dyspepsia (RR 0.17, [0.01 to 3.06], *p* = 0.23), insomnia (RR 0.61, [0.13 to 2.84], *p* = 0.53), nausea (RR 1.69, [0.36 to 7.83], *p* = 0.50, I^2=0%), or lower extremity weakness (RR 3.00 [0.14 to 63.15], *p* = 0.48).
Consistency in results	Consistent, apart from overall symptoms, BPRS/PANSS total and PANSS general psychopathology, positive symptoms <20% improvement on BPRS/PANSS, PANSS cognitive scores.
Precision in results	Imprecise, apart from overall symptoms <50% improvement on BPRS/PANSS and PANSS general, <20% improvement on BPRS/PANSS, positive symptoms endpoint BPRS/PANSS scores, negative symptoms endpoint PANSS total scores, <50% improvement on BPRS/PANSS.
Directness of results	Direct
Comparison 3	**CX516 + antipsychotic medication vs. placebo + antipsychotic medication.**
Summary of evidence	**Low quality evidence (very small sample, imprecise) is unable to determine any benefit of adjunctive ampakine CX516 for study retention.**
Leaving the study early	
No significant differences between groups; 2 RCTs, N = 19, RR = 0.22, 95%CI 0.01 to 4.60, *p* = 0.33, Q = 0.0, *p* = 1.00, I^2 = 0.0%	

Risks	No differences in hypertension (RR 1.80 [0.10 to 31.52], $p = 0.69$) or suicidal thoughts (RR 2.00 [0.10 to 41.37], $p = 0.65$).
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Tsai GE, Lin P

Strategies to Enhance N-Methyl-D-Aspartate Receptor-Mediated Neurotransmission in Schizophrenia, a Critical Review and Meta-Analysis

Current Pharmaceutical Design 2010; 16: 522-537

View review abstract online

Comparison 1	**All glutamate receptor modulators + antipsychotic medication (varying doses) vs. placebo + antipsychotic medication (varying doses) in chronically stable patients with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly consistent, precise, direct) shows adjunctive glutamate receptor agonists were associated with small improvements in mental state when compared to adjunctive placebo. Lower quality evidence (inconsistent) suggests reduction in negative symptom severity following NMDA modulation.**

Symptoms

Significant, small to medium improvements for all mental state scales in patients receiving any adjunctive glutamate compared to adjunctive placebo;

Total psychopathology: 21 RCTs, N = 621, $r = 0.40$, 95% CI 0.22 to 0.58, $p < 0.0001$, Q = 24.32, $p = 0.23$, $I^2 = 17.8\%$

Negative symptoms: 26 RCTs, N = 886, $r = 0.38$, 95% CI 0.19 to 0.56, $p < 0.0001$, Q = 42.39, $p = 0.02$, $I^2 = 41\%$

Positive symptoms: 24 RCTs, N = 717, $r = 0.26$, 95% CI 0.11 to 0.41, $p = 0.006$, Q = 21.58, $p = 0.55$, $I^2 = 0\%$

Cognitive symptoms: 13 RCTs, N = 485, $r = 0.28$, 95% CI 0.10 to 0.47, $p = 0.002$, Q = 7.81, $p = 0.80$, $I^2 = 0\%$

Depressive symptoms: 13 RCTs, N = 416, *r* = 0.40, 95% CI 0.20 to 0.59, *p* < 0.0003, Q = 10.65, *p* = 0.58, I^2 = 0% General psychopathology: 16 RCTs, N = 452, *r* = 0.26, 95% CI 0.07 to 0.45, *p* = 0.006, Q = 13.31, *p* = 0.58, I^2 = 0%	
Risks	No differences in extrapyramidal symptoms (18 RCT, N = 582, *r* = 0.14, 95%CI -0.05 to 0.33, *p* = 0.16) or abnormal Involuntary movement (16 RCT, N = 549, r = 0.18, 95%CI = -0.03 to 0.38, *p* = 0.09).
Consistency in results	Consistent for all outcomes except negative symptoms.
Precision in results	Precise
Directness of results	Direct
Comparison 2	**Glycine + antipsychotic medication (varying doses) vs. placebo + antipsychotic medication (varying doses) in chronically stable patients with schizophrenia.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, unable to assess consistency, imprecise, direct) shows adjunctive glycine may give medium to large improvements in total psychopathology, negative, positive and depressive symptoms when compared to adjunctive placebo.**
Symptoms	
Significant, medium to large improvement for total psychopathology, negative, positive and depressive symptoms. No differences between groups in cognitive symptoms or general psychopathology; Total psychopathology: 4 studies, N = 95, *r* = 0.71, 95% CI 0.00 to 1.42, *p* = 0.05 Negative symptoms: 7 studies, N = 261, *r* = 0.52, 95% CI -0.02 to 1.05, *p* = 0.06 Positive symptoms: 6 studies, N = 145, *r* = 0.42, 95% CI 0.01 to 0.82, *p* = 0.04 Cognitive symptoms: 4 studies, N = 165, *r* = 0.25, 95% CI -0.08 to 0.58, *p* = 0.14 Depressive symptoms: 3 studies, N = 90, *r* = 0.59, 95% CI 0.16 to 1.01, *p* = 0.007 General psychopathology: 2 studies, N = 36, *r* = 0.51, 95% CI -0.25 to 1.26, *p* = 0.19 Q, *p*, I^2 = not reported	
Risks	No differences in extrapyramidal symptoms (4 RCT, N = 101, *r* = 0.23, 95%CI -0.16 to 0.63, *p* = 0.25) or abnormal Involuntary movement (3 RCT, N = 90, *r* = 0.14, 95%CI = -0.28 to 0.55, *p* = 0.52).

Consistency in results	Unable to assess
Precision in results	Imprecise
Directness of results	Direct
Comparison 3	**D-cycloserine + antipsychotic medication (varying doses) vs. placebo + antipsychotic medication (varying doses) in chronically stable patients with schizophrenia.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, unable to assess consistency, imprecise, direct) shows adjunctive D-cycloserine may not improve mental state when compared to adjunctive placebo.**
Symptoms	
No differences between groups in; Total psychopathology: 6 studies, N = 166, *r* = 0.12, 95% CI -0.18 to 0.43, *p* = 0.43 Negative symptoms: 8 studies, N = 317, *r* = 0.15, 95% CI -0.10 to 0.41, *p* = 0.24 Positive symptoms: 7 studies, N = 212, *r* = 0.14, 95% CI -0.13 to 0.41, *p* = 0.31 Depressive symptoms: 2 studies, N = 64, *r* = 0.41, 95% CI -0.09 to 0.90, *p* = 0.11 General psychopathology: 4 studies, N = 131, *r* = 0.03, 95% CI -0.36 to 0.43, *p* = 0.87 Q, *p*, I^2 = not reported	
Risks	No differences in extrapyramidal symptoms (4 RCT, N = 141, *r* = -0.18, 95%CI -0.51 to 0.15, *p* = 0.28) or abnormal Involuntary movement (3 RCT, N = 119, *r* = 0.18, 95%CI = -0.18 to 0.54, *p* = 0.34).
Consistency in results	Unable to assess
Precision in results	Imprecise
Directness of results	Direct
Comparison 4	**D-serine + antipsychotic medication (varying doses) vs. placebo + antipsychotic medication (varying doses) in chronically stable patients with schizophrenia.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, unable to assess consistency, imprecise, direct) shows adjunctive D-serine were associated with small to medium improvements in total psychopathology, negative,**

	cognitive and depressive symptoms when compared to adjunctive placebo.
Symptoms	
Significant, medium improvement in total psychopathology, negative, cognitive and depressive symptoms when compared to adjunctive placebo; Total psychopathology: 5 studies, N = 208, *r* = 0.40, 95% CI 0.07 to 0.73, *p* = 0.02 Negative symptoms: 5 studies, N = 208, *r* = 0.48, 95% CI 0.06 to 0.90, *p* = 0.02 Positive symptoms: 5 studies, N = 208, *r* = 0.21, 95% CI -0.20 to 0.61, *p* = 0.32 Cognitive symptoms: 4 studies, N = 168, *r* = 0.42, 95% CI 0.12 to 0.73, *p* = 0.007 Depressive symptoms: 4 studies, N = 168, *r* = 0.39, 95% CI -0.01 to 0.79, *p* = 0.06 General psychopathology: 4 studies, N = 133, *r* = 0.22, 95% CI -0.13 to 0.56, *p* = 0.22 Q *p*, I^2 = not reported	
Risks	No differences in extrapyramidal symptoms (5 RCT, N = 208, *r* = -0.31, 95%CI -0.15 to 0.78, *p* = 0.19) or abnormal involuntary movement (5 RCT, N = 187, *r* = 0.22, 95%CI = -0.33 to 0.78, *p* = 0.43)
Consistency in results	Unable to assess
Precision in results	Imprecise
Directness of results	Direct
Comparison 5	**Sarcosine + antipsychotic medication (varying doses) vs. placebo + antipsychotic medication (varying doses) in chronically stable patients with schizophrenia.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, unable to assess consistency, imprecise, direct) shows adjunctive sarcosine may give small to medium improvements in total and general psychopathology and negative symptoms when compared to adjunctive placebo.**
Symptoms	
Significant, medium improvement in total psychopathology, negative, and general psychopathology when compared to adjunctive placebo; Total psychopathology: 5 studies, N = 162, *r* = 0.43, 95% CI 0.11 to 0.74, *p* = 0.007 Negative symptoms: 5 studies, N = 162, *r* = 0.33, 95% CI 0.02 to 0.64, *p* = 0.04	

Positive symptoms: 5 studies, N = 162, *r* = 0.25, 95% CI -0.07 to 0.56, *p* = 0.12 Cognitive symptoms: 3 studies, N = 102, *r* = 0.29, 95% CI -0.10 to 0.69, *p* = 0.14 Depressive symptoms: 3 studies, N = 84, *r* = 0.31, 95% CI -0.17 to 0.79, *p* = 0.21 General psychopathology: 5 studies, N = 162, *r* = 0.49, 95% CI 0.18 to 0.81, *p* = 0.002 Q *p*, I^2 = not reported	
Risks	No differences in extrapyramidal symptoms (4 RCT, N = 142, *r* = -0.08, 95%CI -0.25 to 0.41, *p* = 0.63) or abnormal Involuntary movement (4 RCT, N = 121, *r* = -0.04, 95%CI = -0.14 to 0.51, *p* = 0.84).
Consistency in results	Unable to assess
Precision in results	Imprecise
Directness of results	Direct

Veerman SRT, Schulte PFJ, Begemann MJH, Engelsbel F, de Haan L

Clozapine Augmented with Glutamate Modulators in Refractory Schizophrenia: A Review and Meta-analysis

Pharmacopsychiatry 2014; 47: 185-194

View review abstract online

Comparison	**Clozapine plus glutamate modulators compared to clozapine and placebo for people with treatment-resistant schizophrenia.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, inconsistent or imprecise, direct) suggests augmenting clozapine with lamotrigine, topiramate or glycine provides no benefit over clozapine plus placebo.**
Symptoms	
There were no significant differences between clozapine plus lamotrigine and clozapine plus placebo; Overall symptoms: 6 RCTs, N = 185, *g* = 0.31, 95%CI -0.28 to 0.91, *p* = 0.29, I^2 = 75% Positive symptoms: 6 RCTs, N = 185, *g* = 0.31, 95%CI -0.02 to 0.65, *p* = 0.07, I^2 = 26% Negative symptoms: 6 RCTs, N = 185, *g* = 0.37, 95%CI -0.15 to 0.88, *p* = 0.16, I^2 = 68%	

Affective symptoms: 3 RCTs, N = 126, *g* = 0.07, 95%CI -0.39 to 0.53, *p* = 0.77, I^2 = 43% Authors report that after excluding 2 outliers, effect sizes for overall symptoms and negative symptoms increased to trend level and heterogeneity reduced to 0%. *There were no significant differences between clozapine plus topiramate and clozapine plus placebo;* Overall symptoms: 4 RCTs, N = 152, *g* = 0.75, 95%CI -0.06 to 1.56, *p* = 0.07, I^2 = 69% Positive symptoms: 4 RCTs, N = 152, *g* = 0.41, 95%CI -0.15 to 0.98, *p* = 0.15, I^2 = 65% Negative symptoms: 4 RCTs, N = 152, *g* = 0.40, 95%CI -0.39 to 1.19, *p* = 0.32, I^2 = 81% *Clozapine plus glycine showed a worsening of positive symptoms, with no significant differences in overall or negative symptoms;* Overall symptoms (PANSS/BPRS): 3 RCTs, N = 57, *g* = -0.16, 95%CI -0.62 to 0.30, *p* = 0.499, I^2 = 0% Positive symptoms: 3 RCTs, N = 57, *g* = -0.64, 95%CI -1.12 to -0.17, *p* = 0.008, I^2 = 0% Negative symptoms: 3 RCTs, N = 57, *g* = -0.07, 95%CI -0.53 to 0.39, *p* = 0.77, I^2 = 0%	
Consistency in results	Consistent for glycine only.
Precision in results	Precise for glycine overall and negative symptoms, and lamotrigine positive, negative and affective symptoms only.
Directness	Direct

Zheng W, Zhu XM, Zhang QE, Cai DB, Yang XH, Zhou YL, Ungvari GS, Ng CH, He SH, Peng XJ, Ning YP, Xiang YT

Adjunctive memantine for major mental disorders: A systematic review and meta-analysis of randomized double-blind controlled trials

Schizophrenia Research 2019; 209: 12-21

View review abstract online

Comparison	**Adjunctive memantine vs. placebo.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) finds medium-sized improvements in total and negative symptoms with adjunctive memantine, with no significant effects on positive symptoms or general psychopathology. Lower quality evidence (small sample, imprecise) suggests there may also be some improvement in**

	cognitive symptoms.
Total symptoms	
Significant, medium-sized effect of greater improvement in total symptoms with memantine; 7 RCTs, N = 395, SMD = -0.56, 95%CI -1.01 to -0.11, p = 0.01, I^2 = 76%, p = 0.0003 The effect was larger in: Patients on clozapine (-0.95) than other antipsychotics (-0.40) Longer studies (≥12 weeks, -0.75) than shorter studies (<12 weeks, -0.16) Lower quality studies (-0.94) than higher quality studies (-0.39) Younger (<39 years, -1.21) than older patients (≥39 years, -0.21) The effect was similar in subgroup analyses of Chinese vs. non-Chinese studies, in studies with more males than females, and in studies of inpatients or outpatients. Higher PANSS negative symptom scores at baseline were significantly associated with greater efficacy of adjunctive memantine for total psychopathology.	
Negative symptoms	
Significant, medium-sized effect of greater improvement in negative symptoms with memantine; 9 RCTs, N = 501, SMD = -0.71, 95%CI -1.09 to -0.33, p = 0.0003, I^2 = 74%, p = 0.0001 The effect was larger in: Patients on clozapine (-1.13) than other antipsychotics (-0.65) Longer studies (≥12 weeks, -0.85) than shorter studies (<12 weeks, -0.54) Lower quality studies (-1.02) than higher quality studies (-0.54) Younger (<39 years, -1.20) than older patients (≥39 years, -0.41) The effect was similar in subgroup analyses of Chinese vs. non-Chinese studies, in studies with more males than females, and in studies of inpatients or outpatients.	
Positive symptoms	
There was a trend effect for a small improvement in positive symptoms; 9 RCTs, N = 501, SMD = -0.32, 95%CI -0.64 to 0.00, p = 0.05, I^2 = 66%, p = 0.003 This effect was not significant after removal of one outlier. The effect was larger in: Non-Chinese (-0.38) than Chinese studies (0.11) Studies with no sex predominance (-0.41) than studies with male predominance (-0.22)	

Glutamate modulators

Lower quality studies (-0.45) than higher quality studies (-0.28) Younger (<39 years, -0.71) than older patients (≥39 years, 0.00) Inpatients (-0.42) than outpatients (-0.28) The effect was similar in subgroup analyses of clozapine vs. other antipsychotics, and longer vs. shorter studies. Higher PANSS negative symptom scores at baseline were significantly associated with greater efficacy of adjunctive memantine for positive symptoms.	
General psychopathology	
There were no significant differences in general psychopathology; 5 RCTs, N = 236, SMD = -0.27, 95%CI -0.64 to 0.09, $p = 0.14$, $I^2 = 49\%$, $p = 0.10$	
Cognitive symptoms	
A significant effect of greater improvement in cognition (MMSE) with adjunctive memantine; 3 RCTs, N = 93, SMD = 1.07, 95%CI 0.53 to 1.61, $p < 0.0001$, $I^2 = 29\%$, $p > 0.05$	
Risks	There were no significant differences in any adverse event (fatigue, dizziness, insomnia, headache, nausea, constipation, diarrhea, anxiety).
Consistency in results	Inconsistent, apart from cognitive symptoms and general psychopathology.
Precision in results	Precise, apart from cognitive symptoms.
Directness of results	Direct

Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale, CI = confidence interval, CGI = Clinical Global Impressions Scale, *d* = Cohen's d and *g* = Hedges' g = standardised mean differences, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MMSE = Mini-Mental State Examination, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = Positive and Negative Syndrome Scale, Q = Q statistic for the test of heterogeneity, Qw = test for within group differences (heterogeneity in study results within a group of studies – measure of study consistency), QB = test for between group differences (heterogeneity between groups of studies for an outcome of interest), SANS = Scale for the Assessment of Negative Symptoms, SMD = standardised mean difference, vs. = versus

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Glutamate modulators

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[13].

† 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 that 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[13].

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[14]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

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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[13];

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

§ 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[15].

‖ 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.

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