TECHNICAL COMMENTARY

Treatments for medication resistance

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Introduction

Antipsychotic medications provide symptom respite and improvement in quality of life for many people with schizophrenia. However, for a subset of people with schizophrenia, antipsychotic medications do not provide adequate relief from symptoms. Treatment-resistant schizophrenia has many definitions that vary depending on the individual study, but a broad definition includes those patients whose symptoms have not responded to antipsychotic medications, or only partially responded.

Here we summarise the evidence describing the efficacy of antipsychotic medications and other non-antipsychotic therapies for improving symptom severity in people with treatment-resistant schizophrenia.

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 are prioritised 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 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).

Results

We found 14 systematic reviews that met inclusion criteria[3-16].

- Moderate to high quality evidence suggests a general pattern of superiority for olanzapine, clozapine and risperidone over other antipsychotics (first or second generation), although effect sizes were small and there were few significant differences.

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Treatments for medication resistance

- Moderate to low quality evidence suggests a medium to large effect of treatment response in patients receiving clozapine or olanzapine compared to first-generation antipsychotics. There may also be fewer extrapyramidal side effects. Greater benefit of clozapine may be associated with more severe symptoms at baseline, shorter trial duration, and pharmaceutical industry sponsorship.
- Moderate quality evidence suggests augmenting clozapine with aripiprazole may provide some improvement in overall symptoms. Aripiprazole augmentation may result in less weight gain and lower LDL-cholesterol, but it may result in more akathisia, agitation and anxiety.
- Moderate to high quality evidence suggests no improvements in symptoms after augmenting clozapine with lamotrigine or topiramate. Moderate quality evidence also suggests no improvements with glycine, risperidone, or sulpiride. Low quality evidence is unclear as to any effects of augmenting olanzapine therapy with antipsychotic or non-antipsychotic treatments for treatment-resistant patients.

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Barbui C, Signoretti A, Mule S, Boso M, Cipriani A

Does the Addition of a Second Antipsychotic Drug Improve Clozapine Treatment?

Schizophrenia Bulletin 2009; 35(2): 458-468

View review abstract online

Comparison	**Clozapine plus amisulpride, chlorpromazine, pipothiazine, risperidone or sulpiride vs. clozapine alone for treatment-resistant schizophrenia.**
Summary of evidence	**Moderate quality evidence (precise, direct, inconsistent) suggests a small effect of improved symptoms with clozapine polypharmacy for treatment resistant schizophrenia, although this finding was not supported in double-blinded RCTs.**
Symptoms	
A small effect favoring clozapine combination therapy; 14 RCTs (open or blinded), N = 1064, SMD -0.80, 95%CI -1.14 to -0.46, I^2 85.1% *However, subgroup analysis of 6 double-blinded RCTs reported no difference between groups;* N = 227, SMD -0.12, 95%CI -0.57 to 0.32, I^2 63.1%	
Consistency in results‡	Inconsistent
Precision in results§	Precise
Directness of results‖	Direct

Chakos M, Lieberman J, Hoffman E, Bradford D, Sheitman B

Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomised trials

American J Psychiatry 2001; 158(4): 518-526

View review abstract online

Comparison	**Efficacy of second-generation antipsychotics vs. first-**

	generation antipsychotics for improving outcomes in people with chronic, treatment-resistant schizophrenia.
Summary of evidence	**Moderate to low quality evidence (unable to assess consistency or precision, moderate sample size, direct) suggests second-generation antipsychotics clozapine and olanzapine were associated with a medium to large decrease in symptom severity and less drop-out rates, and fewer extrapyramidal effects than first-generation antipsychotics.**
Clinical outcomes	
First vs. second generation antipsychotics 6 of 10 studies favoured second-generation antipsychotics over first-generation for efficacy in treating resistant patients, while four studies found no significant difference between groups. Clozapine vs. other 5 of 7 (N = 1124) studies favoured clozapine over first-generation antipsychotics for BPRS-total score reduction in treatment-resistant patients. This was statistically significant (F = 8.51, $p < 0.05$), SMD = 0.48. This effect was also largest in patients whose baseline scores were higher (F = 28.45, $p < 0.006$). There were no differences between groups on the BPRS-Positive subscale or SANS scores. 7 studies (N = 1124) compared clozapine with a first-generation antipsychotic and found clozapine patients were significantly less likely to drop-out early (OR = 1.49, $p = 0.003$). 5 studies (N = 1028) assessed categorical treatment response (response/non-response) in clozapine and first-generation antipsychotics and found clozapine patients were 2.45 times more likely to meet criteria for a favourable response ($p = 0.001$). 2 studies (N = 115) assessed categorical treatment response (response/non-response) in clozapine and risperidone and found no difference between groups. There were no differences between drop-out rates in clozapine and risperidone. Olanzapine vs. other 2 studies (N = 610) assessed categorical treatment response (response/non-response) in olanzapine and first-generation antipsychotics and found olanzapine patients were 1.71 times more likely to meet criteria for a favourable response ($p = 0.005$). 2 studies found olanzapine patients were significantly less likely than first-generation patients to drop-out early (OR = 1.81, $p = 0.001$).	
Risks	6 studies found that patients treated with clozapine or olanzapine had fewer extrapyramidal effects than those treated with first-generation antipsychotics ($p < 0.002$). 4 studies found no difference between first- and second-generation antipsychotics for tardive dyskinesia.

	1 of 2 studies favoured clozapine over risperidone extrapyramidal symptoms, 1 of 2 studies found no difference between groups.
Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct

Cipriani A, Boso M, Barbui C.

Clozapine combined with different antipsychotic drugs for treatment resistant schizophrenia

Cochrane Database of Systematic Reviews 2009; Issue 3. Art. No.: CD006324. DOI: 10.1002/14651858.CD006324.pub2

View review abstract online

Comparison	**Clozapine plus any antipsychotic vs. clozapine plus any other antipsychotic for treatment-resistant schizophrenia.**
Summary of evidence	**Low quality evidence (very small trials, imprecise) is unable to determine any benefits of clozapine polypharmacy for treatment resistant schizophrenia.**

Symptoms

Measured by clinical response or PANSS

Clozapine plus risperidone vs. clozapine plus sulpiride

A medium to large effect of higher clinical response rate with risperidone + clozapine;

1 RCT, N = 60, RR 2.33, 95%CI 1.29 to 4.23, *p* = 0.005

Better PANSS positive change scores with risperidone + clozapine;

1 RCT, N = 60, MD -2.55, 95%CI -4.64 to -0.46, *p* = 0.02

No differences on PANSS total, PANSS negative, or adverse effects.

Clozapine plus risperidone vs. clozapine plus ziprasidone

1 RCT, N = 23: no differences in clinical response, or PANSS positive

Clozapine plus amisulpride vs. clozapine plus quetiapine

1 RCT, N = 56: no differences in leaving the study early

Risks	The only differences were reported for clozapine plus risperidone vs. clozapine plus ziprasidone (N = 24) where patients on ziprasidone experienced a significant increase of QTc interval (from 387.7 to 403.2 ms, p = 0.043) while patients on risperidone showed a non-significant decrease of QTc interval (from 390.5 to 381.4 ms). The ziprasidone group experienced an improvement from 2.4 to 1.1 (p = 0.013) on extrapyramidal symptom scores while there was no improvement in the risperidone group.
Consistency in results	Not applicable (1 RCT).
Precision in results	Imprecise
Directness of results	Direct

Englisch S, Zink M

Combined antipsychotic treatment involving clozapine and aripiprazole.

Progress in Neuro-Psychopharmacology and Biological Psychiatry 2008; 32: 1386-1392

View review abstract online

Comparison	**Efficacy of second-generation antipsychotics clozapine and aripiprazole combined for improving outcomes in people with treatment-resistant schizophrenia.**
Summary of evidence	**Low quality evidence (unable to assess consistency or precision, direct) is unclear as to any benefits of augmenting clozapine with aripiprazole for improving treatment response.**
11 studies (N = 94) assessed the combined use of aripiprazole and clozapine for treatment-resistance. Augmentation of clozapine with aripiprazole allowed significant reduction of clozapine doses (p < 0.05). 50 of 94 patients (53.2%) experienced an improvement in positive symptoms of psychosis (inconsistently assessed by BPRS, PANSS, other scales). 37 of 94 patients (39.4%) showed improvement in negative symptom severity.	
Risks	53 of 94 patients, (56.4%) found reductions in severity of clozapine-induced side effects. 40 patients observed reduction in body weight. Single cases of nausea, vomiting, headache, insomnia, agitation and anxiety were reported.

Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct

Lerner V, Libov I, Kotler M, Strouss RD

Combination of "atypical" antipsychotic medication in the management of treatment-resistant schizophrenia and schizoaffective disorder

Progress in Neuro-Psychopharmacology and Biological Psychiatry 2004; 29: 89-98

View review abstract online

Comparison	**Efficacy of second-generation antipsychotics combination therapy for improving outcomes in people with treatment-resistant schizophrenia.**
Summary of evidence	**Low quality evidence (unable to assess consistency or precision, direct) is unclear as to any benefits of combining second generation antipsychotics for improving treatment response. Risperidone and sulpiride as adjunct to clozapine may have some benefit for a subset of patients.**

Overall

28 studies (19 case-reports, 8 open studies, 1 placebo-controlled trial, N = 200) assessed combinations of second-generation antipsychotics for treatment efficacy. The studies assessed combinations of clozapine, olanzapine, quetiapine, risperidone, sulpiride, and ziprasidone.

Of these trials, 171 patients (85.5%) found some benefit of combination therapy. Only 22 patients (11%) showed no improvement or worsening of mental state (7 patients have no mental state data).

Clozapine plus risperidone

Of 20 studies (N = 64), only 20 patients (31%) did not respond to the combination of clozapine and risperidone. 20 patients also reported experiencing varying side effects.

Clozapine plus sulpiride

One double-blind study found that 8 patients (50%) receiving clozapine-sulpiride had BPRS improvement compared to only 1 patient (8%) receiving placebo. These results were supported by a smaller open-label trial and a case-study. All patients recorded increases in serum prolactin. Two patients reported hypersalivation and tardive dyskinesia respectively.

Clozapine plus olanzapine

Two case-studies (N = 3) found up to 36% clinical improvement in BPRS scores. No side effects

were reported. Clozapine plus quetiapine An open-label study (N = 65) reported improved glycemic control and weight loss. The most commonly reported side effect was sedation. Clozapine plus ziprasidone An open-label study (N = 11) found that addition of ziprasidone allowed the reduction of clozapine doses and resulted in weight-loss, motivation, apathy and cognitive function. Risperidone plus olanzapine Three case-reports (N = 9) found improvements in symptom severity (BPRS). Risperidone plus quetiapine One case-study found QTc prolongation associated with quetiapine overdose in one patient. Olanzapine plus sulpiride One case-report (N = 6) found that 3 patients (50%) showed marked improvement, two patients had moderate improvement and one had minimal improvement in PANSS scores at 10 weeks.	
Risks	164 of 200 patients (82%) did not experience any side-effects of combination therapy. 36 patients (18%) experienced varying side effects.
Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct

Moncrieff J

Clozapine v. Conventional antipsychotic drugs for treatment-resistant schizophrenia: a re-examination

British Journal of Psychiatry 2003; 183: 161-66

View review abstract online

Comparison	**Efficacy of clozapine compared to other first-generation antipsychotics for improving outcomes in people with treatment-resistant schizophrenia.**
Summary of evidence	**Moderate quality evidence (inconsistent, precise, direct) suggests a small benefit of clozapine over other first-generation**

	antipsychotics for treatment resistant patients. Greater benefit of clozapine was associated with more severe symptoms at baseline, shorter trial duration, and pharmaceutical industry sponsorship.
9 studies (N unclear) found a small benefit of clozapine over typical antipsychotics for treatment response (BPRS scores); SMD = 0.44, 95%CI 0.15 to 0.73, $p < 0.05$, Q = 38.2, $p < 0.001$ Meta-regression analysis identified that shorter trials ($p < 0.01$), higher initial BPRS scores ($p = 0.02$), and financial sponsorship from pharmaceutical industry ($p = 0.003$) were all significant predictors of trial outcome, were all associated with better clozapine response as compared to other first-generation antipsychotics.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Porcelli S, Balzarro B, Seretti A

Clozapine resistance: augmentation strategies

Neuropsychopharmacology 2012; 22: 165-182

View review abstract online

Comparison	**Efficacy of augmented clozapine therapy for improving outcomes in people with treatment-resistant schizophrenia.**
Summary of evidence	**Moderate quality evidence (consistent, imprecise, direct) suggests no benefit of augmenting clozapine therapy with risperidone or lamotrigine (mood stabiliser) compared to augmentation with placebo. Low quality evidence (unable to assess consistency or precision, small samples) is unclear about any benefit of clozapine augmentation with other agents.**
Clozapine plus risperidone *No benefit of augmenting clozapine therapy with risperidone over placebo;* 5 RCTs, N = 225, OR = 1.05, 95%CI 0.55 to 2.01, $p = 0.89$, Q = 5.93, $p = 0.20$, $I^2 = 33\%$ 5 studies (N = 61) of risperidone (no placebo group) found mostly positive results for improvements in symptom severity.	

6 studies (N = 119) assessed the use of aripiprazole (no placebo group) augmentation and found improvements in symptom severity.

5 studies (N = 78) of amisulpride (no placebo group) augmentation also found benefits for improving symptom severity.

Clozapine plus mood stabilisers

No benefit of augmenting clozapine therapy with lamotrigine over placebo;

3 RCTs, N = 97, OR = 1.22, 95%CI 0.47 to 3.17, $p = 0.69$, Q = 1.27, $p = 0.53$, $I^2 = 0\%$

2 of 3 studies (N = 64) found no benefits of topiramate augmentation for improving symptom severity; 1 of 3 studies found positive results for topiramate.

2 of 3 studies (no placebo groups) (N = 111) reported benefits of lithium augmentation for improving symptom severity; 1 study found no benefit of lithium over placebo.

Clozapine plus antidepressants

2 studies (only one with placebo control) (N = 43) reported no additional benefits of augmenting clozapine with fluoxetine.

3 studies (no placebo groups) (N = 42) reported improvements in symptom severity following clozapine augmentation with fluvoxamine.

2 of 3 studies (one placebo controlled) (N = 35) found benefit of mirtazapine for symptom severity; 1 of 3 studies (plus placebo control) (N = 15) found no additional benefits of mirtazapine.

Clozapine plus other agents

2 of 4 RCTs (N = 46) comparing glycine augmentation with placebo found improvements in symptom severity; 2 of 4 RCTs (N = 31) found no benefits of glycine over placebo.

No benefits were reported for augmentation with other glutamate agonists including D-cycloserine (1 study, N = 11), N-methylglycine (1 study, N = 10), or D-serine (1 study, N = 20) compared to placebo.

1 of 2 studies (total N = 69) reported positive results for ampakine CX516 over placebo for improving symptom severity.

2 of 3 studies (N = 56) found greater benefit of clozapine augmentation with omega-3 fatty acid (ethyl-eicosapentaenoic acid) over placebo for improving symptom severity; 1 of 3 studies (N = 75) found no benefit.

1 study (N = 35) found no benefit of modafinil (stimulant) over placebo for improving symptom severity.

1 study (N = 39) found no benefit of mazindol (stimulant) over placebo for improving symptom severity.

1 study (N = 21) found some benefit of memantine (glutamate blocker) over placebo for improving symptom severity.

1 study (N = 16) found no benefit of donepezil (cholinesterase inhibitor) over placebo for improving symptom severity.

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Clozapine plus ECT 3 RCTs (N = 38) found benefits of clozapine augmented with ECT for improving symptom severity.	
Consistency in results	Consistent where applicable.
Precision in results	Imprecise
Directness of results	Direct

Samara MT, Dold M, Gianatsi M, Nikolakopoulou A, Helfer B, Salanti G, Leucht S

Efficacy, Acceptability, and Tolerability of Antipsychotics in Treatment-Resistant Schizophrenia. A Network Meta-analysis

JAMA Psychiatry 2016; 73(3): 199-210

View review abstract online

Comparison	**Antipsychotics vs. placebo for people with insufficient response to treatment.**
Summary of evidence	**Moderate to high quality evidence (consistent, precise, some indirectness, large sample) suggests a general pattern of superiority for olanzapine, clozapine and risperidone over other antipsychotics, with small effect sizes and few significant differences between antipsychotics in general.**

Overall symptoms

Measured by BPRS and PANSS

This review included 40 RCTs, N = 5172

Olanzapine was significantly more effective than;

Quetiapine: g = -0.29, 95%CI -0.56 to -0.02, $p < 0.05$

Haloperidol: g = -0.29, 95%CI -0.44 to 0.13, $p < 0.05$

Sertindole: g = -0.46, 95%CI -0.80 to -0.06, $p < 0.05$

Clozapine was significantly more effective than;

Haloperidol: g = -0.22, 95%CI -0.38 to -0.07, $p < 0.05$

Sertindole: g = -0.40, 95%CI -0.74 to -0.04, $p < 0.05$

Risperidone was significantly more effective than;

Sertindole: g = -0.32, 95%CI -0.63 to -0.01, $p < 0.05$

There were no other significant differences between aripiprazole, clozapine, chlorpromazine, fluphenazine, haloperidol, olanzapine, perphenazine, quetiapine, risperidone, sertindole, thiothixene, or ziprasidone.
Positive symptoms **Measured by BPRS and PANSS**
Risperidone was significantly more efficacious than quetiapine; SMD = -0.43, 95%CI -0.81 to -0.09, $p < 0.05$ *Clozapine was significantly more efficacious than quetiapine;* SMD = -0.40, 95%CI -0.75 to -0.09, $p < 0.05$ *Olanzapine was significantly more efficacious than quetiapine;* SMD = -0.33, 95%CI -0.67 to -0.01, $p < 0.05$ *Risperidone was significantly more efficacious than haloperidol;* SMD = -0.29, 95%CI -0.54 to -0.07, $p < 0.05$ *Clozapine was significantly more efficacious than haloperidol;* SMD = -0.27, 95%CI -0.46 to -0.09, $p < 0.05$
Negative symptoms **Measured by BPRS and PANSS**
Olanzapine was significantly more efficacious than clozapine; SMD = -0.14, 95%CI -0.30 to -0.01, $p < 0.05$ *Olanzapine was significantly more efficacious than risperidone;* SMD = -0.24, 95%CI -0.44 to -0.02, $p < 0.05$ *Olanzapine was significantly more efficacious than haloperidol;* SMD = -0.24, 95%CI -0.40 to -0.04, $p < 0.05$ *Olanzapine was significantly more efficacious than chlorpromazine;* SMD = -0.26, 95%CI -0.51 to -0.02, $p < 0.05$ *Olanzapine was significantly more efficacious than sertindole;* SMD = -0.44, 95%CI -0.81 to -0.08, $p < 0.05$ *Ziprasidone was significantly more efficacious than chlorpromazine;* SMD = -0.26, 95%CI -0.53 to -0.04, $p < 0.05$ *Ziprasidone was significantly more efficacious than sertindole;* SMD = -0.44, 95%CI -0.88 to -0.01, $p < 0.05$

Response to treatment	
Risperidone was significantly more effective than haloperidol; OR = 2.27, 95%CI 1.11 to 4.73, $p < 0.05$ *Clozapine was significantly more effective than haloperidol;* OR = 2.09, 95%CI 1.26 to 3.82, $p < 0.05$ *Olanzapine was significantly more effective than haloperidol;* OR = 2.00, 95%CI 1.16 to 3.76, $p < 0.05$	
All cause treatment discontinuation	
Olanzapine was significantly more effective than haloperidol; OR = 0.56, 95%CI 0.33 to 0.87, $p < 0.05$ *Olanzapine was significantly more effective than fluphenazine;* OR = 0.24, 95%CI 0.03 to 0.87, $p < 0.05$	
Risks	*Weight gain* Risperidone and haloperidol resulted in less weight gain than clozapine and olanzapine. Ziprasidone and quetiapine resulted in less weight gain than olanzapine. *Extrapyramidal side-effects* Clozapine resulted in less antiparkinson medication than risperidone and haloperidol. Ziprasidone, olanzapine and quetiapine resulted in less antiparkinson medication than haloperidol. Fluphenazine resulted in less antiparkinson medication than clozapine. *Sedation* Clozapine resulted in more sedation than ziprasidone, olanzapine quetiapine and risperidone.
Consistency in results	Consistent direct and indirect results after excluding 5 studies.
Precision in results	Precise
Directness	Network analysis; direct and indirect

Sommer IE, Begemann MJH, Temmerman A, Leucht S

Pharmacological Augmentation Strategies for Schizophrenia Patients With

Insufficient Response to Clozapine: A Quantitative Literature Review

Schizophrenia Bulletin 2012; 38(5): 1003-1011

View review abstract online

Comparison	**Clozapine plus antiepileptics, antidepressants, antipsychotics, or glutamatergics vs. placebo for people with insufficient response to clozapine.**
Summary of evidence	**Moderate to high quality evidence (consistent, precise, direct, small to medium size samples) suggests no improvements in symptoms after augmentation with antiepileptics lamotrigine or topiramate.** **Low quality evidence (small samples, imprecise or inconsistent, 1 RCT) is unable to determine any benefits of clozapine augmentation with antidepressants citalopram, fluoxetine, or mirtazapine.** **Moderate to high quality evidence (consistent, precise, direct, medium size samples) suggests no improvements in total or positive symptoms after aripiprazole augmentation. Moderate quality evidence (inconsistent) suggests no improvements with risperidone augmentation, and low quality evidence (small samples, imprecise, 1 RCT) is unable to determine any benefits of sulpiride, amisulpiride or haloperidol augmentation.** **Moderate quality evidence (consistent, precise, direct, small sample) suggests no improvements with glycine augmentation. Low quality evidence (small samples, imprecise, 1 RCT) is unable to determine any benefits of CX516, D-cycloserine, D-serine or sarcosine augmentation.**

Clozapine + antiepileptics

No consistent improvements with lamotrigine augmentation;

Total symptoms (PANSS/BPRS): 5 RCTs, N = 143, g = 0.53, 95%CI 0.03 to 1.04, $p < 0.05$, I^2 60%

Excluding 1 outlier: 4 RCTs, N = 92, g = 0.27, 95%CI -0.10 to 0.65, $p > 0.05$, I^2 0%

Positive symptoms: 5 RCTs, N = 143, g = 0.38, 95%CI -0.02 to 0.78, $p > 0.05$, I^2 39%

Excluding 1 outlier: 4 RCTs, N = 92, g = 0.15, 95%CI -0.22 to 0.52, $p > 0.05$, I^2 0%

Negative symptoms: 5 RCTs, N = 143, g = 0.41, 95%CI -0.13 to 0.94, $p > 0.05$, I^2 64%

Excluding 1 outlier: 4 RCTs, N = 92, g = 0.12, 95%CI -0.25 to 0.49, $p > 0.05$, I^2 0%

No consistent improvements with topiramate augmentation;

Total symptoms (PANSS/BPRS): 3 RCTs, N = 89, *g* = 0.75, 95%CI -0.05 to 1.56, *p* > 0.05, I^2 69%
Excluding 1 outlier: 2 RCTs, N = 57, *g* = 0.27, 95%CI -0.13 to 0.89, *p* > 0.05, I^2 0%
Positive symptoms: 3 RCTs, N = 89, *g* = 0.63, 95%CI 0.03 to 1.23, *p* < 0.05, I^2 47%
Excluding 1 outlier: 2 RCTs, N = 57, *g* = 0.39, 95%CI -0.24 to 1.01, *p* > 0.05, I^2 25%
Negative symptoms: 3 RCTs, N = 89, *g* = 0.66, 95%CI -0.17 to 1.50, *p* > 0.05, I^2 71%
Clozapine + antidepressants
Large effect of improved total and negative symptoms with citalopram augmentation;
Total symptoms (PANSS/BPRS): 1 RCT, N = 61, *g* = 0.81, 95%CI 0.30 to 1.33, *p* < 0.05
Positive symptoms: 1 RCT, N = 61, *g* = 0.28, 95%CI -0.22 to 0.79, *p* > 0.05
Negative symptoms: 1 RCT, N = 61, *g* = 0.81, 95%CI 0.30 to 1.33, *p* < 0.05
No significant improvements with fluoxetine augmentation;
Positive symptoms: 1 RCT, N = 33, *g* = 0.12, 95%CI -0.55 to 0.79, *p* > 0.05
Negative symptoms: 1 RCT, N = 33, *g* = 0.19, 95%CI -0.48 to 0.86, *p* > 0.05
No consistent improvements with mirtazapine augmentation;
Total symptoms (PANSS/BPRS): 2 RCTs, N = 35, *g* = 2.91, 95%CI -2.69 to 8.51, *p* > 0.05, I^2 96%
Positive symptoms: 2 RCTs, N = 35, *g* = 0.04, 95%CI -0.59 to 0.67, *p* > 0.05, I^2 0%
Negative symptoms: 2 RCTs, N = 35, *g* = 1.20, 95%CI -0.25 to 2.66, *p* > 0.05, I^2 76%
Clozapine + other antipsychotics
Significant, large improvements with sulpiride augmentation;
Total symptoms (PANSS/BPRS): 1 RCT, N = 28, *g* = 0.83, 95%CI 0.07 to 1.59, *p* < 0.05
Positive symptoms: 1 RCT, N = 28, *g* = 0.77, 95%CI 0.02 to 1.52, *p* < 0.05
Negative symptoms: 1 RCT, N = 28, *g* = 0.76, 95%CI 0.01 to 1.51, *p* < 0.05
No significant improvements with amisulpride augmentation;
Total symptoms (PANSS/BPRS): 1 RCT, N = 20, *g* = 0.13, 95%CI -0.48 to 0.74, *p* > 0.05
Positive symptoms: 1 RCT, N = 20, *g* = 0.11, 95%CI -0.50 to 0.72, *p* > 0.05
Negative symptoms: 1 RCT, N = 20, *g* = 0.21, 95%CI -0.40 to 0.82, *p* > 0.05
No significant improvements with aripiprazole augmentation;
Total symptoms (PANSS/BPRS): 2 RCTs, N = 268, *g* = 0.12, 95%CI -0.12 to 0.36, *p* > 0.05, I^2 0%
Positive symptoms: 2 RCTs, N = 268, *g* = 0.22, 95%CI -0.02 to 0.46, *p* > 0.05, I^2 0%
Negative symptoms: 2 RCTs, N = 268, *g* = 0.37, 95%CI -0.19 to 0.93, *p* > 0.05, I^2 74%

No consistent improvements with haloperidol augmentation; Total symptoms (PANSS/BPRS): 1 RCT, N = 6, *g* = -0.15, 95%CI -1.51 to 1.21, *p* > 0.05 Positive symptoms: 1 RCT, N = 6, *g* = 0.26, 95%CI -1.11 to 1.62, *p* > 0.05 Negative symptoms: 1 RCT, N = 6, *g* = -0.31, 95%CI -1.68 to 1.06, *p* > 0.05 *No consistent improvements with risperidone augmentation;* Total symptoms (PANSS/BPRS): 5 RCTs, N = 226, *g* = 0.18, 95%CI -0.21 to 0.57, *p* >0.05, I^2 53% Positive symptoms: 5 RCTs, N = 226, *g* = 0.09, 95%CI -0.24 to 0.74, *p* > 0.05, I^2 56% Negative symptoms: 5 RCTs, N = 226, *g* = 0.22, 95%CI -0.14 to 0.57, *p* > 0.05, I^2 43%	
Clozapine + glutamatergics	
Large effect of improved total and negative symptoms with CX516 augmentation; Total symptoms (PANSS/BPRS): 1 RCT, N = 18, *g* = 1.35, 95%CI 0.32 to 2.38, *p* < 0.05 Positive symptoms: 1 RCT, N = 18, *g* = 0.20, 95%CI -0.74 to 1.14, *p* > 0.05 Negative symptoms: 1 RCT, N = 18, *g* = 1.43, 95%CI 0.38 to 2.46, *p* < 0.05 *No significant improvements with D-cycloserine augmentation;* Negative symptoms: 1 RCT, N = 11, *g* = -0.76, 95%CI -1.59 to 0.08, *p* > 0.05 *No consistent improvements with D-serine augmentation;* Positive symptoms: 1 RCT, N = 20, *g* = 0.40, 95%CI -0.45 to 1.24, *p* > 0.05, Negative symptoms: 1 RCT, N = 20, *g* = 0.33, 95%CI -0.52 to 1.17, *p* > 0.05 *No consistent improvements with glycine augmentation;* Total symptoms (PANSS/BPRS): 3 RCTs, N = 68, *g* = -0.16, 95%CI -0.62 to 0.30, *p* > 0.05, I^2 0% Positive symptoms: 3 RCTs, N = 68, *g* = -0.36, 95%CI -1.19 to 0.46, *p* > 0.05, I^2 67% Negative symptoms: 3 RCTs, N = 68, *g* = -0.14, 95%CI -0.60 to 0.32, *p* > 0.05, I^2 0% *No consistent improvements with sarcosine augmentation;* Total symptoms (PANSS/BPRS): 1 RCT, N = 20, *g* = -0.21, 95%CI -1.06 to 0.63, *p* > 0.05 Positive symptoms: 1 RCT, N = 20, *g* = -0.07, 95%CI -0.91 to 0.77, *p* > 0.05 Negative symptoms: 1 RCT, N = 20, *g* = -0.07, 95%CI -0.91 to 0.77, *p* > 0.05	
Consistency in results	Consistent for all antiepileptic analyses without outliers, mirtazapine for positive symptoms, aripiprazole for total and positive symptoms, and glycine for total and negative symptoms.
Precision in results	Precise for all lamotrigine analyses without outliers, aripiprazole for total and positive symptoms, risperidone for total and negative symptoms, and glycine for total symptoms.

Directness	Direct

Srisurapanont M, Suttajit S, Maneeton N, Maneeton B

Efficacy and safety of aripiprazole augmentation of clozapine in schizophrenia: A systematic review and meta-analysis of randomized-controlled trials

Journal of Psychiatric Research 2015; 62: 38-47

View review abstract online

Comparison	**Clozapine plus aripiprazole compared to clozapine plus placebo in people with treatment-resistant schizophrenia.** **Treatment duration was 8 to 24 weeks.**
Summary of evidence	**Moderate quality evidence (inconsistent or imprecise, direct) suggests augmenting clozapine with aripiprazole may provide some improvement in overall symptoms. Aripiprazole augmentation may result in less weight gain and lower LDL-cholesterol but it may result in more akathisia, agitation and anxiety.**
No significant differences in study retention; 4 RCTs, N = 347, RR = 1.41, 95%CI 0.78 to 2.56, $p > 0.05$, $I^2 = 0\%$, $p = 0.78$ *No significant differences in symptoms, although there were trend level effects;* Overall symptoms: 3 RCTs, SMD = -0.40, 95%CI -0.87 to 0.07, $p = 0.09$, $I^2 = 68\%$, $p = 0.03$ Positive symptoms: 3 RCTs, SMD = -1.05, 95%CI -2.39 to 0.29, $p = 0.12$, $I^2 = 94\%$, $p < 0.001$ Negative symptoms: 3 RCTs, SMD = -0.36, 95%CI -0.77 to 0.05, $p = 0.08$, $I^2 = 54\%$, $p = 0.11$	
Risks	Aripiprazole augmentation resulted in less weight change (3 RCTs, mean difference = -1.36kg, 95%CI -2.35 to -0.36, $p = 0.008$, $I^2 = 39\%$, $p = 0.19$), and LDL-cholesterol (3 RCTs, mean difference = -11.06 mg/dL, 95%CI -18.25 to -3.87, $p = 0.003$, $I^2 = 31\%$, $p = 0.23$). However, aripiprazole augmentation resulted in more agitation or akathisia (3 RCTs, RR = 7.59, 95%CI 1.43 to 40.18, $p = 0.02$, $I^2 = 0\%$, $p = 0.95$) and anxiety (1 RCT, RR = 2.70, 95%CI 1.02 to 7.15, $p = 0.05$). There were no differences in fasting plasma glucose, triglycerides, high density lipoprotein, headache or insomnia.

Consistency in results	Consistent for all outcomes apart from overall and positive symptoms.
Precision in results	Imprecise for all outcomes apart from overall and negative symptoms.
Directness	Direct

Tiihonen J, Wahlbeck K, Kiviniemi V

The efficacy of lamotrigine in clozapine-resistant schizophrenia: A systematic review and meta-analysis

Schizophrenia Research 2009; 109(1-3): 10-14

View review abstract online

Comparison	**Anticonvulsant (lamotrigine, dose range 100-400mg/day) plus clozapine (dose unspecified) vs. placebo plus clozapine (dose unspecified) for clozapine-resistant schizophrenia. Treatment duration range 12-24 weeks.**
Summary of evidence	**Moderate quality evidence (consistent, imprecise, direct, small to medium size samples) suggests some benefit of lamotrigine for improving symptom severity in patients receiving clozapine.**

Mental state

Greater improvement in mental state in the lamotrigine group at the end of treatment;

PANSS or BPRS difference scores: 5 RCTs, N = 81, *d* = -0.57, 95%CI -0.89 to -0.25, *p* = 0.0006, Q = 6.35, *p* = 0.17, I^2 = 37%

Positive scales (PANSS, BPRS, SAPS): *d* = 0.34, 95%CI 0.02 to 0.65, *p* = 0.04

Negative scales (PANSS, BPRS, SANS): *d* = 0.43, 95%CI 0.11 to 0.76, *p* = 0.008

Lamotrigine was associated with a significantly higher treatment response rate than placebo;

OR = 0.19, 95%CI 0.09 to 0.43, *p* = 0.001 (NNT 4, CI 3-6)

Leaving the study early

There was no significant difference between groups for study attrition;

5 RCTs, N = 81, OR = 0.59, 95%CI 0.27 to 1.29

Risks	No differences in rates of severe adverse events; OR = 1.58, 95%CI 0.24 to 10.60, $p > 0.05$. There was also no significant difference in risk of rash; OR 1.75, 95%CI 0.39 to 7.94, $p > 0.05$.
Consistency in results	Consistent
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 (inconsistent or imprecise, direct) suggests augmenting clozapine with lamotrigine, topiramate or glycine provides no benefit over clozapine plus placebo.**

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

Wang J, Omori IM, Fenton M, Soares B

Sulpiride augmentation for schizophrenia

Cochrane Database of Systematic Reviews 2010; Issue 1: Art. No.: CD008125

View review abstract online

Comparison	**Efficacy of clozapine plus sulpiride compared to clozapine, with or without placebo, for people with treatment-resistant schizophrenia.** **Note: all participants had schizophrenia that was either treatment resistant or with prominent negative symptoms.**
Summary of evidence	**Moderate to low quality evidence (consistent, imprecise, direct, small samples) suggests augmenting clozapine therapy with sulpiride provides no benefit or risks compared to clozapine alone, with or without placebo.**
No significant difference for: Global state in the short term: N = 193, 3 RCTs, RR 0.58 CI 0.30 to 1.09, *p* = 0.09, Q = 1.23, *p* = 0.54, I^2 = 0% Global state in the long term: N = 70, 1 RCT, RR 0.67 CI 0.42 to 1.08, *p* = 0.099 Psychotic relapse: N = 70, 1 RCT, RR 0.85 CI 0.54 to 1.33, *p* = 0.47 Mental state (endpoint): N = 59, 1 RCT, MD -3.40 CI -6.84 to 0.04, *p* = 0.053	

Positive symptoms (endpoint): N = 28, 1 RCT, RR 0.68 CI 0.45 to 1.03, *p* = 0.071 *Significant improvement in patients receiving sulpiride augmentation for:* Negative symptoms (endpoint): N = 64, 1 RCT, MD -6.90 CI -10.87 to -2.93, *p* = 0.00066 Mental state (change, short term): N = 70, 1 RCT, MD -1.74 CI -3.01 to -0.47, *p* = 0.0071	
Risks	Augmentation of clozapine with sulpiride resulted in increased movement disorders; 1 RCT, N = 70, RR 48.24 CI 3.05 to 762.56, p < 0.05. Augmentation of clozapine with sulpiride resulted in reduced incidence of hypersalivation compared to clozapine alone; 3 RCTs, N = 162, RR 0.49 CI 0.29 to 0.83, I^2 = 43%, *p* = 0.17, and less weight gain; 1 RCT, N = 64, RR 0.30 CI 0.09 to 0.99, less appetite loss; 1 RCT, N = 70, RR 0.09 CI 0.01 to 0.70, NNT 4 CI 4 to 12, Z = 2.31, *p* = 0.02, and less abdominal distension; N = 70, 1 RCT, RR 0.10 CI 0.01 to 0.78, NNT 5 CI 4 to 19, Z = 2.20, *p* = 0.03.
Consistency in results	Consistent for global state in the short term and hypersalivation, not applicable for other outcomes (1 RCT only).
Precision in results	Imprecise
Directness	Direct

Zink M

Augmentation of olanzapine in treatment-resistant schizophrenia

Journal of Psychiatry and Neuroscience 2005; 30(6): 409-415

View review abstract online

Comparison	**Efficacy of clozapine compared to other first-generation antipsychotics for improving outcomes in people with treatment-resistant schizophrenia.**
Summary of evidence	**Low quality evidence (unable to assess consistency or precision, direct) is unclear as to any effects of augmenting olanzapine therapy with antipsychotic or non-antipsychotic treatments.**
14 studies (N = 83) assessed the use of olanzapine combined with another antipsychotic 1 RCT (N = 17) assessed olanzapine and sulpiride and found no benefit for improving psychotic symptoms, but found some improvement in symptoms of depression. 1 open-label trial (N = 6)	

reported improved BPRS symptom severity ratings. 3 case-reports (including one retrospective chart review), N = 39, reported no effects of haloperidol combined with olanzapine for mental state outcomes. 1 case-report (N = 1) reported no effects of fluphenazine plus olanzapine for mental state. 1 case-report (N = 1) reported 40% improvement in BPRS scores following pimozide plus olanzapine. 2 case-reports (N = 3) report improved symptom severity following clozapine plus olanzapine. 1 open-label trial and 1 case-report (N = 6) report improved symptom severity following risperidone plus olanzapine. 3 case reports (including one retrospective chart review), N = 9, report large improvements in symptom severity following amisulpride plus olanzapine. <u>8 studies assessed olanzapine combined with other agents</u> 1 open-label trial (N = 8) report improvements in negative symptoms following olanzapine plus fluvoxamine (antidepressant). 1 RCT (N = 26) found improvements in depression following olanzapine plus reboxetine (antidepressant). 1 RCT (N = 12) assessed olanzapine plus glycine and found improvements in both positive and negative symptoms. 1 open-label trial (N = 3) reported no benefit of lamotrigine (mood stabilizer) combined with olanzapine. 1 open-label trial (N = 3) reported no benefit of topiramate (mood stabilizer) combined with olanzapine. 2 RCT (N = 380) found some benefit of olanzapine plus divalproex (anticonvulsant) for mental state and hostility. 1 open-label trial (N = 10) and 1 retrospective case-report (N = 547) found olanzapine plus valproate (anticonvulsant) reduced hostility and increased treatment persistence.	
Risks	<u>Olanzapine plus other antipsychotics (mixed)</u> Two cases of neuroleptic malignant syndrome, one case of neutropenia, one case of priapism, one case of increased creatine kinase and one case of weight gain. <u>Olanzapine combined with other agents</u> 1 RCT (N = 12) of olanzapine plus glycine reported increased risk of upper gastrointestinal discomfort. 2 RCTs (N = 380) of olanzapine plus divalproex (anticonvulsant) reported some cases of abnormal liver function, asthma, hyperglycemia and rash.
Consistency in results	Unable to assess, no measure of consistency is reported.

Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct

Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale, CI = Confidence Interval, ECT = Electroconvulsive Therapy, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MD = mean difference effect size, N = number of participants, NMS = Neuroleptic Malignant Syndrome, OR = Odds ratio, *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, RCT = randomised controlled trial, RR = relative risk, SMD = standardised mean difference effect size, vs. = versus

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[17].

† 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[17].

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[18]. 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[17];

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

§ 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[19].

‖ 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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