TECHNICAL COMMENTARY

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Treatments for negative symptoms

Introduction

Negative symptoms are referring to an absence of normal functions. This may include (but is not limited to) blunted affect, which is a scarcity of facial expressions of emotion, reduced frequency and range of gestures and voice modulation, and restricted eye contact; alogia (poverty of speech); asociality (reduced social interaction); avolition (reduced motivation and often poor hygiene) and anhedonia, which is reduced experience of pleasure, often manifesting as scarcity of recreation, inability to experience closeness and reduced interest in any sexual activity.

Method

We have included only systematic reviews with detailed literature search, methodology, and inclusion/exclusion criteria that were published in full text, in English, from the year 2000. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Reviews with pooled data are prioritized for inclusion. Reviews reporting fewer than 50% of items on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA[1]) checklist have been excluded from the library. The evidence was graded guided by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach[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 16 systematic reviews that met inclusion criteria[3-18].

Antipsychotics

- Moderate to high quality evidence finds medium-sized effects of greater improvement in negative symptoms with clozapine, zotepine, amisulpride, olanzapine, perphenazine, and asenapine compared to placebo. There were small improvements over placebo with risperidone, paliperidone, sertindole, chlorpromazine, ziprasidone, aripiprazole, cariprazine, quetiapine, lurasidone, haloperidol, brexpiprazole, and iloperidone. There were no significant differences between placebo and flupentixol or zuclopenthixol.
- Moderate quality evidence finds a medium-sized benefit of improved negative symptoms with second-generation antipsychotics in general compared to placebo, but no effect of first-generation antipsychotics in general.
- Moderate to low quality evidence finds a medium-sized benefit of antipsychotics plus psychological interventions compared to antipsychotics alone for improving negative symptoms.
- Moderate quality evidence finds benefits for negative symptoms with cariprazine, olanzapine, or quetiapine over risperidone, and olanzapine over haloperidol.
- For people with first-episode psychosis, moderate quality evidence finds olanzapine and quetiapine may be more efficacious than haloperidol, and clozapine may be more efficacious than chlorpromazine for negative symptoms.
- For children and adolescents with schizophrenia, moderate to low quality evidence finds aripiprazole, asenapine, molindone, olanzapine and risperidone may all have small to medium-sized benefits over placebo for negative symptoms.

Antidepressants

- Moderate quality evidence finds a small benefit of greater improvement in negative symptoms with adjunctive antidepressants, particularly SNRIs and SSRIs. The effect size increased with increased baseline symptom severity.

Glutamatergic agents

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Treatments for negative symptoms

- Moderate quality evidence finds a small benefit of adjunctive glutamatergic agents over placebo for improving negative symptoms.

Other agents

- Moderate to high quality evidence finds adjunctive modafinil, armodafinil or minocycline may improve negative symptoms when compared to placebo.
- Moderate to high quality evidence finds a medium-sized improvement in negative symptoms with anti-dementia medications compared to placebo, particularly galantamine, rivastigmine and memantine.
- Moderate to low quality evidence finds there may also be benefits of other adjunctive agents including aspirin, atomoxetine, celecoxib, cerebrolysin, amotidine, folate, granisetron, insulin, latrepirdine, mazindol, mianserin, mirtazapine, methotrimeprazine, oxytocin, pramipexole, reboxetine, selegiline, sildenafil, sodium benzoate, tropisetron, viloxazine, and vitamin B12.

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Andrade C, Kisely S, Monteiro I, Rao S

Antipsychotic augmentation with modafinil or armodafinil for negative symptoms of schizophrenia: Systematic review and meta-analysis of randomized controlled trials

Journal of Psychiatric Research 2015; 60: 14-21

View review abstract online

Comparison	**Adjunctive modafinil (200 to 300mg/day) or armodafinil (150-200mg/day) vs. placebo.** **Treatment duration 6 – 24 weeks**
Summary of evidence	**Moderate to high quality evidence (medium-sized samples, consistent, precise, direct) suggests adjunctive modafinil or armodafinil may improve negative symptoms but not positive symptoms or attention, with no adverse effects when compared to placebo.**
Negative symptoms	
Small, significant improvement in negative symptoms with modafinil or armodafinil; Negative symptoms (PANSS-N): 6 RCTs, N = 322, SMD = -0.26, 95%CI -0.48 to -0.04, p = 0.02, I^2 = 7%, p = 0.37 Sensitivity analysis excluding an outlier study that included acutely ill patients resulted in non-significant results for negative symptoms (SMD = -0.17, 95%CI -0.51 to 0.06).	
Risks	*No significant differences between groups for;* Insomnia: 5 RCTs, N = 292, RR = 0.83, 95%CI 0.40 to 1.74, p > 0.05, I^2 = 0%, p = 0.60 Dizziness: 4 RCTs, N = 179, RR = 1.24, 95%CI 0.49 to 3.14, p > 0.05 Headache: 4 RCTs, N = 249, RR = 1.50, 95%CI 0.71 to 3.15, p > 0.05 Sexual dysfunction: 2 RCTs, N = 104, RR = 0.86, 95%CI 0.31 to 2.37, p > 0.05 Depression: 2 RCTs, N = 93, RR = 0.78, 95%CI 0.24 to 2.47, p > 0.05 Fatigue: 2 RCTs, N = 593, RR = 1.71, 95%CI 0.35 to 8.31, p > 0.05 Nausea: 2 RCTs, N = 185, RR = 1.82, 95%CI 0.77 to 4.28, p > 0.05
Consistency in results‡	Consistent where reported.

Precision in results[§]	Precise for SMDs, imprecise for RRs.
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 1	**First-generation antipsychotics vs. placebo.**
Summary of evidence	**Moderate quality evidence (unclear sample size, inconsistent, precise, direct) suggests no significant effect of first-generation antipsychotics over placebo for improving negative symptoms.**
Negative symptoms	
Non-significant trend effect of greater improvement in negative symptoms with first-generation antipsychotics; 10 studies, N not reported, SMD = -0.531, 95%CI -1.104 to 0.041, $p = 0.069$, $I^2 = 89.8\%$, $p < 0.001$ 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
Comparison 2	**Second-generation antipsychotics vs. placebo.**
Summary of evidence	**Moderate quality evidence (unclear sample size, inconsistent, precise, direct) suggests a medium-sized effect of second-generation antipsychotics over placebo for improving negative symptoms, but no clinically significant effect.**
Negative symptoms	

A significant, medium-sized effect of greater improvement in negative symptoms with second-generation antipsychotics; 38 studies, N not reported, SMD = -0.579, 95%CI -0.755 to -0.404, $p < 0.001$, $I^2 = 84.7\%$, $p < 0.001$ 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
Comparison 3	**Adjunctive antidepressants vs. placebo.**
Summary of evidence	**Moderate quality evidence (unclear sample size, inconsistent, precise, direct) suggests a small effect of adjunctive antidepressants over placebo for improving negative symptoms, although the effect may not be clinically significant.**
Negative symptoms	
A significant, small effect of greater improvement in negative symptoms with adjunctive antidepressants; 26 studies, N not reported, SMD = -0.349, 95%CI -0.551 to -0.146, $p < 0.001$, $I^2 = 56.3\%$, $p < 0.001$ 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
Comparison 4	**Adjunctive glutamatergic agents vs. placebo.**
Summary of evidence	**Moderate quality evidence (unclear sample size, inconsistent, precise, direct) suggests a small effect of adjunctive glutamatergic agents over placebo for improving negative symptoms, but no clinically significant effect.**
Negative symptoms	

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A significant, small effect of greater improvement in negative symptoms with glutamatergic agents; 26 studies, N not reported, 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
Comparison 5	**Any other adjunctive pharmacological agent (armodafinil, aspirin, atomoxetine, celecoxib, cerebrolysin, donepezil, amotidine, folate, galantamine, granisetron, insulin, latrepirdine, mazindol, methotrimeprazine, minocycline, modafinil, oxytocin, pramipexole, selegiline, sildenafil, sodium benzoate, tropisetron, or vitamin B12) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, inconsistent, precise, indirect) suggests a medium-sized, statistically significant effect of other adjunctive pharmaceutical agents over placebo for improving negative symptoms, but no clinically significant effect.**
Negative symptoms	
A significant, medium-sized effect of greater improvement in negative symptoms with other agents; 33 studies, N not reported, SMD = -0.518, 95%CI -0.757 to -0.279, p < 0.001, I^2 = 80.9%, 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	Indirect (mixed pharmacological agents combined)
Comparison 6	**Effectiveness of antipsychotics alone vs. antipsychotics plus any psychological treatment.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, inconsistent, precise, indirect) suggests a medium-sized, statistically significant effect of antipsychotics plus**

	psychological interventions over antipsychotics alone for improving negative symptoms, but no clinically significant effect.
Negative symptoms	
A significant, small effect of greater improvement in negative symptoms with adjunctive psychological interventions; 27 studies, N not reported, SMD = -0.396, 95%CI -0.563 to -0.229, $p < 0.001$, $I^2 = 57.6\%$, $p < 0.001$ 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	Indirect (psychological interventions combined)

Galling B, Vernon JA, Pagsberg AK, Wadhwa A, Grudnikoff E, Seidman AJ, Tsoy-Podosenin M, Poyurovsky M, Kane JM, Correll CU

Efficacy and safety of antidepressant augmentation of continued antipsychotic treatment in patients with schizophrenia

Acta Psychiatrica Scandinavica 2018; 137: 187-205

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Comparison	**Adjunctive antidepressants vs. placebo.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, precise, indirect) finds a small effect of greater improvement in negative symptoms with adjunctive antidepressants, particularly SNRIs and SSRIs.**
Negative symptoms	
A significant, small effect of improved negative symptoms with adjunctive antidepressants; 34 RCTs, N = 1,413, SMD = -0.28, 95%CI -0.47 to -0.09, $p = 0.003$, $I^2 = 65\%$, $p < 0.0001$ Subgroup analyses found only SNRIs and SSRIs antidepressant classes were significant for negative symptoms and the improvement in negative symptoms was with augmentation with first-	

generation antipsychotics but not second-generation antipsychotics. Meta-regression found lower risk of study bias was associated with larger effect sizes.	
Risks	There was more dry mouth with antidepressant augmentation.
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Indirect (mixed drug classes), direct for subgroup analyses of drug classes.

Hecht EM, Landy DC

Alpha-2 receptor antagonist add-on therapy in the treatment of schizophrenia; a meta-analysis

Schizophrenia Research 2012; 134: 202-206

View review abstract online

Comparison	**Mirtazapine (30 mg/day) or mianserin (15 or 30 mg/day) for 4-8 weeks plus antipsychotics vs. placebo plus antipsychotics.**
Summary of evidence	**Moderate to low quality evidence (medium-sized sample, inconsistent, imprecise, direct) suggests a benefit of mirtazapine or mianserin for improving negative symptoms compared to placebo.**
Negative symptoms	
Large effect of improved negative symptoms with alpha-2 antagonists; 8 RCTs, N = 244, d = 0.84, 95%CI 0.17 to 1.51, $p < 0.05$, Q = 37.4, $p < 0.01$	
Risks	Authors report that the combination treatment of antipsychotics and alpha-2 antagonists were well tolerated, with no serious adverse events reported.
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Helfer B, Samara MT, Huhn M, Klupp E, Leucht C, Zhu Y, Engel RR, Leucht S

Efficacy and safety of antidepressants added to antipsychotics for schizophrenia: A systematic review and meta-analysis

American Journal of Psychiatry 2016; 173: 876-86

View review abstract online

Comparison	**Antidepressants vs. placebo or no adjunctive treatment.**
Summary of evidence	**Moderate quality evidence (large samples, mostly inconsistent, precise, indirect) finds small effects of greater improvement in negative symptoms with adjunctive antidepressants. The effect size increased with increased baseline symptom severity.**
Negative symptoms	
A significant, small effect of improved negative symptoms with adjunctive antidepressants; 48 RCTs, N = 1,905, SMD = -0.30, 95%CI -0.44 to -0.16, $p < 0.0001$, $I^2 = 53\%$, $p < 0.0001$ Subgroup analyses found similar effect sizes for individual antidepressants or drug classes, although there were few studies in some of these subgroup analyses and not all analyses were significant. Meta-regressions showed the effect size for negative symptoms increased with increased baseline symptom severity.	
Risks	Antidepressants were associated with more abdominal pain, constipation, dizziness, and dry mouth.
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Indirect (mixed drug classes), direct for subgroup analyses of drug classes.

Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, Arndt T, Backers L, Rothe P, Cipriani A, Davis J, Salanti G, Leucht S

Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: A systematic review and network meta-analysis

Treatments for negative symptoms

The Lancet 2019; 394: 918 View review abstract online	
Comparison	**All antipsychotics vs. placebo for 3-13 weeks.** **Studies with a high risk of bias were excluded.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, precise, indirect) finds medium-sized effects of greater improvement in negative symptoms with clozapine, zotepine, amisulpride, olanzapine, perphenazine, and asenapine. There were small improvements with risperidone, paliperidone, sertindole, chlorpromazine, ziprasidone, aripiprazole, cariprazine, quetiapine, lurasidone, haloperidol, brexpiprazole, and iloperidone. There were no significant effects of flupentixol or zuclopenthixol.**
Negative symptoms	
Medium-sized effects of more improvement in symptoms with (in descending order of effect size); Clozapine: N = 6,772, SMD = -0.62, 95%CrI -0.84 to -0.39, $p < 0.05$ Zotepine: N = 6,762, SMD = -0.54, 95%CrI -0.77 to -0.31, $p < 0.05$ Amisulpride: N = 7,304, SMD = -0.50, 95%CrI -0.64 to -0.37, $p < 0.05$ Olanzapine: N = 10,837, SMD = -0.45, 95%CrI -0.51 to -0.39, $p < 0.05$ Perphenazine: N = 6,924, SMD = -0.42, 95%CrI -0.59 to -0.25, $p < 0.05$ Asenapine: N = 7,346, SMD = -0.42, 95%CrI -0.55 to -0.29, $p < 0.05$ *Small effects of more improvement in symptoms with (in descending order of effect size);* Risperidone: N = 10,048, SMD = -0.37, 95%CrI -0.43 to -0.31, $p < 0.05$ Paliperidone: N = 7,986, SMD = -0.37, 95%CrI -0.47 to -0.28, $p < 0.05$ Sertindole: N = 7,477, SMD = -0.37, 95%CrI -0.48 to -0.25, $p < 0.05$ Chlorpromazine: N = 7,033, SMD = -0.35, 95%CrI -0.51 to -0.18, $p < 0.05$ Ziprasidone: N = 7,572, SMD = -0.33, 95%CrI -0.43 to -0.23, $p < 0.05$ Aripiprazole: N = 7.966, SMD = -0.33, 95%CrI -0.41 to -0.24, $p < 0.05$ Cariprazine: N = 7,612, SMD = -0.32, 95%CrI -0.44 to -0.20, $p < 0.05$ Quetiapine: N = 9,607, SMD = -0.31, 95%CrI -0.38 to -0.24, $p < 0.05$ Lurasidone: N = 7,778, SMD = -0.29, 95%CrI -0.39 to -0.18, $p < 0.05$ Haloperidol: N = 9,944, SMD = -0.29, 95%CrI -0.35 to -0.29, $p < 0.05$ Brexpiprazole: N = 7,793, SMD = -0.25, 95%CrI -0.36 to -0.14, $p < 0.05$ Iloperidone: N = 7,531, SMD = -0.22, 95%CrI -0.33 to -0.11, $p < 0.05$	

There were no significant effects for flupentixol and zuclopenthixol.	
Risks	*The following antipsychotics were significantly associated with;* <u>More use of antiparkinson drugs</u> Small effects: paliperidone, ziprasidone, risperidone, and lurasidone Medium-sized effects: zotepine, cariprazine, chlorpromazine, sulpiride, perphenazine, molindone, zuclopenthixol, trifluoperazine, flupentixol, loxapine, penfluridol, haloperidol, fluphenazine, and chlorpromazine Large effects: thiotixene and pimozide. There was a large effect of less use of antiparkinson drugs with clozapine. <u>Akathisia</u> Small effects: aripiprazole Medium-sized effects: ziprasidone, thioridazine, asenapine, amisulpride, chlorpromazine, thiotixene, risperidone, cariprazine, loxapine, haloperidol, lurasidone, trifluoperazine, and sulpiride, Large effects: molindone, penfluridol, pimozide, fluphenazine, flupentixol, and zuclopenthixol <u>Weight gain</u> In order of increasing effect (measured in kg): haloperidol, amisulpride, asenapine, risperidone, paliperidone, clozapine, quetiapine, iloperidone, chlorpromazine, sertindole, olanzapine, and zotepine <u>Prolactin elevation</u> Less elevation with aripiprazole, clozapine, and zotepine More elevation with olanzapine, asenapine, lurasidone, sertindole, haloperidol, amisulpride, risperidone, and paliperidone <u>Sedation</u> Small effects: aripiprazole, lurasidone, and haloperidol Medium-sized effects: risperidone, thioridazine, asenapine, loxapine, olanzapine, thiotixene, ziprasidone, quetiapine, perazine, chlorpromazine, sulpiride, clopenthixol, and clozapine Large effects: zotepine and zuclopenthixol <u>QTc prolongation</u> Medium-sized effects: quetiapine, olanzapine, and risperidone Large effects: iloperidone, ziprasidone, amisulpride, and sertindole <u>Anticholinergic side-effects</u> Small effects: haloperidol and olanzapine Medium-sized effects: clozapine, iloperidone, chlorpromazine,

	zotepine, thioridazine, and quetiapine
Consistency in results	Authors state that overall heterogeneity was low to moderate.
Precision in results	Precise
Directness of results	Some indirectness; network meta-analysis.

Jin Y, Wang Q, Wang Y, Liu M, Su A, Geng Z, Lin Y, Li X

Alpha7 nAChR agonists for cognitive deficit and negative symptoms in schizophrenia: A meta-analysis of randomized double-blind controlled trials

Shanghai Archives of Psychiatry 2017; 29: 191-9

View review abstract online

Comparison	**Cholinergic enhancing drugs plus antipsychotic treatment vs. placebo plus antipsychotic treatment.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests no significant benefit of cholinergic medications for improving negative symptoms.**
Negative symptoms	
No significant differences between groups; 8 studies, N = 1,438, SMD = 0.13, 95%CI -0.04 to 0.30, p = 0.13, I^2 = 64%, p = 0.002 The samples in the meta-analysis were not always independent.	
Risks	There were no significant differences in adverse events.
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Kishi T, Ikuta T, Oya K, Matsunaga S, Matsuda Y, Iwata N

Anti-dementia drugs for psychopathology and cognitive impairment in

schizophrenia: A systematic review and meta-analysis **International Journal of Neuropsychopharmacology 2018; 21: 748-57** View review abstract online	
Comparison	**Adjunctive anti-dementia drugs (donepezil, galantamine, rivastigmine, and memantine) vs. adjunctive placebo.** **Note that memantine is a glutaminergic antagonist.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests a medium-sized improvement in negative symptoms with anti-dementia medications compared to placebo, particularly galantamine, rivastigmine and memantine. There were no differences in adverse events.**
Symptoms	
A significant, medium-sized improvement in negative symptoms with anti-dementia medications; Negative symptoms: 24 RCTs, N = 1,077, SMD = -0.62, 95%CI -0.92 to -0.32, p = 0.000045, I^2 = 80% Subgroup analysis of individual agents found only galantamine, rivastigmine, and memantine were significant for improving negative symptoms.	
Risks	There were no differences in adverse events.
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct for individual agents

Krause M, Zhu Y, Huhn M, Schneider-Thoma J, Bighelli I, Nikolakopoulou A, Leucht S

Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis **European Archives of Psychiatry and Clinical Neuroscience 2018; 268: 625-39** View review abstract online	
Comparison	**Antipsychotics vs. placebo or other antipsychotics.** **Authors determined predominant negative symptoms as those occurring in the presence of psychotic symptoms that are mild**

	and well controlled, while prominent negative symptoms are those occurring with any severity of psychotic symptoms.
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, consistent, some imprecision, direct) finds benefits for negative symptoms with amisulpride over placebo, cariprazine, olanzapine or quetiapine over risperidone, and olanzapine over haloperidol.**
Negative symptoms	
For people with predominant negative symptoms, the only significant benefits were for; Amisulpride over placebo: 4 RCTs, N = 590, SMD = 0.47, 95%CI 0.23 to 0.71, p = 0.0001, I^2 = 46%, p = 0.13 Cariprazine over risperidone: 1 RCT, N = 456, SMD = - 0.29, 95%CI - 0.48 to - 0.11, p = 0.002 Olanzapine over haloperidol: 1 RCT, N = 35, SMD = 0.75, 95%CI 0.06 to 1.44, p = 0.03 There were no significant differences between placebo and olanzapine or zotepine, or between olanzapine and amisulpride, asenapine, or haloperidol. *For people with prominent negative symptoms, the only significant benefits were for;* Olanzapine over risperidone: 1 RCT, N = 235, SMD = -0.30, 95%CI -0.56 to -0.04, p = 0.02 Quetiapine over risperidone: 1 RCT, N = 44, SMD = -1.34, 95%CI -2.00 to -0.68, p < 0.0001 There were no significant differences between placebo and sulpride, or between amisulpride and fluphenazine, haloperidol, or ziprasidone. There were also no differences between risperidone and flupenthixol, haloperidol and zotepine, or olanzapine and quetiapine, or haloperidol and clozapine. Amisulpride and zotepine were beneficial for depressive symptoms when compared to placebo.	
Risks	There was a disadvantage of the more dopaminergic compounds for parkinsonism symptoms; fluphenazine-treated patients received antiparkinson medication more frequently than those on amisulpride or risperidone; risperidone-treated patients more frequently than those on quetiapine; risperidone produced more extra-pyramidal symptoms than olanzapine.
Consistency in results	Consistent where applicable.
Precision in results	Precise, apart from olanzapine over haloperidol and quetiapine over risperidone.
Directness of results	Direct

Matthews PRL, Horder J, Pearce M

Selective noradrenaline reuptake inhibitors for schizophrenia

Cochrane Database of Systematic Reviews 2018; 1: CD010219

View review abstract online

Comparison	**Noradrenergic reuptake inhibitors (reboxetine, atomoxetine or viloxazine) plus antipsychotics vs. placebo plus antipsychotics.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, inconsistent, unable to assess precision, direct) suggests some benefit of noradrenergic reuptake inhibitors for negative symptoms in the medium-term (13-26 weeks).**
Negative symptoms	
Short-term (2-12 weeks) *No significant differences between groups;* PANSS negative: 6 RCTs, N = 359, MD = -0.99, 95%CI -2.53 to 0.56, p = 0.21, I^2 = 71%, p = 0.004 Medium-term (13-26 weeks) *A medium-sized effect of greater improvement in negative symptoms with noradrenergic medications;* PANSS negative: 3 RCTs, N = 219, MD = -3.25, 95%CI -4.04 to -2.47, p < 0.00001, I^2 = 0%, p = 0.78	
Risks	There were no differences in all-cause withdrawal or nausea.
Consistency in results	Inconsistent
Precision in results	Unable to assess MDs (not standardised).
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 quality evidence (medium-sized samples, inconsistent, imprecise, direct) suggests a small benefit of adjunctive minocycline for negative symptoms.**
Negative symptoms	
Small, significant effect of improved negative symptoms with adjunctive minocycline; PANSS negative: 4 RCTs, N = 267, SMD = -0.86, 95%CI -1.32 to -0.41, p = 0.0002, I^2 = 66%, p = 0.02	
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 RCTs, N = 189, SMD = -0.32, 95%CI -0.64 to -0.01, p = 0.04, I^2 = 0%).
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Pagsberg AK, Tarp S, Glintborg D, Stenstrom AD, Fink-Jensen A, Correll CU, Christensen R

Acute Antipsychotic Treatment of Children and Adolescents With Schizophrenia-Spectrum Disorders: A Systematic Review and Network Meta-Analysis

Journal of the American Academy of Child and Adolescent Psychiatry 2017; 56(3): 191-202

View review abstract online

Comparison 1	**Antipsychotics vs. placebo in children and adolescents (8 to 19 years) with schizophrenia spectrum disorders.**
Summary of evidence	**Moderate to low quality evidence (unclear sample sizes, unable to assess consistency, precise, indirect) suggests aripiprazole, asenapine, molindone, olanzapine and risperidone may all have small to medium-sized benefits over placebo for the treatment of negative symptoms in children and adolescents with schizophrenia. Only quetiapine is more effective than placebo**

	for depression. **There was more weight gain with all antipsychotics apart from ziprasidone, with olanzapine and quetiapine resulting in the most weight gain. There were more extrapyramidal side effects with paliperidione, ziprasidone, risperidone, and aripiprazole. Olanzapine and quetiapine resulted in increases in triglycerides. There was decreased prolactin with aripiprazole, increased prolactin with risperidone, olanzapine and paliperidione.**
Negative symptoms	
Significant, small to medium-sized effects of improved negative symptoms with the following antipsychotics compared to placebo (all are indirect comparisons); Aripiprazole: unclear sample size, SMD = -0.27, 95%CI -0.52 to -0.02, $p < 0.05$ Asenapine: unclear sample size, SMD = -0.32, 95%CI -0.63 to 0.00, $p = 0.05$ Molindone: unclear sample size, SMD = -0.58, 95%CI -1.06 to -0.09, $p < 0.05$ Olanzapine: unclear sample size, SMD = -0.45, 95%CI -0.77 to -0.12, $p < 0.05$ Risperidone: unclear sample size, SMD = -0.35, 95%CI -0.55 to -0.15, $p < 0.05$ *No differences with placebo were found in indirect comparisons for;* Paliperidone: unclear sample size, SMD = -0.25, 95%CI -0.53 to 0.02, $p > 0.05$ Quetiapine: unclear sample size, SMD = -0.26, 95%CI -0.59 to 0.08, $p > 0.05$ Ziprasidone: unclear sample size, SMD = 0.08, 95%CI -0.24 to 0.40, $p > 0.05$	
Depression symptoms	
Only quetiapine improved depression symptoms, with a small to medium-sized effect (indirect comparison); Quetiapine: unclear sample size, SMD = -0.37, 95%CI -0.71 to -0.04, $p < 0.05$	
Risks	**Weight gain** Large effects were found in direct comparisons with placebo for olanzapine (SMD = 1.32, 95%CI 0.88 to 1.77) and quetiapine (SMD = 0.80, 95%CI 0.51 to 1.09); medium-sized effects were found for paliperidione (SMD = 0.57, 95%CI 0.23 to 0.92), asenapine (SMD = 0.44, 95%CI 0.20 to 0.69), risperidone (SMD = 0.43, 95%CI 0.23 to 0.62), and aripiprazole (SMD = 0.38, 95%CI 0.14 to 0.63), and no effect was found for ziprasidone (SMD = -0.04, 95%CI -0.36 to 0.28). **Extrapyramidal** Large effects were found in direct comparisons with placebo for paliperidione (OR = 29.33, 95%CI 1.74 to 495.11), ziprasidone (OR = 11.45, 95%CI 1.52 to 86.34), risperidone (OR = 4.32, 95%CI 2.31 to

	8.06), and aripiprazole (OR = 3.98, 95%CI 1.51 to 10.51), and no effects were found for quetiapine (OR = 2.63, 95%CI 0.86 to 8.05), asenapine (OR = 2.09, 95%CI 0.68 to 6.41), or olanzapine (OR = 0.72, 95%CI 0.11 to 4.50). For akathasia in particular, no effects were found between any antipsychotic and placebo, apart from risperidone which showed a large effect of more frequent akathasia (OR = 5.64, 95%CI 1.45 to 21.96). Note: indirect network meta-analyses showed more akathisia with aripiprazole, olanzapine, and paliperidone than with placebo. **Triglycerides** No effects were found between any antipsychotic and placebo in direct comparisons, apart from olanzapine (SMD = 0.54, 95%CI 0.05 to 1.02) and quetiapine (SMD = 0.36, 95%CI 0.05 to 0.66), which showed medium-sized effects of greater increase in triglycerides. **Sedation** Large effects were found in indirect comparisons with placebo for olanzapine (OR = 6.77, 95%CI 1.86 to 24.60), paliperidione (OR = 4.91, 95%CI 1.42 to 16.99), risperidone (OR = 6.85, 95%CI 2.00 to 23.50), aripiprazole (OR = 2.96, 95%CI 1.05 to 8.34), and molindone (OR = 10.88, 95%CI 2.36 to 50.17). No effect was found for quetiapine or ziprasidone. **Prolactin** A small effect of decreased prolactin in an indirect comparison with placebo vs. aripiprazole (SMD = -0.30, 95%CI -0.59 to -0.01). Medium-sized effects of increased prolactin with olanzapine (SMD = 0.49, 95%CI 0.09 to 0.87) and paliperidione (SMD = 0.70, 95%CI 0.36 to 1.03), and large effects of increased prolactin with risperidone (SMD = 1.19, 95%CI 0.92 to 1.45. No effect was found for quetiapine, ziprasidone, molindone or asenapine.
Consistency in results	Not able to be assessed for indirect comparisons (no consistency measure is reported).
Precision in results	Precise for SMDs, imprecise for ORs.
Directness of results	Direct for weight gain, extrapyramidal side effects and triglycerides, indirect for negative symptoms, sedation and prolactin levels.
Comparison 2	**Antipsychotics vs. antipsychotics in children and adolescents (8 to 19 years) with schizophrenia spectrum disorders.**
Summary of evidence	**Low quality evidence (unclear sample sizes, unable to assess consistency, mostly imprecise and indirect) is unable to determine the benefits or harms of particular antipsychotics.**

Negative symptoms	
There were no significant differences in comparisons between individual antipsychotics, apart from the following indirect comparisons with medium-sized effects; Molindone over ziprasidone: unclear sample size, SMD -0.66, 95%CI -1.24 to -0.07, $p < 0.05$ Olanzapine over ziprasidone: unclear sample size, SMD -0.53, 95%CI -0.99 to -0.07, $p < 0.05$ Risperidone over ziprasidone: unclear sample size, SMD -0.44, 95%CI -0.82 to -0.06, $p < 0.05$	
Risks	**Weight gain** *The following comparisons were significant for less weight gain;* Molindone over olanzapine (direct SMD = -1.77 [large effect], 95%CI -2.31 to -1.23), quetiapine (indirect SMD = -1.23 [large effect], 95%CI -1.79 to -0.68), paliperidone (indirect SMD = -1.07 [large effect], 95%CI -1.61 to -0.53), risperidone (direct SMD = -0.93 [large effect], 95%CI -1.24 to -0.47), asenapine (indirect SMD = 0.83 [large effect], 95%CI 0.29 to 1.36), and aripiprazole (indirect SMD = 0.65 [medium-sized effect], 95%CI 0.13 to 1.17). Ziprasidone over olanzapine (indirect SMD = 1.25 [large effect], 95%CI 0.77 to 1.74), quetiapine (indirect SMD = 0.89 [large effect], 95%CI 0.46 to 1.32), paliperidone (indirect SMD = 0.73 [medium-large effect], 95%CI 0.33 to 1.14), asenapine (indirect SMD = 0.49 [medium-sized effect], 95%CI 0.09 to 0.89), and risperidone (indirect SMD = 0.46 [medium-sized effect], 95%CI 0.08 to 0.83). Risperidone over olanzapine (direct SMD = 0.60 [medium-sized effect], 95%CI 0.19 to 1.01), and quetiapine (indirect SMD = 0.44 [medium-sized effect], 95%CI 0.08 to 0.79). Aripiprazole over olanzapine (indirect SMD = -0.94 [large effect], 95%CI -1.37 to -0.52), quetiapine (indirect SMD = -0.58 [medium-sized effect], 95%CI -0.94 to -0.22), and paliperidone (direct SMD = -0.50 [medium-sized effect], 95%CI -0.76 to -0.23). Asenapine over olanzapine (indirect SMD = -0.77 [medium-large effect], 95%CI -1.21 to -0.32), and quetiapine (indirect SMD = -0.40 [medium-sized effect], 95%CI -0.78 to -0.03). Paliperidone over olanzapine (indirect SMD = 0.52 [medium-sized effect], 95%CI 0.07 to 0.97). **Extrapyramidal** *The following comparisons were significant for fewer extrapyramidal side effects;* Olanzapine over molindone (direct; all extrapyramidal OR = 4.91, [large effect], 95%CI 1.58 to 15.25). Risperidone over molindone (direct; akathisia OR = 6.84, [large

	effect], 95%CI 2.04 to 22.86). Asenapine over molindone (indirect all extrapyramidal OR = 0.18, [large effect], 95%CI 0.03 to 0.97). Aripiprazole over molindone (indirect; akathisia OR = 0.13, [large effect], 95%CI 0.03 to 0.60). **Triglycerides** *No significant differences between any antipsychotic.* **Prolactin** *The following comparisons were significant for lower prolactin levels;* Aripiprazole over olanzapine (indirect SMD = -0.78, [large effect], 95%CI -1.27 to -0.29). Aripiprazole over paliperidone (indirect SMD = -1.00, [large effect], 95%CI -1.32 to -0.68). Aripiprazole over risperidone (indirect SMD = -1.49, [large effect], 95%CI -1.88 to -1.09). Molindone over risperidone (indirect SMD = -1.11, [large effect], 95%CI -1.62 to -1.61). Olanzapine over risperidone (indirect SMD = -0.71, [medium-large effect], 95%CI -1.11 to -0.31). Paliperidone over risperidone (indirect SMD = -0.49, [medium-sized effect], 95%CI -0.92 to -0.06). Quetiapine over paliperidone (indirect SMD = -0.53, [medium-sized effect], 95%CI -0.01 to -1.05). Quetiapine over risperidone (indirect SMD = -1.02, [large effect], 95%CI -1.50 to -0.54).
Consistency in results	No consistency measure is reported.
Precision in results	Mostly imprecise
Directness of results	Mostly indirect

Sabe M, Kirschner M, Kaiser S

Prodopaminergic drugs for treating the negative symptoms of schizophrenia: Systematic review and meta-analysis of randomized controlled trials

Journal of Clinical Psychopharmacology 2019; 39: 658-64

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Comparison	**Adjunctive prodopaminergic drugs (mean 11 weeks of modafinil, armodafinil, L-dopa, and pramipexole) vs. placebo.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, consistent, precise, direct) finds no effect of adjunctive prodopaminergic drugs over placebo in general, although there was a small improvement in negative symptoms with adjunctive modafinil.**
Negative symptoms	
There were no differences between groups; 10 RCTs, N = 450, SMD = -0.17, 95%CI -0.36 to 0.01, p = 0.07, I^2 = 0% *Subgroup analysis found a small, significant effect of modafinil for improving negative symptoms;* 6 RCTs, N = 176, SMD = -0.32, 95%CI -0.62 to -0.02, p = 0.04, I^2 = 0%	
Risks	There were no differences in adverse events.
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Solmi M, Veronese N, Thapa N, Facchini S, Stubbs B, Fornaro M, Carvalho AF, Correll CU

Systematic review and meta-analysis of the efficacy and safety of minocycline in schizophrenia

CNS Spectrums 2017; 22: 415-26

View review abstract online

Comparison	**Adjunctive minocycline vs. placebo.**
Summary of evidence	**Moderate to high quality evidence (medium-sized samples, some inconsistency, precise, direct) finds a medium-sized effect of greater improvement in negative symptoms with adjunctive minocycline over placebo.**
Negative symptoms	

Significant, a medium-sized effect of greater improvement in negative symptoms with adjunctive minocycline; Negative PANSS scores: 5 RCTs, N = 300, SMD = -0.76, 95%CI -1.21 to -0.31, p = 0.001, I^2 = 69% Negative SANS scores: 4 RCTs, N = 216, SMD = -0.60, 95%CI -0.94 to -0.27, p < 0.001, I^2 = 29%

Risks	There were no differences in discontinuation due intolerability.
Consistency in results	Inconsistent for PANSS negative.
Precision in results	Precise
Directness of results	Direct

Xiang YQ, Zheng W, Wang SB, Yang XH, Cai DB, Ng CH, Ungvari GS, Kelly DL, Xu WY, Xiang YT

Adjunctive minocycline for schizophrenia: A meta-analysis of randomized controlled trials

European Neuropsychopharmacology 2017; 27: 8-18

View review abstract online

Comparison	**Adjunctive minocycline (mean 171.9mg/day for 18.5 weeks) vs. placebo.**
Summary of evidence	**Moderate to high quality evidence (medium to large sample, inconsistent, precise, direct) finds a medium-sized effect of greater improvement in negative symptoms with adjunctive minocycline over placebo.**
Symptoms	
Significant, medium-sized effect of greater improvement in negative symptoms with adjunctive minocycline; Negative PANSS/SANS scores: 8 RCTs, N = 476, SMD = -0.69, 95%CI -0.98 to -0.40, p < 0.00001, I^2 = 56%, p = 0.02	
Risks	There were no differences in movement or extrapyramidal symptoms.
Consistency in results	Inconsistent
Precision in results	Precise

Directness of results	Direct

Zhang J, Gallego JA, Robinson DG, Malhotra AK, Kane JM, Correll CU

Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis

International Journal of Neuropsychopharmacology 2013; 16: 1205-1218

View review abstract online

Comparison	**First generation vs. second-generation antipsychotics for people with first-episode psychosis.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, precise, indirect) suggests olanzapine and quetiapine may be more efficacious than haloperidol, and clozapine may be more efficacious than chlorpromazine. There may be less extrapyramidal side effects and akathisia with olanzapine and risperidone compared to haloperidol, although olanzapine and risperidone may cause more weight gain.** **Moderate to high quality evidence suggests less use of benzodiazapines with olanzapine compared to haloperidol, and moderate quality evidence also suggests less use of anticholinergeric medications and beta-blockers with olanzapine, although cholesterol change is higher than haloperidol. For tryglyceride change, amisulpride resulted in greater change than haloperidol.**
Negative symptoms	
A very small effect of improved negatives symptoms for second-generation antipsychotics; 11 RCTs, N = 1932, *g* 0.16, 95%CI 0.04 to 0.28, $p < 0.01$ Individually, only olanzapine (4 RCTs, N = 653, *g* 0.30, 95%CI 0.15 to 0.46, $p < 0.001$) and quetiapine (1 RCT, N = 207, *g* 0.32, 95%CI 0.05 to 0.59, $p < 0.05$) were superior to haloperidol and clozapine was superior to chlorpromazine (1 RCT, N = 160, *g* 0.41, 95%CI 0.10 to 0.72, $p < 0.01$). Only industry-sponsored studies significantly favouring second generation antipsychotics ($p = 0.001$), while independently funded or government funded studies did not, although between groups analysis (Q_B) was not significant.	
Risks	Overall, second generation antipsychotics resulted in less extrapyramidal side effects (9 RCTs, N = 1338, *g* -0.43, 95%CI -0.64

	to -0.22, $p < 0.01$), which was most evident in individual analyses of olanzapine (4 RCTs, N = 609, *g* -0.69, 95%CI -1.02 to -0.35, $p < 0.01$), and risperidone (3 RCTs, N = 588, *g* -0.33, 95%CI -0.51 to -0.16, $p < 0.01$) compared to haloperidol, and in the comparison of clozapine with chlorpromazine (1 RCT, N = 160, *g* -0.72, 95%CI -1.04 to -0.41, $p < 0.01$). More recent studies had smaller effect sizes for extrapyramidal side effects (*b* 0.04, $p = 0.02$), and higher patient age was associated with larger effect sizes (*b* -0.04, $p = 0.006$). Less akathisia was reported with second generation antipsychotics (7 RCTs, N = 998, *g* -0.48, 95%CI -0.62 to -0.34, $p < 0.01$), particularly for olanzapine (4 RCTs, N = 611, *g* -0.61, 95%CI -0.79 to -0.42, $p < 0.01$), and risperidone (2 RCTs, N = 406, *g* -0.29, 95%CI -0.52 to -0.06, $p < 0.05$) compared to haloperidol. Second generation antipsychotics resulted in less use of anticholinergeric medications (6 RCTs, N = 999, RR 0.47, 95%CI 0.29 to 0.77, $p < 0.01$), particularly for olanzapine compared to haloperidol (3 RCTs, N = 445, RR 0.21, 95%CI 0.09 to 0.51, $p < 0.01$), or molindone (1 RCT, N = 75, RR 0.31, 95%CI 0.13 to 0.76, $p < 0.01$). Less use of benzodiazepines (5 RCTs, N = 816, RR 0.84, 95%CI 0.75 to 0.95, $p < 0.01$), particularly for olanzapine compared to haloperidol (3 RCTs, N = 445, RR 0.83, 95%CI 0.71 to 0.96, $p < 0.05$). Less use of beta-blockers for olanzapine compared to haloperidol (1 RCT, N = 251, RR 0.11, 95%CI 0.03 to 0.40, $p < 0.01$). More patients on first generation antipsychotics in open-label studies took anticholinergics than in double-blind studies. Less anticholinergic use with second generation antipsychotics compared to first generation antipsychotics was associated with smaller sample size, younger age, male sex and longer follow-up. Olanzapine (2 RCTs, N = 362, RR 3.31, 95%CI 1.83 to 5.98, $p < 0.01$) and risperidone (2 RCTs, N = 485, RR 1.61, 95%CI 1.25 to 2.09, $p < 0.01$) caused more weight gain than haloperidol (>7% gain). Larger differences in weight gain were associated with shorter follow-up time, smaller sample size, younger age, female sex and schizophrenia diagnosis. Olanzapine (1 RCT, N = 53, *g* -1.21, 95%CI -1.79 to -0.63, $p < 0.01$), risperidone (1 RCT, N = 58, *g* -1.99, 95%CI -2.61 to -1.36, $p < 0.01$), and clozapine (1 RCT, N = 59, *g* -1.54, 95%CI -2.12 to -0.97, $p < 0.01$), were associated with lower glucose change than sulpiride. Olanzapine resulted in more total cholesterol change than molindone (1 RCT, N = 35, *g* 1.02, 95%CI 1.30 to 1.75, $p < 0.01$), sulpiride (1 RCT, N = 53, *g* 5.12, 95%CI 4.01 to 6.23, $p < 0.01$), and haloperidol (3 RCTs, N = 501, *g* 0.17, 95%CI 0.00 to 0.35, $p = 0.05$). Risperidone resulted in less total cholesterol change than sulpiride (1 RCT, N = 58, *g* -1.36, 95%CI -1.93 to -0.80, $p < 0.01$). For triglyceride change, olanzapine (1 RCT, N = 53, *g* 3.32, 95%CI

	2.49 to 4.15, $p < 0.01$) and clozapine (1 RCT, N = 59, g 5.02, 95%CI 3.98 to 6.05, $p < 0.01$) were worse than sulpiride, and amisulpride was worse than haloperidol (1 RCT, N = 207, g 0.34, 95%CI 0.06 to 0.61, $p < 0.05$). Risperidone was better than sulpiride (1 RCT, N = 58, g -1.18, 95%CI -1.74 to -0.63, $p < 0.01$).
Consistency in results	Authors report inconsistency in results.
Precision in results	Precise for negative symptoms, extrapyramidal side effects, akathisia and use of benzodiazapines, imprecise for other side effects.
Directness of results	Indirect

Explanation of acronyms

CI = confidence interval, d = Cohen's d = standardised mean differences, g = Hedge's g standardised mean difference, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = odds ratio, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RCT = randomised controlled trial, SMD = standardised mean difference, SNRIs = serotonin and norepinephrine reuptake inhibitor, SSRI = Sselective serotonin reuptake inhibitor, RR = relative risk, 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[19].

† 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[19].

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[20]. 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.

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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[19]:

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

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data 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[21].

‖ 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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