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Herbal treatments

Introduction

Herbal treatments have been suggested as an adjunctive therapy which may positively contribute to the treatment of schizophrenia. A supplementary or adjunctive treatment is administered in conjunction with a patient's ongoing antipsychotic therapy in an attempt to treat symptoms or improve functions that are not addressed by antipsychotics alone. Herbal therapies can include traditional Chinese medicines, as well as more common herbal medicines such as gingko biloba.

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 nine reviews that met inclusion criteria[3-11].

- High quality evidence shows adjunctive ginkgo improves symptoms, particularly when combined with chlorpromazine or haloperidol, and when the study is conducted in China. Moderate to high quality evidence suggests adjunctive ginkgo may specifically improve negative symptoms.
- Moderate to high quality evidence shows adjunctive folic acid improves negative

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symptoms, with less risk of adverse events than with placebo.

- Moderate to low quality evidence suggests traditional Chinese herbal medicines (wendon decoction, hirudo seu whitmania, rhizome rheum palmatum, and xingshen) combined with antipsychotics may result in greater improvement in symptoms and better retention in treatment than antipsychotics alone. There may also be fewer side effects with adjunctive Chinese herbal medicines.
- Moderate to low quality evidence suggests traditional Chinese medicine suoquan wan may be more effective than doxepin (an antimuscarinic) for reducing clozapine-induced hypersalivation, and may result in less constipation.
- Moderate to low quality evidence suggests a large benefit of adjunctive withania somnifera extract (ashwagandha) for improving symptoms.
- Moderate to low quality evidence suggests adjunctive Vitamin B may result in a medium-sized improvement in overall symptoms compared to adjunctive placebo.
- Moderate to low quality evidence suggests no benefit of Vitamin E for tardive dyskinesia or mental state, or of probiotics for symptoms.

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Cakici N, van Beveren N, Judge-Hundal G, Koola M, Sommer I

An update on the efficacy of anti-inflammatory agents for patients with schizophrenia: A meta-analysis

Psychological Medicine 2019; 49: 2307-19

View review abstract online

Comparison	**Adjunctive withania somnifera extract (1000mg daily for 12 weeks) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (small sample, imprecise, direct) suggests a large benefit of adjunctive withania somnifera extract for improving symptoms.**
Symptoms	
Large effects of reduced symptom severity with adjunctive Withania somnifera extract: 1 RCT, N = 68, *g* = 0.81, 95%CI 0.32 to 1.30, *p* = 0.001, I^2 = N/A	
Consistency in results‡	Not applicable
Precision in results§	Imprecise
Directness of results‖	Direct

Deng H, Xu J

Wendan decoction (Traditional Chinese medicine) for schizophrenia

Cochrane Database of Systematic Reviews 2017; 6: CD012217

View review abstract online

Comparison	**Adjunctive wendon decoction vs. antipsychotics alone.**
Summary of evidence	**Moderate quality evidence (large samples, consistent, precise, direct, possible publication bias) suggests adjunctive wendon decoction may result in a medium-sized improvement in symptoms and fewer extrapyramidal side effects than antipsychotics alone.**

Mental state	
A medium-sized effect of improved symptoms with adjunctive wendon decoction; 7 RCTs, N = 522, RR = 0.69, 95%CI 0.51 to 0.93, $p < 0.05$, $I^2 = 0\%$ Authors report this evidence is moderate quality.	
Global state	
A medium-sized effect of improved symptoms with adjunctive wendon decoction; 6 RCTs, N = 684, RR = 0.60, 95%CI 0.50 to 0.72, $p < 0.05$, $I^2 = 0\%$ Authors report this evidence is moderate quality.	
Risks	*Fewer extrapyramidal side effects with wendon decoction;* 2 RCTs, N = 308, RR = 0.46, 95%CI 0.30 to 0.70, $p < 0.05$, $I^2 = 0\%$ *Less use of risperidone with wendon decoction;* 1 RCT, N = 107, MD = -0.70, 95%CI -0.87 to -0.53, $p < 0.05$ *No differences in weight gain;* 1 RCT, N = 108, RR = 0.50, 95%CI 0.20 to 1.24, $p < 0.05$
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Firth J, Stubbs B, Sarris J, Rosenbaum S, Teasdale S, Berk M, Yung, AR

The effects of vitamin and mineral supplementation on symptoms of schizophrenia: a systematic review and meta-analysis

Psychological Medicine 201; 47: 1515-27

View review abstract online

Comparison	**Adjunctive vitamin or minerals vs. adjunctive placebo.**
Summary of evidence	**Moderate to low quality evidence (medium-sized samples, inconsistent, imprecise, direct, no publication bias) suggests adjunctive Vitamin B may result in a medium-sized improvement**

	in overall symptoms.
Mental state	
A medium-sized, significant small effect of improved overall symptoms with adjunctive vitamin B (B6, B9 and B12); 7 RCTs, N = 297, *g* = 0.51, 95%CI 0.01 to 1.15, *p* < 0.05, I^2 = 72.3% Shorter illness duration was associated with greater vitamin B effectiveness. There were no effects of vitamin B on individual positive or negative symptoms. There were no effects of vitamins C or E, folate, inositol, chromium or zinc on overall symptoms. Authors report no evidence of publication bias.	
Risks	No serious side effects were reported.
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Ng QX, Soh AYS, Venkatanarayanan N, Ho CYX, Lim DY, Yeo W-S

A systematic review of the effect of probiotic supplementation on schizophrenia symptoms

Neuropsychobiology 2019; 78: 1-6

View review abstract online

Comparison	**Adjunctive probiotics vs. adjunctive placebo.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, consistent, direct) suggests no benefit of adjunctive probiotics over placebo.**
Symptoms	
No significant difference between the groups; 3 studies, N = 172, MD = -0.0884, 95%CI -0.380 to 0.204, *p* = 0.551, I^2 = 0% There were no differences in subgroup analyses of positive and negative symptoms.	
Consistency in results	Consistent

Precision in results	Unable to assess; MDs not standardised.
Directness of results	Direct

Rathbone J, Zhang L, Zhang M, Xia J, Liu X, Yang Y

Chinese herbal medicine for schizophrenia

Cochrane Database of Systematic Reviews 2005; Issue 4. Art. No.: CD003444. DOI: 10.1002/14651858.CD003444.pub2

View review abstract online

Comparison	**Adjunctive Chinese herbal medicine vs. antipsychotics alone.**
Summary of evidence	**Moderate to low quality evidence (medium to large samples, some inconsistency, imprecise or unable to assess, direct) suggests combination herbal medicine and antipsychotics may result in greater improvement in mental state and global state, better retention in treatment and less risk of constipation.**

Mental state

Significant improvement on BPRS scores (short and medium term – up to 12 months) for those receiving combined herbal medicine and antipsychotics, over antipsychotics alone;

Herbal treatments included gingko biloba (3 RCTs, doses unspecified), hirudo seu whitmania and rhizome rheum palmatum (1 RCT, doses unspecified) plus antipsychotics, compared to antipsychotics alone (chlorpromazine, clozapine, sulpiride, perphenazine, or haloperidol, 120-360mg/day), treatment duration ranged from 30 days to 16 weeks with follow-up duration up to 12 months.

Overall BRPS scores: 4 RCTs, N = 724, WMD = -3.33, 95%CI -4.32 to -2.34, $p < 0.00001$, Q = 3.0, $p = 0.08$, $I^2 = 67\%$

Short term (up to 3 months): 2 RCTs, N = 103, WMD = -2.41, 95%CI -3.85 to -0.97, $p = 0.0011$, Q = 5.36, $p = 0.02$, $I^2 = 81\%$

Medium term (up to 12 months): 2 RCTs, N = 621, WMD = -4.17, 95%CI -5.54 to -2.79, $p < 0.00001$, Q = 0.86, $p = 0.35$, $I^2 = 0\%$

Significant improvement on SANS in the medium term for those receiving the combined herbal medicine + antipsychotic treatment over antipsychotics alone;

Herbal treatments included xingshen (30mL, 1 RCT) or gingko biloba (dose unspecified, 2 RCT) plus antipsychotics, compared to antipsychotics alone (chlorpromazine, clozapine, sulpiride, perphenazine, haloperidol, 120-800mg/day), treatment duration range 12 weeks to 6 months.

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3 RCTs, N = 741, WMD = -9.15, 95%CI -12.10 to -6.20, $p < 0.00001$, Q = 6.65, $p = 0.04$, $I^2 = 70\%$ Authors report trials were generally of poor quality.	
Global state	
People receiving both herbal medicine and antipsychotics showed a significant large improvement in global state compared to those receiving antipsychotics alone; Interventions included 12 weeks of either dang gui cheng qi tang or xiao yao san, 100 ml 2-3/day, plus antipsychotics (unclear type/dose); vs. antipsychotics alone (unclear type/dose) 1 RCT, N = 123, RR = 0.19, 95%CI 0.06 to 0.61, $p = 0.0057$, NNT 6, 95%CI = 5 to 11 *People receiving both herbal medicine and antipsychotics showed a significant improvement in global state, compared to those receiving antipsychotics alone;* One RCT compared 8 weeks of ginkgo biloba + antipsychotics (120mg/day first week, then 240mg/day) vs. placebo + antipsychotics (unclear type/dose). The second RCT compared 30 days of hirudo seu Whitmania (Shui zhi) and rhizoma rheum palmatum (da huang) (doses not specified) + chlorpromazine (≤300 mg/day) vs. chlorpromazine alone: dose (≤400mg/day) CGI scores: 2 RCTs, N = 103, WMD = -0.46, 95%CI -0.86 to -0.06, $p = 0.023$, Q = 3.30, $p = 0.07$, $I^2 = 70\%$	
Leaving the study early	
By 12 months, significantly fewer people in the combined herbal medicine + antipsychotic group had left the study early compared to those given antipsychotics alone; 6 RCTs, N = 1004, RR = 0.30, 95%CI 0.16 to 0.58, $p = 0.00030$, NNT 21, 95%CI 18 to 35, Q = 1.02, $p = 0.60$, $I^2 = 0\%$	
Risks	*Fewer reports of constipation with herbal + chlorpromazine;* 1 RCT, N = 67, RR = 0.03, 95%CI 0.00 to 0.45, $p = 0.011$ *No differences in extrapyramidal symptoms;* 1 RCT, N = 67, RR = 0.55, 95%CI 0.18 to 1.65, $p = 0.28$
Consistency in results	Consistent except for short term BPRS and medium term SANS data. Unable to assess 1 RCT.
Precision in results	Precise for all except extrapyramidal symptoms. Unable to assess WMD (standardised measures not reported).
Directness of results	Direct

Sakuma K, Matsunaga S, Nomura I, Okuya M, Kishi T, Iwata N

Folic acid/methylfolate for the treatment of psychopathology in schizophrenia: a systematic review and meta-analysis

Psychopharmacology 2018; 235: 2303-14

View review abstract online

Comparison	**Adjunctive folic acid vs. adjunctive placebo.**
Summary of evidence	**Moderate to high quality evidence (medium-sized sample, consistent, precise, direct,) shows adjunctive folic acid improves negative symptoms with less risk of adverse events.**
Mental state	
There were no differences between groups in overall symptoms; 7 RCTs, N = 340, SMD = -0.20, 95% CI -0.41 to 0.02, p = 0.08, I^2 = 0% *Significant, small effect favoured adjunctive folic acid for negative symptoms;* 5 RCTs, N = 281, SMD = -0.25, 95%CI -0.49 to -0.01, p = 0.04, I^2 = 0%	
Risks	*Lower risk of serious adverse events with folic acid;* 4 RCTs, N = 241, RR = 0.32, 95%CI 0.12 to 0.82, p = 0.02, I^2 = 0%
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Singh V, Singh SP, Chan K

Review and meta-analysis of usage of ginkgo as an adjunct therapy in chronic schizophrenia

International Journal of Neuropsychopharmacology 2010; 13: 257-271

View review abstract online

Comparison	**Adjunctive ginkgo vs. adjunctive placebo.**

Herbal treatments

Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) shows adjunctive ginkgo improved symptoms more than placebo, particularly when combined with chlorpromazine or haloperidol and when the study is conducted in China.** **Moderate to high quality evidence (inconsistent) suggests adjunctive ginkgo may specifically improve negative symptoms.**
Mental state	
Significant, medium-sized effect favoured adjunctive ginkgo for overall symptoms; 6 RCTs, N = 828, SMD = -0.49, 95%CI -0.65 to -0.34, $p < 0.05$, Q = 5.354, $p = 0.374$ *Significant medium-sized effect favoured adjunctive ginkgo for negative symptoms;* 6 RCTs, N = 828, SMD = -0.50, 95%CI -0.81 to -0.18, $p < 0.05$, Q = 15.11, $p = 0.01$ *Studies of first-generation chlorpromazine and haloperidol found a significant improvement in negative and total symptoms with adjunctive ginkgo;* Negative symptoms: 4 RCTs, SMD = -0.38, 95%CI -0.66 to -0.10, $p < 0.05$, Q = 3.79 $p > 0.05$ Total symptoms 4 RCTs, SMD: = -0.43, 95%CI -0.71 to -0.16, $p < 0.05$, Q = 1.97 $p > 0.05$ *Studies of second generation clozapine and olanzapine found no significant differences between groups;* Negative symptoms 2 RCTs, SMD: = -0.38, 95%CI -1.81 to 1.06, $p > 0.05$, Q = 8.52 $p < 0.05$ Total symptoms 2 RCTs, SMD: = -0.42, 95%CI -0.89 to 0.06, $p > 0.05$, Q = 1.28 $p > 0.05$ *Studies conducted in China showed a significant improvement with ginkgo;* Negative symptoms: 4 RCTs, SMD = -0.49, 95%CI -0.63 to -0.34, $p < 0.05$, Q = 6.57, $p > 0.05$ Total symptoms: 4 RCTs, SMD = -0.51, 95%CI -0.66 to -0.37, $p < 0.05$, Q = 3.93, $p > 0.05$ *Studies conducted in Turkey showed no differences between groups;* Negative symptoms: 2 RCTs, SMD = -0.38, 95%CI -1.81 to 1.06, $p > 0.05$, Q = 8.52, $p < 0.05$ Total symptoms: 2 RCTs, SMD = -0.42, 95%CI -0.89 to 0.06, $p > 0.05$, Q = 1.28, $p > 0.05$	
Risks	Not reported
Consistency in results	Consistent for all outcomes except negative symptoms – total, second generation studies, and Turkish studies.
Precision in results	Precise for total and negative symptoms. Imprecise for most subgroup analyses.
Directness of results	Direct

Soares-Weiser K, Maayan N, Bergman H

Vitamin E for antipsychotic-induced tardive dyskinesia

Cochrane Database of Systematic Reviews 2018; 1: CD000209

View review abstract online

Comparison	**Adjunctive vitamin E (600-1600IU/day) vs. adjunctive placebo.**
Summary of evidence	**Moderate to low quality evidence (small poor quality trials, consistent, precise, direct) suggests no benefit of Vitamin E for tardive dyskinesia or mental state.**
Mental state	
No differences between groups; 3 RCTs, N = 165, MD = -0.20, 95%CI -3.21 to 2.82, $p > 0.05$, $I^2 = 38\%$ Authors report this is low quality evidence from poorly randomised trials.	
Tardive dyskinesia	
No significant differences in rates of improvement of tardive dyskinesia symptoms; 6 RCTs, N = 264, RR = 0.95, 95%CI 0.89 to 1.01, $p > 0.05$, $I^2 = 0\%$ Authors report this is low quality evidence from poorly randomised trials.	
Risks	*No differences between groups in any adverse effects;* 9 RCTs, N = 205, RR = 1.21, 95%CI 0.35 to 4.15, $p > 0.05$, $I^2 = 0\%$
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Syed R, Au K, Cahill C, Duggan L, He Y, Udu V, Xia J

Pharmacological interventions for clozapine-induced hypersalivation

Cochrane Database of Systematic Reviews 2008; Issue 3: CD005579

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Comparison	**Suoquan wan (dose 9g/day) plus clozapine (dose range 150-312mg/day) vs. placebo or doxepin (dose range 25-50mg/day) plus clozapine (dose range 150-288mg/day).**
Summary of evidence	**Moderate to low quality evidence (small sample, imprecise, direct) suggests suoquan wan may be more effective than doxepin for hypersalivation, with less risk of constipation.**
Hypersalivation	
Significant, small effect of improved hypersalivation with suoquan wan; 1 RCT, N = 70, RR = 0.31, 95%CI 0.16 to 0.59, *p* = 0.00043	
Risks	*Less risk of constipation with suoquan wan;* 1 RCT, N = 70, RR = 0.02, 95%CI 0.00 to 0.35, *p* = 0.0067
Consistency in results	Not applicable
Precision in results	Imprecise
Directness of results	Direct
Comparison 2	**Wudunsan paste (dose 9g/day) plus clozapine (mean dose 310mg/day) vs. placebo plus clozapine (mean dose 325mg/day).**
Summary of evidence	**Low quality evidence (very small sample, imprecise, direct) is unclear as to any benefit of wudunsan over placebo for improving hypersalivation.**
Hypersalivation	
No significant difference between groups; 1 RCT, N = 16, RR = 0.11, 95%CI 0.01 to 1.78, *p* = 0.12	
Risks	Not reported
Consistency in results	Not applicable
Precision in results	Imprecise
Directness of results	Direct

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Explanation of acronyms

AIMS = Abnormal Involuntary Movement Scale, BPRS = Brief Psychiatric Rating Scale**,** CI = Confidence Interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MD = Mean difference, N = number of participants, NNH = number needed to harm, NNT = number needed to treat, *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, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms, SMD = standardised mean difference, TDRS = Tardive Dyskinesia Rating Scale, vs = versus, WMD = weighted mean difference

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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[12].

† 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[12].

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

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measure the effect of an explanatory variable on the hazard or risk of an event.

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

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[12];

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

§ 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[14].

‖ 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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