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Introduction

Second generation antipsychotics (sometimes referred to as 'atypical' antipsychotics) are a newer class of antipsychotic medication than first generation 'typical' antipsychotics. Second generation antipsychotics are effective for the positive symptoms of schizophrenia. It is sometimes claimed that they are more effective than first generation antipsychotics in treating the negative symptoms of schizophrenia, although the evidence for this is weak. Negative symptoms include a lack of ordinary mental activities such as emotional expression, social engagement, thinking and motivation, whereas positive symptoms include the experiences of perceptual abnormalities (hallucinations) and fixed, false, irrational beliefs (delusions).

Second generation antipsychotics may also cause less extra-pyramidal side effects. These include dyskinesias such as repetitive, involuntary, and purposeless body or facial movements, Parkinsonism (cogwheel muscle rigidity, pill-rolling tremor and reduced or slowed movements), akathisia (motor restlessness, especially in the legs, and resembling agitation) and dystonias such as muscle contractions causing unusual twisting of parts of the body, most often in the neck. These effects are caused by the dopamine receptor antagonist action of these drugs. One explanation for differences in producing these side effects is that high potency first generation antipsychotics are usually selective dopamine receptor antagonists with a high affinity for the dopamine receptor and they induce extrapyramidal effects by the blockade of these dopamine receptors. In contrast, second generation antipsychotics generally have a lower affinity for the dopamine receptor and also block serotonin receptors, both of which mechanisms may play a role in mitigating the effects of dopamine blockade. Amisulpride is an exception to other second generation antipsychotics in that it is a pure dopamine receptor antagonist, however it tends to block dopamine receptors more selectively in the

limbic system relative to the nigrostriatal system, which is the site responsible for inducing extrapyramidal symptoms. In addition to amisulpride, olanzapine and quetiapine also tend to selectively block dopamine receptors in the mesolimbic system but target serotonin receptors.

This table summarises overall group effectiveness of clozapine from information gained from randomised controlled trials (RCTs), however individual treatment programs need to be tailored by trained clinicians as response - both in symptoms and adverse effects - can vary between individuals.

Method

Owing to the vast number of reviews on antipsychotics, we have prioritised information reported in the abstracts of Cochrane systematic reviews³. This is because the Cochrane internal review process ensures a high level of scientific rigor and meta-analyses are usually conducted, giving treatment effect sizes. Data from the abstracts were supplemented from the full text when clarification was required. We have included only Cochrane reviews that have been published from the year 2000 to date to ensure the latest available evidence is presented. When multiple copies of reviews were found and/or when findings conflict, we present the most recent version and the most recent conclusions.

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 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



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that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks⁴. The resulting table represents an objective summary of the evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found eight reviews that met our inclusion criteria^{1, 5-11}.



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Compared to first generation antipsychotics

Efficacy: Moderate to high quality evidence (some inconsistency) suggests clozapine may provide benefit for symptoms, global state, reducing relapse, and increasing study retention for patients who are and who are not resistant to first generation antipsychotics. Clozapine may provide no advantage for outcomes of mortality, ability to work, or suitability for early hospital discharge. Low quality evidence (unable to assess precision, 1RCT with small sample size) is unclear as to the benefit of clozapine for childhood onset schizophrenia.

Adverse effects: Moderate quality evidence (inconsistent) suggests clozapine may be associated with less movement disorders, increased blood problems, increased drowsiness, hypersalivation and temperature compared to first generation antipsychotics.

Compared to other second generation antipsychotics

Efficacy: Moderate quality evidence (imprecise) suggests clozapine may produce better clinically significant response and reduced symptom severity compared to zotepine, as well as fewer hospital admission compared to other second generation antipsychotics. Low quality evidence (unable to assess precision, 1RCT with small sample size) is unclear as to the benefit of clozapine for childhood onset schizophrenia.

Adverse effects: Clozapine was associated with fewer extrapyramidal effects than risperidone and zotepine. More hypersalivation, white blood cell reduction, triglycerides, sedation, seizures, and weight gain are reported with clozapine than risperidone, olanzapine, or quetiapine.

Augmentation of clozapine with sulpiride vs. clozapine alone

Efficacy: Moderate quality evidence (imprecise) suggests no differences in global state or relapse rates between clozapine and clozapine plus sulpiride.

Adverse effects: Moderate quality evidence (imprecise) suggests less hypersalivation, appetite loss, weight gain and abdominal distension with clozapine plus sulpiride. Low quality evidence (very imprecise, 1RCT) is uncertain as to the effect of clozapine plus sulpiride on movement disorders.

[Asenjo Lobos, C, Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Leucht S. Clozapine versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2010, Issue 11: Art. No.: CD006633 DOI: 10.1002/14651858.CD006633.pub2.](#)

The review includes clozapine vs olanzapine (12 RCTs); vs quetiapine (5 RCTs); vs risperidone (9 RCTs); vs ziprasidone (1 RCT); vs zotepine (2 RCTs).

Clozapine had a higher attrition rate due to adverse effects than the olanzapine group (9 RCTs, N =



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1674, RR = 1.60, 95%CI 1.07 to 2.40, $p = 0.021$, $I^2 = 10%$ $p = 0.35$) and the risperidone group (6 RCTs, N = 627, RR = 1.88, 95%CI 1.11 to 3.21 $p = 0.02$, $I^2 = 0%$).

However, fewer participants in the clozapine group left the study early due to inefficacy than in the risperidone group (6 RCTs, N = 627, RR = 0.40 95%CI 0.23 to 0.70 $p = 0.0013$, $I^2 = 0%$).

Fewer participants in the clozapine group had to be hospitalised to avoid suicide attempts compared to the olanzapine group (1 RCT, N = 980, RR = 0.78, 95%CI 0.62 to 0.98, $p = 0.035$).

Clozapine participants had greater improvements in mental state (BPRS total score) compared to the zotepine group (1 RCT, N = 59, MD = -6 95%CI -9.83 to -2.17, $p = 0.0021$) with no significant differences compared to olanzapine, quetiapine, risperidone and ziprasidone.

Quetiapine participants had a greater short term improvement in negative symptoms than clozapine participants (2 RCTs, N = 142, MD = 2.23, 95%CI 0.99 to 3.48, $p = 0.00045$, $I^2 = 0%$), with no significant difference in positive or negative symptoms in clozapine compared to olanzapine or risperidone.

People on risperidone showed greater improvement in social functioning than those on clozapine (1 RCT, N = 19, MD = -47.0, 95%CI -93.55 to -0.45, $p = 0.048$).

<p>Risks</p>	<p>Clozapine produced fewer extrapyramidal side-effects than risperidone (use of antiparkinson medication: 6 RCTs, N = 304, RR = 0.39, 95%CI 0.22 to 0.68, $p < 0.05$, $I^2 = 0%$) and zotepine (1 RCT, N = 59, RR = 0.05, 95%CI 0.00 to 0.86, $p = 0.039$).</p> <p>Clozapine did not alter prolactin levels, whereas olanzapine (for men $p = 0.15$, for women $p < 0.05$), risperidone ($p < 0.005$) and zotepine ($p < 0.005$) prolactin levels increased.</p> <p>Compared to olanzapine, clozapine had greater white blood cell reduction (4 RCTs, N = 1264, $p < 0.05$); hypersalivation (5 RCTs, N = 1333, $p = 0.005$); sedation (7 RCTs, N = 1445, $p = 0.028$); and seizures (4 RCTs, N = 1097, $p = 0.0056$).</p> <p>Compared to risperidone, clozapine had greater hypersalivation (3 RCT, N = 373, $p < 0.05$); sedation (5 RCTs, N = 479, $p = 0.0014$); seizures (2 RCTs, N = 354, $p = 0.010$); weight gain (4 RCTs, N = 459, $p < 0.05$); and triglyceride levels (1 RCT, N = 26, $p < 0.001$).</p> <p>Compared to quetiapine, clozapine had greater hypersalivation (2 RCTs, N = 135, $p < 0.05$); sedation (2 RCTs, N = 135, $p < 0.05$); ECG alterations (1 RCT, N = 72, $p = 0.044$); and triglyceride levels (1 RCT, N = 27, $p < 0.001$).</p>
<p>Consistency in results[‡]</p>	<p>Consistent for all measures except hypersalivation and sedation for olanzapine and weight gain for risperidone. Unable to assess for 1 RCT.</p>
<p>Precision in results[§]</p>	<p>Precise for hospitalisation for olanzapine, imprecise for all other measures. Unable to assess for mental states, triglyceride levels and</p>



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	social functioning as standardised values not reported.
Directness of results	Direct
<p>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.</p>	
<p>This review included 3 RCTs (N = not reported). Authors state that the methodological quality of the included studies was too low to assess the effectiveness of clozapine for treatment resistant schizophrenia. No data reported in abstract.</p>	
Risks	Not reported in abstract.
Consistency in results	Not applicable; all outcomes 1 RCT.
Precision in results	Not reported in abstract.
Directness of results	Direct
<p>Essali A, Al-Haj Haasan N, Li C, Rathbone J. Clozapine versus typical neuroleptic medication for schizophrenia. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD000059. DOI: 10.1002/14651858.CD000059.pub2.</p>	
<p>This review included 42 RCTs (N = 3950). Compared to first generation antipsychotics, clozapine presented improved clinical improvements both in the short term (< 12 weeks, N = 1119, 14 RCTs, RR 0.72 CI 0.66 to 0.79, NNT 6, CI 5 to 8, I² = 0%, p = 0.49) and long term (> 26 weeks, N = 719, 3 RCTs, RR 0.81 CI 0.74 to 0.88, CI 5 to 8, I² = 81%, p = 0.01), with greater reduction of overall symptom reduction in the short term (N = 1145, 16 RCTs, WMD -4.22, CI -5.4 to -3.1, I² = 66%, p = 0.0001) and long term (N = 235, 1 RCT, WMD -6.90, CI -10.66 to -3.14, I² = NA), particularly negative symptoms in the short-term (N = 196, 5 RCTs, WMD -5.92, CI -7.8 to -4.1, I² = 90%, p < 0.00001). Clozapine also resulted in fewer psychotic relapses in the short term (N = 1303, 19 RCTs, RR 0.62, CI 0.5 to 0.8, NNT 21 CI 15 to 49, I² = 14%, p = 0.31) and long term (N = 578, 4 RCTs, RR 0.22, CI 0.14 to 0.34, I² = 76%, p = 0.01), and increased study retention in the long term (N = 982, 16 RCTs, RR 0.60, CI 0.5 to 0.7, NNT 15, CI 12 to 20, I² = 0%, p = 0.42). There were no significant advantages of clozapine over first generation antipsychotics for outcomes of mortality, ability to work, retention in the study in the short term, or suitability for discharge at the end of the study. The effects of clozapine were also beneficial for patients that were resistant to first generation antipsychotics, in terms of global clinical improvement in the short term (N = 370, 4 RCTs, RR 0.71, CI 0.64 to 0.79, NNT 4, CI 3 to 6, I² = 0%, p = 0.83) and longer term (N = 648, 2 RCTs, RR 0.83, CI 0.76 to 0.91, I² = 82%, p = 0.02), overall symptom reduction in the short term (N = 429, 5 RCTs, WMD -7.83, CI -10.01 to -5.64 I² = 65%, p = 0.02) and the long term (N = 235, 1 RCT, WMD -6.90,</p>	



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<p>CI -16.66 to -3.14, $I^2 = NA$), and more retention in the study in the long term (N = 648, 2 RCTs, RR 0.57, CI 0.49 to 0.66, $I^2 = 0\%$, $p = 0.41$). There were no significant advantages of clozapine over first generation antipsychotics for treatment resistant patients for outcomes of mortality, ability to work, retention in the study in the short term, or suitability for discharge at the end of the study.</p>	
Risks	<p>Compared to first generation antipsychotics, blood problems (any blood problem requiring withdrawal of participants from trials, or leukopenia, defined as a white cell count < 3000 per cubic mm, or neutropenia, defined as granulocyte count < 1500 per cubic mm) occurred more frequently in participants receiving clozapine (3.2%) compared with those given first generation antipsychotics (0%) (N = 1031, 13 RCTs, RR 7.09, CI 2.0 to 25.6, $I^2 = 0\%$, $p = 0.87$).</p> <p>Clozapine participants experienced more drowsiness, hypersalivation, or temperature increase, than those given first generation antipsychotics. However, clozapine patients experienced fewer movement disorders (N = 1433, 18 RCTs, RR 0.58, CI 0.5 to 0.7, NNT 5 CI 4 to 6, $I^2 = 76\%$, $p < 0.00001$). There were no differences in cognitive measures.</p>
Consistency in results	Inconsistent for suitability for discharge, ability to work, symptoms, movement disorder and long term clinical improvement and relapse.
Precision in results	Precise for dichotomous outcomes, unable to assess continuous outcomes (standardised values not reported).
Directness of results	Direct
<p>Kennedy E, Kumar A, Datta SS. Antipsychotic medication for childhood-onset schizophrenia. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD004027 DOI: 10.1002/14651858.CD004027.pub2</p>	
<p>This review includes 6 RCTs (N = not reported) - six studies comparing either second generation versus first generation, second generation versus second generation, or first generation versus first generation antipsychotics for childhood-onset schizophrenia.</p> <p>Comparing clozapine to first generation antipsychotic, haloperidol, clozapine was reported to be more effective for treatment resistant childhood-onset schizophrenia on the Childrens Global Assessment Scale (N = 21, WMD 17.00 CI 7.74 to 26.26) and on the Bunney-Hamburg Psychosis Rating Scale (N = 21, WMD -3.60 CI -6.64 to -0.56).</p> <p>No other differences were reported for any outcome.</p>	
Risks	Clozapine had higher incidence of drowsiness (1 RCT, N = 21, RR 3.30 CI 1.23 to 8.85, NNH 2 CI 2 to 17) and neutropenia (1 RCT, N = 21, RR 12, CI 0.75 to 192.86).
Consistency in results	Not applicable; 1 RCT.



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Precision in results	Unable to assess (standardised values are not reported).
Directness of results	Direct
<p>Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Duggan L, Kissling W, Leucht S. Olanzapine versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2010, Issue 3. Art. No.: CD006654 DOI: 10.1002/14651858.CD006654.pub2.</p>	
<p>The review includes 50 RCTs (N = 9476) of olanzapine compared to amisulpride, aripiprazole, clozapine, quetiapine, risperidone or ziprasidone.</p> <p>Olanzapine had no significant benefit over clozapine for improving general mental state (measured by PANSS (7 RCTs, N = 618, WMD -1.97, 95%CI -4.66 to 0.71, I² = 0%, p = 0.95).</p> <p>Olanzapine had more hospital re-admissions compared to clozapine (1 RCT, N = 980, RR 1.28, 95%CI 1.02 to 1.61).</p>	
Risks	Olanzapine increased prolactin more than clozapine (1 RCT, N = 120, WMD 0.57, 95%CI 0.09 to 1.05).
Consistency in results	Consistent
Precision in results	Precise for dichotomous outcome, unable to assess continuous measures.
Directness of results	Direct
<p>Subramanian S, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Kissling W, Leucht S, Komossa K. Zotepine versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2010, Issue 10. Art. No.: CD006628 DOI: 10.1002/14651858.CD006628.pub3.</p>	
<p>This review includes 3 RCTs (N = 289), 2 comparing zotepine vs. clozapine, 1 comparing zotepine vs. clozapine vs. risperidone (at 4 mg and 8 mg) vs. remoxipride.</p> <p>No significant difference in study retention was reported.</p> <p>Compared to clozapine, zotepine had less clinically significant response (N = 59, 1 RCT, RR 8.23, 95%CI 1.14 to 59.17, p = 0.036, NNH 3 CI 2 to 8) and less reduction in symptom severity (BPRS) (N = 59, 1 RCT, MD 6.00, 95%CI 2.17 to 9.83, p < 0.01).</p>	
Risks	Zotepine had higher levels of extrapyramidal symptoms than clozapine, measured as use of antiparkinson medication (N = 116, 2 RCTs, RR 20.96, 95%CI 2.89 to 151.90, p < 0.01, I ² = 0%, p = 0.91) and higher prolactin levels (N = 59, 1 RCT, MD 33.40, 95%CI 14.87 to 51.93, p < 0.01).



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Consistency in results	Inconsistent for clozapine use of antiparkinson medication, unable to assess for 1 RCT.
Precision in results	Imprecise, unable to assess MDs as standardised values are not reported.
Directness of results	Direct
<p><u>Tuunainen A, Wahlbeck K, Gilbody SM. Newer atypical antipsychotic medication versus clozapine for schizophrenia. Cochrane Database of Systematic Reviews 2000, Issue 2. Art. No.: CD000966. DOI: 10.1002/14651858.CD000966</u></p>	
<p>This review includes 8 RCTs (N = not reported).</p> <p>Compared to other second generation antipsychotics, there were no differences reported in global clinical improvement, symptoms or retention in the study. Social functioning as measured by the Social Functioning Scale was better in patients on risperidone (N = 19, 1RCT, MD = -47.01, CI = -93.55 to -0.45) but this finding is based on a single small trial and authors say this should be interpreted with caution.</p>	
Risks	Compared to other second generation antipsychotics, clozapine produced more fatigue than risperidone (N = 86, 1 RCT, RR = 0.55, CI = 0.31 to 0.96), more nausea than olanzapine and risperidone data combined (N = 266, 2 RCTs, RR = 0.42, CI = 0.19 to 0.92, I ² = 73%, p = 0.05), although the effect was more pronounced when compared to olanzapine, more hypersalivation compared to olanzapine (N = 180, 1 RCT, RR = 0.08, CI = 0.02 to 0.31), and orthostatic dizziness (N = 266, 2 RCTs, RR = 0.35, CI = 0.15 to 0.85, I ² = 43%, p = 0.19). Other new second generation antipsychotics (with the exception of olanzapine - where no differences were observed), produced more extrapyramidal symptoms than clozapine (N = 305, 5 RCTs, RR = 3.55, CI = 1.79 to 7.06, I ² = 13%, p = 0.33). There were no differences in sleep problems, weight gain or white blood cell problems.
Consistency in results	Consistent for all outcomes except nausea.
Precision in results	Imprecise, authors report wide confidence intervals.
Directness of results	Direct
<p><u>Wang J, Omori IM, Fenton M, Soares B. Sulpiride augmentation for schizophrenia. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD008125 DOI: 10.1002/14651858.CD008125.pub2.</u></p>	



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This review includes 4 RCTs (N = 221).

Note – this review considers sulpiride augmentation of clozapine in schizophrenia patients who are either treatment resistant or with prominent negative symptoms. All studies compared sulpiride plus clozapine with clozapine alone (with or without a placebo comparison).

No differences were found for sulpiride augmentation of clozapine compared to clozapine alone, for global state in the short term (N = 193, 3 RCTs, RR 0.58 CI 0.3 to 1.09, $I^2 = 0\%$, $p = 0.54$), long-term (N = 70, 1 RCT, RR 0.67 CI 0.42 to 1.08) or for psychotic relapse (N = 70, 1 RCT, RR 0.85 CI 0.5 to 1.3).

Risks	<p>Clozapine augmented with sulpiride resulted in increased movement disorders (N = 70, 1 RCT, RR 48.24 CI 3.05 to 762.56).</p> <p>Augmentation of clozapine resulted in reduced incidence of hypersalivation (N = 162, 3 RCTs, RR 0.49 CI 0.29 to 0.83, $I^2 = 43\%$, $p = 0.17$) and less weight gain (N = 64, 1 RCT, RR 0.30 CI 0.09 to 0.99), less appetite loss (N = 70, 1 RCT, 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, $p = 0.03$).</p>
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 for all outcomes.
Directness of results	Direct

Explanation of acronyms

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, NA = not applicable, NNH = number of patients needed to treat for one to show one negative effect, NNT = number of patients needed to treat for one to show a positive effect, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RR = relative risk, vs = versus, WMD = weighted mean difference

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Explanation of technical terms

† Different effect measures are reported by different reviews.

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. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect³.

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 ¹². InOR 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 are an indication of

prediction, but do not confirm causality due to possible and often unforeseen 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 formula³;

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

§ 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



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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 relaxed¹³.

|| 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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