TECHNICAL COMMENTARY

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Olanzapine

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 olanzapine 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 reviews[1]. 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,

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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, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks[2]. 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 nine reviews that met our inclusion criteria[3-11].

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Olanzapine

Olanzapine

Compared to placebo

Efficacy: High quality evidence (consistent, precise, direct) suggests olanzapine results in greater clinical response and is equally effective at retaining patients in treatment as placebo.

Adverse effects: Moderate quality evidence (imprecise) suggests no differences between olanzapine and placebo in any adverse effect.

Compared to first generation antipsychotics

Efficacy: In general, moderate quality evidence (inconsistent) suggests there no differences in clinical response between olanzapine and first generation antipsychotics. Compared to haloperidol, moderate to low quality evidence (1 small to medium-sized RCT) suggests olanzapine may improve mental state and retain more patients in the study.

Adverse effects: Moderate to high quality evidence (some imprecision) suggests olanzapine may result in less extrapyramidal side effects than first generation antipsychotics.

Compared to other second generation antipsychotics

Efficacy: Compared to risperidone, high quality evidence suggests no differences in global state or symptom severity. Fewer people left the study early with olanzapine than risperidone, aripiprazole, quetiapine, ziprasidone, or clozapine, but not amisulpride or paliperidone. Olanzapine was associated with fewer relapses than risperidone, with no differences in relapse rates when compared to paliperidone. Moderate to high quality evidence suggests olanzapine improves general mental state more than aripiprazole, quetiapine, or ziprasidone, but not amisulpride or clozapine. Olanzapine was associated with fewer hospital admissions than quetiapine and ziprasidone, but more hospital admissions to avoid suicide than clozapine.

Adverse effects: In general, moderate quality evidence (imprecise) suggests olanzapine may result in fewer extrapyramidal symptoms and more weight gain than other second generation antipsychotics, including risperidone, paliperidone, ziprasidone, amisulpride, aripiprazole or quetiapine. Olanzapine also increased prolactin more than aripiprazole, clozapine and quetiapine, but clearly less so than risperidone. Related effects such as increases in glucose and cholesterol levels were also more frequent with olanzapine. Compared to clozapine, olanzapine altered prolactin levels, had fewer participants with decreased white blood cells, and resulted in less hypersalivation, and less seizures. Compared to risperidone and paliperidone, olanzapine showed lower rates of insomnia and sexual dysfunction.

See below for detailed results from nine reviews.

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Asenjo Lobos C, Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S and 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 27 blinded RCTs, N = 3099, twelve compared clozapine with olanzapine. Clozapine had a higher attrition rate due to adverse effects than the olanzapine group (9 RCTs, N = 1674, RR = 1.60, 95%CI 1.07 to 2.40 p = 0.021, I^2 = 10%). 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). No significant difference in mental state (BPRS total score) (5 RCTs, N = 304, MD = 1.31, 95%CI -0.30 to 2.92, p = 0.11, I^2 = 8) or negative symptoms between olanzapine and clozapine (6 RCTs, N = 592, MD = 0.78, 95%CI -0.21 to 1.77, p = 0.12, I^2 = 0).	
Risks	Compared to clozapine, olanzapine altered prolactin levels (men: p = 0.15; women p < 0.05); had less reduction of white blood cells (4 RCTs, N = 1264, p < 0.05); had less hypersalivation (5 RCTs, N = 1333, p = 0.005); less sedation (7 RCTs, N = 1445, p = 0.028); and less seizures (4 RCTs, N = 1097, p = 0.0056).
Consistency in results‡	Consistent for all measures except hypersalivation and sedation. Unable to assess for 1 RCT.
Precision in results§	Precise for hospitalisation imprecise for adverse effects. Unable to assess for mental states, negative symptoms as standardised values not reported.
Directness of results‖	Direct
Duggan L, FentonM, Rathbone J,DardennesR, El-Dosoky A, Indran S. Olanzapine for schizophrenia. Cochrane Database of Systematic Reviews, 2005, Issue 2. Art. No.: CD001359. DOI: 10.1002/14651858.CD001359.pub2	
This review includes 55 RCTs (N = over 10,000). Compared to placebo, olanzapine appeared superior for clinical response at six weeks (2 RCTs N = 418, RR = 0.88, 95%CI 0.8 to 1.0, NNT 8 CI 5 to 27, I^2 = 0%, p = 0.39). Compared to first generation antipsychotics, olanzapine appears equally effective for clinical response (4 RCTs, N = 2778, RR = 0.90, CI 0.76 to 1.06, I^2 = 85%, p = 0.00022). Compared to second generation antipsychotics, olanzapine appears equally effective for clinical response (5 RCTs, N = 1258, RR = 0.93, CI 0.85 to 1.03, I^2 = 0%, p = 0.53). No differences were reported for patients in their first episode of illness, (1 RCT, duration 6 weeks, N = 42). For people with treatment-resistant illness, there were no clear differences in any outcome between	

olanzapine and clozapine, 4 RCTs, N = 457.	
Risks	Compared to placebo, no significant differences in were found weight, dizziness and dry mouth in patients treated with olanzapine. Compared to first generation antipsychotics, olanzapine was associated with fewer extrapyramidal side effects and a non-significant increase in weight, on average four kilograms over 3 to 12 months (4 RCTs, N = 186, WMD = 4.62, CI 0.6 to 8.64, I^2 = 0%, *p* = 0.63). Compared to other second generation antipsychotics, olanzapine was associated with fewer extrapyramidal side effects and a significant increase in weight (1 RCT, N = 980, RR = 1.73, CI 1.49 to 2.00, NNH 5 CI 4 to 7).
Consistency in results	Consistent for all outcomes except for extrapyramidal effects in all comparisons, mental state and weight gain compared to both first generation and second generation antipsychotics, and global effects and study retention in first generation antipsychotic comparison.
Precision in results	Precise for all dichotomous outcomes. Unable to assess continuous outcomes.
Directness of results	Direct
Hamann J, KisslingW, Leucht S, Rummel-Kluge C. New generation antipsychotics for first episode schizophrenia. Cochrane Database of Systematic Reviews 2003, Issue 4. Art. No.: CD004410. DOI: 10.1002/14651858.CD004410	
This review includes 2 RCTs (N = 266). Compared to haloperidol, olanzapine was associated with a clinically significant improvement in mental state, (N = 83, 1 RCT, RR = 0.45 CI 0.3 to 0.7, NNH 3 CI 2 to 6) and had greater study retention (N = 83, 1 RCT, RR = 0.43 CI 0.3 to 0.7, NNH 3 CI 2 to 8). No difference was reported for global effect measures (N = 83, 1 RCT, RR = 0.8 CI 0.5 to 1.1).	
Risks	Compared to haloperidol, patients randomised to olanzapine required significantly less anticholinergic medication for extrapyramidal effects (N = 83, 1 RCT, RR = 0.3 CI 0.2 to 0.7, NNH 4 CI 2 to 14).
Consistency in results	Not applicable, 1 RCT only.
Precision in results	Precise for all outcomes except extrapyramidal effects.
Directness of results	Direct

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Jayaram MB, Hosalli P, Stroup TS. Risperidone versus olanzapine for schizophrenia. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD005237 DOI: 10.1002/14651858.CD005237.pub2.	
This review includes 16 RCTs (N = not reported). Compared to risperidone, there were no differences in short term global effect, (N = 548, 2 RCTs, RR = 1.00 CI 0.88 to 1.15, I^2 = 0%, *p* = 0.52). Olanzapine had a lower relapse rate at 12 months N = 279, 1 RCT, RR = 2.16 CI 1.31 to 3.54, NNH 7 CI 3 to 25). No significant differences were reported for symptom severity and mental state (N = 552, 2 RCTs, RR = 1.01 CI 0.87 to 1.16, I^2 = 0%, *p* = 0.69). Both drugs are associated with high attrition rates; in the long term 66% of those allocated risperidone left the study early compared with 56% given olanzapine (N = 1440, 5 RCTs, RR = 1.17 CI 1.08 to 1.27, NNH 11 CI 7 to 23, I^2 = 7%, *p* = 0.38).	
Risks	Compared to risperidone, insomnia was lower with olanzapine (N = 1588, 5 RCTs, RR = 1.41 CI 1.15 to 1.72, NNH 15 CI 9 to 41, I^2 = 0%, *p* = 0.98). Extrapyramidal symptoms were common with both drugs (N = 893, 3 RCTs, RR = 1.18 CI 0.75 to 1.88, I^2 = 63%, *p* = 0.07); although risperidone patients had increased requirements for medication to alleviate these symptoms (N = 419, 2 RCTs, RR = 1.76 CI 1.25 to 2.48, NNH 8 CI 4 to 25, I^2 = 0%, *p* = 0.44). Patients randomised to risperidone were less likely to gain weight compared to olanzapine (N = 984, 2 RCTs, RR = 0.47 CI 0.36 to 0.61, NNH 7 CI 6 to 10, I^2 = 0%, *p* = 0.98). Patients on risperidone were more likely to experience abnormal ejaculation (N = 370, 2 RCTs, RR = 4.36 CI 1.38 to 13.76, NNH 20 CI 6 to 176, I^2 = 0%, *p* = 0.82).
Consistency in results	Consistent for all outcomes.
Precision in results	Precise for all outcomes except relapse, insomnia, extrapyramidal symptoms, sexual dysfunction.
Directness of results	Direct
Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Silveira da Mota Neto JI, Kissling W, Leucht S. Amisulpride versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD006624. DOI: 10.1002/14651858.CD006624.pub2.	
This review includes 10 RCTs (N = 1549) compared amisulpride to olanzapine, risperidone or ziprasidone No significant difference was reported between any intervention for study attrition No significant differences in efficacy were reported between amisulpride and olanzapine.	

Risks	Compared to olanzapine, amisulpride also induced less weight gain (N = 671, 3 RCTs, MD = -2.11, 95%CI -2.94 to -1.29, I^2 = 0%, *p* = 0.58). Olanzapine was also associated with a higher increase of glucose (N = 406, 2 RCTs, MD = -7.30, 95%CI -7.62 to -6.99, I^2 = 0%, *p* = 0.52).There was no difference in terms of cardiac effects and extra pyramidal symptoms (EPS) compared with olanzapine (akathisia: N = 587, 2 RCTs, RR = 0.66 CI 0.36 to 1.21, I^2 = 0%, *p* = 0.51).
Consistency in results	Consistent for adverse effects, unable to assess efficacy
Precision in results	Imprecise for dichotomous outcomes, unable to assess continuous measures
Directness of results	Direct

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.

The review includes 50 RCTs (N = 9476) of olanzapine compared to amisulpride, aripiprazole, clozapine, quetiapine, risperidone or ziprasidone

Olanzapine had greater improvement of general mental state (measured by PANSS) compared to aripiprazole, (2 RCTs, N = 794, WMD = -4.96, 95%CI -8.06 to -1.85, I^2 = 0%, *p* = 0.66), quetiapine (10 RCTs, N = 1449, WMD = -3.66, 95%CI -5.39 to -1.93, I^2 = 0%, *p* = 0.69), risperidone (15 RCTs, N = 2390, WMD = -1.94, 95%CI -3.31 to -0.58, I^2 = 0%, *p* = 0.65) and ziprasidone (4 RCTs, N = 1291, WMD = -8.32, 95%CI -10.99 to -5.64, I^2 = 0%, *p* = 0.88), but not more than amisulpride or clozapine (1 RCT, N = 980, RR = 1.28, 95%CI 1.02 to 1.61).

Olanzapine had significantly fewer participants leave the study early due to inefficacy compared to quetiapine (8 RCTs, N = 1563, RR = 0.56, 95%CI 0.44 to 0.70, NNT 11, I^2 = 7%, *p* = 0.38), risperidone (14 RCTs, N = 2744, RR = 0.78, 95%CI 0.62 to 0.98, NNT 50, I^2 = 11%, *p* = 0.33) and ziprasidone (5 RCTs, N = 1937, RR = 0.64, 95%CI 0.51 to 0.79, NNT 17, I^2 = 0%, *p* = 0.78).

Olanzapine had fewer hospital re-admissions compared to quetiapine (2 RCTs, N = 876, RR = 0.56, 95%CI 0.41 to 0.77, NNT 11, I^2 = 0%, *p* = 0.98) and ziprasidone (2 RCTs, N = 766, RR = -0.06, 95%CI -0.11 to -0.01, NNT 17, I^2 = 0%, *p* = 0.77), but not clozapine (1 RCT, N = 980, RR = 1.28, 95%CI 1.02 to 1.61).

Risks	Olanzapine induced more weight gain compared to amisulpride (3 RCTs, N = 671,WMD = 2.11kg, 95%CI 1.29kg to 2.94kg, I^2 = 0%, *p* = 0.58); aripiprazole (1 RCT, N = 90, WMD = 5.60kg, 95%CI 2.15kg to 9.05kg); quetiapine (7 RCTs, N = 1173, WMD = 2.68kg, 95%CI 1.10kg to 4.26kg, I^2 = 76%, *p* = 0.00036); risperidone (13 RCTs, N =

	2116,WMD = 2.61kg, 95%CI 1.48kg to 3.74kg, I^2 = 83%, p < 0.00001); ziprasidone (5 RCTs, N = 1659, WMD = 3.82kg, 95%CI 2.96kg to 4.69kg, I^2 = 59%, p = 0.04). Related effects such as increases in glucose and cholesterol levels were also more frequent with olanzapine. Olanzapine was associated with slightly more extrapyramidal side effects than quetiapine, measured as the use of antiparkinson medication (6 RCTs, N = 1090, RR = 2.05, 95%CI 1.26 to 3.32, NNH 25, I^2 = 0%, p = 0.52), but less than risperidone (13 RCTs, N = 2599, RR = 0.78, 95%CI 0.65 to 0.95, NNH 17, I^2 = 28%, p = 0.17) and ziprasidone (4 RCTs, N = 1732, RR = 0.70, 95%CI 0.50 to 0.97, I^2 = 43%, p = 0.15). Olanzapine also increased prolactin more than aripiprazole (1 RCT, N = 317, RR = 3.74, 95%CI 1.68 to 8.33), clozapine (1 RCT, N = 120, WMD = 0.57, 95%CI 0.09 to 1.05) and quetiapine (5 RCTs, N = 1021, WMD = 5.89, 95%CI 0.16 to 11.62, I^2 = 59%, p = 0.04), but clearly less so than risperidone (6 RCTs, N = 1291, WMD = -22.84, 95%CI -27.98 to -17.69, I^2 = 65%, p = 0.01).
Consistency in results	Consistent for all except weight gain compared to quetiapine, risperidone and ziprasidone, and prolactin compared to risperidone.
Precision in results	Precise for dichotomous outcomes, unable to assess continuous measures.
Directness of results	Direct
Komossa K, Rummel-Kluge C, Schmid F, Hunger H, Schwarz S, Srisurapanont M, Kissling W, Leucht S. Quetiapine versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD006625 DOI: 10.1002/14651858.CD006625.pub2.	
This review includes 21 RCTs (N = 4101). No significant difference in study attrition was reported between the interventions, all had high numbers of participants leaving the study early. Compared to olanzapine, quetiapine had lower efficacy for reducing symptom severity (10 RCTs, N = 1449, WMD = 3.66, 95%CI 1.93 to 5.39, I^2 = 0%, p = 0.69).	
Risks	Compared to olanzapine, quetiapine produced fewer movement disorders (as measured by use of antiparkinson medication, 6 RCTs, N = 1090, RR = 0.49, 95%CI 0.3 to 0.79, NNH 25, I^2 = 0%, p = 0.52) and less weight gain (7 RCTs, N = 1173, WMD = -2.68, 95%CI -4.26 to -1.10, I^2 = 76%, p = 0.00036), but more QTc prolongation (3 RCTs, N =

	643, WMD = 4.81, 95%CI 0.34 to 9.28, I^2 = 0%, *p* = 0.68).
Consistency in results	Consistent for all except side effects.
Precision in results	Unable to assess continuous outcomes, imprecise for dichotomous outcomes.
Directness of results	Direct
Marriott RG, Neil W, Waddingham S. Antipsychotic medication for elderly people with schizophrenia. Cochrane Database of Systematic Reviews 2006; Issue 1. Art. No.: CD005580 DOI: 10.1002/14651858.CD005580.	
This review includes 3 RCTs (N = 252 elderly people with schizophrenia). Compared with second generation antipsychotic, risperidone there were no differences in global state (N = 171, 1 RCT, RR = 1.26 CI 0.8 to 1.9) and mental state (N =171, RR = 0.98 CI 0.76 to 1.26).	
Risks	Not reported.
Consistency in results	Not applicable; 1 RCT.
Precision in results	Imprecise
Directness of results	Direct
Nussbaum A, Stroup TS. Oral paliperidone for schizophrenia. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD006369. DOI: 10.1002/14651858.CD006369.pub2	
This review included 5 RCTs (N = not reported). Compared to second generation antipsychotic paliperdone, no differences are reported for study retention, (N = 1332, 3 RCTs, RR = 1.04 CI 0.89 to 1.21, I^2 = 0%, *p* = 0.49), or psychotic relapse (N = 1327, 3 RCTs, RR = 1.07, CI 0.64 to 1.76, I^2 = 53%, *p* = 0.12).	
Risks	Compared to paliperidone, olanzapine was more likely to produce a weight change (N = 660, 3 RCTs, WMD = -0.88 CI -1.38 to -0.37, I^2 = 10%, *p* = 0.33), however paliperidone may be more likely to cause extrapyramidal symptoms (N = 1327, 3 RCTs, RR = 2.99 CI 1.44 to 6.18, I^2 = 0%, *p* = 0.77).
Consistency in results	Consistent.
Precision in results	Precise for study retention only.

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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, 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

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 effect[1].

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]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an 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.

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‡ 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[1];

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

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§ 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[13].

‖ 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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