TECHNICAL COMMENTARY

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Mood stabilisers

Introduction

Mood stabilisers such as lithium and anticonvulsants (e.g. carbamazepine) have been proposed as an alternative therapy to standard antipsychotic treatments when individuals have sub-optimal responses to treatment.

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[2]. 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)[3]. 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 three systematic reviews that met our inclusion criteria[1, 4, 5].

- Moderate to high quality evidence suggests a large effect of greater improvement in overall symptoms with antipsychotics than with lithium.
- Moderate quality evidence suggests a medium-sized increased risk of leaving the study early for any reason or due to inefficacy of treatment with lithium than with antipsychotics. Lithium may result in less sleepiness, but more toxic confusion than antipsychotics.
- Moderate to low quality evidence suggests a large effect of less need for additional anticholinergic drugs with carbamazepine than with antipsychotics.

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Baethge C

Long-term treatment of schizoaffective disorder: review and recommendations

Pharmacopsychiatry 2003; 36(2): 45-56

View review abstract online

Comparison 1	**Carbamazepine vs. lithium (dose not reported) in people with schizoaffective disorder.**
Summary of evidence	**Low quality evidence (small sample, unable to assess consistency and precision, direct) is unable to determine any benefits of carbamazepine over lithium.**
All outcomes	
2 open-label RCTs and one retrospective study (N = 140) reported no differences between groups for up to 6.8 years. 1 open trial of carbamazepine (N = 6) without any comparison group found significantly increased relapse-free interval for up to 5.2 years after treatment commencement.	
Risks	Not reported
Consistency in results‡	Unable to assess, no measure of consistency is reported.
Precision in results§	Unable to assess, no measure of precision is reported.
Directness of results‖	Direct
Comparison 2	**Valproate alone or valproate + lithium (dose not reported) in people with schizoaffective disorder.**
Summary of evidence	**Low quality evidence (small sample, unable to assess consistency and precision, direct) is unable to determine any benefits of valproate with or without lithium.**
All outcomes	
3 studies (N = 25) reported some improvement for up to 3 years following treatment commencement.	
Risks	Not reported

Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct
Comparison 3	**Lithium vs. placebo, antipsychotics or antidepressants (doses not reported) in people with schizoaffective disorder.**
Summary of evidence	**Low quality evidence (small samples, unable to assess consistency and precision, direct) is unable to determine any benefits of lithium over any comparison.**
All outcomes	
Placebo: 1 study (N = 6) reported no significant differences between lithium and placebo for 2 years following treatment commencement. Antipsychotics: 3 studies (N = 111) reported no significant differences between lithium and antipsychotics for up to 5 years following treatment commencement. Antidepressants: 1 study (N = 35) reported no significant differences between lithium and antidepressants for 1.4 years following treatment commencement.	
Risks	Not reported
Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct

Leucht S, Kissling W, McGrath J

Lithium for schizophrenia

Cochrane Database of Systematic Reviews 2007; (3): CD001258

View review abstract online

Comparison 1	**Lithium (plasma level range 0.8-1.4 mEq/L) vs. placebo for up to 8 weeks.**
Summary of evidence	**Moderate to low quality evidence (small samples, consistent, imprecise, direct) finds no benefits of lithium over placebo.**

Leaving the study early
No significant difference between groups; 3 RCTs, N = 65, RR = 1.14, 95%CI 0.29 to 4.44, *p* = 0.85, Q = 0.0, *p* = 1.00, I^2 = 0%
Global state – no clinically important response
No significant difference between groups; 2 RCTs, N = 54, RR = 1.15, 95%CI 0.73 to 1.81, *p* = 0.54, Q = 0.0, *p* = 0.96, I^2 = 0%
Mental state – schizophrenia symptoms
No significant difference in New Haven Schizophrenia Index scores between groups: Less than 20% reduction: 1 RCT, N = 15, RR = 1.17, 95%CI 0.60 to 2.27, *p* = 0.65 Less than 35% reduction: 1 RCT, N = 15, RR = 1.17, 95%CI 0.60 to 2.27, *p* = 0.65 Less than 50% reduction: 1 RCT, N = 15, RR = 1.17, 95%CI 0.60 to 2.27, *p* = 0.65 *No significant difference in global Manchester Scale scores between groups;* Less than 20% reduction: 1 RCT, N = 39, RR = 1.20, 95%CI 0.46 to 3.13, *p* = 0.71 Less than 35% reduction: 1 RCT, N = 39, RR = 1.18, 95%CI 0.61 to 2.28, *p* = 0.62 Less than 50% reduction: 1 RCT, N = 39, RR = 1.14, 95%CI 0.63 to 2.07, *p* = 0.66 *No significant difference in Manchester Scale negative symptom scores between groups;* Less than 20% reduction: 1 RCT, N = 39, RR = 0.93, 95%CI 0.58 to 1.48, *p* = 0.76 Less than 35% reduction: 1 RCT, N = 39, RR = 1.00, 95%CI 0.64 to 1.56, *p* = 1.00 Less than 50% reduction: 1 RCT, N = 39, RR = 1.00, 95%CI 0.64 to 1.56, *p* = 1.00 *No significant difference in Manchester Scale positive symptom scores between groups;* Less than 20% reduction: 1 RCT, N = 39, RR = 2.14, 95%CI 0.81 to 5.67, *p* = 0.13 Less than 35% reduction: 1 RCT, N = 39, RR = 1.14, 95%CI 0.63 to 2.07, *p* = 0.66 Less than 50% reduction: 1 RCT, N = 39, RR = 1.14, 95%CI 0.63 to 2.07, *p* = 0.66
Mental state – depressive symptoms
No significant difference in Montgomery-Asberg Depression Rating Scale scores between groups; Less than 20% reduction: 1 RCT, N = 39, RR = 0.76, 95%CI 0.37 to 1.56, *p* = 0.46 Less than 35% reduction: 1 RCT, N = 39, RR = 0.95, 95%CI 0.50 to 1.81, *p* = 0.88 Less than 50% reduction: 1 RCT, N = 39, RR = 0.79, 95%CI 0.47 to 1.32, *p* = 0.37

Mental state – mania symptoms	
No significant difference in Bech-Rafaelsen scale scores between groups; Less than 20% reduction: 1 RCT, N = 39, RR = 0.98, 95%CI 0.44 to 2.17, *p* = 0.96 Less than 35% reduction: 1 RCT, N = 39, RR = 0.93, 95%CI 0.58 to 1.48, *p* = 0.76 Less than 50% reduction: 1 RCT, N = 39, RR = 0.99, 95%CI 0.67 to 1.47, *p* = 0.96	
Risks	Not reported.
Consistency in results	Consistent where applicable (> 1 RCT).
Precision in results	Imprecise
Directness of results	Direct
Comparison 2	**Lithium (various doses) vs. first generation antipsychotic medication (various doses) for 3 weeks to 1 year.**
Summary of evidence	**Moderate to high quality evidence (medium-sized sample, consistent where applicable, precise, direct) suggests a large improvement in overall symptoms with antipsychotics compared to lithium.** **Moderate quality evidence (medium-sized sample, consistent where applicable, imprecise, direct) suggests a medium-sized increased risk of leaving the study early for any reason or due to inefficacy of treatment with lithium. A large effect suggests lithium may result in less somnolence, but more toxic confusion than antipsychotics.** **Low quality evidence (small samples, inconsistent where applicable, imprecise, direct) is unable to determine any differences for global state, specific symptoms of schizophrenia or for depressive or manic type symptoms or other adverse effects.**
Leaving the study early	
People receiving lithium had a significant, medium-sized increased risk of leaving the study early for any reason or due to inefficacy of treatment, but not adverse effects; All reasons: 8 RCTs, N = 270, RR = 1.83, 95%CI 1.15 to 2.93, *p* = 0.011, Q = 6.15, *p* = 0.29, I^2 = 19% Due to inefficacy of treatment: 4 RCTs, N = 178, RR = 3.01, 95%CI 1.16 to 7.80, *p* = 0.023, Q = 0.85, *p* = 0.36, I^2 = 0%	

Due to adverse effects: 4 RCTs, N = 178, RR = 1.24, 95%CI 0.08 to 19.21, *p* = 0.88, Q = 0, *p* = 1.00, I^2 = 0%
Global state
No significant difference between groups; No clinically important response: 3 RCTs, N = 80, RR = 1.28, 95%CI 0.74 to 2.20, *p* = 0.38, Q = 5.00, *p* = 0.08, I^2 = 60% Not improved or worse: 2 RCTs, N = 36, RR = 2.72, 95%CI 0.05 to 135.10, *p* = 0.62, Q = 7.31, *p* = 0.01, I^2 = 86% Relapse: 1 RCT, N = 14, RR = 6.00, 95%CI 0.95 to 37.76, *p* = 0.056
Mental state – schizophrenia symptoms
Significant, large effect shows less improvement in the lithium group on; Manchester Scale and BPRS endpoint scores combined: 4 RCTs, N = 136, SMD = 0.81, 95%CI 0.46 to 1.17, *p* < 0.00001, Q = 5.57, *p* = 0.13, I^2 = 46% BPRS endpoint score: 3 RCTs, N = 92, SMD = 0.89, 95%CI 0.45 to 1.33, *p* = 0.000076, Q = 5.25, *p* = 0.07, I^2 = 62% Less than 20% reduction on Manchester Scale overall: 1 RCT, N = 44, RR = 3.83, 95%CI 0.89 to 16.44, *p* = 0.07 Less than 35% reduction on Manchester Scale overall: 1 RCT, N = 44, RR = 2.41, 95%CI 1.00 to 5.79, *p* = 0.049 Less than 50% reduction on Manchester Scale overall*:* 1 RCT, N = 44, RR = 2.19, 95%CI 1.00 to 4.78, *p* = 0.049 Manchester Scale endpoint score: 1 RCT, N = 44, SMD = 0.67, 95%CI 0.06 to 1.28, *p* = 0.031 Less than 20% reduction Manchester Scale negative*:* 1 RCT, N = 44, RR = 14.24, 95%CI 2.03 to 99.68, *p* = 0.0075 Less than 35% reduction Manchester Scale negative: 1 RCT, N = 44, RR = 7.67, 95%CI 1.97 to 29.82, *p* = 0.0033 Less than 50% reduction Manchester Scale negative: 1 RCT, N = 44, RR = 7.67, 95%CI 1.97 to 29.82, *p* = 0.0033 Less than 20% reduction Manchester Scale positive: 1 RCT, N = 44, RR = 10.95, 95%CI 1.53 to 78.43, *p* = 0.017 Less than 35% reduction Manchester Scale positive: 1 RCT, N = 44, RR = 4.38, 95%CI 1.43 to 13.40, *p* = 0.0096 Less than 50% reduction Manchester Scale positive: 1 RCT, N = 44, RR = 4.38, 95%CI 1.43 to 13.40, *p* = 0.0096

No significant differences on Structured Clinical Interview endpoint scores: 1 RCT, N = 11, MD = -2.00, 95%CI -81.29 to 77.29, *p* = 0.96	
Mental state – depressive symptoms	
No significant difference in Montgomery-Asberg Depression Rating Scale scores between groups; Less than 20% reduction: 1 RCT, N = 44, RR = 1.75, 95%CI 0.68 to 4.52, *p* = 0.25 Less than 35% reduction: 1 RCT, N = 44, RR = 1.56, 95%CI 0.73 to 3.36, *p* = 0.25 Less than 50% reduction: 1 RCT, N = 44, RR = 1.51, 95%CI 0.75 to 3.01, *p* = 0.25	
Mental state – mania symptoms	
No significant difference in Bech-Rafaelsen scale scores between groups; Less than 20% reduction: 1 RCT, N = 44, RR = 1.25, 95%CI 0.55 to 2.85, *p* = 0.59 Less than 35% reduction: 1 RCT, N = 44, RR = 1.42, 95%CI 0.80 to 2.53, *p* = 0.23 Less than 50% reduction: 1 RCT, N = 44, RR = 1.64, 95%CI 0.96 to 2.82, *p* = 0.071	
Risks	Significantly less somnolence was reported in the lithium group (1 RCT, N = 83, RR = 0.18, 95%CI 0.04 to 0.73, *p* = 0.017). Significantly less toxic confusion was reported in the antipsychotic group (2 RCTs, N = 104, RR = 9.27, 95%CI 1.22 to 70.55, *p* = 0.03, Q = 0.10, *p* = 0.75, I^2 = 0%). Increase in white blood cell count was reported in the lithium group (1 RCT, N = 21, RR = 17.42, 95%CI 1.14 to 265.34, *p* = 0.040) and slight decrease in the antipsychotic group (1 RCT, N = 21, RR = 0.07, 95%CI 0.00 to 1.11, *p* = 0.059). No differences between groups are reported for rates of blurred vision (N = 83, RR = 0.62, 95%CI 0.12 to 3.21, *p* = 0.57), dry mouth (N = 83, RR = 0.68, 95%CI 0.28 to 1.16, *p* = 0.40), constipation (N = 83, RR = 0.31, 95%CI 0.07 to 1.38, *p* = 0.12), dizziness (N = 83, RR = 0.62, 95%CI 0.12 to 3.21, *p* = 0.57), ataxia (N = 83, RR = 0.62 0.12 to 3.21, *p* = 0.57), hyperactive reflexes (N = 83, RR = 8.66, 95%CI 0.46 to 162.49, *p* = 0.15), muscle weakness (N = 83, RR = 1.24, 95%CI 0.18 to 8.42, *p* = 0.82), slurred speech (N = 83, RR = 0.83, 95%CI 0.15 to 4.70, *p* = 0.83), pruritus (N = 83, RR = 0.41, 95%CI 0.02 to 9.83, *p* = 0.58), dehydration (N = 83, RR = 3.71, 95%CI 0.16 to 88.51, *p* = 0.42), nausea (N = 83, RR = 0.62, 95%CI 0.12 to 3.21, *p* = 0.57), vomiting (N = 83, RR = 0.83, 95%CI 0.15 to 4.70, *p* = 0.83), parkinsonism (N = 83, RR = 0.25, 95%CI , 95%CI 0.01 to 5.00, *p* = 0.36), tremor (N = 83, RR = 2.18, 95%CI 0.69 to 6.87, *p* = 0.19),and proteinuria (N = 21, RR = 4.58, 95%CI 0.25 to 85.35, *p* = 0.31).
Consistency in results	Consistent where applicable, apart from not improved or worse global

	state.
***P*recision in results**	Precise for Manchester Scale and BPRS endpoint scores combined only.
Directness of results	Direct

Leucht S, Kissling W, McGrath J, White P

Carbamazepine for schizophrenia

Cochrane Database of Systematic Reviews 2007; (3): CD001258

View review abstract online

Comparison 1	**Antiepileptics alone (carbamazepine, 800-1200mg/day) over 95 days vs. placebo.**
Summary of evidence	**Low quality evidence (small sample, imprecise, direct) is unable to determine any benefit of carbamazepine over placebo.**
Leaving the study early	
No difference between groups; 1 RCT, N = 31, RR = 1.07, 95%CI 0.17 to 6.64, *p* = 0.94	
Relapse	
No difference between groups by 3 months. Both groups reported very high rates of relapse (13 participants relapsing per group); 1 RCT, N = 31, RR = 1.07, 95%CI 0.78 to 1.45, *p* = 0.68	
Mental state	
No difference in BPRS score reduction between groups; 1 RCT, N = 31, RR = 0.99, 95%CI 0.75 to 1.30, *p* = 0.94 *No difference in average BPRS endpoint scores between groups by 3 months;* 1 RCT, N = 27, WMD = -0.07, 95%CI -0.46 to 0.32, *p* = 0.72	
Risks	1 RCT, N = 31, reported no difference in rate of allergic reaction (RR 7.44, 95%CI 0.42 to 132.95), or blood dyscrasia (RR 3.19, 95%CI

	0.14 to 72.69)
Consistency in results	Not applicable; 1 RCT.
Precision in results	Imprecise for all, except unable to assess WMD.
Directness of results	Direct
Comparison 2	**Antiepileptics alone (carbamazepine, mean dose 1374mg/day) vs. any antipsychotics alone (perphenazine, mean dose 53mg/day); cross-over design, 3 weeks of each treatment.**
Summary of evidence	**Moderate to low quality evidence (small sample, precise, direct) suggests a large effect for less need of additional anticholinergic drugs to treat side effects in people receiving carbamazepine.** **Low quality evidence (imprecise) is unable to determine any benefit of carbamazepine for study attrition, mental state, and other adverse effects.**
Leaving the study early	
No difference between groups; 1 RCT, N = 38, RR = 4.52, 95%CI 0.23 to 88.38, *p* = 0.32	
Mental state	
No difference in average BPRS endpoint scores between groups; 1 RCT, N = 38, WMD = 2.30, 95%CI -3.84 to 8.44, *p* = 0.46 *No difference in degree of BPRS score reduction between groups;* Less than 20% reduction: 1 RCT, N = 38, RR = 1.29, 95%CI 0.62 to 2.66, *p* = 0.50 Less than 35% reduction: 1 RCT, N = 38, RR = 1.67, 95%CI 0.86 to 3.24, *p* = 0.13 Less than 50% reduction: 1 RCT, N = 38, RR = 1.23, 95%CI 0.78 to 1.92, *p* = 0.37 *After exclusion of people with schizoaffective disorder, the results favoured the antipsychotic group;* Less than 20% BPRS reduction: 1 RCT, N = 28, RR = 3.09, 95%CI 1.22 to 7.84, *p* = 0.017 Less than 35% BPRS reduction: 1 RCT, N = 28, RR = 2.32, 95%CI 1.15 to 4.67, *p* = 0.019 Less than 50% BPRS reduction: 1 RCT, N = 28, RR = 1.40, 95%CI 0.94 to 2.09, *p* = 0.094 (trend)	
Risks	1 RCT, N = 38, reported significantly reduced rates of parkinsonism (RR 0.03, 95%CI 0.00 to 0.43, *p* = 0.01) and use of anticholinergic drugs (RR 0.23, 95%CI 0.09 to 0.55, *p* = 0.001) in patients receiving

	carbamazepine compared to antipsychotics alone. No difference was reported in rate of akathisia (RR 0.13, 95%CI 0.01 to 2.34), tremor (RR 0.30, 95%CI 0.01 to 6.97), blurred vision (RR 0.45, 95%CI 0.04 to 4.55), collapse (RR 0.30, 95%CI 0.03 to 2.63), constipation (RR 0.45, 95%CI 0.04 to 4.55), dizziness (RR 4.52, 95%CI 0.23 to 88.38), dry mouth (RR 0.45, 95%CI 0.04 to 4.55), fatigue (RR 5.40, 95%CI 0.72 to 40.66), nausea (RR 2.71, 95%CI 0.12 to 62.70), salivation (RR 2.71, 95%CI 0.12 to 62.70), tachycardia (RR 0.75, 95%CI 0.28 to 2.04).
Consistency in results	Not applicable; 1 RCT.
Precision in results	Imprecise for all except anticholinergic drugs, unable to assess WMD.
Directness of results	Direct

Explanation of acronyms

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), N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic for the test of heterogeneity, RR = Risk ratio, vs. = versus, WMD = weighted mean difference

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[6].

† 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[6].

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[7]. 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[6];

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

§ 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[8].

‖ 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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