



Polypharmacy

Introduction

Medication combination treatment, also called polypharmacy, has been utilised in clinical practice for patients who are unresponsive or partially responsive to monotherapies. This topic covers antipsychotic, mood stabiliser, and/or antidepressant combinations for people with bipolar disorder.

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 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, the most recent and/or most comprehensive review 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 that describes a preferred way to present a meta-analysis¹. Reviews reporting less than 50% of items 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 five reviews that met our inclusion criteria³⁻⁷.

Any combination therapy vs. any monotherapy or placebo

- Moderate quality evidence suggests fewer relapses with combination therapy than with monotherapy or placebo. The risk of relapse is highest in the first year of treatment.

Antipsychotic olanzapine + antidepressant fluoxetine vs. placebo, olanzapine or anticonvulsant lamotrigine

- Moderate to high quality evidence suggests greater improvement in depression with combined olanzapine + fluoxetine therapy.

Second-generation antidepressants + mood stabilisers or antipsychotics vs. placebo + mood stabilisers or antipsychotics

- Moderate to high quality evidence suggests adjunctive second generation



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antidepressants were associated with a small, significant effect of greater improvement in depressive symptoms, but only over the short-term (< 12 weeks). There was also an increased risk of switching to mania/hypomania in the longer term (~52 weeks).

Mood stabilisers + antipsychotics vs. mood stabilisers

- Moderate to high quality evidence suggests mood stabilisers + antipsychotics resulted in small effects of better response and remission, and improved mania and depression symptoms. However, there are also increased rates of discontinuation due to adverse effects, in particular, sleepiness, somnolence, weakness, faintness, dizziness, appetite, weight gain, tremor, use of antiparkinsonian drugs, dry mouth and thirst, and changes in triglycerides, fasting glucose, and HbA1c levels.

Mood stabilisers + antipsychotics vs. antipsychotics

- Moderate quality evidence suggests mood stabilisers + antipsychotics results in small effects of better response and remission, and improved mania but not depression. However, there are medium-sized to large effects of more tremor, sleepiness, and vomiting.



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Farooq S, Singh SP

Fixed dose-combination products in psychiatry: Systematic review and meta-analysis

Journal of Psychopharmacology 2015; 29: 556-64

[View review abstract online](#)

Comparison	7-8 weeks of olanzapine + fluoxetine vs. placebo, olanzapine or lamotrigine.
Summary of evidence	Moderate to high quality evidence (large samples, imprecise, consistent, direct) suggests greater improvement in depression with combined olanzapine + fluoxetine therapy than with placebo, olanzapine or lamotrigine.
Depression	
<p><i>Greater improvement in depression scores with combination therapy;</i> 3 RCTs, N = 1,300, SMD = -0.32, 95%CI -0.45 to -0.19, $p < 0.001$, NNT = 16 <i>Results were similar in each comparison/trial;</i> Olanzapine + fluoxetine vs. placebo; 1 RCT, N = 463, SMD = -0.44, 95%CI 0.68 to -0.20, $p < 0.001$ Olanzapine + fluoxetine vs. lamotrigine; 1 RCT, N = 381, SMD = -0.27, 95%CI 0.47 to -0.07, $p = 0.01$ Olanzapine + fluoxetine vs. olanzapine; 1 RCT, N = 456, SMD = -0.26, 95%CI -0.50 to -0.03, $p = 0.03$</p>	
Risks	Not reported
Consistency in results[†]	Consistent
Precision in results[§]	Imprecise
Directness of results	Direct for individual comparisons.

Frecka E, Kovacs AI, Balla P, Falussy L, Ferencz A, Varga Z

The message of the survival curves: I. Composite analysis of long-term treatment studies in bipolar disorder



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<p>Neuropsychopharmacologia Hungarica 2012; 14: 155-64 View review abstract online</p>	
Comparison	Any combination therapy vs. any monotherapy vs. placebo.
Summary of evidence	Moderate quality evidence (large sample, precise for NNTs, unable to assess consistency, indirect) suggests fewer relapses with any combination therapy than any monotherapy or placebo. The risk of relapse is highest in the first year.
Relapse	
<p style="text-align: center;">28 studies, N = 5,231</p> <p style="text-align: center;"><i>Fewer relapses with combination therapy than with placebo or monotherapy;</i></p> <p style="text-align: center;">Combination vs. placebo: $\chi^2 = 283.3, p < 0.0001$</p> <p style="text-align: center;">Combination vs. monotherapy: $\chi^2 = 55.2, p < 0.001$</p> <p style="text-align: center;">Monotherapy NNT = 6, 95%CI 5.9 to 6.1</p> <p style="text-align: center;">Combination NNT = 3, 95%CI 2.9 to 3.1</p> <p style="text-align: center;">By 1 year: 48% relapsed with monotherapy vs. 35% with combination therapy</p> <p style="text-align: center;">By 2 years: 57% relapsed with monotherapy vs. 42% with combination therapy</p> <p style="text-align: center;">Authors report that from 12 to 28 months, relapse rates decrease, with rates being similar between the three groups; 15% with monotherapy, 14% with combination therapy, 14% with placebo. However, within the group of patients who remained stable until 1 year, the NNTs after one year were 14 with monotherapy and 8 with combination therapy.</p>	
Risks	Not reported
Consistency in results	No measure of consistency is reported.
Precision in results	NNTs appear precise.
Directness of results	Indirect

Galling B, Garcia MA, Osuchukwu U, Hagi K, Correll CU

Safety and tolerability of antipsychotic-mood stabilizer co-treatment in the management of acute bipolar disorder: results from a systematic review and exploratory meta-analysis

Expert Opinion on Drug Safety 2015; 14: 1181-99

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Comparison 1	3-12 weeks of mood stabilisers + antipsychotics vs. mood stabilisers alone.
Summary of evidence	Moderate to high quality evidence (large samples, imprecise or inconsistent, direct) suggests that compared to mood stabilisers alone, mood stabilisers + antipsychotics results in increased discontinuation due to adverse effects, in particular; more tremor and use of antiparkinsonian drugs; dry mouth/thirst; sleepiness, weakness, and faintness/dizziness; greater appetite and weight gain; and more change in triglycerides, fasting glucose, and HbA1c levels.
Discontinuation	
<i>Small effect of more discontinuation due to adverse effects with combination therapy;</i> 15 RCTs, N = 3,997, RR = 1.541, 95%CI 1.095 to 2.171, $p = 0.013$, test for heterogeneity $p = 0.041$	
Movement disorders	
<i>Small to medium-sized effects of more extrapyramidal adverse effects with combination therapy, in particular tremor and use of antiparkinsonian drugs;</i> At least one extrapyramidal adverse effect: 10 RCTs, N = 2,448, RR = 1.804, 95%CI 1.144 to 2.845, $p = 0.011$, test for heterogeneity $p < 0.001$ Tremor: 14 RCTs, N = 3,950, RR = 1.354, 95%CI 1.067 to 1.717, $p = 0.013$, test for heterogeneity $p = 0.501$ Use of antiparkinsonian drugs: 6 RCTs, N = 1990, RR = 2.839, 95%CI 1.983 to 4.065, $p < 0.001$, test for heterogeneity $p = 0.911$ There were no significant differences between groups in levels of akathisia, dyskinesia, hypokinesia, dystonia, parkinsonism, rigidity, or tardive dyskinesia.	
Anticholinergic	
<i>Medium-sized effect of more thirst or dry mouth with combination therapy;</i> Thirst, dry mouth: 11 RCTs, N = 2311, RR = 3.241, 95%CI 2.197 to 4.781, $p < 0.001$, test for heterogeneity $p = 0.173$ There were no significant differences between groups in levels of blurred vision.	
Arousal	
<i>Medium-sized effect of more sleepiness or somnolence with combination therapy;</i> Sleepiness/somnolence: 15 RCTs, N = 3,875, RR = 2.830, 95%CI 2.226 to 3.598, $p < 0.001$, test for heterogeneity $p = 0.130$	



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There were no significant differences between groups in levels of excitement, insomnia, or sedation.
Cardiovascular
<p><i>Small effect of more faintness or dizziness with combination therapy;</i> Faintness/dizziness: 12 RCTs, N = 2,908, RR = 1.838, 95%CI 1.360 to 2.483, $p < 0.001$, test for heterogeneity $p = 0.949$</p> <p>There were no significant differences between groups in levels of electrocardiography abnormalities, orthostasis, or QTc average change.</p>
Central nervous system
<p><i>Small effect of more weakness or fatigue with combination therapy;</i> 8 RCTs, N = 1,885, RR = 1.693, 95%CI 1.155 to 2.480, $p = 0.007$, test for heterogeneity $p = 0.344$</p> <p>There were no significant differences between groups in levels of anxiety, nervousness, depression, mania, or headache.</p>
Appetite and weight adverse events
<p><i>Medium-sized effects of more appetite and weight gain with combination therapy;</i> Increased appetite: 5 RCTs, N = 1,297, RR = 2.366, 95%CI 1.539 to 3.637, $p < 0.001$, test for heterogeneity $p = 0.612$</p> <p>Any weight gain: 9 RCTs, N = 2,484, RR = 2.905, 95%CI 1.746 to 4.835, $p < 0.001$, test for heterogeneity $p = 0.131$</p> <p>Weight gain > 7%: 9 RCTs, N = 2,413, RR = 3.674, 95%CI 2.273 to 5.939, $p < 0.001$, test for heterogeneity $p = 0.075$</p>
Metabolic and endocrine
<p><i>Small effects of more change in triglycerides, fasting glucose and HbA1c with combination therapy;</i> Triglycerides: 5 RCTs, N = 1271, SMD = 0.212, 95%CI 0.102 to 0.323, $p < 0.001$, test for heterogeneity $p = 0.507$</p> <p>Fasting glucose: 5 RCTs, N = 1340, SMD = 0.201, 95%CI 0.085 to 0.317, $p = 0.001$, test for heterogeneity $p = 0.333$</p> <p>HbA1c: 3 RCTs, N = 911, SMD = 0.252, 95%CI 0.082 to 0.421, $p = 0.004$, test for heterogeneity $p = 0.193$</p> <p>There were no differences between groups in levels of cholesterol, fasting glucose, insulin, prolactin or ALT levels.</p>
Other adverse events



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There were no differences between groups in levels of gastrointestinal, exanthema/Rash, rhinitis/nasopharyngitis/, upper respiratory tract infection or oedema.	
Consistency in results	Consistent, apart from extrapyramidal adverse effects and discontinuation.
Precision in results	Imprecise, apart from metabolic and endocrine.
Directness of results	Direct
Comparison 2	3-6 weeks of mood stabilisers + antipsychotics vs. antipsychotics alone.
Summary of evidence	Moderate quality evidence (medium-sized samples, imprecise, direct) suggests that, compared to antipsychotics alone, mood stabilisers + antipsychotics results in increased medium-sized to large effects of more tremor, sleepiness, and vomiting.
Movement disorders	
<i>Medium-sized effect of more tremor with combination therapy;</i> Tremor: 1 RCT, N = 356, RR = 3.173, 95%CI 1.537 to 6.554, $p = 0.002$	
Arousal	
<i>Medium-sized effect of more sleepiness with combination therapy;</i> Sleepiness/somnolence: 1 RCT, N = 356, RR = 2.327, 95%CI 1.135 to 4.772, $p = 0.021$	
Gastrointestinal	
<i>Large effect of more vomiting with combination therapy;</i> Vomiting: 1 RCT, N = 356, RR = 17.977, 95%CI 1.045 to 309.1, $p = 0.047$ There were no differences between groups in levels of constipation, diarrhea, nausea, and dyspepsia	
Other adverse events	
There were no differences between groups in levels of discontinuation, thirst, dry mouth, insomnia, cardiovascular factors, central nervous system factors, appetite and weight, prolactin, and exanthema/rash factors.	
Consistency in results	Not applicable; 1 RCT.
Precision in results	Imprecise
Directness of results	Direct



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McGirr A, Vohringer PA, Ghaemi SN, Lam RW, Yatham LN

Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials

The Lancet Psychiatry 2016; 3: 1138-46

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Comparison	6-12 weeks of adjunctive second-generation antidepressants (+ mood stabilisers or second-generation antipsychotics) vs. adjunctive placebo (+ mood stabilisers or second-generation antipsychotics) in people with bipolar depression.
Summary of evidence	Moderate to high quality evidence (large samples, imprecise, consistent, direct) suggests adjunctive second-generation antidepressants (+ mood stabilisers or antipsychotics) were associated with a small, significant effect of greater improvement in depressive symptom scores than with placebo (+ mood stabilisers or antipsychotics), but only over the short-term (< 12 weeks). There is also an increased risk of mania/hypomania switching in the longer term (~52 weeks).
Symptoms	
<p><i>Adjunctive second-generation antidepressants (+ mood stabilisers or antipsychotics) were associated with a small, significant effect of greater improvement in depressive symptom scores than with placebo (+ mood stabilisers or antipsychotics), but only over the short-term;</i></p> <p>6 RCTs, N = 1,383, SMD = 0.165, 95%CI 0.051 to 0.278, $p = 0.004$, $I^2 = 0\%$, $p < 0.05$</p> <p>There were no differences between groups in clinical response or remission rates, and meta-regression found decreasing efficacy with increasing trial duration.</p> <p>Authors report no evidence of publication bias.</p>	
Risks	There were no differences between groups in risk of treatment-emergent mania or hypomania in the short term (6-12 weeks), but in the longer term (follow-up ~52 weeks) there was a small increased risk of emergent mania/hypomania (2 RCTs, N = 463, OR = 1.774, 95%CI 1.018 to 3.091, $p = 0.043$).
Consistency in results	Consistent
Precision in results	Imprecise



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Directness of results	Direct for adjunctive antidepressants.
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Ogawa Y, Tajika A, Takeshima N, Hayasaka Y, Furukawa TA

Mood stabilizers and antipsychotics for acute mania: a systematic review and meta-analysis of combination/augmentation therapy versus monotherapy

CNS Drugs 2014; 28: 989-1003

[View review abstract online](#)

Comparison 1	3-12 weeks of mood stabilisers + antipsychotics vs. mood stabilisers alone.
Summary of evidence	Moderate to high quality evidence (large samples, some inconsistency or imprecision, direct) suggests small effects of better response and remission rates, and improved mania and depression symptoms with combined mood stabilisers + antipsychotics compared to mood stabilisers alone. However, more participants in the combination therapy group experienced at least one side effect, in particular somnolence and weight gain. Adding haloperidol or aripiprazole significantly increased extrapyramidal symptoms.
Response and remission	
<p><i>Small, significant effects of better response and remission rates with mood stabilisers + antipsychotics than mood stabilisers alone;</i></p> <p>Remission: 12 RCTs, N = 3,164, RR = 1.17, 1.07 to 1.28, $p < 0.05$, $I^2 = 23\%$</p> <p>Response: 11 RCTs, (N not reported), RR 1.25, 1.14 to 1.36, $p < 0.05$, $I^2 = 6\%$</p>	
Mania	
<p><i>Small, significant effect of improved mania symptoms with mood stabilisers + antipsychotics than mood stabilisers alone;</i></p> <p>12 RCTs, N = 3,164, SMD = -0.26, 95%CI -0.36 to -0.15, $p < 0.05$, $I^2 = 47\%$, $p = 0.03$</p> <p>Results were similar for individual adjunctive antipsychotics haloperidol, asenapine, olanzapine, quetiapine, risperidone and ziprasidone. Results for adjunctive aripiprazole and paliperidone were not significantly different to mood stabilisers alone.</p>	
Depression	



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<p><i>Small, significant effect of improved depression symptoms with mood stabilisers + antipsychotics than mood stabilisers alone;</i></p> <p>6 RCTs, (N not reported), SMD = -0.21, 95%CI -0.37 to -0.06, $p < 0.05$, I^2 not reported</p> <p>This result was particularly relevant for mood stabilisers + olanzapine.</p>	
Risks	<p>The dropout rates due to inefficacy showed a statistically significant superiority for the combination therapy (12 RCTs, N = 3,164, RR = 0.62, 95%CI 0.47 to 0.82, $p < 0.05$, I^2 not reported). However, significantly more participants in the combination therapy group experienced at least one side effect (8 RCTs, RR = 1.18, 95%CI 1.08 to 1.30, $p < 0.05$, $I^2 = 28%$), in particular somnolence (9 RCTs, RR = 2.46, 95%CI 1.91 to 3.18, $p < 0.05$, $I^2 = 0%$) and weight gain (7 RCTs, RR = 3.72, 95%CI 2.46 to 5.63, $p < 0.05$, $I^2 = 0%$). Adding haloperidol (2 RCTs, RR = 6.01, 95%CI 1.55 to 23.4, $p < 0.05$, I^2 not reported) and aripiprazole (1 RCT, RR = 2.03, 95%CI 1.26 to 3.25, $p < 0.05$) significantly increased extrapyramidal symptoms.</p> <p>There were no differences between groups in tremor and depression.</p>
Consistency in results	Inconsistent for mania symptoms.
Precision in results	Precise, apart from somnolence, weight gain, and extrapyramidal symptoms.
Directness of results	Direct
Comparison 2	3-6 weeks of mood stabilisers + antipsychotics vs. antipsychotics alone.
Summary of evidence	Moderate quality evidence (medium-sized samples, some inconsistency or imprecision, direct) suggests small effects of better response and remission rates, and improved mania with combined mood stabilisers + antipsychotics compared to antipsychotics alone.
Response and remission	
<p><i>Small, significant effects of better response and remission rates with lithium or valproate + antipsychotics than antipsychotics alone;</i></p> <p>Response: 4 RCTs, (N not reported), RR = 1.24, 1.11 to 1.39, $p < 0.05$, I^2 not reported</p> <p>Remission: 2 RCTs, (N not reported), RR = 1.28, 1.12 to 1.47, $p < 0.05$, I^2 not reported</p>	
Mania	
<p><i>Small, significant effects of more improved symptoms with lithium + antipsychotics than antipsychotics alone;</i></p>	



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<p>3 RCTs, N = 426, SMD -0.31, 95%CI -0.50 to -0.12, $p = 0.001$, $I^2 = 0\%$, $p > 0.05$ <i>Medium-sized, significant effects of more improved symptoms with valproate + antipsychotics than antipsychotics alone;</i> 1 RCT, N = 136, SMD -0.50, 95%CI -0.85 to -0.16, $p = 0.004$</p>	
<p>Depression</p>	
<p><i>No significant differences between lithium + quetiapine vs. quetiapine;</i> 1 RCT, N not reported, SMD = -0.15, 95%CI -0.35 to 0.06, $p > 0.05$</p>	
<p>Risks</p>	<p>Adding lithium to quetiapine increased tremor (1 RCT, N not reported, RR = 3.17, 95%CI 1.54 to 6.55, $p < 0.05$) and somnolence (1 RCT, N not reported, RR = 2.33, 95%CI 1.13 to 4.77, $p < 0.05$). There were no differences between groups in extrapyramidal symptoms, depression or weight gain.</p>
<p>Consistency in results</p>	<p>Consistent where reported (mania).</p>
<p>Precision in results</p>	<p>Precise for symptoms and response, imprecise for side effects.</p>
<p>Directness of results</p>	<p>Direct</p>

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), N = number of participants, NNT = number needed to treat, OR = odds ratio, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RCT = randomised controlled trial, RR = risk ratio, SMD = standardised mean difference, vs. = versus



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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 small⁸.

† 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).

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 effect⁸.

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 ⁹. InOR stands for logarithmic OR where a InOR 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 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 formula⁸;

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

§ 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 relaxed¹⁰.

|| 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 that 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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