TECHNICAL COMMENTARY

Haloperidol

Introduction

First generation 'typical' antipsychotics are an older class of antipsychotic than second generation 'atypical' antipsychotics. They are used primarily to treat positive symptoms including the experiences of perceptual abnormalities (hallucinations) and fixed, false, irrational beliefs (delusions).

First generation antipsychotics may cause side effects which can differ depending on which antipsychotic is being administered and on individual differences in reaction to the drug. Reactions may 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.

This table summarises overall group effectiveness of haloperidol from information gained from randomised controlled trials (RCTs). 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 included only 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, 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 11 reviews that met our inclusion criteria[3-13] . See below for detailed results.

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Haloperidol

Compared to placebo

Efficacy: High quality evidence (consistent, precise, direct, large sample) shows haloperidol results in greater clinical improvement and study retention than placebo. Moderate to high quality evidence (mostly consistent and precise, direct) suggests haloperidol is more effective for sedation and agitation.

Adverse effects: Moderate quality evidence (imprecise) suggests haloperidol may cause more movement disorders than placebo and may increase the risk of one or more other adverse effects within 24 hours of administration.

Comparing discontinuing haloperidol (switching to placebo) with continuing haloperidol

Efficacy: Moderate to low quality evidence (inconsistent, imprecise, direct, small samples) suggests participants allocated to discontinuing haloperidol were more likely to show no improvement in global state and those who continued haloperidol treatment were less likely to experience a relapse. Study retention was similar between groups.

Compared to other first generation antipsychotics

Efficacy: High quality evidence (consistent, precise, direct, large sample) shows no differences in clinical improvement when compared to chlorpromazine. Moderate to low quality evidence (imprecise) suggests no differences in clinical response or leaving the study for any reason when compared to low-potency first generation antipsychotics.

Adverse effects: Moderate to low quality evidence (imprecise) suggests more movement disorders, but less sedation, dizziness, orthostasis problems and weight gain with haloperidol than with low-potency first generation antipsychotics.

Compared to second generation antipsychotics

Efficacy: Moderate quality evidence (1 RCT, medium-sized sample) suggests haloperidol is associated with less improvement in mental state and less study retention than olanzapine. Olanzapine had benefits over haloperidol for sedation, and ziprasidone had benefits over haloperidol for global state. Haloperidol was more effective than risperidone for sedation and aggression and required fewer injections than aripiprazole. Haloperidol plus promethazine was more effective than haloperidol alone for inducing sleep by 20 minutes.

Adverse effects: Moderate quality evidence (large sample size, imprecise, consistent) suggests haloperidol caused more insomnia, dyspepsia, dystonia, and extrapyramidal effects, but less nausea, than aripiprazole. Haloperidol resulted in more risk of dystonia and extrapyramidal effects than olanzapine. Haloperidol resulted in less heartbeat change, but more akathisia than risperidone. Haloperidol resulted in more risk of any adverse event, particularly movement disorders, than ziprasidone.

Comparing different doses of haloperidol

Efficacy: Moderate to high quality evidence (consistent, precise, direct, medium-sized sample) suggests no differences between 3 to 7.5mg/day and 15 to 35mg/day. Low quality evidence (imprecise, small sample, 1 RCT) is unable to determine differences in global state

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between 3 to 7.5mg/day and 7.5 to 15mg/day. **Adverse effects: High quality evidence (consistent, precise, direct, large sample) suggests more extrapyramidal side effects with 15 to 35mg/day than 3 to 15mg/day. Moderate to low quality evidence (imprecise, small to medium-sized samples) also suggests more extrapyramidal side effects with 7.5 to 15mg/day than 3 to 7.5mg/day.** **See below for detailed results from 11 reviews.**
Bergman H, Rathbone J, Agarwal V, Soares-Weiser K. Antipsychotic reduction and/or cessation and antipsychotics as specific treatments for tardive dyskinesia. Cochrane Database of Systematic Reviews 2018; 2: CD000459.
There was greater clinical improvement in tardive dyskinesia with switching to quetiapine than switching to haloperidol (1 RCT, N = 45, RR 0.45, 95%CI 0.21 to 0.96, $p < 0.05$).

Consistency in results	Not applicable; 1 RCT.
Precision in results	Imprecise
Directness of results	Direct

Essali A, Turkmani K, Aboudamaah S, AbouDamaah A, Diaa Aldeen MR, Marwa ME, AlMounayer N. Haloperidol discontinuation for people with schizophrenia. Cochrane Database of Systematic Reviews 2019; 4: CD011408.
This review included 5 RCTs (N = 232). Participants allocated to discontinuing haloperidol treatment were more likely to show no improvement in global state compared with those in the haloperidol continuation group (N = 49, 1 RCT, RR 2.06, 95% CI 1.33 to 3.20). Those who continued haloperidol treatment were less likely to experience a relapse compared to people who discontinued taking haloperidol (N = 165, 4 RCTs, RR 1.80, CI 1.18 to 2.74, $I^2 = 72\%$). Leaving the study early was similar between groups.

Consistency in results	Inconsistent where applicable (>1 RCT).
Precision in results	Imprecise
Directness of results	Direct

Hamann J, Kissling W, 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 included 2 RCTs (N = 266). Compared to second generation antipsychotic olanzapine, haloperidol was associated with less improvement in mental state (N = 83, 1 RCT, RR 0.45 CI 0.3 to 0.7, NNH 3 CI 2 to 6), and less 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 olanzapine, haloperidol was associated with more use of 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
Huf G, Alexander J, Allen MH, Raveendran NS. Haloperidol plus promethazine for psychosis-induced aggression. Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD005146. DOI: 10.1002/14651858.CD005146	
This review included 4 RCTs (N = 1107). All studies had one arm in which haloperidol could be given by intramuscular injection. Comparing haloperidol plus the sedative promethazine with the sedative midazolam alone suggests haloperidol plus promethazine was not as effective as midazolam alone for sedation by 30 minutes (N = 301, 1 RCT, RR 2.9 CI 1.75 to 4.80, NNH5 CI 3 to 12). There were no differences by 2 to 3 hours (N = 301, 1 RCT, RR 1.73 CI 0.70 to 4.26, NNH5 CI 3 to 12). Comparing haloperidol plus the sedative promethazine with the sedative lorazepam alone suggests that haloperidol plus promethazine was more effective than lorazepam alone for sedation by 30minutes (N = 200, 1 RCT, RR 0.26 CI 0.10 to 0.68, NNT 8 CI 6 to 17). There were no differences by 4 hours (N = 200, 1 RCT, RR 1.00 CI 0.26 to 3.89). Comparing haloperidol plus the sedative promethazine with haloperidol alone suggests intramuscular haloperidol plus promethazine was more effective than intramuscular haloperidol alone for sedation by 20 minutes (1 RCT, N = 316, RR 0.65 CI 0.49 to 0.87, NNT 7 CI 5 to 17). At 2 hours, differences were also significant (but not at 40 minutes or 1 hour) (1 RCT, N = 316, RR 0.55 CI 0.32 to 0.96). Comparing haloperidol plus the sedative promethazine with second generation olanzapine suggests no differences at 15 minutes (1 RCT, N = 300, RR 0.74 CI 0.38 to 1.41), but by 1 hour olanzapine was less sedating (1 RCT, N = 300, RR 0.11 CI 0.01 to 0.87) requiring additional drugs within 4 hours (1 RCT, N = 300, RR 0.48 CI 0.33 to 0.69, NNT 5 CI 4 to 8) and to be re-assessed by the doctor (1 RCT, N = 300, RR 0.47 CI 0.30 to 0.73, NNT 6 CI 5 to 12).	
Risks	Comparing haloperidol plus the sedative promethazine with the sedative midazolam, there were no differences in the number of serious adverse effects by 30 minutes (1 RCT, N = 301, RR 1.01 CI 0.06 to 15.95). Comparing haloperidol plus the sedative promethazine with the sedative lorazepam, there were no differences in the number of

	serious adverse effects by 30 minutes (1 RCT, N = 200, RR 0.33 CI 0.01 to 8.09). Comparing haloperidol plus the sedative promethazine with haloperidol alone suggests haloperidol plus promethazine is associated with fewer serious adverse effects by 24 hours (1 RCT, N = 298, RR 0.09 CI 0.01 to 0.66, NNH 15 CI 14 to 40). Comparing haloperidol plus the sedative promethazine with second generation olanzapine there were no differences in the number of adverse effects by 4 hours (1 RCT, N = 300, RR 0.33 CI 0.04 to 3.17).
Consistency in results	Not applicable; all outcomes have only 1 RCT.
Precision in results	Precise for sedation by 20 minutes in the comparison of haloperidol plus promethazine with haloperidol and requiring additional drugs within 4 hours in comparison of haloperidol plus promethazine with olanzapine.
Directness of results	Direct
Irving CB, Adams CE, Lawrie S. Haloperidol versus placebo for schizophrenia. Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD003082. DOI: 10.1002/14651858.CD003082.pub2.	
This review includes 21 RCTs, (N = 1519). Compared to placebo, those on haloperidol clinically improved (< 6 weeks, 3 RCTs, N = 159, RR 0.44 CI 0.31 to 0.62, NNT 3 CI 2 to 5, I^2 = 0%, *p* = 0.40, 6-24 weeks, 8 RCTs, N = 308 RR 0.68 CI 0.59 to 0.81 NNT 3 CI 2.5 to 5, I^2 = 25%, *p* = 0.23), and showed increased treatment retention (< 6 weeks, 12 RCTs, N = 898, RR 0.83 CI 0.73 to 0.95, NNT 59 CI 38 to 200, I^2 = 0%, *p* = 0.59).	
Risks	Compared to placebo, haloperidol may cause movement disorders, at least in the short term (dystonia, 3 RCTs, N = 109, RR 8.52 CI 1.66 to 43.85, NNH 5 CI 3 to 9, I^2 = 0%, *p* = 0.99, akathisia, 4 RCTs, N = 333, RR 2.57 CI 1.39 to 4.75, NNH 7 CI 3 to 25, I^2 = 0%, *p* = 0.55 and parkinsonism, 4 RCTs, N = 163, RR 11.65 CI 2.88 to 47.11, NNH 3 CI 2 to 5 I^2 = 0%, *p* = 0.91).
Consistency in results	Consistent
Precision in results	Precise for efficacy outcomes, imprecise for adverse effects.
Directness of results	Direct
Leucht C, Kitzmantel M, Kane J, Leucht S, Chua WL. Haloperidol versus chlorpromazine for	

schizophrenia. Cochrane Database of Systematic Reviews 2008; Issue 1. Art. No.: CD004278. DOI: 10.1002/14651858.CD004278.pub2.
This review includes 14 RCTs (total N = 794). Nine compared oral formulations of both compounds, and five compared intramuscular formulations. Compared to first generation antipsychotic chlorpromazine, more people left the study early if they were taking haloperidol (13 RCTs, N = 476, RR 0.26 CI 0.08 to 0.82, I^2 = 0%, *p* = 0.88). There were no significant differences in clinical improvement (9 RCTs, N = 400, RR 0.81 CI 0.64 to 1.04, I^2 = 59%, *p* = 0.01). Authors state that similar trends were found when studies comparing intramuscular formulations and studies comparing oral formulations were analysed separately.

Risks	Compared to first generation antipsychotic chlorpromazine, movement disorders were more frequent in the haloperidol groups (6 RCTs, N = 212, RR 2.2 CI 1.11 to 4.40, NNH5 CI 3 to 33 I^2 = 43%, *p* = 0.14), while chlorpromazine was associated with more hypotension (5 RCTs, N = 175, RR 0.31 CI 0.11 to 0.88, NNH 7 CI 4 to 25 I^2 = 0%, *p* = 0.73). Authors state that similar trends were found when studies comparing intramuscular formulations and studies comparing oral formulations were analysed separately.
Consistency in results	Consistent for all outcomes except clinical improvement.
Precision in results	Imprecise for all outcomes except clinical improvement.
Directness of results	Direct

Marriott RG, Neil W, Waddingham S. Antipsychotic medication for elderly people with schizophrenia. Cochrane Database of Systematic Reviews 2006; (1):CD005580
This review includes 3 RCTs (N = 252 elderly people with schizophrenia). Compared to second generation antipsychotic olanzapine there were no differences in mental state (1 RCT, N = 59, WMD -3.60 CI -10.8 to 3.6; and WMD -6.00 CI -18.3 to 6.3).

Risks	Not reported.
Consistency in results	Not applicable; 1 RCT.
Precision in results	Unable to assess; standardised measures are not reported.
Directness of results	Direct

Ostinelli EG, Brooke-Powney MJ, Li X, Adams CE. Haloperidol for psychosis-induced aggression or agitation (rapid tranquillisation). Cochrane Database of Systematic Reviews

2017; 7: CD009377	
This review includes 41 RCTs in total (N = 4933). Compared to placebo, more people in the haloperidol group were asleep by two hours (2 RCTs, N = 220, RR 0.88, 95% CI 0.82 to 0.95, I^2 = 76%, *p* = 0.04), and had reduced agitated behaviour (2 RCTs, N = 425, RR 1.62, 95%CI 1.28 to 2.07, I^2 = 0%, *p* = 0.81). Compared to first-generation antipsychotic chlorpromazine there was a benefit of haloperidol for any global improvement (2 RCTs, N = 89, RR 0.15, CI 0.05 to 0.49, I^2 = 0%, *p* = 0.76), and for study retention (4 RCTs, N = 153, RR 0.21, CI 0.07 to 0.71, I^2 = 0%, *p* = 0.35). Compared to second-generation antipsychotic aripiprazole, people in the haloperidol group required fewer injections (2 RCTs, N = 473, RR 0.78, CI 0.62 to 0.99, I^2 = 0%, *p* = 0.40). Compared to olanzapine, haloperidol was less effective for sedation (1 RCT, N = 257, RR 1.16, 95%CI 1.02 to 1.32), and less effective than ziprasidone for global state (CGI-S) (1 RCT, N = 132, RR 0.34, 95%CI 0.13 to 0.55). Compared to risperidone, haloperidol was more effective for sedation (1 RCT, N = 162, RR 0.84, 95%CI 0.74 to 0.95), and aggression (1 RCT, N = 147, MD -0.50, 95%CI -0.58 to -0.42). Haloperidol plus promethazine was more effective than haloperidol alone for inducing sleep by 20 minutes (1 RCT, N = 316, RR 1.60, 95%CI 1.18 to 2.16).	
Risks	Compared to placebo, haloperidol increased the risk of one or more adverse effects within 24 hours (2 RCTs, N = 395, RR 1.64, CI 1.22 to 2.20, I^2 = 0%), particularly over sedation and extrapyramidal symptoms. Compared to chlorpromazine, haloperidol had decreased risk of drowsiness (1 RCT, N = 39, RR 0.06, CI 0.01 to 0.42). Compared to aripiprazole, haloperidol had increased insomnia (1 RCT, N = 360, RR 2.08, CI 1.01 to 4.27), dyspepsia (1 RCT, N = 477, RR 10.41, CI 1.36 to 79.76), dystonia (2 RCTs, N = 477, RR 6.63, CI 1.52 to 28.86, I^2 = 0%), extrapyramidal (1 RCT, N = 360, RR 9.46, CI 1.22 to 73.13), and less nausea (2 RCTs, N = 477, RR 0.18, CI 0.05 to 0.60, I^2 = 0%). Compared to loxapine, haloperidol had increased risk of drowsiness (1 RCT, N = 35, RR 33.16, CI 2.15 to 511.57). Compared to olanzapine, haloperidol had increased risk of dystonia (2 RCTs, N = 343, RR 12.92, CI 1.67 to 99.78, I^2 = 0%) and extrapyramidal effects (2 RCTs, N = 343, RR 7.65, CI 1.78 to 32.98, I^2 = 0%. Compared to risperidone, haloperidol had less heartbeat change (1 RCT, N = 162, MD -9.40, CI -9.99 to -8.81), but more akathisia (1 RCT, N = 162, RR 0.30, CI 0.24 to 0.36). Compared to thiothixene, haloperidol had more risk of drowsiness (2 RCTs, N = 74, RR 1.72, CI 1.02 to 2.90, I^2 = 0%).

	Compared to ziprasidone, haloperidol had more risk of any adverse event (3 RCTs, N = 739, RR 1.77, CI 1.49 to 2.11, I^2 = 67%), particularly movement disorders. Compared to lorazepam, haloperidol had more risk of extrapyramidal side effects (1 RCT, N = 66, RR 15.00, CI 2.11 to106.49). Compared to haloperidol plus promethazine, haloperidol resulted in more adverse effects (2 RCTs, N = 316, RR = 2.01, 95%CI 1.07-3.80, I^2 = 82%), particularly dystonia (1 RCT, N = 316, RR = 19.48, 95%CI 1.14 -331.92). Compared to risperidone plus clonazepam, haloperidol resulted in less overall adverse effects (1 RCT, N = 205, RR = 1.72, 95%CI 1.29-2.29), particularly extrapyramidal symptoms (1 RCT, N = 205, RR = 2.22, 95%CI 1.52-3.23).
Consistency in results	Consistent where applicable.
Precision in results	Imprecise
Directness of results	Direct
Tardy M, Huhn M, Kissling W, Engel RR, Leucht S. Haloperidol versus low-potency first-generation antipsychotic drugs for schizophrenia. Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD009268. DOI: 10.1002/14651858.CD009268.pub2	
This review includes 17 RCTs, (N = 877). There were no significant differences between haloperidol and low-potency antipsychotic drugs in terms of clinical response (14 RCTs, N = 574, RR 1.11, CI 0.86 to 1.44, *p* = 0.42, I^2 = 33%, *p* = 0.11), or leaving the studies early due to any reason (11 RCTs, N = 408, RR 0.82, CI 0.38 to 1.77 *p* = 0.62, I^2 = 43%, *p* = 0.08).	
Risks	More participants from the low-potency drug group experienced sedation (2 RCTs, N = 44, RR 0.30, CI 0.11 to 0.82, *p* = 0.019, I^2 = 0%, *p* = 0.95), dizziness (2 RCTs, N = 127, RR 0.36, CI 0.21 to 0.62, *p* = 0.00023, I^2 = 0%, *p* = 0.77), orthostasis problems (1 RCT, N = 41, RR 0.35, CI 0.16 to 0.78, *p* = 0.11) and weight gain (3 RCTs, N = 88, RR 0.22, CI 0.06 to 0.81, *p* = 0.23, I^2 = 0%, *p* = 0.46). In contrast, the outcome 'at least one movement disorder' was more frequent in the haloperidol group (5 RCTs, N = 170, RR 1.64, CI 1.22 to 2.21, *p* = 0.00097, I^2 = 24%, *p* = 0.26).
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Waraich PS, Adams CE, Roqué I, Figuls M, Hamill KM, Marti J. Haloperidol dose for the acute phase of schizophrenia. Cochrane Database of Systematic Reviews 2002, Issue 2. Art. No.: CD001951. DOI: 10.1002/14651858.CD001951.	
This review included 16 RCTs (N = not reported) Comparing low dose haloperidol 3 to 7.5mg/day with 7.5 to 15mg/day, no differences in global state were reported (N = 48, 1 RCT, RR 1.09 CI 0.67 to 1.75). Comparing haloperidol dose of 3 to 7.5mg/day with 15 to 35mg/day, no differences in global state were reported (N = 81, 2 RCTs, RR 0.95 CI 0.75 to 1.19, I^2 = 0%, *p* = 0.75). Authors state that all other comparisons did not yield significant differences, but several, particularly with lower dose ranges, were underpowered to detect clinically meaningful differences.	
Risks	Comparing low dose haloperidol 3 to 7.5mg/day with 7.5 to 15mg/day, 3 to 7.5 mg/day had a lower rate of extrapyramidal adverse effects (N = 64, 2 RCTs, RR 0.12 CI 0.01 to 2.12, I^2 = 0%, *p* = 1.00). Comparing haloperidol dose of 3 to 7.5mg/day with 15 to 35mg/day, 3 to 7.5 mg/day had a lower rate of extrapyramidal adverse effects (N = 144, 3 RCTs RR 0.59 CI 0.45 to 0.78, NNH 3 CI 2, I^2 = 0%, *p* = 0.48). Comparing low dose haloperidol 3 to 7.5mg/day with 35mg/day, 3 to 7.5 mg/day had a lower rate of extrapyramidal adverse effects (N = 86, 2 RCTs, RR 0.70 CI 0.45 to 1.09, I^2 = 35%, *p* = 0.21).
Consistency in results	Consistent where applicable (> 1 RCT).
Precision in results	Precise for comparisons of > 3 to 7.5mg/day with > 15 to 35mg/day only.
Directness of results	Direct.

Explanation of acronyms

CGI = Clinical Global Improvement, 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[14]. 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[15].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared to C and B was compared to 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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