TECHNICAL COMMENTARY

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Benzodiazapines

Introduction

Benzodiazepines have been proposed as an alternative therapy to standard antipsychotic treatments in an attempt to improve functional outcomes and treat symptoms that are not addressed by the antipsychotic medications. Benzodiazepine medications induce anxiolytic, sedative, muscle relaxant, and amnesic effects when used therapeutically. They bind to a subset of $GABA_A$ receptors (benzodiazepine receptors) in the central nervous system, increasing its affinity for the GABA neurotransmitter. This enhances the inhibitory GABA response in these cells, leading to a decrease in brain cell (neuron) excitability and resulting in the sedative and anxiolytic effects. However, peripheral benzodiazepine receptors are found throughout the body, facilitating many of the side-effects associated with benzodiazepine administration.

Benzodiazepines may be implemented as a short-term therapy in order to treat acute symptoms of psychosis, such as agitation or aggression. They have also been suggested as an ongoing treatment regime, as they may have fewer side effects than antipsychotics. However, the efficacy of benzodiazepines for reducing side effects of antipsychotics is unclear, as they may be associated with adverse effects of their own. Benzodiazepines are also associated with well-established patterns of tolerance and dependence and are prescribed with caution.

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[1]. 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)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion

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of staff of NeuRA (Neuroscience Research Australia).

Results

We found four systematic reviews that met our inclusion criteria[3-6].

- High quality evidence shows a lower risk of extrapyramidal side effects with benzodiazepines than with antipsychotics.
- Moderate quality evidence showed benzodiazepines were associated with a faster rate of sedation and more improvement in global state than antipsychotics. Moderate to low quality evidence suggests less excitation with antipsychotics than with benzodiazepines. No differences were found between benzodiazepines and antipsychotics in study attrition, behavioural improvement, mental state, need for additional medication or restraint, agitation, service use, hospital discharge, or relapse.
- Compared to placebo, moderate to low quality evidence suggests greater clinical improvement but a significantly increased risk of side effects such as low energy levels and ataxia with benzodiazepines. No differences were found between benzodiazepines and placebo in study attrition, relapse, anxiety, or other adverse effects.

Dold M, Li C, Tardy M, Khorsand V,Gillies D, Leucht S

Benzodiazepines for schizophrenia

CochraneDatabase of Systematic Reviews 2012; 11: Art. No.: CD006391. DOI: 10.1002/14651858.CD006391.pub2

View review abstract online

Comparison	**Benzodiazepines (diazepam, chlordiazepoxide, midazolam, alpidem) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, inconsistent, imprecise, direct) suggests people receiving benzodiazepines showed significantly greater clinical improvement than placebo, and some benefit for improving mental state (BPRS).** **Moderate quality evidence (consistent) suggests significantly increased risk of side effects, including reduced energy levels and ataxia. There were no differences in study attrition, relapse, mental state, anxiety, and other adverse effects.**

Leaving the study early

No difference between groups in the short term (up to 24 hours);

7 RCTs, N = 417, RR = 0.89, 95%CI 0.57 to 1.38, $p = 0.59$, $I^2 = 0\%$

Global state

A medium-sized effect of greater clinical improvement with benzodiazepines;

5 RCTs, N = 382, RR = 0.67, 95%CI 0.44 to 1.02, $p = 0.059$, $I^2 = 62\%$

No difference between groups in rate of relapse after one year;

2 RCTs, N = 58, RR = 0.84, 95%CI 0.41 to 1.74, $p = 0.65$, $I^2 = 81\%$

Mental state

Significantly lower mean BPRS score in the benzodiazepine group at 3 weeks post-treatment reported in one trial;

1 RCT, N = 66, WMD = -17.60, 95%CI -22.61 to -12.59, $p < 0.00001$

No difference between groups on;

BPRS: 1 RCT, N = 60, RR = 1.0, 95%CI 0.73 to 1.36, $p = 1.0$

MMS: 1 RCT, N = 60, RR = 0.90, 95%CI 0.52 to 1.57, *p* = 0.71 Anxiety: 1 RCT, N = 39, RR = 1.16, 95%CI 0.63 to 2.15, *p* = 0.64	
Risks	One RCT (N = 100) suggests the benzodiazepine group were significantly more likely to show any side effect, 1 RCT, RR = 1.44, 95%CI 1.02 to 2.04, *p* = 0.037. This includes a significantly increased risk of sleepiness or motor inhibition, 2 RCTs, N = 222, RR = 2.18, 95%CI 1.38 to 3.43, *p* = 0.00079, I^2 = 0%. A large effect size suggests a significantly increased risk of ataxia with benzodiazepines (RR = 8.18, 95%CI 1.35 to 49.74, *p* = 0.022, I^2 = 0%). There was no significant difference in risk of an autonomic reaction (flushing, dry mouth, 1 RCT, RR 1.71, 95%CI 0.75 to 3.93), cardiovascular reaction (stats not reported), anorexia (stats not reported), depression (stats not reported), increased energy levels (2 RCTs, RR 0.62, 95%CI 0.02 to 22.78), gastrointestinal reaction (3 RCTs, RR 0.99, 95%CI 0.29 to 3.37), headache (2 RCTs, RR 0.75, 95%CI 0.20 to 2.81), insomnia (1 RCT, RR 1.14, 95%CI 0.05 to 27.28), sedation (2 RCTs, RR 3.00, 95%CI 0.15 to 61.74).
Consistency in results	Consistent for all except clinical improvement, unable to assess outcomes with 1 RCT.
Precision in results	Imprecise
Directness of results	Direct
Comparison 2	**Benzodiazepines alone (lorazepam, diazepam, clonazepam, chlordiazepoxide, midazolam) vs. antipsychotics alone (haloperidol, fluphenazine, chlorpromazine, thioridazine).**
Summary of evidence	**Moderate to high quality evidence (small to medium-sized samples, consistent, precise, direct) suggests people receiving benzodiazepines were significantly more likely to be asleep or tranquil (within 60 minutes) than those on antipsychotics.** **Moderate quality evidence (imprecise) suggests no differences in study attrition, clinical improvement, relapse, mental state, side effects, sedation, aggression or hospitalisation.**
Leaving the study early	
A trend for higher attrition in the benzodiazepine group due to side effects in the ultra-short term (up to 24 hours); 3 RCTs, N = 351, RR = 13.00, 95%CI 0.78 to 216.39, *p* = 0.074, I^2 = 0% *No difference between groups in leaving the study early for any reason in the ultra-short term;*	

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7 RCTs, N = 514, RR = 0.67, 95%CI 0.33 to 1.36, *p* = 0.27, I^2 = 6%
No difference between groups in leaving the study early for any reason in the short term (up to 10 weeks);
4 RCTs, N = 161, RR = 0.65, 95%CI 0.27 to 1.56, *p* = 0.34, I^2 = 0%
No difference between groups in leaving the study early for any reason in the long term (up to 3 years);
2 RCTs, N = 63, RR = 5.00, 95%CI 0.26 to 96.13, *p* = 0.29, I^2 = 0%
Global state
No difference between benzodiazepines and antipsychotics in the degree of clinical improvement in the short term;
30 minutes (similar results at 60 minutes): 1 RCT, N = 44, RR = 0.91, 95%CI 0.58 to 1.43, *p* = 0.69
12 hours: 1 RCT, N = 66, RR = 0.99, 95%CI 0.71 to 1.38, *p* = 0.94
2 weeks: 1 RCT, N = 52, RR = 1.11, 95%CI 0.39 to 3.19, *p* = 0.84
A small effect of lower CGI scores in the benzodiazepine group 1 hour post-treatment, that was not maintained at 4 hours;
1 hour: 1 RCT, N = 37, RR = -0.67, 95%CI -1.09 to -0.25, *p* = 0.002
4 hours: 1 RCT, N = 37, RR = -0.62, 95%CI -1.36 to 0.12, *p* = 0.10
No difference between groups in rate of relapse by one year;
2 RCTs, N = 63, RR = 2.02, 95%CI 0.37 to 11.04, *p* = 0.42, I^2 = 83%
Mental state
Significant reductions in the antipsychotic group on psychosis-specific BPRS items at 1 hour post-treatment only;
1 RCT, WMD = 6.00, 95%CI 0.68 to 11.32, *p* = 0.027
No difference between groups for improvements in mental state on;
BPRS: 1 RCT, N = 60, RR = 2.50, 95%CI 0.60 to 10.34, *p* = 0.21
BPRS: 1 RCT, N = 37, WMD = -1.73, 95%CI -9.60 to 6.14, *p* = 0.67
MMS: 1 RCT, N = 60, RR = 1.13, 95%CI 0.60 to 2.13, *p* = 0.72
Sedation
A medium-sized effect of more likelihood to be tranquil or asleep at 20 minutes with benzodiazepines, a trend was maintained up to 60 minutes, and there were no differences between groups at 2 or 12 hours;
20 minutes: 1 RCT, N = 301, RR = 1.32, 95%CI 1.16 to 1.49, *p* = 0.000015

60 minutes: 2 RCT, N = 345, RR = 1.07, 95%CI 1.00 to 1.15, p = 0.056, I^2 = 0% 12 hours: 1 RCT, N = 66, RR = 0.75, 95%CI 0.44 to 1.30, p = 0.31 *No difference in level of sedation at 2 hours;* 1 RCT, N = 16, WMD = 0.10, 95%CI -0.98 to 1.18, p = 0.86	
Behaviour	
No difference in aggressive behaviour following treatment; Needing restraint within 2 hours: 1 RCT, N = 301, RR = 0.82, 95%CI 0.55 to 1.22, p = 0.33 Use of tranquilising drugs within 2 hours: 1 RCT, N = 301, RR = 0.28, 95%CI 0.06 to 1.34, p = 0.11 Any episode of aggression by 24 hours: 1 RCT, N = 301, RR = 1.12, 95%CI 0.78 to 1.62, p = 0.54 Mean aggression score (ABS) after 12 hours: 1 RCT, N = 66, WMD = 3.00, 95%CI -2.32 to 8.32, p = 0.27	
Service use	
No difference in the likelihood of hospital discharge by 2 weeks; 1 RCT, N = 301, RR = 0.96, 95%CI 0.77 to 1.18, p = 0.68	
Risks	2 RCT (N = 118) reported no significant difference in risk of any side effect, RR = 0.73, 95%CI 0.45 to 1.17, p = 0.19, I^2 = 0%. Specifically, there was no significant difference in risk of movement disorder (including ataxia, 2 RCT RR 0.80, 95%CI 0.11 to 5.60), respiratory depression (1 RCT, RR 2.98, 95%CI 0.23 to 72.58), dry mouth (2 RCT, RR 1.36, 95%CI 0.35 to 5.33), cardiovascular reaction (stats not reported), anorexia (1 RCT, RR 0.19, 95%CI 0.01 to 3.69), depression (1 RCT, RR 0.19, 95%CI 0.01 to 3.69), dizziness (1 RCT, RR 1.13, 95%CI 0.25 to 5.19), change in energy levels (decreased:1 RCT, RR 0.56, 95%CI 0.24 to 1.30; increased: 1 RCT, RR 0.93, 95%CI 0.06 to 14.03), gastrointestinal reaction (stats not reported), headache (1 RCT, RR 0.19, 95%CI 0.01 to 3.69), insomnia (no stats reported), sedation (1 RCT, RR 1.76, 95%CI 0.33 to 9.36), seizure (1 RCT, RR 0.33, 95%CI 0.01 to 8.06).
Consistency in results	Consistent, unable to assess if 1 RCT.
Precision in results	Imprecise for all except tranquil or asleep (20-60 mins), unable to assess WMD.
Directness of results	Direct

Gillies D, Beck A, McCloud A, Rathbone J

Benzodiazepines for psychosis-induced aggression or agitation

Cochrane Database of Systematic Reviews 2005; 4: Art. No.: CD003079. DOI: 10.1002/14651858.CD003079.pub2

View review abstract online

Comparison	**Benzodiazepines alone (lorazepam, clonazepam, flunitrazepam, diazepam) of 1-6 doses spread up to 24 hours vs. any antipsychotics alone (haloperidol, olanzapine, clotiapine), for acute psychosis. Both oral and intramuscular medications reported.** **Note – this review contains a mixed sample of people with acute psychosis, including schizophrenia spectrum, bipolar, acute agitation.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, consistent, imprecise, direct) showed no differences in sedation, study attrition, behavioural improvement or mental and global state, or need for additional medication.** **High quality evidence (large sample, consistent, precise, direct) shows a significantly lower risk of extrapyramidal effects in the benzodiazepine group.** **Moderate to low quality evidence (unable to assess consistency or precision, direct) favoured the antipsychotic group for reducing excitation levels.**
Global state	
No difference between groups in the need for additional medication for up to 48 hours after admission; 2 RCTs, N = 216, RR = 1.28, 95%CI 0.51 to 3.22, p = 0.60, Q = 14.69, p = 0.00013, I^2 = 93% *No difference in change in CGI scores for up to 48 hours after admission;* 2 RCTs, N = 189, WMD = 0.20, 95%CI -0.07 to 0.47, p = 0.16, Q = 1.19, p = 0.28, I^2 = 16%	
Leaving the study early	

No difference in the number of people leaving the study early for up to 48 hours; 4 RCTs, N = 254, RR = 1.70, 95%CI 0.11 to 27.35, *p* = 0.71, Q = 2.19, *p* = 0.14, I^2 = 54%	
Sedation	
No difference in the number of people rated as under sedation; 6 RCTs, N = 324, RR = 0.76, 95%CI 0.48 to 1.21, *p* = 0.25, Q = 1.41, *p* = 0.92, I^2 = 0%	
Behaviour	
No difference in behavioural improvements using the Overt Aggression Scale (OAS) for up to 48 hours; 1 RCT, N = 28, RR = 2.60, 95%CI 0.31 to 22.05, *p* = 0.38	
Mental state	
Fewer people in the antipsychotic group rated high on excitation scores (PANSS-subscale) for up to 48 hours; 1 RCT, N = 150, RR = 1.84, 95%CI 1.06 to 3.18, *p* = 0.03 *Greater improvement on PANSS excitation scores in the antipsychotic group;* 1 RCT, N = 149, WMD = 2.85, 95%CI 1.14 to 4.56, *p* = 0.0011 *Greater improvement on PANSS total change scores in the antipsychotic group;* 1 RCT, N = 146, WMD = 5.64, 95%CI 2.20 to 9.08, *p* = 0.0013 *Greater improvement on BPRS-total change scores in the benzodiazepine group for up to 48 hours;* 1 RCT, N = 20, WMD = -7.60, 96%CI -13.87 to -1.33, *p* = 0.017 *No difference mental state using the Inpatients Multidimensional Psychiatric Scale –(IMPS) for up to 48 hours;* 1 RCT, N = 16, RR = 1.50, 95%CI 0.34 to 6.70, *p* = 0.60, I^2 = NA *No difference in average BPRS score;* Up to 1 hour: 1 RCT, N = 37, WMD = -3.26, 95%CI -10.65 to 4.13, I^2 = NA Up to 48 hours: 1 RCT, N = 37, = WMD = -4.07, 95%CI -10.76 to 2.62, I^2 = NA *No difference in BPRS psychosis subscale scores for up to 48 hours;* 1 RCT, N = 66, WMD = -0.30, 95%CI -4.65 to 4.05, *p* = 0.89	
Risks	From 7 RCTs, a large effect size suggests the risk of extrapyramidal effects was significantly lower in the benzodiazepine group (N = 391, RR = 0.17, 95%CI 0.06 to 0.43, *p* = 0.00023, I^2 = 0%). From 2 RCTs,

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	there was no significant difference between groups for risk of ataxia (1 RCT, RR 2.26, 95%CI 0.22 to 23.71), dizziness (2 RCTs, RR 1.39, 95%CI 0.63 to 3.07), dry mouth (1 RCT, RR 1.88, 95%CI 0.49 to 7.24), nausea (1 RCT, RR 7.76, 95%CI 0.89 to 67.67), or speech disorder (1 RCT, RR 0.56, 95%CI 0.11 to 2.87).
Consistency in results	Consistent for all except 'need for additional medication', and not applicable for outcomes with 1 RCT.
Precision in results	Imprecise for all binary outcomes (RR), unable to assess WMD.
Directness of results	Direct

Huf G, Alexander J, Allen MH

Haloperidol plus promethazine for psychosis induced aggression

Cochrane Database of Systematic Reviews 2005; (1): CD005146

View review abstract online

Comparison	**Intramuscular haloperidol plus promethazine (phenergan) vs. benzodiazepines for reducing psychosis-induced aggression.** **Note – this review contains a mixed sample of people with acute psychosis, including schizophrenia spectrum, bipolar, and acute agitation.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, mostly consistent, imprecise, direct) suggests no differences in the need for additional medication or restraint, or for relapse of aggression. There were no differences in service use, hospital discharge, or study attrition. The haloperidol plus promethazine group showed greater immediate clinical improvement, but this effect was lost by 2 to 4 hours post-treatment.**

Sedation

2 RCTs report conflicting findings on the risk of not being tranquil or asleep in the short term (up to 2 hours), I^2 = 84% (pooled effect size not reported).

1 RCT (N = 301) favours haloperidol plus promethazine for likelihood of sedation by 2 hours (RR = 1.73, 95%CI 0.70 to 4.26, *p* not reported); however 1 RCT (N = 200) favours benzodiazepines for likelihood of sedation by 2 hours (RR = 0.25, 95%CI 0.07 to 0.86, *p* not reported).

Aggression	
No difference in need for additional tranquilising drugs for up to 2 hours; 2 RCTs, N = 501, RR = 1.67, 95%CI 0.62 to 4.54, *p* = 0.31, Q = 2.02, *p* = 0.15, I^2 = 51% *No difference in the need for restraint or seclusion for up to 2 hours;* 2 RCTs, N = 501, RR = 1.09, 95%CI 0.77 to 1.56, *p* = 0.63, Q = 1.08, *p* = 0.30, I^2 = 7% *No difference in the occurrence of a second aggressive episode for up to 24 hours;* 1 RCT, N = 301, RR = 0.89, 95%CI 0.62 to 1.29, *p* = 0.54	
Global state	
Higher rate of clinically significant improvement in the haloperidol plus promethazine group at 30 minutes, 1 hour, and 2 hours, which was not maintained at 4 hours; 30 mins: 1 RCT, N = 200, RR = 0.40, 95%CI 0.25 to 0.66, *p* = 0.0003 1 hour: 1 RCT, N = 200, RR = 0.50, 95%CI 0.32 to 0.79, *p* = 0.0031 2 hours: 1 RCT, N = 200, RR = 0.46, 95%CI 0.25 to 0.86, *p* = 0.015 4 hours: 1 RCT, N = 200, RR = 0.93, 95%CI 0.46 to 1.87, *p* = 0.84 *Greater average improvement in CGI scores in the haloperidol plus promethazine group at 30 minutes and 1 hour, which was not maintained at 2 or 4 hours;* 30 mins: 1 RCT, N = 200, WMD = -0.60, 95%CI -0.86 to -0.34, *p* < 0.00001 1 hour: 1 RCT, N = 200, WMD = -0.33, 95%CI -0.54 to -0.12, *p* = 0.0018 2 hours: 1 RCT, N = 200, WMD = -0.23, 95%CI -0.51 to 1.05, *p* = 0.11 4 hours: 1 RCT, N = 200, WMD = -0.09, 95%CI -0.32 to 0.14, *p* = 0.45	
Service outcomes	
No difference in the need for doctor supervision within 24 hours; 2 RCTs, N = 501, RR = 0.82, 95%CI 0.60 to 1.10, *p* = 0.18, Q = 0.19, *p* = 0.67, I^2 = 0% *No difference in the patients' willingness to receive oral medications within 2 weeks;* 2 RCTs, N = 501, RR = 1.00, 95%CI 0.59 to 1.72, *p* = 0.99, Q = 2.26, *p* = 0.13, I^2 = 56% *No difference in the patients' likelihood of hospital discharge within 2 weeks;* 2 RCTs, N = 501, RR = 1.08, 95%CI 0.91 to 1.28, *p* = 0.39, Q = 0.19, *p* = 0.67, I^2 = 0% *No difference in the likelihood of leaving the study early within 2 weeks;* 2 RCTS, N = 501, RR = 0.91, 95%CI 0.41 to 2.05, *p* = 0.83, Q = 1.98, *p* = 0.16, I^2 = 50%	
Risks	2 RCTs (N = 501) report no significant difference in risk of a serious adverse event by 30 minutes post-treatment, RR = 0.60, 95%CI 0.08

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	to 4.52, p = 0.62, I^2 = 0%, and no difference was maintained over 4 hours. There was also no significant difference in the risk of extrapyramidal effects, assessed by Simpson-Angus scale, RD = 0.0, 95%CI -0.02 to 0.02, p = 1.0.
Consistency in results	Consistent for all (where applicable) except sedation.
Precision in results	Imprecise for all except hospital discharge, unable to assess WMD.
Directness of results	Direct

Explanation of acronyms

ABS = Agitated Behaviour Scale, BPRS = Brief Psychiatric Rating Scale, CGI = clinical global improvement scale, CI = confidence interval, IMPS = Inpatients Multidimensional Psychiatric Scale, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, NA = not applicable, OAS = Overt Aggression Scale, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), MMS = Malamud-Sands Scale, PANSS = Positive and Negative Syndrome Scale, Q = Q statistic for the test of heterogeneity, RCT = Randomised Controlled Trial, RR = Relative Risk, 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[7].

† 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[7].

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[8]. 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[7];

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

§ 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[9].

‖ 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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