TECHNICAL COMMENTARY

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Anti-inflammatory medications

Introduction

Growing evidence suggests that inflammatory processes may contribute to the development of schizophrenia. This suggests a potential role for anti-inflammatory medications, such as non-steroidal agents (e.g., aspirin) which may be potentially useful therapeutic strategies, particularly in combination with ongoing antipsychotic medication.

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, and PsycINFO. 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 that 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 of staff of NeuRA (Neuroscience Research Australia).

Results

We found nine systematic reviews that met inclusion criteria[3-11].

- Moderate to high quality evidence suggests a large benefit of adjunctive N-acetylcysteine and medium-sized benefits of adjunctive oestrogen and minocycline for improving symptoms. There was also a small benefit of adjunctive aspirin for symptom improvement.
- Moderate quality evidence suggests medium to large benefits of adjunctive melatonin, withania somnifera extract, pioglitazone, piracetam, and pregnenolone for improving symptoms.
- Moderate quality evidence suggests a medium-sized benefit of adjunctive celecoxib for improving symptoms in first-episode, but not chronic patients.

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- Moderate quality evidence suggests improved executive functioning with adjunctive minocycline and improved working memory with adjunctive N-acetylcysteine.
- There were no significant benefits of adjunctive fatty acids, statins, davunetide, bexarotene, dextromethorphan, or varenicline.

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Cakici N, van Beveren N, Judge-Hundal G, Koola M, Sommer I

An update on the efficacy of anti-inflammatory agents for patients with schizophrenia: A meta-analysis

Psychological Medicine 2019; 49: 2307-19

View review abstract online

Comparison	**Adjunctive anti-inflammatory medications vs. placebo.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests a large benefit of adjunctive N-acetylcysteine and medium-sized benefits of adjunctive oestrogen and minocycline for improvement in symptoms. There was also a small benefit of adjunctive aspirin for symptoms.** **Moderate quality evidence (small samples, consistent, imprecise, direct) suggests large benefits of adjunctive melatonin, withania somnifera extract, pioglitazone, and piracetam for improving symptoms.** **There were no significant benefits of adjunctive fatty acids, celecoxib, statins, davunetide, bexarotene, dextromethorphan, pregnenolone, or varenicline.**

Symptoms

Large effects of reduced symptom severity with;

N-acetylcysteine (600 to 3600mg daily for 8 to 52 weeks): 5 RCTs, N = 442, g = 1.00, 95%CI 0.60 to 1.41, $p < 0.001$, I^2 = 75%

Melatonin (3mg daily for 8 weeks): 1 RCT, N = 36, g = 2.82, 95%CI 1.91 to 3.74, $p < 0.001$, I^2 = N/A

Withania somnifera extract (1000mg daily for 12 weeks): 1 RCT, N = 68, g = 0.81, 95%CI 0.32 to 1.30, p = 0.001, I^2 = N/A

Pioglitazone (30mg daily for 8 weeks): 1 RCT, N = 42, g = 0.79, 95%CI 0.17 to 1.41, p = 0.012, I^2 = N/A

Piracetam (3200mg daily for 8 weeks): 1 RCT, N = 30, g = 0.77, 95%CI 0.05 to 1.50, p = 0.036, I^2 = N/A

Medium-sized effects of reduced symptom severity with;

Oestrogen (0.05 to 2mg daily) or raloxifene (60 to 120 mg daily): 11 RCTs, N = 723, g = 0.57,

95%CI 0.25 to 0.90, p = 0.001, I^2 = 74% Minocycline (100 to 300mg daily for 2 to 12 months): 11 RCTs, N = 946, g = 0.40, 95%CI 0.11 to 0.68, p = 0.007, I^2 = 77% *A small effect of reduced symptom severity with;* Aspirin (1000mg daily for 3 to 4 months): 2 RCTs, N = 270, g = 0.30, 95%CI 0.06 to 0.54, p = 0.01, I^2 = 0% *No significant differences for;* Fatty acids eicosapentaenoic (0.5g daily), docosahexaenoic (4g daily), or omega-3 (0.4 to 2.2g daily): 11 RCTs, N = 652, g = 0.19, 95%CI -0.02 to 0.40, p = 0.07, I^2 = 41% Celecoxib (400mg daily for 5 to 11 weeks): 5 RCTs, N = 465, g = 0.15, 95%CI -0.67 to 0.96, p = 0.73, I^2 = 93% Statins (40mg daily for 8-12 weeks): 2 RCTs, N = 126, g = 0.50, 95%CI -0.25 to 1.25, p = 0.19, I^2 = 78% Davunetide (5 or 30mg daily for 3 months): 1 RCT, N = 85, g = -0.24, 95%CI -0.65 to 0.19, p = 0.70, I^2 = N/A Bexarotene (75 mg daily for 6 weeks): 1 RCT, N = 90, g = 0.37, 95%CI -0.05 to 0.78, p = 0.08, I^2 = N/A Dextromethorphan (60 mg daily for 11 weeks): 1 RCT, N = 149, g = 0.11, 95%CI -0.29 to 0.52, p = 0.58, I^2 = N/A Pregnenolone (50mg daily for 8 weeks): 1 RCT, N = 52, g = 0.16, 95%CI -0.34 to 0.67, p = 0.53, I^2 = N/A Varenicline (1-4mg daily for 8 weeks): 2 RCTs, N = 151, g = 0.24, 95%CI -0.13 to 0.61, p = 0.20, I^2 = 24%	
Consistency in results‡	Inconsistent for N-acetylcysteine, oestrogen, minocycline, fatty acids, celecoxib, and statins.
Precision in results§	Imprecise for melatonin, withania somnifera extract, pioglitazone, piracetam, celecoxib, and statins.
Directness of results‖	Direct

Cho M, Lee TY, Kwak YB, Yoon YB, Kim M, Kwon JS

Adjunctive use of anti-inflammatory drugs for schizophrenia: A meta-analytic investigation of randomized controlled trials

Australian and New Zealand Journal of Psychiatry 2019; 53: 742-59

Anti-inflammatory medications

View review abstract online	
Comparison	**Adjunctive anti-inflammatory medications vs. placebo.**
Summary of evidence	**Moderate quality evidence (medium-sized samples, mostly inconsistent, mostly precise, direct) suggests medium to large benefits of adjunctive N-acetylcysteine, oestrogen, raloxifene, aspirin, and pregnenolone for symptoms. Functioning and cognition may also be improved.**
Symptoms	
Medium to large-sized effects of reduced symptom severity with; All anti-inflammatory agents: 57 RCTs, N > 2,000, g = 0.41, 95%CI 0.26 to 0.56, $p < 0.05$, I^2 = 74% The result was significant for positive and negative symptoms. N-acetylcysteine: 2 RCTs, N = 182, g = 0.65, 95%CI 0.13 to 1.18, $p < 0.05$, I^2 = 56% The result was significant for negative but not positive symptoms. Oestrogen: 7 RCTs, N = 327, g = 0.47, 95%CI 0.13 to 0.81, $p < 0.05$, I^2 = 66% The result was significant for positive and negative symptoms. Raloxifene: 9 RCTs, N = 583, g = 0.40, 95%CI 0.10 to 0.70, $p < 0.05$, I^2 = 74% The result was significant for positive but not negative symptoms. Minocycline: 6 RCTs, N = 310, g = 0.93, 95%CI 0.42 to 1.44, $p < 0.05$, I^2 = 78% The result was significant for negative (above) but not positive or total symptoms. Aspirin: 3 RCTs, N = 130, g = 1.31, 95%CI 0.25 to 2.37, $p < 0.05$, I^2 = 89% The result was significant for positive and negative symptoms. Pregnenolone: 4 RCTs, N = 101, g = 0.52, 95%CI 0.05 to 0.99, $p < 0.05$, I^2 = 0% The result was not significant for positive or negative symptoms. *No significant differences for;* Omega-3 fatty acids: 20 RCTs, N = 778, g = 0.03, 95%CI -0.14 to 0.20, $p > 0.05$, I^2 = 21% The result was similar for positive and negative symptoms. Celecoxib: 4 RCTs, N = 195, g = 0.44, 95%CI -0.05 to 0.93, $p > 0.05$, I^2 = 67% The result was similar for positive and negative symptoms. Erythropoietin: 1 RCT, N = 37, g = -0.48, 95%CI -1.12 to 0.15, $p > 0.05$, I^2 = N/A The result was similar for positive and negative symptoms.	
Functioning	

Small effect of improved functioning; All anti-inflammatory agents: 9 RCTs, N not reported, g = 0.22, 95%CI 0.04 to 0.40, $p < 0.05$, I^2 = 20%	
Cognition	
Small effect of improved cognition with; Minocycline: 10 RCTs, N not reported, g = 0.21, 95%CI 0.04 to 0.38, $p < 0.05$, $I^2 < 20\%$ Pregnenolone: 20 RCTs, N not reported, g = 0.19, 95%CI 0.08 to 0.29, $p < 0.05$, $I^2 < 63\%$	
Risks	There were no differences in extrapyramidal side effects.
Consistency in results	Inconsistent, apart from pregnenolone, omega-3, functioning, and cognition (minocycline).
Precision in results	Imprecise for aspirin and erythropoietin.
Directness of results	Direct

Oya K, Kishi T, Iwata N

Efficacy and tolerability of minocycline augmentation therapy in schizophrenia: a systematic review and meta-analysis of randomized controlled trials

Human Psychopharmacology: Clinical and Experimental 2014; 29: 483-491

View review abstract online

Comparison	**Minocycline + antipsychotics vs. placebo + antipsychotics. Mean treatment duration 25 weeks.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, inconsistent, imprecise, direct) suggests a small benefit of adjunctive minocycline for overall and negative symptoms, but not positive or depressive symptoms.**
Symptoms **PANSS, SANS, CGI, CDSS, HDRS, GAF**	
Small, significant effect of improved overall and negative symptoms with adjunctive minocycline; PANSS total: 4 RCTs, N = 267, SMD = -0.70, 95%CI -1.31 to -0.08, p = 0.03, I^2 81%, p = 0.0002	

PANSS general: 4 RCTs, N = 267, SMD = -0.50, 95%CI = -0.99 to -0.01, p = 0.05, I^2 72%, p = 0.007 PANSS negative: 4 RCTs, N = 267, SMD = -0.86, 95%CI -1.32 to -0.41, p = 0.0002, I^2 66%, p = 0.02 SANS: 2 RCTs, N = 133, SMD = -0.74, 95%CI -1.23 to -0.25, p = 0.003, I^2 44%, p not reported CGI: 3 RCTs, N = 227, SMD = -0.47, 95%CI -0.82 to -0.13, p = 0.007, I^2 34%, p not reported *No differences for positive or depression symptoms;* PANSS positive: 4 RCTs, N = 267, SMD = -0.26, 95%CI -0.55 to 0.02, p = 0.07, I^2 22%, p not reported Depression CDSS symptoms: 2 RCTs, N = 94, SMD = -0.28, 95%CI = -0.70 to 0.14, p = 0.20, I^2 = 0%, p not reported Authors report no evidence of publication bias	
Risks	Minocycline and placebo did not differ on discontinuation rates for inefficacy or any adverse event. Minocycline was superior to placebo in Extrapyramidal Symptom Rating Scale/Abnormal Involuntary Movement Scale scores (3 RCT, N = 189, SMD = -0.32, 95%CI -0.64 to -0.01, p = 0.04, I^2 = 0%).
Consistency in results	Inconsistent for PANSS scales only.
Precision in results	Some imprecision.
Directness of results	Direct

Schmidt L, Phelps E, Friedel J, Shokraneh F

Acetylsalicylic acid (Aspirin) for schizophrenia

Cochrane Database of Systematic Reviews 2019; 8: Art. No.: CD012116. DOI: 10.1002/14651858.CD012116.pub2

View review abstract online

Comparison	**Adjunctive aspirin vs. adjunctive placebo.**
Summary of evidence	**Moderate quality evidence (small to medium-sized sample, consistent, unable to assess precision, direct) suggests improved symptoms with adjunctive aspirin.**
Symptoms	

PANSS	
Significant effect of improved overall symptoms with adjunctive aspirin; PANSS total: 2 RCTs, N = 130, MD = -6.56, 95%CI -12.04 to -1.08, p = 0.02, I^2 = 0%	
Risks	Authors report that adverse reactions and discontinuation rates were similar between aspirin and placebo.
Consistency in results	Consistent
Precision in results	Unable to assess MDs (not standardised).
Directness of results	Direct

Solmi M, Veronese N, Thapa N, Facchini S, Stubbs B, Fornaro M, Carvalho AF, Correll CU

Systematic review and meta-analysis of the efficacy and safety of minocycline in schizophrenia

CNS Spectrums 2017; 22: 415-26

View review abstract online

Comparison	**Adjunctive minocycline vs. placebo.**
Summary of evidence	**Moderate quality evidence (medium-sized samples, mostly inconsistent, mostly precise, direct) finds medium-sized effects of greater improvement in overall and negative symptoms with adjunctive minocycline over placebo, with no differences in positive or depression symptoms. There was also some improvement in executive functioning.**
Symptoms	
Significant, medium-sized effects of greater improvement in overall and negative symptoms with adjunctive minocycline; Total PANSS scores: 5 RCTs, N = 300, SMD = -0.59, 95%CI -1.15 to -0.03, p = 0.04, I^2 = 81% General PANSS scores: 5 RCTs, N = 300, SMD = -0.44, 95%CI -0.88 to 0.00, p = 0.05, I^2 = 69% Clinical global impression: 4 RCTs, N = 277, SMD = -0.50, 95%CI -0.78 to -0.22, p < 0.0001, I^2 = 23%	

Negative PANSS scores: 5 RCTs, N = 300, SMD = -0.76, 95%CI -1.21 to -0.31, p = 0.001, I^2 = 69% Negative SANS scores: 4 RCTs, N = 216, SMD = -0.60, 95%CI -0.94 to -0.27, p < 0.001, I^2 = 29% *No differences for positive or depressive symptoms;* Positive PANSS scores: 5 RCTs, N = 300, SMD = -0.22, 95%CI -0.50 to 0.06, p = 0.13, I^2 = 29% Depression CDSS, HDRS, BDI scores: 4 RCTs, N = 177, SMD = -0.12, 95%CI -0.42 to -0.18, p = 0.43, I^2 = 0%
Cognition
A small effect of improved executive functioning with adjunctive minocycline; 2 RCTs, N = 183, SMD = 0.22, 95%CI 0.01 to 0.44, p = 0.04, I^2 = 42% There were no significant differences in attention, memory or motor speed.

Risks	There were no differences in discontinuation due intolerability.
Consistency in results	Inconsistent for PANSS total, general and negative symptoms.
Precision in results	Precise, apart from PANSS total.
Directness of results	Direct

Xiang YQ, Zheng W, Wang SB, Yang XH, Cai DB, Ng CH, Ungvari GS, Kelly DL, Xu WY, Xiang YT

Adjunctive minocycline for schizophrenia: A meta-analysis of randomized controlled trials

European Neuropsychopharmacology 2017; 27: 8-18

View review abstract online

Comparison	**Adjunctive minocycline (mean 171.9mg/day for 18.5 weeks) vs. placebo.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, mostly inconsistent, precise, direct) finds medium-sized effects of greater improvement in overall and negative symptoms, and a small effect for positive symptoms with adjunctive minocycline over placebo. There were no differences in depression, functioning, cognition or extrapyramidal symptoms.**

Symptoms
Significant, medium-sized effects of greater improvement in overall and negative symptoms, and a small effect for positive symptoms with adjunctive minocycline; Total PANSS/BPRS scores: 8 RCTs, N = 476, SMD = -0.64, 95%CI -1.02 to -0.27, p = 0.0008, I^2 = 74%, p = 0.0002 General PANSS scores: 6 RCTs, N = 300, SMD = -0.45, 95%CI -0.82 to -0.09, p = 0.02, I^2 = 63%, p = 0.01 Clinical global impression: 4 RCTs, N = 274, SMD = -0.53, 95%CI -0.82 to -0.24, p = 0.0003, I^2 = 25%, p = 0.26 Negative PANSS/SANS scores: 8 RCTs, N = 476, SMD = -0.69, 95%CI -0.98 to -0.40, p < 0.00001, I^2 = 56%, p = 0.02 Positive PANSS scores: 8 RCTs, N = 476, SMD = -0.22, 95%CI -0.41 to -0.03, p = 0.02, I^2 = 7%, p = 0.38 *No differences for depressive symptoms or functioning;* Depression CDSS scores: 2 RCTs, N = 104, SMD = -0.32, 95%CI -0.72 to 0.08, p = 0.12, I^2 = 0%, p = 0.46 Functioning GAF scores: 2 RCTs, N = 150, SMD = 0.01, 95%CI -0.63 to 0.64, p = 0.96, I^2 = 89%, p = 0.04 The effects were larger in studies of Chinese samples, adjunctive treatment with risperidone, and in older samples (>32yrs). There were no effects of study blinding vs. open label, trial duration (<24weeks vs. >24weeks), gender or study quality.
Cognition
There was no significant difference for any cognitive function (attention, memory, learning, problem solving).

Risks	There were no differences in movement or extrapyramidal symptoms.
Consistency in results	Inconsistent for total, general, negative symptoms and functioning, consistent for positive and depression symptoms.
Precision in results	Precise
Directness of results	Direct

Yolland COB, Hanratty D, Neill E, Rossell SL, Berk M, Dean OM, Castle DJ, Tan

EJ, Phillipou A, Harris AWF, Barreiros AR, Hansen A, Siskind D

Meta-analysis of randomised controlled trials with N-acetylcysteine in the treatment of schizophrenia

Australian and New Zealand Journal of Psychiatry 2019; Jan: doi: 10.1177/0004867419893439

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Comparison	**Adjunctive N-acetylcysteine vs. adjunctive placebo.**
Summary of evidence	**Moderate to high quality evidence (small to medium-sized sample, consistent, precise, direct) suggests improved symptoms and working memory with adjunctive N-acetylcysteine.**
Symptoms **PANSS**	
A large, significant effect of improved total symptoms with adjunctive N-acetylcysteine; 7 RCTs, N = 220, SMD = -0.92, 95%CI -1.27 to -0.58, $p < 0.0001$, $I^2 = 49\%$, $p = 0.10$ The effect was larger for negative than for positive symptoms.	
Cognition	
A large, significant effect of improved total working memory with adjunctive N-acetylcysteine; 3 RCTs, N = 136, SMD = 0.56, 95%CI 0.17 to 0.94, $p = 0.005$, $I^2 = 0\%$, $p = 0.40$ There was no difference in processing speed.	
Risks	Not reported
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Zheng W, Cai DB, Yang XH, Ungvari GS, Ng CH, Muller N, Ning YP, Xiang YT

Adjunctive celecoxib for schizophrenia: A meta-analysis of randomized,

double-blind, placebo-controlled trials

Journal of Psychiatric Research 2017; 92: 139-46

View review abstract online

Comparison	**Adjunctive celecoxib vs. adjunctive placebo.**
Summary of evidence	**Moderate quality evidence (medium to large samples, consistent, precise, direct) suggests a medium-sized benefit of adjunctive celecoxib for improving symptoms in first-episode patients, but not chronic patients.**
Symptoms	
There were no significant differences between celecoxib and placebo in total symptoms; 8 RCTs, N = 613, SMD = -0.22, 95%CI -0.54 to 0.10, p = 0.17, I^2 = 68% Results were similar for positive and negative symptom subscales. *Subgroup analysis of first-episode and chronic patients showed greater improvements in total symptoms only in first-episode patients receiving celecoxib vs. placebo (medium-sized effect);* First-episode: 3 RCTs, N = 180, SMD = -0.47, 95%CI -0.81 to -0.14, p = 0.005, I^2 = 18% Chronic patients: 4 RCTs, N = 398, SMD = -0.16, 95%CI -0.67 to 0.34, p = 0.75, I^2 = 75%	
Risks	Authors report that adverse reactions and discontinuation rates were similar between celecoxib and placebo.
Consistency in results	Inconsistent for all patients, consistent for first-episode patients.
Precision in results	Precise
Directness of results	Direct

Zheng W, Zhu X-M, Zhang Q-E, Cheng G, Cai D-B, He J, Ng CH, Ungvari GS, Peng X-J, Ning Y-P, Xiang Y-T

Adjunctive minocycline for major mental disorders: A systematic review

Journal of Psychopharmacology 2019; 33: 1215-26

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Comparison	**Adjunctive minocycline vs. adjunctive placebo.**
Summary of evidence	**Moderate to high quality evidence (sample, inconsistent, precise, direct) suggests a medium-sized benefit of adjunctive minocycline for improving symptoms, particularly negative symptoms.**
Symptoms	
A medium-sized effect of improved symptoms with adjunctive minocycline; 16 RCTs, N = 1,357, SMD = -0.45, 95%CI -0.73 to -0.16, p = 0.002, I^2 = 77% Results were significant for positive and negative symptoms, but the effect was larger for negative symptoms.	
Risks	Authors report that minocycline caused less headache.
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

BDI = Beck Depression Inventory, CDSS = Calgary Depression Scale for Schizophrenia, CI = confidence interval, HDRS = Hamilton Depression Rating Scale, g = Hedge's g, standardised mean difference, 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), RCT = randomised controlled trial, 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 small.

† 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[12].

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[13]. 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 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[12];

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

§ 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[14].

‖ 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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