TECHNICAL COMMENTARY

Cholinesterase inhibitors

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Introduction

A supplementary, or adjunctive, treatment is administered in conjunction with a patient's ongoing antipsychotic therapy.

Cholinesterase inhibitors (ChEIs), or anti-cholinesterase, have been proposed as an additional therapy to standard antipsychotic treatments, in an attempt to improve functional outcomes and treat symptoms that are not addressed by the antipsychotic medication alone. Cholinesterase inhibitors work by blocking the cholinesterase enzymes that break down acetylcholine neurotransmitters (AChs), increasing the neurotransmitter action. Their action is in contrast to anti-cholinergic medications, which have an opposite effect, and block the action of cholinergic neurotransmitters on their receptors.

There are two key forms of cholinesterase enzymes, acetyl cholinesterase (AChE) and butyryl cholinesterase (BChE). There are several different cholinesterase inhibitor drugs that target these enzymes, and which vary in their specificity for each of these enzymes ('single-action' or 'dual-action'). Essentially, cholinesterase inhibitors work by blocking the cholinesterase enzyme from metabolising ACh, resulting in increased availability of ACh in neuron synapses and increasing ACh activity on cholinergic receptors (called nicotinic and muscarinic receptors). These receptors are known to be involved in cognition, and the use of cholinesterase inhibitors has previously shown some efficacy for improving cognition in Alzheimer's disease. Aspects of cognition are known to be impaired in schizophrenia (See Cognition topics). It is important to consider that any effects of ChEIs may be biased by the younger age of the schizophrenia population. Cholinesterase inhibitors have also been proposed as treatments for visual hallucinations, possibly due to depleted ACh levels in the cortex including regions involved in visual processing and interpretation.

Trials of ChEI efficacy are limited by considerable heterogeneity of both sample population and neuropsychological assessment, as well as potentially confounding effects such as the smoking status of patients (as nicotine affects cholinergic receptors and may interfere with ChEI mechanism of action), as well as medication heterogeneity (such as the concomitant use of anti-cholinergic medications, which may 'cancel out' any effects). Specifically, most antipsychotics affect the ACh system; however this possible confound has not been formally investigated by the available evidence.

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

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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 seven systematic reviews that met our inclusion criteria[3-9].

- Moderate to high quality evidence finds small to medium-sized effects of improved overall, negative and positive symptoms with adjunctive AChEIs compared to placebo.
- Moderate to high quality evidence shows medium-sized improvements in memory, attention, processing speed and motor functioning with adjunctive AChEIs (particularly single-action). There may also be a small benefit for language functioning.
- Moderate to low quality evidence finds no differences in tardive dyskinesia.

Choi K, Wykes T, Kurtz M

Adjunctive pharmacotherapy for cognitive deficits in schizophrenia: meta-analytical investigation of efficacy

The British Journal of Psychiatry 2013; 203: 172-178

View review abstract online

Comparison	**Adjunctive donepezil or galantamine plus antipsychotics vs. antipsychotics plus placebo.**
Summary of evidence	**Moderate to high quality evidence (unclear sample sizes, consistent, precise, direct) suggests a medium-sized benefit of adjunctive donepezil or galantamine for improving overall and negative symptoms, with no benefit for cognitive functioning other than a small trend effect for verbal learning and memory.**

Symptoms

Significant, medium-sized effects of improved overall symptoms in those taking adjunctive donepezil or galantamine, with negative symptoms showing the most improvement;

Negative symptoms: 5 RCTs (N unclear), d = 0.54, 95%CI 0.10 to 0.98, p = 0.016, Q_W = 5.82, p = 0.21

Positive symptoms: 5 RCTs (N unclear), d = 0.01, 95%CI -0.42 to 0.44, p = 0.961, Q_W = 0.84, p = 0.93

Overall symptoms: 5 RCTs (N unclear), d = 0.46, 95%CI 0.04 to 0.88, p = 0.032, Q_W = 3.40, p = 0.49

Cognition

A trend effect for a small improvement in verbal learning and memory;

Verbal learning and memory: 9 RCTs (N unclear), d = 0.23, 95%CI -0.01 to 0.46, p = 0.062, Q_W = 6.85, p = 0.55

No significant differences in;

Overall function: 13 RCTs, N = 577, d = 0.05, 95%CI -0.16 to 0.27, p = 0.630 Q_W = 4.63, p = 0.97

Attention/vigilance: 11 RCTs (N unclear), d = -0.12, 95%CI -0.35 to 0.10, p = 0.284, Q_W = 8.87, p = 0.54

Verbal working memory 9 RCTs (N unclear), d = -0.08, 95%CI -0.32 to 0.16, p = 0.517, Q_W = 12.02, p = 0.15

Spatial learning and memory: 5 RCTs (N unclear), *d* = 0.21, 95%CI -0.15 to 0.57, *p* = 0.253, Q_W = 10.45, *p* = 0.03 Spatial working memory 3 RCTs (N unclear), *d* = 0.16, 95%CI -0.19 to 0.50, *p* = 0.371, Q_W = 0.97, *p* = 0.62 Reasoning/problem-solving: 8 RCTs (N unclear), *d* = -0.11, 95%CI -0.38 to 0.16, *p* = 0.418, Q_W = 4.46, *p* = 0.73 Speed of processing: 8 RCTs (N unclear), *d* = 0.06, 95%CI -0.19 to 0.31, *p* = 0.659, Q_W = 10.22, *p* = 0.17	
Consistency in results‡	Consistent, apart from spatial learning and memory.
Precision in results§	Precise
Directness of results‖	Direct

Chouinard S, Sepehry AA, Stip E

Oral cholinesterase inhibitor add-on therapy for cognitive enhancement in schizophrenia: a quantitative systematic review, Part I

Clinical Neuropharmacology 2007; 30(3): 169-82

View review abstract online

Comparison 1	**Cognitive function before and after treatment with oral cholinesterase inhibitors plus standard antipsychotic treatment.** **Pre-post assessment for 6-24 weeks.**
Summary of evidence	**Moderate to high quality evidence (unclear sample sizes, consistent, precise, direct) suggests a small benefit of adjunctive acetylcholinesterase inhibitors (AChEIs) for improving motor function and attention, particularly with single action AChEIs.**
Cognitive functioning	
Significant, small improvements in motor function and attention with AChEIs, with no significant benefit for executive functioning or language; Motor: 4 studies, *g* = 0.239, (N unclear), 95%CI -0.014 to 0.465, *p* = 0.038, Q_W = NS (after removal of an outlier) Attention: 10 studies, *g* = 0.261, (N unclear), 95%CI 0.074 to 0.448, *p* = 0.006, Q_W = 4.024, *p* =	

0.910 Executive functioning: 7 studies, *g* = -0.039, (N unclear), 95%CI -0.241 to 0.163, *p* = 0.704, Q_W = 2.202, *p* = 0.900 Language: 6 studies, *g* = 0.247, (N unclear), 95%CI -0.088 to 0.583, *p* = 0.148, Q_W = 7.346, *p* = 0.196 *Single action AChEIs (donepezil and galantamine) improved attention, but not language;* Attention: *g* = 0.241, (N unclear), 95%CI 0.029 to 0.452, *p* = 0.026 Language: *g* = 0.054, (N unclear), 95%CI -0.191 to 0.299, *p* = 0.667 *There were no benefits of dual action AChEI (rivastigmine);* Attention: *g* = 0.314 (N and CI not reported, authors report results are NS) Language: *g* = 0.391, 95%CI -0.566 to 1.348, *p* = 0.423	
Risks	Possible side effects include nausea, diarrhoea, dizziness, depression.
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct
Comparison 2	**Cognitive functioning following oral cholinesterase inhibitors vs. placebo plus standard antipsychotic treatment.**
Summary of evidence	**Moderate to high quality evidence (unclear sample sizes, consistent precise and direct) suggests a small benefit of placebo over adjunctive AChEI treatment for language. No differences for motor function, or executive function, although there may be some benefit for improving attention.**
Cognitive functioning	
Small effect size favours placebo group for improving language, with no differences in executive functioning, motor or attention (for all studies combined); Language: 4 studies, *g* = -0.393, (N unclear), 95%CI -0.644 to -0.141, *p* = 0.002, Q_W = 1.158, *p* = 0.763 Attention: 5 studies, *g* = 0.175, (N unclear), 95%CI -0.125 to 0.475, p = 0.253, Q_W = 4.813, *p* = 0.307 Note; with the exclusion of one RCT which represented > 50% of total sample, the results became significant, favouring AChEI (*g* = 0.441, CI not reported, *p* = 0.038) Executive function: 4 studies, *g* = 0.073, (N unclear), 95%CI -0.500 to 0.354, *p* = 0.737, Q_W = 5.275, *p* = 0.153 Motor: 3 studies, *g* = 0.428, (N unclear), 95%CI -0.465 to 1.322, *p* = 0.347, Q_W = 12.994, *p* = 0.002	

Risks	Possible side effects include nausea, diarrhoea, dizziness, depression.
Consistency in results	Consistent for all except motor functioning.
Precision in results	Precise for all except executive function and motor functioning.
Directness of results	Direct

Jin Y, Wang Q, Wang Y, Liu M, Su A, Geng Z, Lin Y, Li X

Alpha7 nAChR agonists for cognitive deficit and negative symptoms in schizophrenia: A meta-analysis of randomized double-blind controlled trials

Shanghai Archives of Psychiatry 2017; 29: 191-9

View review abstract online

Comparison	**Cholinergic drugs plus antipsychotic treatment vs. placebo plus antipsychotic treatment.** **ix different kinds of α7-nicotinic agonist were used** **as the intervention, varenicline,[12,13] tropisetron,[14,15]** **ABT-126,[7] encenicline,[8] TC-5619,[16] and RG3487**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests no significant benefit of cholinergic medications for improving negative symptoms or cognition.**
Negative symptoms	
No significant differences between groups; 8 studies, N = 1,438, SMD = 0.13, 95%CI -0.04 to 0.30, p = 0.13, I^2 = 64%, p = 0.002 The samples in the meta-analysis were not always independent.	
Cognition	
No significant differences between groups; 5 studies, N = 1,299, SMD = -0.10, 95%CI -0.46 to 0.25, p = 0.57, I^2 = 88%, p < 0.00001	

Risks	There were no significant differences in adverse events.
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Kishi T, Ikuta T, Oya K, Matsunaga S, Matsuda Y, Iwata N

Anti-dementia drugs for psychopathology and cognitive impairment in schizophrenia: A systematic review and meta-analysis

International Journal of Neuropsychopharmacology 2018; 21: 748-57

View review abstract online

Comparison	**Adjunctive anti-dementia drugs (donepezil, galantamine, rivastigmine, and memantine) vs. adjunctive placebo.** **Note that memantine is a glutaminergic antagonist.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, some inconsistency, precise, direct) suggests a medium-sized improvement in negative symptoms, and small improvements in overall and affective symptoms with anti-dementia medications compared to placebo. For individual cholinesterase inhibitors, only galantamine and rivastigmine were significant for improving negative symptoms, and none were significant for overall symptoms. There was a small improvement in verbal learning with anti-dementia medications.** **There were no differences in positive symptoms, clinical improvement, other cognitive domains, or adverse events.**

Symptoms

A significant, medium-sized improvement in negative symptoms and small improvements in overall symptoms and affective symptoms with anti-dementia medications;

Negative symptoms: 24 RCTs, N = 1,077, SMD = -0.62, 95%CI -0.92 to -0.32, p = 0.000045, I^2 = 80%

Overall symptoms: 24 RCTs, N = 1,069, SMD = -0.34, 95%CI -0.61 to -0.08, p = 0.01, I^2 = 74%

Anxiety/depressive symptoms: 12 RCTs, N = 483, SMD = -0.20, 95%CI -0.39 to -0.02, p = 0.03, I^2 = 4%

Subgroup analysis of individual agents found only galantamine, rivastigmine, and memantine were significant for improving negative symptoms. Only memantine was significant for improving overall symptoms. *There were no significant differences in;* Positive symptoms: 21 RCTs, N = 805, SMD = -0.21, 95%CI -0.45 to 0.04, p = 0.10, I^2 = 60% PANSS general: 12 RCTs, N = 367, SMD = -0.23, 95%CI -0.62 to 0.16, p = 0.24, I^2 = 68% Clinical global impression: 8 RCTs, N = 356, SMD = -0.03, 95%CI -0.38 to 0.32, p = 0.87, I^2 = 53%
Cognition
A significant, small improvement in verbal learning with anti-dementia medications; 14 RCTs, N = 487, SMD = -0.23, 95%CI -0.44 to -0.01, p = 0.04, I^2 = 57% *There were no significant differences in;* Overall cognition: 6 RCTs, N = 532, SMD = -0.02, 95%CI -0.22 to 0.18, p = 0.83, I^2 = 37% Working memory: 15 RCTs, N = 501, SMD = 0.08, 95%CI -0.18 to 0.34, p = 0.53, I^2 = 65% Speed of processing: 12 RCTs, N = 417, SMD = 0.16, 95%CI -0.08 to 0.40, p = 0.19, I^2 = 33% Attention/vigilance: 9 RCTs, N = 330, SMD = -0.13, 95%CI -0.38 to 0.13, p = 0.34, I^2 = 28% Reasoning/problem solving: 4 RCTs, N = 130, SMD = -0.10, 95%CI -0.45 to 0.24, p = 0.56, I^2 = 0% Executive functioning: 10 RCTs, N = 279, SMD = 0.02, 95%CI -0.27 to 0.31, p = 0.90, I^2 = 45% Social cognition: 2 RCTs, N = 64, SMD = 0.06, 95%CI -0.43 to 0.55, p = 0.82, I^2 = 0% Visual learning: 5 RCTs, N = 181, SMD = -0.03, 95%CI -0.26 to 0.21, p = 0.82, I^2 = 0%

Risks	There were no differences in adverse events.
Consistency in results	Some inconsistency
Precision in results	Precise
Directness of results	Direct for anti-dementia class

Ribeiz SRI, Bassitt DP, Arrais JA, Steffens DC, Bottino CMC

Cholinesterase inhibitors as adjunctive therapy in patients with schizophrenia and schizoaffective disorder: a review and meta-analysis of the literature

CNS Drugs 2010; 24(4): 303-17

TECHNICAL COMMENTARY

Cholinesterase inhibitors

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Comparison	**Efficacy of adjunctive AChEIs (rivastigmine, donepezil or galantamine for 8-24 weeks) vs. placebo for cognitive functioning and psychopathology.**
Summary of evidence	**Moderate quality evidence (small samples, consistent, precise, direct) finds a medium-sized improvement in the trail making test and a small improvement in memory. There may also be a small improvement in positive symptoms.**
Cognitive functioning	
A significant, medium effect improvement on the trail making test and a small improvement in memory with adjunctive AChEIs; Trail making test: 4 RCTs, N = 93, *g* = -0.68, 95%CI -1.14 to -0.23, *p* = 0.003, Q_W = 3.41, *p* = 0.33 Memory: 3 RCTs, N = 146, *g* = 0.28, 95%CI 0.06 to 0.50, *p* = 0.014, Q_W = 12.82, *p* = 0.12 *No significant difference in;* Executive functioning: 6 RCTs, N = 199, *g* = 0.05, 95%CI -0.26 to 0.35, *p* = 0.75, Q_W = 4.85, *p* = 1.0 Language: 4 RCTs, N = 63, *g* = 0.24, 95%CI -0.12 to 0.59, *p* = 0.19, Q_W = 4.78, *p* = 0.57	
Symptoms	
A significant, small improvement in positive symptoms with adjunctive AChEIs; Positive PANSS: 7 RCTs, N = 364, *g* = 0.28, 95%CI 0.07 to 0.50, *p* = 0.01, Q_W = 1.91, *p* = 0.93 *No significant difference in;* Total PANSS: 6 RCTs, N = 119, *g* = 0.09, 95%CI -0.32 to 0.50, *p* = 0.67, Q_W = 1.05, *p* = 0.96 Negative PANSS: 8 RCTs, N = 377, *g* = -0.17, 95%CI -0.68 to 0.33, *p* = 0.50, Q_W = 21.47, *p* = 0.003 Extrapyramidal symptoms: 3 RCT, N = 158, *g* = -0.57, 95%CI -1.16 to -0.02, *p* = 0.06, Q_W = 19.85, *p* = 0.001	
Consistency in results	Consistent for all except extrapyramidal and negative symptoms.
Precision in results	Precise for all except trail making and extrapyramidal symptoms.
Directness of results	Direct

Santos B, Gonzalez-Fraile E, Zabala A, Guillen V, Rueda JR, Ballesteros J

Cognitive improvement of acetylcholinesterase inhibitors in schizophrenia

Journal of psychopharmacology 2018; 32: 1155-66

View review abstract online

Comparison	**Efficacy of adjunctive AChEIs (rivastigmine, donepezil or galantamine for 6-48 weeks) vs. placebo for cognitive functioning.**
Summary of evidence	**Moderate to high quality evidence (medium-sized samples, consistent, precise, direct) finds medium-sized effects of improved processing speed and attention with adjunctive AChEIs, with no effect on working memory.**
Cognitive functioning	
Significant, medium-sized effects of better speed of processing and attention with adjunctive AChEIs; Speed of processing: 6 RCTs, N = 219, SMD = -0.52, 95%CI -0.79 to -0.25, p = 0.0002, I^2 = 0%, p = 0.70 Attention: 8 RCTs, N = 252, SMD = -0.43, 95%CI -0.72 to -0.13, p = 0.005, I^2 = 23%, p = 0.24 *No significant differences in working memory;* 8 RCTs, N = 273, -0.14, 95%CI -0.51 to 0.24, p = 0.47, I^2 = 54%, p = 0.03	
Consistency in results	Consistent except working memory.
Precision in results	Precise
Directness of results	Direct

Stip E, Sepehry AA, Chouinard S

Add-on therapy with acetylcholinesterase inhibitors for memory dysfunction in schizophrenia: a systematic quantitative review, part 2

Clinical Neuropharmacology 2007; 30(4): 218-29

View review abstract online

Comparison 1	**Change in memory function after 6-24 weeks of adjunctive AChEIs.**

Summary of evidence	**Moderate to high quality evidence (small to medium-sized samples, consistent, mostly precise, direct) suggests a small, improvement in long-term memory with AChEIs. Only donepezil may confer some benefit for short-term memory.**
Memory	
A small significant improvement in long-term but not short-term memory with AChEIs; Long-term: 8 studies, N = 192, *g* = 0.362, 95%CI 0.0617 to 0.663, p = 0.019, Q = 11.984, *p* = 0.101 Short-term: 9 studies, N = 191, *g* = 0.226, 95%CI -0.003 to 0.454, *p* = 0.117, Q = 12.927, *p* = 0.114 *Subgroup analysis shows significant improvement in short-term memory with single-action donepezil only;* Short-term: Single action donepezil*:* 4 studies, *g* = 0.246, 95%CI 0.019 to 0.473, *p* = 0.034 Short-term: Dual action rivastigmine: 4 studies, *g* = 0.299, 95%CI -0.182 to 0.780, *p* = 0.223 Long-term: Single action donepezil*:* 5 studies, *g* = -0.352, 95%CI -0.060 to 0.765, *p* = 0.094 Long-term: Dual action rivastigmine: 2 studies, *g* = 0.383, 95%CI -0.333 to 1.099, *p* = 0.294 There were no significant differences in subgroup analyses of antipsychotic type (first or second-generation antipsychotics).	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct
Comparison 2	**Long-term memory and short-term memory following acetylcholinesterase inhibitors plus antipsychotics vs. placebo plus antipsychotics.**
Summary of evidence	**Moderate to high quality evidence (medium or unclear sample sizes, consistent, precise, direct) suggests no significant difference between AChEI and placebo.**
Memory	
No significant difference between groups; Long-term: 3 studies, N not reported, *g* = -0.240, 95%CI -0.492 to 0.011, *p* = 0.061, Q = 0.769, *p* = 0.681 Short-term: 4 studies, N = 263, *g* = -0.236, 95%CI -0.604 to 0.132, *p* = 0.208, Q = 4.214, *p* = 0.239	
Consistency in results	Consistent

Precision in results	Precise
Directness of results	Direct

Tammenmaa-Aho I, Asher R, Soares-Weiser K, Bergman H

Cholinergic medication for antipsychotic-induced tardive dyskinesia

Cochrane Database of Systematic Reviews 2018; 3: CD000207

View review abstract online

Comparison	**Acetylcholinesterase-inhibitors vs. placebo.** **See the adjunctive cholinergic topic for details on these medications.**
Summary of evidence	**Moderate to low quality evidence (mostly very small samples, imprecise, consistent where applicable, direct) suggests no differences between groups for tardive dyskinesia or adverse effects.**
Tardive dyskinesia	
No significant differences between groups in a 50% improvement in tardive dyskinesia symptoms; Donepezil: 1 RCT, N = 10, RR = 1.00, 95%CI 0.70 to 1.43, p = 1.00 *No significant differences between groups in AIMS scores;* Galantamine: 1 RCT, N = 35, MD = 1.50, 95%CI -0.44 to 3.44, p = 0.13 Rivastigmine: 1 RCT, N = 40, MD = 2.20, 95%CI -1.16 to 5.56, p = 0.20 Donepezil: 1 RCT, N = 10, MD = 1.10, 95%CI -4.22 to 6.42, p = 0.69	
Risks	There were no differences in any adverse event.
Consistency in results	Consistent where applicable (> 1 RCT).
Precision in results	Imprecise, unable to assess MDs.
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences, 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, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = Positive and Negative Syndrome Scale, Q = Q statistic for the test of heterogeneity, Q_w = test for within group differences (heterogeneity in study results within a group of studies – measure of study consistency), Q_B = test for between group differences (heterogeneity between groups of studies for an outcome of interest), RR = risk ratio, SMD = standardised mean difference, vs. = versus

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[10].

† 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[10].

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[11]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

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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[10];

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

§ 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[12].

‖ 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.

References

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