TECHNICAL COMMENTARY

Drug and alcohol use

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Introduction

Substance use is a concern for people with a mental illness due to the association with poor clinical and social outcomes. Substance use places additional burden on patients, families, psychiatric services, and government resources due to high rates of treatment non-adherence and relapse.

Substance abuse leads to risk-taking behaviour, illegal activity, interpersonal problems and a loss of interest in usual activities. Abuse jeopardises physical health and neglect of important commitments at home, school or work.

Substance dependence involves having a strong physical or psychological need for the substance. Not taking it leads to withdrawal symptoms within a few hours of stopping, such as nausea, vomiting, tremors, chills, sweating, low blood pressure, irritability, depression, anxiety or confused thinking.

This topic presents the rates and the effects of substance use on the course and outcome of bipolar disorder. Please also see the treatment topics for people with a dual diagnosis of bipolar and substance use disorders.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2010 that report results for people with a diagnosis of bipolar or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. Reviews with pooled data were given priority for inclusion. When multiple copies of reviews assessing the same topic were found, only the most recent review was included.

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 < 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 ten reviews that met our inclusion criteria[3-12].

- Moderate quality evidence suggests a medium to large increased risk of bipolar

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disorder in people with a substance use disorder. In children and youth with bipolar disorder, moderate to low quality evidence suggests the rate of substance use disorder is around 31%. Rates were significantly higher in youth than in children, and in youth with comorbid PTSD or disruptive behaviour disorder.

- There is a greater risk of drug or alcohol dependence than risk of drug or alcohol abuse in people with bipolar disorder. Having a substance use disorder was associated with a greater risk of hospitalisation, and high levels of alcohol intake increased the risk of a mood recurrence or rapid-cycling.
- High quality evidence suggests there is greater risk of substance use disorders with greater number of manic episodes. Moderate quality evidence also suggests greater risk of substance use disorders with male sex, a history of suicide behaviour, a diagnosis of bipolar I disorder (rather than bipolar II), and having an early age of onset of bipolar disorder (<18 years).
- Moderate quality evidence suggests around one-quarter of people with bipolar disorder report using cannabis. Cannabis use was more common than having a cannabis use disorder. Use was associated with younger age, male gender, single marital status, having fewer years of education, an earlier onset of affective symptoms, psychotic symptoms, suicide attempts, use of tobacco, alcohol, and other substances.
- Moderate to high quality evidence found cannabis use was associated with greater risk of treatment non-adherence, depression, anxiety, and mania symptom severity, more mood episodes, suicide attempts, and more insomnia or hypersomnia in people with bipolar disorder and comorbid cannabis use compared to people with bipolar disorder and no cannabis use.

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Bartoli F, Crocamo C, Carra G

Cannabis use disorder and suicide attempts in bipolar disorder: A meta-analysis

Neuroscience and Biobehavioral Reviews 2019; 103: 14-20

View review abstract online

Comparison	**Relationship between cannabis use and suicide attempts in people with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) finds a small increased risk of suicide attempts in cannabis users vs. non-users.**

Suicide attempts and cannabis use

Small, significant increased risk of suicide attempts in people with bipolar disorder and cannabis use compared to people with bipolar disorder and no cannabis use;

The random-effects meta-analysis, based on

11 studies, N = 6,375, OR = 1.35, 95%CI 1.08 to 1.70, $p = 0.01$, $I^2 = 41.7\%$

Meta-regression found this result was not influenced by moderators (year of publication, geographical area, sample size, proportion of subjects with bipolar I disorder, mean age, females proportion, timeframe considered for cannabis use disorder, quality of methods to assess cannabis use disorder and suicide attempts, and published vs. unpublished findings).

Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Foglia E, Schoeler T, Klamerus E, Morgan K, Bhattacharyya S

Cannabis use and adherence to antipsychotic medication: a systematic review and meta-analysis

Psychological Medicine 2017; 47: 1691-705

View review abstract online

Comparison	**Cannabis use and adherence to antipsychotic medication in**

	people with bipolar disorder (72% of the sample had bipolar I disorder or other affective disorders, the remainder had a psychotic disorder).
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, imprecise, direct) finds a medium-sized increased risk of non-adherence to antipsychotics in cannabis users vs. non-users. At follow-up (mean 2.3 years) the effect size was large, suggesting greater increased risk of non-adherence with continued cannabis use.**
Treatment non-adherence	
A significant, medium-sized effect of increased non-adherence in cannabis users vs. non-users; 11 studies, N = 3,055, OR = 2.46, 95%CI 1.97 to 3.07, $p < 0.00001$, $I^2 = 0\%$ Results were similar in subgroup analyses of first-episode vs. chronic patients; in affective vs. non-affective psychosis; and in studies that controlled vs. those that did not control for baseline symptom severity. There were no moderating effects of age, gender or follow-up period (6 months to 8 years; mean 2.3 years). At follow-up the effect size was large, suggesting greater increased risk of non-adherence with continued cannabis use. There was no evidence of publication bias.	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Frias A, Palma C, Farriols N

Comorbidity in pediatric bipolar disorder: prevalence, clinical impact, etiology and treatment

Journal of Affective Disorders 2015; 174: 378-89

View review abstract online

Comparison	**Substance use in children and youth with bipolar disorder.**
Summary of evidence	**Moderate to low quality evidence (inconsistent, imprecise, direct, unclear sample size) suggests the overall prevalence of substance use disorders in children or youth with bipolar disorder is around 31%. Rates were significantly higher in youth than in children, and in youth with comorbid PTSD or disruptive behaviour disorder.**

Substance use disorders	
8 studies, N = not reported, overall mean prevalence rate = 31% (range 16% to 48%) The proportion of bipolar youth diagnosed with a comorbid substance use disorder was significantly higher in the adolescent group than in the childhood-onset group (OR = 8.8). Rates were higher in prospective studies than in cross-sectional studies and were higher in bipolar youth with comorbid PTSD or disruptive behaviour disorder. There was greater functional impairment in bipolar youth with comorbid substance use disorders than in bipolar youth without comorbid substance use disorder, particularly around legal and academic issues.	
Consistency in results	Authors report the data are inconsistent.
Precision in results	Imprecise
Directness of results	Direct

Hunt GE, Malhi GS, Cleary M, Lai HMX, Sitharthan T

Comorbidity of bipolar and substance use disorders in national surveys of general populations, 1990-2015: Systematic review and meta-analysis

Journal of Affective Disorders 2016; 206: 321-30

View review abstract online

Comparison	**Rates of bipolar disorder in people with vs. without comorbid substance use.**
Summary of evidence	**Moderate quality evidence (inconsistent, imprecise, direct, large sample size) suggests a medium to large effect of increased rates of bipolar disorder in people with any substance use. Rates of bipolar disorder were higher in people with illicit drug or alcohol dependence than in people with illicit drug or alcohol abuse. Rates of bipolar disorder were higher in people with lifetime alcohol use than in people with 12 month alcohol use, with no differences for illicit drug use. Rates of bipolar I disorder were higher than rates of bipolar II disorder in people with drug use, with no differences for alcohol use.**
Illicit drug use	
Medium to large increased risk of bipolar disorder in people with illicit drug use compared to people without illicit drug use;	

22 point estimates, N ~218,397, OR = 4.956, 95%CI 3.984 to 6.167, $p < 0.01$, $I^2 = 92.1\%$ *The effect size for drug dependence was significantly larger than for abuse;* Drug dependence: 9 point estimates**,** OR = 7.869, 95%CI 5.207 to 11.891 Drug abuse: 8 point estimates, OR = 3.733, 95%CI 2.628 to 5.303 *Rates for bipolar I disorder were higher than for bipolar II disorder;* Bipolar I disorder: 12 point estimates, OR = 7.475, 95%CI 5.411 to 10.326 Bipolar II disorder: 10 point estimates, OR = 3.302, 95%CI 2.634 to 4.139 *There were no significant differences between lifetime and 12 month drug use;* 12 months: 8 point estimates, OR = 6.494, 95%CI 4.302 to 9.803 Lifetime: 14 point estimates, OR = 4.683, 95%CI 3.395 to 6.459
Alcohol misuse
Medium to large increased risk of bipolar disorder in people with alcohol use compared to people without alcohol use; 21 point estimates, N ~218,397, OR = 4.088, 95%CI 3.368 to 4.963, $p < 0.001$, $I^2 = 86.2\%$ *The effect size for alcohol dependence was significantly larger than for abuse;* Alcohol dependence: 7 point estimates, OR = 5.783, 95%CI 4.300 to 7.777 Alcohol abuse: 9 point estimates, OR = 3.248, 95%CI 2.081 to 5.068 *Rates for lifetime misuse were higher than for 12 month misuse;* Lifetime: 11 point estimates, OR = 5.127, 95%CI 3.883 to 6.769 12 months: 10 point estimates, OR = 2.829, 95%CI 1.986 to 4.030 *There were no significant differences between bipolar I disorder and bipolar II disorder;* Bipolar I disorder: 13 point estimates, OR = 3.780, 95%CI 2.621 to 5.452 Bipolar II disorder: 8 point estimates, OR = 3.821, 95%CI 3.001 to 4.867

Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Hunt GE, Malhi GS, Cleary M, Lai HMX, Sitharthan T

Prevalence of comorbid bipolar and substance use disorders in clinical settings, 1990-2015: Systematic review and meta-analysis

Journal of Affective Disorders 2016; 206: 331-49

View review abstract online	
Comparison	**Rates of substance use in people with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (inconsistent, imprecise, direct, large sample size) suggests small effects of increased rates of substance use disorders in men with bipolar disorder compared to women with bipolar disorder. People with bipolar I disorders had more substance use disorders, particularly alcohol use disorders, than people with bipolar II disorder. There was an earlier age at onset and more hospitalisations in people with bipolar disorder and comorbid substance use disorders.**
Substance use disorders	
Small effect of increased rates of substance use disorders in men with bipolar disorder than women with bipolar disorder; Men: substance use disorders prevalence = 51.5% Women: substance use disorders prevalence = 34.4% 17 studies, N = 16,454, OR = 2.180, 95%CI 1.788 to 2.657, $p < 0.001$, $I^2 = 65.4\%$ Results were similar regardless of diagnosis of substance use disorder (abuse or dependence), substance type (cannabis, alcohol, or any substance), study setting (inpatient, outpatient or mixed) and study quality. *Small effect of increased rates of substance use disorders in people with bipolar I disorder than people with bipolar II disorder;* Bipolar I disorder: substance use disorders prevalence = 35.7% Bipolar II disorder: substance use disorders prevalence = 28.1% 17 studies, N = 4,414, OR = 1.334, 95%CI 1.013 to 1.757, $p < 0.05$, I^2 not reported When substance type was analysed separately, only alcohol use disorders, and not drug use disorders, remained significantly increased in people with bipolar I disorder compared to people with bipolar II disorder. *Small effect of increased rates of earlier age of onset of bipolar disorder in people with bipolar disorder and a substance use disorder compared to people with bipolar disorder without a substance use disorder;* Age at bipolar onset with substance use = 20.7 years Age at bipolar onset without substance use = 24 years 10 studies, N = 2,065, OR = 2.043, 95%CI 1.595 to 2.613, $p < 0.001$, I^2 not reported When type of substance use disorder was analysed separately, only people with drug use disorders, and not alcohol or cannabis use disorders, showed an earlier age of onset. *Small effect of increased rates of hospitalisations in people with bipolar disorder and a substance use disorder compared to people with bipolar disorder without a substance use disorder;* 9 studies, N = 6,819, OR = 1.355, 95%CI 1.239 to 1.482, $p < 0.001$, I^2 not reported	

Mean number of hospitalisations with substance use = 4.5 Mean number of hospitalisations without substance use = 3.1 Results were similar regardless of substance type (alcohol, or any substance), or study quality.	
Consistency in results	Inconsistent where reported.
Precision in results	Imprecise
Directness of results	Direct

Joslyn C, Hawes DJ, Hunt C, Mitchell PB

Is age of onset associated with severity, prognosis, and clinical features in bipolar disorder? A meta-analytic review

Bipolar Disorders 2016; 18: 389-403

View review abstract online

Comparison	**Association between age at onset and substance use disorders.**
Summary of evidence	**Moderate quality evidence (inconsistent and imprecise, direct, large samples) suggests early age of onset was associated with substance use and alcohol use disorders.**
Substance use disorders	
Significant, small effects of early age of onset and increased risk of substance use disorders; Substance use disorder: 10 studies, N = 4,808, OR = 1.80, 95%CI 1.39 to 2.35, $p < 0.001$, $I^2 = 50\%$ Alcohol use disorder: 9 studies, N = 4,752, OR = 1.35, 95%CI 1.04 to 1.76, $p = 0.023$, $I^2 = 62\%$	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Mammen G, Rueda S, Roerecke M, Bonato S, Lev-Ran S, Rehm J

Association of cannabis with long-term clinical symptoms in anxiety and mood disorders: A systematic review of prospective studies

Journal of Clinical Psychiatry 2018; 79(4) View review abstract online	
Comparison	**The association between cannabis use and symptoms in people with bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, unable to assess precision, direct) suggests cannabis use is associated with greater depression, anxiety, and mania symptom severity, more mood episodes, and more insomnia or hypersomnia in people with bipolar disorder and comorbid cannabis use compared to people with bipolar disorder and no cannabis use.**
Symptoms	
All five included studies reported significant adverse effects of cannabis use on symptoms in people with bipolar disorder; 1 study (N = 2,577) reported significantly more depression symptoms (β = 0.62, p = 0.0019), more anhedonia symptoms (β = 2.62, p = 0.0048), and more insomnia or hypersomnia (β = 2.302, p = 0.0055) in patients with a cannabis use disorder vs. no cannabis use. There was no association with remission. 1 study (N = 3,426) reported significantly higher overall symptoms (β = 0.13, p = 0.004), and mania symptoms (β = 0.15, p = 0.001), in patients with any cannabis use vs. no cannabis use, with no significant associations with depression symptoms. 1 study (N = 1,922) reported significantly greater odds of a mania episode (OR = 1.59, p = 0.048) and shorter time to recurrence of a mania episode (OR = 1.47, p = 0.034) in patients with any cannabis use vs. never used. 1 study (N = 307) reported significantly higher depression (β = 1.24, p < 0.001) and anxiety (β = 0.80, p < 0.001) scores in patients with any cannabis use in the previous month vs. no use in the past month. 1 study (N = 144) reported significantly more affective episodes (p = 0.004), more manic episodes (p = 0.06), more mixed episodes (p = 0.03), and more rapid cycling (p = 0.04) in patients with cannabis use disorder vs. no cannabis use disorder.	
Consistency in results	Consistent
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Messer T, Lammers G, Muller-Siecheneder F, Schmidt RF, Latifi S

Substance abuse in patients with bipolar disorder: A systematic review

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and meta-analysis **Psychiatry Research 2017; 253: 338-50** View review abstract online	
Comparison	**Risk factors for substance use disorders in people with bipolar disorder.**
Summary of evidence	**High quality evidence (consistent, precise, direct, large sample) shows a small effect of increased number of manic episodes is related to increased risk of substance use disorders. Moderate quality evidence (inconsistent and imprecise) suggests small effects of male gender and suicidality.**
Risk factors	
Small effects of increased risk of comorbid substance use disorder with the following factors; Increased number of manic episodes: 6 studies, N = 3,005, SMD = 0.202, 95%CI 0.078 to 0.327, p = 0.001, I^2 = 10% Male gender: 7 studies, N = 3,252, OR = 2.191, 95%CI 1.121 to 4.281, p = 0.022, I^2 = 85% History of suicidality: 4 studies, N = 2,695, OR = 1.758, 95%CI 1.156 to 2.674, p = 0.008, I^2 = 39% There were no significant associations with age, subtype of bipolar disorder, hospitalisation, comorbid anxiety disorders, or psychotic symptoms.	
Consistency in results	Consistent for number of manic episodes only.
Precision in results	Precise for number of manic episodes only.
Directness of results	Direct

Pinto JV, Medeiros LS, Santana da Rosa G, Santana de Oliveira CE, Crippa JADS, Passos IC, Kauer-Sant'Anna, M.

The prevalence and clinical correlates of cannabis use and cannabis use disorder among patients with bipolar disorder: A systematic review with meta-analysis and meta-regression

Neuroscience and Biobehavioral Reviews 2019; 101: 78-84

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Comparison	**Prevalence and clinical correlates of cannabis use or a cannabis use disorder in people with bipolar disorder.**

Summary of evidence	**Moderate quality evidence (inconsistent, appears imprecise, direct, large sample) suggests around one-quarter of people with bipolar disorder reported using cannabis. Cannabis use was more common than having a cannabis use disorder. High heterogeneity across studies was explained by sample differences, with those reporting highest cannabis use with younger age, male gender, single marital status, having fewer years of education, an earlier onset of affective symptoms, psychotic symptoms, suicide attempts, use of tobacco, alcohol and other substances.**
Prevalence and clinical correlates	
Around one-quarter of people with bipolar disorder reported using cannabis; All cannabis use: 53 studies, N = 51,756, prevalence = 24%, 95%CI 18% to 29%, I^2 = 99.8% Cannabis use: 10 studies, N = 2,482, prevalence = 30%, 95%CI 19% to 41%, I^2 = 96.8% Cannabis use disorder: 28 studies, N = 49,554, prevalence = 20%, 95%CI 14% to 25%, I^2 = 96.8% Heterogeneity was explained by the following moderators: younger age, male gender, single marital status, having fewer years of education, an earlier onset of affective symptoms, psychotic symptoms, suicide attempts, use of tobacco, alcohol, and other substances.	
Consistency in results	Inconsistent
Precision in results	Appears imprecise.
Directness of results	Direct

Rakofsky JJ, Dunlop BW

Do alcohol use disorders destabilize the course of bipolar disorder?

Journal of Affective Disorders 2013; 145: 1-10

View review abstract online

Comparison	**Alcohol use on the course and outcomes of bipolar disorder.**
Summary of evidence	**Moderate to low quality evidence (inconsistent, direct, unable to assess precision, large sample) suggests that while alcohol may not prolong an index mood episode, high levels of alcohol intake may increase the risk of a mood recurrence with higher risk of rapid-cycling.**
Effects of alcohol use	

Overall 23 studies were included, N = 10,408 3/5 studies found that alcohol did not prolong index mood episodes of any type. 6/11 studies found that high levels of alcohol intake increased the risk of a mood recurrence. 5/7 studies found that increased alcohol use preceded the development of new mood episodes. 4/5 studies found alcohol use disorders were associated with higher rates of rapid-cycling.	
Consistency in results	Appears inconsistent.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Explanation of acronyms

β = beta coefficient, CI = confidence cnterval, *g* = Hedges'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, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), 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[13].

† 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) that 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[13].

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 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[13];

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

§ 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[15].

‖ 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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