TECHNICAL COMMENTARY

Sleep disturbance

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Introduction

People with a mental illness may show disturbances in the amount or quality of sleep. Typically sleep follows a characteristic pattern of four stages, where stage 1 is a state of drowsiness and early sleep; stage 2 comprises the largest component of the sleep cycle and is the first complete loss of awareness of the external environment; stage 3 is a deep, slow-wave sleep; and the fourth stage is rapid eye movement (REM) sleep where memorable dreaming and muscle paralysis occurs.

Sleep disturbance can be measured in many ways, including the total sleep time, the sleep latency (the length of time it takes from full wakefulness to sleep), and the sleep efficiency index (the amount of time spent asleep while in bed). Sleep latency can have varying definitions, particularly regarding the definition of “asleep” – some studies define this more strictly as the time from lights out until 10 consecutive minutes of stages 2, 3 or 4, while other studies define the latency more leniently as the time from lights out until the first signs of stage 2 sleep.

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 separately 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. When multiple copies of review topics were found, only the most recent and comprehensive 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. Reviews were assigned a low, medium or high possibility of reporting bias* depending on how many items were checked. Reviews rated as having less than 50% of items checked have now 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, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[1]. 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 six systematic reviews that met our inclusion criteria[2-7].

- Moderate to high quality evidence suggests around 30% of people with bipolar disorder have hypersomnia.

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- There were large effects of more time in bed and poorer sleep quality; medium-sized effects of less sleep efficacy, more sleep time (particularly stage 1), and more awakenings; small effects of more sleep latency and wakefulness in people with euthymic bipolar disorder than controls. The effects were similar in different mood phases of the disorder. The sleep disturbances were greater in people with bipolar disorder than in people with schizophrenia.
- These sleep disturbances may be apparent prior to the onset of bipolar disorder, including during childhood or adolescence. A decreased need for sleep may precede a manic episode, while hypersomnia may precede a depressive episode. Insomnia can precede either a manic or a depressive episode.
- Moderate quality evidence suggests a medium-sized effect of lower relative amplitude of the sleep-wake cycle in people with bipolar disorder than people at familial or clinical risk of bipolar disorder.

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De Crescenzo F, Economou A, Sharpley AL, Gormez A, Quested DJ

Actigraphic features of bipolar disorder: A systematic review and meta-analysis

Sleep Medicine Reviews 2017; 33: 58-69

View online review abstract

Comparison	**Sleep efficacy in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate quality evidence (medium to large sample sizes, direct, mostly inconsistent, imprecise) suggests small to medium-sized effects of longer sleep duration, more latency, more time awake after sleep onset and less sleep efficiency in people with bipolar disorder, regardless of illness phase.**
Sleep variables	
Small to medium-sized effects of longer sleep duration, more time awake, longer latency, and lower sleep efficiency in people with bipolar disorder; Sleep duration: 11 studies, N = 258, g = 0.62, 95%CI 0.38 to 0.85, $p < 0.00001$, I^2 = 42%, p = 0.07 Time awake after sleep onset: 9 studies, N = 208, g = 0.55, 95%CI 0.13 to 0.98, p = 0.01, I^2 = 78%, p < 0.0001 Sleep latency: 8 studies, N = 179, g = 0.29, 95%CI 0.09 to 0.50, p = 0.005, I^2 = 5%, p = 0.39 Sleep efficiency: 9 studies, N = 202, g = -0.39, 95%CI -0.71 to -0.08, p = 0.01, I^2 = 58%, p = 0.01 Subgroup analyses revealed similar results in patients in euthymic or mood phases.	
Consistency in results	Inconsistent, apart from sleep latency.
Precision in results	Precise
Directness of results	Direct

Grigolon RB, Trevizol AP, Cerqueira RO, Lee Y, Mansur RB, McIntyre RS, Brietzke E

Hypersomnia and Bipolar Disorder: A systematic review and meta-analysis of proportion

Journal of Affective Disorders 2019; 246: 659-66

View online review abstract	
Comparison	**Rates of hypersomnia in people with bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests around 30% of people with bipolar disorder have hypersomnia.**
Hypersomnia	
Around 30% of people with bipolar disorder have hypersomnia; 10 studies, N = 1,824, proportion = 29.9%, 95%CI 25.8% to 34.1%, I^2 = 59.2%, $p < 0.05$ There were no significant associations between hypersomnia rates and mood state, disorder type, use of medication, age, diagnostic criteria, and hypersomnia criteria.	
Consistency in results	Inconsistent
Precision in results	Appears precise
Directness of results	Direct

Meyer N, Faulkner SM, McCutcheon RA, Pillinger T, Dijk DJ, MacCabe JH

Sleep and circadian rhythm disturbance in remitted schizophrenia and bipolar disorder: A systematic review and meta-analysis

Schizophrenia Bulletin 2020; 46: 1126-43

View online review abstract

Comparison	**Sleep and circadian rhythm disturbance in people with bipolar disorder vs. controls and vs. people with schizophrenia.** **Both groups were in a non-acute phase of the illness.**
Summary of evidence	**Moderate quality evidence (large sample, mostly inconsistent and imprecise, direct) found large effects of more total sleep time, more time in bed, more time awake after sleep onset, and more motor activity, and a medium to large effect of more sleep latency in people with bipolar disorder compared to controls. These effects were greater in people with bipolar disorder compared to controls than in people with schizophrenia compared to controls. There were no significant differences in the number of awakenings, relative amplitude, interdaily stability or variability of circadian rhythms or acrophose (timing of peak**

	intensity of circadian activity) in either patient group compared to controls.
Sleep disturbance	
15 bipolar studies, N = 1,091, 15 schizophrenia studies, N = 679 *A large effect of more total sleep time in people with bipolar disorder vs. controls, and a medium-sized effect of more total sleep time in people with schizophrenia vs. controls;* Bipolar disorder vs. controls: SMD = 1.26, 95%CI 0.73 to 1.79, $p < 0.001$ Schizophrenia vs. controls: SMD = 0.46, 95%CI 0.32 to 0.60, $p < 0.001$ These effect sizes were significantly different ($p < 0.001$) *A medium to large effect of more sleep latency in people with bipolar disorder vs. controls, and a small effect of more sleep latency in people with schizophrenia vs. controls;* Bipolar disorder vs. controls: SMD = 0.74, 95%CI 0.34 to 1.14, $p < 0.001$ Schizophrenia vs. controls: SMD = 0.24, 95%CI 0.04 to 0.44, $p < 0.05$ These effect sizes were significantly different ($p = 0.02$) *A large effect of more wake after sleep onset in people with bipolar disorder vs. controls, and a small effect of more wake after sleep onset in people with schizophrenia vs. controls;* Bipolar disorder vs. controls: SMD = 0.90, 95%CI 0.15 to 1.66, $p < 0.05$ Schizophrenia vs. controls: SMD = 0.24, 95%CI 0.10 to 0.37, $p < 0.001$ These effect sizes were significantly different ($p = 0.002$) *A large effect of more time in bed in people with bipolar disorder vs. controls, and a medium-sized effect of more time in bed in people with schizophrenia vs. controls;* Bipolar disorder vs. controls: SMD = 1.05, 95%CI 0.40 to 1.71, $p < 0.01$ Schizophrenia vs. controls: SMD = 0.65, 95%CI 0.37 to 0.92, $p < 0.001$ These effect sizes were not significantly different ($p > 0.05$) *There were no significant differences in sleep efficacy between people with bipolar disorder and controls, but a small effect of less sleep efficacy in people with schizophrenia vs. controls;* Bipolar disorder vs. controls: SMD = -0.39, 95%CI -0.86 to 0.08, $p > 0.05$ Schizophrenia vs. controls: SMD = -0.16, 95%CI -0.30 to -0.03, $p < 0.05$ These effect sizes were not significantly different ($p > 0.05$) *There were no significant differences in the number of awakenings for either patient group vs. controls;* Bipolar disorder vs. controls: SMD = 0.55, 95%CI -0.32 to 1.42, $p > 0.05$ Schizophrenia vs. controls: SMD = -0.12, 95%CI -0.48 to 0.23, $p > 0.05$ These effect sizes were not significantly different ($p > 0.05$) Meta-regression showed higher antipsychotic dose was related to longer total sleep time and longer	

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sleep latency. A greater proportion of the sample being prescribed sedative antipsychotics predicted shortened sleep latency.
Circadian rhythm disturbance
Large effects of lower motor activity in people with bipolar disorder vs. controls, and in people with schizophrenia vs. controls; Bipolar disorder vs. controls: SMD = -0.86, 95%CI -1.22 to -0.51, $p < 0.001$ Schizophrenia vs. controls: SMD = -0.75, 95%CI -1.20 to -0.29, $p < 0.01$ These effect sizes were not significantly different ($p > 0.05$) *There were no significant differences in relative amplitude for either patient group vs. controls;* Bipolar disorder vs. controls: SMD = -0.50, 95%CI -1.15 to 0.16, $p > 0.05$ Schizophrenia vs. controls: SMD = -0.25, 95%CI -0.56 to 0.05, $p > 0.05$ These effect sizes were not significantly different ($p > 0.05$) *There were no significant differences in interdaily stability for either patient group vs. controls;* Bipolar disorder vs. controls: SMD = 0.27, 95%CI -0.42 to 0.96, $p > 0.05$ Schizophrenia vs. controls: SMD = -0.10, 95%CI -1.01 to 0.82, $p > 0.05$ These effect sizes were not significantly different ($p > 0.05$) *There were no significant differences in interdaily variability for either patient group vs. controls;* Bipolar disorder vs. controls: SMD = -0.47, 95%CI -1.25 to 0.31, $p > 0.05$ Schizophrenia vs. controls: SMD = 0.30, 95%CI -0.33 to 0.94, $p > 0.05$ These effect sizes were not significantly different ($p > 0.05$) *There were no significant differences in acrophase for either patient group vs. controls;* Bipolar disorder vs. controls: SMD = 0.32, 95%CI -0.01 to 0.65, $p > 0.05$ Schizophrenia vs. controls: SMD = -1.67, 95%CI -4.14 to 0.81, $p > 0.05$ These effect sizes were not significantly different ($p > 0.05$) Increasing age predicted decreasing relative amplitude.

Consistency in results	Authors report some inconsistencies in the analyses
Precision in results	Mostly imprecise
Directness of results	Direct

Ng TH, Chung KF, Ho FY, Yeung WF, Yung KP, Lam TH

Sleep-wake disturbance in interepisode bipolar disorder and high-risk individuals: a systematic review and meta-analysis

Sleep Medicine Reviews 2015; 20: 46-58

View online review abstract

Comparison 1	**Sleep efficacy in people with bipolar disorder in the euthymic phase vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium sample sizes, mostly consistent, precise, direct) suggests large effects of more time in bed and poorer sleep quality; medium-sized effects of less sleep efficacy, more sleep time (particularly stage 1), and more awakenings; small effects of more sleep latency and wakefulness in people with bipolar disorder than controls.**

Sleep variables

Significant, large effects of more time in bed and poor sleep quality in people with bipolar disorder;

Time in bed (actigraphy): 2 studies, N = 118, SMD = 0.87, 95%CI 0.26 to 1.48, $p = 0.005$, $I^2 = 60\%$, $p = 0.11$

Sleep quality, Pittsburgh Sleep Quality index: 3 studies, N = 268, SMD = 1.55, 95%CI 1.27 to 1.82, $p < 0.00001$, $I^2 = 0\%$, $p = 0.88$

Sleep quality, Insomnia Severity index: 2 studies, N = 95, SMD = 1.28, 95%CI 0.83 to 1.72, $p < 0.00001$, $I^2 = 0\%$, $p = 0.70$

Significant, medium-sized effects of less sleep efficacy and quality, sleep time (particularly stage 1), but more awakenings in people with bipolar disorder;

Sleep efficacy (sleep diary): 5 studies, N = 274, SMD = -0.77, 95%CI -1.16 to -0.39, $p < 0.0001$, $I^2 = 52\%$, $p = 0.08$

Sleep quality, Epworth Sleepiness Scale: 2 studies, N = 187, SMD = 0.50, 95%CI 0.20 to 0.79, $p < 0.001$, $I^2 = 1\%$, $p = 0.32$

Sleep time (actigraphy): 8 studies, N = 383, SMD = 0.65, 95%CI 0.30 to 1.00, $p = 0.0002$, $I^2 = 63\%$, $p = 0.008$

Stage 1 sleep (polysomnography): 2 studies, N = 64, SMD = 0.55, 95%CI 0.05 to 1.05, $p = 0.03$, $I^2 = 0\%$, $p = 0.39$

Number of awakenings (sleep diary): 3 studies, N = 237, SMD = 0.65, 95%CI 0.27 to 1.03, $p = 0.0007$, $I^2 = 55\%$, $p = 0.11$

Significant, small effects of more sleep latency and wakefulness in people with bipolar disorder;

Sleep latency (actigraphy): 8 studies, N = 383, SMD = 0.37, 95%CI 0.16 to 0.59, $p = 0.0006$, $I^2 =$

9%, *p* = 0.36 Awake after sleep onset (actigraphy): 8 studies, N = 383, SMD = 0.26, 95%CI 0.07 to 0.46, *p* = 0.009, I^2 = 0%, *p* = 0.90	
Consistency in results	Consistent, apart from sleep time.
Precision in results	Precise
Directness of results	Direct
Comparison 2	**Sleep efficacy in people with bipolar disorder in the euthymic phase vs. people at high risk of the disorder (family history and questionnaire scores).**
Summary of evidence	**Moderate quality evidence (small to medium sample size, consistent, precise, direct) suggests a medium-sized effect of lower relative amplitude of the sleep-wake cycle in people with bipolar disorder.**
Sleep variables	
Significant, medium-sized effect of lower relative amplitude of the sleep-wake cycle in people with bipolar disorder; 3 studies, N = 174, SMD = -0.43, 95%CI -0.83 to -0.02, *p* = 0.04, I^2 = 43%, *p* = 0.17 There were no significant differences in sleep time, efficacy, latency, or wakefulness.	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct
Comparison 3	**Sleep efficacy in people with bipolar disorder in the euthymic phase vs. people with a primary diagnosis of insomnia.**
Summary of evidence	**Moderate quality evidence (small to medium sample sizes, consistent, precise, direct) suggests more sleep time and better sleep efficacy in people with bipolar disorder. Moderate to low quality evidence (inconsistent and imprecise) also suggests less wakefulness. There were no differences in sleep latency.**
Sleep variables	
Significant, large effects of more sleep time, better sleep efficacy and less wakefulness in people with bipolar disorder; Sleep time (actigraphy): 2 studies, N = 67, SMD = 0.87, 95%CI 0.07 to 1.67, *p* = 0.03, I^2 = 53%, *p* =	

0.15 Sleep efficacy (sleep diary): 3 studies, N = 168, SMD = 0.57, 95%CI 0.18 to 0.96, p = 0.004, I^2 = 18%, p = 0.30 Wake after sleep onset (sleep diary): 3 studies, N = 168, SMD = -0.76, 95%CI -1.45 to -0.06, p = 0.03, I^2 = 70%, p = 0.03 There were no significant differences in sleep latency.	
Consistency in results	Consistent, apart from wakefulness.
Precision in results	Precise, apart from wakefulness.
Directness of results	Direct

Pancheri C, Verdolini N, Pacchiarotti I, Samalin L, Delle Chiaie R, Biondi M, Carvalho AF, Valdes M, Ritter P, Vieta E, Murru A

A systematic review on sleep alterations anticipating the onset of bipolar disorder

European Psychiatry 2019; 58: 45-53

View online review abstract

Comparison	**Rates of sleep alterations prior to the onset of bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests sleep disturbances may be apparent prior to the onset of bipolar disorder, often during childhood or adolescence. A decreased need for sleep may precede a manic episode, while hypersomnia may precede a depressive episode. Insomnia can precede either a manic or a depressive episode.**
Sleep disturbances	
16 studies, N = 34,563 Authors report that sleep disturbances frequently appear one year before the onset of bipolar disorder and are often apparent during childhood or adolescence. A decreased need for sleep may precede a manic episode, while hypersomnia may precede a depressive episode. Insomnia can precede either a manic or a depressive episode.	
Consistency in results	Unable to assess; no measure of consistency is reported.

Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Tazawa Y, Wada M, Mitsukura Y, Takamiya A, Kitazawa M, Yoshimura M, Mimura M, Kishimoto T

Actigraphy for evaluation of mood disorders: A systematic review and meta-analysis

Journal of Affective Disorders 2019; 253: 257-69

View online review abstract

Comparison	**Sleep efficacy in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, direct, mostly consistent, precise) suggests small to medium-sized effects of longer sleep duration, more latency, more time awake after sleep onset in people with bipolar disorder.**
Sleep variables	
Small to medium-sized effects showed euthymic bipolar patients had more; Total sleep time: 9 studies, N = 595, SMD = -0.37, 95%CI -0.61 to -0.13, p = 0.003, I^2 = 46.2%, p = 0.06 Sleep latency: 8 studies, N = 507, SMD = -0.24, 95%CI -0.47 to -0.02, p = 0.03, I^2 = 30.8%, p = 0.18 Wake after sleep onset: 7 studies, N = 469, SMD = -0.21, 95%CI -0.39 to -0.03, p = 0.025, I^2 = 0%, p = 0.97 *There were no significant differences in:* Sleep efficacy: 7 studies, N = 467, SMD = 0.16, 95%CI -0.02 to 0.35, p = 0.083, I^2 = 0%, p = 0.81 Daily activity: 2 studies, N = 108, SMD = 0.61, 95%CI -0.49 to 1.70, p = 0.279, I^2 = 86%, p = 0.008	
Consistency in results	Consistent, apart from sleep time and daily activity.
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, *g* = Hedges 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), 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[8].

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† 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.

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. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large treatment effect[8].

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).

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, an 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. An 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[9]. 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

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between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent 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 substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

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

§ 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[10].

‖ 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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