TECHNICAL COMMENTARY

Smoking

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Introduction

Tobacco smoking is very common among people with schizophrenia, who often show particularly heavy usage. This poses considerable health risks, potential interference with the metabolism of antipsychotic medications[1], as well as financial burden for the individuals.

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. Due to the high volume of systematic reviews we have now limited inclusion to systematic meta-analyses. Where no systematic meta-analysis exists for a topic, systematic reviews without meta-analysis are included for that topic. 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.

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[2]. Reviews reporting less than 50% of items 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).[3] 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 two systematic reviews that met inclusion criteria[4, 5]. These are presented below in alphabetical order.

Conclusions

- Moderate to high quality evidence suggests buproprion improves short-term, but not long-term, smoking abstinence.
- Moderate to low quality evidence suggests contingency reinforcement in combination with transdermal nicotine is more effective than contingency reinforcement alone or self-quit for reducing smoking.

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Banham L, Gilbody S

Smoking cessation in severe mental illness: what works?

Addiction 2010; 105: 1176-1189

View review abstract online

Comparison 1	**Bupropion for smoking cessation vs. placebo.**
Summary of evidence	**Moderate quality evidence (consistent, imprecise, direct, medium-sized sample) suggests buproprion increased smoking abstinence in the short term compared with placebo, but this was not maintained at follow-up.**

Smoking abstinence

Participants receiving buproprion alone showed a significant, medium sized increase in smoking abstinence compared to placebo at the end of treatment;.

5 RCTs, N = 212, RR 2.76, 95%CI 1.48 to 5.16, $p < 0.05$, I^2 0%

Bupropion in addition to group therapy showed significantly greater rates of smoking abstinence compared to placebo plus group therapy, however this was not maintained at follow-up;

End of trial: 3 RCTs, N = 103, RR 4.18, 95%CI 1.30 to 13.42, $p < 0.05$, I^2 0%

1 month follow-up: 2 RCTs, N = 71, RR 5.04, 95%CI 0.38 to 23.68

3 month follow-up: 2 RCTs, N = 71, RR 8.96, 95%CI 0.08 to 161.23

6 month follow-up: 1 RCT, N = 71, RR 1.12-2, 95%CI 0.07 to 52.44

24 month follow-up: 1 RCT, N = 18, RR 1.00, 95%CI 0.18 to 5.63

3 RCT (N = 103) reported improvements in symptom severity scores following bupropion (BPRS, PANSS positive, HAM-D) and 1 RCT (N = 53) reported increased cognitive scores. 1 RCT (N = 18) reported increased weight loss in the bupropion group at 6 months, $p < 0.01$.

Bupriopion in addition to group therapy and NRT showed significantly greater rates of smoking abstinence compared to placebo plus group therapy plus NRT; however this was not maintained beyond the short term;

End of treatment: 2 RCTs, N = 109, RR 2.34, 95%CI 1.12 to 4.91, $p < 0.05$, $I^2 = 0\%$

3 month follow-up: 1 RCT, N = 51, RR 1.87, 95%CI 0.73 to 4.82

6 month follow-up: 1 RCT, N = 51, RR 2.60, 95%CI 0.55 to 12.19

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15 month follow-up: 1 RCT, N = 51, RR 1.56, 95%CI 0.28 to 8.56 1 RCT (N = 51) reported the bupropion group was associated with lower severity of extrapyramidal symptoms.	
Risks	1 RCT (N = 53) reported 1 withdrawal due to a medical allergy and 2 withdrawals due to suicide ideation, and 1 RCT (N = 51) reported 4 withdrawals due to medication side effects.
Consistency in results‡	Consistent where applicable (>1 RCT)
Precision in results§	Imprecise
Directness of results‖	Direct
Comparison 2	**Smoking reduction using nicotine replacement therapy (NRT) vs. placebo.**
Summary of evidence	**Low quality evidence (1 small RCT) is unclear as to any benefits of NRT for smoking reduction compared to placebo.**
Smoking reduction	
1 RCT (N = 10) reported no difference in mean expired CO in people receiving NRT, however they showed significant increases on Abnormal Involuntary Movement Scale at day 2, $p < 0.05$.	
Consistency in results	Not applicable
Precision in results	Unable to assess
Directness of results	Direct
Comparison 3	**Specialised smoking program plus NRT vs. standard smoking group therapy plus NRT.**
Summary of evidence	**Low quality evidence (imprecise, 1 small RCT) suggests no sustained benefits of specialised mental health smoking abstinence programs over standard smoking abstinence programs.**
Smoking abstinence	
There was no difference between groups at the end of the trial, but at 8 month follow up the standard program showed higher rates of abstinence; *End of trial (3 months):* 1 RCT, N = 45, RR 1.01, 95%CI 0.45 to 2.28	

8.5 month follow-up: 1 RCT, N = 45, RR 0.61, 95%CI 0.14 to 2.67, $p > 0.05$	
Consistency in results	Not applicable
Precision in results	Imprecise
Directness of results	Direct
Comparison 4	**Individual therapy plus NRT vs. usual care.**
Summary of evidence	**Moderate to low quality evidence (imprecise, 1 RCT, medium-sized sample) suggests no sustained benefits of individual therapy over usual care for smoking abstinence but a significant reduction in total cigarettes over 1 year.**
Smoking abstinence and reduction	
A medium effect size suggests significantly better abstinence in those receiving individual therapy plus NRT, compared to usual care. This was not maintained at follow up; *End of trial (4 months):* 1 RCT, N = 298, RR 2.74, 95%CI 1.10 to 6.81, $p < 0.05$ *3 month post-treatment:* 1 RCT, N = 298, RR 2.74, 95%CI 0.74 to 10.12, $p > 0.05$ *9 month post-treatment:* 1 RCT, N = 298, RR 5.14, 95%CI 0.61 to 43.44 , $p > 0.05$ *A medium effect suggests a significant increase in smoking reduction (≥50% reduction from baseline cigarettes/day) in people receiving individual therapy plus NRT;* *4 month follow-up:* 1 RCT, N = 298, RR 2.62, 95%CI 1.76 to 3.93 *7 month follow-up:* 1 RCT, N = 298, RR 1.61, 95%CI 1.07 to 2.44 *13 months:* 1 RCT, N = 298, RR 1.75, 95%CI 1.15 to 2.66 This RCT also reported depression and anxiety in those receiving individual therapy, $p < 0.01$	
Consistency in results	Unable to assess consistency
Precision in results	Unable to assess precision
Directness of results	Direct

Tsoi DT, Porwal M, Webster AC

Interventions for smoking cessation and reduction in individuals with

schizophrenia

Cochrane Database of Systematic Reviews 2010; 6: Art. No.: CD007253

View review abstract online

Comparison 1	**Atypical antidepressant bupropion (150-300 mg/day) plus antipsychotics (not specified) vs. placebo plus antipsychotics for reducing smoking in people with schizophrenia. Treatment duration range 3-12 weeks.** **Note - many groups also received weekly group therapy sessions in addition to ongoing antipsychotics. Several groups also included transdermal nicotine patches (same as NRT above) with bupriopion treatment.**
Summary of evidence	**High quality evidence (direct, consistent, precise) shows no difference in mental state severity between the bupropion and placebo groups.** **Moderate to high quality evidence (direct, consistent, unable to assess precision) suggests that people with schizophrenia who smoke and are treated with bupropion may reduce their smoking (CO level and number of cigarettes smoked each day) by the end of treatment. However low to moderate quality evidence (direct, inconsistent, unable to assess precision) suggests no difference at 6 months follow up.** **Moderate quality evidence (direct, consistent, imprecise) suggests that people with schizophrenia who smoke and are treated with bupropion had a higher rate of abstinence from smoking overall by the end of the treatment, however there is no difference at 6 months, and no difference when also treated with transdermal NRT.**

Mental state

No difference in symptom severity was reported between the bupropion group and the placebo group at the end of treatment;

Positive symptoms: 2 RCTs, N = 85, *d* = -0.24, 95%CI -0.66 to 0.19, *p* = 0.28, Q_w = 0.43, *p* = 0.51, I^2 = 0%

Negative symptoms: 3 RCTs, N = 136, *d* = -0.12, 95%CI -0.46 to 0.22, *p* = 0.49, Q_w = 0.25, *p* = 0.88, I^2 = 0%

Depressive symptoms: 3 RCTs, N = 136, *d* = -0.16, 95%CI -0.50 to 0.18, *p* = 0.35, Q_w = 0.44, *p* = 0.80, I^2 = 0%

Smoking reduction
A significant medium to large effect size favoured bupropion alone compared to placebo to improving abstinence from smoking, immediately following treatment. This effect was not reported for bupropion in combination with a transdermal nicotine patch (NRT), compared to placebo (plus NRT);
Bupropion alone: 5 RCTs, N = 230, RR = 3.21, 95%CI 1.51 to 6.81, *p* = 0.0024, Q_w = 2.43, *p* = 0.66, I^2 = 0%
Bupropion plus NRT: 2 RCTs, N = 110, RR = 2.92, 95%CI 0.75 to 11.33, *p* = 0.12, Q_w = 1.72, *p* = 0.19, I^2 = 42%
Overall: 7 RCTs, N = 340, RR = 2.84, 95%CI 1.61 to 4.99, *p* = 0.0003, Q_w = 4.40, *p* = 0.62, I^2 = 0%
At 6 month follow-up, there was no significant difference in smoking abstinence following bupropion alone, or in combination with NRT, compared to placebo;
Bupropion alone: 3 RCTs, N = 104, RR = 2.19, 95%CI 0.50 to 9.63, *p* = 0.30, Q_w = 0.34, *p* = 0.85, I^2 = 0%
Bupropion plus NRT: 2 RCTs, N = 110, RR = 3.41, 95%CI 0.87 to 13.30, *p* = 0.078, Q_w = 0.56, *p* = 0.46, I^2 = 0%
However, pooled measures show a medium effect size that significantly favoured the bupropion group for a higher rate of abstinence compared to the placebo group at 6 month follow-up;
Overall: 5 RCTs, N = 214, RR = 2.78, 95%CI 1.02 to 7.58, *p* = 0.045, Q_w = 1.08, *p* = 0.90, I^2 = 0%
The bupropion group showed a significant reduction in expired carbon monoxide (CO) level compared to the placebo group, at the end of treatment;
Endpoint levels: 2 RCTs, N = 104, MD = -6.10, 95%CI -10.71 to -1.49, *p* = 0.0094, Q_w = 0.18, *p* = 0.67, I^2 = 0%
Change from baseline: 1 RCT, N = 19, MD = -14.80, 95%CI -28.15 to -1.45, *p* = 0.03
Overall: 3 RCTs, N = 123, MD = -7.03, 95%CI -11.38 to -2.67, *p* = 0.0016, Q_w = 1.64, *p* = 0.44, I^2 = 0%
However, no difference was reported at 6 month follow up in the overall or endpoint scores, though 1 RCT showed significant difference from baseline levels;
Endpoint levels: 2 RCTs, N = 104, MD = -2.08, 95%CI -17.76 to 13.59, *p* = 0.79, Q_w = 9.12, *p* = 0.003, I^2 = 89%
Change from baseline: 1 RCT, N = 19, MD = -14.30, 95%CI -27.20 to -1.40, *p* = 0.03
Overall: 3 RCTs, N = 123, MD = -5.55, 95%CI -17.89 to 6.78, *p* = 0.38, Q_w = 11.77, *p* = 0.003, I^2 =

83% *Bupropion was associated with a significant reduction in number of cigarettes smoked per at the end of treatment compared to placebo, but this difference was not maintained at 6 month follow up;* *End of treatment*: 3 RCTs, N = 184, MD = -10.77, 95%CI -16.52 to -5.01, *p* = 0.00025, Q_w = 3.36, *p* = 0.19, I^2 = 40% *Follow-up*: 2 RCTs, N = 104 MD = 0.40, 95%CI -5.72 to 6.53, *p* = 0.90, Q_w = 0.43, *p* = 0.51, I^2 = 0%	
Consistency in results‡	Consistent for all except CO level at 6 months follow-up.
Precision in results§	Imprecise for all measures except mental states. Unable to assess for non-standardised values.
Directness of results‖	Direct
Comparison 2	**High dose transdermal NRT (42mg) vs. regular dose transdermal NRT (21mg) in people with schizophrenia who want to quit smoking.**
Summary of evidence	**Low quality evidence (direct, small sample, unable to assess consistency or precision) is unclear as to benefits of higher-dose NRT for smoking abstinence.**
Smoking abstinence	
1 RCT (N = 51) found that at 8 weeks the abstinence rates were not significantly different between high dose group (32%) and the regular dose group (23%).	
Consistency in results	No measure of consistency reported.
Precision in results	No measure of precision reported.
Directness of results	Direct
Comparison 3	**Contingent Reinforcement (CR) using money with transdermal NRT vs. CR alone vs. no active intervention (self-quit) for aiding smoking cessation in people with schizophrenia.**
Summary of evidence	**Moderate to low (direct, 1 RCT, unable to assess consistency) suggests that CR in combination with NRT is more effective than either CR alone or self-quit at reducing smoking in people with schizophrenia.**

Smoking abstinence	
1 RCT, N = 80, showed 32.5% of participants expressed an interest in quitting smoking. Abstinence rates were significantly higher in the CR with NRT (50%) compared to the CR group (27.8%) or the self-quit group (10%) at the end of the 36 week trial. The CR with NRT group had significantly lower nicotine dependence at 20 and 36 weeks compared to both comparison groups. The CR with NRT group had significantly lower expired carbon monoxide level at the end of the trial compared to self-quit, but not CR alone.	
Cigarettes smoked per day (CPD)	
CPD was lower at week 36 in the CR with NRT group compared to the self-quit group. CR alone showed no difference to either comparison group by the end of the trial. No data reported	
Consistency in results	No measures of consistency reported
Precision in results	No measure of precision reported
Directness of results	Direct
Comparison 4	**American Lung Association (ALA) group program vs. specialised smoking cessation group therapy designed for schizophrenia (both with transdermal NRT).**
Summary of evidence	**Moderate to low quality evidence (direct, unable to assess consistency or precision) suggests people with schizophrenia who smoke may have a higher abstinence rate when treated with an ALA group program compared to a specialized smoking cessation group therapy at a 6 month follow up. They may have a higher abstinence rate if they are treated with second generation compared to first generation antipsychotics.**
Smoking abstinence **Measured by continuous abstinence for the past 4 weeks**	
1 study (N = 45) reported a trend-level reduction in smoking in the ALA program compared to the specialised therapy group; 23.5% vs. 32.1, $p = 0.06$. At 6 month follow up, the ALA therapy group had significantly lower rates of smoking than the specialised therapy group; 17.6% vs. 10.7% ($p < 0.03$). This effect was stronger in participants receiving atypical antipsychotics compared to first-	

generation medications. No difference between groups in expired carbon monoxide (CO) level, psychiatric symptoms, medication side effects.	
Consistency in results	No measure of consistency reported.
Precision in results	No measure of precision reported.
Directness of results	Direct
Comparison 5	**Smoking cessation individual therapy plus transdermal NRT vs. routine care.**
Summary of evidence	**Low quality evidence (direct, imprecise unable to assess consistency) is unclear as to any benefit of individual therapy plus NRT for reducing smoking.**
Smoking reduction	
1 RCT (N = 169) showed a significant reduction in total smoking in the therapy group compared to routine care at 3 months, this was no sustained at 6 or 12 months. OR = 3.96, 99%CI 1.53 to 10.23, $p < 0.01$ There were no significant differences in number of participants abstinent from smoking at 3 months, 6 months or 12 months. 1 RCT (N = 78) compared motivational interviewing, psychoeducation, and routine care, and found no difference in expired CO at one week and one month after intervention.	
Consistency in results	Unable to assess
Precision in results	Imprecise where applicable
Directness of results	Direct
Comparison 6	**Transdermal NRT alone for smoking reduction in schizophrenia vs. placebo.**
Summary of evidence	**Low quality evidence (direct, unable to assess consistency or precision) is unclear as to any benefit of transdermal NRT for reducing smoking.**
Smoking reduction	

1 RCT (N = 10) assessed smoking reduction over 32 hours and found no difference between groups in expired CO level or psychiatric symptoms, though NRT showed some reduction in expired CO in the heaviest smokers. The NRT group had significantly increased involuntary movement, with 6 out of 10 subjects having abnormal movement. 1 RCT (N = 14) reported smoking reduction over 7 hours and found that participants receiving NRT smoked significantly fewer cigarettes than the placebo group, $p < 0.05$.	
Consistency in results	No measure of consistency reported.
Precision in results	No measure of precision reported.
Directness of results	Direct
Comparison 7	**Smoking reduction in schizophrenia patients treated with other pharmaceutical interventions vs. placebo.**
Summary of evidence	**Low quality evidence (direct, unable to assess consistency or precision) is clear as to any benefit of clozapine, galantamine, atomoxetine or topiramate for reducing smoking in people with schizophrenia.**
Clozapine (antipsychotic)	
1 study (N not reported) found that people treated with clozapine (>200ng/ml) showed a significant decline in number of cigarettes smoked and expired CO. Those receiving 50-150ng/ml (sub-therapeutic dose) showed no difference, however they also had a lower CO levels at baseline. 1 study reported no difference in smoking in people with schizophrenia treated with clozapine.	
Galantamine (acetylcholinesterase inhibitor)	
1 study reported no significant difference between groups in expired CO level, but found a significant increase in nicotine dependence in people given galantamine compared to placebo.	
Atomoxetine (noradrenaline reuptake inhibitor)	
1 study reported no significant difference in expired CO level or cigarette consumption between those receiving atomoxetine and the placebo.	
Topiramate (anticonvulsant)	

1 RCT (N = 24) found no difference in expired CO level or psychiatric symptoms between topiramate and placebo at 8 weeks.	
Consistency in results	No measure of consistency reported.
Precision in results	No measure of precision reported.
Directness of results	Direct

Explanation of acronyms

ALA = American Lung Association, BPRS = Brief Psychiatric Rating Scale, CI = Confidence Interval, CO = carbon monoxide, CPD = cigarettes per day, CR = contingency reinforcement, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences (see below for interpretation of effect size), HAM-D = Hamilton rating scale for Depression, 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, NRT = Nicotine Replacement Therapy, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = Positive and Negative Syndrome Scale, RCT = randomised controlled trial, RR = relative risk, 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[6].

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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.

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).

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[6].

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[7]. 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.

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‡ 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.

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§ 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[8].

‖ 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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