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Proportion attributable to contextual effects in general medicine: a meta-epidemiological study based on Cochrane reviews

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Abstract

Objectives Our objectives were to examine the magnitude of the proportion attributable to contextual effects (PCE), which shows what proportion of the treatment arm response can be achieved by the placebo arm across various interventions, and to examine PCE variability by outcome type and condition.

Design We conducted a meta-epidemiological study.

Setting We searched the Cochrane Database of Systematic Reviews with the keyword 'placebo' in titles, abstracts and keywords on 1 January 2020.

Participants We included reviews that showed statistically significant beneficial effects of the intervention over placebo for the first primary outcome.

Main outcome measures We performed a random-effects meta-analysis to calculate PCEs based on the pooled result of each included review, grouped by outcome type and condition. The PCE quantifies how much of the observed treatment response can be achieved by the contextual effects.

Public and patient involvement statement No patient or member of the public was involved in conducting this research.

Results We included 328 out of 3175 Cochrane systematic reviews. The results of meta-analyses showed that PCEs varied greatly depending on outcome type ($I^2=98%$) or condition ($I^2=98%$), but mostly lie between 0.40 and 0.95. Overall, the PCEs were 0.65 (95% CI 0.59 to 0.72) on average. Subjective outcomes were 0.50 (95% CI 0.41 to 0.59), which was significantly smaller than those of semiobjective (PCE 0.78; 95% CI 0.72 to 0.85) or objective outcomes (PCE 0.94; 95% CI 0.91 to 0.97).

Conclusions The results suggest that much of the observed benefit is not just due to the specific effect of the interventions. The specific effects of interventions may be larger for subjective outcomes than for objective or semiobjective outcomes. However, PCEs were exceptionally variable. When we evaluate the magnitude of PCEs, we should consider each PCE individually, for each condition, intervention and outcome in its context, to assess the importance of an intervention for each specific clinical setting.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although the proportion attributable to contextual effects (PCE) is highly important to interpreting the results of clinical trials and selecting the appropriate treatment in the clinical setting, a comprehensive review of PCEs among several outcome types and conditions was not yet available.

WHAT THIS STUDY ADDS

⇒ This study showed that the overall PCE was 0.65 (95% CI 0.59 to 0.72).
⇒ The PCE of subjective outcomes was 0.50 (95% CI 0.41 to 0.59), while that of semiobjective and objective outcomes were 0.78 (95% CI 0.72 to 0.85) and 0.94 (95% CI, 0.91 to 0.97), respectively.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ The results suggest that much of the observed benefits in clinical trials are actually due to factors other than specific intervention effects. A smaller PCE may indicate that the effect of interventions on subjective outcomes is larger than on different types of outcomes.
⇒ We should consider each PCE individually, for each condition, intervention and outcome in its context, to assess the importance of an intervention for each specific clinical setting.

Introduction

Placebo has long been used as a dummy treatment in control groups of randomised controlled trials (RCTs) to control for non-specific factors.^{1 2} Improvement seen in the intervention group (treatment response) can often be seen in the placebo group and is understood to be due to three contextual effects: the placebo effect, the natural course of the disease or regression to the mean.³ While the

nature and degree of the placebo effect itself have been controversial,⁴⁻⁶ assessing the amount of response due to contextual effects helps to explain the benefits specific to an intervention.

The proportion attributable to contextual effects (PCE) is a metric indicating what proportion of the treatment arm response can be achieved by the placebo arm. Response may be beneficial for a dichotomous outcome (eg, survival, remission) or a beneficial change for a continuous outcome (eg, reduction in pain, increase in quality of life (QoL)). Therefore, the PCE corresponds with the contextual effects (placebo effect +natural course +regression to the mean) divided by the intervention arm response (specific effect +placebo effect +natural course +regression to the mean). The PCE ranges from 0 to 1. A score of 0 means that none of the treatment response is due to the contextual effects. Conversely, a PCE score of 1 means that all of the treatment response is due to the contextual effects. A larger PCE reflects a larger contextual effect, or a smaller specific effect of the intervention.⁷⁻⁹

An RCT usually focuses on the specific treatment effect, which is the difference in the outcome between the treatment arm and the placebo arm. However, in clinical practice, the overall treatment effect includes not only the specific treatment effect, but also the contextual effects. As a result, a treatment that did not show a large specific effect in an RCT, can still show a larger response in clinical practice than a treatment with large beneficial contextual effects. This phenomenon is called the Efficacy Paradox.¹⁰ Therefore, clinicians and patients should consider both the overall treatment effect and the PCE to interpret clinical trials properly and select appropriate treatments. A large PCE means that a large amount of response seen in patients receiving the treatment can also be seen in patients without receiving the active intervention. Some studies have shown that the PCE might reach 0.65–0.75.^{11 12} However, there has been no systematic attempt to review PCEs across various current healthcare interventions.

In this study, we examine the magnitude of PCEs. This will inform how much of an intervention's beneficial effect can be achieved by the contextual effects. In addition, we evaluate PCE variability by outcome type and condition when contextual effects also show a beneficial effect. To achieve this, we systematically surveyed all relevant Cochrane reviews, calculated the PCEs in all fields of medicine, and compared them by the outcome, condition and degree of the certainty of evidence from existing reviews.

Methods

We followed the published reporting guideline for a meta-epidemiological study.¹³

Eligibility criteria

We included all systematic reviews (SRs) of randomised placebo-controlled trials published in the Cochrane Database of Systematic Reviews that showed statistically significant beneficial effects of the intervention over placebo in the first primary outcome. We regarded a two-tailed $p < 0.05$ as statistically significant. We excluded interventions whose efficacy is not established because it would be meaningless to examine PCEs for non-beneficial interventions. When there were multiple comparisons for the first primary outcome due to multiple intervention arms in a review, we selected the first comparison. We included reviews that reported a risk ratio (RR) or an OR for dichotomous outcomes. We excluded reviews reporting other effect sizes, such as HRs in survival analyses. For continuous outcomes, we were able to calculate PCE only when: (1) the meta-analysis reported change scores, (2) the weighted mean of both intervention and control arm showed the same direction of change and (3) larger changes

in the outcome equated to more beneficial changes. We excluded initial reviews that had been updated (ie, we included only the most recent version), reviews of studies other than placebo-controlled trials (eg, sham-controlled trials, non-RCTs, diagnostic test accuracy studies or prognostic studies), overviews of reviews and methodological reviews. We extracted the numerical data from the forest plot of the first meta-analysis. Therefore, we were obliged to exclude reviews that did not show the forest plot of their primary outcome.

Search strategy and study selection

We searched the Cochrane Database of Systematic Reviews with the keyword 'placebo' in titles, abstracts and keywords on 1 January 2020 and selected all the available reviews, regardless of the publication date. Two authors independently performed the initial screening of the titles and abstracts of all studies identified by the search and examined the potential eligibility for inclusion. After initial screening, the same authors assessed the eligibility based on a full-text review. Disagreements were resolved by discussion between the authors, with another author acting as an arbiter when necessary.

Data extraction

Two authors independently used a structured data extraction form to collect data from the included studies. Differences were resolved by consensus. We extracted the pooled RR, SE, and 95% CI when the review reported RR. We extracted the pooled OR, SE, 95% CI and the average control event rate (CER) when the review reported OR. When the review reported a mean difference (MD) of change scores, we extracted the change score and the number of participants for the intervention and placebo arms separately. When the review reported the standardised MD, we extracted the change score of the outcome, SE and the number of participants for the intervention and placebo arms separately.

In addition, we extracted the following information: the number of participants and trials in the meta-analysis of the first primary outcome, the sample size of intervention and placebo arms, outcome data type (dichotomous or continuous), outcome type, condition, intervention type (pharmacological or non-pharmacological), Cochrane review group and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) category of the outcome.

We categorised outcome types and conditions following the categories used in previous studies.¹³⁻¹⁵ We modified the category of outcome types, in which we translated harmful outcomes into equivalent beneficial outcomes (eg, from mortality to survival).

We categorised outcome types as follows, following typologies used in the literature.¹⁴⁻¹⁶

Objective outcome

Survival.

Semiobjective outcomes

No major morbidity events, improved obstetric outcomes, less resource use/shorter hospital stay, improved internal structure (structural outcome within the internal body such as radiograph outcomes), improved external structure (structural outcomes which can be externally observed such as eczema), improved biological markers, no unpleasant composite endpoint, no composite mortality/morbidity events, less drop-out from the treatment, no adverse events and others

Subjective outcomes

Pain relief, QoL improvement, mental health improvement, less consumption/satisfaction with care, cure of condition, no new signs of infection/disease and others

We categorised conditions as follows^{14–16}: cardiovascular, central nervous system/musculoskeletal, digestive system, infectious disease, mental health and behavioural conditions, obstetrics and gynaecology, respiratory disease, urogenital and others.

Statistical analyses

The definition of beneficial and harmful outcome measures

Some reviews used an outcome measure in which the higher number of events is better (eg, survival), while others examined the same outcome but used the opposite measure in which the lower number of events is better (eg, death). We defined the outcome measure in which the higher number of events is better as a beneficial outcome and the outcome measure in which the lower number of events is better as a harmful outcome.

Calculation of the CE for each intervention over placebo

We defined and calculated the PCE to designate how much of the beneficial outcome observed in the intervention group is realised in the placebo group. We assumed the independence between the specific treatment effect and the contextual effects.

Beneficial dichotomous outcomes

When the meta-analysis reported an RR for a beneficial outcome (RR >1 expected), we defined the PCE as follows:

$$PCE = \frac{\text{Control event rate (CER)}}{\text{Experimental event rate (EER)}} \quad (1)$$

where the CER refers to the proportion of outcome events in the placebo group, and the experimental event rate (EER) refers to the proportion of outcome events in the intervention group. We calculated PCE as the inverse of the pooled RR.

When the meta-analysis reported an OR, we first converted the OR to an RR using the average CER obtained in the meta-analysis:

$$RR = \frac{OR}{1 - CER \times (1 - OR)} \quad (2)$$

PCE was then calculated using the RR according to the formula (1).

Harmful dichotomous outcomes

When the meta-analysis reported an RR for a harmful outcome, we converted the RR to an OR using the CER:

$$OR = \frac{RR \times (CER - 1)}{RR \times CER - 1} \quad (3)$$

Then we converted the OR of harmful outcomes to that of beneficial outcomes. For example, ORs for mortality were converted to ORs for survival, taking the inverse of the OR. Finally, we calculated the PCE using formulae (2) and (1).

When the meta-analysis reported an OR, we took the inverse of the OR to represent the OR for a beneficial outcome. Then we calculated the PCE using formulae (2) and (1).

For RRs and ORs, we calculated the 95% CI and SEs of the PCE using a formula for the variance estimators of log(RR) and log(OR), respectively. For dichotomous outcomes, the PCE means that the probability, given an individual had a positive outcome after treatment, would also have had a positive outcome after placebo.

Continuous outcomes

We define the PCE for the continuous outcome as follows in accordance with a previous study.⁷

$$PCE = \frac{\text{the mean change score of the placebo arm}}{\text{the mean change score of the intervention arm}} \quad (4)$$

In this study, we calculated the mean change score of each arm based on multiple studies rather than a single study. Therefore, we first calculated the standardised weighted change score means for both the intervention and placebo arms by meta-analysis, using the DerSimonian-Laird method for continuous outcomes.¹⁷

The PCE was then calculated as:

$$PCE = \frac{\text{weighted standardized mean change score of the placebo arm}}{\text{weighted standardized mean change score of the intervention arm}} \quad (5)$$

The conditions to calculate PCEs by formula (5) were that both groups showed the same direction of change (same positive or negative direction), and the change in the treatment group was greater than the change in the placebo group. Therefore, we excluded Cochrane reviews when the weighted mean of the intervention and control arms did not show the same direction of change or when the weighted standardised mean change score of the placebo arm was greater than that of the intervention arm.

To construct the CI of PCE, the ordinary Wald-type CI is unsuitable for the original scale because PCE is a ratio measure and usually has an asymmetric sample distribution. Thus, we adopted the approximate CI for log-transformed PCE. Using the Delta method, we obtained the SE estimator of the log(PCE) as follows¹⁸:

$$SE [\log(PCE)] = \sqrt{\frac{SE_{intervention}^2}{WSM_{intervention}^2} + \frac{SE_{placebo}^2}{WSM_{placebo}^2}} \quad (6)$$

where SE [log(PCE)] was the SE of log(PCE), SE_{intervention} and SE_{placebo} represent the SE of the weighted change score means of the intervention and placebo arms, respectively. WSM_{intervention} and WSM_{placebo} were the weighted standardised change score means of the intervention and placebo arms, respectively. The weighted standardised means were defined as pooled summaries of standardised mean change scores from the intervention and placebo arms of individual studies. The weights were defined by the corresponding meta-analysis methods. We could then obtain the Wald-type 95% CI for log(PCE) by the conventional normal approximation.¹⁹ The 95% CI of PCE can be calculated by back-transformation (exponential transformation) of the confidence limits.

Meta-analyses of PCEs

We pooled the logarithm-transformed PCEs for each outcome type, condition and GRADE category, using the DerSimonian-Laird method.¹⁷ We performed all analyses using meta (V.4.15–1) package of R V.4.0.0.^{20 21}

Changes from the protocol

The study protocol was uploaded to the Department of Health Promotion and Human Behaviour website, Kyoto University Graduate School of Medicine/School of Public Health (<http://ebmh.med.kyoto-u.ac.jp/r-meta.html>), attached as online supplemental file 1) on 4 September 2018. Changes to the protocol are listed in online supplemental file 2, and all were minor.

Patient and public involvement

No patient or member of the public was involved in conducting this research.

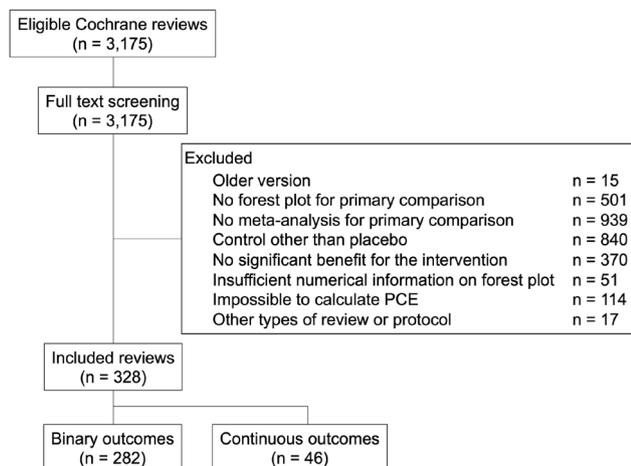


Figure 1 The flow chart for study selection. PCE, proportion attributable to contextual effect.

Results

Selected studies

Figure 1 shows the flowchart for study selection. The initial search identified 3175 Cochrane reviews, from which we excluded 2847 for reasons seen in figure 1. The final selection included 328 reviews. Of these, 282 reviews represent 1755 trials, with 2 625 184 participants reporting dichotomous outcomes. The remaining 46 reviews represent 259 trials, with 42 156 participants reporting continuous outcomes.

Over half of the reviews were published within the past 10 years. Approximately 70% of the included reviews reported subjective outcomes. Mental health and behaviour conditions was the most popular condition (table 1). Online supplemental file 3 shows all included SRs and their outcomes, conditions and PCEs calculated from the results of the meta-analysis from each review. For example, Bennett *et al*²² examined the effect of tranexamic acid on mortality for upper gastrointestinal bleeding. They reported an RR of 0.6. The CER for mortality was 8.4% and converted to a positive outcome CER for survival at 91.6%. The EER of survival was 95.0%. Dividing the CER of survival by the EER of survival gives a PCE of 0.96. By contrast, Derry *et al*²³ examined the effect of ibuprofen plus codeine for acute postoperative pain and showed an RR of 4.1. Their CER for a 50% reduction of maximum pain was 18.0%, and the EER was 64.0%. Thus, the calculated PCE was 0.24.

PCEs by outcome types, conditions and GRADE categories

Outcome types

We first pooled PCEs across all outcome types, including both dichotomous and continuous outcomes (figure 2, table 2). The pooled PCE across all outcomes was 0.65 (95% CI 0.59 to 0.72). When the outcome types were divided into subgroups, objective outcomes showed a PCE of 0.94 (95% CI 0.91 to 0.97), which was higher than that of semiobjective outcomes (PCE 0.78; 95% CI 0.72 to 0.85, $I^2=90\%$) and subjective outcomes (PCE 0.50; 95% CI 0.41 to 0.59, $I^2=99\%$). The PCE of typical patient-reported outcomes such as pain, QoL, and mental health outcomes ranged between 0.44 and 0.74.

We next pooled PCEs across all outcome types when the outcomes were dichotomous (online supplemental figure S1) or continuous (online supplemental figure S2).

Conditions

Figure 3 shows the PCE by condition. PCEs ranged widely from 0.40 in 'anaesthesia' to 0.89 in 'cardiovascular disease' ($I^2=98\%$). Online supplemental figure S3 and S4 present the results for dichotomous and continuous outcomes separately.

Grade categories

Among 156 Cochrane reviews that had reported a GRADE in the summary of findings table, the PCEs did not appear to be appreciably influenced by the certainty of evidence (online supplemental figure S5, $I^2 = 54\%$). Online supplemental figures S6 and S7 present these results for dichotomous and continuous outcomes separately.

Discussion

Key findings

Based on 328 Cochrane reviews representing 2014 trials and 2 667 340 participants, the overall PCE for various interventions in contemporary medicine was 0.65 (0.59 to 0.72). PCEs ranged from 0.28 to 0.94. The subjective outcomes showed lower PCEs than objective or semiobjective outcomes. They also varied depending on the condition. GRADE ratings did not appear to influence PCEs. These results suggest that PCEs should be considered according to the outcome type and condition when interpreting study results and determining the importance of interventions.

Comparisons with the previous literature

As previously stated, there is no study examining the PCE of several semiobjective outcomes. In our study, PCEs of the objective and semisubjective outcomes were mostly larger than 0.70. Several studies have reported PCEs for patient-reported outcomes in the literature. One study revealed a PCE of 0.72 for pain among burning mouth syndrome patients,²⁴ while another showed a PCE of 0.82 for antidepressant trials for depression.²⁵ When we examined PCEs for various patient-reported outcomes and conditions, the average PCE seemed to lie in the medium range between 0.40 and 0.75, which was lower than those reported in previous studies. The effects of the intervention on the subjective outcomes may be larger than those for the other types of outcomes. Previous studies suggest larger placebo effects for subjective outcomes than for objective outcomes.^{6 26} These findings are in line with the current findings of contextual effects. This is because, regardless of the magnitude of the placebo effect, PCEs represent the proportion of the contextual effects of the improvements observed in the active intervention arm.

Clinical interpretations

The contextual effects have been known to contribute to the treatment response.^{10 27} However, the magnitude of PCEs had not been examined in detail or quantified in the literature until this study. Our study presented the average PCEs across outcome types and conditions.

We found that subjective outcomes, including typical patient-reported outcomes such as pain, QoL, and mental health outcomes, showed PCEs of 0.44–0.74. This may reflect the fact that the specific intervention effect seen in subjective outcomes are likely to be of moderate magnitude and clinically important. On the other hand, 'hard' outcomes, including survival or morbidity events, showed PCEs above 0.80 or even 0.90. We assume PCEs seen in objective and semiobjective outcomes may reflect the fact that the natural disorder course plays a strong role in those outcomes. It would

Table 1 Characteristics of included studies

	Dichotomous outcome (n=282)	Continuous outcome (n=46)
No of included primary studies per meta-analysis, median (IQR)	4 (2–7)	4 (3–7)
No of included participants per meta-analysis, median (IQR)	557 (283–1490)	511 (229–1094.5)
Years of publication (%)		
1998–2000	14 (5.0)	0 (0)
2001–2005	27 (9.6)	10 (21.7)
2006–2010	57 (20.2)	7 (15.2)
2011–2015	101 (35.8)	12 (26.1)
2016–2019	83 (29.4)	17 (37.0)
Outcome type (%)		
Objective outcome		
Survival	7 (2.5)	0 (0)
Semiobjective outcomes		
No major morbidity event	14 (5.0)	0 (0)
Less drop-outs from the treatment	11 (3.9)	0 (0)
Improved obstetric outcomes	9 (3.2)	0 (0)
Less resource use/shorter hospital stay	9 (3.2)	0 (0)
Improved internal structure	5 (1.8)	2 (4.3)
Improved biological markers	4 (1.4)	6 (13.0)
Improved external structure	4 (1.4)	1 (2.2)
No unpleasant composite endpoint	4 (1.4)	0 (0)
No adverse events	3 (1.1)	0 (0)
No composite mortality/morbidity events	0 (0)	0 (0)
Others (semiobjective)	1 (0.4)	6 (13.0)
Subjective outcomes		
Pain relief	72 (25.5)	9 (19.6)
Cure of condition	71 (25.2)	4 (8.7)
Mental health outcomes improvement	35 (12.4)	12 (26.1)
No new signs of infection/disease	17 (6.0)	0 (0.0)
Quality of life	13 (4.6)	6 (13.0)
Less consumption, satisfaction with care	1 (0.4)	0 (0.0)
Others (Subjective)	2 (0.7)	0 (0.0)
Conditions (%)		
Mental health and behavioural conditions	56 (19.9)	12 (26.1)
Anaesthesia	48 (17.0)	3 (6.5)
Central nervous system/ musculoskeletal	47 (16.7)	7 (15.2)
Digestive system	29 (10.3)	0 (0)
Infectious disease	26 (9.2)	1 (2.2)
Respiratory disease	19 (6.7)	3 (6.5)
Obstetrics and gynaecology	16 (5.7)	2 (4.3)
Cardiovascular	12 (4.3)	7 (15.2)
Urogenital	7 (2.5)	4 (8.7)
Others	22 (7.8)	7 (15.2)
GRADE category (%)*		
High	35 (25.9)	2 (9.5)
Moderate	53 (39.3)	5 (23.8)
Low	36 (26.7)	13 (61.9)
Very low	11 (8.1)	1 (4.8)

*A total of 147 dichotomous outcomes and 25 continuous outcomes did not report the GRADE category in their summary of findings table. GRADE, Grading of Recommendations Assessment, Development and Evaluation.

be relatively difficult for an intervention to show large effects in these 'hard' outcomes.

The pooled estimates are approximate indicators of how much PCE we can expect for each subgroup. However, the average PCEs are only a rough guide, and a starting point for clinical evaluation of an intervention effect. Generally, the higher the PCE, the greater the contextual effects. Therefore, watchful waiting or careful observation with follow-ups may be a reasonable choice,

rather than an active intervention, because much of the benefit can be expected from the placebo intervention. However, this general judgement should be tempered by the gravity of the outcome (eg, a small decrease in death may be as valuable as or even more valuable than a large decrease in some non-life-threatening consequences) and the burdens (side-effects and costs) of the alternative treatments. Moreover, our study revealed that PCEs were highly heterogeneous. We must consider the individual

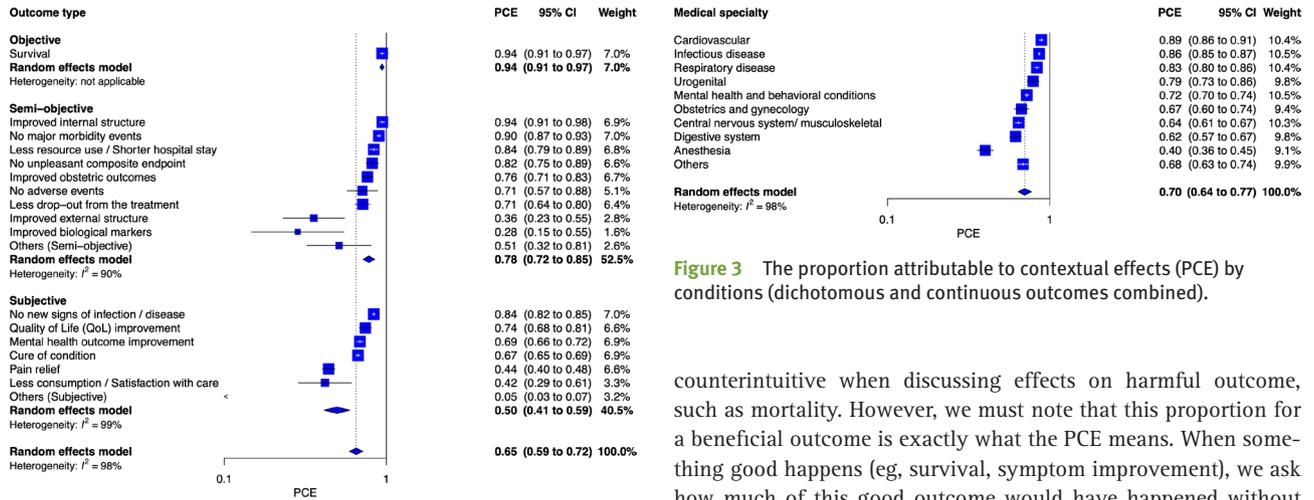


Figure 2 The proportion attributable to contextual effects (PCE) by outcome type (continuous and dichotomous outcomes combined)

condition, intervention and outcome when we evaluate the clinical significance of the PCE.

We also found that PCEs were diverse over several conditions, partly reflecting outcome types commonly used in each condition. For example, the PCEs of cardiovascular disease, infectious disease, and respiratory disease were over 0.80. Trials examining these conditions usually select objective or semiobjective outcomes such as survival, major morbidity, composite endpoints or severity of symptoms as the primary outcome. In fact, 30 of 68 included reviews among these conditions reported objective or semiobjective outcomes. On the other hand, conditions with subjective main outcomes, such as pain, mental health or behaviour conditions, showed moderate PCEs.

Additionally, we found no remarkable diversity of PCEs depending on the GRADE category. However, over half of the included reviews did not report the GRADE category with a summary of findings table of their first primary outcome, which led to the loss of power in this analysis. We also found that out of 328 Cochrane reviews, 282 reported a dichotomous outcome, such as mortality, as their first primary outcome, and we were only able to identify 46 Cochrane reviews with a primary continuous outcome reported first.

Strengths and limitations

There are some weaknesses to our study. First, we calculated a PCE as the proportion of the contextual effects over the intervention response for a beneficial outcome. This might appear

Figure 3 The proportion attributable to contextual effects (PCE) by conditions (dichotomous and continuous outcomes combined).

counterintuitive when discussing effects on harmful outcome, such as mortality. However, we must note that this proportion for a beneficial outcome is exactly what the PCE means. When something good happens (eg, survival, symptom improvement), we ask how much of this good outcome would have happened without the intervention (ie, it can be explained by the contextual effects). Second, we were unable to calculate PCE when the intervention showed improvement from baseline while the placebo group showed deterioration, or when the intervention showed deterioration while the placebo group showed greater deterioration. This may have led to overestimation or underestimation of PCE. This was inevitable, given the definition of PCE above. We wanted to quantify when something good happens following treatment and how much of that good could happen without the intervention. Third, there is intrinsic heterogeneity among outcomes belonging to the same type (eg, morbidity event) or used in the same condition (eg, respiratory disease). Each outcome may have different clinical importance depending on the context. Because PCE is a relative measure, the CER may also influence the absolute benefit. In other words, the absolute benefit is larger for events with large CERs, and smaller for events with smaller CERs for a given PCE. Therefore, each PCE of an intervention must be interpreted in its specific context and, ultimately, under each patient's preferences and values. However, it is scientifically meaningful to know the overall averages even when the apparent heterogeneity may be high. Fourth, measurement errors (random errors) are larger for subjective outcomes than semiobjective or objective outcomes. How such measurement errors may have contributed to the estimates of PCEs is not straightforward. However, by pooling across SRs, the overall averages would be less affected by such random errors. Fifth, our study calculated PCEs by outcome types and conditions independently. PCE is highly dependent on both the condition and outcome. For example, the PCE for pain in 'cardiovascular' may be larger than that in 'mental health and behavioural conditions' because the pain in cardiovascular is more likely

Table 2 The proportion attributable to contextual effects by outcome type

		Outcome category		All
		Dichotomous	Continuous	
Outcome type	Objective	0.94 (0.91 to 0.97) (NA)	NA	0.94 (0.91 to 0.97) (NA)
	Semiobjective	0.81 (0.75 to 0.87) (0.64 to 1.00)	0.54 (0.38 to 0.77) (0.15 to 1.00)	0.78 (0.72 to 0.85) (0.60 to 1.00)
	Subjective	0.49 (0.41 to 0.59) (0.26 to 0.94)	0.60 (0.54 to 0.66) (0.46 to 0.79)	0.50 (0.41 to 0.59) (0.26 to 0.94)
All	0.67 (0.61 to 0.74) (0.45 to 0.99)	0.59 (0.53 to 0.66) (0.47 to 0.75)	0.65 (0.59 to 0.72) (0.44 to 0.97)	

(Parentheses) show 95% CIs, and (brackets) show 95% prediction intervals.
NA, not applicable.

due to an organic cause. Finer subgroup analyses examining their interactions were impossible in the current study, as we had too many subgroups, but this would be desirable for future research. Finally, the specific and contextual effects are not independent of each other but may interact with each other when, for example, the side effects of the intervention may enhance the non-specific effects.²⁸ Thus, the same outcome for the same disease may show different PCEs depending on the intervention. We did not have enough variability in the interventions in our dataset to appreciate such interactions. Further research would be warranted to clarify the nature and degree of the relationships between specific effects and contextual effects.

Our study also has several strengths. First, to the best of our knowledge, this is the first study to examine PCEs comprehensively across outcome types and conditions. Second, our study is based on Cochrane reviews which are considered the best resources of evidence. We searched all the Cochrane reviews that had reported the results of head-to-head meta-analyses of interventions against placebo. We pooled these meta-analyses to calculate the PCEs by outcome type, condition and GRADE category.

Conclusions

In conclusion, our study showed that the overall PCE was 0.65 (95% CI 0.59 to 0.72). PCEs were smaller for subjective outcomes than for objective or semiobjective outcomes. The results suggest that much of the observed benefit is actually due to factors including the placebo effect, the natural course of the disease, and regression to the mean, rather than just the specific effect of the interventions. Specific effects of interventions may be larger for subjective than for objective or semiobjective outcomes. However, PCEs were exceptionally variable. When we evaluate the magnitude of PCEs, we should consider each PCE individually, for each condition, intervention and outcome in its context, to assess the importance of an intervention for each specific clinical setting.

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responsible for writing the protocol. YTsut, YTsuj, AT, KO, TF, AO, YK, MK, ES, EGO extracted the data. YTsut analysed the data. HN supervised the statistical analyses. TAF supervised the research. All authors contributed to draft the manuscript and gave final approval of the manuscript before submission. TAF is the guarantor of the study.

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Supplement 1. The original protocol of the study

Fixed and uploaded on September 4, 2018

The Placebo Attributable Fraction in General Medicine: Protocol for a meta-epidemiological Study of Cochrane Reviews

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INTRODUCTION

Placebo has long been used as dummy treatment in the “control group” in randomized controlled trials to ensure methodological validity (1,2). Placebo-controlled group may show similar response to active treatment especially for subjective outcomes. This is known as placebo response and, sometimes, placebo response may reach up to about 40% of active treatment response (3–5).

Placebo response consists of placebo effect and other factors such as natural course of the disease and regression to the mean (6). Among these, placebo effect is the change of the status caused by placebo and the existence and degree of this effect was controversial (7–9). No matter how much placebo effect exists, the magnitude of placebo response attributable to active treatment response, which called the placebo-attributable fraction, is highly important for the implications of clinical trials and treatment choice in clinical setting.

In this study, we will systematically review Cochrane reviews to examine the placebo-attributable fraction in all fields of medicine and reveal the difference of the size of the placebo-attributable fraction according to specialties and intervention methods.

METHODS

Types of studies included

We will select all the systematic review of randomized placebo-controlled trials published in the Cochran Database of Systematic Reviews. Among selected studies, we will include reviews which showed the significant beneficial effect of intervention arm compared to placebo for their first primary outcome. If there are multiple comparison regarding the first primary outcome due to multiple intervention arms, we will select the first comparison.

We will define placebo-attributable fraction (P-AF) as follows:

For dichotomous beneficial outcome,

$$\frac{\text{the proportion of beneficial event in the placebo arm}}{\text{the proportion of beneficial event in the intervention arm}}$$

For dichotomous harmful outcome,

$$\frac{1 - \text{the proportion of harmful event in the placebo arm}}{1 - \text{the proportion of harmful event in the intervention arm}}$$

For continuous beneficial outcome

$$\frac{\text{the change of score or scale in the placebo arm}}{\text{the change of score or scale in the placebo arm}}$$

We will exclude interventions whose aim is to prevent deterioration in the continuous score (i.e. either increase in bad outcome scale or decrease in good outcome scale, as this would complicate interpretation of placebo-attributable fraction.

To calculate the P-AF defined above, we will use the average proportion or change score in the control group in the numerator, and the event rate or the change score in the intervention group based on the pooled OR or SMD/MD in the denominator. Therefore, we will exclude reviews that did not perform meta-analysis, did not report the change of score (if first primary outcome is continuous), did not report the number of participants and events for each arm (if first primary outcome is dichotomous), using outcome measure other than MD or SMD for first primary outcome. We will also exclude systematic reviews of studies other than pill placebo-controlled trials (e.g. sham-controlled trials, non-randomized controlled trials, diagnostic test accuracy studies and prognostic studies), overview of reviews, or methodological reviews.

Search strategy

We will search Cochrane Central Register Controlled Trials (CENTRAL) using “placebo” as keyword in Title, Abstract, Keywords in Cochrane Reviews

Study selection

Two authors will independently perform the initial screening of the titles and abstracts of all studies identified by the search and will examine the potential eligibility for inclusion. After initial screening, same authors will assess the eligibility based on a full-text review. We will resolve disagreements by discussion between the authors, with another author acting as an arbiter.

Data extraction

Two authors will use structured data extraction form to independently collect the data from included studies. If the review reported RR, we will extract pooled RR of each review. If the review reported MD, we will extract the change of the outcome and the number of participants for each of intervention and placebo arm of included trials separately. If the review reported SMD, we will extract the change of the outcome with standard deviation and the number of participants for each of intervention and placebo arm of included trials separately. We will also extract the following information: number of participants and trials in meta-analysis of first primary outcome, sample size of intervention and placebo arm, outcome data type (dichotomous or continuous), outcome type, medical specialty, Intervention type (pharmacological or non-pharmacological) and Cochrane review group.

We will categorize outcome types as below: (10–12)

Objective outcome

·All-cause mortality,

Semi objective outcomes

· Major morbidity event

· Obstetric outcomes

· Resource use and Hospital stay/process measures

· Internal and external structure related outcomes

· Biological markers

· Other semi-objective outcomes including cause-specific mortality, composite (mortality / morbidity only), and withdrawals/dropouts

Subjective outcomes

·Pain

·Quality of life/functioning

- Mental health outcomes
- Various subjectively measured outcomes including consumption, satisfaction with care, composite (at least 1 non-mortality/morbidity) and surgical/device related success/failure
- General health-related outcomes including general physical health and adverse events
- Signs/symptoms reflecting continuation/end of condition and Infection/onset of new acute/chronic disease

Others

- Other outcomes

We will categorize medical specialty as follows: cancer, cardiovascular, central nervous system/ musculoskeletal, digestive system, infectious disease, mental health and behavioral conditions, obstetrics and gynecology, pathological conditions, respiratory disease, urogenital and others (10–12).

Statistical analysis

First, we will calculate P-AF for each review as described above. Next, we will compute the weighted mean of P-AF of each review to show the overall P-AF across general clinical condition.

Additionally, we will perform sub-group analyses and meta-regression analyses to examine any heterogeneity of P-AF across outcome types, intervention types, medical specialty, overall risk of bias and Cochrane review groups.

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Supplement 2. Changes to the protocol

1. We revised category names of outcome type as the name indicates beneficial outcome rather than harmful outcome (e.g. from all-cause mortality to survival).
2. We revised the detailed definition of placebo attributable fraction (PAF) to cope with the variation of outcome measure (dichotomous or continuous, beneficial or harmful, and risk ratio or odds ratio)
3. We add the detailed method to calculate PAF for continuous outcomes. As described in the Method section, we calculate weighted standardized mean of intervention and placebo arm of each Cochran SR by performing meta-analysis, and then calculate PAF and its standard error using Delta method.
4. We add the detailed method to calculate PAF by outcome type, medical specialty and GRADE rating. As described in the Method section, we performed meta-analysis to calculate.
5. We categorized other types of outcomes into others (semi-objective) and others (subjective).
6. We changed the term PAF to the proportion attributable to contextual effect (PCE) throughout the manuscript.
7. We slightly modified the category of medical specialty, in which we delete pathological condition and cancer, and added anaesthesia.

Supplement 3. All of included Cochrane reviews and its PCE. Created by authors.

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Paracetamol/acetaminophen (single administration) for perineal pain in the early postpartum period	2013	Chou D	Adequate pain relief as reported by women.	dichotomous	Pain relief	Anesthesia	0.47
Single dose oral lornoxicam for acute postoperative pain in adults	2009	Hall PE	Participants with at least 50% pain relief over 6 hours	dichotomous	Pain relief	Anesthesia	0.43
Single dose oral gabapentin for established acute postoperative pain in adults	2010	Straube S	Participants with $\geq 50\%$ pain relief over 6 hours	dichotomous	Pain relief	Anesthesia	0.41
Single dose oral etodolac for acute postoperative pain in adults	2009	Tirunagari SK	Participants with at least 50% pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.58
Single dose oral ibuprofen plus oxycodone for acute postoperative pain in adults	2013	Derry S	Participants with $\geq 50\%$ pain relief at 6 hours	dichotomous	Pain relief	Anesthesia	0.28
Single dose oral dihydrocodeine for acute postoperative pain	2000	Moore RA	Patients with at least 50% pain relief	dichotomous	Pain relief	Anesthesia	0.63
Single dose oral ibuprofen plus codeine for acute postoperative pain in adults	2015	Derry S	Participants with $\geq 50\%$ pain relief	dichotomous	Pain relief	Anesthesia	0.24
Single dose oral naproxen and naproxen sodium for acute postoperative pain in adults	2009	Derry CJ	Participants with at least 50% pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.35

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Single dose oral flurbiprofen for acute postoperative pain in adults	2009	Sultan A	Participants with $\geq 50\%$ pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.14
Single dose oral lumiracoxib for postoperative pain in adults	2010	Roy YM	Participants with at least 50% pain relief at 6 hours	dichotomous	Pain relief	Anesthesia	0.15
Single dose oral celecoxib for acute postoperative pain in adults	2013	Derry S	At least 50% pain relief over 4-6 hours	dichotomous	Pain relief	Anesthesia	0.06
Oral non-steroidal anti-inflammatory drugs (single dose) for perineal pain in the early postpartum period	2016	Wuytack F	Adequate pain relief (4 hours after administration)	dichotomous	Pain relief	Anesthesia	0.52
Single dose oral ibuprofen for acute postoperative pain in adults	2009	Derry CJ	Participants with at least 50% pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.22
Intravenous or intramuscular parecoxib for acute postoperative pain in adults	2009	Lloyd R	Participants with at least 50% pain relief	dichotomous	Pain relief	Anesthesia	0.20
Topical NSAIDs for acute musculoskeletal pain in adults	2015	Derry S	Clinical success	dichotomous	Pain relief	Anesthesia	0.63
Single dose oral mefenamic acid for acute postoperative pain in adults	2011	Moll R	$\geq 50\%$ pain relief over 4 to 6 h	dichotomous	Pain relief	Anesthesia	0.47
Single dose oral paracetamol (acetaminophen) for postoperative pain in adults	2008	Toms L	Participants with at least 50% pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.41
Muscle relaxants for non-specific low-back pain	2003	van Tulder MW	Pain	dichotomous	Pain relief	Anesthesia	0.29

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Therapeutic ultrasound for postpartum perineal pain and dyspareunia	1998	Hay-Smith J	No improvement (self-report) post-treatment	dichotomous	Pain relief	Anesthesia	0.88
Lacosamide for neuropathic pain and fibromyalgia in adults	2012	Hearn L	Moderate benefit ($\geq 2/10$ on NRS or $\geq 30\%$ on visual analogue scale (VAS) pain intensity reduction)	dichotomous	Pain relief	Anesthesia	0.78
Oxycodone for neuropathic pain in adults	2016	Gaskell H	At least moderate pain relief	dichotomous	Pain relief	Anesthesia	0.60
Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults	2009	Toms L	Participants with at least 50% pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.16
Salicylate-containing rubefacients for acute and chronic musculoskeletal pain in adults	2014	Derry S	Clinical success (eg 50% reduction in pain)	dichotomous	Pain relief	Anesthesia	0.52
Topical clonidine for neuropathic pain	2015	Wrzosek A	Pain relief $\geq 30\%$	dichotomous	Pain relief	Anesthesia	0.74
Single fixed-dose oral dexketoprofen plus tramadol for acute postoperative pain in adults	2016	Derry S	Participants with $\geq 50\%$ pain relief over 6 hours	dichotomous	Pain relief	Anesthesia	0.49
Single dose oral diclofenac for acute postoperative pain in adults	2015	Derry S	At least 50% of maximum pain relief over 6 hours	dichotomous	Pain relief	Anesthesia	0.06

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Tramadol for postoperative pain treatment in children	2015	Schnabel A	Number of patients requiring rescue analgesia (PACU)	dichotomous	Pain relief	Anesthesia	0.32
Single dose oral ibuprofen plus caffeine for acute postoperative pain in adults	2015	Derry S	At least 50% maximum pain relief.	dichotomous	Pain relief	Anesthesia	0.18
Non-surgical interventions for the management of chronic pelvic pain	2014	Cheong YC	Improvement in pain score at end of treatment	dichotomous	Pain relief	Anesthesia	0.81
Single dose oral fenoprofen for acute postoperative pain in adults	2011	Traa MX	≥50% total pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.24
Tramadol for neuropathic pain in adults	2017	Duehmke RM	Participants with ≥ 50% pain intensity reduction	dichotomous	Pain relief	Anesthesia	0.46
Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain	2013	Derry CJ	Participants with ≥50% pain relief	dichotomous	Pain relief	Anesthesia	0.10
Single dose oral diflunisal for acute postoperative pain in adults	2010	Wasey JO	Participants with ≥50% pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.35
Carbamazepine for chronic neuropathic pain and fibromyalgia in adults	2014	Wiffen PJ	Any pain improvement	dichotomous	Pain relief	Anesthesia	0.15
Lidocaine for reducing propofol-induced pain on induction of anaesthesia in adults	2016	Euasobhon P	High-intensity pain	dichotomous	Pain relief	Anesthesia	0.75

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Single dose oral codeine, as a single agent, for acute postoperative pain in adults	2010	Derry S	Participants with $\geq 50\%$ pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.67
Gabapentin for chronic neuropathic pain in adults	2017	Wiffen PJ	At least 50% pain reduction over baseline	dichotomous	Pain relief	Anesthesia	0.59
Single dose oral etoricoxib for acute postoperative pain in adults	2014	Clarke R	Participants with at least 50% pain relief over 6 hours	dichotomous	Pain relief	Anesthesia	0.18
Combination pharmacotherapy for the treatment of neuropathic pain in adults	2012	Chaparro LE	At least moderate/good pain relief	dichotomous	Pain relief	Anesthesia	0.77
Single dose dipyrone (metamizole) for acute postoperative pain in adults	2016	Hearn L	Participants with $\geq 50\%$ pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.42
Single-dose intravenous diclofenac for acute postoperative pain in adults	2018	McNicol ED	Number of participants with at least 50% pain relief at 4 hours	dichotomous	Pain relief	Anesthesia	0.35
Milnacipran for pain in fibromyalgia in adults	2015	Cording M	At least 30% pain relief	dichotomous	Pain relief	Anesthesia	0.72
Paracetamol for pain relief after surgical removal of lower wisdom teeth	2007	Weil K	Number of people with at least 50% pain relief at 4 hours	dichotomous	Pain relief	Anesthesia	0.35
Single dose oral ketoprofen or dexketoprofen for acute postoperative pain in adults	2017	Gaskell H	Participants with $\geq 50\%$ pain relief over 6 hours	dichotomous	Pain relief	Anesthesia	0.24

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Single dose oral dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain	1999	Moore RA	No. patients experiencing at least 50% pain relief (>50% maxTOTPAR)	dichotomous	Pain relief	Anesthesia	0.68
Single dose oral piroxicam for acute postoperative pain	2000	Moore RA	Participants with at least 50% pain relief	dichotomous	Pain relief	Anesthesia	0.41
Single dose oral rofecoxib for acute postoperative pain in adults	2009	Bulley S	Participants with at least 50% pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.20
Single dose intravenous paracetamol or intravenous propacetamol for postoperative pain	2016	McNicol ED	Number of participants with > 50% pain relief over 4 hours	dichotomous	Pain relief	Anesthesia	0.40
Non-steroidal anti-inflammatory drugs for low back pain	2008	Roelofs PDDM	Change in Pain Intensity from baseline on 100mmVAS	continuous	Pain relief	Anesthesia	0.86
Non-steroidal anti-inflammatory drugs for chronic low back pain	2016	Enthoven WTM	Change in pain intensity from baseline on 100 mm visual analogue scale (VAS)	continuous	Pain relief	Anesthesia	0.41
Analgesia for relief of pain due to uterine cramping/involution after birth	2011	Deussen AR	Pain Reduction	continuous	Pain relief	Anesthesia	0.54
Phlebotonics for venous insufficiency	2016	Martinez-Zapata MJ	Oedema in the lower legs (dichotomous variable)	dichotomous	Cure of condition	Cardiovascular	0.71

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Naftidrofuryl for intermittent claudication	2012	de Backer TLM	Responder rate	dichotomous	Cure of condition	Cardiovascular	0.82
Vitamin E for intermittent claudication	1998	Kleijnen J	Subjective assessment of no change or deterioration after 40 weeks or 8 months	dichotomous	Cure of condition	Cardiovascular	0.59
Blood pressure lowering efficacy of renin inhibitors for primary hypertension	2017	Musini VM	Systolic blood pressure	continuous	Improved biological markers	Cardiovascular	0.70
Rosuvastatin for lowering lipids	2014	Adams SP	Total cholesterol	continuous	Improved biological markers	Cardiovascular	0.12
Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus	2008	Hartweg J	Triglycerides	continuous	Improved biological markers	Cardiovascular	0.09
Blood pressure-lowering efficacy of loop diuretics for primary hypertension	2015	Musini VM	Systolic blood pressure	continuous	Improved biological markers	Cardiovascular	0.41
Long-term effects of weight-reducing drugs in people with hypertension	2016	Siebenhofer A	Change in systolic blood pressure from baseline to endpoint	continuous	Improved biological markers	Cardiovascular	0.74
Blood pressure-lowering efficacy of reserpine for primary hypertension	2016	Shamon SD	Weighted mean change in systolic blood pressure	continuous	Improved biological markers	Cardiovascular	0.39
Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants	2018	Ohlsson A	Failure to close a patent ductus arteriosus (after 3 doses)	dichotomous	Improved internal structure	Cardiovascular	0.75

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Peroxisome proliferator-activated receptor gamma agonists for preventing recurrent stroke and other vascular events in people with stroke or transient ischaemic attack	2019	Liu J	Recurrence of stroke	dichotomous	No major morbidity events	Cardiovascular	0.97
Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery	2019	Felder S	All venous thromboembolism (VTE)	dichotomous	No major morbidity events	Cardiovascular	0.91
Pentasaccharides for the prevention of venous thromboembolism	2016	Dong K	Total venous thromboembolism (VTE)	dichotomous	No major morbidity events	Cardiovascular	0.93
Prevention of infection in arterial reconstruction	2006	Stewart A	Wound infection	dichotomous	No new signs of infection / disease	Cardiovascular	0.88
Buflomedil for intermittent claudication	2013	de Backer TLM	Pain free walking distance	continuous	Pain relief	Cardiovascular	0.70
Phosphodiesterase 5 inhibitors for pulmonary hypertension	2019	Barnes H	Improvement in World Health Organization (WHO) functional class	dichotomous	Quality of Life (QoL) improvement	Cardiovascular	0.95
First-line drugs for hypertension	2018	Wright JM	Total mortality	dichotomous	Survival	Cardiovascular	0.99
Antiplatelet agents for intermittent claudication	2011	Wong PF	All cause mortality	dichotomous	Survival	Cardiovascular	0.98
Adrenaline and vasopressin for cardiac arrest	2019	Finn J	Survival to hospital discharge	dichotomous	Survival	Cardiovascular	0.69
Losigamone add-on therapy for focal epilepsy	2019	Chen H	50% or greater reduction in seizure frequency	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.57
Surgical interventions for lumbar disc prolapse	2007	Gibson JNA	No success at 6 wks - patient rated	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.59

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Vigabatrin for refractory partial epilepsy	2013	Hemming K	50% responders	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.39
Pregabalin add-on for drug-resistant focal epilepsy	2019	Panebianco M	50% or greater reduction in seizure frequency	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.44
Tiagabine add-on therapy for drug-resistant focal epilepsy	2019	Bresnahan R	50% or greater reduction in seizure frequency	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.32
Gabapentin add-on treatment for drug-resistant focal epilepsy	2018	Panebianco M	Reduction in seizure frequency \geq 50%	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.53
Pharmacological interventions for epilepsy in people with intellectual disabilities	2015	Jackson CF	Responder rate (\geq 50% reduction in overall seizure frequency)	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.91
Topiramate add-on therapy for drug-resistant focal epilepsy	2019	Bresnahan R	50% reduction in seizure frequency	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.23
Rufinamide add-on therapy for refractory epilepsy	2018	Panebianco M	50% reduction in seizure frequency	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.56
Lacosamide add-on therapy for partial epilepsy	2015	Weston J	50% reduction in seizure frequency	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.71
Antiepileptic drugs for the treatment of infants with severe myoclonic epilepsy	2017	Brigo F	\geq 50% reduction in seizure frequency	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.10

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Immunosuppressive agents for myasthenia gravis	2007	Hart IK	Improvement or lack of improvement at six months	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.41
Iron for the treatment of restless legs syndrome	2019	Trotti LM	Change in IRLS severity scale score	continuous	Cure of condition	Central nervous system/ musculoskeletal	0.47
Strontium ranelate for preventing and treating postmenopausal osteoporosis	2006	O'Donnell S	Vertebral fractures	dichotomous	Improved internal structure	Central nervous system/ musculoskeletal	0.97
Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women	2008	Wells GA	Vertebral Fractures	dichotomous	Improved internal structure	Central nervous system/ musculoskeletal	0.95
Huperzine A for Alzheimer's disease	2008	Li J	The change of general cognitive function measured by MMSE	continuous	Mental health outcome improvement	Central nervous system/ musculoskeletal	0.03
Rofecoxib for osteoarthritis	2005	Garner SE	Adverse events	dichotomous	No adverse events	Central nervous system/ musculoskeletal	0.87
Gamma aminobutyric acid (GABA) modulators for amyotrophic lateral sclerosis/motor neuron disease	2017	Diana A	Adverse events	dichotomous	No adverse events	Central nervous system/ musculoskeletal	0.36
Interferon in relapsing-remitting multiple sclerosis	2001	Rice GPA	Patients with at least one exacerbation until 1 yr	dichotomous	No major morbidity events	Central nervous system/ musculoskeletal	0.63
Dimethyl fumarate for multiple sclerosis	2015	Xu Z	The proportion of patients with at least one relapse at two years	dichotomous	No major morbidity events	Central nervous system/ musculoskeletal	0.75

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Antibiotics for preventing infection in open limb fractures	2004	Gosselin RA	Early wound infection	dichotomous	No new signs of infection / disease	Central nervous system/ musculoskeletal	0.93
Leflunomide for the treatment of rheumatoid arthritis	2002	Osiri M	Treatment responder - The American College of Rheumatology (ACR) 20	dichotomous	No unpleasant composite endpoint	Central nervous system/ musculoskeletal	0.84
Celecoxib for rheumatoid arthritis	2017	Fidahic M	Clinical improvement: American College of Rheumatology 20% improvement criteria (ACR20)	dichotomous	No unpleasant composite endpoint	Central nervous system/ musculoskeletal	0.65
Photodynamic therapy for neovascular age-related macular degeneration	2007	Wormald R	Loss of 3 or more lines (15 or more letters) visual acuity at 12 months	dichotomous	Others (Semi-objective)	Central nervous system/ musculoskeletal	0.83
Scopolamine (hyoscine) for preventing and treating motion sickness	2011	Spinks A	Prevention of sickness symptoms (nausea)	dichotomous	Others (Subjective)	Central nervous system/ musculoskeletal	0.05
Botulinum toxin type A therapy for hemifacial spasm	2005	Costa J	Improvement	dichotomous	Others (Subjective)	Central nervous system/ musculoskeletal	0.07
Ketoprofen for episodic tension-type headache in adults	2016	Veys L	Pain-free at 2 hours	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.59
Sumatriptan (subcutaneous route of administration) for acute migraine attacks in adults	2012	Derry CJ	Pain-free at 2 h	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.21

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Ibuprofen with or without an antiemetic for acute migraine headaches in adults	2013	Rabbie R	Pain-free at 2 hours.	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.51
Drugs for the acute treatment of migraine in children and adolescents	2016	Richer L	Pain-free	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.53
Aspirin for acute treatment of episodic tension-type headache in adults	2017	Derry S	Participants using rescue medication	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.81
Naproxen with or without an antiemetic for acute migraine headaches in adults	2013	Law S	Pain-free response at two hours	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.49
Sumatriptan (intranasal route of administration) for acute migraine attacks in adults	2012	Derry CJ	Headache relief at 1 h	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.71
Aspirin with or without an antiemetic for acute migraine headaches in adults	2013	Kirithi V	Pain free at 2 hours	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.48
Sumatriptan plus naproxen for the treatment of acute migraine attacks in adults	2016	Law S	Pain-free at two hours	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.36
Zolmitriptan for acute migraine attacks in adults	2014	Bird S	Pain-free at 2 h	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.36
Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults	2013	Derry S	Pain-free at 2 hours	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.56
Ibuprofen for acute treatment of episodic tension-type headache in adults	2015	Derry S	Pain-free at 2 hours	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.66
Diclofenac with or without an antiemetic for acute migraine headaches in adults	2013	Derry S	Pain-free at 2 hours	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.50

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults	2013	Linde M	Responders (patients with \geq 50% reduction in headache frequency)	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.85
Zonisamide add-on therapy for focal epilepsy	2018	Brigo F	50% responder rate - whole treatment period	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.54
Paracetamol (acetaminophen) for acute treatment of episodic tension-type headache in adults	2016	Stephens G	Pain-free at 2 hours	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.79
Sumatriptan (oral route of administration) for acute migraine attacks in adults	2012	Derry CJ	Pain-free at 2 h	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.38
Electromagnetic fields for treating osteoarthritis	2013	Li S	Pain	continuous	Pain relief	Central nervous system/ musculoskeletal	0.56
Celecoxib for osteoarthritis	2017	Puljak L	Pain	continuous	Pain relief	Central nervous system/ musculoskeletal	0.83
Paracetamol versus placebo for knee and hip osteoarthritis	2019	Leopoldino AO	Pain	continuous	Pain relief	Central nervous system/ musculoskeletal	0.83
Corticosteroids or ACTH for acute exacerbations in multiple sclerosis	2000	Citterio A	Worse or unimproved within 5 weeks from randomisation	dichotomous	Quality of Life (QoL) improvement	Central nervous system/ musculoskeletal	0.62

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Pyridoxal 5 phosphate for neuroleptic-induced tardive dyskinesia	2015	Adelufosi AO	Global: Clinical efficacy - significant reduction in Extrapyramidal Symptoms Rating Scale (ESRS) scores from baseline	dichotomous	Quality of Life (QoL) improvement	Central nervous system/ musculoskeletal	0.05
Endothelin receptor antagonists for subarachnoid hemorrhage	2012	Guo J	The development of Delayed ischemic neurological deficit (DIND)	dichotomous	Quality of Life (QoL) improvement	Central nervous system/ musculoskeletal	0.94
Edaravone for acute ischaemic stroke	2011	Feng S	Improvement of neurological deficit at the end of treatment	dichotomous	Quality of Life (QoL) improvement	Central nervous system/ musculoskeletal	0.50
Methotrexate for treating juvenile idiopathic arthritis	2001	Takken T	Improvement in limited joint range score	continuous	Quality of Life (QoL) improvement	Central nervous system/ musculoskeletal	0.48
Nimodipine for primary degenerative, mixed and vascular dementia	2002	Birks J	The Sandoz Clinical Assessment Geriatric Scale (SCAG) score	continuous	Quality of Life (QoL) improvement	Central nervous system/ musculoskeletal	0.21
Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)	2012	Miller RG	Percent mortality at 12 months	dichotomous	Survival	Central nervous system/ musculoskeletal	0.85
Adalimumab for induction of remission in Crohn's disease	2019	Abbass M	Failure to achieve clinical remission at 4 weeks:	dichotomous	Cure of condition	Digestive system	0.39

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn's disease	2014	Lev-Tzion R	Relapse rate at one year	dichotomous	Cure of condition	Digestive system	0.83
Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease	2008	Behm BW	Clinical Remission	dichotomous	Cure of condition	Digestive system	0.40
Non surgical therapy for anal fissure	2012	Nelson RL	Non-healing of fissure (persistence or recurrence)	dichotomous	Cure of condition	Digestive system	0.58
Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis	2016	Wang Y	Failure to Induce global / clinical remission	dichotomous	Cure of condition	Digestive system	0.59
Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis	2016	Wang Y	Failure to Maintain Clinical or Endoscopic Remission	dichotomous	Cure of condition	Digestive system	0.70
Budesonide for maintenance of remission in Crohn's disease	2014	Kuenzig ME	Maintenance of clinical remission	dichotomous	Cure of condition	Digestive system	0.80
Vedolizumab for induction and maintenance of remission in ulcerative colitis	2014	Bickston SJ	Failure to induce clinical remission	dichotomous	Cure of condition	Digestive system	0.40
Mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care	2018	Candy B	Rescue-free laxation within 24 hours of dose	dichotomous	Cure of condition	Digestive system	0.36
Prokinetics for functional dyspepsia	2018	Pittayanon R	Not symptom-free or no symptom improvement	dichotomous	Cure of condition	Digestive system	0.65

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-esophageal reflux disease-like symptoms and endoscopy negative reflux disease	2013	Sigterman KE	Heartburn remission	dichotomous	Cure of condition	Digestive system	0.35
Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease	2015	Chande N	Maintenance of remission	dichotomous	Cure of condition	Digestive system	0.80
Anti-tuberculous therapy for maintenance of remission in Crohn's disease	2016	Patton PH	Relapse	dichotomous	Cure of condition	Digestive system	0.54
Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis	2006	Lawson MM	Clinical remission at 8 weeks	dichotomous	Cure of condition	Digestive system	0.31
Azathioprine and 6-mercaptopurine for maintenance of surgically-induced remission in Crohn's disease	2019	Gjuladin-Hellon T	Clinical relapse at 12 to 36 months	dichotomous	Cure of condition	Digestive system	0.73
Antibiotics for induction and maintenance of remission in Crohn's disease	2019	Townsend CM	Failure to enter clinical remission at week 10 or 12	dichotomous	Cure of condition	Digestive system	0.47
Oral budesonide for induction of remission in ulcerative colitis	2015	Sherlock ME	Remission (combined clinical and endoscopic remission)	dichotomous	Cure of condition	Digestive system	0.44
Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis	2012	Marshall JK	Symptomatic remission	dichotomous	Cure of condition	Digestive system	0.45
Certolizumab pegol for induction of remission in Crohn's disease	2019	Yamazaki H	Clinical remission at week 8	dichotomous	Cure of condition	Digestive system	0.74

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Traditional corticosteroids for induction of remission in Crohn's disease	2008	Benchimol EI	Remission rate (Late, 15+ weeks)	dichotomous	Cure of condition	Digestive system	0.50
Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents	2011	Fedorowicz Z	Rate of admission to hospital (during ED stay)	dichotomous	Less resource use / Shorter hospital stay	Digestive system	0.94
Probiotics for the prevention of pediatric antibiotic-associated diarrhea	2019	Guo Q	Incidence of diarrhea	dichotomous	No major morbidity events	Digestive system	0.90
Arginine supplementation for prevention of necrotising enterocolitis in preterm infants	2017	Shah PS	Necrotising enterocolitis(N EC) any stage	dichotomous	No major morbidity events	Digestive system	0.79
Antibiotics versus placebo for prevention of postoperative infection after appendicectomy.	2005	Andersen BR	Wound infection	dichotomous	No new signs of infection / disease	Digestive system	0.90
Non-Steroid anti-inflammatory drugs for biliary colic	2016	Fraquelli M	Lack of pain relief	dichotomous	Pain relief	Digestive system	0.27
Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis	2010	Marshall JK	Symptomatic Improvement	dichotomous	Quality of Life (QoL) improvement	Digestive system	0.75
Tegaserod for the treatment of irritable bowel syndrome and chronic constipation	2007	Evans BW	Subjects Global Assessment (SGA) of relief at endpoint	dichotomous	Quality of Life (QoL) improvement	Digestive system	0.84
Tranexamic acid for upper gastrointestinal bleeding	2014	Bennett C	Mortality	dichotomous	Survival	Digestive system	0.96
Vaccines for preventing rotavirus diarrhoea: vaccines in use	2019	Soares-Weiser K	Rotavirus diarrhoea: severe (up to 1 year follow-up)	dichotomous	Cure of condition	Infectious disease	0.99
Antibiotic treatment for travellers' diarrhoea	2000	de Bruyn G	Number cured at 72 hours	dichotomous	Cure of condition	Infectious disease	0.58

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Antibiotics for acute rhinosinusitis in adults	2018	Lemiengre MB	Cure in adults with clinically diagnosed acute rhinosinusitis	dichotomous	Cure of condition	Infectious disease	0.86
Antibiotics versus placebo for acute bacterial conjunctivitis	2012	Sheikh A	Clinical remission (early)	dichotomous	Cure of condition	Infectious disease	0.74
Topical antifungal treatments for tinea cruris and tinea corporis	2014	El-Gohary M	Mycological cure	dichotomous	Cure of condition	Infectious disease	0.35
Hepatitis B vaccination for patients with chronic renal failure	2004	Schroth RJ	Seroconversion to anti-Hepatitis B (HB)s	dichotomous	Improved biological markers	Infectious disease	0.04
Drugs for treating <i>Schistosoma mansoni</i> infection	2013	Danso-Appiah A	Parasitological failure at one month	dichotomous	Improved biological markers	Infectious disease	0.32
Interventions for treating genital <i>Chlamydia trachomatis</i> infection in pregnancy	2017	Cluver C	Microbiological cure	dichotomous	Improved biological markers	Infectious disease	0.38
Topical treatments for fungal infections of the skin and nails of the foot.	2007	Crawford F	Short term (2 weeks) treatment failure	dichotomous	Improved external structure	Infectious disease	0.47
Imiquimod for anogenital warts in non-immunocompromised adults	2014	Grillo-Ardila CF	Complete regression after treatment	dichotomous	Improved external structure	Infectious disease	0.25
Vaccines for preventing hepatitis B in health-care workers	2005	Chen W	Hepatitis B events at maximum follow-up	dichotomous	No major morbidity events	Infectious disease	0.97
Prophylactic antibiotics for preventing pneumococcal infection in children with sickle cell disease	2017	Rankine-Mullings AE	Incidence of pneumococcal infection, for initiation or withdrawal of treatment.	dichotomous	No new signs of infection / disease	Infectious disease	0.94

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Vaccines for preventing cholera: killed whole cell or other subunit vaccines (injected)	2010	Graves PM	Cholera cases	dichotomous	No new signs of infection / disease	Infectious disease	1.00
Drugs for treating urinary schistosomiasis	2014	Kramer CV	Parasitological failure	dichotomous	No new signs of infection / disease	Infectious disease	0.15
Interventions for the prevention and treatment of herpes simplex virus in patients being treated for cancer	2009	Glenny AM	The herpes simplex virus (HSV) oral lesions (by mode of administration)	dichotomous	No new signs of infection / disease	Infectious disease	0.58
Vaccines for preventing influenza in healthy children	2018	Jefferson T	Influenza	dichotomous	No new signs of infection / disease	Infectious disease	0.83
Isoniazid for preventing tuberculosis in non-HIV infected persons	1999	Smieja M	Active tuberculosis	dichotomous	No new signs of infection / disease	Infectious disease	0.99
Amantadine and rimantadine for influenza A in adults	2006	Jefferson T	Influenza cases	dichotomous	No new signs of infection / disease	Infectious disease	0.92
Mefloquine for preventing malaria during travel to endemic areas	2017	Tickell-Painter M	Clinical cases of malaria	dichotomous	No new signs of infection / disease	Infectious disease	0.81
Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children	2013	Andabaka T	Hospitalisation for RS virus (RSV) infection	dichotomous	No new signs of infection / disease	Infectious disease	0.95
Treatment of latent tuberculosis infection in HIV infected persons	2010	Akolo C	Incidence of active tuberculosis (TB)	dichotomous	No new signs of infection / disease	Infectious disease	0.98
Oral antiviral therapy for prevention of genital herpes outbreaks in immunocompetent and nonpregnant patients	2014	Le Cleach L	Participants with at least 1 clinical recurrence	dichotomous	No new signs of infection / disease	Infectious disease	0.08

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Anabolic steroids for the treatment of weight loss in HIV-infected individuals	2005	Johns KKJ	Change from baseline in lean body mass	continuous	Others (Semi-objective)	Infectious disease	0.27
Corticosteroids as standalone or add-on treatment for sore throat	2012	Hayward G	Complete resolution of pain at 24 hours	dichotomous	Pain relief	Infectious disease	0.32
Topical analgesia for acute otitis media	2006	Foxlee R	50% reduction in ear pain	dichotomous	Pain relief	Infectious disease	0.47
Antihistamines for the common cold	2015	De Sutter AI	Change in severity of overall symptoms	dichotomous	Quality of Life (QoL) improvement	Infectious disease	0.84
Micronutrient supplementation for children with HIV infection	2013	Irlam JH	All-cause mortality	dichotomous	Survival	Infectious disease	0.78
Interventions to reduce harm from continued tobacco use	2016	Lindson-Hawley N	Reduction in cigarettes/day of > 50% of baseline or cessation	dichotomous	Cure of condition	Mental health and behavioral conditions	0.57
Interventions for smoking cessation and reduction in individuals with schizophrenia	2013	Tsoi DT	Abstinence at 6-month follow-up	dichotomous	Cure of condition	Mental health and behavioral conditions	0.36
Pharmacological interventions for clozapine-induced hypersalivation	2008	Syed R	No Effect / not cured / not markedly improved	dichotomous	Cure of condition	Mental health and behavioral conditions	0.22
Clonidine for smoking cessation	2004	Gourlay SG	Smoking Cessation	dichotomous	Cure of condition	Mental health and behavioral conditions	0.61
Megestrol acetate for treatment of anorexia-cachexia syndrome	2013	Ruiz Garcia V	Appetite improvement	dichotomous	Cure of condition	Mental health and behavioral conditions	0.46

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Nicotine receptor partial agonists for smoking cessation	2016	Cahill K	Continuous/sustained abstinence at longest follow-up (24+ weeks)	dichotomous	Cure of condition	Mental health and behavioral conditions	0.94
Opioid antagonists for alcohol dependence	2010	Rösner S	Return to heavy drinking	dichotomous	Cure of condition	Mental health and behavioral conditions	0.79
Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder	2013	Cipriani A	Study withdrawal due to episode of mood disorder.	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.82
Oral paliperidone for schizophrenia	2008	Nussbaum AM	Leaving the study early	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.79
Quetiapine for schizophrenia	2004	Srisurapanont M	Leaving the study early	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.80
Treatment for amphetamine withdrawal	2009	Shoptaw SJ	Discontinuation rates	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.77
Antipsychotic medications for cocaine dependence	2016	Indave BI	Dropouts	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.77
Haloperidol alone or in combination for acute mania	2006	Cipriani A	Failure to complete treatment - total dropouts	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.90
Depot haloperidol decanoate for schizophrenia	1999	Quraishi SN	Not completing the study	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.31
Azapirones versus placebo for panic disorder in adults	2014	Imai H	Dropouts for any reason	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.47

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Paliperidone palmitate for schizophrenia	2012	Nussbaum AM	Leaving the study early	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.82
Antipsychotic medication for early episode schizophrenia	2011	Bola JR	Leaving the study early	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.63
Amisulpride for schizophrenia	2002	Silveira da Mota Neto JI	Leaving the study early - overall	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.73
Aripiprazole (intramuscular) for psychosis-induced aggression or agitation (rapid tranquillisation)	2018	Ostinelli EG	Repeated need for tranquillisation	dichotomous	Less resource use / Shorter hospital stay	Mental health and behavioral conditions	0.69
Pharmacotherapy for anxiety disorders in children and adolescents	2009	Ipser JC	Clinical Global Impressions scale - Improvement item (CGI-I)	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.49
Thioridazine for schizophrenia	2007	Fenton M	Global state: no change or worse	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.64
Lithium for maintenance treatment of mood disorders	2001	Burgess SSA	All relapses	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.56
Olanzapine for schizophrenia	2005	Duggan L	Global effect: no important clinical response - by 6 weeks	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.68
Antidepressants versus placebo for panic disorder in adults	2018	Bighelli I	Failure to respond	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.74
Amitriptyline versus placebo for major depressive disorder	2012	Leucht C	Response	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.81

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Tryptophan and 5-Hydroxytryptophan for depression	2002	Shaw KA	Numbers of responders	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.81
Risperidone versus placebo for schizophrenia	2016	Ratthalli RD	Mental state: no clinically significant response in psychotic symptoms (defined by various scale total score change) - short term (up to 12 weeks)	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.55
Penfluridol for schizophrenia	2006	Soares BGO	No marked improvement	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.41
Interventions for preventing relapse and recurrence of a depressive disorder in children and adolescents	2012	Cox GR	Number relapsed	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.56
Vortioxetine for depression in adults	2017	Koesters M	Response	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.74
Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults	2015	McCloud TL	Response rate	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.09
St John's wort for major depression	2008	Linde K	Responder	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.68
Comparative effectiveness of continuation and maintenance treatments for persistent depressive disorder in adults	2019	Machmutow K	Relapse/recurrence	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.77

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Valproate for acute mania	2019	Jochim J	Response rate (adults)	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.85
Lithium for acute mania	2019	McKnight RF	The Young Mania Rating Scale (YMRS) decrease by =>50% at end of trial	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.82
Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders	2006	Ipser JC	Clinical Global Impression (CGI-I) scale response	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.32
Risperidone for autism spectrum disorder	2007	Jesner OS	Number of participants improved/very much improved	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.21
Antidepressant treatment for postnatal depression	2014	Molyneaux E	Response rate at post-treatment	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.70
Trifluoperazine versus placebo for schizophrenia	2014	Koch K	Global state - clinical improvement	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.16
Antidepressants versus placebo for people with bulimia nervosa	2003	Bacaltchuk J	Remission	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.43
Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD)	2013	Williams K	Proportion improved for Clinical Global Impression Improvement (CGI-I)	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.08
Tricyclic antidepressants for attention deficit hyperactivity disorder (ADHD) in children and adolescents	2014	Otasowie J	Clinical Global Impression (CGI) (response rate)	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.92

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Second-generation antidepressants for preventing seasonal affective disorder in adults	2019	Gartlehner G	Onset of major depressive episode	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.87
Pharmacotherapy for anxiety and comorbid alcohol use disorders	2015	Ipser JC	Treatment response	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.45
Polyunsaturated fatty acids (PUFA) for attention deficit hyperactivity disorder (ADHD) in children and adolescents	2012	Gillies D	Improvement in in attention deficit hyperactivity disorder (ADHD) symptoms	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.46
Benzodiazepines versus placebo for panic disorder in adults	2019	Breilmann J	Treatment response	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.61
Antidepressants for depression in physically ill people	2010	Rayner L	Response to treatment (4-5 weeks)	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.81
Ziprasidone for schizophrenia and severe mental illness	2000	Bagnall AM	No response (The Clinical Global Impression Improvement:C GI-I score >2 at last observation)	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.65
Antidepressants versus placebo for the depressed elderly	2001	Wilson K	Recovered	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.49
Hydroxyzine for generalised anxiety disorder	2010	Guaiana G	Number of patients who did not show a response	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.57

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Ketamine and other glutamate receptor modulators for depression in adults	2015	Caddy C	Response rate	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.97
Trifluoperazine for schizophrenia	2004	Marques LDO	No substantial improvement (defined as slight improvement or worse)	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.09
Haloperidol versus placebo for schizophrenia	2013	Adams CE	No marked global improvement	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.63
Second-generation antipsychotics for anxiety disorders	2010	Depping AM	Response - as defined by original studies	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.45
Donepezil for vascular cognitive impairment	2004	Malouf R	The cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) completers	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.27
Olanzapine alone or in combination for acute mania	2003	Rendell JM	Mean change in Young Mania Rating Scale (YMRS)	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.59
Atypical antipsychotics for disruptive behaviour disorders in children and youths	2017	Loy JH	Aggression: the Aberrant Behaviour Checklist (ABC) irritability	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.35
Active placebos versus antidepressants for depression	2004	Moncrieff J	Change in mood after treatment period	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.86

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Antidepressants for depression in adults with HIV infection	2018	Eshun-Wilson I	The Hamilton Depression Rating Scale (HAM-D) score	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.54
Pharmacological interventions for apathy in Alzheimer's disease	2018	Ruthirakuhan MT	Change in apathy from baseline as measured by the apathy evaluation scale (AES)	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.14
Risperidone alone or in combination for acute mania	2006	Rendell JM	Mean change in Young Mania Rating Scale (YMRS) - all participants	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.57
Nicergoline for dementia and other age associated forms of cognitive impairment	2001	Fioravanti M	The Sandoz Clinical Assessment Geriatric Scale (SCAG) total scores	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.53
Aripiprazole for autism spectrum disorders (ASD)	2016	Hirsch LE	Aberrant Behavior Checklist (ABC) - Irritability subscale	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.51
Kava extract versus placebo for treating anxiety	2003	Pittler MH	Improvement of the Hamilton Anxiety (HAM-A) score	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.71
Aripiprazole alone or in combination for acute mania	2013	Brown R	Young Mania Rating Scale	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.70

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Benzodiazepines for alcohol withdrawal	2010	Amato L	Alcohol withdrawal seizures	dichotomous	No major morbidity events	Mental health and behavioral conditions	0.93
Hydergine for dementia	2000	Schneider L	Patient status	dichotomous	Quality of Life (QoL) improvement	Mental health and behavioral conditions	0.29
Pharmacological interventions for sleepiness and sleep disturbances caused by shift work	2014	Liira J	Total sleep time	continuous	Quality of Life (QoL) improvement	Mental health and behavioral conditions	0.92
Progesterone receptor modulators for endometriosis	2017	Fu J	Dysmenorrhoea at three months	dichotomous	Cure of condition	Obstetrics and gynecology	0.66
The effects of antimicrobial therapy on bacterial vaginosis in non-pregnant women	2009	Oduyebo OO	Clinical failure	dichotomous	Cure of condition	Obstetrics and gynecology	0.55
Bioidentical hormones for women with vasomotor symptoms	2016	Gaudard AMIS	Frequency of hot flushes	continuous	Cure of condition	Obstetrics and gynecology	0.54
Medical interventions for high-grade vulval intraepithelial neoplasia	2015	Pepas L	Response to treatment at 5-6 months	dichotomous	Improved external structure	Obstetrics and gynecology	0.08
Combined oral contraceptive pills for treatment of acne	2012	Arowojolu AO	Mean change in total lesion count	continuous	Improved external structure	Obstetrics and gynecology	0.52
Interventions for helping to turn term breech babies to head first presentation when using external cephalic version	2015	Cluver C	Cephalic presentation at birth	dichotomous	Improved obstetric outcomes	Obstetrics and gynecology	0.60
Prophylactic oral betamimetics for reducing preterm birth in women with a twin pregnancy	2015	Yamasmit W	Preterm labour	dichotomous	Improved obstetric outcomes	Obstetrics and gynecology	0.88
Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth	2013	Dodd JM	Perinatal mortality	dichotomous	Improved obstetric outcomes	Obstetrics and gynecology	0.95

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Treatment of vaginal bleeding irregularities induced by progestin only contraceptives	2013	Abdel-Aleem H	Continued irregular bleeding during treatment	dichotomous	Improved obstetric outcomes	Obstetrics and gynecology	0.38
Metformin during ovulation induction with gonadotrophins followed by timed intercourse or intrauterine insemination for subfertility associated with polycystic ovary syndrome	2017	Bordewijk EM	Live birth rate (per woman)	dichotomous	Improved obstetric outcomes	Obstetrics and gynecology	0.85
Combined hormonal contraceptives for heavy menstrual bleeding	2019	Lethaby A	Response to treatment	dichotomous	Improved obstetric outcomes	Obstetrics and gynecology	0.97
Medical treatment for early fetal death (less than 24 weeks)	2019	Lemmers M	Complete miscarriage	dichotomous	Improved obstetric outcomes	Obstetrics and gynecology	0.24
Betamimetics for inhibiting preterm labour	2014	Neilson JP	Birth within 48 hours of treatment	dichotomous	Improved obstetric outcomes	Obstetrics and gynecology	0.83
Progestational agents for treating threatened or established preterm labour	2014	Su LL	Preterm delivery	dichotomous	Improved obstetric outcomes	Obstetrics and gynecology	0.70
Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems	2018	Hofmeyr GJ	High blood pressure (with or without proteinuria)	dichotomous	No major morbidity events	Obstetrics and gynecology	0.92
Antibiotic prophylaxis for elective hysterectomy	2017	Ayeleke RO	Total postoperative infections - early and late	dichotomous	No new signs of infection / disease	Obstetrics and gynecology	0.46
Transcutaneous electrical nerve stimulation for primary dysmenorrhoea	2002	Proctor M	Pain relief - overall experience	dichotomous	Pain relief	Obstetrics and gynecology	0.14
Oral contraceptive pill for primary dysmenorrhoea	2009	Wong CL	Pain improvement	dichotomous	Pain relief	Obstetrics and gynecology	0.87

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Brivaracetam add-on therapy for drug-resistant epilepsy	2019	Bresnahan R	50% or greater reduction in seizure frequency (responder rate)	dichotomous	Cure of condition	Others	0.55
Medical and surgical interventions for the treatment of usual-type vulval intraepithelial neoplasia	2016	Lawrie TA	Response to treatment at 5 to 6 months	dichotomous	Cure of condition	Others	0.08
Ketanserin for Raynaud's phenomenon in progressive systemic sclerosis	1998	Pope J	Number of patients who improved	dichotomous	Cure of condition	Others	0.81
Local corticosteroid injection for carpal tunnel syndrome	2007	Marshall SC	Clinical improvement	dichotomous	Cure of condition	Others	0.39
Corticosteroids for the treatment of idiopathic acute vestibular dysfunction (vestibular neuritis)	2011	Fishman JM	Complete caloric recovery at 1 month	dichotomous	Cure of condition	Others	0.36
Antibiotics for sore throat	2013	Spinks A	Symptom of sore throat on day 3	dichotomous	Cure of condition	Others	0.61
Interventions for impetigo	2012	Koning S	Cure/improvement	dichotomous	Cure of condition	Others	0.45
Natalizumab for induction of remission in Crohn's disease	2018	Nelson SML	Failure to induce remission at 2 weeks	dichotomous	Cure of condition	Others	0.64
Cannabinoid type 1 receptor antagonists for smoking cessation	2011	Cahill K	Prolonged abstinence at wk 50	dichotomous	Cure of condition	Others	0.67
Chinese herbal medicines for type 2 diabetes mellitus	2002	Liu JP	Normalisation of fasting blood glucose (< 7.2 mmol/L)	dichotomous	Improved biological markers	Others	0.49

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Chinese herbal medicine for atopic eczema	2013	Gu S	Total effectiveness rate (number of participants recovered and significantly improved)	dichotomous	Improved external structure	Others	0.48
Rapamycin and rapalogs for tuberous sclerosis complex	2016	Sasongko TH	Response to tumour size	dichotomous	Improved internal structure	Others	0.04
Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women	2008	Wells GA	Vertebral Fractures	dichotomous	Improved internal structure	Others	0.97
Interventions for restoring patency of occluded central venous catheter lumens	2012	van Miert C	Restored patency of central venous catheter (CVC) following one or two installations of study drug	dichotomous	Less resource use / Shorter hospital stay	Others	0.48
Steroids for improving recovery following tonsillectomy in children	2011	Steward DL	Emesis	dichotomous	No adverse events	Others	0.75
Intravenous dexamethasone for extubation of newborn infants	2001	Davis PG	Endotracheal reintubation	dichotomous	No major morbidity events	Others	0.92
Local interventions for the management of alveolar osteitis (dry socket)	2012	Daly B	Presence of dry socket	dichotomous	No major morbidity events	Others	0.86
Interventions for preventing high altitude illness: Part 1. Commonly-used classes of drugs	2017	Nieto Estrada VH	Incidence of acute mountain sickness	dichotomous	No major morbidity events	Others	0.86
Anakinra for rheumatoid arthritis	2009	Mertens M	American College of Rheumatology (ACR) 20	dichotomous	No unpleasant composite endpoint	Others	0.72

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Chromium picolinate supplementation for overweight or obese adults	2013	Tian H	Change in weight at 12-16 weeks	continuous	Others (Semi-objective)	Others	0.38
Rimonabant for overweight or obesity	2006	Curioni C	Weight change	continuous	Others (Semi-objective)	Others	0.33
Dexamethasone as an adjuvant to peripheral nerve block	2017	Pehora C	Duration of sensory block	continuous	Others (Semi-objective)	Others	0.73
Long-term pharmacotherapy for obesity and overweight	2003	Padwal RS	Change in Weight	continuous	Others (Semi-objective)	Others	0.59
Amitriptyline for fibromyalgia in adults	2015	Moore RA	Third-tier efficacy	dichotomous	Pain relief	Others	0.35
Bisphosphonates for Paget's disease of bone in adults	2017	Corral-Gudino L	Number of participants whose bone pain disappeared completely	dichotomous	Pain relief	Others	0.29
Hyaluronic acid and other conservative treatment options for osteoarthritis of the ankle	2015	Witteveen AGH	The Ankle Osteoarthritis Scale (AOS) total (combined pain and function score) at 6months	continuous	Pain relief	Others	0.54
Acetyl-L-carnitine for the treatment of diabetic peripheral neuropathy	2019	Rolim LCSP	Pain at 6 to 12 months' follow-up	continuous	Pain relief	Others	0.57
Spirolactone versus placebo or in combination with steroids for hirsutism and/or acne	2009	Brown J	Subjective improvement in hair growth	dichotomous	Quality of Life (QoL) improvement	Others	0.88

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Betahistine for symptoms of vertigo	2016	Murdin L	Proportion of patients with improvement according to global judgement of patient	dichotomous	Quality of Life (QoL) improvement	Others	0.77
Interventions for treating sexual dysfunction in patients with chronic kidney disease	2010	Vecchio M	Sexual function using the overall International Index of Erectile Function-5 (IIEF-5)	continuous	Quality of Life (QoL) improvement	Others	0.56
Terlipressin for acute esophageal variceal hemorrhage	2003	Ioannou GN	Mortality	dichotomous	Survival	Others	0.84
Corticosteroids for preventing relapse following acute exacerbations of asthma	2007	Rowe BH	Relapse rates	dichotomous	Cure of condition	Respiratory disease	0.88
Umeclidinium bromide versus placebo for people with chronic obstructive pulmonary disease (COPD)	2017	Ni H	Number of participants with exacerbations requiring steroids, antibiotics, or both	dichotomous	Cure of condition	Respiratory disease	0.94
Antibiotics for acute bronchitis	2017	Smith SM	Number of participants with cough	dichotomous	Cure of condition	Respiratory disease	0.73
Pelargonium sidoides extract for treating acute respiratory tract infections	2013	Timmer A	Failure to recover by day seven (complete resolution of all symptoms)	dichotomous	Cure of condition	Respiratory disease	0.13

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Tiotropium for stable chronic obstructive pulmonary disease	2005	Barr RG	Exacerbations	dichotomous	Cure of condition	Respiratory disease	0.92
Intranasal steroids for acute sinusitis	2013	Zalmanovici Trestioreanu A	Proportion of participants with resolution of symptoms or improved	dichotomous	Cure of condition	Respiratory disease	0.91
Macrolide antibiotics for bronchiectasis	2018	Kelly C	≥ 1 exacerbation	dichotomous	Cure of condition	Respiratory disease	0.53
Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children	2010	Ducharme FM	Patients with exacerbations requiring oral steroids	dichotomous	Cure of condition	Respiratory disease	0.96
Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease	2019	Poole P	Participants with no exacerbations in study period	dichotomous	Cure of condition	Respiratory disease	0.84
Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)	2018	Herath SC	Number of people with one or more exacerbations	dichotomous	Cure of condition	Respiratory disease	0.74
Glucocorticoids for croup in children	2018	Gates A	Croup score	continuous	Cure of condition	Respiratory disease	0.43
Beclomethasone versus placebo for chronic asthma	2005	Adams NP	forced expiratory volume in one second (FEV1) (L) and FEV1 (% predicted)	continuous	Improved internal structure	Respiratory disease	0.76
Ketotifen alone or as additional medication for long-term control of asthma and wheeze in children	2004	Bassler D	Reduction of bronchodilator use	dichotomous	Less consumption / Satisfaction with care	Respiratory disease	0.42

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Epinephrine for bronchiolitis	2011	Hartling L	Admissions at enrollment or < 24 hours (outpatients only)	dichotomous	Less resource use / Shorter hospital stay	Respiratory disease	0.93
Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease	2014	Walters JAE	Need to intensify therapy/ emergency department (ED) or hospital admission Follow-up: 3-30 days	dichotomous	Less resource use / Shorter hospital stay	Respiratory disease	0.84
Magnesium sulfate for treating exacerbations of acute asthma in the emergency department	2000	Rowe BH	Admission to hospital	dichotomous	Less resource use / Shorter hospital stay	Respiratory disease	0.72
Early emergency department treatment of acute asthma with systemic corticosteroids	2001	Rowe BH	Admitted to hospital (all times)	dichotomous	Less resource use / Shorter hospital stay	Respiratory disease	0.75
Intravenous magnesium sulfate for treating children with acute asthma in the emergency department	2016	Griffiths B	Hospital admissions	dichotomous	Less resource use / Shorter hospital stay	Respiratory disease	0.48
Corticosteroids for hospitalised children with acute asthma	2003	Smith M	Discharge at first re-examination (4h)	dichotomous	Less resource use / Shorter hospital stay	Respiratory disease	0.94
Probiotics for preventing acute upper respiratory tract infections	2015	Hao Q	The number of participants who experienced upper respiratory tract infections (URTI) episodes: at least 1 event	dichotomous	No new signs of infection / disease	Respiratory disease	0.86

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Antibiotics for exacerbations of chronic obstructive pulmonary disease	2018	Vollenweider DJ	Treatment failure up to 4 weeks	dichotomous	No unpleasant composite endpoint	Respiratory disease	0.89
Nebulized epinephrine for croup in children	2013	Bjornson C	Croup score (change baseline - 30 minutes)	continuous	Others (Semi-objective)	Respiratory disease	0.45
5-FU for genital warts in non-immunocompromised individuals	2010	Batista CS	Cure	dichotomous	Cure of condition	Urogenital	0.85
Topical corticosteroids for treating phimosis in boys	2014	Moreno G	Resolution of phimosis (complete or partial)	dichotomous	Cure of condition	Urogenital	0.41
Prostaglandin E1 for treatment of erectile dysfunction	2004	Urcioli R	At least one success	dichotomous	Cure of condition	Urogenital	0.85
Sildenafil for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia	2017	Jung JH	Urologic symptom scores (short term)	continuous	Cure of condition	Urogenital	0.63
Botulinum toxin injections for adults with overactive bladder syndrome	2011	Duthie JB	Change in post void residual volume (PVR) at 4-6 weeks	continuous	Improved internal structure	Urogenital	0.04
5-alpha-reductase inhibitors for prostate cancer prevention	2008	Wilt TJ	Prostate cancer detected "for-cause"	dichotomous	No major morbidity events	Urogenital	0.99
Antibiotic prophylaxis for transrectal prostate biopsy	2011	Zani EL	Bacteriuria	dichotomous	No new signs of infection / disease	Urogenital	0.88
Pygeum africanum for benign prostatic hyperplasia	1998	Wilt TJ	Symptoms improvement: overall improvement	dichotomous	Quality of Life (QoL) improvement	Urogenital	0.48

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Anticholinergic drugs versus placebo for overactive bladder syndrome in adults	2006	Nabi G	Patient perception of cure or improvement.	dichotomous	Quality of Life (QoL) improvement	Urogenital	0.72
Finasteride for benign prostatic hyperplasia	2010	Tacklind J	Total symptom score	continuous	Quality of Life (QoL) improvement	Urogenital	0.99
Phosphodiesterase inhibitors for lower urinary tract symptoms consistent with benign prostatic hyperplasia	2018	Pattanaik S	Change in the International Prostate Symptom Score (IPSS) - total	continuous	Quality of Life (QoL) improvement	Urogenital	0.60

Supplement 4. Worked examples of PCE calculation from Cochrane reviews

Abbreviations

RR, risk ratio; OR, odds ratio; CER, control event rate; PCE, the proportion attributable to contextual effects; n, number of patients; SE, standard error; SD, standard deviation; WSM, weighted standardized mean; 95% CI, 95% confidence interval

Dichotomous harmful outcome

Example: Fenton M et al. Thioridazine for schizophrenia. CD005170.pub2

The results of this review were as follows;

RR 0.66, 95% CI 0.44 to 0.98.

CER 35/56 = 0.625 (CER on harmful outcome)

1. Converting harmful RR to harmful OR

We used formula (3) in the manuscript.

$$OR = \frac{RR \times (CER - 1)}{RR \times CER - 1} = \frac{0.66 \times (35/56 - 1)}{0.66 \times 35/56 - 1} = 0.42$$

2. Converting harmful OR to beneficial OR

We took the reciprocal.

$$\text{beneficial OR} = \frac{1}{\text{harmful OR}} = \frac{1}{0.42} = 2.38$$

3. Converting beneficial OR to beneficial RR

We used formula (2) in the manuscript (in this case, CER must be a CER of the beneficial outcome, that is 1-CER on the harmful outcome).

$$RR = \frac{OR}{1 - CER \times (1 - OR)} = \frac{2.38}{1 - (1 - 35/56) \times (1 - 2.38)} = 1.57$$

4. Calculating the PCE

Based on the definition, PCE was calculated as follows:

$$PCE = \frac{1}{\text{beneficial RR}} = \frac{1}{1.57} = 0.64$$

5. Calculating the SE of log (PCE)

We performed the same conversions as above to compute the upper and lower 95% confidence interval of the PCE. The upper 95% CI was 0.97, and the lower 95% CI was 0.52

We then calculated the SE of PCE by the following formula:

$$\text{SE of log (PCE)} = \frac{\log(\text{upper 95\% CI}) - \log(\text{lower 95\% CI})}{3.92} = \frac{\log(0.97) - \log(0.52)}{3.92} = 0.16$$

Continuous outcome

Example: Jung JH et al. Silodosin for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia. CD012615.pub2

The results of the review were as follows;

SMD -2.65, 95% CI -3.23 to -2.08

Included studies in the original meta-analysis

Study ID	Mean change (SD) in the intervention arm	Number of patients on the intervention arm	Mean change (SD) in the placebo arm	Number of patients on the placebo arm
Chapple 2011	-7.1 (5.31)	371	-4.9 (5.42)	185
Kawabe 2006a	-8.3 (6.4)	175	-5.3 (6.7)	89
Marks 2009	-6.4 (6.63)	466	-3.5 (5.84)	457

For each primary study,

Standardized mean change = mean change / SD

SE of standardized mean change = $1/\sqrt{n}$

1. Calculating the weighted standardized mean change of each arm by meta-analysis

We used the DerSimonian-Laird method. The results of the meta-analyses were as follows:

Weighted standardized mean change of intervention arm (SE): -1.20 (0.13)

Weighted standardized mean change of placebo arm (SE): -0.76 (0.11)

We performed the meta-analyses by `metagen` from the package `meta` in R.

2. Calculating the PCE

We used formula (5) in the manuscript.

$$\text{PCE} = \frac{\text{weighted standardized mean change score of the placebo arm}}{\text{weighted standardized mean change score of the intervention arm}} = \frac{-0.76}{-1.20} = 0.63$$

3. Calculating the SE of log(PCE)

We used formula (6) for calculating the SE based on the Delta method.

$$\text{SE of log(PCE)} = \sqrt{\frac{\text{SE}_{\text{intervention}}^2}{\text{WSM}_{\text{intervention}}^2} + \frac{\text{SE}_{\text{placebo}}^2}{\text{WSM}_{\text{placebo}}^2}} = \sqrt{\frac{(0.13)^2}{(-1.20)^2} + \frac{(0.11)^2}{(-0.76)^2}} = 0.17$$

Figure S1. PCE by outcome type (binary outcomes). Created by the authors.

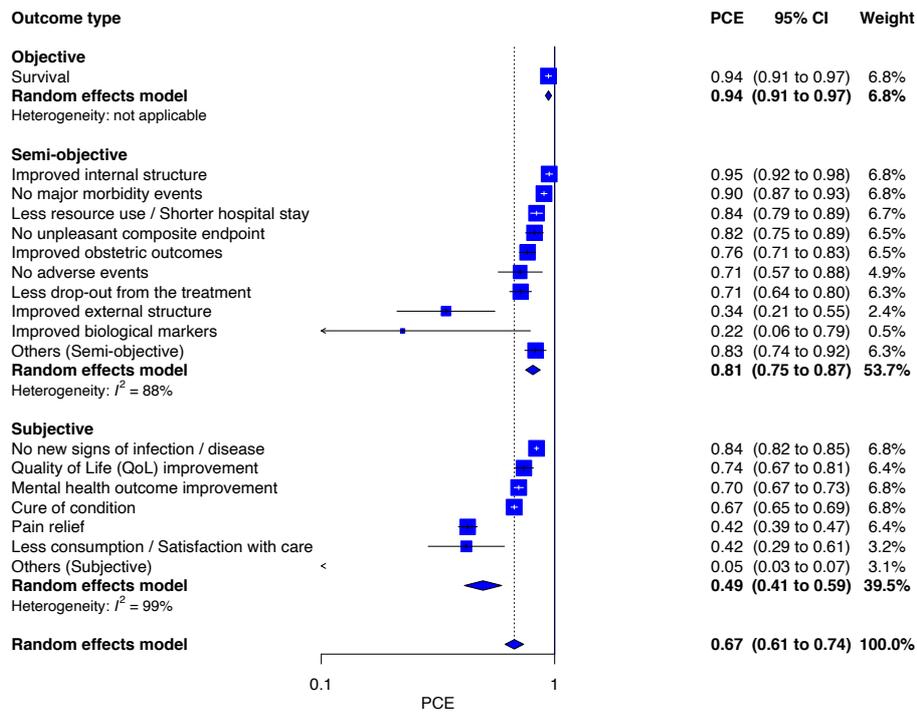


Figure S2. PCE by outcome type (continuous outcomes). Created by the authors.

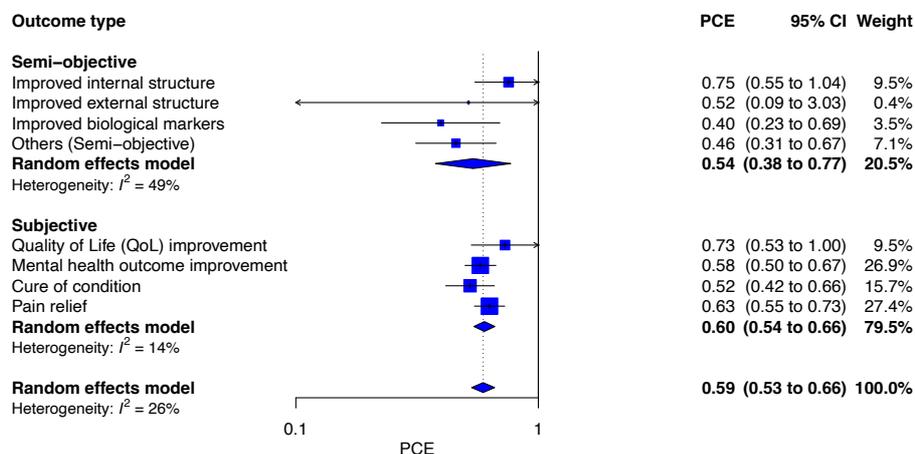


Figure S3. PCE by conditions (binary). Created by the authors.

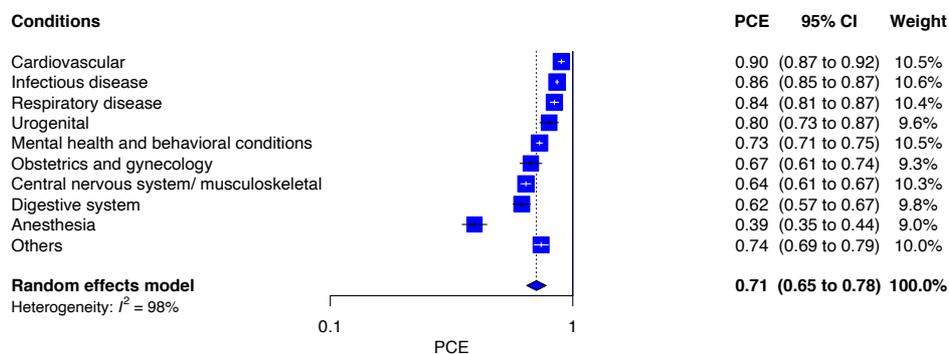


Figure S4. PCE by conditions (continuous). Created by the authors.

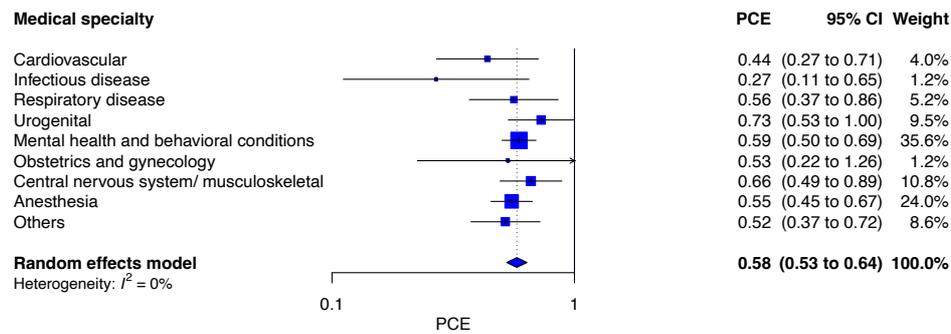


Figure S5. PCE by GRADE category (total). Created by the authors

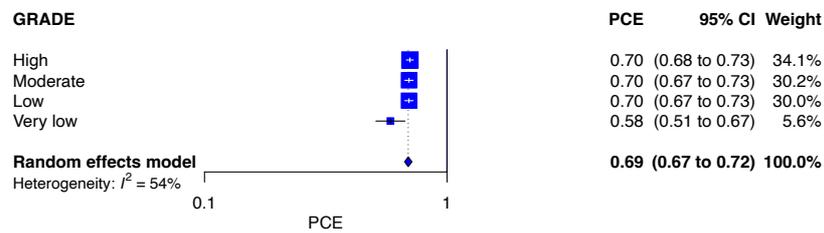


Figure S6. PCE by GRADE category (binary). Created by the authors.

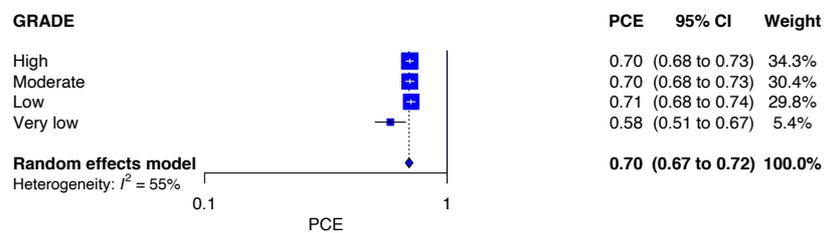
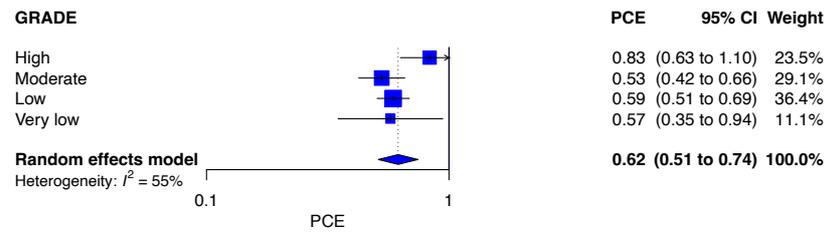


Figure S7. PCE by GRADE category (continuous). Created by the authors.



Supplement 1. The original protocol of the study

Fixed and uploaded on September 4, 2018

The Placebo Attributable Fraction in General Medicine: Protocol for a meta-epidemiological Study of Cochrane Reviews

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INTRODUCTION

Placebo has long been used as dummy treatment in the “control group” in randomized controlled trials to ensure methodological validity (1,2). Placebo-controlled group may show similar response to active treatment especially for subjective outcomes. This is known as placebo response and, sometimes, placebo response may reach up to about 40% of active treatment response (3–5).

Placebo response consists of placebo effect and other factors such as natural course of the disease and regression to the mean (6). Among these, placebo effect is the change of the status caused by placebo and the existence and degree of this effect was controversial (7–9). No matter how much placebo effect exists, the magnitude of placebo response attributable to active treatment response, which called the placebo-attributable fraction, is highly important for the implications of clinical trials and treatment choice in clinical setting.

In this study, we will systematically review Cochrane reviews to examine the placebo-attributable fraction in all fields of medicine and reveal the difference of the size of the placebo-attributable fraction according to specialties and intervention methods.

METHODS

Types of studies included

We will select all the systematic review of randomized placebo-controlled trials published in the Cochran Database of Systematic Reviews. Among selected studies, we will include reviews which showed the significant beneficial effect of intervention arm compared to placebo for their first primary outcome. If there are multiple comparison regarding the first primary outcome due to multiple intervention arms, we will select the first comparison.

We will define placebo-attributable fraction (P-AF) as follows:

For dichotomous beneficial outcome,

$$\frac{\text{the proportion of beneficial event in the placebo arm}}{\text{the proportion of beneficial event in the intervention arm}}$$

For dichotomous harmful outcome,

$$\frac{1 - \text{the proportion of harmful event in the placebo arm}}{1 - \text{the proportion of harmful event in the intervention arm}}$$

For continuous beneficial outcome

$$\frac{\text{the change of score or scale in the placebo arm}}{\text{the change of score or scale in the placebo arm}}$$

We will exclude interventions whose aim is to prevent deterioration in the continuous score (i.e. either increase in bad outcome scale or decrease in good outcome scale, as this would complicate interpretation of placebo-attributable fraction.

To calculate the P-AF defined above, we will use the average proportion or change score in the control group in the numerator, and the event rate or the change score in the intervention group based on the pooled OR or SMD/MD in the denominator. Therefore, we will exclude reviews that did not perform meta-analysis, did not report the change of score (if first primary outcome is continuous), did not report the number of participants and events for each arm (if first primary outcome is dichotomous), using outcome measure other than MD or SMD for first primary outcome. We will also exclude systematic reviews of studies other than pill placebo-controlled trials (e.g. sham-controlled trials, non-randomized controlled trials, diagnostic test accuracy studies and prognostic studies), overview of reviews, or methodological reviews.

Search strategy

We will search Cochrane Central Register Controlled Trials (CENTRAL) using “placebo” as keyword in Title, Abstract, Keywords in Cochrane Reviews

Study selection

Two authors will independently perform the initial screening of the titles and abstracts of all studies identified by the search and will examine the potential eligibility for inclusion. After initial screening, same authors will assess the eligibility based on a full-text review. We will resolve disagreements by discussion between the authors, with another author acting as an arbiter.

Data extraction

Two authors will use structured data extraction form to independently collect the data from included studies. If the review reported RR, we will extract pooled RR of each review. If the review reported MD, we will extract the change of the outcome and the number of participants for each of intervention and placebo arm of included trials separately. If the review reported SMD, we will extract the change of the outcome with standard deviation and the number of participants for each of intervention and placebo arm of included trials separately. We will also extract the following information: number of participants and trials in meta-analysis of first primary outcome, sample size of intervention and placebo arm, outcome data type (dichotomous or continuous), outcome type, medical specialty, Intervention type (pharmacological or non-pharmacological) and Cochrane review group.

We will categorize outcome types as below: (10–12)

Objective outcome

·All-cause mortality,

Semi objective outcomes

· Major morbidity event

· Obstetric outcomes

· Resource use and Hospital stay/process measures

· Internal and external structure related outcomes

· Biological markers

· Other semi-objective outcomes including cause-specific mortality, composite (mortality / morbidity only), and withdrawals/dropouts

Subjective outcomes

·Pain

·Quality of life/functioning

- Mental health outcomes
- Various subjectively measured outcomes including consumption, satisfaction with care, composite (at least 1 non-mortality/morbidity) and surgical/device related success/failure
- General health-related outcomes including general physical health and adverse events
- Signs/symptoms reflecting continuation/end of condition and Infection/onset of new acute/chronic disease

Others

- Other outcomes

We will categorize medical specialty as follows: cancer, cardiovascular, central nervous system/ musculoskeletal, digestive system, infectious disease, mental health and behavioral conditions, obstetrics and gynecology, pathological conditions, respiratory disease, urogenital and others (10–12).

Statistical analysis

First, we will calculate P-AF for each review as described above. Next, we will compute the weighted mean of P-AF of each review to show the overall P-AF across general clinical condition.

Additionally, we will perform sub-group analyses and meta-regression analyses to examine any heterogeneity of P-AF across outcome types, intervention types, medical specialty, overall risk of bias and Cochrane review groups.

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Supplement 2. Changes to the protocol

1. We revised category names of outcome type as the name indicates beneficial outcome rather than harmful outcome (e.g. from all-cause mortality to survival).
2. We revised the detailed definition of placebo attributable fraction (PAF) to cope with the variation of outcome measure (dichotomous or continuous, beneficial or harmful, and risk ratio or odds ratio)
3. We add the detailed method to calculate PAF for continuous outcomes. As described in the Method section, we calculate weighted standardized mean of intervention and placebo arm of each Cochran SR by performing meta-analysis, and then calculate PAF and its standard error using Delta method.
4. We add the detailed method to calculate PAF by outcome type, medical specialty and GRADE rating. As described in the Method section, we performed meta-analysis to calculate.
5. We categorized other types of outcomes into others (semi-objective) and others (subjective).
6. We changed the term PAF to the proportion attributable to contextual effect (PCE) throughout the manuscript.
7. We slightly modified the category of medical specialty, in which we delete pathological condition and cancer, and added anaesthesia.

Supplement 3. All of included Cochrane reviews and its PCE. Created by authors.

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Paracetamol/acetaminophen (single administration) for perineal pain in the early postpartum period	2013	Chou D	Adequate pain relief as reported by women.	dichotomous	Pain relief	Anesthesia	0.47
Single dose oral lornoxicam for acute postoperative pain in adults	2009	Hall PE	Participants with at least 50% pain relief over 6 hours	dichotomous	Pain relief	Anesthesia	0.43
Single dose oral gabapentin for established acute postoperative pain in adults	2010	Straube S	Participants with $\geq 50\%$ pain relief over 6 hours	dichotomous	Pain relief	Anesthesia	0.41
Single dose oral etodolac for acute postoperative pain in adults	2009	Tirunagari SK	Participants with at least 50% pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.58
Single dose oral ibuprofen plus oxycodone for acute postoperative pain in adults	2013	Derry S	Participants with $\geq 50\%$ pain relief at 6 hours	dichotomous	Pain relief	Anesthesia	0.28
Single dose oral dihydrocodeine for acute postoperative pain	2000	Moore RA	Patients with at least 50% pain relief	dichotomous	Pain relief	Anesthesia	0.63
Single dose oral ibuprofen plus codeine for acute postoperative pain in adults	2015	Derry S	Participants with $\geq 50\%$ pain relief	dichotomous	Pain relief	Anesthesia	0.24
Single dose oral naproxen and naproxen sodium for acute postoperative pain in adults	2009	Derry CJ	Participants with at least 50% pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.35

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Single dose oral flurbiprofen for acute postoperative pain in adults	2009	Sultan A	Participants with \geq 50% pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.14
Single dose oral lumiracoxib for postoperative pain in adults	2010	Roy YM	Participants with at least 50% pain relief at 6 hours	dichotomous	Pain relief	Anesthesia	0.15
Single dose oral celecoxib for acute postoperative pain in adults	2013	Derry S	At least 50% pain relief over 4-6 hours	dichotomous	Pain relief	Anesthesia	0.06
Oral non-steroidal anti-inflammatory drugs (single dose) for perineal pain in the early postpartum period	2016	Wuytack F	Adequate pain relief (4 hours after administration)	dichotomous	Pain relief	Anesthesia	0.52
Single dose oral ibuprofen for acute postoperative pain in adults	2009	Derry CJ	Participants with at least 50% pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.22
Intravenous or intramuscular parecoxib for acute postoperative pain in adults	2009	Lloyd R	Participants with at least 50% pain relief	dichotomous	Pain relief	Anesthesia	0.20
Topical NSAIDs for acute musculoskeletal pain in adults	2015	Derry S	Clinical success	dichotomous	Pain relief	Anesthesia	0.63
Single dose oral mefenamic acid for acute postoperative pain in adults	2011	Moll R	\geq 50% pain relief over 4 to 6 h	dichotomous	Pain relief	Anesthesia	0.47
Single dose oral paracetamol (acetaminophen) for postoperative pain in adults	2008	Toms L	Participants with at least 50% pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.41
Muscle relaxants for non-specific low-back pain	2003	van Tulder MW	Pain	dichotomous	Pain relief	Anesthesia	0.29

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Therapeutic ultrasound for postpartum perineal pain and dyspareunia	1998	Hay-Smith J	No improvement (self-report) post-treatment	dichotomous	Pain relief	Anesthesia	0.88
Lacosamide for neuropathic pain and fibromyalgia in adults	2012	Hearn L	Moderate benefit ($\geq 2/10$ on NRS or $\geq 30\%$ on visual analogue scale (VAS) pain intensity reduction)	dichotomous	Pain relief	Anesthesia	0.78
Oxycodone for neuropathic pain in adults	2016	Gaskell H	At least moderate pain relief	dichotomous	Pain relief	Anesthesia	0.60
Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults	2009	Toms L	Participants with at least 50% pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.16
Salicylate-containing rubefacients for acute and chronic musculoskeletal pain in adults	2014	Derry S	Clinical success (eg 50% reduction in pain)	dichotomous	Pain relief	Anesthesia	0.52
Topical clonidine for neuropathic pain	2015	Wrzosek A	Pain relief $\geq 30\%$	dichotomous	Pain relief	Anesthesia	0.74
Single fixed-dose oral dexketoprofen plus tramadol for acute postoperative pain in adults	2016	Derry S	Participants with $\geq 50\%$ pain relief over 6 hours	dichotomous	Pain relief	Anesthesia	0.49
Single dose oral diclofenac for acute postoperative pain in adults	2015	Derry S	At least 50% of maximum pain relief over 6 hours	dichotomous	Pain relief	Anesthesia	0.06

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Tramadol for postoperative pain treatment in children	2015	Schnabel A	Number of patients requiring rescue analgesia (PACU)	dichotomous	Pain relief	Anesthesia	0.32
Single dose oral ibuprofen plus caffeine for acute postoperative pain in adults	2015	Derry S	At least 50% maximum pain relief.	dichotomous	Pain relief	Anesthesia	0.18
Non-surgical interventions for the management of chronic pelvic pain	2014	Cheong YC	Improvement in pain score at end of treatment	dichotomous	Pain relief	Anesthesia	0.81
Single dose oral fenoprofen for acute postoperative pain in adults	2011	Traa MX	≥50% total pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.24
Tramadol for neuropathic pain in adults	2017	Duehmke RM	Participants with ≥ 50% pain intensity reduction	dichotomous	Pain relief	Anesthesia	0.46
Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain	2013	Derry CJ	Participants with ≥50% pain relief	dichotomous	Pain relief	Anesthesia	0.10
Single dose oral diflunisal for acute postoperative pain in adults	2010	Wasey JO	Participants with ≥50% pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.35
Carbamazepine for chronic neuropathic pain and fibromyalgia in adults	2014	Wiffen PJ	Any pain improvement	dichotomous	Pain relief	Anesthesia	0.15
Lidocaine for reducing propofol-induced pain on induction of anaesthesia in adults	2016	Euasobhon P	High-intensity pain	dichotomous	Pain relief	Anesthesia	0.75

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Single dose oral codeine, as a single agent, for acute postoperative pain in adults	2010	Derry S	Participants with $\geq 50\%$ pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.67
Gabapentin for chronic neuropathic pain in adults	2017	Wiffen PJ	At least 50% pain reduction over baseline	dichotomous	Pain relief	Anesthesia	0.59
Single dose oral etoricoxib for acute postoperative pain in adults	2014	Clarke R	Participants with at least 50% pain relief over 6 hours	dichotomous	Pain relief	Anesthesia	0.18
Combination pharmacotherapy for the treatment of neuropathic pain in adults	2012	Chaparro LE	At least moderate/good pain relief	dichotomous	Pain relief	Anesthesia	0.77
Single dose dipyrone (metamizole) for acute postoperative pain in adults	2016	Hearn L	Participants with $\geq 50\%$ pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.42
Single-dose intravenous diclofenac for acute postoperative pain in adults	2018	McNicol ED	Number of participants with at least 50% pain relief at 4 hours	dichotomous	Pain relief	Anesthesia	0.35
Milnacipran for pain in fibromyalgia in adults	2015	Cording M	At least 30% pain relief	dichotomous	Pain relief	Anesthesia	0.72
Paracetamol for pain relief after surgical removal of lower wisdom teeth	2007	Weil K	Number of people with at least 50% pain relief at 4 hours	dichotomous	Pain relief	Anesthesia	0.35
Single dose oral ketoprofen or dexketoprofen for acute postoperative pain in adults	2017	Gaskell H	Participants with $\geq 50\%$ pain relief over 6 hours	dichotomous	Pain relief	Anesthesia	0.24

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Single dose oral dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain	1999	Moore RA	No. patients experiencing at least 50% pain relief (>50% maxTOTPAR)	dichotomous	Pain relief	Anesthesia	0.68
Single dose oral piroxicam for acute postoperative pain	2000	Moore RA	Participants with at least 50% pain relief	dichotomous	Pain relief	Anesthesia	0.41
Single dose oral rofecoxib for acute postoperative pain in adults	2009	Bulley S	Participants with at least 50% pain relief over 4 to 6 hours	dichotomous	Pain relief	Anesthesia	0.20
Single dose intravenous paracetamol or intravenous propacetamol for postoperative pain	2016	McNicol ED	Number of participants with > 50% pain relief over 4 hours	dichotomous	Pain relief	Anesthesia	0.40
Non-steroidal anti-inflammatory drugs for low back pain	2008	Roelofs PDDM	Change in Pain Intensity from baseline on 100mmVAS	continuous	Pain relief	Anesthesia	0.86
Non-steroidal anti-inflammatory drugs for chronic low back pain	2016	Enthoven WTM	Change in pain intensity from baseline on 100 mm visual analogue scale (VAS)	continuous	Pain relief	Anesthesia	0.41
Analgesia for relief of pain due to uterine cramping/involution after birth	2011	Deussen AR	Pain Reduction	continuous	Pain relief	Anesthesia	0.54
Phlebotonics for venous insufficiency	2016	Martinez-Zapata MJ	Oedema in the lower legs (dichotomous variable)	dichotomous	Cure of condition	Cardiovascular	0.71

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Naftidrofuryl for intermittent claudication	2012	de Backer TLM	Responder rate	dichotomous	Cure of condition	Cardiovascular	0.82
Vitamin E for intermittent claudication	1998	Kleijnen J	Subjective assessment of no change or deterioration after 40 weeks or 8 months	dichotomous	Cure of condition	Cardiovascular	0.59
Blood pressure lowering efficacy of renin inhibitors for primary hypertension	2017	Musini VM	Systolic blood pressure	continuous	Improved biological markers	Cardiovascular	0.70
Rosuvastatin for lowering lipids	2014	Adams SP	Total cholesterol	continuous	Improved biological markers	Cardiovascular	0.12
Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus	2008	Hartweg J	Triglycerides	continuous	Improved biological markers	Cardiovascular	0.09
Blood pressure-lowering efficacy of loop diuretics for primary hypertension	2015	Musini VM	Systolic blood pressure	continuous	Improved biological markers	Cardiovascular	0.41
Long-term effects of weight-reducing drugs in people with hypertension	2016	Siebenhofer A	Change in systolic blood pressure from baseline to endpoint	continuous	Improved biological markers	Cardiovascular	0.74
Blood pressure-lowering efficacy of reserpine for primary hypertension	2016	Shamon SD	Weighted mean change in systolic blood pressure	continuous	Improved biological markers	Cardiovascular	0.39
Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants	2018	Ohlsson A	Failure to close a patent ductus arteriosus (after 3 doses)	dichotomous	Improved internal structure	Cardiovascular	0.75

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Peroxisome proliferator-activated receptor gamma agonists for preventing recurrent stroke and other vascular events in people with stroke or transient ischaemic attack	2019	Liu J	Recurrence of stroke	dichotomous	No major morbidity events	Cardiovascular	0.97
Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery	2019	Felder S	All venous thromboembolism (VTE)	dichotomous	No major morbidity events	Cardiovascular	0.91
Pentasaccharides for the prevention of venous thromboembolism	2016	Dong K	Total venous thromboembolism (VTE)	dichotomous	No major morbidity events	Cardiovascular	0.93
Prevention of infection in arterial reconstruction	2006	Stewart A	Wound infection	dichotomous	No new signs of infection / disease	Cardiovascular	0.88
Buflomedil for intermittent claudication	2013	de Backer TLM	Pain free walking distance	continuous	Pain relief	Cardiovascular	0.70
Phosphodiesterase 5 inhibitors for pulmonary hypertension	2019	Barnes H	Improvement in World Health Organization (WHO) functional class	dichotomous	Quality of Life (QoL) improvement	Cardiovascular	0.95
First-line drugs for hypertension	2018	Wright JM	Total mortality	dichotomous	Survival	Cardiovascular	0.99
Antiplatelet agents for intermittent claudication	2011	Wong PF	All cause mortality	dichotomous	Survival	Cardiovascular	0.98
Adrenaline and vasopressin for cardiac arrest	2019	Finn J	Survival to hospital discharge	dichotomous	Survival	Cardiovascular	0.69
Losigamone add-on therapy for focal epilepsy	2019	Chen H	50% or greater reduction in seizure frequency	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.57
Surgical interventions for lumbar disc prolapse	2007	Gibson JNA	No success at 6 wks - patient rated	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.59

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Vigabatrin for refractory partial epilepsy	2013	Hemming K	50% responders	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.39
Pregabalin add-on for drug-resistant focal epilepsy	2019	Panebianco M	50% or greater reduction in seizure frequency	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.44
Tiagabine add-on therapy for drug-resistant focal epilepsy	2019	Bresnahan R	50% or greater reduction in seizure frequency	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.32
Gabapentin add-on treatment for drug-resistant focal epilepsy	2018	Panebianco M	Reduction in seizure frequency \geq 50%	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.53
Pharmacological interventions for epilepsy in people with intellectual disabilities	2015	Jackson CF	Responder rate (\geq 50% reduction in overall seizure frequency)	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.91
Topiramate add-on therapy for drug-resistant focal epilepsy	2019	Bresnahan R	50% reduction in seizure frequency	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.23
Rufinamide add-on therapy for refractory epilepsy	2018	Panebianco M	50% reduction in seizure frequency	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.56
Lacosamide add-on therapy for partial epilepsy	2015	Weston J	50% reduction in seizure frequency	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.71
Antiepileptic drugs for the treatment of infants with severe myoclonic epilepsy	2017	Brigo F	\geq 50% reduction in seizure frequency	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.10

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Immunosuppressive agents for myasthenia gravis	2007	Hart IK	Improvement or lack of improvement at six months	dichotomous	Cure of condition	Central nervous system/ musculoskeletal	0.41
Iron for the treatment of restless legs syndrome	2019	Trotti LM	Change in IRLS severity scale score	continuous	Cure of condition	Central nervous system/ musculoskeletal	0.47
Strontium ranelate for preventing and treating postmenopausal osteoporosis	2006	O'Donnell S	Vertebral fractures	dichotomous	Improved internal structure	Central nervous system/ musculoskeletal	0.97
Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women	2008	Wells GA	Vertebral Fractures	dichotomous	Improved internal structure	Central nervous system/ musculoskeletal	0.95
Huperzine A for Alzheimer's disease	2008	Li J	The change of general cognitive function measured by MMSE	continuous	Mental health outcome improvement	Central nervous system/ musculoskeletal	0.03
Rofecoxib for osteoarthritis	2005	Garner SE	Adverse events	dichotomous	No adverse events	Central nervous system/ musculoskeletal	0.87
Gamma aminobutyric acid (GABA) modulators for amyotrophic lateral sclerosis/motor neuron disease	2017	Diana A	Adverse events	dichotomous	No adverse events	Central nervous system/ musculoskeletal	0.36
Interferon in relapsing-remitting multiple sclerosis	2001	Rice GPA	Patients with at least one exacerbation until 1 yr	dichotomous	No major morbidity events	Central nervous system/ musculoskeletal	0.63
Dimethyl fumarate for multiple sclerosis	2015	Xu Z	The proportion of patients with at least one relapse at two years	dichotomous	No major morbidity events	Central nervous system/ musculoskeletal	0.75

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Antibiotics for preventing infection in open limb fractures	2004	Gosselin RA	Early wound infection	dichotomous	No new signs of infection / disease	Central nervous system/ musculoskeletal	0.93
Leflunomide for the treatment of rheumatoid arthritis	2002	Osiri M	Treatment responder - The American College of Rheumatology (ACR) 20	dichotomous	No unpleasant composite endpoint	Central nervous system/ musculoskeletal	0.84
Celecoxib for rheumatoid arthritis	2017	Fidahic M	Clinical improvement: American College of Rheumatology 20% improvement criteria (ACR20)	dichotomous	No unpleasant composite endpoint	Central nervous system/ musculoskeletal	0.65
Photodynamic therapy for neovascular age-related macular degeneration	2007	Wormald R	Loss of 3 or more lines (15 or more letters) visual acuity at 12 months	dichotomous	Others (Semi-objective)	Central nervous system/ musculoskeletal	0.83
Scopolamine (hyoscine) for preventing and treating motion sickness	2011	Spinks A	Prevention of sickness symptoms (nausea)	dichotomous	Others (Subjective)	Central nervous system/ musculoskeletal	0.05
Botulinum toxin type A therapy for hemifacial spasm	2005	Costa J	Improvement	dichotomous	Others (Subjective)	Central nervous system/ musculoskeletal	0.07
Ketoprofen for episodic tension-type headache in adults	2016	Veys L	Pain-free at 2 hours	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.59
Sumatriptan (subcutaneous route of administration) for acute migraine attacks in adults	2012	Derry CJ	Pain-free at 2 h	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.21

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Ibuprofen with or without an antiemetic for acute migraine headaches in adults	2013	Rabbie R	Pain-free at 2 hours.	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.51
Drugs for the acute treatment of migraine in children and adolescents	2016	Richer L	Pain-free	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.53
Aspirin for acute treatment of episodic tension-type headache in adults	2017	Derry S	Participants using rescue medication	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.81
Naproxen with or without an antiemetic for acute migraine headaches in adults	2013	Law S	Pain-free response at two hours	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.49
Sumatriptan (intranasal route of administration) for acute migraine attacks in adults	2012	Derry CJ	Headache relief at 1 h	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.71
Aspirin with or without an antiemetic for acute migraine headaches in adults	2013	Kirithi V	Pain free at 2 hours	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.48
Sumatriptan plus naproxen for the treatment of acute migraine attacks in adults	2016	Law S	Pain-free at two hours	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.36
Zolmitriptan for acute migraine attacks in adults	2014	Bird S	Pain-free at 2 h	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.36
Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults	2013	Derry S	Pain-free at 2 hours	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.56
Ibuprofen for acute treatment of episodic tension-type headache in adults	2015	Derry S	Pain-free at 2 hours	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.66
Diclofenac with or without an antiemetic for acute migraine headaches in adults	2013	Derry S	Pain-free at 2 hours	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.50

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults	2013	Linde M	Responders (patients with \geq 50% reduction in headache frequency)	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.85
Zonisamide add-on therapy for focal epilepsy	2018	Brigo F	50% responder rate - whole treatment period	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.54
Paracetamol (acetaminophen) for acute treatment of episodic tension-type headache in adults	2016	Stephens G	Pain-free at 2 hours	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.79
Sumatriptan (oral route of administration) for acute migraine attacks in adults	2012	Derry CJ	Pain-free at 2 h	dichotomous	Pain relief	Central nervous system/ musculoskeletal	0.38
Electromagnetic fields for treating osteoarthritis	2013	Li S	Pain	continuous	Pain relief	Central nervous system/ musculoskeletal	0.56
Celecoxib for osteoarthritis	2017	Puljak L	Pain	continuous	Pain relief	Central nervous system/ musculoskeletal	0.83
Paracetamol versus placebo for knee and hip osteoarthritis	2019	Leopoldino AO	Pain	continuous	Pain relief	Central nervous system/ musculoskeletal	0.83
Corticosteroids or ACTH for acute exacerbations in multiple sclerosis	2000	Citterio A	Worse or unimproved within 5 weeks from randomisation	dichotomous	Quality of Life (QoL) improvement	Central nervous system/ musculoskeletal	0.62

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Pyridoxal 5 phosphate for neuroleptic-induced tardive dyskinesia	2015	Adelufosi AO	Global: Clinical efficacy - significant reduction in Extrapyramidal Symptoms Rating Scale (ESRS) scores from baseline	dichotomous	Quality of Life (QoL) improvement	Central nervous system/ musculoskeletal	0.05
Endothelin receptor antagonists for subarachnoid hemorrhage	2012	Guo J	The development of Delayed ischemic neurological deficit (DIND)	dichotomous	Quality of Life (QoL) improvement	Central nervous system/ musculoskeletal	0.94
Edaravone for acute ischaemic stroke	2011	Feng S	Improvement of neurological deficit at the end of treatment	dichotomous	Quality of Life (QoL) improvement	Central nervous system/ musculoskeletal	0.50
Methotrexate for treating juvenile idiopathic arthritis	2001	Takken T	Improvement in limited joint range score	continuous	Quality of Life (QoL) improvement	Central nervous system/ musculoskeletal	0.48
Nimodipine for primary degenerative, mixed and vascular dementia	2002	Birks J	The Sandoz Clinical Assessment Geriatric Scale (SCAG) score	continuous	Quality of Life (QoL) improvement	Central nervous system/ musculoskeletal	0.21
Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)	2012	Miller RG	Percent mortality at 12 months	dichotomous	Survival	Central nervous system/ musculoskeletal	0.85
Adalimumab for induction of remission in Crohn's disease	2019	Abbass M	Failure to achieve clinical remission at 4 weeks:	dichotomous	Cure of condition	Digestive system	0.39

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn's disease	2014	Lev-Tzion R	Relapse rate at one year	dichotomous	Cure of condition	Digestive system	0.83
Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease	2008	Behm BW	Clinical Remission	dichotomous	Cure of condition	Digestive system	0.40
Non surgical therapy for anal fissure	2012	Nelson RL	Non-healing of fissure (persistence or recurrence)	dichotomous	Cure of condition	Digestive system	0.58
Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis	2016	Wang Y	Failure to Induce global / clinical remission	dichotomous	Cure of condition	Digestive system	0.59
Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis	2016	Wang Y	Failure to Maintain Clinical or Endoscopic Remission	dichotomous	Cure of condition	Digestive system	0.70
Budesonide for maintenance of remission in Crohn's disease	2014	Kuenzig ME	Maintenance of clinical remission	dichotomous	Cure of condition	Digestive system	0.80
Vedolizumab for induction and maintenance of remission in ulcerative colitis	2014	Bickston SJ	Failure to induce clinical remission	dichotomous	Cure of condition	Digestive system	0.40
Mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care	2018	Candy B	Rescue-free laxation within 24 hours of dose	dichotomous	Cure of condition	Digestive system	0.36
Prokinetics for functional dyspepsia	2018	Pittayanon R	Not symptom-free or no symptom improvement	dichotomous	Cure of condition	Digestive system	0.65

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-esophageal reflux disease-like symptoms and endoscopy negative reflux disease	2013	Sigterman KE	Heartburn remission	dichotomous	Cure of condition	Digestive system	0.35
Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease	2015	Chande N	Maintenance of remission	dichotomous	Cure of condition	Digestive system	0.80
Anti-tuberculous therapy for maintenance of remission in Crohn's disease	2016	Patton PH	Relapse	dichotomous	Cure of condition	Digestive system	0.54
Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis	2006	Lawson MM	Clinical remission at 8 weeks	dichotomous	Cure of condition	Digestive system	0.31
Azathioprine and 6-mercaptopurine for maintenance of surgically-induced remission in Crohn's disease	2019	Gjuladin-Hellon T	Clinical relapse at 12 to 36 months	dichotomous	Cure of condition	Digestive system	0.73
Antibiotics for induction and maintenance of remission in Crohn's disease	2019	Townsend CM	Failure to enter clinical remission at week 10 or 12	dichotomous	Cure of condition	Digestive system	0.47
Oral budesonide for induction of remission in ulcerative colitis	2015	Sherlock ME	Remission (combined clinical and endoscopic remission)	dichotomous	Cure of condition	Digestive system	0.44
Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis	2012	Marshall JK	Symptomatic remission	dichotomous	Cure of condition	Digestive system	0.45
Certolizumab pegol for induction of remission in Crohn's disease	2019	Yamazaki H	Clinical remission at week 8	dichotomous	Cure of condition	Digestive system	0.74

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Traditional corticosteroids for induction of remission in Crohn's disease	2008	Benchimol EI	Remission rate (Late, 15+ weeks)	dichotomous	Cure of condition	Digestive system	0.50
Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents	2011	Fedorowicz Z	Rate of admission to hospital (during ED stay)	dichotomous	Less resource use / Shorter hospital stay	Digestive system	0.94
Probiotics for the prevention of pediatric antibiotic-associated diarrhea	2019	Guo Q	Incidence of diarrhea	dichotomous	No major morbidity events	Digestive system	0.90
Arginine supplementation for prevention of necrotising enterocolitis in preterm infants	2017	Shah PS	Necrotising enterocolitis(N EC) any stage	dichotomous	No major morbidity events	Digestive system	0.79
Antibiotics versus placebo for prevention of postoperative infection after appendicectomy.	2005	Andersen BR	Wound infection	dichotomous	No new signs of infection / disease	Digestive system	0.90
Non-Steroid anti-inflammatory drugs for biliary colic	2016	Fraquelli M	Lack of pain relief	dichotomous	Pain relief	Digestive system	0.27
Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis	2010	Marshall JK	Symptomatic Improvement	dichotomous	Quality of Life (QoL) improvement	Digestive system	0.75
Tegaserod for the treatment of irritable bowel syndrome and chronic constipation	2007	Evans BW	Subjects Global Assessment (SGA) of relief at endpoint	dichotomous	Quality of Life (QoL) improvement	Digestive system	0.84
Tranexamic acid for upper gastrointestinal bleeding	2014	Bennett C	Mortality	dichotomous	Survival	Digestive system	0.96
Vaccines for preventing rotavirus diarrhoea: vaccines in use	2019	Soares-Weiser K	Rotavirus diarrhoea: severe (up to 1 year follow-up)	dichotomous	Cure of condition	Infectious disease	0.99
Antibiotic treatment for travellers' diarrhoea	2000	de Bruyn G	Number cured at 72 hours	dichotomous	Cure of condition	Infectious disease	0.58

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Antibiotics for acute rhinosinusitis in adults	2018	Lemiengre MB	Cure in adults with clinically diagnosed acute rhinosinusitis	dichotomous	Cure of condition	Infectious disease	0.86
Antibiotics versus placebo for acute bacterial conjunctivitis	2012	Sheikh A	Clinical remission (early)	dichotomous	Cure of condition	Infectious disease	0.74
Topical antifungal treatments for tinea cruris and tinea corporis	2014	El-Gohary M	Mycological cure	dichotomous	Cure of condition	Infectious disease	0.35
Hepatitis B vaccination for patients with chronic renal failure	2004	Schroth RJ	Seroconversion to anti-Hepatitis B (HB)s	dichotomous	Improved biological markers	Infectious disease	0.04
Drugs for treating <i>Schistosoma mansoni</i> infection	2013	Danso-Appiah A	Parasitological failure at one month	dichotomous	Improved biological markers	Infectious disease	0.32
Interventions for treating genital <i>Chlamydia trachomatis</i> infection in pregnancy	2017	Cluver C	Microbiological cure	dichotomous	Improved biological markers	Infectious disease	0.38
Topical treatments for fungal infections of the skin and nails of the foot.	2007	Crawford F	Short term (2 weeks) treatment failure	dichotomous	Improved external structure	Infectious disease	0.47
Imiquimod for anogenital warts in non-immunocompromised adults	2014	Grillo-Ardila CF	Complete regression after treatment	dichotomous	Improved external structure	Infectious disease	0.25
Vaccines for preventing hepatitis B in health-care workers	2005	Chen W	Hepatitis B events at maximum follow-up	dichotomous	No major morbidity events	Infectious disease	0.97
Prophylactic antibiotics for preventing pneumococcal infection in children with sickle cell disease	2017	Rankine-Mullings AE	Incidence of pneumococcal infection, for initiation or withdrawal of treatment.	dichotomous	No new signs of infection / disease	Infectious disease	0.94

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Vaccines for preventing cholera: killed whole cell or other subunit vaccines (injected)	2010	Graves PM	Cholera cases	dichotomous	No new signs of infection / disease	Infectious disease	1.00
Drugs for treating urinary schistosomiasis	2014	Kramer CV	Parasitological failure	dichotomous	No new signs of infection / disease	Infectious disease	0.15
Interventions for the prevention and treatment of herpes simplex virus in patients being treated for cancer	2009	Glenny AM	The herpes simplex virus (HSV) oral lesions (by mode of administration)	dichotomous	No new signs of infection / disease	Infectious disease	0.58
Vaccines for preventing influenza in healthy children	2018	Jefferson T	Influenza	dichotomous	No new signs of infection / disease	Infectious disease	0.83
Isoniazid for preventing tuberculosis in non-HIV infected persons	1999	Smieja M	Active tuberculosis	dichotomous	No new signs of infection / disease	Infectious disease	0.99
Amantadine and rimantadine for influenza A in adults	2006	Jefferson T	Influenza cases	dichotomous	No new signs of infection / disease	Infectious disease	0.92
Mefloquine for preventing malaria during travel to endemic areas	2017	Tickell-Painter M	Clinical cases of malaria	dichotomous	No new signs of infection / disease	Infectious disease	0.81
Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children	2013	Andabaka T	Hospitalisation for RS virus (RSV) infection	dichotomous	No new signs of infection / disease	Infectious disease	0.95
Treatment of latent tuberculosis infection in HIV infected persons	2010	Akolo C	Incidence of active tuberculosis (TB)	dichotomous	No new signs of infection / disease	Infectious disease	0.98
Oral antiviral therapy for prevention of genital herpes outbreaks in immunocompetent and nonpregnant patients	2014	Le Cleach L	Participants with at least 1 clinical recurrence	dichotomous	No new signs of infection / disease	Infectious disease	0.08

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Anabolic steroids for the treatment of weight loss in HIV-infected individuals	2005	Johns KKJ	Change from baseline in lean body mass	continuous	Others (Semi-objective)	Infectious disease	0.27
Corticosteroids as standalone or add-on treatment for sore throat	2012	Hayward G	Complete resolution of pain at 24 hours	dichotomous	Pain relief	Infectious disease	0.32
Topical analgesia for acute otitis media	2006	Foxlee R	50% reduction in ear pain	dichotomous	Pain relief	Infectious disease	0.47
Antihistamines for the common cold	2015	De Sutter AI	Change in severity of overall symptoms	dichotomous	Quality of Life (QoL) improvement	Infectious disease	0.84
Micronutrient supplementation for children with HIV infection	2013	Irlam JH	All-cause mortality	dichotomous	Survival	Infectious disease	0.78
Interventions to reduce harm from continued tobacco use	2016	Lindson-Hawley N	Reduction in cigarettes/day of > 50% of baseline or cessation	dichotomous	Cure of condition	Mental health and behavioral conditions	0.57
Interventions for smoking cessation and reduction in individuals with schizophrenia	2013	Tsoi DT	Abstinence at 6-month follow-up	dichotomous	Cure of condition	Mental health and behavioral conditions	0.36
Pharmacological interventions for clozapine-induced hypersalivation	2008	Syed R	No Effect / not cured / not markedly improved	dichotomous	Cure of condition	Mental health and behavioral conditions	0.22
Clonidine for smoking cessation	2004	Gourlay SG	Smoking Cessation	dichotomous	Cure of condition	Mental health and behavioral conditions	0.61
Megestrol acetate for treatment of anorexia-cachexia syndrome	2013	Ruiz Garcia V	Appetite improvement	dichotomous	Cure of condition	Mental health and behavioral conditions	0.46

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Nicotine receptor partial agonists for smoking cessation	2016	Cahill K	Continuous/sustained abstinence at longest follow-up (24+ weeks)	dichotomous	Cure of condition	Mental health and behavioral conditions	0.94
Opioid antagonists for alcohol dependence	2010	Rösner S	Return to heavy drinking	dichotomous	Cure of condition	Mental health and behavioral conditions	0.79
Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder	2013	Cipriani A	Study withdrawal due to episode of mood disorder.	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.82
Oral paliperidone for schizophrenia	2008	Nussbaum AM	Leaving the study early	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.79
Quetiapine for schizophrenia	2004	Srisurapanont M	Leaving the study early	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.80
Treatment for amphetamine withdrawal	2009	Shoptaw SJ	Discontinuation rates	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.77
Antipsychotic medications for cocaine dependence	2016	Indave BI	Dropouts	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.77
Haloperidol alone or in combination for acute mania	2006	Cipriani A	Failure to complete treatment - total dropouts	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.90
Depot haloperidol decanoate for schizophrenia	1999	Quraishi SN	Not completing the study	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.31
Azapirones versus placebo for panic disorder in adults	2014	Imai H	Dropouts for any reason	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.47

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Paliperidone palmitate for schizophrenia	2012	Nussbaum AM	Leaving the study early	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.82
Antipsychotic medication for early episode schizophrenia	2011	Bola JR	Leaving the study early	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.63
Amisulpride for schizophrenia	2002	Silveira da Mota Neto JI	Leaving the study early - overall	dichotomous	Less drop-out from the treatment	Mental health and behavioral conditions	0.73
Aripiprazole (intramuscular) for psychosis-induced aggression or agitation (rapid tranquillisation)	2018	Ostinelli EG	Repeated need for tranquillisation	dichotomous	Less resource use / Shorter hospital stay	Mental health and behavioral conditions	0.69
Pharmacotherapy for anxiety disorders in children and adolescents	2009	Ipser JC	Clinical Global Impressions scale - Improvement item (CGI-I)	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.49
Thioridazine for schizophrenia	2007	Fenton M	Global state: no change or worse	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.64
Lithium for maintenance treatment of mood disorders	2001	Burgess SSA	All relapses	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.56
Olanzapine for schizophrenia	2005	Duggan L	Global effect: no important clinical response - by 6 weeks	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.68
Antidepressants versus placebo for panic disorder in adults	2018	Bighelli I	Failure to respond	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.74
Amitriptyline versus placebo for major depressive disorder	2012	Leucht C	Response	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.81

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Tryptophan and 5-Hydroxytryptophan for depression	2002	Shaw KA	Numbers of responders	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.81
Risperidone versus placebo for schizophrenia	2016	Ratthalli RD	Mental state: no clinically significant response in psychotic symptoms (defined by various scale total score change) - short term (up to 12 weeks)	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.55
Penfluridol for schizophrenia	2006	Soares BGO	No marked improvement	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.41
Interventions for preventing relapse and recurrence of a depressive disorder in children and adolescents	2012	Cox GR	Number relapsed	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.56
Vortioxetine for depression in adults	2017	Koesters M	Response	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.74
Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults	2015	McCloud TL	Response rate	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.09
St John's wort for major depression	2008	Linde K	Responder	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.68
Comparative effectiveness of continuation and maintenance treatments for persistent depressive disorder in adults	2019	Machmutow K	Relapse/recurrence	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.77

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Valproate for acute mania	2019	Jochim J	Response rate (adults)	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.85
Lithium for acute mania	2019	McKnight RF	The Young Mania Rating Scale (YMRS) decrease by =>50% at end of trial	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.82
Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders	2006	Ipser JC	Clinical Global Impression (CGI-I) scale response	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.32
Risperidone for autism spectrum disorder	2007	Jesner OS	Number of participants improved/very much improved	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.21
Antidepressant treatment for postnatal depression	2014	Molyneaux E	Response rate at post-treatment	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.70
Trifluoperazine versus placebo for schizophrenia	2014	Koch K	Global state - clinical improvement	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.16
Antidepressants versus placebo for people with bulimia nervosa	2003	Bacaltchuk J	Remission	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.43
Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD)	2013	Williams K	Proportion improved for Clinical Global Impression Improvement (CGI-I)	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.08
Tricyclic antidepressants for attention deficit hyperactivity disorder (ADHD) in children and adolescents	2014	Otasowie J	Clinical Global Impression (CGI) (response rate)	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.92

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Second-generation antidepressants for preventing seasonal affective disorder in adults	2019	Gartlehner G	Onset of major depressive episode	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.87
Pharmacotherapy for anxiety and comorbid alcohol use disorders	2015	Ipser JC	Treatment response	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.45
Polyunsaturated fatty acids (PUFA) for attention deficit hyperactivity disorder (ADHD) in children and adolescents	2012	Gillies D	Improvement in in attention deficit hyperactivity disorder (ADHD) symptoms	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.46
Benzodiazepines versus placebo for panic disorder in adults	2019	Breilmann J	Treatment response	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.61
Antidepressants for depression in physically ill people	2010	Rayner L	Response to treatment (4-5 weeks)	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.81
Ziprasidone for schizophrenia and severe mental illness	2000	Bagnall AM	No response (The Clinical Global Impression Improvement: C GI-I score >2 at last observation)	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.65
Antidepressants versus placebo for the depressed elderly	2001	Wilson K	Recovered	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.49
Hydroxyzine for generalised anxiety disorder	2010	Guaiana G	Number of patients who did not show a response	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.57

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Ketamine and other glutamate receptor modulators for depression in adults	2015	Caddy C	Response rate	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.97
Trifluoperazine for schizophrenia	2004	Marques LDO	No substantial improvement (defined as slight improvement or worse)	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.09
Haloperidol versus placebo for schizophrenia	2013	Adams CE	No marked global improvement	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.63
Second-generation antipsychotics for anxiety disorders	2010	Depping AM	Response - as defined by original studies	dichotomous	Mental health outcome improvement	Mental health and behavioral conditions	0.45
Donepezil for vascular cognitive impairment	2004	Malouf R	The cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) completers	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.27
Olanzapine alone or in combination for acute mania	2003	Rendell JM	Mean change in Young Mania Rating Scale (YMRS)	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.59
Atypical antipsychotics for disruptive behaviour disorders in children and youths	2017	Loy JH	Aggression: the Aberrant Behaviour Checklist (ABC) irritability	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.35
Active placebos versus antidepressants for depression	2004	Moncrieff J	Change in mood after treatment period	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.86

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Antidepressants for depression in adults with HIV infection	2018	Eshun-Wilson I	The Hamilton Depression Rating Scale (HAM-D) score	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.54
Pharmacological interventions for apathy in Alzheimer's disease	2018	Ruthirakuhan MT	Change in apathy from baseline as measured by the apathy evaluation scale (AES)	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.14
Risperidone alone or in combination for acute mania	2006	Rendell JM	Mean change in Young Mania Rating Scale (YMRS) - all participants	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.57
Nicergoline for dementia and other age associated forms of cognitive impairment	2001	Fioravanti M	The Sandoz Clinical Assessment Geriatric Scale (SCAG) total scores	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.53
Aripiprazole for autism spectrum disorders (ASD)	2016	Hirsch LE	Aberrant Behavior Checklist (ABC) - Irritability subscale	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.51
Kava extract versus placebo for treating anxiety	2003	Pittler MH	Improvement of the Hamilton Anxiety (HAM-A) score	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.71
Aripiprazole alone or in combination for acute mania	2013	Brown R	Young Mania Rating Scale	continuous	Mental health outcome improvement	Mental health and behavioral conditions	0.70

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Benzodiazepines for alcohol withdrawal	2010	Amato L	Alcohol withdrawal seizures	dichotomous	No major morbidity events	Mental health and behavioral conditions	0.93
Hydergine for dementia	2000	Schneider L	Patient status	dichotomous	Quality of Life (QoL) improvement	Mental health and behavioral conditions	0.29
Pharmacological interventions for sleepiness and sleep disturbances caused by shift work	2014	Liira J	Total sleep time	continuous	Quality of Life (QoL) improvement	Mental health and behavioral conditions	0.92
Progesterone receptor modulators for endometriosis	2017	Fu J	Dysmenorrhoea at three months	dichotomous	Cure of condition	Obstetrics and gynecology	0.66
The effects of antimicrobial therapy on bacterial vaginosis in non-pregnant women	2009	Oduyebo OO	Clinical failure	dichotomous	Cure of condition	Obstetrics and gynecology	0.55
Bioidentical hormones for women with vasomotor symptoms	2016	Gaudard AMIS	Frequency of hot flushes	continuous	Cure of condition	Obstetrics and gynecology	0.54
Medical interventions for high-grade vulval intraepithelial neoplasia	2015	Pepas L	Response to treatment at 5-6 months	dichotomous	Improved external structure	Obstetrics and gynecology	0.08
Combined oral contraceptive pills for treatment of acne	2012	Arowojolu AO	Mean change in total lesion count	continuous	Improved external structure	Obstetrics and gynecology	0.52
Interventions for helping to turn term breech babies to head first presentation when using external cephalic version	2015	Cluver C	Cephalic presentation at birth	dichotomous	Improved obstetric outcomes	Obstetrics and gynecology	0.60
Prophylactic oral betamimetics for reducing preterm birth in women with a twin pregnancy	2015	Yamasmit W	Preterm labour	dichotomous	Improved obstetric outcomes	Obstetrics and gynecology	0.88
Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth	2013	Dodd JM	Perinatal mortality	dichotomous	Improved obstetric outcomes	Obstetrics and gynecology	0.95

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Treatment of vaginal bleeding irregularities induced by progestin only contraceptives	2013	Abdel-Aleem H	Continued irregular bleeding during treatment	dichotomous	Improved obstetric outcomes	Obstetrics and gynecology	0.38
Metformin during ovulation induction with gonadotrophins followed by timed intercourse or intrauterine insemination for subfertility associated with polycystic ovary syndrome	2017	Bordewijk EM	Live birth rate (per woman)	dichotomous	Improved obstetric outcomes	Obstetrics and gynecology	0.85
Combined hormonal contraceptives for heavy menstrual bleeding	2019	Lethaby A	Response to treatment	dichotomous	Improved obstetric outcomes	Obstetrics and gynecology	0.97
Medical treatment for early fetal death (less than 24 weeks)	2019	Lemmers M	Complete miscarriage	dichotomous	Improved obstetric outcomes	Obstetrics and gynecology	0.24
Betamimetics for inhibiting preterm labour	2014	Neilson JP	Birth within 48 hours of treatment	dichotomous	Improved obstetric outcomes	Obstetrics and gynecology	0.83
Progestational agents for treating threatened or established preterm labour	2014	Su LL	Preterm delivery	dichotomous	Improved obstetric outcomes	Obstetrics and gynecology	0.70
Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems	2018	Hofmeyr GJ	High blood pressure (with or without proteinuria)	dichotomous	No major morbidity events	Obstetrics and gynecology	0.92
Antibiotic prophylaxis for elective hysterectomy	2017	Ayeleke RO	Total postoperative infections - early and late	dichotomous	No new signs of infection / disease	Obstetrics and gynecology	0.46
Transcutaneous electrical nerve stimulation for primary dysmenorrhoea	2002	Proctor M	Pain relief - overall experience	dichotomous	Pain relief	Obstetrics and gynecology	0.14
Oral contraceptive pill for primary dysmenorrhoea	2009	Wong CL	Pain improvement	dichotomous	Pain relief	Obstetrics and gynecology	0.87

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Brivaracetam add-on therapy for drug-resistant epilepsy	2019	Bresnahan R	50% or greater reduction in seizure frequency (responder rate)	dichotomous	Cure of condition	Others	0.55
Medical and surgical interventions for the treatment of usual-type vulval intraepithelial neoplasia	2016	Lawrie TA	Response to treatment at 5 to 6 months	dichotomous	Cure of condition	Others	0.08
Ketanserin for Raynaud's phenomenon in progressive systemic sclerosis	1998	Pope J	Number of patients who improved	dichotomous	Cure of condition	Others	0.81
Local corticosteroid injection for carpal tunnel syndrome	2007	Marshall SC	Clinical improvement	dichotomous	Cure of condition	Others	0.39
Corticosteroids for the treatment of idiopathic acute vestibular dysfunction (vestibular neuritis)	2011	Fishman JM	Complete caloric recovery at 1 month	dichotomous	Cure of condition	Others	0.36
Antibiotics for sore throat	2013	Spinks A	Symptom of sore throat on day 3	dichotomous	Cure of condition	Others	0.61
Interventions for impetigo	2012	Koning S	Cure/improvement	dichotomous	Cure of condition	Others	0.45
Natalizumab for induction of remission in Crohn's disease	2018	Nelson SML	Failure to induce remission at 2 weeks	dichotomous	Cure of condition	Others	0.64
Cannabinoid type 1 receptor antagonists for smoking cessation	2011	Cahill K	Prolonged abstinence at wk 50	dichotomous	Cure of condition	Others	0.67
Chinese herbal medicines for type 2 diabetes mellitus	2002	Liu JP	Normalisation of fasting blood glucose (< 7.2 mmol/L)	dichotomous	Improved biological markers	Others	0.49

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Chinese herbal medicine for atopic eczema	2013	Gu S	Total effectiveness rate (number of participants recovered and significantly improved)	dichotomous	Improved external structure	Others	0.48
Rapamycin and rapalogs for tuberous sclerosis complex	2016	Sasongko TH	Response to tumour size	dichotomous	Improved internal structure	Others	0.04
Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women	2008	Wells GA	Vertebral Fractures	dichotomous	Improved internal structure	Others	0.97
Interventions for restoring patency of occluded central venous catheter lumens	2012	van Miert C	Restored patency of central venous catheter (CVC) following one or two installations of study drug	dichotomous	Less resource use / Shorter hospital stay	Others	0.48
Steroids for improving recovery following tonsillectomy in children	2011	Steward DL	Emesis	dichotomous	No adverse events	Others	0.75
Intravenous dexamethasone for extubation of newborn infants	2001	Davis PG	Endotracheal reintubation	dichotomous	No major morbidity events	Others	0.92
Local interventions for the management of alveolar osteitis (dry socket)	2012	Daly B	Presence of dry socket	dichotomous	No major morbidity events	Others	0.86
Interventions for preventing high altitude illness: Part 1. Commonly-used classes of drugs	2017	Nieto Estrada VH	Incidence of acute mountain sickness	dichotomous	No major morbidity events	Others	0.86
Anakinra for rheumatoid arthritis	2009	Mertens M	American College of Rheumatology (ACR) 20	dichotomous	No unpleasant composite endpoint	Others	0.72

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Chromium picolinate supplementation for overweight or obese adults	2013	Tian H	Change in weight at 12-16 weeks	continuous	Others (Semi-objective)	Others	0.38
Rimonabant for overweight or obesity	2006	Curioni C	Weight change	continuous	Others (Semi-objective)	Others	0.33
Dexamethasone as an adjuvant to peripheral nerve block	2017	Pehora C	Duration of sensory block	continuous	Others (Semi-objective)	Others	0.73
Long-term pharmacotherapy for obesity and overweight	2003	Padwal RS	Change in Weight	continuous	Others (Semi-objective)	Others	0.59
Amitriptyline for fibromyalgia in adults	2015	Moore RA	Third-tier efficacy	dichotomous	Pain relief	Others	0.35
Bisphosphonates for Paget's disease of bone in adults	2017	Corral-Gudino L	Number of participants whose bone pain disappeared completely	dichotomous	Pain relief	Others	0.29
Hyaluronic acid and other conservative treatment options for osteoarthritis of the ankle	2015	Witteveen AGH	The Ankle Osteoarthritis Scale (AOS) total (combined pain and function score) at 6months	continuous	Pain relief	Others	0.54
Acetyl-L-carnitine for the treatment of diabetic peripheral neuropathy	2019	Rolim LCSP	Pain at 6 to 12 months' follow-up	continuous	Pain relief	Others	0.57
Spirolactone versus placebo or in combination with steroids for hirsutism and/or acne	2009	Brown J	Subjective improvement in hair growth	dichotomous	Quality of Life (QoL) improvement	Others	0.88

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Betahistine for symptoms of vertigo	2016	Murdin L	Proportion of patients with improvement according to global judgement of patient	dichotomous	Quality of Life (QoL) improvement	Others	0.77
Interventions for treating sexual dysfunction in patients with chronic kidney disease	2010	Vecchio M	Sexual function using the overall International Index of Erectile Function-5 (IIEF-5)	continuous	Quality of Life (QoL) improvement	Others	0.56
Terlipressin for acute esophageal variceal hemorrhage	2003	Ioannou GN	Mortality	dichotomous	Survival	Others	0.84
Corticosteroids for preventing relapse following acute exacerbations of asthma	2007	Rowe BH	Relapse rates	dichotomous	Cure of condition	Respiratory disease	0.88
Umeclidinium bromide versus placebo for people with chronic obstructive pulmonary disease (COPD)	2017	Ni H	Number of participants with exacerbations requiring steroids, antibiotics, or both	dichotomous	Cure of condition	Respiratory disease	0.94
Antibiotics for acute bronchitis	2017	Smith SM	Number of participants with cough	dichotomous	Cure of condition	Respiratory disease	0.73
Pelargonium sidoides extract for treating acute respiratory tract infections	2013	Timmer A	Failure to recover by day seven (complete resolution of all symptoms)	dichotomous	Cure of condition	Respiratory disease	0.13

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Tiotropium for stable chronic obstructive pulmonary disease	2005	Barr RG	Exacerbations	dichotomous	Cure of condition	Respiratory disease	0.92
Intranasal steroids for acute sinusitis	2013	Zalmanovici Trestioreanu A	Proportion of participants with resolution of symptoms or improved	dichotomous	Cure of condition	Respiratory disease	0.91
Macrolide antibiotics for bronchiectasis	2018	Kelly C	≥ 1 exacerbation	dichotomous	Cure of condition	Respiratory disease	0.53
Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children	2010	Ducharme FM	Patients with exacerbations requiring oral steroids	dichotomous	Cure of condition	Respiratory disease	0.96
Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease	2019	Poole P	Participants with no exacerbations in study period	dichotomous	Cure of condition	Respiratory disease	0.84
Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)	2018	Herath SC	Number of people with one or more exacerbations	dichotomous	Cure of condition	Respiratory disease	0.74
Glucocorticoids for croup in children	2018	Gates A	Croup score	continuous	Cure of condition	Respiratory disease	0.43
Beclomethasone versus placebo for chronic asthma	2005	Adams NP	forced expiratory volume in one second (FEV1) (L) and FEV1 (% predicted)	continuous	Improved internal structure	Respiratory disease	0.76
Ketotifen alone or as additional medication for long-term control of asthma and wheeze in children	2004	Bassler D	Reduction of bronchodilator use	dichotomous	Less consumption / Satisfaction with care	Respiratory disease	0.42

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Epinephrine for bronchiolitis	2011	Hartling L	Admissions at enrollment or < 24 hours (outpatients only)	dichotomous	Less resource use / Shorter hospital stay	Respiratory disease	0.93
Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease	2014	Walters JAE	Need to intensify therapy/ emergency department (ED) or hospital admission Follow-up: 3-30 days	dichotomous	Less resource use / Shorter hospital stay	Respiratory disease	0.84
Magnesium sulfate for treating exacerbations of acute asthma in the emergency department	2000	Rowe BH	Admission to hospital	dichotomous	Less resource use / Shorter hospital stay	Respiratory disease	0.72
Early emergency department treatment of acute asthma with systemic corticosteroids	2001	Rowe BH	Admitted to hospital (all times)	dichotomous	Less resource use / Shorter hospital stay	Respiratory disease	0.75
Intravenous magnesium sulfate for treating children with acute asthma in the emergency department	2016	Griffiths B	Hospital admissions	dichotomous	Less resource use / Shorter hospital stay	Respiratory disease	0.48
Corticosteroids for hospitalised children with acute asthma	2003	Smith M	Discharge at first re-examination (4h)	dichotomous	Less resource use / Shorter hospital stay	Respiratory disease	0.94
Probiotics for preventing acute upper respiratory tract infections	2015	Hao Q	The number of participants who experienced upper respiratory tract infections (URTI) episodes: at least 1 event	dichotomous	No new signs of infection / disease	Respiratory disease	0.86

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Antibiotics for exacerbations of chronic obstructive pulmonary disease	2018	Vollenweider DJ	Treatment failure up to 4 weeks	dichotomous	No unpleasant composite endpoint	Respiratory disease	0.89
Nebulized epinephrine for croup in children	2013	Bjornson C	Croup score (change baseline - 30 minutes)	continuous	Others (Semi-objective)	Respiratory disease	0.45
5-FU for genital warts in non-immunocompromised individuals	2010	Batista CS	Cure	dichotomous	Cure of condition	Urogenital	0.85
Topical corticosteroids for treating phimosis in boys	2014	Moreno G	Resolution of phimosis (complete or partial)	dichotomous	Cure of condition	Urogenital	0.41
Prostaglandin E1 for treatment of erectile dysfunction	2004	Urciuoli R	At least one success	dichotomous	Cure of condition	Urogenital	0.85
Sildenafil for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia	2017	Jung JH	Urologic symptom scores (short term)	continuous	Cure of condition	Urogenital	0.63
Botulinum toxin injections for adults with overactive bladder syndrome	2011	Duthie JB	Change in post void residual volume (PVR) at 4-6 weeks	continuous	Improved internal structure	Urogenital	0.04
5-alpha-reductase inhibitors for prostate cancer prevention	2008	Wilt TJ	Prostate cancer detected "for-cause"	dichotomous	No major morbidity events	Urogenital	0.99
Antibiotic prophylaxis for transrectal prostate biopsy	2011	Zani EL	Bacteriuria	dichotomous	No new signs of infection / disease	Urogenital	0.88
Pygeum africanum for benign prostatic hyperplasia	1998	Wilt TJ	Symptoms improvement: overall improvement	dichotomous	Quality of Life (QoL) improvement	Urogenital	0.48

Title	Year	First author	Outcome	Dichotomous or continuous	Outcome type	Conditions	PCE
Anticholinergic drugs versus placebo for overactive bladder syndrome in adults	2006	Nabi G	Patient perception of cure or improvement.	dichotomous	Quality of Life (QoL) improvement	Urogenital	0.72
Finasteride for benign prostatic hyperplasia	2010	Tacklind J	Total symptom score	continuous	Quality of Life (QoL) improvement	Urogenital	0.99
Phosphodiesterase inhibitors for lower urinary tract symptoms consistent with benign prostatic hyperplasia	2018	Pattanaik S	Change in the International Prostate Symptom Score (IPSS) - total	continuous	Quality of Life (QoL) improvement	Urogenital	0.60

Supplement 4. Worked examples of PCE calculation from Cochrane reviews

Abbreviations

RR, risk ratio; OR, odds ratio; CER, control event rate; PCE, the proportion attributable to contextual effects; n, number of patients; SE, standard error; SD, standard deviation; WSM, weighted standardized mean; 95% CI, 95% confidence interval

Dichotomous harmful outcome

Example: Fenton M et al. Thioridazine for schizophrenia. CD005170.pub2

The results of this review were as follows;

RR 0.66, 95% CI 0.44 to 0.98.

CER 35/56 = 0.625 (CER on harmful outcome)

1. Converting harmful RR to harmful OR

We used formula (3) in the manuscript.

$$OR = \frac{RR \times (CER - 1)}{RR \times CER - 1} = \frac{0.66 \times (35/56 - 1)}{0.66 \times 35/56 - 1} = 0.42$$

2. Converting harmful OR to beneficial OR

We took the reciprocal.

$$\text{beneficial OR} = \frac{1}{\text{harmful OR}} = \frac{1}{0.42} = 2.38$$

3. Converting beneficial OR to beneficial RR

We used formula (2) in the manuscript (in this case, CER must be a CER of the beneficial outcome, that is 1-CER on the harmful outcome).

$$RR = \frac{OR}{1 - CER \times (1 - OR)} = \frac{2.38}{1 - (1 - 35/56) \times (1 - 2.38)} = 1.57$$

4. Calculating the PCE

Based on the definition, PCE was calculated as follows:

$$PCE = \frac{1}{\text{beneficial RR}} = \frac{1}{1.57} = 0.64$$

5. Calculating the SE of log (PCE)

We performed the same conversions as above to compute the upper and lower 95% confidence interval of the PCE. The upper 95% CI was 0.97, and the lower 95% CI was 0.52

We then calculated the SE of PCE by the following formula:

$$\text{SE of log (PCE)} = \frac{\log(\text{upper 95\% CI}) - \log(\text{lower 95\% CI})}{3.92} = \frac{\log(0.97) - \log(0.52)}{3.92} = 0.16$$

Continuous outcome

Example: Jung JH et al. Silodosin for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia. CD012615.pub2

The results of the review were as follows;

SMD -2.65, 95% CI -3.23 to -2.08

Included studies in the original meta-analysis

Study ID	Mean change (SD) in the intervention arm	Number of patients on the intervention arm	Mean change (SD) in the placebo arm	Number of patients on the placebo arm
Chapple 2011	-7.1 (5.31)	371	-4.9 (5.42)	185
Kawabe 2006a	-8.3 (6.4)	175	-5.3 (6.7)	89
Marks 2009	-6.4 (6.63)	466	-3.5 (5.84)	457

For each primary study,

Standardized mean change = mean change / SD

SE of standardized mean change = $1/\sqrt{n}$

1. Calculating the weighted standardized mean change of each arm by meta-analysis

We used the DerSimonian-Laird method. The results of the meta-analyses were as follows:

Weighted standardized mean change of intervention arm (SE): -1.20 (0.13)

Weighted standardized mean change of placebo arm (SE): -0.76 (0.11)

We performed the meta-analyses by metagen from the package meta in R.

2. Calculating the PCE

We used formula (5) in the manuscript.

$$\text{PCE} = \frac{\text{weighted standardized mean change score of the placebo arm}}{\text{weighted standardized mean change score of the intervention arm}} = \frac{-0.76}{-1.20} = 0.63$$

3. Calculating the SE of log(PCE)

We used formula (6) for calculating the SE based on the Delta method.

$$\text{SE of log(PCE)} = \sqrt{\frac{\text{SE}_{\text{intervention}}^2}{\text{WSM}_{\text{intervention}}^2} + \frac{\text{SE}_{\text{placebo}}^2}{\text{WSM}_{\text{placebo}}^2}} = \sqrt{\frac{(0.13)^2}{(-1.20)^2} + \frac{(0.11)^2}{(-0.76)^2}} = 0.17$$

Figure S1. PCE by outcome type (binary outcomes). Created by the authors.

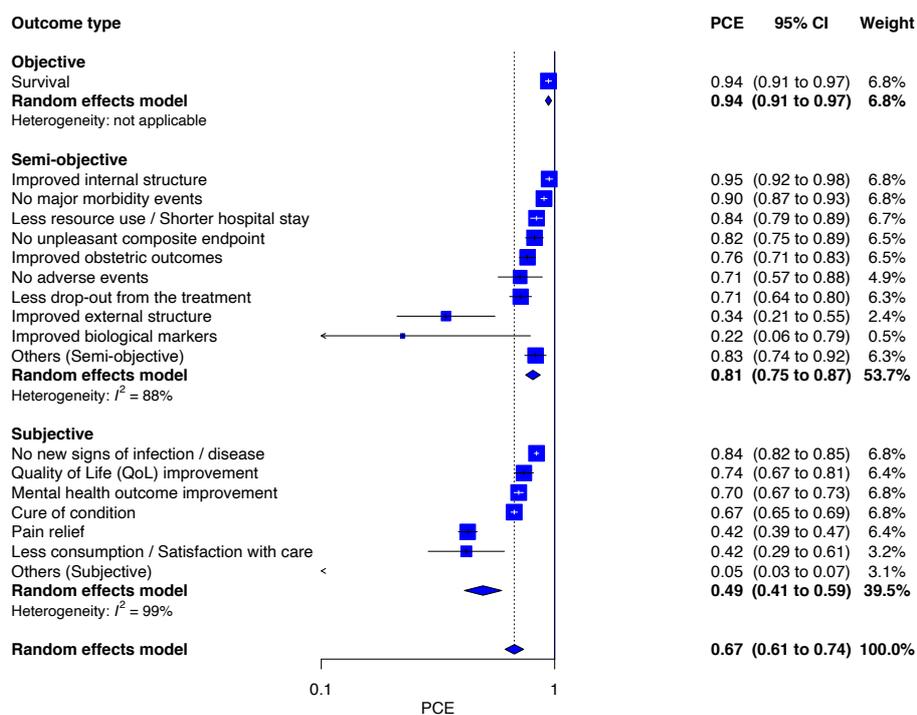


Figure S2. PCE by outcome type (continuous outcomes). Created by the authors.

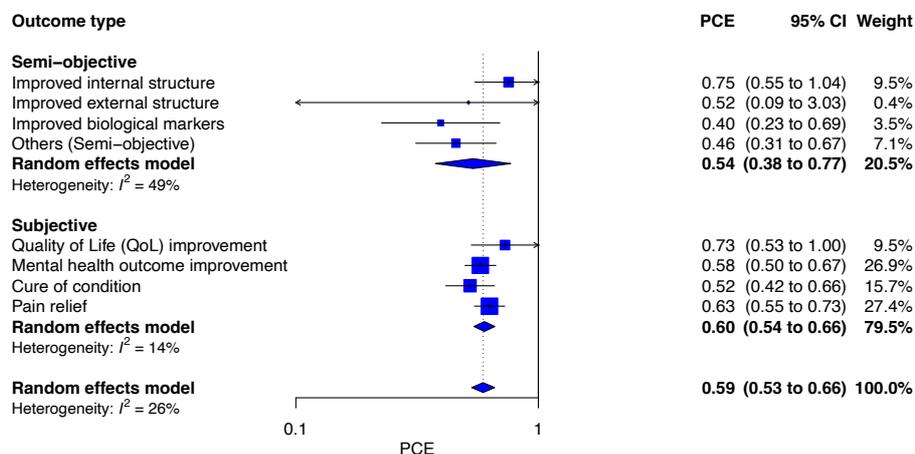


Figure S3. PCE by conditions (binary). Created by the authors.

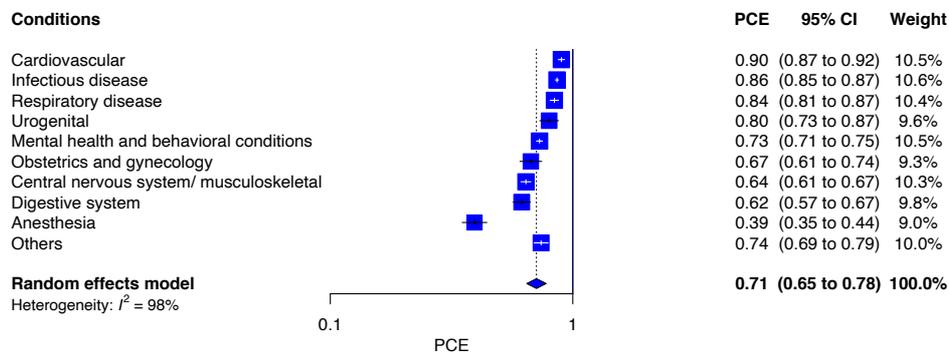


Figure S4. PCE by conditions (continuous). Created by the authors.

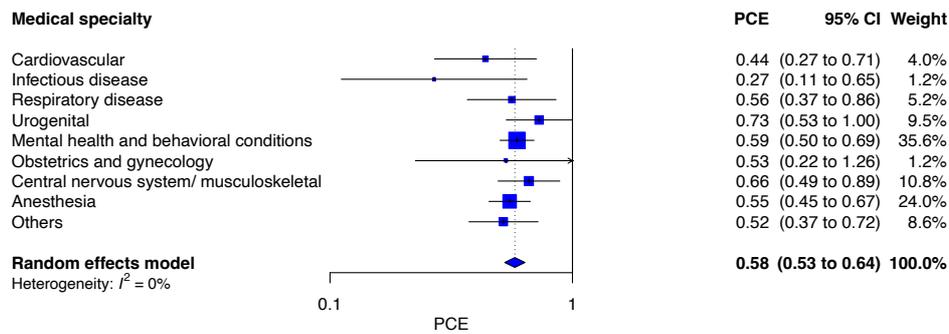


Figure S5. PCE by GRADE category (total). Created by the authors

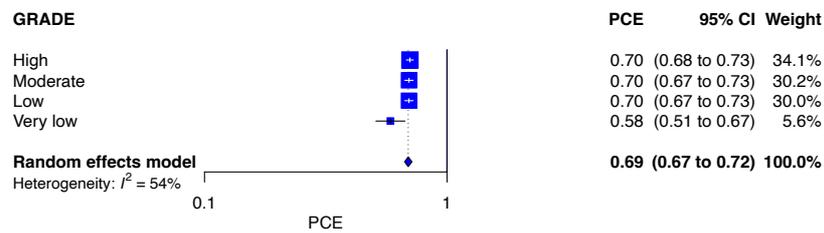


Figure S6. PCE by GRADE category (binary). Created by the authors.

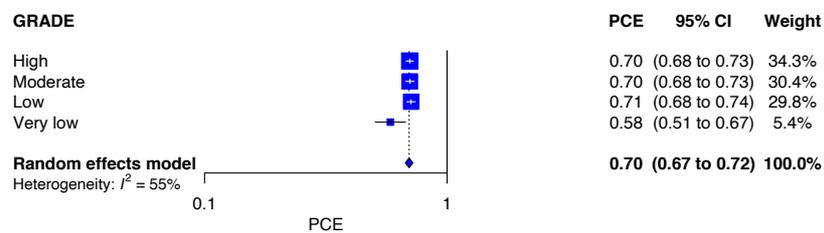


Figure S7. PCE by GRADE category (continuous). Created by the authors.

