Meta-analysis: Factors Affecting Placebo Response Rate in Irritable Bowel Syndrome.

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TITLE PAGE

Title: Meta-analysis: Factors Affecting Placebo Response Rate in Irritable Bowel Syndrome.

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Abbreviations:

5-HT	5-hydroxytryptamine
b.i.d.	twice daily
CI	confidence interval
GI	gastrointestinal
IBS	irritable bowel syndrome
MeSH	medical subject headings
o.d.	once daily
q.i.d.	four times daily
RCT	randomised controlled trial
t.i.d.	three times daily

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SUMMARY

Background: Irritable bowel syndrome (IBS) is a functional disorder of the gastrointestinal tract. Magnitude of placebo response rate in treatment trials for IBS, and what factors may influence this, is important.

Aims: To conduct a systematic review and meta-analysis examining this.

Methods: MEDLINE, EMBASE, and the Cochrane central register of controlled trials were searched to identify randomised controlled trials (RCTs) comparing pharmacological therapies with placebo in adult IBS patients. Studies reported either global assessment of IBS symptom cure or improvement, or abdominal pain cure or improvement. Data were extracted as intention-to-treat analyses with drop-outs assumed to be treatment failures, and pooled using a random effects model. Proportion of placebo patients experiencing symptom improvement or resolution was reported, with a 95% confidence interval (CI). Effect of trial characteristics on magnitude of placebo response was examined.

Results: 73 RCTs were eligible, including 8364 patients with IBS allocated to placebo. Pooled placebo response rate across all RCTs was 37.5% (95% CI 34.4%-40.6%). Rates were higher in European RCTs, RCTs that used physician-reported outcomes, and RCTs using shorter duration of therapy.

Conclusions: Placebo response rates across RCTs of pharmacological therapies in IBS were high. Future research should identify patient characteristics predicting placebo response.

INTRODUCTION

Irritable bowel syndrome (IBS) is a common functional gastrointestinal (GI) disorder consisting of abdominal pain in association with a disturbance in bowel habit. [1] The condition follows a chronic relapsing and remitting course. [2, 3] Sufferers represent a significant burden to the health service due to the consumption of medical resources, such as consultations in primary and secondary care, [3-6] investigations, [7] drugs, [8] and unnecessary surgical procedures. [9]

Despite evidence from recent meta-analyses demonstrating that some pharmaceutical agents, including antispasmodic drugs, peppermint oil, antidepressants, and drugs acting on the 5-hydroxytryptamine (5-HT) receptor are of benefit for the treatment of IBS in the short-term, [10-12] there is no medical intervention proven to alter the long-term natural history of the condition, and there is no agreement on a gold-standard for the treatment of IBS.

As a result, whenever a new pharmaceutical agent is developed for IBS it is compared with placebo in a randomised controlled trial (RCT). There is no structural abnormality that can be corrected by successful therapy and response to treatment is therefore assessed by improvement in symptoms. This is a subjective outcome and, in an effort to standardise research, the Rome foundation has made recommendations as to how best to assess response to therapy in treatment trials conducted in IBS and the other functional GI disorders. [13]

Evidence from the systematic review literature suggests that a significant proportion of patients assigned to placebo will respond to therapy, even in RCTs of therapies for organic GI conditions such as inflammatory bowel disease or peptic ulcer, where mucosal or ulcer healing are the outcomes of interest. [14, 15] In functional

GI disorders, where trial endpoints are likely to be less tangible than this, the placebo response rate may be even higher. However, despite the fact that there have been numerous published RCTs of pharmacological therapies in IBS this issue has not been well studied. This is important, as high placebo response rates will statistically reduce the possibility of seeing a positive impact of active therapy, and RCTs should be designed to minimise placebo response. We have therefore conducted a systematic review and meta-analysis in order to assess the magnitude of the placebo response rate in treatment trials of IBS, and have examined trial characteristics and features of design that may influence this.

MATERIALS AND METHODS

Search Strategy and Trial Selection

Studies were identified through a search developed to inform an updated monograph on the management of IBS for the American College of Gastroenterology. [16] A search of the medical literature was conducted using MEDLINE (1950 to January 2010), EMBASE (1980 to January 2010), and the Cochrane central register of controlled trials (2009). Randomised controlled trials examining the effect of pharmacological therapies in adult patients (over the age of 16 years) with IBS were eligible for inclusion (Box 1). The first period of cross-over RCTs were also eligible for inclusion. In the case of all RCTs the control arm were required to receive placebo. Duration of therapy had to be at least 7 days. The diagnosis of IBS could be based on either a physician's opinion or symptom-based diagnostic criteria, supplemented by the results of investigations to exclude organic disease, where trials deemed this necessary.Trials had to report either a global assessment of IBS symptom cure or improvement, or abdominal pain cure or improvement, after completion of therapy, preferably as reported by the patient, but if this was not recorded then as documented by the investigator or via questionnaire data. Where RCTs included patients with other functional GI disorders, or did not report these types of dichotomous data, but were otherwise eligible for inclusion in the systematic review, we attempted to contact the original investigators in order to obtain further information.

Placebo-controlled trials in irritable bowel syndrome were identified with the terms *irritable bowel syndrome* and *functional diseases, colon* (both as medical subject heading (MeSH) and free text terms), and *IBS*, *spastic colon*, *irritable colon*, and *functional* adj5 *bowel* (as free text terms). These were combined using the set

operator AND with studies identified with the terms: *parasympatholytics*, *scopolamine*, *trimebutine*, *muscarinic antagonists*, *butylscopolammonium bromide, psychotropic drugs*, *antidepressive agents*, *antidepressive agents (tricyclic)*, *desipramine*, *imipramine*, *trimipramine*, *doxepin, dothiepin, nortriptyline*, *amitriptyline*, *selective serotonin re-uptake inhibitors*, *paroxetine, sertraline, fluoxetine, citalopram, venlafaxine, serotonin antagonists, serotonin agonists, cisapride, receptors (serotonin, 5-HT_3),* and *receptors (serotonin, 5-HT_4)* (both as MeSH terms and free text terms), and the following free text terms: *spasmolytics*, *spasmolytic agents*, *antispasmodics*, *mebeverine*, *alverine*, *pinaverium bromide*, *otilonium bromide*, *cimetropium bromide*, *hyoscine butyl bromide*, *butylscopolamine*, *peppermint oil*, *colpermin, 5-HT_3, 5-HT_4, alosetron, cilansetron, ramosetron, tegaserod,* and *renzapride*.

There were no language restrictions and abstracts of the papers identified by the initial search were evaluated by the lead reviewer for appropriateness to the study question, and all potentially relevant papers were obtained and evaluated in detail. Foreign language papers were translated where necessary. Abstract books of conference proceedings between 2001 and 2009 were hand-searched to identify potentially eligible RCTs published only in abstract form. We also contacted pharmaceutical companies and searched the Food and Drug Administration Agency (FDA) website to obtain data from unpublished RCTs. The bibliographies of all identified relevant trials were used to perform a recursive search of the literature. Articles were independently assessed by two reviewers using pre-designed eligibility forms, according to the prospectively defined eligibility criteria. Any disagreement between investigators was resolved by consensus.

Outcome Assessment

The primary outcome assessed was the magnitude of the placebo response rate, in terms of improvement in, or resolution of, global IBS symptoms or abdominal pain, in all RCTs of pharmacological therapies conducted in IBS after cessation of therapy. Secondary outcomes included assessing placebo response rate according to various trial characteristics (see below).

Data Extraction

All data were extracted independently by two reviewers on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes (global IBS symptoms absent or improved, or abdominal pain absent or improved in the placebo arms of the included RCTs) (Box 2). In addition, the following clinical data were extracted for each trial: year of publication, geographical location, setting (primary, secondary, or tertiary care), number of centres, criteria used to define IBS, IBS subtype according to predominant stool pattern reported by the patient (diarrhoea-predominant, constipation-predominant, or alternating bowel habit), dosing schedule of the placebo, duration of therapy, proportion of trial patients receiving placebo, active pharmacological therapy used, primary outcome measure used to define symptom improvement or cure following therapy (patient versus physician-reported and global IBS symptoms versus abdominal pain or discomfort), whether the method used to generate the randomisation schedule was stated, whether the method of concealment of allocation was stated, and overall trial quality (assessed using the Jadad scale, Box 3). [17] Data were extracted as intention-to-treat analyses, with all drop-outs assumed to be

treatment failures, wherever trial reporting allowed this.

Data Synthesis and Statistical Analysis

Data were pooled using a random effects model, to give a more conservative estimate of the magnitude of the placebo response rate, allowing for any heterogeneity between trials. [18] Outcomes were expressed as the pooled proportion of patients assigned to placebo with global IBS symptoms or abdominal pain absent or improved after completion of therapy, with a 95% confidence interval (CI).

The results of individual RCTs can be diverse, and this inconsistency within a single meta-analysis can be quantified with a statistical test of heterogeneity, to assess whether the variation across trials is due to true heterogeneity, or chance. This quantity is termed I^2, and its value ranges from 0% to 100%, with 0% representing no observed heterogeneity, and larger values indicating increasing heterogeneity. A value below 50% was chosen to represent low levels of heterogeneity. [19]

Subgroup analyses were conducted according to year of publication geographical location, trial setting, single versus multi-centre trials, criteria used to define IBS, predominant stool pattern reported by the patient, dosing schedule of the placebo, duration of therapy, proportion of trial patients receiving placebo, active pharmacological therapy used, primary outcome measure used to define symptom improvement or cure following therapy (patient versus physician-reported and global IBS symptoms versus abdominal pain or discomfort), whether method of randomisation or concealment of allocation were reported, and trial quality according to the Jadad scale. We did not performed meta-regression in this systematic review and meta-analysis, but rather subgroup analyses according to individual trial characteristics, because the former technique evaluates the average of patient

characteristics within each trial, and this summary data may misrepresent individual patients within each treatment arm. The technique is therefore vulnerable to giving spurious results due to the ecological fallacy. [20]

StatsDirect version 2.4.4 (StatsDirect Ltd, Sale, Cheshire, England) was used to generate Forest plots of the pooled proportions of patients assigned to placebo with global IBS symptoms or abdominal pain absent or improved after completion of therapy, with 95% confidence intervals. Pooled placebo response rates were compared between the pre-defined subgroups using the Cochran Q statistic in order to assess for any heterogeneity between placebo response rates for the different subgroup analyses we conducted and, due to multiple analyses, a P value of < 0.01 was considered statistically significant.

RESULTS

The search strategy generated 3383 citations of which 177 appeared to be relevant to the systematic review and were retrieved for further assessment (Figure 1). Of these 177 RCTs, 104 were excluded for various reasons leaving 73 eligible trials, [21-92] containing 8364 individuals with IBS who were randomised to receive placebo. Five of these RCTs were published in abstract form only, [73-75, 82, 83] and data from two placebo-controlled trials of tegaserod in IBS (B307 and B351) were published in a single document on the FDA website. [84] We contacted original investigators in seven of the studies to clarify data or obtain supplementary information. [42, 49, 72, 82, 83, 85, 87] Agreement between reviewers for assessment of trial eligibility was good (kappa statistic = 0.90). Characteristics of individual RCTs, including the magnitude of the placebo response in each trial, are provided in Table 1.

Placebo Response Rate in All Trials

The pooled placebo response rate in the 73 RCTs we identified was 37.5% (95% CI 34.4% to 40.6%), with considerable heterogeneity between trials (I^2 = 86.2%, P < 0.001). The placebo response rate in individual RCTs varied from 0% in two trials, [21, 23] to 91.7%. [57] (Figure 2)

Placebo Response Rate According to Year of Publication, Trial Location, Setting, and Number of Centres

Trials were divided into those published before 1999, and those published in 1999 or later, as accepted endpoints for evaluating the success of therapy in IBS treatment trials changed around this point in time. There was, however, no significant

difference in placebo response rates between these two time periods (Cochran Q = 0.60, P = 0.44) (Table 2). The majority of RCTs were conducted in Europe, [21, 22, 24, 26-31, 34-37, 39-41, 46, 48, 49, 51, 53-56, 58, 61, 81, 85, 87-91] and the pooled placebo response rate was highest in these trials at 42.7% (Table 2). This rate was significantly higher than that in RCTs conducted in Asia (25.0%, Cochran Q = 8.8, P = 0.003), [23, 25, 50, 67, 70, 80] the Middle-East (23.0%, Cochran Q = 9.4, P = 0.002), [44, 52, 66, 69] and North America (33.0%, Cochran Q = 7.3, P = 0.007). [38, 42, 45, 47, 59, 60, 62-65, 68, 71, 75, 78, 86, 92] However, the number of Asian and Middle Eastern studies was low (n = 6 and n = 4 respectively) and the differences observed between Asian, Middle-Eastern, and North American RCTs were not statistically significant (Table 2). When the effect of trial setting and number of centres was examined, pooled placebo response rate was very similar in RCTs based in secondary and tertiary care, and in single and multi-centre trials, with no statistically significant difference detected (Cochran Q = 0.08, P = 0.78 for both analyses) (Table 2).

Placebo Response Rate According to Diagnostic Criteria Used to Define IBS and Predominant Stool Pattern Reported by the Patient

A clinical diagnosis (usually according to a physician's assessment) of IBS was the most frequent criteria used to define the presence of the condition, [21-25, 27-32, 34, 36-41, 45, 48, 50, 51, 53-57, 89] and pooled placebo response rate was highest in trials that used this definition at 42.0% (Table 2), compared with the Rome I or II criteria (36.0% and 34.4% respectively). However, the difference between these rates was not statistically significant (Cochran Q = 1.3, P = 0.25 and Cochran Q = 2.15, P = 0.14 respectively). There were few trials that reported the predominant stool pattern reported by the patient, but some trials recruited diarrhoea or constipation-predominant patients

exclusively, [32, 44, 52, 64, 67, 70, 71, 73-78, 80, 82-84, 86-91] allowing us to examine the effect of this patient characteristic on pooled placebo response rates. No statistically significant difference, in terms of pooled placebo response rate, between RCTs recruiting constipation-predominant or diarrhoea-predominant IBS patients was detected (Cochran Q = 0.6, P = 0.45) (Table 2).

Placebo Response Rate According to Criteria and Symptom Data Used to Define Response

There were only four RCTs that used a physician-reported outcome to define response to therapy, [34, 36, 37, 56] and the pooled placebo response rate was significantly higher in these trials compared to those that used a patient-reported outcome (53.0% versus 37.4%, Cochran Q = 7.8, P = 0.005) (Table 2). In terms of symptom data used to define response, the majority of studies used improvement or relief of global IBS symptoms, though 13 used improvement or relief of abdominal pain or discomfort. [25, 32, 44, 45, 54, 59, 61-63, 69, 71, 72, 87] There was no significant difference in pooled placebo response rate according to the symptom data used to define response (Cochran Q = 0.6, P = 0.43) (Table 2).

Placebo Response Rate According to Dosing Schedule, Duration of Therapy, and Proportion of Trial Patients Assigned to Placebo

The commonest dosing schedule used in eligible RCTs was three times daily, [24, 27-33, 35-37, 39-41, 54, 56, 58, 69, 73-75, 87-90] and pooled placebo response rate was highest in these trials at 43.0%, compared with RCTs that used a once or twice daily schedule (32.2% and 36.0% respectively) (Table 2), but again these differences did not reach formal statistical significance (Cochran Q = 4.7, P = 0.03 and Cochran Q = 3.2, P =

0.07 respectively). Duration of therapy varied from 1 week to 48 weeks. Pooled placebo response rate was highest in trials using 1 to 4 weeks of therapy at 46.0%, [24, 25, 27, 30, 32, 34, 36, 38-41, 51, 54-57, 77, 86, 92] which was significantly higher than in RCTs that used more than 8 weeks of therapy (34.0%, Cochran Q = 8.5, P = 0.004), [21-23, 28, 29, 33, 35, 37, 42-44, 47, 53, 58-67, 70-76, 78-84, 87-91] but not trials using 5 to 8 weeks of therapy (39.8%, Cochran Q = 0.8, P = 0.37) (Table 2). [26, 31, 45, 46, 48-50, 52, 68, 69, 85] The majority of trials assigned patients to active therapy or placebo in a 1:1 ratio, and pooled placebo response rate was higher in these RCTs compared with trials where fewer patients received placebo than received active therapy, [42, 59-61, 64, 70, 71, 76, 77, 82-87] although this difference was not statistically significant (Cochran Q =2.3, P = 0.13) (Table 2).

Placebo Response Rate According to Active Pharmacological Therapy Used

Antispasmodic drugs were the active pharmacological agent used in the greatest number of trials. [21, 22, 27-41, 54-57] Pooled placebo response rates were highest in RCTs that used antispasmodics or mixed 5-HT_3 antagonists / 5-HT_4 agonists (45.0% for both). Whilst there was a trend for the observed response rate to be higher in RCTs that used antispasmodics compared with those using peppermint oil, 5-HT_3 antagonists, or 5-HT_4 agonists these differences were not statistically significant (Cochran Q = 4.5, P = 0.03 for peppermint oil and Cochran Q = 3.1, P = 0.08 for both 5-HT_3 antagonists and 5-HT_4 agonists) (Table 2). There was also a trend for the response rate to be higher in RCTs that used mixed 5-HT_3 antagonists / 5-HT_4 agonists compared with those that used peppermint oil, but again this difference did not reach statistical significance (Cochran Q = 3.2, P = 0.07) (Table 2).

Placebo Response Rate According to Reporting of Method Used to Generate the Randomisation Schedule or to Conceal Allocation

The majority of RCTs did not report either of these features of their design. Pooled placebo response rate was slightly lower in trials that stated the method used to generate the randomisation schedule, but this difference was not statistically significant (Cochran Q = 1.4, P = 0.24) (Table 2). The pooled placebo response rate was almost identical when RCTs were subgrouped according to whether or not the method used to conceal treatment allocation was reported.

Placebo Response Rate According to Trial Quality

Most RCTs scored 4 or more on the Jadad scale. When pooled placebo response rates according to trial quality were assessed, these were highest in those with a score of 3 (40.0%), but the response rate was not significantly lower in studies with a score of 4 (37.8%, Cochran Q = 0.15, P = 0.70) or 5 (36.0%, Cochran Q = 0.51, P = 0.47).

DISCUSSION

This systematic review and meta-analysis of placebo-controlled randomised trials conducted in IBS patients has demonstrated a pooled placebo response rate of 37.5%. The rate was significantly higher in European RCTs compared with those conducted in Asia, the Middle-East, or North America, in trials with a treatment duration from 1 to 4 weeks compared with those that used 8 weeks or more of therapy, and in RCTs that used a physician-reported outcome to define response to therapy compared with those that used a patient-reported endpoint, though in the latter case there were only four studies that used a physician-reported outcome that provided data for the analysis.

Pooled placebo response rates were generally higher in RCTs using clinical criteria to define the presence of IBS, compared with those that used the Rome I or II criteria, trials that used a three times daily dosing schedule, trials that assigned patients to placebo or active therapy in a 1:1 ratio, trials of antispasmodics and mixed 5-HT_3 antagonists / 5-HT_4 agonists, and trials of lower quality according to the Jadad scale, but none of these differences reached formal statistical significance. Specific features of RCT design such as trial setting, number of involved centres, predominant stool pattern of recruited patients, as well as whether or not investigators reported the method used to generate the randomisation schedule and to conceal treatment allocation appeared to have little effect on pooled placebo response rates in our analyses, nor did the year of publication of the trial.

Strengths of the present study include the search strategy, which was exhaustive, and the fact that we contacted original investigators in order to obtain supplementary data in some cases, in order to maximise the number of identified

RCTs providing data for these analyses. We assessed the impact of individual trial characteristics on pooled placebo response rates in subgroup analyses. We also performed an intention-to-treat analysis, where all drop-outs were assumed to be treatment failures, and used a random effects model to provide a more conservative estimate of the pooled placebo response rate, meaning that the magnitude of this effect is unlikely to have been overestimated. Weaknesses of the study include the fact that there was statistically significant heterogeneity when trial data were pooled, which was not explained by any of our subgroup analyses, and the fact that, without access to individual patient data it is difficult to draw any conclusions about specific patient characteristics that may have contributed to the findings of our study.

There has been a previously published systematic review and meta-analysis that has examined this issue. [93] The authors identified 45 placebo-controlled trials, containing 3352 individuals with IBS who were randomised to receive placebo. They reported a placebo response rate of 40% when data for all eligible trials were pooled. The response rate was significantly lower in studies that used the Rome criteria to define the presence of IBS, but there were no other features of the studies identified that they examined, including trial duration, score on the Jadad scale, and type of active pharmacological therapy, which predicted placebo response rate. There are several limitations of this study. Firstly, there has been a considerable amount of data published in the 5 years since this meta-analysis was conducted. Secondly, the authors included RCTs of therapies for IBS that are not accepted as conventional treatments for the condition, such as activated charcoal, loxiglumide, and naloxene. Thirdly, they included cross-over studies in which data extraction according to initial treatment allocation was not possible. Finally, they missed eligible studies that were published and available at the time their meta-analysis was conducted. The present study

therefore provides new and important information about the magnitude of the placebo response rate in IBS, as well as examining a larger number of trial characteristics and features of design that may influence this.

The finding that placebo response rates were significantly higher in RCTs conducted in European populations is novel. Possible explanations for this are speculative, but it may be that there are cultural differences that influence the magnitude of the placebo effect. The fact that trials with a duration of therapy of between 1 and 4 weeks reported a significantly larger placebo effect than trials using more than 8 weeks is interesting, and suggests that any observed benefit of placebo in the treatment of IBS may ameliorate over time. The trend towards a higher placebo response rate seen with an increase in dosing schedule is a phenomenon that has also been described when data from healing rates in duodenal ulcer trials were examined. [14] There is evidence from the systematic review literature that RCTs that do not report the method used to generate the randomisation schedule and to conceal allocation tend to overestimate the efficacy of the active therapy. [94] It could therefore be expected that placebo response rates would be lower in trials that did not report these features of their design, and it is therefore interesting to note that in our analyses these had no statistically significant effect on the magnitude of the placebo response.

The number of IBS patients achieving response or remission of their symptoms with placebo in this study appears to be somewhere between one in two and one in three. This information is important for the conduct of future RCTs in the condition, as it may be helpful in informing power calculations on which to base trial recruitment. Recent trials of renzapride and citalopram in IBS both failed to demonstrate any significant benefit of these drugs, [68, 95] partly due to the high response rates observed in the placebo arms of the trials, which meant that the studies

were underpowered to detect a statistically significant difference, and in the case of renzapride led the pharmaceutical company that had developed the drug to abandon further investment in its clinical development. [96] Trials that use a longer duration of treatment, and use medication given once or twice daily, might be expected to reduce the placebo response rate, and may have a better ability to demonstrate the benefit of active therapy.

In conclusion, this systematic review and meta-analysis has demonstrated a pooled placebo response rate in all available RCTs of pharmacological therapies in IBS of 37.5%. Future research should concentrate on identifying patient characteristics that predict such a response to treatment, perhaps using trial data at the individual patient level.

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Box 1. Eligibility criteria.

Randomised controlled trials

Adults (participants aged > 16 years)

Diagnosis of irritable bowel syndrome based on either a clinician's opinion, or meeting specific diagnostic criteria*, supplemented by negative investigations where trials deemed this necessary.

Compared pharmacological therapies† with placebo.

Minimum duration of therapy 7 days.

Global assessment of irritable bowel syndrome symptoms or abdominal pain following therapy.‡

*Manning, Kruis score, Rome I, II, or III.

†Antispasmodics, peppermint oil, antidepressants, 5-HT_3 antagonists, 5-HT_4 agonists, and mixed 5-HT_3 antagonists / 5-HT_4 agonists.

‡Preferably patient-reported, but if this was not available then as assessed by a physician or questionnaire data.

Box 2. Data extraction methodology.

Outcome of interest: improvement in or absence of global irritable bowel syndrome symptoms preferable, if not reported then improvement in or absence of abdominal pain.

Reporting of outcomes: patient-reported preferable, if not available then investigator-reported.

Time of assessment: upon completion of therapy.

Denominator used: true intention-to-treat analysis, if not available then all evaluable patients.

Box 3. Jadad score calculation

Item	Score
Was the study described as randomised?	1
Was the method used to generate the sequence of randomisation described and appropriate (random numbers, computer-generated, etc)?	1
Was the study described as double-blind?	1
Was the method of double-blinding described and appropriate (identical placebo, active placebo, dummy, etc)?	1
Was there a description of withdrawals and drop-outs?	1
Deduct one point if method used to generate sequence of randomisation described, but inappropriate (allocated alternately, or according to date of birth, or hospital number).	-1
Deduct one point if study described as double-blind, but method of blinding inappropriate.	-1

FIGURES

Figure 1. Flow Diagram of Assessment of Trials Identified in the Systematic Review.

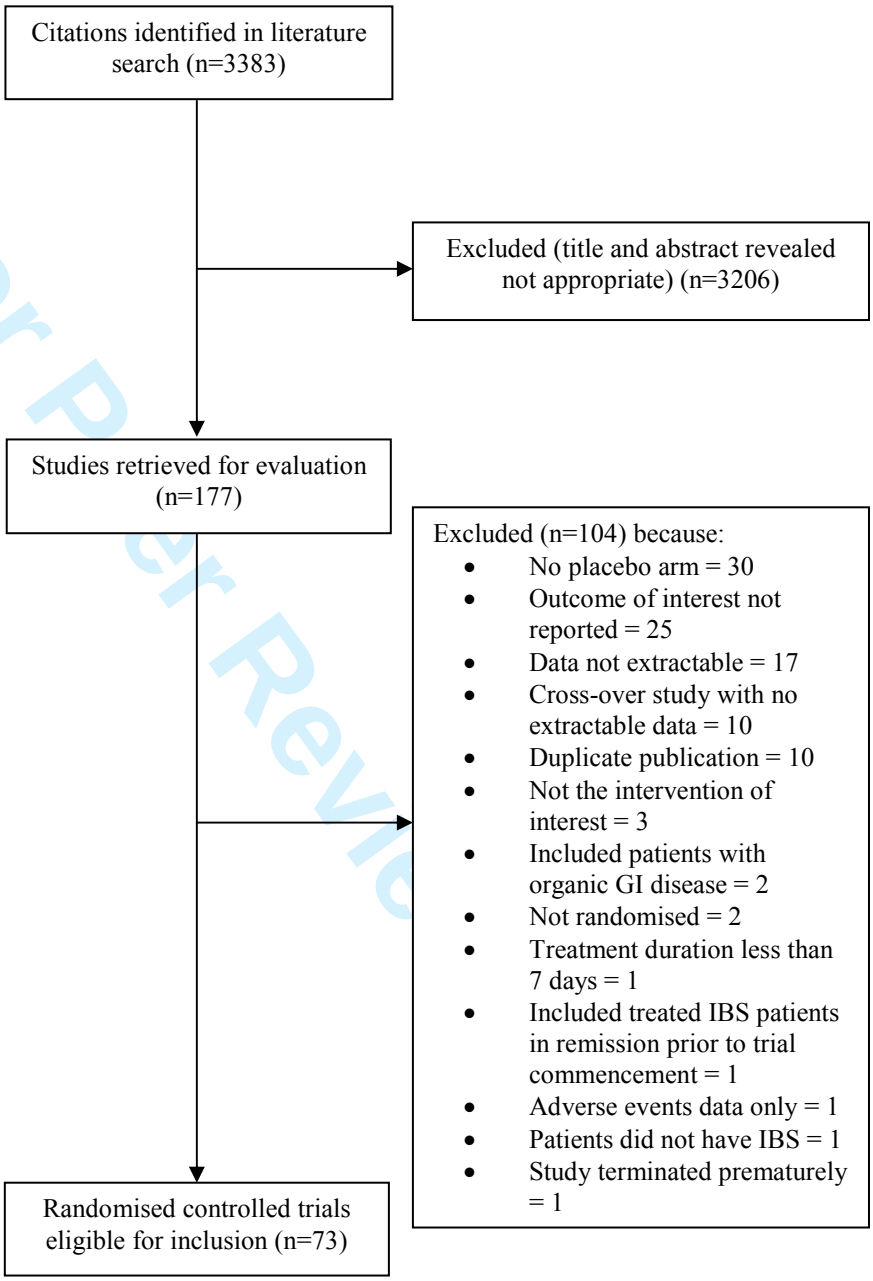
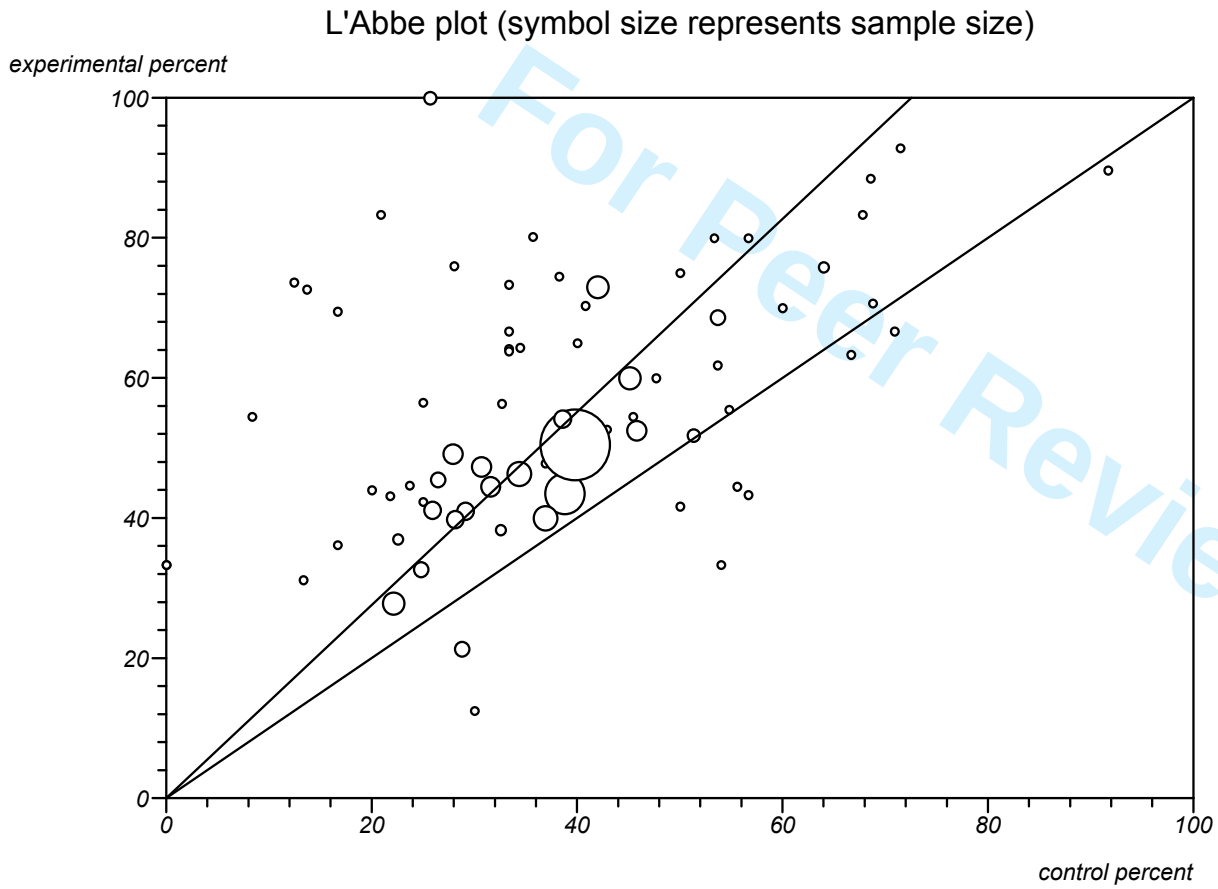


Figure 2. L'Abbe Plot of Placebo Response Rates (The Solid Line Represents Equality Between Experimental Treatment and Control, with Circles Above this Line Representing Trials Where Experimental Treatment was Superior to Control).



TABLES

Table 1. Characteristics of Included Trials.

Trial	Geographical location	Number of centres	Criteria used to define IBS*	Active treatment	Duration of therapy	Dosing schedule†	Sample size	Placebo response rate (%)	Jadad score
Heefner 1978 [45]	North America	Multiple	Clinical	Desimipramine	8 weeks	o.d.	44	10/22 (45.5)	4
Myren 1982 [51]	Europe	Multiple	Clinical	Trimipramine	4 weeks	o.d.	61	21/31 (67.7)	2
Nigam 1984 [23]	Asia	Single	Clinical	Amitriptyline	12 weeks	o.d.	42	0/21 (0)	3
Boerner 1988 [48]	Europe	Single	Clinical	Doxepin	8 weeks	o.d.	83	22/41 (53.7)	4
Bergmann 1991 [53]	Europe	Single	Clinical	Trimipramine	12 weeks	o.d.	35	2/16 (12.5)	2
Vij 1991 [50]	Asia	Single	Clinical	Doxepin	6 weeks	o.d.	50	5/25 (20.0)	5
Drossman 2003 [42]	North America	Multiple	Rome I	Desipramine	12 weeks	o.d.	172	21/57 (36.8)	5
Kuiken 2003 [46]	Europe	Single	Rome I	Fluoxetine	6 weeks	o.d.	40	9/21 (42.9)	5
Tabas 2004 [47]	North America	Single	Rome I	Paroxetine	12 weeks	o.d.	90	10/46 (21.7)	5
Vahedi 2005 [44]	Middle East	Single	Rome II	Fluoxetine	12 weeks	o.d.	44	3/22 (13.6)	5
Tack 2006 [49]	Europe	Single	Rome II	Citalopram	6 weeks	o.d.	23	1/12 (8.3)	4

Talley 2008 [43]	Australasia	Multiple	Rome II	Citalopram and imipramine	12 weeks	o.d.	33	11/16 (68.8)	5
Vahedi 2008 [52]	Middle East	Single	Rome II	Amitriptyline	8 weeks	o.d.	54	11/27 (40.7)	5
Abdul-Baki 2009 [66]	Middle East	Single	Rome II	Imipramine	12 weeks	Titrated	107	12/48 (25.0)	5
Masand 2009 [65]	North America	Multiple	Rome II	Paroxetine	12 weeks	o.d.	72	6/36 (16.7)	4
Ladabaum 2010 [68]	North America	Multiple	Rome II	Citalopram	8 weeks	o.d.	54	15/27 (55.6)	5
Levy 1977 [39]	Europe	Single	Clinical	Pinaverium	2 weeks	t.i.d.	50	7/25 (28.0)	3
Moshal 1979 [32]	Africa	Single	Clinical	Trimebutine	4 weeks	t.i.d.	20	6/10 (60.0)	4
Piai 1979 [36]	Europe	Single	Clinical	Prifinium	3 weeks	t.i.d.	18	3/9 (33.3)	4
Ritchie 1979 [21]	Europe	Single	Clinical	Hyoscine	12 weeks	q.i.d.	24	0/12 (0)	4
D'Arienzo 1980 [40]	Europe	Single	Clinical	Octilonium	4 weeks	t.i.d.	28	10/14 (71.4)	3
Fielding 1980 [37]	Europe	Single	Clinical	Trimebutine	24 weeks	t.i.d.	60	17/30 (56.7)	3
Delmont 1981 [56]	Europe	Single	Clinical	Pinaverium	4 weeks	t.i.d.	60	17/30 (56.7)	4
Page 1981 [38]	North America	Multiple	Clinical	Dicycloverine	2 weeks	q.i.d.	97	16/49 (32.7)	4
Baldi 1983 [54]	Europe	Single	Clinical	Otilonium	4 weeks	t.i.d.	30	8/15 (53.3)	4
Ghidini 1986 [31]	Europe	Single	Clinical	Rociverine and trimebutine	8 weeks	t.i.d.	60	20/30 (66.7)	3

Kruis 1986 [22]	Europe	Single	Clinical	Mebeverine	16 weeks	q.i.d.	80	12/40 (30.0)	4
Virat 1987 [41]	Europe	Single	Clinical	Pinaverium	1 week	t.i.d.	78	13/39 (33.3)	2
Centonze 1988 [28]	Europe	Single	Clinical	Cimetropium	24 weeks	t.i.d.	48	5/24 (20.8)	4
Gilvarry 1989 [34]	Europe	Single	Clinical	Pirenzipine	4 weeks	b.i.d.	24	6/12 (50.0)	4
Passaretti 1989 [30]	Europe	Single	Clinical	Cimetropium	4 weeks	t.i.d.	40	8/20 (40.0)	4
Dobrilla 1990 [29]	Europe	Single	Clinical	Cimetropium	12 weeks	t.i.d.	70	24/35 (68.6)	4
Schafer 1990 [27]	Europe	Single	Clinical	Hyoscine	4 weeks	t.i.d.	360	114/178 (64.0)	3
Castiglione 1991 [55]	Europe	Single	Clinical	Otilonium	4 weeks	Not stated	60	10/30 (33.3)	2
Pulpeiro 2000 [57]	South America	Single	Clinical	Propinox	4 weeks	Not stated	75	33/36 (91.7)	3
Glende 2002 [33]	Multiple	Multiple	Rome I	Otilonium	15 weeks	t.i.d.	317	36/160 (22.5)	3
Mitchell 2002 [35]	Europe	Multiple	Rome II	Alverine	12 weeks	t.i.d.	107	23/54 (42.6)	5
Lech 1988 [24]	Europe	Single	Clinical	Peppermint oil	4 weeks	t.i.d.	47	6/24 (25.0)	3
Liu 1997 [25]	Asia	Single	Clinical	Peppermint oil	4 weeks	q.i.d.	110	21/55 (38.2)	4
Capanni 2005 [58]	Europe	Single	Rome II	Peppermint oil	12 weeks	t.i.d.	178	31/87 (35.6)	5
Cappello 2007 [26]	Europe	Single	Rome II	Peppermint oil	8 weeks	b.i.d.	57	10/29 (34.5)	5
Merat 2010 [69]	Middle East	Single	Rome II	Peppermint oil	8 weeks	t.i.d.	90	6/45 (13.3)	5
Camilleri 1999 [59]	North America	Multiple	Rome I	Alosetron	12 weeks	b.i.d.	370	26/80 (32.5)	4

Bardhan 2000 [61]	Europe	Multiple	Rome I	Alosetron	12 weeks	b.i.d.	462	60/117 (51.3)	4
Camilleri 2000 [62]	North America	Multiple	Rome I	Alosetron	12 weeks	b.i.d.	647	94/323 (29.1)	5
Camilleri 2001 [63]	North America	Multiple	Rome I	Alosetron	12 weeks	b.i.d.	626	82/317 (25.9)	5
Lembo 2001 [60]	North America	Multiple	Rome II	Alosetron	12 weeks	b.i.d.	801	113/269 (42.0)	4
Chey 2004 [72]	Multiple	Multiple	Rome I	Alosetron	48 weeks	b.i.d.	714	166/363 (45.7)	4
Chang 2005 [71]	North America	Single	Rome I	Alosetron	12 weeks	b.i.d.	662	51/128 (39.8)	4
Krause 2007 [64]	North America	Multiple	Rome II	Alosetron	12 weeks	b.i.d.	705	54/176 (30.7)	5
Bradette 2004 [73]	Not stated	Not stated	Rome‡	Cilansetron	24 weeks	t.i.d.	792	179/397 (45.1)	3
Miner 2004 [75]	North America	Not stated	Rome‡	Cilansetron	12 weeks	t.i.d.	692	97/348 (27.9)	3
Francisconi 2006 [74]	Not stated	Not stated	Rome‡	Cilansetron	12 weeks	t.i.d.	745	116/368 (31.5)	3
Matsueda 2008 [67]	Asia	Multiple	Rome II	Ramosetron	12 weeks	o.d.	539	71/269 (26.4)	4
Matsueda 2008 [70]	Asia	Multiple	Rome II	Ramosetron	12 weeks	o.d.	418	28/109 (25.7)	4
Hamling 1998 [82]	Not stated	Multiple	Rome I	Tegaserod	20 weeks	b.i.d.	123	9/38 (23.7)	3
Langaker 1998 [83]	Not stated	Multiple	Rome I	Tegaserod	12 weeks	b.i.d.	547	28/113 (24.8)	3
Muller-Lissner 2001 [76]	Multiple	Multiple	Rome I	Tegaserod	12 weeks	b.i.d.	881	99/288 (34.4)	4
Novick 2002 [78]	North America	Multiple	Rome I	Tegaserod	12 weeks	b.i.d.	1519	292/752 (38.8)	5
Kellow 2003 [79]	Multiple	Multiple	Rome II	Tegaserod	12 weeks	b.i.d.	520	140/261 (53.6)	5

Nyhlin 2004 [81]	Europe	Multiple	Rome II	Tegaserod	12 weeks	b.i.d.	647	90/320 (28.1)	5
Tack 2005 [77]	Multiple	Multiple	Rome II	Tegaserod	4 weeks	b.i.d.	2660	209/525 (39.8)	5
Harish 2007 [80]	Asia	Single	Rome II	Tegaserod	12 weeks	b.i.d.	40	10/20 (50.0)	5
Chey 2008 [92]	North America	Multiple	Rome II	Tegaserod	4 weeks	b.i.d.	661	128/332 (38.6)	5
B307 [84]	Multiple	Multiple	Rome I	Tegaserod	12 weeks	b.i.d.	845	105/285 (36.8)	4
B351 [84]	Multiple	Multiple	Rome I	Tegaserod	12 weeks	b.i.d.	799	59/267 (22.1)	4
Camilleri 2004 [86]	North America	Single	Rome II	Renzapride	2 weeks	o.d.	48	2/12 (16.7)	4
George 2008 [87]	Europe	Multiple	Rome II	Renzapride	12 weeks	o.d.	510	36/125 (28.8)	4
Spiller 2008 [85]	Europe	Multiple	Rome II	Renzapride	8 weeks	o.d.	168	23/42 (54.8)	5
Van Outryve 1991 [89]	Europe	Single	Clinical	Cisapride	12 weeks	t.i.d.	69	11/33 (33.3)	4
Schutze 1997 [88]	Europe	Multiple	Rome I	Cisapride	12 weeks	t.i.d.	96	34/48 (70.8)	4
Farup 1998 [91]	Europe	Multiple	Rome I	Cisapride	12 weeks	t.i.d.	70	20/37 (54.1)	4
Ziegenhagen 2004 [90]	Europe	Multiple	Rome I	Cisapride	12 weeks	t.i.d.	82	20/42 (47.6)	4

*Irritable bowel syndrome

†o.d. once daily, b.i.d. twice daily, t.i.d. three times daily, q.i.d. four times daily

‡Iteration of Rome criteria not specified

Table 2. Effect of Trial Characteristics on Magnitude of the Placebo Response.

	Number of trials	Number of patients receiving placebo	Pooled placebo response rate (%)	95% confidence interval	I^2 (%)	P value for I^2
All trials	73	8364	37.5	34.4 – 40.6	86.2	< 0.001
Year of publication						
Before 1999	33	1700	39.0	33.0 – 46.0	86.5	< 0.001
1999 or later	40	6706	36.1	32.7 – 39.5	86.2	< 0.001
Trial location						
Asia	6	499	25.0	16.0 – 36.0	80.5	< 0.001
Europe	33	1622	42.7	36.6 – 48.8	82.7	< 0.001
Middle-East	4	142	23.0	13.0 – 35.0	61.5	0.05
North America	16	2974	33.0	30.0 – 37.0	73.8	< 0.001

Trial setting						
Secondary care	21	663	39.0	31.0 – 48.0	79.2	< 0.001
Tertiary care	20	673	37.0	26.2 – 48.4	88.6	< 0.001
Number of centres						
Single	37	1301	36.9	30.1 – 44.0	85.2	< 0.001
Multi	33	5950	38.0	34.0 – 41.0	86.8	< 0.001
Criteria used to define IBS*						
Clinical	28	906	42.0	33.0 – 51.0	85.9	< 0.001
Rome I	19	3482	36.0	31.0 – 41.0	86.6	< 0.001
Rome II	23	2863	34.4	29.8 – 39.2	82.6	< 0.001
Predominant stool pattern						
Constipation	16	2617	36.0	31.0 – 42.0	82.7	< 0.001
Diarrhoea	8	1822	33.0	28.0 – 39.0	83.0	< 0.001

Criteria used to define response						
Patient-reported	66	8122	37.4	34.2 – 40.6	87.0	< 0.001
Physician-reported	4	81	53.0	42.0 – 63.0	0	0.64
Symptom data used to define response						
Abdominal pain	13	1622	35.0	29.0 – 42.0	83.8	< 0.001
Global symptoms	54	6175	38.0	35.0 – 42.0	87.4	< 0.001
Dosing schedule†						
o.d.	20	977	32.2	25.2 – 39.7	81.1	< 0.001
b.i.d.	21	5015	36.0	32.0 – 40.0	85.8	< 0.001
t.i.d.	25	2102	43.0	37.0 – 50.0	87.2	< 0.001

Duration of therapy						
1 – 4 weeks	19	1446	46.0	39.0 – 54.0	83.8	< 0.001
5 – 8 weeks	11	321	39.8	28.7 – 51.4	78.3	< 0.001
> 8 weeks	43	6597	34.0	31.0 – 37.0	86.8	< 0.001
Proportion of trial patients assigned to placebo						
Approximately 50%	57	5733	38.7	34.7 – 42.7	87.7	< 0.001
Significantly less than 50%	16	2631	34.0	30.0 – 39.0	79.0	< 0.001

Active pharmacological therapy						
Antidepressant	16	468	32.0	22.4 – 42.5	82.4	< 0.001
Antispasmodic	21	852	45.0	35.0 – 55.0	87.9	< 0.001
Peppermint oil	5	240	30.0	21.0 – 40.0	62.1	0.03
5-HT_3 antagonist	13	3264	35.0	30.0 – 40.0	87.6	< 0.001
5-HT_4 agonist	11	3201	35.0	30.0 – 40.0	88.3	< 0.001
Mixed 5-HT_3 antagonists / 5-HT_4 agonists	7	339	45.0	31.0 – 58.0	83.2	< 0.001
Generation of randomisation schedule						
Stated	27	3811	35.0	31.0 – 40.0	83.0	< 0.001
Not stated or unclear	46	4553	38.8	34.5 – 43.3	87.8	< 0.001

Concealment of allocation						
Stated	7	895	37.0	29.0 – 45.0	74.2	< 0.001
Not stated or unclear	66	7469	37.5	34.2 – 40.9	87.0	< 0.001
Score on Jadad scale						
3	14	1782	40.0	30.0 – 50.0	93.9	< 0.001
4	32	2894	37.8	33.3 – 42.5	81.7	< 0.001
5	23	3572	36.0	31.0 – 40.0	81.9	< 0.001

*Irritable bowel syndrome

†o.d. once daily, b.i.d. twice daily, t.i.d. three times daily

Section/topic	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sourc participants, and interventions; study appraisal and synthesis methods; results; limitations; implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, i outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), ar registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with stud additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic rev included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in dupl for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specificati done at the study or outcome level), and how this information is to be used in any data syn
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including (e.g., I^2) for each meta-analysis.

Section/topic	#	Checklist item
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., public reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regr which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PIC provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summ intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures c

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-reg
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; co key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implicat
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of da systematic review.

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