The placebo response rate in pharmacological trials in patients with irritable bowel syndrome: a systematic review and meta-analysis

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The placebo response rate in pharmacological trials in patients with irritable bowel syndrome: a systematic review and meta-analysis

Michelle Bosman, Sigrid Elsenbruch, Maura Corsetti, Jan Tack, Magnus Simrén, Bjorn Winkens, Thimo Boumans, Ad Masclee, Daniel Keszthelyi

Summary

Background Clinical trials in irritable bowel syndrome are associated with high placebo response rates. We aimed to identify the magnitude of the placebo response and the contributing factors to this occurrence.

Methods We did a systematic review and meta-analysis with a search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials between April 1, 1959, and April 30, 2020. We included all randomised controlled trials that compared an active pharmacotherapeutic agent with placebo and had a dichotomous outcome of response to therapy (in terms of global improvement or improvement in abdominal pain) in adults (aged ≥ 18 years) with irritable bowel syndrome. Exclusion criteria were trials reporting on treatment satisfaction as a dichotomous outcome of response to therapy or clinician-reported outcomes and a treatment duration of less than 4 weeks. Our main outcome was identification of the magnitude of the pooled placebo response rate for the following endpoints: global improvement, abdominal pain, and US Food and Drug Administration (FDA) endpoints. We extracted information from published reports and pooled proportions through meta-analysis with random effects. The study was registered with PROSPERO, CRD42020170908.

Findings Of the 6863 publications identified, 70 articles describing 73 randomised controlled trials were included in our analysis. The pooled placebo response rate was 27.3% (95% CI 24.3–30.9) using the global improvement endpoint, 34.4% (31.2–37.8) using the abdominal pain endpoint, and 17.9% (15.2–21.0) using the composite FDA endpoint responder definition, all with substantial heterogeneity between the trials. Studies published before 2006, and those done in Europe, with a parallel design, a run-in period of 2 weeks or less, a dose schedule of three times a day or more, or a smaller sample size of the control group were significantly associated with an increased pooled placebo response rate.

Interpretation More than a quarter of patients with irritable bowel syndrome had a placebo response in terms of global improvement, with multiple associated moderators. We recommend future trials apply a run-in period of at least 2 weeks and dose once or twice a day to minimise the placebo response rate.

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Introduction

Irritable bowel syndrome (IBS) is a common disorder of gut–brain interaction characterised by recurrent abdominal pain associated with defecation or a change in bowel habits.^{1,2} The estimated prevalence in a recent study is 4.6% in the USA, Canada, and UK (according to the Rome IV criteria).³ IBS is not only associated with a substantial effect on an individuals' functioning and quality of life, but also with substantial costs to patients, health-care systems, and society.^{4,5} The treatment of IBS is commonly known to represent a clinical challenge, in part because of varying efficacy of different therapies.^{1,6} To improve therapeutic outcomes, more in-depth understanding of the mechanisms relevant to existing strategies is necessary, including the role of placebos in trials for IBS. Generally, pharmacological therapies are considered efficacious if they are superior to placebos in clinical trials.² The magnitude of the placebo response therefore has

profound effects on the outcomes of these trials. Previous pharmacological trials in disorders of gut–brain interaction, including IBS, have shown that there is a substantial proportion of patients that benefits from placebo intervention.⁷ A previous meta-analysis⁸ of the placebo response in IBS showed a pooled placebo response rate of 37.5% (95% CI 34.4–40.6; with a wide range between 0% to 91.7%). Due to the high placebo response rate in IBS trials, the assay sensitivity (ie, the ability of a trial to successfully differentiate between an efficacious and an inefficacious treatment) is generally low.

Placebo responses in IBS have received increasing attention.⁹ The placebo effect has been identified as a phenomenon influenced by multiple factors of the psychosocial treatment context, including patient characteristics and communication between doctor and patient, as well as the normal symptom fluctuation over time in many diseases. In the context of randomised controlled

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Research in context

Evidence before this study

Trials in irritable bowel syndrome are characterised by a high placebo response (a 2010 meta-analysis showed a pooled placebo response rate of 37.5%), which largely influences the success of these trials. However, previous systematic reviews have shown conflicting results for the factors affecting the placebo response rate in clinical trials. Additionally, these analyses predate the irritable bowel syndrome responder definition by the US Food and Drug Administration (FDA) and European Medicines Agency. We did a systematic review and meta-analysis to identify the pooled placebo response rate in pharmacological randomised controlled trials in adult patients with irritable bowel syndrome to better understand the factors affecting the placebo response rate. We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials between April 1, 1959, and April 30, 2020, using search terms "irritable bowel syndrome", "IBS", "irritable colon", "spastic colon", "spastic bowel", in combination with "placebo", and "placebo effect" with no language restrictions. Only studies that reported a dichotomous outcome of response to therapy with a minimal therapy duration of 4 weeks were included.

Added value of this study

This meta-analysis of 73 randomised controlled trials highlights different moderators that are associated with an increased pooled placebo response rate in pharmacological trials in

irritable bowel syndrome. Additionally, we found a decrease in the pooled placebo response rate after the introduction of the composite FDA endpoint, but the therapeutic gain remained unaltered. These findings could help optimise trial design in irritable bowel syndrome.

Implications of all the available evidence

Based on the findings in this meta-analysis, we suggest future pharmacological trials in irritable bowel syndrome to apply a run-in period of at least 2 weeks (preferably without a placebo therapy pending further research on this topic), and a dose of one or two times a day, to minimise the placebo response rate. There is a reporting and assessment gap in factors affecting patients' treatment expectancies, causing an inadequate assessment of the influence of these factors on the pooled placebo response rate. Adequate assessment and reporting of these factors in the future is needed.

Despite the unaltered therapeutic gain after the introduction of the FDA endpoint, advantages of the FDA endpoint are its contribution to harmonisation of irritable bowel syndrome trials and also that the endpoint seems less sensitive to the sample size of the placebo group. At this point, we believe that the introduction of the FDA endpoint represents a step in the right direction to bring uniformity to irritable bowel syndrome trials, but further investigation of its performance is required.

trials in IBS, study or trial characteristics, including trial duration and number of study visits, have been identified as moderators of the placebo response.¹⁰ Several systematic reviews have attempted to identify specific moderators of the placebo response in IBS, but with conflicting results.^{8,11,12} Improved knowledge regarding moderators in clinical trials is therefore needed to minimise the magnitude of the placebo response in clinical trials by optimising trial designs.¹⁰ This knowledge is especially called for given the publication of the 2016 Rome IV guidance that generated substantial advances in several aspects of clinical trial design,² and publication of the European Medicines Agency (EMA)¹³ and the US Food and Drug Administration (FDA)¹⁴ standards for responder definition in IBS clinical trials. As far as we know, the effects of these novel definitions and recommendations on the placebo response rate have not yet been studied, even though a large number of trials have been done since then.

Therefore, we did a systematic review and meta-analysis that aimed to characterise the pooled placebo response rate in pharmacological randomised controlled trials in patients with IBS and to identify the moderators of the magnitude of the placebo response rate.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis was done in accordance with the guidance provided by the Cochrane

Handbook for Systematic Reviews of Interventions¹⁵ and PRISMA.¹⁶ The protocol is registered in PROSPERO, CRD42020170908.¹⁷ We searched the medical literature to identify potential studies using MEDLINE (April 1, 1959, to April 30, 2020), EMBASE (Jan 1, 1974, to April 30, 2020), and the Cochrane Central Register of Controlled Trials (April 1, 1959 to April 30, 2020). Foreign language papers were translated where necessary. Eligible trials were randomised controlled trials that examined the effect of pharmacological therapies compared with a control arm with a placebo (as a pill, tablet, or capsule). The participants of the study population had to be adult (≥ 18 years) with the diagnosis of IBS (based on either symptom-based diagnostic criteria [ie, Rome criteria] or a physician's assessment). A minimum treatment duration of 4 weeks of active therapy was required (in line with recommendations for treatment trials for disorders of gut-brain interaction).^{2,13} Trials had to report a dichotomous outcome of response to therapy, in terms of global improvement or improvement in abdominal pain. The outcome had to be reported by the patient.² The first period of crossover randomised controlled trials were eligible for inclusion if the authors provided data before crossover. We excluded trials that had treatments other than pharmacological therapies (eg, dietary interventions, food supplements, or psychological therapies), reported on treatment satisfaction as dichotomous outcome of response to therapy,¹⁸ duplicated or reanalysed previously

obtained trial data, and any publication type that was not a full-text article (eg, conference abstract, due to incomplete data for our outcome assessment). There were no language restrictions. Corresponding authors of the studies were contacted if the full-text article was not available and to provide additional information on individual studies when required.

The search was independently done by TB and MB. A medical librarian was contacted for supervision of the search. Trials in IBS were identified using the search terms “irritable bowel syndrome” (as medical subject heading and free-text term), combined, using the set operator “OR”, with “irritable colon”, “IBS”, “spastic colon”, or “spastic bowel” (as free-text terms). These terms were then combined using the set operator “AND” with studies identified using the terms “placebo” or “placebo effect” (both as medical subject heading and free-text terms). Articles identified by the search were assessed and extracted by their abstract, independently by TB and MB, according to the predefined eligibility criteria. Subsequently, all potentially relevant articles were obtained and evaluated independently by TB and MB in greater detail to assess eligibility. Disagreement between the investigators was resolved by discussion with a third investigator (DK).

Data analysis

The primary outcome assessed was the magnitude of the placebo response rate. For the primary outcome assessment, we distinguished between a global improvement responder (ie, patients reporting global improvement) after therapy with placebo, an abdominal pain responder (ie, relief of abdominal pain) after therapy with placebo, and a responder according to the composite FDA endpoint after therapy with placebo (defined as a $\geq 30\%$ reduction in abdominal pain and increase of ≥ 1 complete spontaneous bowel movement from baseline in the same week [IBS with constipation] or a $\geq 50\%$ reduction in the number of days per week with at least one stool that has a consistency of type six or seven on the Bristol stool scale compared with baseline [IBS with diarrhoea] for at least 50% of the weeks of treatment).¹⁴ The composite FDA endpoint was also assessed separately for the abdominal pain responder (ie, a $\geq 30\%$ reduction in abdominal pain) and for the bowel symptom responder (ie, the change in stool frequency and consistency) according to the FDA endpoint definitions. The secondary outcome assessed was the effect of various trial and patient characteristics (ie, moderators) on the pooled placebo response rate, according to the combined responder definition (ie, the primary outcome of each specific trial [either global improvement, improvement in abdominal pain, or the US FDA endpoint], because the trials were generally powered for their specific primary endpoints). The moderators assessed were identified from previous systematic reviews: year of publication, geographical

setting, trial setting (single vs multicentre and primary vs secondary or tertiary care), study design (parallel vs crossover), run-in phase (duration and use of placebo), study size, randomisation ratio, mean age, sex, criteria used to define irritable bowel syndrome, subtype of irritable bowel syndrome, mean duration of diagnosis or symptoms, baseline abdominal pain, type of active therapy, duration of therapy, dosing schedule or escalating dose, number of face-to-face visits, proportion of side-effects, dropouts in the control group, and therapeutic response in the active treatment group. Data for these moderators in each trial were extracted when available.

For all included trials, data were extracted independently by TB and MB into a Microsoft Excel spreadsheet as dichotomous outcomes (responder vs non-responder). Data were extracted as intention-to-treat analyses, with dropouts assumed to be treatment failures, whenever trial reporting allowed this, in accordance with the guidance provided by the Cochrane Handbook for Systematic Reviews of Interventions.¹⁵

The Cochrane Risk of Bias Tool was used to assess the risk of bias at the individual study level.¹⁹ This assessment was done by DK and MB independently. Disagreements were resolved by discussion. Bias was assessed as a judgement (low, unclear, or high risk of bias) for six domains of bias (sequence generation, allocation

Figure 1: Study profile

concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias). Criteria for the judgement of high risk of bias were either one domain with high risk of bias or four domains with unclear risk of bias. Studies with a high risk of bias were then excluded from further assessment.

Data were analysed using R (version 4.0.1). Data were pooled from the placebo arms of the clinical trials using a random-effects model based on logit transformation, allowing for any heterogeneity between trials. Separate analyses were run to evaluate the pooled placebo response rate across all studies for the global improvement responder, abdominal pain responder, combined endpoint (ie, the primary outcome of each specific trial [either global improvement, improvement in abdominal pain, or the US FDA endpoint], composite FDA endpoint, the FDA endpoint abdominal pain responder and the FDA endpoint bowel symptom responder, with 95% CI. Data were presented in forest plots and funnel plots were included for detecting publication bias. Some variables (ie, IBS with diarrhoea and IBS with constipation) were examined separately in a subgroup analysis, with 95% CI. Post-hoc, we also did the previously described analyses for each of the endpoints for the intervention arms of the clinical trials to obtain the intervention response rate. To obtain the therapeutic gain, the difference between the intervention response rate and placebo response rate was calculated separately for each trial and subsequently pooled using a random-effects model.

Each moderator was examined in a separate meta-regression model rather than in a combined model to avoid overfitting of data and listwise deletion (ie, some moderators were measured in one study but not in another study). Results were expressed as odds ratios with a 95% CI. Heterogeneity was evaluated using the I^2 statistic (interpreted as low heterogeneity [$<25\%$], moderate heterogeneity [$25\text{--}50\%$] and high heterogeneity [$>50\%$]) and homogeneity was evaluated using the Q statistic (with $p<0.10$ considered statistically significant).²⁰ A p value of 0.05 or less was considered statistically significant.

Role of the funding source

There was no funding source for this study.

Results

The search strategy generated 6863 article citations, 279 of which appeared to be relevant on the basis of screening the title or abstract, or both, and were retrieved for further assessment (figure 1). Of these, 198 articles were excluded, leaving 81 eligible articles that met our inclusion criteria. The risk of bias was assessed for each study and 11 articles^{21–31} were excluded because of a high

Figure 2: Forest plot of the proportion of placebo responders with the endpoint of global improvement responder*

*60 trials with this endpoint.

	Number of trials with this variable	Placebo		Intervention		Therapeutic gain (95% CI)
		Response rate (95% CI)	<i>I</i> ²	Response rate (95% CI)	<i>I</i> ²	
Global improvement responder endpoint	60	27.3% (24.3–30.9)	90.7%	42.5% (38.7–46.4)	95.4%	13.8% (11.4–16.1)
IBS-D	20	27.2% (22.4–32.7)	89.4%	39.8% (32.7–47.4)	96.5%	..
IBS-C	22	23.3% (19.3–27.9)	93.2%	37.4% (32.8–42.1)	95.4%	..
Abdominal pain responder endpoint	48	34.4% (31.2–37.8)	89.4%	46.8% (43.5–50.2)	93.5%	12.0% (9.3–14.7)
IBS-D	23	33.6% (30.1–37.4)	81.6%	46.7% (43.1–50.3)	87.9%	..
IBS-C	13	31.5% (25.1–38.7)	94.6%	40.1% (34.4–46.0)	95.7%	..
Combined responder endpoint	73	31.3% (28.2–34.5)	91.6%	45.9% (42.4–49.5)	95.5%	13.0% (10.9–15.0)
US FDA endpoint responder						
Composite	20	17.9% (15.2–21.0)	82.8%	29.1% (26.0–32.4)	88.6%	11.7% (9.5–13.9)
IBS-D	9	21.1% (16.6–26.4)	84.0%	31.6% (26.3–37.5)	91.1%	..
IBS-C	10	15.7% (12.6–19.4)	80.9%	27.3% (23.6–31.4)	87.1%	..
Abdominal pain	19	35.1% (30.6–39.9)	89.1%	45.7% (41.2–50.2)	92.4%	10.9% (6.4–15.5)
IBS-D	8	37.0% (29.5–45.1)	90.3%	49.9% (44.3–55.6)	88.4%	..
IBS-C	9	34.6% (28.4–41.5)	90.9%	42.7% (35.7–50.1)	95.0%	..
Bowel symptom	19	28.3% (23.4–33.8)	92.7%	42.6% (37.4–47.9)	95.0%	13.3% (10.2–16.5)
IBS-D	9	29.2% (20.9–39.3)	94.2%	42.8% (33.9–52.2)	96.2%	..
IBS-C	10	27.4% (21.6–34.1)	91.9%	42.4% (36.1–48.8)	93.9%	..

US FDA=US Food and Drug Administration. IBS-C=irritable bowel syndrome with constipation. IBS-D=irritable bowel syndrome with diarrhoea. *Primary outcome of each specific study (either global improvement, improvement in abdominal pain, or the US FDA endpoint).

Table 1: Placebo response rate, intervention response rate, and the therapeutic gain of the primary outcome assessment

risk for bias. 73 randomised controlled trials, described in 70 articles,^{32–101} were included in the meta-analysis. Detailed characteristics of individual trials are provided in the appendix (pp 2–4). The bias assessment of all articles is reported in the appendix (p 5). The risk of bias was low for most of the included articles (58 of the 70 articles). However, selection bias was unclear for several included articles because the allocation concealment might have been compromised by treatment-specific side-effects. Additionally, in some articles a high drop-out ratio of 1 (20%) out of 5 patients was reported or the sample size calculation was unclear.

60 trials provided data for the outcome assessment of proportion of patients who were global improvement responders (figure 2; table 1; appendix p 6). The placebo response rate ranged from 4.7% to 68.6%, with an overall pooled placebo response rate of 27.3% (95% CI 24.3–30.9), with substantial heterogeneity between the trials ($I^2=90.7\%$). The pooled intervention response rate for this endpoint was 42.5% (95% CI 38.7–46.4), with substantial heterogeneity between the trials ($I^2=95.4\%$), resulting in a therapeutic gain of 13.8% (95% CI 11.4–16.1).

48 trials provided data for the outcome assessment of proportion of patients who were abdominal pain responders (figure 3; table 1; appendix p 7). The placebo response rate ranged from 13.3% to 63.7%, with an overall pooled placebo response rate of 34.4% (95% CI 31.2–37.8), with substantial heterogeneity between the

trials ($I^2=89.4\%$). The pooled intervention response rate for this endpoint was 46.8% (95% CI 43.5–50.2), with substantial heterogeneity between the trials ($I^2=93.5\%$), resulting in a therapeutic gain of 12.0% (95% CI 9.3–14.7).

20 trials provided data for the outcome assessment of proportion of patients who were composite FDA endpoint responders (figure 4; table 1; appendix p 8). The overall pooled placebo response rate was 17.9% (95% CI 15.2–21.0), with substantial heterogeneity between the trials ($I^2=82.8\%$). The pooled intervention response rate for this endpoint was 29.1% (95% CI 26.0–32.4), with substantial heterogeneity between the trials ($I^2=88.6\%$), resulting in a therapeutic gain of 11.7% (95% CI 9.5–13.9).

19 trials provided data for the outcome assessment of proportion of patients who were FDA endpoint abdominal pain responders (table 1). The overall pooled placebo response rate was 35.1% (95% CI 30.6–39.9), with substantial heterogeneity between the trials ($I^2=89.1\%$). The pooled intervention response rate on this endpoint was 45.7% (95% CI 41.2–50.2), with substantial heterogeneity between the trials ($I^2=92.4\%$), resulting in a therapeutic gain of 10.9% (95% CI 6.4–15.5).

19 trials provided data for the outcome assessment of proportion of patients who were FDA endpoint bowel symptom responders (table 1). The overall pooled placebo response rate was 28.3% (95% CI 23.4–33.8),

See Online for appendix

Figure 3: Forest plot of the proportion of placebo responders with the endpoint of abdominal pain responder*
*48 trials with this endpoint.

with substantial heterogeneity between the trials ($I^2=92.7\%$). The pooled intervention response rate on this endpoint was 42.6% (95% CI 37.4–47.9), with

substantial heterogeneity between the trials ($I^2=95.0\%$), resulting in a therapeutic gain of 13.3% (95% CI 10.2–16.5).

For all analyses, similar results were seen in trials that assessed IBS with diarrhoea or IBS with constipation subtypes.

Figure 5 shows the response rates in the intervention group against the response rates in the placebo group as defined by the combined endpoint. There were multiple moderators associated with the magnitude of the placebo response rate as defined by the combined endpoint (table 2). There was a significant effect of the year of publication on the placebo response rate. Specifically, the trials published before 2006 (ie, corresponding to the publication of the Rome III criteria,² which was used as a surrogate marker of the process of increased scientific rigor of clinical trial conduct and quality of reporting) had a larger pooled placebo response rate compared with trials published in or after 2006 (37.2% [95% CI 32.7–42.0] vs 28.9% [25.5–33.0], $p=0.032$). The trial location also had a significant effect on the placebo response rate. Trials done in Europe had a significantly larger pooled placebo response rate compared with trials done in America (38.9% [32.3–45.9] vs 25.7% [21.3–30.5], $p=0.0032$) and a non-significant larger pooled placebo response rate compared with trials done in Asia (30.3% [25.2–35.8], $p=0.068$). Some active pharmacological agents were significantly related to the placebo response rate. For IBS with diarrhoea, trials with 5-HT₃ antagonists had a significant larger pooled placebo response rate compared with trials with opioid receptor agonists as the active agent (32.3% [27.8–37.3] vs 16.2% [12.3–21.0], $p<0.0001$). For IBS with constipation, trials with 5-HT₄ agonist had a significant larger pooled placebo response rate compared with trials with secretagogues as active agent (36.1% [29.9–42.9] vs 20.8% [14.5–28.9], $p=0.0030$).

Trial setting (single vs multicentre and primary vs secondary or tertiary care) was not significantly related to the placebo response rate. By contrast, there was a significant effect of the study design on the placebo response rate. Crossover studies had a significant lower pooled placebo response rate than parallel studies (18.4% [95% CI 14.6–23.0] vs 32.8% [29.4–36.0], $p=0.0081$). There was a positive association between the duration of the run-in period and the placebo response. For trials with a run-in period of 2 weeks or less, the placebo response rate was significantly higher than in trials with a run-in period of more than 2 weeks (34.6% [30.9–38.5] vs 19.4% [13.7–26.6], $p=0.0001$). However, there was no significant association between placebo run-in versus no treatment in the run-in period ($p=0.10$). There was a significant effect of the dose schedule on the placebo response rate. Trials with a dose schedule of once or twice a day had a significantly lower pooled placebo response rate compared with trials with a dose schedule of three times a day or more (29.4% [26.2–32.8] vs 40.1% [32.9–47.7], $p=0.025$). The use of an escalating dose,

mean age, the duration of irritable bowel syndrome symptoms or time since diagnosis, the proportion of patients assigned to placebo, and the level of bias were not significantly related to the placebo response rate.

Finally, we did the meta-regression analysis of numeric variables for the combined responder definition (table 3). We found a significant association between the size of the placebo group and the placebo response rate ($p=0.016$), indicating that larger trials were more likely to have a lower placebo response. There was no significant association when comparing the size of the placebo group with the therapeutic gain (appendix p 9). Also, the duration of therapy (against the proportion of placebo responders and the therapeutic gain), the study visits, the proportion of men, the baseline abdominal pain, and proportion of side-effects and dropouts were not associated with the placebo response rate. We did the same meta-regression analysis for the FDA endpoint responder outcome (table 3; appendix p 9). However, there was no significant relationship between any of the aforementioned variables.

Discussion

In this meta-analysis of 73 IBS randomised controlled trials, the magnitude of the placebo response rate was 27.3% using the global improvement responder definition, 34.4% using the abdominal pain responder definition, and 17.9% using the FDA endpoint composite responder definition. When subdividing the FDA composite endpoint, the pooled placebo response rate was 35.1% using the FDA endpoint abdominal pain responder definition and 28.3% using the FDA endpoint bowel symptom responder definition. Studies published before 2006, with a parallel design, a run-in period of 2 weeks or less, a dose schedule of three times or more a day, studies done in Europe, and a smaller study size in the control group were significantly associated with a higher placebo response rate.

This meta-analysis was prompted by the fact that the recent introduction of novel trial endpoints and diagnostic criteria have changed the landscape for IBS trials. Several findings from our analysis are in line with the most recent meta-analysis on the subject⁸ (eg, higher placebo response in trials done in Europe and in trials that used a higher daily dosing schedule). Other similarities were found in the moderators that had no or only modest effects on the pooled placebo response rate—eg, the trial setting and patients' predominant stool pattern. The finding that the pooled placebo response rates in trials that used antispasmodics as the active agent were not statistically significantly higher than in trials that used peppermint oil as the active agent, is another similarity. Contrary to our study, Ford and Moayyedi found no significant effect of the year of publication on the placebo response rate, which could be related to the 10-year time gap between their and our meta-analyses.

Figure 4: Forest plot of the proportion of placebo responders with the endpoint of composite FDA endpoint responder*

FDA=Food and Drug Administration. *20 trials with this endpoint.

Figure 5: L'Abbe plot of the response rate, defined as the combined endpoint, in the intervention group against the response rate in the placebo group. The equality line (solid line) and overall effect line (dashed line) are shown. Circle size represents sample size.

The pooled placebo response rates in this meta-analysis are lower than reported before, with pooled placebo response rates of 36.0% (95% CI not shown),¹¹ 37.5%

	Number of trials with this variable	Pooled placebo response rate (95% CI)	I ²	Combined I ²	Q statistic	Odds ratio (95% CI)	p value
Year of publication							
Before 2006	21	37.2% (32.7–42.0)	87.3%	..	..	..	..
2006 or later	52	28.9% (25.5–33.0)	92.1%	..	..	..	..
Before 2006 vs 2006 or later	..	..	..	92.9%	4.6095	1.47 (1.03–2.08)	0.032
Geographical location							
Europe	23	38.9% (32.3–45.9)	89.1%	..	..	..	..
America	27	25.7% (21.3–30.5)	92.9%	..	..	..	..
Asia	15	30.3% (25.2–35.8)	82.8%	..	..	..	..
Europe vs America	..	..	..	92.8%	8.6817	1.84 (1.23–2.75)	0.0032
Europe vs Asia	..	..	..	88.0%	3.3224	1.47 (0.97–2.22)	0.068
Trial setting							
Multicentre	60	31.4% (28.1–34.8)	92.8%	..	..	..	..
Single centre	13	30.3% (21.8–40.5)	72.2%	..	..	..	..
Primary	6	40.0% (28.9–52.3)	92.5%	..	..	..	..
Secondary or tertiary	32	34.3% (29.5–39.5)	83.9%	..	..	..	..
Multicentre vs single centre	..	..	..	93.5%	0.0429	1.05 (0.66–1.69)	0.84
Primary vs secondary or tertiary	..	..	..	88.4%	0.7017	1.28 (0.72–2.29)	0.40
Study design							
Parallel	68	32.8% (29.4–36.0)	91.0%	..	..	..	..
Crossover	5	18.4% (14.6–23.0)	78.9%	..	..	..	..
Parallel vs crossover	..	..	..	92.6%	7.0033	2.22 (1.23–4.01)	0.0081
Duration run-in period							
≤2 weeks	47	34.6% (30.9–38.5)	90.4%	..	..	..	..
>2 weeks	13	19.4% (13.7–26.6)	96.2%	..	..	..	..
≤2 weeks vs >2 weeks	..	..	..	93.0%	15.0432	2.19 (1.47–3.26)	0.0001
Placebo run-in							
Yes	3	46.2% (31.5–61.6)	86.9%	..	..	..	..
No	70	30.6% (27.8–33.9)	91.4%	..	..	..	..
Yes vs no	..	..	..	93.15%	2.693	1.95 (0.88–4.33)	0.10
Assignment ratio (placebo:intervention)							
Balanced ratio	41	33.8% (29.5–38.4)	91.6%	..	..	..	..
Unbalanced ratio	32	28.3% (24.2–32.7)	90.9%	..	..	..	..
Balanced ratio vs unbalanced ratio	..	..	..	93.1%	2.462	1.30 (0.94–1.79)	0.12
Mean age							
≤40 years	17	34.9% (27.2–43.4)	85.8%	..	..	..	..
>40 years	54	29.9% (26.6–33.4)	92.6%	..	..	..	..
≤40 years vs >40 years	..	..	..	93.4%	1.2136	1.25 (0.84–1.87)	0.27
Sex							
>30% of patients male	27	31.8% (26.9–37.1)	85.4%	..	..	..	..
<30% of patients male	46	30.9% (27.2–35.1)	93.3%	..	..	..	..
>30% of patients male vs <30% of patients male	..	..	..	93.4%	0.0515	1.04 (0.74–1.47)	0.82
Duration of IBS symptoms or diagnosis							
≤5 years	7	37.6% (27.9–48.4)	89.3%	..	..	..	..
>5 years	28	30.3% (26.5–34.4)	88.4%	..	..	..	..
≤5 years vs >5 years	..	..	..	91.1%	1.7228	1.39 (0.85–2.26)	0.19
Use of Rome criteria							
No	5	45.4% (29.6–62.2)	84.3%	..	..	..	..
Yes	68	30.4% (27.3–33.7)	91.8%	..	..	..	..
No vs yes	..	..	..	93.1%	3.6051	1.90 (0.98–3.69)	0.058

(Table 2 continues on next page)

	Number of trials with this variable	Pooled placebo response rate (95% CI)	I^2	Combined I^2	Q statistic	Odds ratio (95% CI)	p value
(Continued from previous page)							
Dosage schedule							
Three times or more a day	14	40.1% (32.9–47.7)	84.1%	..	..	..	..
Once or twice a day	59	29.4% (26.2–32.8)	91.9%	..	..	..	..
Three times or more a day vs once or twice a day	..	..	..	92.9%	5.0302	1.59 (1.06–2.38)	0.025
Escalating dose							
Yes	10	36.4% (28.7–45.0)	66.8%	..	..	..	..
No	63	30.6% (27.4–34.0)	92.5%	..	..	..	..
Yes vs no	..	..	..	93.4%	0.9737	1.28 (0.78–2.10)	0.33
Level of bias							
Unclear	12	38.9% (32.6–45.7)	69.0%	..	..	..	..
Low	62	30.5% (27.2–33.9)	92.4%	..	..	..	..
Unclear vs low	..	..	..	93.1%	1.9165	1.38 (0.88–2.16)	0.17
Active therapy							
Antidepressant	8	42.5% (31.4–54.5)	68.6%	..	..	..	..
Antispasmodic†	9	41.7% (33.6–50.2)	83.8%	..	..	..	..
5-HT4 agonist‡	11	36.1% (29.9–42.9)	92.0%	..	..	..	..
5-HT3 antagonist†	13	32.3% (27.8–37.3)	84.6%	..	..	..	..
Peppermint oil	4	30.2% (20.4–42.2)	61.1%	..	..	..	..
Secretagogues‡	12	20.8% (14.5–28.9)	95.7%	..	..	..	..
Opioid receptor agonist (peripherally acting)†	5	16.2% (12.3–21.0)	70.1%	..	..	..	..
5-HT3 antagonist plus antispasmodic plus opioid receptor agonist (peripherally acting)†	27	31.5% (27.1–36.3)	90.4%	..	..	..	..
5-HT4 agonist plus secretagogues‡	23	27.6% (22.6–33.2)	95.1%	..	..	..	..
Antispasmodic vs peppermint oil	..	..	..	83.1%	2.1409	1.68 (0.84–3.34)	0.14
Antidepressant vs peppermint oil	..	..	..	68.0%	1.9833	1.74 (0.80–3.76)	0.16
5-HT3 antagonist vs opioid receptor agonist (peripherally acting)	..	..	..	84.0%	16.5223	2.50 (1.61–3.88)	<0.0001
Antispasmodic vs 5-HT3 antagonist	..	..	..	86.0%	3.8122	1.49 (1.0–2.23)	0.051
5-HT4 agonist vs secretagogues	..	..	..	94.7%	8.8291	2.20 (1.31–3.70)	0.0030
5-HT3 antagonist plus antispasmodic plus opioid receptor agonist (peripherally acting) vs 5-HT4 agonist plus secretagogues	..	..	..	94.7%	0.8997	1.20 (0.82–1.76)	0.34
IBS=irritable bowel syndrome. IBS-C=irritable bowel syndrome with constipation. IBS-D=irritable bowel syndrome with diarrhoea. *The primary endpoint of each specific trial, either global improvement, improvement in abdominal pain, or the US Food and Drug Administration endpoint. †Agents used in IBS-D. ‡Agents used in IBS-C.							
Table 2: Moderators with categorical variables of the placebo response rate for the composite endpoint*							

(34.4–40.6),⁸ and 40.2% (35.9–44.4).¹² This finding could be explained by the number of trials included in this meta-analysis, the distinction between different responder definitions (in particular the novel FDA definitions), and the inclusion of a considerable number of recent trials. Our results have shown that more recent studies have a significantly lower pooled placebo

response rate. This trend appears to be at odds with the increase of pooled placebo response rates observed in other disorders, such as depression, schizophrenia, and neuropathic pain.^{102,103} The fact that more recent clinical trials in IBS had larger sample sizes,¹⁰ and modifications in study design based on new guidelines (including the Rome III and later Rome IV criteria² and the EMA¹³ and

	Number of trials with this variable	Combined I ²	Q statistic	Odds ratio (95% CI)	p value
Primary endpoint					
Number of participants in the placebo group	73	92.6%	5.7793	0.999 (0.998–0.9998)	0.016
Face-to-face study visits	55	94.4%	0.1482	0.98 (0.87–1.09)	0.70
Baseline abdominal pain†	45	93.6%	0.5367	0.93 (0.78–1.12)	0.46
Proportion of side-effects	51	94.8%	0.3682	1.38 (0.49–3.93)	0.54
Proportion of dropouts	69	93.4%	1.5641	0.38 (0.08–1.72)	0.21
Duration of therapy, weeks	73	93.3%	0.9809	0.99 (0.96–1.01)	0.32
Proportion male patients	73	93.4%	0.4644	1.25 (0.66–2.39)	0.50
FDA endpoint					
Number of participants in the placebo group	20	90.6%	0.0019	1.00 (0.998–1.002)	0.96
Face-to-face study visits	20	90.7%	0.0417	1.02 (0.86–1.21)	0.84
Baseline abdominal pain†	18	89.1%	2.3257	0.77 (0.55–1.08)	0.13
Proportion of side-effects	19	90.7%	0.0004	0.98 (0.18–5.25)	0.98
Proportion of dropouts	20	90.6%	0.0231	1.29 (0.05–35.19)	0.88
Duration of therapy, weeks	20	90.2%	0.2065	1.00 (0.99–1.01)	0.65
Proportion male patients	20	90.6%	0.0119	0.90 (0.13–6.26)	0.91

FDA=US Food and Drug Administration. *The primary outcome of each specific trial, either global improvement, improvement in abdominal pain, or the US FDA endpoint. †Measured using an 11-point Numeric Rating Scale.

Table 3: Moderators with numeric variables of the placebo response rate for the composite endpoint*

FDA¹⁴ recommendations) have favoured the trend towards lower placebo response rates in IBS. As a result, we consider it futile to compare studies before 2006 with studies done in 2006 or later.

For the following variables, our results on the association between the moderators and the placebo response rates are in line with previous studies: the significant effect of studies done in Europe,^{8,104} a parallel design,^{103,105} and a dose schedule of three times or more a day,^{8,11} and no significant effect of sex,^{10,106,107} age,^{106,107} and trial setting^{8,11,12} on the placebo response rate. For study duration,^{8,10,11,108} disease severity, and disease duration,^{102,103,106,109,110} previous findings have shown incongruent results, which could be related to different selection criteria. Our results did not show a significant association between these moderators and the pooled placebo response rate. Therefore, together these findings do not support the idea that there might be placebo responders or non-responders based on individual characteristics (age, sex), which would mean that trials should select participants based on criteria to reduce placebo responses. Our findings suggest that trial design and characteristics are more important than individual characteristics to modify to minimise the placebo response rate.

We have shown that longer run-in phases are significantly associated with a lower pooled placebo response rate, in line with previous studies.^{11,12} However, the translation to daily practice becomes more difficult as the run-in period is extended. Therefore, we recommend future trials to apply a run-in phase of at least 2 weeks to

reduce the placebo response rate. The use of a placebo run-in is questionable.¹¹¹ The purpose of a placebo run-in is eliminating patients who respond to placebo during run-in and thereby decreasing placebo response rates following randomisation in the active treatment phase. It is interesting to note that, in line with studies in other disorders,^{112–114} our results showed no benefit of a placebo run-in on the placebo response rate. Additionally, a placebo run-in creates a selection bias and a discrepancy between the trial population and the clinical patient population.^{106,111,115} Because of the risk of underestimating the overall effect size,² and the lack of evidence for a placebo run-in decreasing the placebo response rate, there appears to be insufficient reason for the use of a placebo run-in in future trials. However, it is important to note that these results are based only on the three trials with a placebo run-in. Therefore, further research is needed to establish the exact effects of placebo run-ins on overall placebo response rates before establishing a firm recommendation.

In May, 2012, the FDA published interim endpoints for IBS trials.¹⁴ Although harmonisation of trial design in IBS was warranted, it has been a matter of debate whether the quantification of only two, albeit key, IBS symptoms (abdominal pain and disordered defecation), is able to integrate the multidimensional aspect of IBS symptoms to a sufficient degree,¹¹⁶ and it has been suggested that less robust endpoints might be superior or at least equal in clinical decision making.¹¹⁷ Our results (table 1; figure 5) showed an approximately 10% lower placebo response rate for the composite FDA endpoint by comparison with the historically commonly applied endpoints (ie, global improvement responder endpoint). However, the intervention response rate has a similar trend, with an estimated 13% reduction for the composite FDA endpoint by comparison with the global improvement responder endpoint, resulting in a therapeutic gain nearly the same (13.8% vs 11.7%). Identical results were observed for the abdominal pain responder endpoints, in which the placebo response rates and intervention response rates remained the same after introduction of the FDA endpoint, resulting in no changes in the therapeutic gain. This would imply no apparent advantage of the FDA endpoint in showing the efficacy of active therapy. Conversely, the FDA endpoint seems less dependent on specific moderators, such as the sample size of the placebo group. At this point, we believe that the introduction of the FDA endpoint represents a step in the right direction to bring uniformity to IBS trials, but further investigation of the performance of this endpoint is required.

Previous studies have not shown an association between the sample size of the placebo group and the placebo response rate.^{8,11,12} Our findings showed such an association, which was significant, when assessing the combined responder endpoint. This association was not found for the FDA composite endpoint, which suggests that this endpoint is less sensitive to sample size. No

association was found between sample size and therapeutic gain for any of the endpoints.

Notably, we found a higher pooled placebo response rate with the abdominal pain responder endpoints compared with the global improvement responder endpoints and the bowel symptom responder endpoint, which is in line with previous findings.¹¹ We speculate that this finding might be because it is easier for patients to delineate an improvement specifically for abdominal pain, rather than for a much broader symptom complex with different elements, such as global improvement. Additionally, the symptom of abdominal pain is more modifiable by placebo mechanisms (cognitive factors), is more easily remembered, or is most salient to the patient, especially if the treatment information refers to improvement specifically for this symptom. Finally, the abdominal pain responder defined according to the FDA endpoint (ie, 30% improvement in abdominal pain) might be a substantial hurdle allowing a large placebo response.¹¹⁵ Indeed, in some studies exploring a higher pain improvement threshold generated a bigger margin over placebo.^{86,97}

In our analyses, we did not focus on the symptoms of bloating and abdominal discomfort because of the widespread nature and the less well defined nature of these symptoms.¹¹⁸ Abdominal discomfort has also been removed from the Rome IV criteria. Additionally, an improvement in the symptom of bloating or abdominal discomfort, subsequently associated with a higher pooled placebo response, is neither sensitive nor specific for IBS alone, even in trials before Rome IV, resulting in an erroneously higher placebo response rate.

As for moderators of the placebo response, treatment expectations, in terms of behavioural, psychobiological, and contextual factors (eg, conditioning, patient–clinician relationship), appear to be relevant.^{10,13,119} A higher pooled placebo response rate is associated with an unbalanced randomisation in multiple neurological and psychiatric conditions,^{10,106} and a higher number of study visits.^{11,106} However, our results did not show this association. An explanation might be that most trials did not report (or measure) these potential moderators. Although adequate assessment of these moderators might be difficult, we advocate for more accurate and detailed reporting of these in future trials.¹⁰ Additionally, assessing possible unblinding can also provide insight into treatment expectation, which can be accomplished, in line with FDA recommendations,¹²⁰ by including a single item at the end of the trial to ask patients to identify the clinical trial arm in which they believe they participated.

Previous studies have shown that patients are more likely to report symptom improvement if they subjectively perceive an effect of the drug (including side-effects), while patients without any side-effects might believe the therapy is ineffective and for this reason might drop out of the trial.^{2,10,121,122} We found no such association in our results. However, these phenomena are complex and

might include a multitude of underlying mechanisms including the content and mode of delivery of information during informed consent, driving a delicate balance between placebo and nocebo effects, thereby modifying treatment expectations in both positive and negative directions.¹⁰⁶ These phenomena can also have profound effects on symptom experience, patient expectations about the active pharmacological therapy used, and reporting in the context of clinical trials. The complexity of these phenomena does not allow us to draw firm conclusions based on the current analyses.^{121,122}

The strengths of this study include the magnitude and detailed assessment of various moderators influencing the pooled placebo response rate. Furthermore, IBS with diarrhoea and IBS with constipation were included as a subanalysis rather than a separate primary analysis given the intent of the study. It is important to note, however, that regulatory agencies currently only recognise IBS by subcategory; drugs can only be evaluated for either IBS with diarrhoea or IBS with constipation. Future scrutiny of the IBS definitions currently used by regulatory agencies is required.

There are, however, some limitations of our study. First, 12 (17%) of the 70 articles had an unclear risk of bias, which might have influenced results. Considering the fact that we did not find an effect of the level of bias on the placebo response rate, it is more likely that these deficiencies relate to the lack of reporting of design details assessed in The Cochrane Risk of Bias Tool, rather than true design defects. Second, variability in patient behaviour during the trial period (eg, diet, exercise, stress) and clinical evolution of the disorder during studies could not be extracted from the trials but might influence the placebo response. Third, our results rely on the reporting of the included trials and as mentioned earlier, some moderators, particularly in older trials, have been inadequately reported. There is substantial heterogeneity in trial design, endpoints, and reporting, which makes pooling of results for a meta-analysis inherently difficult. Therefore, for the primary outcome of these analyses, we analysed different study endpoints separately. For the moderator analysis, we chose to perform analysis according to the primary outcomes for which the particular trial was powered, allowing some correction for differences in study design.

In conclusion, the magnitude of the pooled placebo response rate in pharmacological trials in IBS is 27·3% for the global improvement responder endpoint. After the introduction of the interim composite FDA endpoint, the pooled placebo response decreased to 17·9%, but the therapeutic gain remained unaltered. However, the introduction of the FDA endpoint contributes to the harmonisation of trial designs in IBS trials and the FDA endpoint itself seems less sensitive to the sample size of the placebo group. Multiple moderators were associated with a higher pooled placebo response rate. On the basis of our findings, we suggest future pharmacological

trials in IBS should use a run-in period of at least 2 weeks (preferably without a placebo therapy pending further research on this topic) and a daily dose of one or two times a day to minimise the pooled placebo response rate. Sample size calculations should consider a therapeutic gain of 11–15%, when using a dichotomous outcome, depending on the outcome parameter chosen. Additionally, adequate assessment and reporting in the future is needed for variables associated with treatment expectancies (both positive and negative) before and during treatment.

Contributors

DK conceptualised the review project and MB developed the study protocol under the supervision of DK. MB and TB did the literature search, screened and reviewed all the published literature, and did the data extraction. MB did the data analysis. MB and DK did the data interpretation and MB drafted the manuscript and prepared the tables and figures. SE, MC, JT, MS, AM, and DK provided a constructive review of the manuscript. BW provided a critical analyses of the data analysis. MB and DK have verified the underlying data. DK supervised all study phases. All authors approved the final version of the manuscript before its submission. All authors had full access to all the data in the study and have accepted responsibility to submit for publication.

Declaration of interests

SE reports grants from Deutsche Forschungsgemeinschaft (German Research Foundation), outside the submitted work. MC serves as a consultant for Sanofi, Allergan, Arena, Kiowa Kyrin, Reckitt Benckiser, outside the submitted work. JT reports personal fees from Adare, Arena, Christian Hansen, Devintec, Ironwood, Shire, Truvion, Abbott, and Menarini; and grants from Shire, Tsumura, Sofar, Mylan, outside the submitted work. MS reports grants and personal fees from Danone Nutricia Research, and Glycom; personal fees from Nestlé, Ironwood, Menarini, Biocodex, Arena, Adnovate, Shire, Tillotts, Kyowa Kirin, Takeda, Alimentray Health, AlfaSigma, and Falk Foundation; and grants from Genetic Analysis, outside the submitted work. AM reports grants from ZonMw, Will Pharma, Allegan, Grünenthal, Pentax Europe, and the Dutch Cancer Society; and financial compensation to their institution for giving scientific advice to Bayer, Kyowa Kirin, and Takeda, outside the submitted work. DK reports grants from Allergan, Will Pharma, Grünenthal, ZonMw, United European Gastroenterology, and Maag-Lever-Darmstichting, outside the submitted work. MB, BW, and TB declare no competing interests.

Data sharing

There are no individual participant data available for this review. Other documents—ie, statistical analysis plan and analytic code—will be available immediately following publication with no end date for researchers who provide a methodologically sound proposal with the purpose of achieving aims in the approved proposal. The master list of the trials included in this study is available upon request. Proposals and requests should be directed to m.bosman@maastrichtuniversity.nl to gain access; data requestors will need to sign a data access agreement.

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