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

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Summary

Background – Clinical trials in irritable bowel syndrome (IBS) are associated with high placebo response rates. We aimed to identify the magnitude and the contributing factors to this placebo response rate in pharmacological trials in IBS.

Methods – We conducted a systematic review and meta-analysis with a medical search on MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials between 01/04/1959 and 30/04/2020. We included all randomized controlled trials (RCTs) with a dichotomous outcome of response to therapy (in terms of global improvement or improvement in abdominal pain) in adult patients with IBS that compare an active pharmacotherapeutic agent with placebo. Exclusion criteria were trials reporting on treatment satisfaction as outcome or clinician-reported outcomes and a treatment duration of less than four weeks. The main outcome assessed was the identification of the magnitude of the pooled placebo response rate, for the following endpoints: global improvement responder, abdominal pain responder and the FDA endpoints. We extracted information from published reports and pooled proportions through meta-analysis with random effects. In addition, several variables were examined to investigate the moderating effect on the placebo response. The study was registered with PROSPERO, CRD42020170908.

Findings – Of the 6863 publications identified, 73 RCTs were included in our analysis. The pooled placebo response rate was 27·3% (95% CI 24·3%-30·9%) using the global improvement-, 34·4% (95% CI 31·2%-37·8%) using the abdominal pain- and 17·9% (95% CI 15·2%-21·0%) using the composite FDA endpoint responder definition, all with substantial heterogeneity between the trials. Studies published prior to 2006, conducted in Europe, with a parallel design, a run-in period of ≤ two weeks, a dosage schedule of ≥ three times a day, and a smaller sample size of the control group were significantly associated with a higher pooled placebo response rate.

Interpretation – The pooled placebo response rate in pharmacological trials in IBS is 27·3% for the global improvement responder endpoint. Multiple moderators were associated with the pooled placebo response rate; we recommend future trials to apply a run-in period of at least two weeks and a daily dosage of one or two times a day with the purpose of minimizing the placebo response rate.

Funding – None received.

Introduction

Irritable bowel syndrome (IBS) is a common disorder of gut-brain interaction characterized 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 Western world (according to the Rome IV criteria).[3] IBS is not only associated with a significant impact on an individuals' functioning and quality of life, but also with substantial costs to patients, healthcare systems and society.[4,5] The treatment of IBS is commonly known to represent a clinical challenge, in part due to varying efficacy of different therapies.[1,6] In order to improve therapeutic outcomes, furthermore in-depth understanding of the mechanisms relevant to existing strategies is necessary, including the role of placebo in trials for IBS. In general, pharmacological therapies are considered efficacious if they are superior to placebo in clinical trials.[2] The magnitude of the placebo response therefore has profound effects on the outcomes. Previous pharmacological trials in disorders of gut-brain interaction, including IBS, have shown that there is a significant proportion of patients that benefits from placebo intervention.[7] The previous meta-analysis in the placebo response in IBS by Ford and Moayyedi (2010) showed a pooled placebo response rate of 37·5% (95% CI 34·4%-40·6%, with a wide range between 0% to 91·7%).[8] Due to the high placebo response rate in IBS trials, the assay sensitivity (i.e., the ability of a trial to successfully differentiate between an effective and an ineffective treatment) is generally low.

Placebo responses in IBS have received increasing attention over the years.[9] The placebo effect has been identified as a phenomenon influenced by multiple factors of the psychosocial treatment context, including patient characteristics and doctor-patient communication, as well as the normal symptom fluctuation over time in many diseases. In the context of RCTs (randomized clinical trials) in IBS, study or trial characteristics, including trial duration and number of study visits, have been identified.[10] In this respect, a number of systematic reviews in the past have attempted to identify specific moderators of the placebo response in IBS, but with conflicting results.[8,11,12] An improved knowledge regarding moderators in clinical trials therefore remains warranted in order to minimize the magnitude of the placebo response in clinical trials by optimizing trial designs to increase the likelihood of demonstrating the effectiveness of pharmacological treatment.[10] This is especially called for given the recent publication of the Rome IV (2016) guidance that generated substantial advances in several aspects of clinical trial design[2], and publication of the European Medicines Agency (EMA)[13] and the 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, despite the fact that a large number of trials have been conducted since then.

Therefore, we conducted a systematic review and meta-analysis with the aim to characterize the pooled placebo response rate in pharmacological RCTs of IBS and to identify the moderators, based on those previously described by existing systematic reviews, of the magnitude of the placebo response rate.

Methods

This systematic review and meta-analysis was performed in accordance with the guidance provided by *the Cochrane Handbook for Systematic Reviews of Interventions*[15] and the PRISMA guidelines[16]. The search was registered in PROSPERO, the International Prospective Register of Systematic Reviews (registration number: CRD42020170908).[17]

Search strategy and selection criteria

We conducted a search of the medical literature to identify potential studies using MEDLINE (April 1959 – April 2020), EMBASE (January 1974 – April 2020), and the Cochrane Central Register of Controlled Trials (April 1959 – April 2020). Eligible trials were RCTs that examined the effect of pharmacological therapies compared to a control arm with a placebo (as a pill/tablet/capsule). The participants of the study population had to be adult (18 year or older) with the diagnosis IBS (based on either symptom-based diagnostic criteria, i.e., Rome criteria, or a physicians' assessment). A minimum treatment duration of four weeks in which active therapy was given 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 cross-over RCTs was eligible for inclusion if the authors provided data prior to cross-over. We excluded trials with treatments other than pharmacological therapies (e.g. dietary interventions, food supplements or psychological therapies), reporting on treatment satisfaction as outcome[18], duplicates or reanalysis of previously obtained trial data, and a publication type of the article other than a full-text article (e.g. 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.

The search was independently conducted by two investigators (T.B. and M.B.). A medical librarian was contacted for supervision of the search. Trials in IBS were identified using the following terms: *irritable bowel syndrome* (as medical subject heading and free-text term), *irritable colon, IBS, spastic colon or spastic bowel* (as free-text terms, combined using the set operator "OR"). These terms were then combined using the set operator "AND" with studies identified using the following 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 two investigators (T.B. and M.B.), according to the predefined eligibility criteria. Subsequently, all potentially relevant papers were obtained and evaluated independently by the two investigators in greater detail in order to assess eligibility. Disagreement between the investigators was resolved by discussion with a third investigator (D.K.).

Data analysis

The primary outcome assessed was the magnitude of the placebo response rate. For the primary outcome assessment, we distinguished between (i) a global improvement responder (i.e. patients reporting global improvement) after therapy with placebo, (ii) an abdominal pain responder (i.e. relief of abdominal pain) after therapy with placebo, and (iii) a responder according to the composite FDA endpoint after therapy with placebo (defined as: ≥30% abdominal pain reduction and increase ≥1 CSBM from baseline in the same week (IBS-C) or

a ≥50% reduction in the number of days per week with at least one stool that has a consistency of type six or seven compared with baseline (IBS-D) for at least 50% of the weeks of treatment)[14]. The composite FDA endpoint was also assessed separately for pain response and 'bowel symptom response' (i.e. the change in stool frequency or consistency). The secondary outcome assessed was the effect of moderators (various trial and patient characteristics, based on moderators identified from previous systematic reviews, see below) on the pooled placebo response rate, according to the combined responder definition (i.e. the primary endpoint of each specific trial, either global improvement, improvement in abdominal pain or the FDA endpoint, as the trials were generally powered for their specific primary endpoints).
For all included trials, data were extracted independently by two investigators (T.B. and M.B.) into a Microsoft Excel spreadsheet as dichotomous outcomes (responder versus non-responder). The following data were also extracted for each trial, where available: year of publication, geographical setting, trial setting (single versus multicenter and primary versus secondary/tertiary care), study design (parallel versus cross-over), run-in phase (duration and use of placebo), study size, randomization ratio, mean age, sex, criteria used to define IBS, subtype of IBS, mean duration of diagnosis/symptoms, baseline abdominal pain, type of active therapy, duration of therapy, dosing schedule/escalating dose, number of face-to-face visits, proportion of side effects, and dropouts in the control group, therapeutic response in the active treatment group. Corresponding authors of studies were contacted to provide additional information on individual studies where required. Foreign language papers were translated where necessary. Data were extracted as intention-to-treat analyses, with dropouts assumed to be treatment failures, wherever 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 access the risk of bias at the individual study level.[19] This was performed by two investigators independently (D.K. and M.B.). 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 concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias). Criteria for the judgement of high risk of bias were either 1 domain with high risk of bias or 4 domains with unclear risk of bias. Studies at high risk of bias were then excluded from further assessment.

Data were stored and analyzed using R version 4.0.1 (R Core Team [2020]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). 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 across all studies for the global improvement responder, abdominal pain responder, combined endpoint (primary outcome - either global improvement or abdominal pain responder - of the specific study), composite FDA endpoint and the FDA endpoint abdominal pain responder, with a 95% confidence interval (CI). Data were presented in forest plots and funnel plots were included for detecting publication bias. Some variables (i.e. IBS-D and IBS-C) were examined separately in a subgroup analysis, with a 95% confidence interval (CI). Post hoc, previous analyses were also conducted for the intervention arms of the clinical trials. In order 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.

Moderators were extracted as beforementioned (predefined). Each moderator was examined in a separate meta-regression model rather than in a combined model to avoid overfitting of data and listwise deletion (i.e. some moderators are measured in one study but not in another study). Results were expressed in odds ratios with a 95% confidence interval (CI). Heterogeneity was evaluated using I^2-statistics (interpreted as low heterogeneity (<25%), moderate heterogeneity (25%-50%) and high heterogeneity (>50%)) and homogeneity was evaluated using the Q-statistics (with $P < 0{\cdot}10$ considered statistically significant).[20] A p-value of $\leq 0{\cdot}05$ was considered statistically significant.

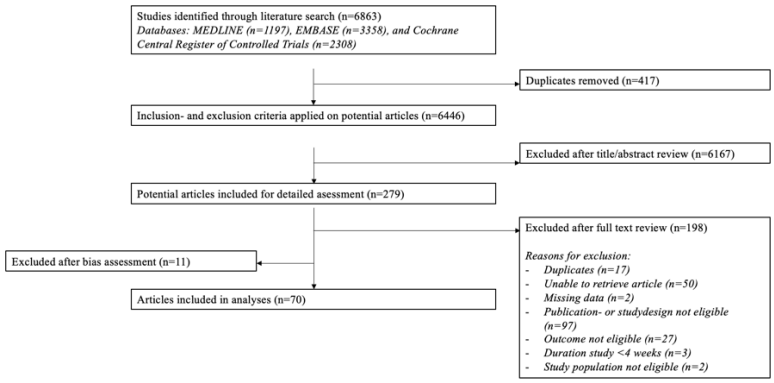
Role of the funding source

There was no funding received for this study. All authors have confirmed they had full access to all the data in the study and have accepted responsibility to submit for publication.

Results

The search strategy (Figure 1.) generated 6863 citations, 279 of which appeared to be relevant based on screening title and/or abstract and were retrieved for further assessment. Of these, 198 trials were excluded for various reasons, leaving 81 eligible trials that met our inclusion criteria. Each study's risk of bias was assessed, after which 11[21-31] additional trials were excluded due to high risk for bias. Eventually, 73 RCTs (described in 70 articles[32-101]) were included in the meta-analysis. Detailed characteristics of individual trials are provided in the Supplementary (see Supplementary page 2 and 4). The bias assessment of all trials is reported in the Supplementary (see Supplementary page 5). The risk of bias was low for most of the included trials (58 of the 70 trials). However, selection bias is unclear for several included studies because the allocation concealment may be compromised by treatment-specific side effects. In addition, in a number of trials a high drop-out ratio (1 (20%) of 5 patients) was reported or the sample size calculation was unclear.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis Analysis) flow diagram of trials identified, excluded and included in the meta-analysis



Sixty trials provided data for the outcome assessment of proportion of patients who were global improvement responders (Figure 2a. and 2b., Table 1.). 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 90·73%). 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 95·37%), resulting in a therapeutic gain of 13·8% (95% CI 11·4%-16·1%). Out of these sixty trials, twenty trials provided data from the IBS with diarrhea subtype with a pooled placebo response rate of 27·2% (95% CI 22·4%-32·7%) and twenty-two trials provided data from the IBS with constipation subtype with a pooled placebo response rate of 23·3% (95% CI 19·3%-27·9%).
Forty-eight trials provided data for the outcome assessment of proportion of patients who were abdominal pain responders (Figure 2c. and 2d., Table 1.). 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 89·37%). 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 93·53%), resulting in a therapeutic gain of 12·0% (95% CI 9·3%-14·7%). Out of these forty-eight trials, twenty-three trials provided data from the IBS with diarrhea subtype with a pooled placebo response rate of 33·6% (95% CI 30·1%-37·4%) and thirteen trials provided data from the IBS with constipation subtype with a pooled placebo response rate of 31·5% (95% CI 25·1%-38·7%).

Figure 2a. Forest plot of proportion of placebo responders, with endpoint global improvement responder (total of articles with this endpoint: n = 60).

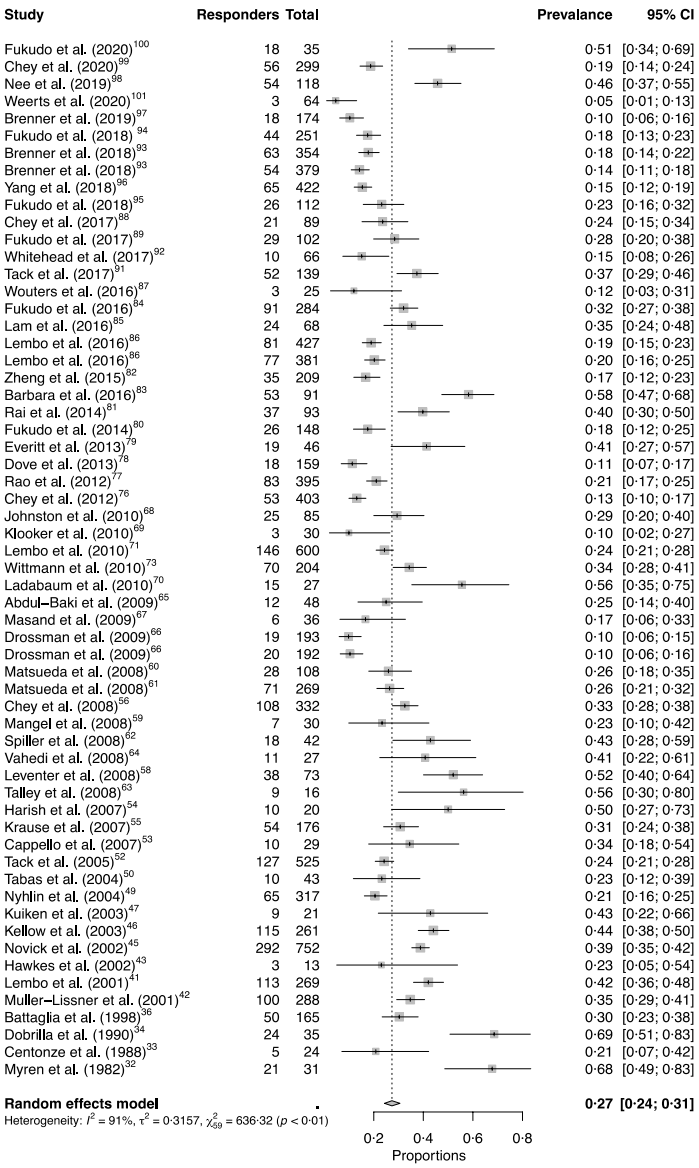


Figure 2b. Funnel plot of proportion of placebo responders, with endpoint global improvement responder (total of articles with this endpoint: n = 60).

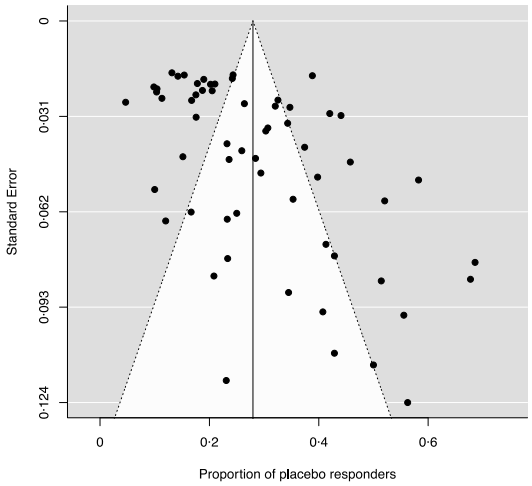


Figure 2c. Forest plot of proportion of placebo responders, with endpoint abdominal pain responder (total of articles with this endpoint: n = 48).

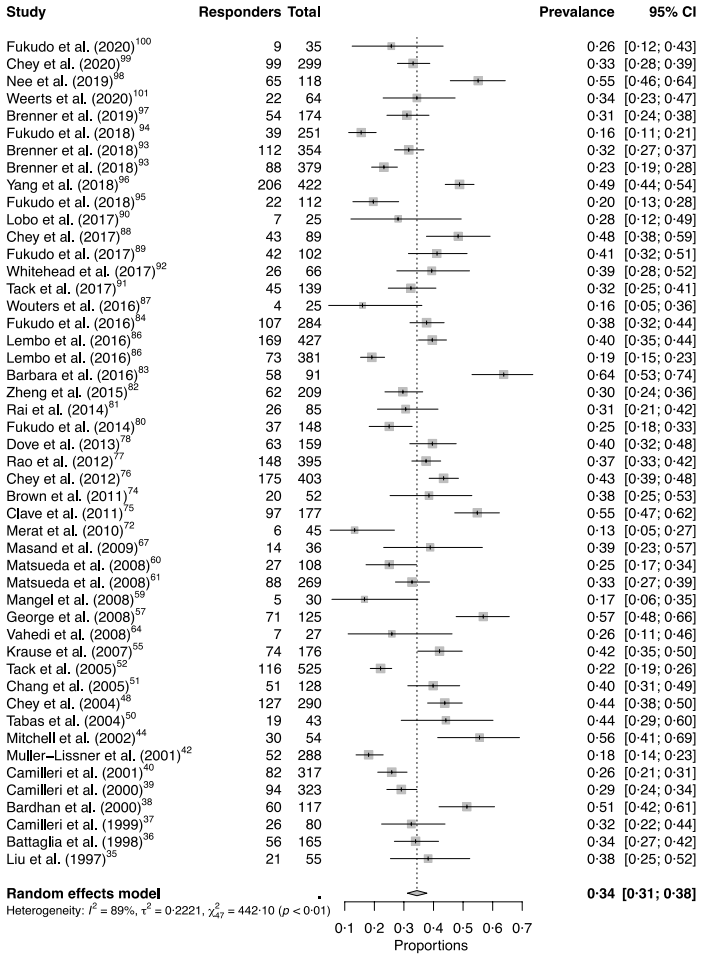
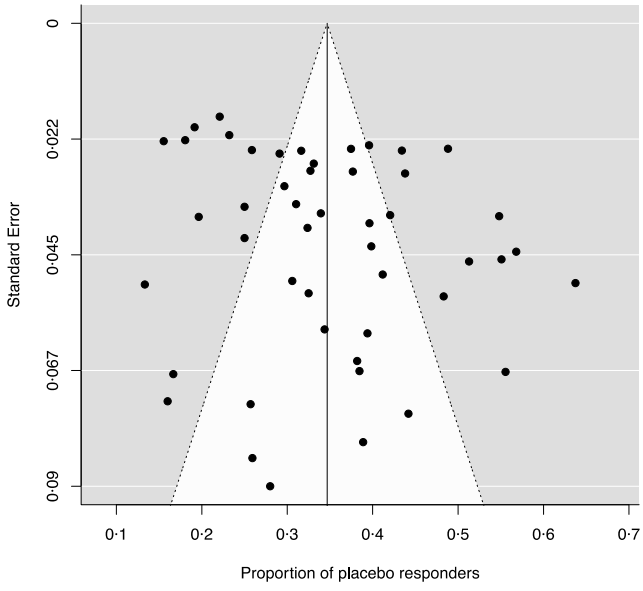


Figure 2d. Funnel plot of proportion of placebo responders, with endpoint abdominal pain responder (total of articles with this endpoint: n = 48).



Twenty trials provided data for the outcome assessment of proportion of patients who were composite FDA endpoint responders (Figure 3a. and 3b., Table 1.). The overall pooled placebo response rate was 17·9% (95% CI 15·2%-21·0%), with substantial heterogeneity between the trials (I^2 82·84%). 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 88·55%), resulting in a therapeutic gain of 11·7% (95% CI 9·5%-13·9%). Out of these twenty trials, nine trials provided data from the IBS with diarrhea subtype with a pooled placebo response rate of 21·1% (95% CI 16·6%-26·4%) and ten trials provided data from the IBS with constipation subtype with a pooled placebo response rate of 15·7% (95% CI 12·6%-19·4%).

Nineteen 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 89·06%). 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 92·42%), resulting in a therapeutic gain of 10·9% (95% CI 6·4%-15·5%). Out of these nineteen trials, eight trials provided data from the IBS with diarrhea subtype with a pooled placebo response rate of 37·0% (95% CI 29·5%-45·1%) and nine trials provided data from the IBS with constipation subtype with a pooled placebo response rate of 34·6% (95% CI 28·4-41·5%).

Nineteen 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%), with substantial heterogeneity between the trials (I^2 92·73%). 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 95·04%), resulting in a therapeutic gain of 13·3% (95% CI 10·2%-16·5%). Out of these nineteen trials, nine trials provided data from the IBS with diarrhea subtype with a pooled placebo response rate of 29·2% (95% CI 20·%-39·3%) and ten trials provided data from the IBS with constipation subtype with a pooled placebo response rate of 27·4% (95% CI 21·6%-34·1%).

Figure 3a. Forest plot of proportion of placebo responders, with endpoint composite FDA endpoint responder (total of articles with this endpoint: n = 20)

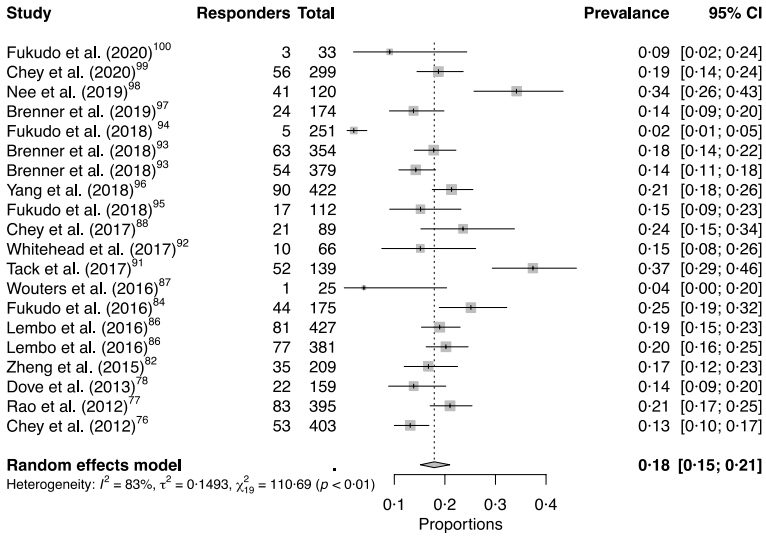
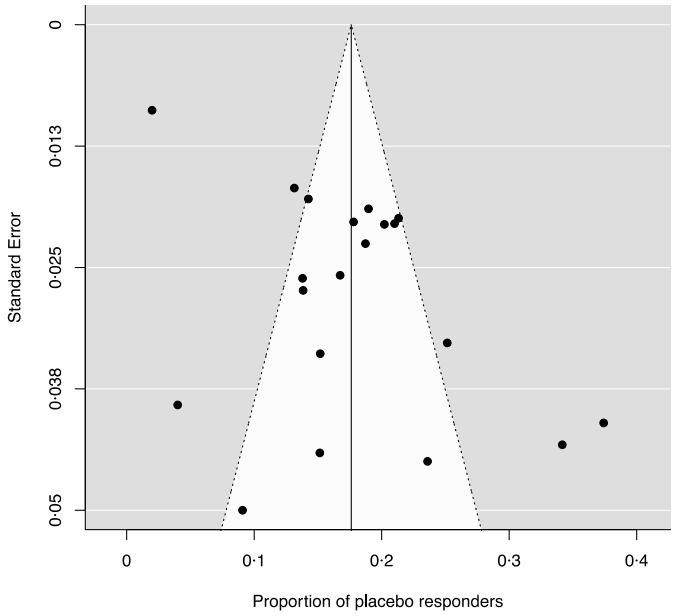


Figure 3b. Funnel plot of proportion of placebo responders, with endpoint composite FDA endpoint responder (total of articles with this endpoint: n = 20)



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 (i.e. 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% vs. 28·9% respectively, p=0·032). The trial location also had a significant effect on the place response rate. Trials conducted in Europe had a significant larger pooled placebo response rate compared with trials conducted in the United States (38·9% vs. 25·7% respectively, p=0·0032) and a non-significant larger pooled placebo response rate compared with trials conducted in Asia (38·9% vs. 30·3% respectively, p=0·068). Some active pharmacological agents were significantly related to the placebo response rate. Further specified; in active agents used for IBS-D, trials with 5-HT3 antagonists had a significant larger pooled placebo response rate compared with trials with opioid receptor agonists as active agent (32·3% vs. 16·2% respectively, p=<0·0001). In active agents used for IBS-C, trials with 5-HT4 antagonists had a significant larger pooled placebo response rate compared with trials with secretagogues as active agent (36·1% vs. 20·8% respectively, p=0·0030).
The trial setting (single versus multicenter and primary versus secondary/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. Cross-over studies had a significant lower pooled placebo response rate compared with parallel-studies (18·4% vs. 32·8% respectively, 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 trials with a run-in period of more than 2 weeks (34·6% vs. 19·4% respectively, 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 dosage schedule on the placebo response rate. Trials with a dosage schedule of once or twice a day had a significant lower pooled placebo

response rate compared with trials with a dosage schedule of three times a day or more (29·4% vs. 40·1% respectively, p=0·025). The use of an escalating dose, mean age, the duration of IBS symptoms/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 performed 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 (see Supplementary page 6). Also, the duration of therapy (against the proportion of placebo responders and the therapeutic gain), the study visits, the proportion of males, the baseline abdominal pain, and proportion of side effects and dropouts were not associated with the placebo response rate. We performed the same meta-regression analysis for the FDA endpoint responder outcome (Table 3.) (see Supplementary page 6). However, there was no significant relationship between any of the abovementioned variables.

Discussion

In this meta-analysis describing 73 IBS RCT's, the magnitude of the placebo response rate was 27·3% using the global improvement responder definition, 34·4% using the abdominal pain responder definition, 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 prior to 2006, with a parallel design, a run-in period of two weeks or less, a dosage schedule of three times or more a day, studies conducted 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 the novel trial endpoints and diagnostic criteria have changed the landscape for IBS trials. A number of findings of our current analysis are in line with the most recent meta-analysis on the subject[8], i.e. the higher placebo response in trials conducted 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, namely the trial setting and patients' predominant stool pattern. In addition, the finding that the pooled placebo response rates were highest in trials that used antispasmodics as active agent, not statistically significant though when compared with peppermint oil as active agent, is another resemblance. 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 the two meta-analyses.

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 mentioned)[11], 37·5% (95% CI 34·4%-40·6%)[8] and 40·2% (95% CI 35·9%-44·4%)[12]. This 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. Interestingly, this trend appears to be at odds with the increase of the 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 the modifications in study design based on new guidelines, including the Rome III and later Rome IV criteria[2], EMA[13] and FDA[14] recommendations, have favored the development towards lower placebo response rates in IBS. As a result, we consider it futile to compare studies before 2006 with studies performed 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 conducted in Europe[8,104], a parallel design,[103,105] and a dosage 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 the 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 notion that there may be placebo "responders" or "non-responders" based on individual characteristics (age, sex) – which would mean that trials

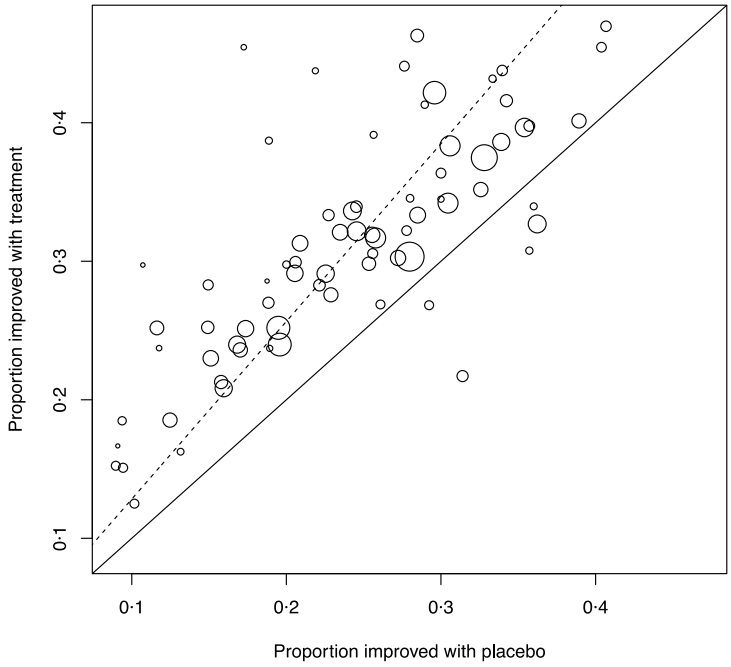
should select participants based on criteria to reduce placebo responses. With the present data, it becomes clearer that it is not the individual but rather the trial design and trial characteristics that are important to modify.

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 the 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 two 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 the placebo during run-in and thereby decreasing placebo response rates following randomization in the active treatment phase. It is interesting to note that, in line with studies in other disorders[112-114], our results demonstrated no benefit of a placebo run-in on the placebo response rate. In addition, 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 of the placebo run-in in decreasing the placebo response rate, there appears to be insufficient substantiation 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 prior to establishing a firm recommendation.

In May 2012, the FDA[14] published interim endpoints for IBS trials. Although harmonization of trial design in IBS was warranted, it has been a matter of debate whether the quantification of only two, albeit cardinal, IBS symptoms, namely abdominal pain and disordered defecation, is able to integrate the multidimensional aspect of the IBS symptoms to a sufficient degree[116], and it is has been suggested that less robust endpoints might be superior or at least equal in clinical decision-making.[117] Our results (Table 1. and Figure 4.) demonstrated an approximately 10% lower placebo response rate for the composite FDA endpoint in comparison with the historically commonly applied improvement responder endpoint. However, the intervention response rate has a similar trend, with an estimated 13% reduction, resulting in a therapeutic gain nearly the same (13·8% versus 11·7%) as before the introduction of the FDA endpoints. Identical results were observed for the abdominal pain responder endpoint. This would imply no apparent advantage of the FDA endpoint in demonstrating the efficacy of the 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 an excellent step in the right direction to uniformization in IBS trials, but further investigation of the performance of this endpoint is required.

Previous studies have not been able to demonstrate an association between the sample size of the placebo group and the placebo response rate.[8,11,12] Our findings did show such an association, which was significant, when assessing the combined responder endpoint. Interestingly, this association was not found for the FDA composite endpoint, which suggests that this endpoint is less sensitive to the sample size. On the other hand, no association was found between sample size and therapeutic gain for any of the endpoints.

Figure 4. L'Abbe plot of the response rate in the intervention group against the response rate in the placebo group. ***Continuous line: equality line. Dotted line: overall effect. Symbol size represents sample size.***



Interestingly, we found a higher pooled placebo response rate with the abdominal pain responder endpoints compared to the global improvement responder endpoints and the symptom bowel responder endpoint, which is in line with previous findings[11]. We speculate that this might be due to the fact that it is easier and more accessible for patients to delineate an improvement specifically for abdominal pain, rather than for a much broader symptom complex with different elements, as in global improvement. In addition, it could also be the case that the symptom of abdominal pain is more modifiable by placebo mechanisms (cognitive factors), is more easily remembered, or that it is most in the center of attention for the patient due to its salience, especially if the treatment information refers to improvement specifically for this symptom. Finally, the 30% improvement in abdominal pain, which defines the pain responder according to the FDA endpoint, may be 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]

Of note is further that, for the purposes of the current analyses, we did not focus on the symptoms of bloating and abdominal discomfort because of the widespread nature and the less well-defined character of these symptoms.[118] Indeed, abdominal discomfort has also been removed from the Rome IV criteria. In addition, 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 pre-Rome IV trials, resulting in an unjustified higher placebo response.

As for moderators of the placebo response, treatment expectations, denominated in behavioral, psychobiological, and contextual factors (e.g. conditioning, patient-clinician relationship), appear to be relevant.[10,13,119] A higher pooled placebo response rate is associated with an unbalanced randomization 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 may be that most trials did not report (or measure) these potential moderators towards the treatment expectation. Although this may be difficult to objectify, in order to make an adequate assessment about these moderators affecting treatment expectations, we advocate for more accurate and detailed reporting of these in future trials.[10] In addition, assessing possible unblinding can also provide insight in treatment expectation. This 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 may believe the therapy is ineffective and for this reason may drop out.[2,10,121,122] We found no such association in our results. However, these phenomena are complex and may 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, hereby modifying treatment expectations in both directions, positive and negative.[106] This 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 to draw firm conclusions on the basis of the current analyses.[121,122]

The strength of this study includes the magnitude and detailed assessment of various moderators influencing the pooled placebo response rate. Furthermore, IBS-D and IBS-C were included as a sub-analysis rather than a separate primary analyses given the intent of the study. It is important to note, however, that regulatory agencies do not currently recognize "IBS" as a separate identity. Instead, drugs can only be evaluated for either IBS-D or IBS-C and this calls for future scrutiny of the IBS definitions currently used by regulatory agencies.
There are, however, some limitations to be noted. First, 12 of the 80 trials were at unclear risk of bias, which may have influenced results on the pooled placebo response rate. 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 objectify lack of reporting of design details assessed in The Cochrane Risk of Bias Tool, rather than true design defects. Second, variability in subject behavior during trial period (diet, exercise, stress) and clinical evolution of the disorder during studies could not be extracted from the trials but may influence the placebo response. Thirdly, our results rely on the reporting of the included trials and as mentioned above, some moderators, particularly in older trials, have been inadequately reported. There is substantial heterogeneity in trial design, endpoints and reporting, making pooling of results for purposes of a meta-analysis inherently difficult. Therefore, for the primary outcome of these analyses, we analyzed different study endpoints separately. As for the moderator analysis, we chose to perform analysis according to the primary outcomes for which the particular trial was powered for, 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 showed a decline to 17·9%, but the therapeutic gain remained unaltered. On the other hand, it tributes to the harmonization in IBS trials and the introduction of the FDA endpoint, as this seems less sensitive to the sample size of the placebo group. Multiple moderators were associated with a higher pooled

placebo response rate. Based on the current findings, we suggest future pharmacological trials in IBS, with the purpose of minimizing the pooled placebo response rate, to apply a run-in period of at least two weeks (preferably without a placebo-therapy pending further research on this topic), and a daily dosage of one or two times a day. Sample size calculations should consider a therapeutic gain of 11-15%, when using a dichotomous outcome, depending on the outcome parameter chosen. In addition, an adequate assessment and reporting in the future is needed on variables associated with treatment expectancies (both positive and negative) prior to as well as during treatment.

Research in context

Evidence before this study

It is well-established that trials in Irritable Bowel Syndrome (IBS) are characterized by a high placebo response (the previous meta-analysis (2010) showed a pooled placebo response rate of 37·5%), which largely influences the success of these trials. As for the factors affecting placebo response in clinical trials, previous systematic reviews have shown conflicting results. In addition, all these analyses predate the recent FDA/EMA responder definition. We conducted a systematic review and meta-analysis to identify the pooled placebo response rate in pharmacological randomized controlled trials (RCTs) in adult patients with IBS in order to better understand the factors affecting the placebo response rate and to control them. We searched MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials between the 1st of April 1959 and 30th April 2020 using search terms for IBS (*irritable bowel syndrome, IBS, irritable colon, spastic colon and spastic bowel*) and placebo response (*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 four weeks were included.

Added value of this study

This meta-analysis of 73 RCTs highlights different moderators that are associated with a higher pooled placebo response rate in pharmacological trials in IBS. In addition, 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 fill an important knowledge gap on the subject and can therefore represents a contribution to the field in optimizing trial design in IBS, not only for clinical gastroenterologist but also for the pharmaceutical industry.

Implications of all the available evidence

Based on the findings in this meta-analysis, we suggest future pharmacological trials in IBS, with the purpose of minimizing the pooled placebo response rate, to apply a run-in period of at least two weeks (preferably without a placebo-therapy pending further research on this topic), and a daily dosage of one or two times a day. 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. An 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 endpoints are the contribution to the harmonization in IBS trials and the FDA 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 an excellent step in the right direction to uniformization in IBS trials, but further investigation of the performance of this endpoint is required.

Contributors

DK conceptualized the review project and MB developed the study protocol under the supervision of DK. MB and TB conducted the literature search, screened and reviewed all the published literature and conducted the data extraction. MB conducted the data analysis. MB and DK conducted 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.

Declaration of interests

MB, BW and TB declare no competing interests. SE reports grants from Deutsche Forschungsgemeinschaft (DFG, German Research Foundation), outside the submitted work. MC serves as a consultant for Sanofi, for Allergan, for Arena and for Kiowa Kyrin, for RB, outside the submitted work. JT reports personal fees from Adare, personal fees from Arena, personal fees from Christian Hansen, personal fees from Devintec, personal fees from Ironwood, personal fees from Shire, personal fees from Truvion, personal fees from Abbott, personal fees from Menarini, grants from Shire, grants from Tsumura and grants from Sofar, grants from Mylan, outside the submitted work. MS reports grants and personal fees from Danone Nutricia Research, grants and personal fees from Glycom A/S, personal fees from Nestlé, personal fees from Ironwood, personal fees from Menarini, personal fees from Biocodex, grants from Genetic Analysis AS, personal fees from Arena, personal fees from Adnovate, personal fees from Shire, personal fees from Tillotts, personal fees from Kyowa Kirin, personal fees from Takeda, personal fees from Alimentray Health, personal fees from AlfaSigma and personal fees from Falk Foundation, outside the submitted work. AM reports grants from ZonMw, The Netherlands Organization for Health Research and Development, health care efficiency grant to evaluate efficacy of peppermint oil in IBS, grants from unrestricted research grant from Will Pharma S.A, grants from research funding from Allegan and Grünenthal on IBS topics, grants from funding from Pentax Europe GmBH, grants from funding from the Dutch Cancer Society related to endoscopy and to colorectal polyps and scientific advice with financial compensation to institution to Bayer (topic: IBS), to Kyowa Kirin (topic: constipation) and to Takeda (topic: gastroparesis), outside the submitted work. DK reports grants from Allergan, grants from Will Pharma, grants from Grunenthal, grants from ZonMw, grants from United Europe Gastroenterology and grants from Maag-Lever-Darmstichting, outside the submitted work.

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Data sharing statement

There are no individual participant data available for this review. The study protocol is available via the PROSPERO database (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=170908). Other documents, i.e. statistical analysis plan and analytic code, will be available immediately following publication with no end date for researcher who provide a methodologically sound proposal with the purpose of achieving

aims in the approved proposal. Proposals 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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