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TITLE PAGE

Title: Placebo Response Rates in Trials of Licensed Drugs for Irritable Bowel Syndrome with Constipation or Diarrhea: Meta-Analysis

Short title: Placebo Response Rate in IBS.

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Abbreviations:

5-HT	5-hydroxytryptamine
BSFS	Bristol stool form scale
CI	confidence interval
CSBM	complete spontaneous bowel movement
FDA	Food and Drug Administration
IBS	irritable bowel syndrome
IBS-C	IBS with constipation
IBS-D	IBS with diarrhea

MeSH	medical subject heading
NNT	number needed to treat
RCT	randomized controlled trial

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ABSTRACT

Objectives: There are several licensed drugs for irritable bowel syndrome (IBS) that have proven efficacy in randomized controlled trials (RCTs) but placebo response rates are high. We conducted a systematic review and meta-analysis of licensed drugs to estimate magnitude of placebo response rate according to Food and Drug Administration (FDA)-recommended endpoints, and to assess how this varies with stringency of the endpoint used to define response.

Methods: We searched MEDLINE, EMBASE CLASSIC and EMBASE, and the Cochrane central register of controlled trials (through January 2021) to identify RCTs comparing licensed drugs with placebo in adult IBS patients. Studies assessed efficacy according to at least one of composite response, abdominal pain response, or stool response. Data were extracted as intention-to-treat analyses with dropouts assumed to be treatment failures and pooled using a random effects model.

Results: There were 17 RCTs of licensed drugs versus placebo in IBS-C (4603 patients placebo) and 17 trials in IBS-D (3908 patients placebo). In IBS-C, according to FDA criteria, pooled composite, abdominal pain, and stool response rates with placebo over ≥6 of 12 weeks were 18.9%, 34.6%, and 30.1%, respectively. Evaluating response rates over ≥9 of 12 weeks led to placebo response rates of 4.3% for the composite endpoint, 24.5% for abdominal pain, and 7.7% for stool. In IBS-D, pooled placebo response rates according to FDA criteria were 16.2% for the composite endpoint, 40.2% for abdominal pain, and 16.2% for stool. Increasing the threshold used to define abdominal pain response from a ≥30% improvement to ≥40% or ≥50% led to lower placebo response rates of 34.5% and 23.4%.

Conclusions: Future RCTs should adhere to current FDA-recommended endpoints for IBS as these lead to lower placebo response rates. However, consideration should be given to further refining some of these to better differentiate between active drug and placebo.

Key words: Irritable bowel syndrome, Meta-analysis, Randomized controlled trials, Placebo

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common disorders of gut-brain interaction, previously called functional gastrointestinal disorders, characterized by altered stool form or frequency in association with abdominal pain.(1, 2) Several risk factors including genetics, diet, disturbances in the gut microbiome, gastrointestinal infection, and psychological factors have been proposed to exert influence, via the bi-directional brain–gut axis.(3) The diagnosis of IBS, in the absence of a diagnostic test or biomarker, is facilitated by symptom-based diagnostic criteria, the latest of which are the Rome IV criteria.(1, 4) According to these criteria, IBS affects between 3% and 5% of the general population globally.(5) Conventionally, IBS is categorized into four subtypes based on the predominant stool form or frequency reported: IBS with constipation (IBS-C); IBS with diarrhea (IBS-D); IBS with mixed bowel habit; or IBS unclassified, where stool form or frequency cannot classify the patient accurately into one of the other three subtypes.(1)

As there is no cure for IBS, treatment aims to improve symptoms, social functioning, and quality of life. Whenever novel drugs are tested in IBS, and because there is no gold standard treatment, their efficacy is examined in a randomized placebo-controlled trial. Although there is evidence from meta-analyses of randomized controlled trials (RCTs) that treatments including secretagogues, drugs acting on 5-hydroxytryptamine (5-HT) or opioid receptors, non-absorbable antibiotics, antispasmodics, and gut-brain neuromodulators are superior to placebo in IBS,(6-9) placebo response rates are high. Previous estimates range between 15% and 72%,(10, 11) with a pooled placebo response rate of 37.5% in a prior meta-analysis.(12) This high placebo response can impair the assessment of drug efficacy in trials, because it might statistically reduce the possibility of seeing a positive impact of the active drug. RCTs should be designed to optimize placebo response in relation to the response in the active drug arm.

An adequate measure of treatment efficacy should capture improvement in the most important IBS symptoms using precise and standardized endpoints. In the early 2000s many drug trials in IBS assessed efficacy using subjective global assessment of relief of IBS symptoms, which

was felt to be clinically relevant and to correlate with improvement in quality of life.(13) However, in 2012, the Food and Drug Administration (FDA) recommended use of endpoints in IBS-C and IBS-D that assessed improvement in abdominal pain, bowel habit, or a combination of both.(14) Since the publication of these recommendations, most RCTs of novel drugs have adhered to these endpoints,(15-17) although some have approximated them,(18, 19) and some have used even more stringent criteria.(15, 20-23) However, to our knowledge, there has been no systematic assessment of placebo response rates using these endpoints in RCTs of licensed drugs. This information is important, as it can be used to inform sample size calculations for future RCTs. In addition, because the magnitude of the placebo response may affect likelihood of a new drug demonstrating significant efficacy over placebo and, given the expense in developing novel drugs for IBS and bringing them to market, the selection of endpoints used to confirm efficacy could decide whether a drug succeeds or fails. We have, therefore, conducted an up-to-date systematic review and meta-analysis of licensed drugs for IBS to estimate magnitude of the placebo response rate according to FDA-recommended endpoints, as well as to assess how this varies with the stringency of the endpoint used to define response.

METHODS

Search Strategy and Study Selection

We searched the medical literature using MEDLINE (1946 to January 2021), EMBASE CLASSIC and EMBASE (1947 to January 2021), and the Cochrane central register of controlled trials (Issue 2, January 2021). To identify potentially eligible studies published only in abstract form we searched conference proceedings (Digestive Disease Week, American College of Gastroenterology, and United European Gastroenterology Week) between 2010 and 2020. We also searched clinicaltrials.gov to obtain data from unpublished trials.

RCTs examining efficacy of licensed drugs for IBS-C (linaclotide, lubiprostone, plecanatide, tegaserod, or tenapanor) or IBS-D (alosetron, eluxadoline, ramosetron, or rifaximin) in adult patients (≥18 years) were eligible. Eligibility criteria are provided in Box 1. The control arm was required to receive placebo. A minimum treatment duration of 12 weeks was required, in line with FDA recommendations for the design of treatment trials for IBS. All endpoints were extracted at 12 weeks, even for RCTs providing efficacy data at other time points. The diagnosis of IBS could be based on any iteration of the Rome criteria, supplemented by results of investigations to exclude organic disease, where trials deemed this necessary. Studies had to report a dichotomous assessment of response to therapy, using composite endpoints for improvement, improvement in abdominal pain, or improvement in stool consistency or frequency in IBS-C or IBS-D. We preferentially extracted data according to FDA-recommended measures of these endpoints, but approximations of these endpoints were permitted. We contacted first and senior authors of studies to provide additional information on trials, where required. Details of the search strategy are provided in the Supplementary Methods.

Outcome Assessment

The primary outcome was the magnitude of the placebo response rate, in terms of the proportion of patients achieving the composite endpoints for IBS-C or IBS-D, according to patient self-report. The FDA-recommended endpoint for composite response in IBS-C consists of a ≥30% improvement in abdominal pain accompanied by an increase of ≥1 complete spontaneous bowel movement (CSBM) per week from baseline for ≥50% of weeks. For IBS-D this consists of a ≥30% improvement in abdominal pain and a ≥50% reduction in number of days per week with at least one stool that has a consistency of type 6 or 7 on the Bristol stool form scale (BSFS) compared with baseline. For both IBS-C and IBS-D abdominal pain response consists of a ≥30% improvement in abdominal pain for ≥50% of weeks. For IBS-C a stool response consists of an increase of ≥1 CSBM per week from baseline for ≥50% of weeks. For IBS-D a stool response consists of a ≥50% reduction in number of days per week with at least one stool that has a consistency of type 6 or 7 on the BSFS compared with baseline for ≥50% of weeks. We judged all these as meeting a "strict" FDA definition of response. For studies that used other endpoints to assess composite, abdominal pain, or stool response that approximated these definitions, we included these in the main analysis but omitted them in a sensitivity analysis. Secondary outcomes included assessing placebo response rate according to other more stringent endpoints, where reported (for example achieving one of the FDA endpoints reported above for ≥75% of weeks or achieving a ≥40% or ≥50% improvement in abdominal pain for ≥50% of weeks).

Data Extraction

Data were extracted independently by two investigators (CJB and ACF, or BB and ACF) on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA, USA), as dichotomous outcomes (FDA composite endpoint response achieved or not achieved, abdominal pain response achieved or not achieved, and stool response achieved or not achieved) in the placebo arms of the included RCTs. We resolved any discrepancies by consensus. In addition, the following

clinical data were extracted for each trial: publication year, geographical location, number of centers, criteria used to define IBS, dosing schedule of placebo, duration of therapy, active drug used, and endpoints used to define symptom improvement following therapy. We extracted all data as intention-to-treat analyses, with dropouts assumed to be treatment failures, wherever trial reporting allowed this. If this was not clear from the original article, we performed an analysis on all patients with reported evaluable data.

Quality Assessment and Risk of Bias

We used the Cochrane Risk of Bias tool to assess the quality of studies.(24) Two investigators (CJB and ACF) assessed study quality independently, with disagreements resolved by discussion. For all RCTs we recorded method used to generate the randomization schedule and conceal treatment allocation, whether participants, personnel, and outcome assessments were blinded, whether there was evidence of incomplete patient outcome data, and whether there was evidence of selective reporting of patient outcomes.

Data Synthesis and Statistical Analysis

We pooled the proportion of patients assigned to placebo achieving each of the endpoints in each study for IBS-C or IBS-D at 12 weeks to give a pooled placebo response rate for all studies by IBS subtype. We assessed heterogeneity between studies using the I^2 statistic. The I^2 measure ranges between 0% and 100%. Values of 25% to 49%, 50% to 74%, and ≥75% are considered low, moderate, and high levels of heterogeneity, respectively.(25) We used StatsDirect version 3.2.7 (StatsDirect Ltd, Sale, Cheshire, England) to generate Forest plots of pooled placebo response rates at 12 weeks, with 95% confidence intervals (CIs). We measured therapeutic gain of active drug over placebo according to each endpoint of interest for IBS-C and IBS-D using the number needed to treat (NNT). We calculated the NNT, with a 95% CI, using the formula NNT = 1 / (assumed control risk x (1 – relative risk)).

RESULTS

We updated our previous systematic reviews and meta-analyses of licensed drugs for IBS-C and IBS-D.(6-8) The search strategy generated 4,334 citations, 136 of which appeared to be relevant. Thirty of these fulfilled eligibility criteria (Figure 1). Of these, 15 articles reported on 17 RCTs of licensed drugs versus placebo in IBS-C,(15-18, 20, 21, 26-34) and 15 articles reported on 17 trials in IBS-D.(19, 22, 23, 35-46) The 17 trials in IBS-C contained 4603 patients assigned to placebo. There were two RCTs, reported in one article,(18) of lubiprostone in IBS-C, six trials of linaclotide,(15, 21, 26-29) three RCTs of plecanatide, reported in two articles,(17, 30) three RCTs of tenapanor,(16, 20, 31) and three trials of tegaserod.(32-34) The 17 trials in IBS-D contained 3908 patients randomized to placebo. There were six RCTs of alosetron,(35-40) five trials of ramosetron,(19, 41-44) four RCTs of eluxadoline, reported in three articles,(22, 23, 45) and two trials of rifaximin, reported in one article.(46) Agreement between investigators for study eligibility was excellent (kappa statistic = 0.88). Detailed characteristics of individual RCTs are provided in Supplementary Tables 1 and 2. Risk of bias items for all included trials are reported in Supplementary Tables 3 and 4. Eleven trials in IBS-C were at low risk of bias, reported in nine articles,(15-18, 21, 26, 27, 29, 31) and 11 RCTs, reported in nine articles,(22, 23, 37, 40, 42-46) in IBS-D.

Placebo Response Rates in Randomized Controlled Trials in IBS-C

Composite Response

Sixteen trials, reported in 14 articles, used a composite response of an improvement in abdominal pain accompanied by an improvement in stool frequency or consistency,(15-18, 20, 21, 26, 28-34) of which 11, reported in 10 articles, used the strict FDA definition consisting of a ≥30% improvement in abdominal pain accompanied by an increase of ≥1 CSBM per week from baseline for ≥6 of 12 weeks.(15-17, 20, 21, 26, 28-31) In addition, five trials reported this endpoint for ≥9 of

12 weeks of treatment.(15, 20, 21, 26, 31) The pooled placebo response rate according to the composite endpoint for ≥6 weeks in all 16 studies was 19.0% (95% CI 15.8%-22.4%), with high heterogeneity (I^2 = 86.9%, p<0.0001). When we restricted to the 11 trials that used the strict FDA definition of a composite response the pooled placebo response rate was almost identical (18.9%; 95% CI 16.8%-21.1%), but with moderate heterogeneity (I^2 = 55.7%, p=0.01). The pooled placebo composite response rate for ≥9 of 12 weeks was much lower in five trials (4.3%; 95% CI 3.4%-5.4%) with no heterogeneity (I^2 = 4.8%, p=0.38). NNTs were 8 irrespective of whether the strict FDA definition of a composite response for ≥6 of 12 weeks was used or not but increased to 11 when composite response was measured over ≥9 weeks.

Abdominal Pain Response

When we pooled data from 15 studies, reported in 13 articles,(15-18, 20, 21, 26, 28, 29, 31-34) using a ≥30% improvement in abdominal pain for ≥6 of 12 weeks as an endpoint the pooled placebo response rate was 37.1% (95% CI 28.8%-45.8%) with high heterogeneity (I^2 = 97.1%, p<0.0001). Restricting this to 12 studies, reported in 10 articles,(15-18, 20, 21, 26, 28, 29, 31) which used the strict FDA definition for an abdominal pain response the pooled placebo response rate was slightly lower (34.6%; 95% CI 29.9%-39.4%) with high heterogeneity (I^2 = 86.5%, p<0.0001). The pooled placebo response rate based on a ≥30% improvement in abdominal pain for ≥9 of 12 weeks, reported in six trials,(15, 20, 21, 26, 29, 31) was 24.5% (95% CI 20.0%-29.3%), but again with high heterogeneity (I^2 =81.5%, p<0.0001). NNTs were 8 or 9, irrespective of whether the strict FDA definition of abdominal pain response was used or not, or whether the response was measured over ≥6 or ≥9 of 12 weeks.

Stool Response

Pooling data from 12 trials, reported in 11 articles,(15-17, 20, 26, 28, 29, 31-34) that examined response rate using an improvement in stool frequency or consistency, the placebo response rate was 38.0% (95% CI 28.8%-47.7%). We observed high heterogeneity between studies (I^2 = 97.3%, p<0.0001). Restricting to the nine RCTs that used the strict FDA definition of an increase of ≥1 CSBM per week from baseline for ≥6 of 12 weeks, reported in eight articles,(15-17, 20, 26, 28, 29, 31) the pooled placebo response rate was 30.1% (95% CI 27.3%-33.0%) with moderate heterogeneity (I^2 = 56.9%, p=0.023). The pooled placebo response rate in seven trials that examined this endpoint for ≥9 of 12 weeks was much lower (7.7%; 95% CI 5.4%-10.4%) with borderline high heterogeneity between studies (I^2 = 76.1%, p=0.0003).(15, 20, 21, 26, 27, 29, 31) NNTs were 6 irrespective of whether the strict FDA definition of stool response for ≥6 of 12 weeks was used or not but increased to 8 when measured over ≥9 of 12 weeks.

Placebo Response Rates in Randomized Controlled Trials in IBS-D

Composite Response

Ten RCTs, reported in eight articles,(22, 23, 35, 37, 40, 43, 45, 46) in IBS-D included a composite endpoint, and five, reported in four articles,(22, 23, 43, 45) used the FDA composite for ≥6 of 12 weeks. In all trials, the pooled placebo response rate was 24.4% (95% CI 18.4%-31.0%, I^2 = 92.2%, p<0.0001). When we only included the five RCTs that used the strict FDA definition of composite response the placebo response rate was 16.2% (95% CI 12.4%-20.4%) with high heterogeneity between studies (I^2 = 74.0%, p=0.0039). The NNT was 9 whether the strict FDA definition of a composite response was used or not.

Abdominal Pain Response

All seventeen studies reported the placebo response rate for abdominal pain in 15 articles,(19, 22, 23, 35-46) and five, reported in four articles,(22, 23, 43, 45) used the FDA criteria of a ≥30% improvement in abdominal pain for ≥6 of 12 weeks. Among all studies, the pooled placebo response rate for abdominal pain was 33.9% (95% CI 29.9%-38.0%, I^2 = 86.3%, p<0.0001). When only trials that used the strict FDA definition of abdominal pain response were included the placebo response rate increased to 40.2% (95% CI 37.0%-43.4%), but with low heterogeneity among studies (I^2 = 29.4%, p=0.23). There were three RCTs, reported in two articles,(22, 23) that applied an even more stringent endpoint of a ≥40% or ≥50% improvement in abdominal pain for ≥6 weeks. Pooled placebo response rate with a ≥40% improvement was 34.5% (95% CI 30.4%-38.8%), and 23.4% (95% CI 11.8%-37.5%) with a ≥50% improvement. The NNT was 14.5 when the strict FDA definition of abdominal pain response was used, compared with 11 when this was approximated. The NNT was 13 when a ≥40% improvement in abdominal pain was used, but when a ≥50% improvement in abdominal pain was used the therapeutic gain over placebo was no longer statistically significant.

Stool Response

Ten articles, reporting on 12 RCTs,(19, 22, 23, 40-46) examined stool response rates. Five trials, reported in four articles,(22, 23, 43, 45) used a stool response according to strict FDA recommendations. The placebo response rate in all trials was 24.4% (95% CI 18.4%-31.0%) with high heterogeneity (I^2 = 92.2%, p<0.0001). When only RCTs that used the strict FDA definition of stool response were included the placebo response rate was 16.2% (95% CI 12.4%-20.4%) with moderate heterogeneity (I^2 = 74.0%, p=0.0039). The NNT was 6 when the strict FDA definition of stool response was used and 7 when it was approximated.

DISCUSSION

We have conducted an up-to-date systematic review and meta-analysis of licensed drugs for IBS-C and IBS-D to estimate magnitude of the placebo response rate according to FDA-recommended endpoints, as well as to assess how this varies with stringency of the endpoint used. In IBS-C, pooled placebo response rates and NNTs were similar for both the composite endpoint and abdominal pain, irrespective of whether trials used strict FDA criteria. In both cases, placebo response rates fell substantially, and NNTs increased, when pooled placebo composite response rates were evaluated for ≥9 of 12 weeks. Stool response rates were higher when strict FDA criteria were not applied (38% vs. 30%), but NNTs were identical, although again pooled placebo response decreased dramatically, and NNT increased slightly, when stool response was assessed over ≥9 of 12 weeks. In IBS-D, pooled placebo response rates were lower for composite response and stool response when only trials using strict FDA criteria were pooled, although NNTs remained similar in both instances. For abdominal pain response, pooled placebo response rates increased when strict FDA criteria were applied, and the NNT increased from 11 to 14.5. When the threshold for improvement in abdominal pain was increased to ≥40% both pooled placebo response rates and the NNT decreased but using a threshold of ≥50%, although the placebo response rate decreased further, there was no longer a significant therapeutic gain of active drug over placebo.

We used a comprehensive literature search, augmented by searching the gray literature, to maximize likelihood of identifying pertinent trials. The literature search, eligibility assessment, and data extraction were undertaken independently by two reviewers, with discrepancies resolved by consensus. We contacted original investigators to obtain supplementary data in some cases, to maximize the number of eligible RCTs. We assessed impact of individual trial characteristics on pooled placebo response rates in subgroup analyses. We also performed an intention-to-treat analysis, where all dropouts were assumed to be treatment failures, and used a random effects model to provide a more conservative estimate of the pooled placebo response rate, meaning the magnitude of this effect is unlikely to have been overestimated. We extracted multiple different

endpoints across trials, where reported, to provide a thorough assessment of how the placebo response in IBS-C and IBS-D varies according to the criteria used to judge treatment efficacy.

Weaknesses include the fact that there was statistically significant heterogeneity when trial data were pooled, and that, without access to individual patient data it is difficult to draw conclusions about specific patient characteristics that may have contributed to our findings. Unlike in our previous meta-analysis,(12) we did not assess individual trial characteristics that may influence the magnitude of the placebo response, other than endpoints used to assess efficacy. In our prior meta-analysis the pooled placebo response rate was 37.5%,(12) and was higher in RCTs using a physician-reported outcome to define response to therapy, compared with those that used a patient-reported endpoint, in RCTs using clinical criteria to define IBS, compared with those that used the Rome I or II criteria, in European, compared with non-European, trials, in RCTs that used a three times daily, compared with a once or twice daily, dosing schedule, and in trials of 4 weeks duration or less, compared with RCTs over 4 weeks. However, in the current study we included a relatively homogeneous group of trials, in terms of their design and patient population. All studies used the Rome criteria to define IBS, all used patient-reported endpoints, we extracted data after an identical duration of treatment for all trials, and all drugs are licensed for the treatment of IBS-C or IBS-D in various parts of the world. Finally, there were insufficient studies to pool data at 26 weeks to examine placebo response rates according to European Medicines Agency endpoints.

There has been another, more recent, meta-analysis examining placebo response rates in drug trials in IBS.(47) This demonstrated a pooled placebo response of 27.3% according to global symptom measures, 34.4% for abdominal pain, and 17.9% according to the FDA composite endpoint. This meta-analysis included RCTs of non-licensed drugs for IBS, including placebo-controlled trials of mesalazine,(48) gut-brain neuromodulators,(49, 50) crofelemer,(51) and ibodutant,(52) where placebo response rates ranged from 37.4% to 63.7%.(48) This could have led to an increase in the pooled placebo response rate observed. Response rates, as recorded in the trials we included in the current study, are likely to be more rigorous in a trial of a drug under

investigation for a licensed indication than for some of the investigator-initiated trials included in the aforementioned meta-analysis. Hence, our meta-analysis complements this earlier work, and can be used to inform future drug development in IBS. However, it is perhaps less clinically relevant. Most clinicians judge treatment efficacy in practice based on whether the individual patient feels better, or their symptoms have improved, akin to global symptom relief or adequate relief, rather than the stringent FDA endpoints. The latter are intended to reduce placebo response rates and would be challenging to apply in everyday practice, yet clinicians often make judgements as to whether a drug will be effective for their own patients, based on the therapeutic gain over placebo according to these endpoints, from phase 3 trials. A prior systematic review of response rates in painful conditions demonstrated that placebo had a beneficial effect over no treatment,(53) which may, in part, explain the higher placebo response rates for abdominal pain we observed compared with those for stool frequency or consistency. Placebo response rates were higher for IBS-D than IBS-C. Although this difference is unlikely to be significant, given the 95% CIs overlapped, others have shown differences in abdominal pain characteristics according to IBS subtype, with those with IBS-C reporting more frequent and severe pain compared with IBS-D.(54)

The number of IBS-C patients achieving response with a placebo in this study appears to be somewhere between one in three and one in five, according to FDA-recommended endpoints. When response rates were assessed over ≥9 of 12 weeks stool response rates fell to less than 10%, compared with around 25% for abdominal pain, leading to composite response rates of less than 5%. Although this may be too stringent for a composite endpoint, with a NNT of 11 for active drug over placebo, a combination of abdominal pain response judged over ≥6 of 12 weeks with stool response over ≥9 of 12 weeks may be worthy of consideration as a future endpoint. In IBS-D, composite and stool response rates with placebo were again lower when FDA-recommended endpoints were used, although this was not the case for abdominal pain. Abdominal pain response rates were lower using a threshold of ≥40% improvement, and the NNT was lower than with a

≥30% improvement. Again, this may be an endpoint worth considering in practice in the future, both individually and as part of the composite endpoint in IBS-D.

The information provided by this meta-analysis is potentially important for the conduct of future RCTs in IBS. It may be helpful in informing power calculations on which to base projected sample sizes. Trials of various drugs in IBS, including renzapride,(55) asimadoline,(56) ibodutant (NCT02107196 and NCT02120027) and, more recently, minesapride,(57) have failed to demonstrate any significant benefit of these drugs, partly due to high response rates observed in the placebo arms of the trials, which meant that the studies were underpowered to detect a statistically significant difference. This was despite, in some cases, a therapeutic gain over placebo of around 7% to 8%,(55, 57) which is similar to that for some other licensed drugs in IBS.(58) In the case of renzapride, asimadoline, and ibodutant the pharmaceutical companies that had developed the drugs abandoned further investment in their clinical development for IBS. Given the expense involved in developing and testing a drug, as well as bringing it to market, endpoints selected, and sample sizes recruited are likely to be instrumental in deciding whether a drug achieves a licensed indication for IBS.

In summary, this systematic review and meta-analysis has demonstrated that, in all available RCTs of licensed drugs in IBS-C, and using strict FDA-recommended endpoints, one-in-five patients responded to placebo based on a composite endpoint, and one-in-three based on either abdominal pain or stool frequency or consistency. In all available trials of licensed drugs in IBS-D, one-in-six patients responded to placebo according to either a composite endpoint or stool frequency or consistency, whereas 40% responded in terms of an improvement in abdominal pain. Our results suggest that future RCTs, irrespective of the drug under study, should adhere to current FDA-recommended endpoints as, for the most part, these lead to lower placebo response rates, but that consideration should be given to further refining some of these to better differentiate between active drug and placebo.

Box 1. Eligibility criteria.

Randomized controlled trials.

Adults (participants aged ≥18 years)

Diagnosis of irritable bowel syndrome based on specific diagnostic criteria*, supplemented by negative investigations where trials deemed this necessary.

Compared licensed drugs† with placebo.

Minimum duration of therapy of 12 weeks.

Assessed efficacy of drugs according to at least one of composite response, abdominal pain response, or stool response, which were patient-reported.

*Rome I, II, III, or IV criteria.

†Secretagogues, 5-HT_4 agonists, 5-HT_3 antagonists, mixed opioid receptor agonists, or non-absorbable antibiotics.

FIGURE LEGENDS

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

Figure 2. Placebo Response Rates According to Criteria Used to Define Response in Randomized Controlled Trials of Licensed Drugs in IBS-C.

Figure 3. Placebo Response Rates According to Criteria Used to Define Response in Randomized Controlled Trials of Licensed Drugs in IBS-D.

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Table 1. Placebo Response Rates According to Criteria Used to Define Response in Randomized Controlled Trials of Licensed Drugs in IBS-C.

	Number of trials	Number of patients receiving placebo	Pooled placebo response rate (%)	95% CI	NNT (95% CI) for active drug versus placebo	I^2 (%)	P value for χ^2
Composite response*							
≥6 of 12 weeks (≥50% of weeks)	16	4518	19.0	15.8 – 22.4	8 (7 – 10)	86.9	<0.0001
≥6 of 12 weeks (≥50% of weeks) using strict FDA criteria	11	3128	18.9	16.8 – 21.1	8 (6 – 10)	55.7	0.01
≥9 of 12 weeks (≥75% of weeks)	5	1846	4.3	3.4 – 5.4	11 (8 – 16)	4.8	0.38
Abdominal pain response							
30% improvement for ≥6 of 12 weeks (≥50% of weeks)	15	4433	37.1	28.8 – 45.8	8 (6 – 14)	97.1	<0.0001
30% improvement for ≥6 of 12 weeks (≥50% of weeks) using strict FDA criteria†	12	3206	34.6	29.9 – 39.4	8.5 (7 – 11)	86.5	<0.0001
30% improvement for ≥9 of 12 weeks (≥75% of weeks)	6	1912	24.5	20.0 – 29.3	9 (6 – 15)	81.5	<0.0001
Stool response							
≥6 of 12 weeks (≥50% of weeks)	12	3848	38.0	28.8 – 47.7	6 (4 – 10.5)	97.3	<0.0001
≥6 of 12 weeks (≥50% of weeks) using strict FDA criteria±	9	2621	30.1	27.3 – 33.0	6 (4.5 – 10)	56.9	0.023
≥9 of 12 weeks (≥75% of weeks)	7	1997	7.7	5.4 – 10.4	8 (6 – 11)	76.1	0.0003

*The FDA-recommended endpoint for composite response in IBS-C consists of a ≥30% improvement in abdominal pain accompanied by an increase of ≥1 complete spontaneous bowel movement (CSBM) per week from baseline for ≥50% of weeks.

†The FDA-recommended endpoint for abdominal pain response in IBS-C consists of a ≥30% improvement in abdominal pain from baseline for ≥50% of weeks.

±The FDA-recommended endpoint for stool response in IBS-C consists of an increase of ≥1 complete spontaneous bowel movement (CSBM) per week from baseline for ≥50% of weeks.

Table 2. Placebo Response Rates According to Criteria Used to Define Response in Randomized Controlled Trials of Licensed Drugs in IBS-D.

	Number of trials	Number of patients receiving placebo	Pooled placebo response rate (%)	95% CI	NNT (95% CI) for active drug versus placebo	I^2 (%)	P value for χ^2
Composite response							
≥6 of 12 weeks (≥50% of weeks)	10	2361	24.4	18.4 – 31.0	9 (7 – 12)	92.2	<0.0001
≥6 of 12 weeks (≥50% of weeks) using strict FDA criteria*	5	1330	16.2	12.4 – 20.4	9 (6.5 – 13)	74.0	0.0039
Abdominal pain response							
30% improvement for ≥6 of 12 weeks (≥50% of weeks)	17	3908	33.9	29.9 – 38.0	11 (8 – 16)	86.3	<0.0001
30% improvement for ≥6 of 12 weeks (≥50% of weeks) using strict FDA criteria†	5	1330	40.2	37.0 – 43.4	14.5 (8 – 41)	29.4	0.23
40% improvement for ≥6 of 12 weeks (≥50% of weeks)	2	983	34.5	30.4 – 38.8	13 (6.5 – 95)	30.5	0.23
50% improvement for ≥6 of 12 weeks (≥50% of weeks)	2	983	23.4	11.8 – 37.5	N/A‡	93.0	0.0002
Stool response							
≥6 of 12 weeks (≥50% of weeks)	12	2770	24.4	18.4 – 31.0	7 (5 – 9)	92.2	<0.0001
≥6 of 12 weeks (≥50% of weeks) using strict FDA criteria±	5	1330	16.2	12.4 – 20.4	6 (5 – 9)	74.0	0.0039

*The FDA-recommended endpoint for composite response in IBS-D consists of a ≥30% improvement in abdominal pain and a ≥50% reduction in the number of days per week with at least one stool that has a consistency of type 6 or 7 on the Bristol stool form scale (BSFS) compared with baseline for ≥50% of weeks.

†The FDA-recommended endpoint for abdominal pain response in IBS-D consists of a ≥30% improvement in abdominal pain from baseline for ≥50% of weeks.

±The FDA-recommended endpoint for stool response in IBS-D consists of a ≥50% reduction in the number of days per week with at least one stool that has a consistency of type 6 or 7 on the BSFS compared with baseline for ≥50% of weeks.

‡N/A; not applicable, result not statistically significant in favor of active drug.