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TITLE PAGE

Title: Adverse Events in Trials of Licensed Drugs for Irritable Bowel Syndrome with Constipation or Diarrhea: Systematic Review and Meta-Analysis.

Short running head: Adverse Events in Trials of Licensed Drugs 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

Background: Nocebo effects occurring in patients receiving placebo frequently impact on adverse events reported in randomized controlled trials (RCTs) in irritable bowel syndrome (IBS). Therefore, we conducted a systematic review and meta-analysis to assess the proportion of patients randomized to placebo or active drug experiencing any adverse event in trials of licensed drugs for IBS with constipation (IBS-C) or diarrhea (IBS-D), and to estimate the risk of developing adverse events among patients randomized to placebo.

Methods: We searched MEDLINE, EMBASE CLASSIC and EMBASE, and the Cochrane central register of controlled trials (through June 2021) to identify RCTs comparing licensed drugs with placebo in adults with IBS-C or IBS-D. We generated Forest plots of pooled adverse event rates in both active drug and placebo arms and pooled risk differences (RDs) with 95% confidence intervals (CIs).

Key results: There were 21 RCTs of licensed drugs versus placebo in IBS-C (5953 patients placebo) and 17 in IBS-D (3854 patients placebo). Overall, 34.9% and 46.9% of placebo patients in IBS-C and IBS-D trials, respectively, developed at least one adverse event, with a statistically significantly higher risk of any adverse event and withdrawal due to an adverse event with active drug. In IBS-C and IBS-D trials, rates of each individual adverse event were generally higher with active drug. However, in IBS-C trials, only diarrhea or headache were significantly more common with active drug (RD 0.066 (95% CI 0.043-0.088) and RD 0.011 (95% CI 0.002-0.021), respectively), and in IBS-D trials only constipation, nausea, or abdominal pain (RD 0.096 (95% CI 0.054-0.138), 0.014 (95% CI 0.002-0.027), and 0.018 (95% CI 0.002-0.034), respectively).

Conclusions & Inferences: Patients with IBS randomized to placebo have a high risk of reporting adverse events, which might relate to both nocebo and non-nocebo factors. Although patients' expectations and psychosocial factors may be involved, further understanding of the mechanisms are important to control or optimize these effects in RCTs, as well as in clinical practice.

Key words: Irritable bowel syndrome, Meta-analysis, Randomized controlled trials, Adverse events, Nocebo

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common disorders of gut-brain interaction, estimated to affect between 3% and 5% of the general population globally.[1] It is characterized by altered stool form or frequency in association with abdominal pain.[2] Some people experience predominantly constipation (IBS-C), some mostly diarrhea (IBS-D), and others a mixture of the two.[2,3] No medical therapy is proven to alter the natural history of IBS and no gold standard treatment is recognized, therefore whenever novel drugs are tested in IBS their efficacy is usually examined in a randomized placebo-controlled trial.[4-7] In IBS, treatment should be directed towards the predominant symptom with a realistic discussion with patients of the limitations of available therapies to manage expectations.[8] In fact, most therapies improve symptoms in only 25% to 30% of patients.[9]

Patients' expectations may also have a determinant role regarding unwanted adverse events during drug treatment, which are often influenced by non-pharmacological effects.[10,11] For instance, many adverse events and symptoms reported by patients in randomized controlled trials (RCTs) may not be attributable directly to the medication, because unwanted adverse effects can also occur in the placebo arm of the trial.[10] Conventionally, adverse events occurring in patients receiving inert therapy have been attributed to worsening of the underlying condition, or the "nocebo" effect, defined as negative consequences arising from a patient's expectations or triggered by neurobiological, psychosomatic, psychosocial, or contextual factors.[12,13]

This nocebo effect could impact substantially on tolerability, and therefore patients' adherence to therapy and treatment efficacy, playing a major role in their withdrawal from a potentially beneficial drug.[14] Substantial nocebo effects may lead to inaccurate estimation of treatment-related adverse events due to either an increased proportion of adverse events in the placebo arm or an increased proportion of treatment-unrelated adverse events in patients receiving

the active drug.[15] All of this may have important implications for both drug development and future RCTs.

To the best of our knowledge, although understanding and minimizing the nocebo effect is fundamental for clinical trial design, there has been no systematic examination of the magnitude of this phenomenon in IBS. Therefore, we performed a systematic review and meta-analysis to assess the proportion of patients randomized to placebo or active drug experiencing any adverse event in trials of licensed drugs for IBS-C or IBS-D, and to estimate the risk of developing adverse events among patients randomized to placebo. In addition, we aimed to evaluate the proportion of adverse events leading to study withdrawal, as well as individual adverse events, where reported. A greater knowledge of the potential magnitude of the nocebo effect might draw attention to the importance of adequate design of RCTs in IBS to minimize such unwanted and non-treatment related adverse events. Moreover, the findings might improve physicians' awareness of ways by which they unintentionally induce nocebo effect, and thereby communicate effectively with patients with IBS to optimize the tolerability, and thereby the benefits, of drugs for the condition.

METHODS

Search Strategy and Study Selection

We searched the medical literature using MEDLINE (1946 to January 2021), EMBASE CLASSIC and EMBASE (1947 to June 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 2021. We also searched clinicaltrials.gov to obtain data from unpublished trials.

RCTs examining the 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) and assessing adverse events were eligible for inclusion. The eligibility criteria are provided in Box 1. In the case of all RCTs, 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 data were extracted at the end of treatment for each trial. The diagnosis of IBS could be based on any iteration of the Rome criteria, supplemented by the results of investigations to exclude organic disease, where trials deemed this necessary. Studies had to report data on adverse events with both active drug and placebo.

The literature search was conducted independently by two investigators (CJB and ACF). We identified studies on IBS with the terms: *irritable bowel syndrome* and *functional disease(s), colon* (both as medical subject headings (MeSH) and free text terms), and *IBS, spastic colon, irritable colon,* or *functional* adj5 *bowel* (as free text terms). For IBS-C, we combined these using the set operator AND with studies identified with the following terms: *lubiprostone* (both as a MeSH and free text term), and *Amitiza, linaclotide, Constella, Linzess, plecanatide, Trulance, tegaserod*, *Zelnorm*, and *tenapanor* (as free text terms). For IBS-D, we combined these using the set operator

AND with studies identified with the following terms: *alosetron, Lotronex, eluxadoline, Viberzi, Truberzi*, *ramosetron, Irribow, rifaximin*, and *Xifaxan* (all as free text terms).

There were no language restrictions. We screened titles and abstracts of all citations identified by our search for potential suitability and retrieved those that appeared relevant to examine them in more detail. We translated foreign language papers, where required. We performed a recursive search of the literature using bibliographies of all relevant studies. Eligibility assessment was performed independently by two investigators (CJB and ACF), using pre-designed eligibility forms. We resolved any disagreement between investigators by consensus and measured the degree of agreement with a kappa statistic. Ethical approval was not required.

Outcome Assessment

The primary outcome assessed was the proportion of patients randomized to placebo or active drug experiencing any adverse event in IBS-C and IBS-D trials separately. Secondary outcomes included adverse events leading to study withdrawal with active drug or placebo, as well as individual adverse events (abdominal distension, abdominal pain, constipation, diarrhea, headache, or nausea), where individual trials reported these data.

Data Extraction

Data were extracted independently by two investigators (CJB and ACF) on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA, USA), as dichotomous outcomes (adverse event experienced or not experienced) in the active drug and placebo arms of the included RCTs. Again, we resolved any discrepancies by consensus. In addition, the following clinical data were extracted for each trial: year of publication, geographical location, number of centers, criteria used to define IBS, active drug used, dosing schedule of the placebo and active drug, duration of therapy, total number of adverse events, number of adverse events leading to withdrawal, and number of individual adverse events in both the active drug and placebo arms. We

extracted all data with the denominators consisting of the safety populations reported; that is all patients receiving at least one dose of the study drug.

Quality Assessment and Risk of Bias

We used the Cochrane Risk of Bias tool to assess the quality of studies.[16] Two investigators (CJB and ACF) assessed study quality independently, with disagreements resolved by discussion. For all RCTs we recorded the 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 randomized to placebo or active drug experiencing adverse events separately for IBS-C and IBS-D trials. We used a random effects model to pool data to provide a conservative estimate of the frequency of adverse events, according to the methodology of DerSimonian and Laird.[17] We assessed heterogeneity between studies using the I^2 statistic, which ranges between 0% and 100%. We considered values of 25% to 49%, 50% to 74%, and ≥75% to represent low, moderate, and high levels of heterogeneity, respectively.[18] We performed subgroup analyses according to the individual drugs and dosages, dosing schedule, and trial duration (12 or 26 weeks).

We used StatsDirect version 3.2.7 (StatsDirect Ltd, Sale, Cheshire, England) to generate Forest plots of pooled adverse event rates both in the active drug and in the placebo arms and pooled risk differences (RDs) with 95% confidence intervals (CIs). Zero event rates were extremely rare due to the rigour of reporting of adverse events in the individual trials that were included. In all instances where they occurred, adding 0.5 to each cell made no difference to the point estimates for the RDs and the 95% CIs observed. We therefore used the raw data from each trial in our analysis.

We planned to assess for evidence of publication bias by applying Egger's test to funnel plots of RDs,[19] where at least 10 studies were available.[20]

RESULTS

The search strategy generated 4,334 citations, 140 articles of which we retrieved for further assessment as they appeared to be relevant. In total, 34 of these articles, reporting on 38 RCTs, fulfilled the eligibility criteria (Figure 1). Of these, 19 articles reported on 21 RCTs of licensed drugs versus placebo in IBS-C,[21-39] and 15 articles reported on 17 trials in IBS-D.[40-54] The 21 trials in IBS-C contained a total of 5,953 patients assigned to placebo and a total of 7,026 patients assigned to active drug. There were seven RCTs of tegaserod 6mg b.i.d. in IBS-C,[28-34] six trials of linaclotide 290mcg o.d.,[21-27] three trials of tenapanor 50mg b.i.d.[35-37] three RCTs, reported in two articles, of lubiprostone 8mcg b.i.d.,[38,39] and two RCTs of plecanatide 3mg or 6mg o.d., reported in one article.[27] The 17 trials in IBS-D contained a total of 3,854 patients randomized to placebo and 5,010 patients randomized to active drug. There were six RCTs of alosetron 1mg b.i.d.,[40-45] three trials of ramosetron 5mcg o.d.,[49-51] one trial of ramosetron 2.5mcg o.d.,[52] one trial of ramosetron 5mcg or 2.5mcg o.d.,[53] four RCTs of eluxadoline 75 or 100mg b.i.d., reported in three articles,[46-48] and two trials of rifaximin 550mg t.i.d., reported in one article.[54] Agreement between investigators for assessment of 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. Twelve trials in IBS-C, reported in 11 articles,[21-24,26,27,33,35,36,38,39] were at low risk of bias and 11 RCTs, reported in nine articles, in IBS-D.[41,45-48,51,52,54]

Adverse Event Rates in Randomized Controlled Trials in IBS-C

Any Adverse Event

Comparing 5,758 patients receiving any active drug with 4,613 patients receiving placebo in 16 studies, reported in 13 articles,[21-27,30,32,35-37,39] 40.1% (95% CI 31.3% to 49.2%) of patients in the active drug arms and 34.9% (95% CI 26.4% to 43.8%) of patients in the placebo arms developed at least one adverse event (Figure 2). There was a statistically significantly higher risk of any adverse events with treatment (RD 0.046, 95% CI 0.030 to 0.063) (Table 1), with minimal heterogeneity between studies (I^2=0.0%, p=0.66) and no evidence of funnel plot asymmetry (Egger test, p=0.18). In subgroup analyses according to individual drug, pooled proportions of patients with any adverse event was significantly higher in the active drug arms, compared with the placebo arms, in trials of linaclotide 290mcg o.d., tenapanor 50mg b.i.d., and plecanatide 3mg o.d. The highest rates of reporting of any adverse event were found in two trials that randomized 1,094 patients to tegaserod 6mg b.i.d. and 1,072 patients to placebo (57.3% (95% CI 54.4% to 60.2%) in the active drug arms and 53.2% (95% 47.7% to 58.8%) in the placebo arms).[30,32]

Adverse Events Leading to Withdrawal

Comparing 7,096 patients receiving any active drug with 5,953 patients receiving placebo in 21 studies, reported in 19 articles,[21-39] 5.2% (95% CI 3.9% to 6.6%) of patients in the active drug arms and 2.4% (95% CI 1.6% to 3.3%) of patients in the placebo arms developed an adverse event leading to withdrawal, with a RD of 0.027 (95% CI 0.016 to 0.039, I^2=74.4%, p<0.0001) (Table 1), and no evidence of funnel plot asymmetry (Egger test, p=0.09). All drugs, except lubiprostone 8mcg b.i.d., showed a statistically significantly higher risk of adverse events leading to withdrawal compared with placebo. The highest rates of adverse events leading to withdrawal were reported in

three trials that randomized 701 patients to tenapanor 50mg b.i.d. and 700 patients to placebo (7.4% (95% CI 5.6% to 9.5%) in the active drug arms and 1.3% (95% CI 0.4% to 2.7%) in the placebo arms).[35-37]

Individual Adverse Events

We also pooled data concerning individual adverse events, including diarrhea, abdominal pain, abdominal distension, nausea, or headache (Table 1). Overall, rates of each of these adverse events was generally higher in the active drug arms than in the placebo arms. Rates of diarrhea were significantly higher in RCTs of linaclotide 290mcg o.d., tenapanor 50mg b.i.d., and plecanatide 3mg or 6mg o.d. Rates of nausea were significantly higher in trials of lubiprostone 8mcg b.i.d., and rates of headache significantly higher in RCTs of tegaserod 6mg b.i.d. Rates of abdominal pain or abdominal distension were no higher in the active drug arms with any of the individual drugs. In two trials of lubiprostone 8mcg b.i.d. more patients in the placebo arms reported abdominal pain or headache than those in the active drug arms (6.5% versus 6.0% and 6.5% versus 4.3%, respectively).[38,39] Similarly, in three trials of linaclotide 290mcg o.d. the proportion of patients who reported nausea was higher in the placebo arms (2.9% versus 2.0%).[21,25,26] More patients complained of headache with placebo in one trial of tenapanor 50mg b.i.d. (5.6% versus 3.4%).[35] Finally, more patients in the placebo arm experienced abdominal distension in one trial of lubiprostone 8mcg b.i.d. (10.4% versus 1.9%).[38]

Further subgroup analyses according to how many times daily a drug was administered, and trial duration (12 or 26 weeks) are provided in Supplementary Table 5. Overall, the prevalence of adverse events, adverse events leading to withdrawal, and diarrhea were higher with active drug in all of these analyses, although rates of all these events were generally higher with both active drug and placebo in trials of 26 weeks duration, versus those of 12 weeks.

Adverse Event Rates in Randomized Controlled Trials in IBS-D

Any Adverse Event

Comparing 5,110 patients receiving any active drug with 3,896 patients receiving placebo in 16 studies, reported in 14 articles,[41-54] 54.1% (95% CI 47.1% to 61.1%) of patients in the active drug arms and 46.9% (95% CI 39.6% to 54.3%) of patients in the placebo arms reported at least one adverse event (Figure 3). There was a statistically significantly higher risk of any adverse event with treatment (RD 0.064, 95% CI 0.029 to 0.099) with moderate heterogeneity between studies (I^2=66.6%, p<0.0001) (Table 2), and no evidence of funnel plot asymmetry (Egger test, p=0.52). In subgroup analyses according to individual drug, pooled proportions of patients with any adverse event was significantly higher in the active drug arms, compared with the placebo arms, in trials of alosetron 1mg b.i.d.[41-45] and ramosetron 2.5mcg o.d. The highest rates of reporting of any adverse event were found in five trials that randomized 1,469 patients to alosetron 1mg b.i.d. and 1,210 patients to placebo (62.7% (95% CI 47.3% to 76.7%) in the active drug arms and 50.7% (95% 31.2% to 70.1%) in the placebo arms), with a RD of 0.113 (95% CI 0.062 to 0.165, I^2=48.2%, p=0.10).[41-45]

Adverse Events Leading to Withdrawal

Comparing 5,010 patients receiving any active drug with 3,854 patients receiving placebo in 16 studies, reported in 14 articles,[40-43,45-54] 6.5% (95% CI 4.4% to 8.9%) of patients in the active drug arms and 3.9% (95% CI 2.7% to 5.4%) of patients in the placebo arms developed an adverse event leading to withdrawal, with a RD of 0.026 (95% CI 0.007 to 0.046, I^2=85.1%, p<0.0001) (Table 2), and no evidence of funnel plot asymmetry (Egger test, p=0.07). Alosetron 1mg b.i.d. and eluxadoline 75mg or 100mg b.i.d. demonstrated a statistically significantly higher risk of adverse

events leading to withdrawal, compared with placebo. The highest rates of adverse events leading to withdrawal were found in five trials that randomized 1,414 patients to alosetron 1mg b.i.d. and 1,165 patients to placebo (13.8% (95% CI 10.4% to 17.6%) in the active drug arms and 5.9% (95% 2.1% to 11.5%) in the placebo arms), with a RD of 0.078 (95% CI 0.051 to 0.106, I^2=34.0%, p=0.19).[40-43,45]

Individual Adverse Events

Pooled prevalence of individual adverse events, including constipation, headache, abdominal pain, or nausea in IBS-D trials are provided in Table 2. Again, rates of individual adverse events were generally higher with active drug in all these analyses. Rates of constipation were significantly higher with all active drugs, except for rifaximin 550mg t.i.d., where those in the placebo arm were significantly more likely to report constipation. Rates of abdominal pain were significantly higher with eluxadoline at any dose, but not with either 75mg or 100mg b.i.d. individually, and with alosetron 1mg b.i.d. Rates of nausea were significantly higher in trials of eluxadoline 75mg or 100mg b.i.d. Rates of headache were no higher in active drug arms with any of the individual drugs. In fact, the proportion of patients who reported headache was higher in the placebo arms in four trials of alosetron 1mg b.i.d.[40,43,44,45] (7.8% versus 6.9%) and in two trials, reported in one article,[54] of rifaximin 550mg t.i.d. (6.7% versus 6.2%). Finally, more patients in the placebo arms complained of abdominal pain than those in the active drug arms in two trials of rifaximin 550mg t.i.d. (5.5% versus 4.7%).[54]

Further subgroup analyses according to how many times daily a drug was administered, and the duration of treatment (12 or 26 weeks) are provided in Supplementary Table 6. Overall, the prevalence of adverse events, adverse events leading to withdrawal, and constipation was higher with active drug versus placebo for several of these analyses. In contrast to trials in IBS-C, rates of

all these events were generally higher with both active drug and placebo in trials of 12 weeks duration, versus those of 26 weeks.

DISCUSSION

We have conducted a systematic review and meta-analysis of licensed drugs for IBS-C and IBS-D to estimate magnitude of prevalence of adverse events in active drug and placebo arms and, therefore, to evaluate potential nocebo effects in IBS. In IBS-C trials, 40.1% of patients in the active drug arms and 34.9% of patients in the placebo arms developed at least one adverse event, with a statistically significantly higher risk of any adverse event with active treatment. In particular, the highest rates of reporting of any adverse event were found in two trials of tegaserod 6mg b.i.d., while the highest rates of adverse events leading to withdrawal were reported in three trials of tenapanor 50mg b.i.d. Overall, rates of each individual adverse event were generally higher with active drug. However, in IBS-C trials, only diarrhea or headache were significantly more common with any active drug, and in IBS-D trials only constipation, nausea, or abdominal pain. Statistically higher rates of any adverse event and diarrhea were found in trials of linaclotide, plecanatide, and tenapanor, and significantly higher rates of adverse events leading to withdrawal with all drugs other than lubiprostone. Rates of nausea were significantly higher with lubiprostone and headache with tegaserod. In IBS-D trials, 54.1% of patients in the active drug arms and 46.9% of patients in the placebo arms reported at least one adverse event, with a statistically significantly higher risk of any adverse event with active treatment. The highest rates of reporting of any adverse event were found in five trials of alosetron 1mg b.i.d., where we also found the highest rates of adverse events leading to withdrawal. Statistically higher rates of any adverse event were found in trials of alosetron and ramosetron, and significantly higher rates of adverse events leading to withdrawal with alosetron and eluxadoline. Rates of constipation were significantly higher with all drugs other than rifaximin, rates of abdominal pain significantly higher with alosetron and eluxadoline, and rates of nausea significantly higher with eluxadoline.

We used a comprehensive literature search, augmented by searching the gray literature, to maximize the likelihood of identifying all pertinent trials, and to minimize bias. The literature search, eligibility assessment, and data extraction for this meta-analysis were undertaken

independently by two reviewers, with any discrepancies resolved by consensus. We used a random effects model to pool data to provide a more conservative estimate of the proportion of adverse events in RCTs of licensed drugs for IBS-C or IBS-D, and assessed for publication bias, where sufficient studies existed. Finally, to minimize influence of heterogeneity on our results, we performed subgroup analyses according to the different types and dosages of drugs, type of adverse event, dosing schedule, and trial duration.

Weaknesses include the fact that there was significant heterogeneity between studies in some analyses. This precludes firm conclusions being drawn from some of the pooled estimates we report, particularly those across all licensed drugs pooled together. The drug and dose-specific estimates may, therefore, be preferable and, in many instances, heterogeneity was not present in these subgroup analyses. However, in some instances this may be because there were fewer studies and therefore power to detect heterogeneity was lower. In addition, we were unable to capture differences in adverse events reporting methodology as a potential source of heterogeneity. Furthermore, we did not assess predictors of reporting adverse events in our meta-analysis, although it is likely this would need patient level data. Moreover, although we were able to extract the proportion of patients experiencing each adverse event, it is also plausible that there are some patients who experience multiple adverse events and this patient subset cannot be characterized by a study such as ours. Some trials were conducted and reported by a single group of investigators, and published within a single article, meaning that pooling them as separate studies in a meta-analysis could be questioned by some. Finally, we did not include trials of non-licensed drugs, complementary therapies, probiotics, or dietary interventions, although differentiating nocebo effects in the placebo group from the active treatment arm may be biased in studies of complementary therapies, given their unclear treatment effect.

The influence of the nocebo effect has not been well studied in drug trials in IBS, despite these patients being prone to “subjective” gastrointestinal symptoms, including nausea, abdominal pain, and abdominal bloating or distension, which may be influenced by patient expectations. To

the best of our knowledge, therefore, this is the first meta-analysis assessing this issue. Other studies have demonstrated a strong nocebo effect with individual food items, including fermentable carbohydrates and gluten.[55,56] This can lead to self-perpetuating beliefs, with some patients developing nutritional or energy deficiencies because they exclude more and more foods, as they try to link flares of their symptoms with specific food items.[57] In fact, more than 80% of patients with IBS report that their symptoms are related to the food they ingest.[57-59] Despite this, in a study evaluating the role of different exclusion or restrictive diets in patients with IBS, including a diet that eliminated food components by choice, gluten-free, dairy-free, or low FODMAP diets, individuals on an exclusion or restrictive diet had more severe symptoms.[60] Knowledge of the potential magnitude of the nocebo effect, and determinants of it, is an important issues, given that elucidating the role and relevance of treatment expectations on response to gastrointestinal symptoms in patients with IBS is still an unfulfilled need.

Our findings highlight how the nocebo response is important for the interpretation of safety data in IBS. To avoid potentially biased interpretations, some measures to minimize this should be considered when designing and reporting RCTs in IBS. First, we expect that adverse events that are spontaneously reported by trial participants might be less influenced by suggestion than adverse events that are identified from a checklist provided to patients. For instance, it is well known that patients treated with statins can experience myalgias.[61] In fact, in a *post hoc* analysis, when both patients and physicians were blinded to treatment assignment, muscle-related adverse events occurred with similar frequency in patients receiving active drug or placebo, whereas during the open-label extension phase, when treatment assignment was unblinded, these events were reported at a significantly higher rate by patients receiving active drug.[61] This finding was hypothesized to be related to muscle-related adverse events with statins, which have been highly publicized. For example, looking at IBS therapies, it is well known that patients taking lubiprostone might experience nausea. Our results showed that 11.7% of patients treated with lubiprostone and 6.8% of those in the placebo arms reported nausea as side effects. These high percentages may be influenced

by prior knowledge of the possibility of these adverse events, since they are generally the most frequent.

This raises questions about how physicians, nurses, and other healthcare professionals inform patients about potential side effects of drugs. Such information should, perhaps, be combined with a detailed explanation of the intended therapeutic benefits of the drug. In addition, providing less information about rare, or irrelevant, side effects might be a good method to minimize nocebo effects. Proof of causality is also crucial; that is how accurate investigators are at establishing a causal relationship between an adverse event and a studied drug. Many RCTs included in our meta-analysis reported abdominal distension or abdominal pain as adverse events during active or inert treatment.[38,43-45] Given that in many RCTs they occurred with almost equal frequency in patients receiving placebo, it is more likely that these adverse outcomes are related to a worsening of the underlying condition itself, rather than an adverse effect of the active drug. Informing patients about the possible risk of worsening disease-related symptoms may, therefore, reduce negative expectations of experiencing drug-related adverse events.

There may be other explanations for reporting adverse events in trials in IBS. In a previous study by Thiwan *et al.* examining data from a large trial of desipramine, a tricyclic antidepressant, in women with functional bowel disorders, many of the symptoms reported as side effects, and which were unchanged in severity or began to improve after 2 weeks of desipramine treatment, were present before starting treatment.[11] In addition, levels of psychological distress, but not blood levels of desipramine, correlated with likelihood of adverse event reporting. Therefore, potentially, some patients may not be aware that often the symptoms they attribute to the medication they receive in clinical trials were present before the initiation of the drug. Frequently, these symptoms appear related to anxiety, worries about taking the drug, or other psychosocial factors that may increase the tendency to report symptoms. These considerations further highlight the importance of effective communication between physician and patient to optimize the tolerability, and potentially beneficial effects, of medications.

In conclusion, our systematic review and meta-analysis demonstrated that 40.1% and 54.1% of patients in the active drug arms, and 34.9% and 46.9% of patients in the placebo arms in IBS-C and IBS-D trials, respectively, developed at least one adverse event. Therefore, patients with IBS randomized to placebo have a high risk of reporting adverse events, which might be related to both nocebo and non-nocebo factors. Understanding the mechanism behind the nocebo effect is important. Although patients' expectations and psychosocial factors may be involved, further insights are critical to be able to control or optimize these effects in clinical trials, as well as in clinical practice.

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CONFLICTS OF INTEREST/STUDY SUPPORT

Guarantor of the article: ACF is guarantor.

Specific author contributions: BB, EVS, CJB, and ACF conceived and drafted the study. BB, CJB, and ACF collected and interpreted the data. BB and ACF analyzed the data. BB and ACF drafted the manuscript. All authors have approved the final draft of the manuscript.

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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 the proportion of patients randomized to placebo or active drug experiencing any adverse event in IBS-C and IBS-D trials separately.

*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. Forest Plot of Risk Difference for Any Adverse Event in Patients Receiving Active Drug Versus Placebo in Randomized Controlled Trials in IBS-C.

Figure 3. Forest Plot of Risk Difference for Any Adverse Event in Patients Receiving Active Drug Versus Placebo in Randomized Controlled Trials in IBS-D.

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Table 1. Pooled Proportion of Patients Experiencing Adverse Events in the Placebo and Active Drug Arms and Pooled Risk Difference in Adverse Events in Randomized Controlled Trials in IBS-C.

	Number of Studies	Total Number of Patients in Placebo Arms	Pooled Proportion of Patients with AEs in Placebo Arms (95% CI)	Total Number of Patients in Active Drug Arms	Pooled Proportion of Patients with AEs in Active Drug Arms (95% CI)	Pooled Risk Difference (95% CI) with Active Drug Versus Placebo	I^2 (p value for χ^2)
Any adverse event							
Any drug	16	4,613	0.349 (0.264 – 0.438)	5,758	0.401 (0.313 – 0.492)	0.046 (0.030 – 0.063)	0.0% (0.66)
Linaclotide 290mcg o.d±	6	1,681	0.355 (0.233 – 0.487)	1,682	0.426 (0.292 – 0.566)	0.055 (0.023 – 0.087)	0.0% (0.66)
Lubiprostone 8mcg b.i.d⁑	3	436	0.271 (0.105 – 0.479)	835	0.324 (0.163 – 0.510)	0.042 (-0.002 – 0.085)	0% (0.49)
Tenapanor 50mg b.i.d.	3	691	0.356 (0.236 – 0.485)	691	0.445 (0.346 – 0.546)	0.093 (0.043 – 0.143)	0.0% (0.80)
Plecanatide any dosing	2	733	0.185 (0.158 – 0.216)	1,456	0.419 (0.384 – 0.455)	0.234 (0.188 – 0.278)	N/A*
Plecanatide 3mg o.d.	2	733	0.185 (0.158 – 0.216)	728	0.238 (0.207 – 0.370)	0.052 (0.010 – 0.094)	N/A*
Plecanatide 6mg o.d.	2	733	0.185 (0.158 – 0.216)	728	0.198 (0.169 – 0.229)	0.012 (-0.028 – 0.053)	N/A*
Tegaserod 6mg b.i.d.	2	1,072	0.532 (0.477 – 0.588)	1,094	0.573 (0.544 – 0.602)	0.033 (-0.009 – 0.075)	0.0% (0.59)

Adverse events leading to withdrawal							
Any drug	21	5,953	0.024 (0.016 – 0.033)	7,096	0.052 (0.039 – 0.066)	0.027 (0.016 – 0.039)	74.4% (<0.0001)
Tegaserod 6mg b.i.d.	7	2,403	0.029 (0.017 – 0.045)	2,422	0.051 (0.028 – 0.080)	0.023 (0.002 – 0.044)	70.5% (0.002)
Linaclotide 290mcg o.d.	6	1,681	0.020 (0.014 – 0.027)	1,682	0.057 (0.028 – 0.096)	0.039 (0.007 – 0.071)	84.6% (<0.0001)
Lubiprostone 8mcg b.i.d.	3	436	0.058 (0.034 – 0.087)	835	0.051 (0.037 – 0.066)	-0.004 (-0.037 – 0.029)	31.1% (0.23)
Tenapanor 50mg b.i.d.	3	700	0.013 (0.004 – 0.027)	701	0.074 (0.056 – 0.095)	0.058 (0.030 – 0.086)	40.4% (0.19)
Plecanatide any dosing	2	733	0.004 (0.001 – 0.012)	1,456	0.045 (0.031 – 0.062)	0.041 (0.027 – 0.058)	N/A*
Plecanatide 3mg o.d.	2	733	0.004 (0.001 – 0.012)	728	0.025 (0.015 – 0.039)	0.021 (0.009 – 0.038)	N/A*
Plecanatide 6mg o.d.	2	733	0.004 (0.001 – 0.012)	728	0.022 (0.013 – 0.035)	0.018 (0.007 – 0.032)	N/A*
Diarrhea							
Any drug	19	5,656	0.025 (0.017 – 0.035)	6,798	0.086 (0.063 – 0.112)	0.064 (0.041 – 0.087)	91.1% (<0.0001)
Linaclotide 290mcg o.d.	6	1,681	0.022 (0.015 – 0.030)	1,682	0.134 (0.081 – 0.199)	0.117 (0.058 – 0.175)	91.1% (<0.0001)
Tegaserod 6mg b.i.d.	5	2,115	0.029 (0.009 – 0.060)	2,134	0.055 (0.028 – 0.092)	0.025 (-0.013 – 0.063)	90.7% (<0.0001)
Lubiprostone 8mcg b.i.d.	3	436	0.056 (0.036 – 0.079)	835	0.073 (0.050 – 0.101)	0.065 (-0.012 – 0.045)	5.9% (0.34)
Tenapanor 50mg b.i.d.	3	691	0.019 (0.005 – 0.043)	691	0.149 (0.123 – 0.176)	0.124 (0.096 – 0.153)	0.0% (0.92)
Plecanatide any dosing	2	733	0.010 (0.004 – 0.019)	1,456	0.042 (0.029 – 0.057)	0.032 (0.011 – 0.053)	66.1% (0.09)
Plecanatide 3mg o.d.	2	733	0.010 (0.004 – 0.019)	728	0.043 (0.024 – 0.068)	0.033 (0.003 – 0.062)	69.3% (0.07)
Plecanatide 6mg o.d.	2	733	0.010 (0.004 – 0.019)	728	0.041 (0.028 – 0.057)	0.030 (0.014 – 0.046)	0.0% (0.40)

Abdominal pain							
Any drug	14	4,128	0.040 (0.025 – 0.059)	4,353	0.051 (0.034 – 0.071)	0.005 (-0.002 – 0.013)	0.0% (0.85)
Linaclotide 290mcg o.d.	6	1, 681	0.028 (0.021 – 0.038)	1, 682	0.038 (0.027 – 0.051)	0.008 (-0.004 – 0.019)	0.0% (0.47)
Tegaserod 6mg b.i.d	5	2,115	0.053 (0.019 – 0.103)	2,134	0.062 (0.024 – 0.114)	0.003 (-0.007 – 0.014)	0.0% (0.54)
Lubiprostone 8mcg b.i.d	2	242	0.065 (0.038 – 0.100)	448	0.060 (0.040 – 0.083)	-0.003 (-0.041 – 0.034)	0.0% (0.71)
Tenapanor 50mg b.i.d	1	90	0.022 (0.003 – 0.078)	89	0.045 (0.012 – 0.111)	0.023 (-0.038 – 0.091)	N/A*
Nausea							
Any drug	13	3,401	0.039 (0.024 – 0.056)	3,824	0.051 (0.030 – 0.077)	0.010 (-0.002 – 0.023)	54.1% (0.01)
Tegaserod 6mg b.i.d	5	2,115	0.038 (0.016 – 0.069)	2,134	0.046 (0.018 – 0.087)	0.008 (-0.008 – 0.024)	50.9% (0.09)
Linaclotide 290mcg o.d.	3	459	0.029 (0.009 – 0.059)	457	0.020 (0.009 – 0.035)	-0.006 (-0.032 – 0.019)	34.0% (0.22)
Lubiprostone 8mcg b.i.d	3	436	0.068 (0.042 – 0.100)	835	0.117 (0.079 – 0.161)	0.047 (0.016 – 0.077)	0.0% (0.60)
Tenapanor 50mg b.i.d	2	391	0.018 (0.007 – 0.033)	398	0.030 (0.015 – 0.049)	0.012 (-0.008 – 0.032)	0.0% (0.59)
Headache							
Any drug	13	3,706	0.058 (0.032 – 0.091)	3,927	0.065 (0.039 – 0.096)	0.011 (0.002 – 0.021)	0.0% (0.65)
Linaclotide 290mcg o.d.	5	1,259	0.026 (0.012 – 0.046)	1,265	0.038 (0.027 – 0.050)	0.012 (-0.001 – 0.024)	0.0% (0.91)
Tegaserod 6mg b.i.d	5	2,115	0.092 (0.037 – 0.169)	2,134	0.111 (0.055 – 0.184)	0.019 (0.004 – 0.034)	0.0% (0.51)
Lubiprostone 8mcg b.i.d	2	242	0.065 (0.037 – 0.099)	439	0.043 (0.026 – 0.064)	-0.019 (-0.055 – 0.016)	0.0% (0.57)
Tenapanor 50mg b.i.d	1	90	0.056 (0.018 – 0.125)	89	0.034 (0.007 – 0.112)	-0.022 (0.001 – 2.365)	N/A*

Abdominal distension							
Any drug	8	1,908	0.018 (0.008 – 0.030)	1,919	0.023 (0.017 – 0.030)	0.007 (-0.006 – 0.019)	48.8% (0.06)
Linaclotide 290 mcg o.d	5	1,259	0.016 (0.007 – 0.028)	1,265	0.019 (0.012 – 0.028)	0.004 (-0.007 – 0.016)	24.1% (0.26)
Tenapanor 50 mg b.i.d	2	601	0.010 (0.001 – 0.027)	602	0.031 (0.019 – 0.047)	0.020 (-0.0008 – 0.041)	44.2% (0.18)
Lubiprostone 8 mcg b.i.d	1	48	0.104 (0.035 – 0.227)	52	0.019 (0.0 – 0.102)	-0.085 (-0.206 – 0.011)	N/A*

± o.d.; once daily

⁑b.i.d.; twice daily

N/A*; not applicable, too few studies.

Table 2. Pooled Proportion of Patients Experiencing Adverse Events in the Placebo and Active Drug Arms and Pooled Risk Difference in Adverse Events in Randomized Controlled Trials in IBS-D.

	Number of Studies	Total Number of Patients in Placebo Arms	Pooled Proportion of Patients with AEs in Placebo Arms (95% CI)	Total Number of Patients in Active Drug Arms	Pooled Proportion of Patients with AEs in Active Drug Arms (95% CI)	Pooled Risk Difference (95% CI) with Active Drug Versus Placebo	I^2 (p value for χ^2)
Any adverse event							
Any drug	16	3,896	0.469 (0.396 – 0.543)	5,110	0.541 (0.471 – 0.611)	0.064 (0.029 – 0.099)	66.6% (<0.0001)
Alosetron 1mg b.i.d‡‡	5	1,210	0.507 (0.312 – 0.701)	1,469	0.627 (0.473 – 0.767)	0.113 (0.062 – 0.165)	48.2% (0.10)
Ramosetron any dosing	5	912	0.488 (0.431 – 0.546)	1,015	0.563 (0.509 – 0.616)	0.075 (0.002 – 0.147)	59.7% (0.04)
Ramosetron 2.5mcg o.d±	2	386	0.420 (0.371 – 0.470)	396	0.533 (0.483 – 0.581)	0.113 (0.044 – 0.183)	0.0% (0.95)
Ramosetron 5mcg o.d.	4	628	0.513 (0.467 – 0.559)	619	0.589 (0.499 – 0.676)	0.079 (-0.044 – 0.202)	78.8% (0.003)
Eluxadoline any dosing	4	1,140	0.499 (0.348 – 0.592)	2,002	0.473 (0.328 – 0.620)	0.024 (-0.012 – 0.060)	0.0% (0.37)
Eluxadoline 100mg b.i.d.	4	1,140	0.469 (0.348 – 0.592)	1,195	0.469 (0.335 – 0.606)	0.015 (-0.025 – 0.055)	0.0% (0.47)
Eluxadoline 75mg b.i.d.	2	808	0.557 (0.522 – 0.591)	807	0.602 (0.567 – 0.636)	0.045 (-0.003 – 0.093)	N/A*
Rifaximin 550mg t.i.d.§	2	634	0.332 (0.296 – 0.369)	624	0.319 (0.274 – 0.367)	-0.013 (-0.064 – 0.039)	0.0% (0.76)

Adverse events leading to withdrawal							
Any drug	16	3,854	0.039 (0.027 – 0.054)	5,010	0.065 (0.045 – 0.089)	0.027 (0.007 – 0.046)	85.1% (<0.0001)
Alosetron 1mg b.i.d	5	1,165	0.059 (0.021 – 0.115)	1,414	0.138 (0.104 – 0.176)	0.078 (0.051 – 0.106)	34.0% (0.19)
Ramosetron any dosing	5	912	0.037 (0.026 – 0.050)	1,015	0.034 (0.022 – 0.048)	-0.005 (-0.021 – 0.011)	0.0% (0.72)
Ramosetron 2.5mcg o.d.	2	386	0.033 (0.018 – 0.053)	396	0.020 (0.008 – 0.036)	-0.013 (-0.034 – 0.008)	0.0% (0.73)
Ramosetron 5mg o.d.	4	628	0.041 (0.027 – 0.058)	619	0.044 (0.029 – 0.061)	0.002 (-0.020 – 0.023)	0.0% (0.55)
Eluxadoline any dosing	4	1,142	0.039 (0.027 – 0.053)	1,956	0.071 (0.054 – 0.091)	0.031 (0.009 – 0.054)	44.8% (0.14)
Eluxadoline 75mg b.i.d.	2	809	0.043 (0.030 – 0.058)	810	0.080 (0.062 – 0.100)	0.037 (0.014 – 0.060)	0.0% (0.83)
Eluxadoline 100mg b.i.d.	4	1,142	0.039 (0.027 – 0.053)	1,146	0.070 (0.048 – 0.095)	0.031 (0.003 – 0.059)	55.8% (0.08)
Rifaximin 550mg t.i.d.	2	635	0.015 (0.003 – 0.034)	625	0.009 (0.001 – 0.053)	-0.005 (-0.014 – 0.005)	0.0% (0.32)

Constipation							
Any drug	16	3,662	0.035 (0.022 – 0.051)	4,874	0.123 (0.074 – 0.182)	0.096 (0.054 – 0.138)	95.2% (<0.0001)
Alosetron 1mg b.i.d.	6	1,290	0.049 (0.019 – 0.092)	1,542	0.246 (0.176 – 0.323)	0.194 (0.146 – 0.242)	71.0% (0.004)
Ramosetron any dosing	5	912	0.031 (0.016 – 0.051)	1,015	0.084 (0.042 – 0.139)	0.048 (0.019 – 0.077)	56.2% (0.06)
Ramosetron 2.5mcg o.d.	2	386	0.051 (0.032 – 0.075)	396	0.113 (0.084 – 0.146)	0.062 (0.024 -0.100)	0.0% (0.87)
Ramosetron 5mg o.d.	4	628	0.026 (0.011 – 0.048)	619	0.087 (0.027 – 0.175)	0.055 (0.005 – 0.104)	78.8% (0.003)
Eluxadoline any dosing	4	1,140	0.024 (0.016 – 0.033)	2,002	0.071 (0.053 – 0.091)	0.050 (0.036 – 0.064)	0.0% (0.46)
Eluxadoline 75mg b.i.d.	2	808	0.025 (0.015 – 0.038)	807	0.074 (0.057 – 0.095)	0.050 (0.029 – 0.072)	N/A*
Eluxadoline 100mg b.i.d.	4	1,140	0.024 (0.016 – 0.033)	1,195	0.071 (0.049 – 0.097)	0.051 (0.032 – 0.069)	9.6% (0.33)
Rifaximin 550mg t.i.d.	1	320	0.025 (0.011 – 0.049)	315	0.003 (0.0 – 0.018)	-0.022 (-0.046 - -0.004)	N/A*
Headache							
Any drug	10	1,870	0.044 (0.022 – 0.072)	2,220	0.044 (0.028 – 0.064)	0.007 (-0.003 – 0.017)	0.3% (0.44)
Alosetron 1mg b.i.d.	4	653	0.078 (0.031 – 0.145)	910	0.069 (0.036 – 0.112)	0.003 (-0.027 – 0.034)	38.1% (0.18)
Eluxadoline 100mg b.i.d	2	332	0.021 (0.001 – 0.064)	336	0.032 (0.016 – 0.054)	0.011 (-0.020 – 0.042)	42.8% (0.19)
Ramosetron any dosing	2	251	0.005 (0.0 – 0.015)	350	0.015 (0.003 – 0.036)	0.011 (-0.005 – 0.027)	0.0% (0.81)
Ramosetron 2.5mcg o.d.	1	102	0.0 (0.0 – 0.0)	104	0.0 (0.0 – 0.0)	0.000 (-0.036 – 0.036)	N/A*
Ramosetron 5mcg o.d.	2	251	0.006 (0.0 – 0.020)	246	0.024 (0.009 – 0.047)	0.016 (-0.004 – 0.037)	0.0% (0.76)
Rifaximin 550mg t.i.d.	2	634	0.067 (0.040 – 0.099)	624	0.062 (0.045 – 0.082)	-0.004 (-0.030 – 0.023)	0.0% (0.36)

Abdominal pain							
Any drug	10	2,616	0.041 (0.029 – 0.056)	3,734	0.063 (0.042 – 0.087)	0.018 (0.002 – 0.034)	58.2% (0.01)
Eluxadoline any dosing	4	1,140	0.031 (0.017 – 0.048)	2,002	0.040 (0.016 – 0.075)	0.017 (0.003 – 0.031)	0.0% (0.38)
Eluxadoline 75mg b.i.d.	2	808	0.041 (0.028 – 0.057)	807	0.058 (0.043 – 0.077)	0.017 (-0.004 – 0.039)	N/A*
Eluxadoline 100mg b.i.d.	4	1,140	0.031 (0.017– 0.048)	1,195	0.042 (0.015 – 0.082)	0.017 (-0.003 – 0.036)	36.5% (0.21)
Alosetron 1mg b.i.d.	3	573	0.056 (0.032 – 0.086)	838	0.123 (0.077 – 0.180)	0.065 (0.015 – 0.115)	62.3% (0.07)
Rifaximin 550mg t.i.d.	2	634	0.055 (0.026 – 0.095)	624	0.047 (0.022 – 0.080)	-0.008 (-0.031 – 0.015)	0.0% (0.80)
Ramosetron 5mcg o.d.	1	269	0.019 (0.006 – 0.043)	270	0.026 (0.010 – 0.053)	0.007 (-0.020 – 0.036)	N/A*
Nausea							
Any drug	9	2,321	0.039 (0.028 – 0.052)	3,537	0.051 (0.035 – 0.069)	0.014 (0.002 – 0.027)	49.3% (0.07)
Eluxadoline any dosing	4	1,140	0.047 (0.036 – 0.060)	2,002	0.075 (0.063 – 0.086)	0.025 (0.008 – 0.042)	0.0% (0.80)
Eluxadoline 75mg b.i.d.	2	808	0.051 (0.037 – 0.068)	807	0.080 (0.063 – 0.101)	0.030 (0.006 – 0.054)	N/A*
Eluxadoline 100mg b.i.d.	4	1,140	0.047 (0.036 – 0.060)	1,195	0.070 (0.057 – 0.085)	0.023 (0.004 – 0.041)	0.0% (0.83)
Alosetron 1mg b.i.d.	2	445	0.046 (0.029 – 0.068)	708	0.060 (0.044 – 0.079)	0.016 (-0.009 – 0.042)	0.0% (0.43)
Rifaximin 550mg t.i.d	2	634	0.039 (0.025 – 0.056)	624	0.040 (0.004 – 0.111)	0.004 (-0.047 – 0.055)	81.7% (0.02)
Ramosetron any dosing	1	102	0.0 (0.0 – 0.0)	203	0.015 (0.003 – 0.043)	0.015 (-0.022 – 0.043)	N/A*
Ramosetron 2.5mcg o.d.	1	102	0.0 (0.0 – 0.0)	104	0.0 (0.0 – 0.0)	0.000 (-0.036 – 0.036)	N/A*
Ramosetron 5mcg o.d.	1	102	0.0 (0.0 – 0.0)	99	0.030 (0.006 – 0.086)	0.030 (-0.007 – 0.085)	N/A*

± o.d.; once daily

‡b.i.d.; twice daily

§t.i.d.; three times daily

N/A*; not applicable, too few studies.