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TITLE PAGE

Title: Systematic Review and Network Meta-analysis: Efficacy of Licensed Drugs for Abdominal Bloating in Irritable Bowel Syndrome with Constipation.

Short running head: IBS-C and Bloating: A Network Meta-analysis.

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Abbreviations:

5-HT	5-hydroxytryptamine
b.d.	twice daily
CI	confidence interval
FDA	Food and Drug Administration
IBS	irritable bowel syndrome

IBS-C	irritable bowel syndrome with constipation
MeSH	medical subject heading
NNT	number needed to treat
o.d.	once daily
RCT	randomised controlled trial
RR	relative risk

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Word count: 4120

SUMMARY

Background: Although bloating is a highly prevalent and troublesome symptom in irritable bowel syndrome with constipation (IBS-C), treatment is empirical with no specific guidelines for its management.

Aim: To conduct a pairwise and network meta-analysis, using a frequentist approach, of Food and Drug Administration-licensed drugs for IBS-C comparing their efficacy for abdominal bloating as a specific endpoint.

Methods: We searched the medical literature through December 2020 to identify randomised controlled trials (RCTs) in IBS-C, with abdominal bloating reported as a dichotomous assessment. Efficacy of each drug was reported as a pooled relative risk (RR) with 95% confidence intervals (CIs) to summarise effect of each comparison tested. Treatments were ranked according to their P-score.

Results: We identified 13 eligible RCTs, containing 10,091 patients. Linaclotide 290mcg o.d., lubiprostone 8mcg b.d., tenapanor 50mg b.d., and tegaserod 6mg b.d. were all superior to placebo for abdominal bloating in patients with IBS-C, in both pairwise and the network meta-analyses. Linaclotide demonstrated the greatest improvement in abdominal bloating in both pairwise and network meta-analysis (RR of failure to achieve an improvement in abdominal bloating = 0.78; 95% CI 0.74 to 0.83, number needed to treat = 7, P-score 0.97). Indirect comparison revealed no significant differences between individual drugs.

Conclusions: We found all licensed drugs for IBS-C to be superior to placebo for abdominal bloating. Linaclotide appeared to be the most efficacious at relieving abdominal bloating. Further research is needed to assess long-term efficacy of these agents and to better understand the precise mechanism of improving bloating.

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders, now termed disorders of gut-brain interaction, with a pooled global prevalence of between 4% and 9% in the general population, depending on the criteria used. [1,2] The Rome IV criteria define IBS as the presence of abdominal pain related to defecation in association with altered stool frequency and/or form. [3] Although not part of the formal Rome IV definition, abdominal bloating is the second most bothersome symptom reported by patients, after abdominal pain, and together these symptoms help predict severity of IBS. [4-7]

Abdominal bloating is a sensation of gassiness or fullness. [3,5] It frequently co-occurs with visible abdominal distension, although these symptoms can exist separately. [3,5,8] The two symptoms are reported in 67% to 90% of patients with IBS with constipation (IBS-C). [4,6,9] The pathophysiology of abdominal bloating and distension is complex and poorly understood. Dietary factors, alterations in the gut microbiome, abnormalities in gastrointestinal transit and gas handling, changes in visceral sensation, and abdomino-phrenic dyssynergia are just a few of the pathophysiological processes that may play a role in symptom development. [5,8,10-12] The economic impact of abdominal bloating in patients with IBS-C is substantial, due to an increased number of physician visits, and reduced workplace productivity. [13-15]

As there is no validated management algorithm for bloating in patients with IBS-C, treatment is often empirical. Although fibre appears beneficial in IBS, many patients report that bloating worsens with increased fibre intake. [16-18] Laxatives are frequently recommended to patients with IBS-C; however, they do not improve abdominal bloating. [19,20] Probiotics may improve bloating symptoms in some IBS patients. [17,21] For example, in a study of patients with IBS-C, *Bifidobacterium lactis* improved abdominal distension by accelerating gastrointestinal transit. [22] Dietary interventions, such as a diet low in fermentable

oligosaccharides, disaccharides, monosaccharides, and polyols, may improve bloating in some patients, although large RCTs have not been carried out specifically in IBS-C populations. [23,24] Finally, some behavioural interventions, such as biofeedback, may be beneficial for abdominal bloating. [25]

There are currently five Food and Drug Administration (FDA)-licensed drugs available for the treatment of IBS-C. Lubiprostone, a prostaglandin E_1 derivative, acts on chloride channels. [26,27] Linaclotide and plecanatide are peptides that stimulate the guanylate cyclase-C receptor. [28,29] Tenapanor is a small molecule that inhibits the sodium-hydrogen exchanger-3. [30] Although their precise mechanisms of action differ, these four drugs are all secretagogues and treat constipation via electrolyte shifts, with water influx into the intestinal lumen, improving stool consistency and accelerating gastrointestinal transit. The fifth agent, tegaserod, is a prokinetic agent and acts as an agonist at the 5-hydroxytryptamine-4 ($5\text{-}HT_4$) receptor. [31] This drug was withdrawn in 2007, due to a small excess number of cardiovascular and cerebrovascular events, but was re-approved for use in the USA in 2018 for women ≤65 years of age with IBS-C with ≤1 cardiovascular risk factor. [32]

A network meta-analysis of randomised controlled trials (RCTs), updated in light of the re-introduction of tegaserod, examined the comparative efficacy of all these drugs, according to FDA-recommended composite endpoints for drug trials in IBS-C. [33,34] All drugs were found to be superior to placebo, and of similar efficacy, but data for abdominal bloating were limited at the time this was conducted. [33] In the interim, additional studies have been performed, and data provided in a report for the FDA Gastrointestinal Drugs Advisory Committee in support of the re-introduction of tegaserod have become available. [32,35,36] We therefore examined the efficacy of all these drugs for abdominal bloating in IBS-C in a pairwise and network meta-analysis.

METHODS

Search Strategy and Study Selection

We searched the medical literature through December 15th 2020, using Pubmed (1964 to present), EMBASE (1974 to present), Scopus (1960 to present), and the Cochrane central register of controlled trials and Web of Science (since inception). We also searched clinicaltrials.gov (1964 to present), for unpublished trials, or supplementary data for potentially eligible studies. The searches for the meta-analysis were conducted by an expert librarian with additional input from the authors. Studies on IBS-C were identified using *irritable bowel syndrome* or *constipation* (both as medical subject headings (MeSH) and free text terms), and c*onstipation, bloating, linaclotide, plecanatide, lubiprostone, tenapanor, tegaserod, irritable colon,* or *randomized control trial* (as free text terms). These were then combined with specific set of operators 'AND/OR' to obtain multiple combinations for identification of the abstracts based on the following: *irritable bowel syndrome AND constipation* (both as MeSH and free text terms), and *linaclotide OR plecanatide OR lubiprostone OR tenapanor OR tegaserod* (as free text terms). An example of the search is provided in the Supplementary Materials. There were no language restrictions; foreign language articles were translated, where required.

Adult patients (≥18 years) in eligible RCTs had to have a diagnosis of IBS-C, based on any iteration of the Rome criteria (I, II, III, or IV) (Supplementary Table 1). Studies recruiting patients with chronic idiopathic constipation, opioid-induced constipation, or mixed populations of patients with IBS-C, chronic idiopathic constipation, or opioid-induced constipation were ineligible for inclusion, unless data were reported separately for all patients with IBS-C. Only RCTs that examined the efficacy of current FDA-licensed doses of lubiprostone, linaclotide, plecanatide, tenapanor, or tegaserod compared with each other, or with placebo, were eligible. All RCTs had to report a dichotomous assessment of efficacy of

these drugs, in terms of improvement, or no improvement, in abdominal bloating. To maintain homogeneity between clinical trials, data were extracted at 12 weeks, even for studies conducted over a longer period. For studies where dichotomous data for abdominal bloating were not available in the original publication, we requested further information from the pharmaceutical companies responsible for conducting the trial.

Two investigators (ADN and NSL) evaluated each of the abstracts and titles identified from the search independently. Full text articles were obtained for all potentially relevant abstracts. These were then evaluated according to the eligibility criteria by two investigators (ADN and ACF) independently, using pre-defined eligibility forms. Disagreements were resolved by consensus. Inter-rater agreement was assessed using the kappa statistic.

Outcome Assessment

We assessed the efficacy of all drugs, compared with each other or with placebo, in terms of failure of abdominal bloating to respond to therapy, with the endpoints of interest used to define response reported below. We did not assess safety, as there were no new data since our previous network meta-analyses. [33,34]

Data Extraction

All data were extracted independently by two investigators (ACF and CJB) on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes (improvement or no improvement in abdominal bloating). For all included studies, the following data were also extracted for each trial, where available: country of origin, number of centres, criteria used to define IBS-C, proportion of female patients, and dose and duration of therapy. Data were extracted as intention-to-treat analyses, with dropouts assumed to be treatment failures (i.e., no improvement in abdominal bloating),

wherever trial reporting allowed. 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

Two investigators (ADN and ACF) performed this independently at the study level. Disagreements were resolved by discussion. The Cochrane handbook (ROB 1.0) was used to assess risk of bias, by recording the method used to generate the randomization schedule and conceal treatment allocation, whether blinding was implemented for participants, personnel, and outcomes assessment, whether there was evidence of incomplete outcomes data, and whether there was evidence of selective reporting of outcomes. [37]

Data Synthesis and Statistical Analysis

We first performed a pairwise meta-analysis pooling data using a random effects model, to provide a more conservative estimate of the effect of each drug on abdominal bloating in IBS-C. [38] The impact of different interventions was expressed as a relative risk (RR) of abdominal bloating not improving with each drug versus placebo with 95% confidence intervals (CI). We calculated the number needed to treat (NNT), with a 95% CI, using the formula NNT = 1 / (assumed control risk x (1 – RR)). Heterogeneity, which is variation between individual study results arising because of differences in study participants or methodology, was assessed using the I^2 statistic. The I^2 ranges between 0% and 100%, and is typically considered low, moderate, and high for values of 25% to 49%, 50% to 74%, and ≥75% respectively. [39] Review Manager version 5.4.1 (RevMan for Windows 2020, the Nordic Cochrane Centre, Copenhagen, Denmark) was used to generate Forest plots of pooled RRs with 95% CIs, as well as funnel plots. The latter were assessed for evidence of asymmetry, and therefore possible publication bias or other small study effects, using the

Egger test, if there were sufficient (≥10) studies included in the meta-analysis, in line with recommendations. [40,41]

We also performed a network meta-analysis using the frequentist model, with the statistical package "netmeta" (version 0.9-0, https://cran.r-project.org/web/packages/netmeta/index.html) in R (version 4.0.2), and reported according to the PRISMA extension statement for network meta-analyses, to explore indirect treatment comparisons of the efficacy and safety of each medication. Network meta-analysis results usually give a more precise estimate, compared with results from standard, pairwise analyses, and can also rank treatments to inform clinical decisions. [42-45]

We examined the symmetry and geometry of the evidence by producing a network plot with node and connection size corresponding to the number of study subjects and number of studies, respectively. We produced a comparison adjusted funnel plot to explore publication bias or other small study effects, for all available comparisons versus placebo, using Stata version 14 (Stata Corp., College Station, TX, USA). This is a scatterplot of effect size versus precision, measured via the inverse of the standard error. Symmetry around the effect estimate line indicates the absence of publication bias, or small study effects. [46] We produced a pooled RR with 95% CIs to summarise the effect of each comparison tested, again using a random effects model as a conservative estimate. As there were no direct comparisons between the active treatment groups, we were unable to perform consistency modelling to check the correlation between direct and indirect evidence. [47]

Global statistical heterogeneity across all these comparisons was assessed using the I^2 measure from the "netmeta" statistical package, using the cut-offs defined above. We ranked the treatments according to their P-score. The P-score is a value between 0 and 1, with a higher score indicating a greater probability of the treatment being ranked as best. [48] However, the magnitude of the P-score should be considered, as well as the treatment rank.

The mean value of the P-score is always 0.5, so if treatments cluster around this value they are likely to be of similar efficacy.

RESULTS

The search strategy generated 565 citations, 23 of which appeared to be relevant to the systematic review and these were retrieved for further assessment (Figure 1). Eleven of these were excluded for various reasons, leaving a total of 12 eligible articles. These reported on 13 trials, which contained a total of 10,091 patients, 5928 of whom were randomised to active treatment. There were two RCTs, reported in one article, of lubiprostone in IBS-C, [49] four trials of linaclotide, [50-53] three RCTs of tenapanor, [54-56] and four trials of tegaserod, [32,35,36,57] three of which reported *post hoc* data for abdominal bloating in a report for the FDA Gastrointestinal Drugs Advisory Committee in 2018, [32,35,36] which led to the decision to reintroduce the drug. Two trials of plecanatide, reported in a single paper, collected abdominal bloating data, but did not report a dichotomous response. [58] We attempted to obtain these data from Salix Pharmaceuticals, but were unsuccessful. The lubiprostone article was a *post hoc* analysis of the two phase III RCTs of lubiprostone, which reported efficacy according to FDA-recommended endpoints. [49] Agreement between investigators for trial eligibility for the 23 articles retrieved was excellent (kappa statistic = 0.83). Detailed characteristics of individual RCTs are provided in Table 1. Risk of bias for all included trials is reported in Supplementary Table 2. Eight trials, reported in seven papers, were at low risk of bias. [49-52,54,55,57]

No trials were identified comparing one drug versus another head-to-head, meaning that direct evidence was only available in comparison with placebo. Active medications could, therefore, only be compared with each other in the network meta-analysis using indirect evidence. Some of the included eligible RCTs used different primary endpoints. However, all trials of linaclotide and tenapanor used an identical endpoint for abdominal bloating, which consisted of a ≥30% decrease in abdominal bloating score for 6 out of 12 weeks. [50-56] The RCTs of lubiprostone applied similar criteria (a ≥30% decrease in abdominal

bloating score from baseline) retrospectively to a subset of patients in the two phase III studies, [49] while three of the tegaserod trials used a ≥25% decrease in abdominal bloating score from baseline retrospectively in a subset of patients in three trials, [32,35,36] and one used a ≥1-point decrease in abdominal bloating score from baseline *a priori* in all participants. [57]

Efficacy in Terms of Failure to Achieve an Improvement in Abdominal Bloating in the Pairwise Meta-analysis

All four medications were found to be superior to placebo in terms of improvement in abdominal bloating. The RR of failure to achieve an improvement in abdominal bloating in two trials of lubiprostone 8mcg b.d., containing 470 patients, was significantly lower with lubiprostone compared with placebo (RR = 0.85; 95% CI 0.74 to 0.99, NNT = 8; 95% CI 5 to 126) (Figure 2), [49] but with borderline moderate heterogeneity between studies (I^2 = 44%). There were four RCTs of linaclotide 290mcg o.d., containing 3061 patients, with a RR of failure to achieve an improvement in abdominal bloating of 0.78 (95% CI 0.74 to 0.83) (NNT = 7; 95% CI 6 to 8), with no heterogeneity between studies (I^2 = 0%). [50-53] Tenapanor 50mg b.d. was also superior to placebo, in three trials containing 1428 patients (RR = 0.86; 95% CI 0.80 to 0.93, NNT = 10; 95% CI 7 to 21), again with no heterogeneity between studies (I^2 = 0%). [54-56] Finally, tegaserod 6mg b.d. was significantly more efficacious than placebo, with a RR of failure to achieve an improvement in abdominal bloating of 0.85 (95% CI 0.80 to 0.90) (NNT = 13; 95% CI 10 to 20) in four trials containing 5132 patients, with no heterogeneity between studies (I^2 = 0%). [32,35,36,57] There were insufficient numbers of trials of each drug to assess for publication bias, or other small study effects, in the pairwise meta-analysis.

Efficacy in Terms of Failure to Achieve an Improvement in Abdominal Bloating

in the Network Meta-analysis

The network plot is provided in Supplementary Figure 1. When data were pooled there was no statistical heterogeneity (I^2 = 0%), and no evidence of publication bias, or other small study effects (Supplementary Figure 2). All medications studied were more efficacious than placebo, with linaclotide 290mcg o.d. ranked as the most efficacious treatment (RR = 0.78; 95% CI 0.74 to 0.83, P-score 0.97) (Table 2 and Figure 3). This means that the probability of linaclotide 290mcg o.d. being the most efficacious drug, when all treatments, including placebo, were compared with each other, was 97%. Indirect comparison of active treatments revealed no significant differences between individual drugs. However, 95% CIs for linaclotide 290mcg o.d. versus tenapanor 50mg b.d. and versus tegaserod 6mg b.d. approached statistical significance as they incorporated 1.0.

DISCUSSION

This systematic review and meta-analysis has demonstrated that the secretagogues lubiprostone, linaclotide, and tenapanor, and the 5-HT_4 agonist tegaserod, were all significantly more efficacious than placebo for abdominal bloating in patients with IBS-C. In the pairwise meta-analysis, the NNTs were lower for linaclotide and lubiprostone (7 and 8, respectively), compared with tenapanor and tegaserod (10 and 13, respectively). This implies that fewer patients would need to be treated with either linaclotide or lubiprostone to improve symptoms of bloating in patients with IBS-C, compared with tenapanor or tegaserod. However, it is inappropriate to make comparisons of efficacy between individual drugs in a pairwise meta-analysis in the absence of a direct head-to-head study. A network meta-analysis can provide valuable information to allow indirect comparisons to be made between treatments, which is important when formulating clinical guidelines. [45,46] In the current network meta-analysis, linaclotide 290mcg o.d. was likely to be the most efficacious drug for treating abdominal bloating, when compared with all other treatments and placebo, with a P-score of 0.97. Although linaclotide was ranked first in the network meta-analysis, the CIs for relative efficacy showed no difference when compared with lubiprostone, tegaserod, or tenapanor, although in the case of the latter two drugs they incorporated 1.0.

In patients with IBS-C, bloating is more likely to be accompanied by abdominal distension than in patients with IBS-D, suggesting its pathophysiology may differ between IBS sub-types, and even between patients within the same sub-type. [3,5,8] Indeed, in patients with IBS-C and abdominal bloating and distension, gastrointestinal transit is significantly delayed, [8] compared with IBS-C patients with no abdominal distension. This suggests that medications that accelerate transit, such as secretagogues or prokinetic agents, should theoretically improve both abdominal bloating and distension in some patients. Data from

this meta-analysis support this, with all three secretagogues and tegaserod being more effective at improving abdominal bloating compared with placebo.

Abdominal bloating and distension may also, in part, be a manifestation of visceral hypersensitivity in patients with IBS. [10,59] It is therefore of interest that the secretagogues, linaclotide and plecanatide, have been shown to improve visceral pain in animal models and clinical studies. [60-63] A *post hoc* analysis of two phase 3 studies of linaclotide demonstrated significant improvements in severe abdominal bloating, in addition to symptoms of abdominal pain or discomfort. [64] Other data to support effects of guanylate cyclase-C agonists on visceral sensation come from a study showing that the endogenous guanylate cyclase-C agonist, uroguanylin, which is released after meal ingestion in humans, inhibits colonic nociceptors, thereby improving abdominal pain and discomfort by suppressing the sensory response to food. [60] These findings may explain, in part, why linaclotide was likely to be the most efficacious agent for improving bloating in patients with IBS-C. Although less extensively studied, tenapanor, which acts on the sodium-hydrogen exchanger-3, reduced colonic hypersensitivity in an animal model, with normalization of colonic sensory neuronal excitability. [65] Finally, tegaserod alters gastrointestinal motility and visceral sensation via its effects on 5-HT receptors. [66]

It is possible that the different mechanisms of action of these drugs may explain, in part, the differences in improvement in abdominal bloating in these studies. Other possible mechanisms that might explain disparities in efficacy include individual differences in impaired gas clearance, alterations in the gut microbiome, dietary factors, or co-existing pelvic floor dysfunction. [67-70] Alternatively, the differences may reflect variations in study design, especially considering that the tegaserod studies were performed earlier than the RCTs of secretagogues. Direct, head to-head mechanistic studies involving all these agents could help elucidate whether accelerating intestinal transit, or modulating visceral sensory

afferents, is the most important factor for improving symptoms of abdominal bloating and distension in patients with IBS-C. In addition, the observation that tegaserod has beneficial effects on abdominal bloating suggests that continuing development and testing of other 5-HT_4 agonists in IBS-C, such as minesapride or prucalopride, may be worthwhile. [71,72]

Recognizing that no medication is approved solely for the treatment of abdominal bloating, and that bloating is just one facet of the symptom complex reported by patients with IBS-C, understanding the comparative merits of various treatments is important for clinicians. To our knowledge, this is the first systematic review and meta-analysis to evaluate the relative efficacy of FDA-licensed drugs for the treatment of abdominal bloating in patients with IBS-C. We conducted an exhaustive search, with the help of a trained librarian, and included data obtained from pharmaceutical company reports, allowing us to analyse data from 13 separate RCTs, recruiting over 10,000 patients. The literature review and data extraction were conducted independently by two reviewers, based on strict inclusion criteria, which were pre-defined. We used an intention-to-treat analysis, wherever trial reporting allowed, and pooled data using a random effect model to provide a more conservative estimate of the efficacy of each medication. We also extracted data at an identical time point in all trials, even in those where treatment duration was longer than 12 weeks. Importantly, there was little evidence of heterogeneity in any of our analyses, or of publication bias, or other small study effects, in the network meta-analysis.

All research studies have limitations, and ours is no exception. Because there were no trials making head-to-head comparisons between different drugs, the comparisons made are based on indirect, rather than direct data. All trials used historical definitions of IBS, and the trials of tegaserod used different, and perhaps less rigorous, endpoints to judge improvement in abdominal bloating, rather than those recommended by the FDA currently. In addition, the trials of lubiprostone applied an approximation of these recommendations retrospectively to a

subset of recruited patients. These factors may have led to an overestimation of the efficacy of tegaserod and lubiprostone, relative to linaclotide and tenapanor; the latter was ranked last in the network meta-analysis. In addition, in all studies efficacy was evaluated at 12 weeks, except for two trials that continued treatment out to 26 weeks, [50,56] and so the longer-term efficacy of these treatments is unknown. A network meta-analysis based on these two studies would have been unlikely to provide robust results. Except for four RCTs that were conducted in multiple countries, [32,35,52,57] the majority of the RCTs were conducted in North America, which may affect the generalizability of the results of this network meta-analysis to patients with IBS-C living in other countries. One of the core assumptions in network meta-analysis relates to transitivity, where indirect comparisons between treatments assume that any patient included in the network could, theoretically, have been recruited to any of the trials and assigned to any of the treatments. These comparisons are not protected by randomization. Therefore, confounding due to underlying differences between RCTs, including patient characteristics, IBS severity, and diagnostic criteria over the 20-year range these trials were conducted is possible. The Rome IV criteria are more specific than their predecessors, [73] but seem to select a group of patients with more severe symptoms and higher levels of psychological comorbidity. [74] Whether the findings of this study are applicable to those with Rome IV criteria IBS is unclear. Finally, we could not obtain abdominal bloating data for plecanatide from the relevant pharmaceutical company, meaning that the relative efficacy of this drug, versus the other four licensed therapies, for abdominal bloating is unknown.

Despite these limitations, we believe that this study provides important clinical data for a symptom that is difficult to treat. At the time our prior network meta-analysis was conducted, [33,34] there were only five RCTs reporting dichotomous efficacy data for abdominal bloating, reported in four papers, and involving only 2257 patients. [49-51,54] We have now been

able to assemble data from a further eight trials of FDA-licensed drugs for IBS, containing an additional 7834 patients, including two RCTs of tenapanor, two trials of linaclotide, and four RCTs of tegaserod. [32,35,36,52,53,55-57] In our previous network meta-analysis, tenapanor 50mg b.d. ranked first for improvement in abdominal bloating, with a P-score of 0.79. However, this was based on only a single phase II RCT, and the 95% CIs were wide, with both the P-score and RR being similar to that for linaclotide 290mcg o.d., studied in two trials. The addition of two large phase III studies of tenapanor in this updated network meta-analysis led to a change in its ranking, although it was still more efficacious than placebo, and the endpoint used to determine efficacy for abdominal bloating was more rigorous than for either lubiprostone or tegaserod.

In conclusion, abdominal bloating is a bothersome and prevalent symptom in patients with IBS-C. This systematic review and network meta-analysis has demonstrated that current licensed therapies for the treatment of IBS-C are more efficacious at improving symptoms of abdominal bloating than placebo, with linaclotide ranked first. A number of the drugs studied in this meta-analysis are not widely available, and the results of this analysis suggest access to them should be improved. Whether these findings are applicable to patients with abdominal bloating associated with other disorders of gut-brain interaction, or specifically to patients with functional abdominal bloating or distension, is uncertain. The precise mechanisms by which these agents improve abdominal bloating in patients with IBS-C are unclear but may relate to improvements in gastrointestinal transit and modulation of visceral sensation, which likely differs from patient to patient. Further studies to elucidate the pathophysiological processes involved are needed, as the results may translate into better treatments for this burdensome symptom of IBS-C. [75]

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CONFLICTS OF INTEREST/STUDY SUPPORT

Guarantor of the article: ACF is guarantor.

Specific author contributions: ADN, CJB, BEL, and ACF conceived and drafted the study. ADN and NSL screened abstracts, ACF and CJB collected all data. CJB, LAH, and ACF analysed and interpreted the data. ADN, BEL, and ACF drafted the manuscript. All authors commented on drafts of the paper. All authors have approved the final draft of the manuscript.

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FIGURE LEGENDS

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

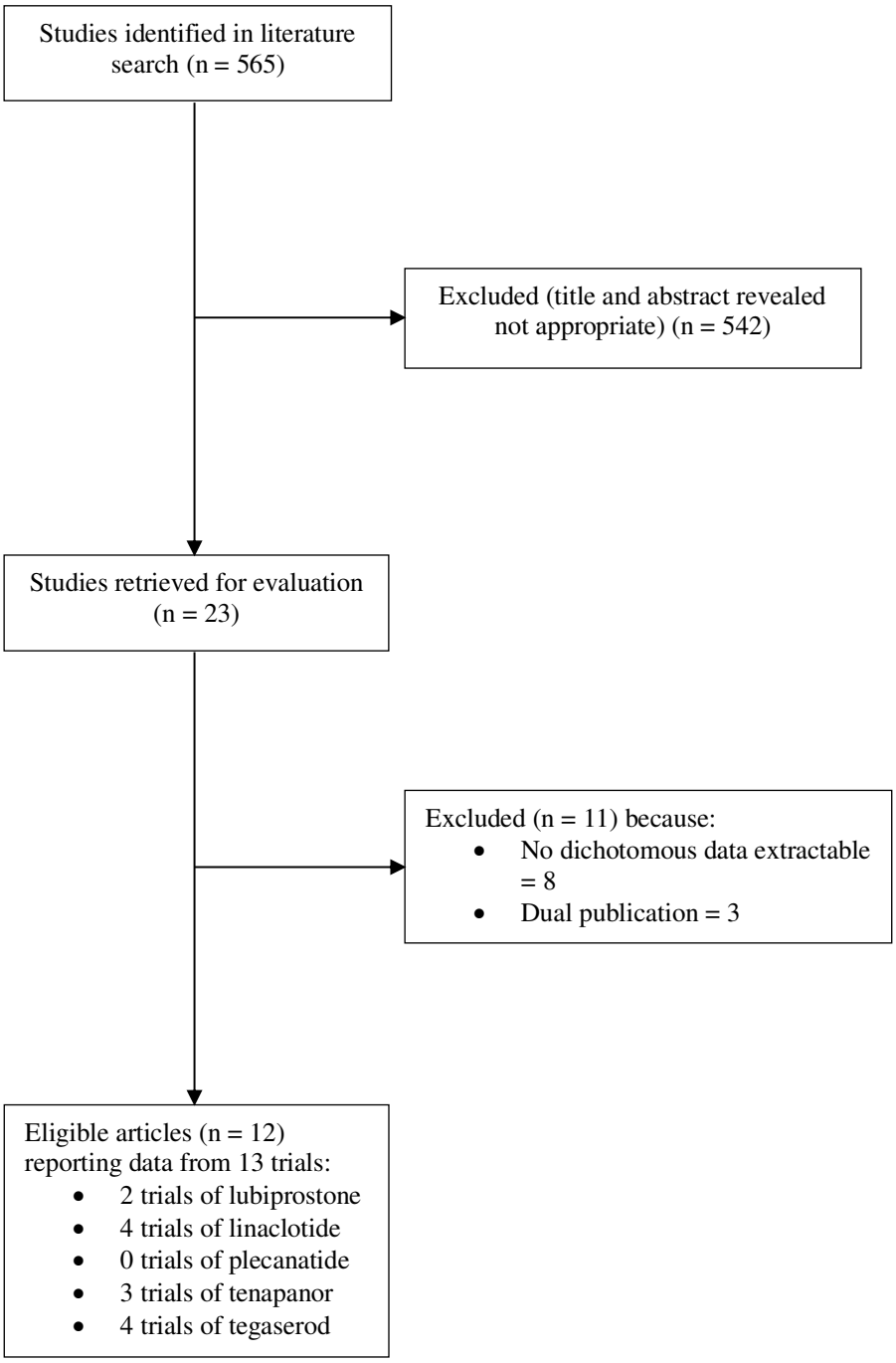


Figure 2. Forest Plot of Pairwise Comparisons for Failure to Achieve an Improvement in Abdominal Bloating in IBS-C.

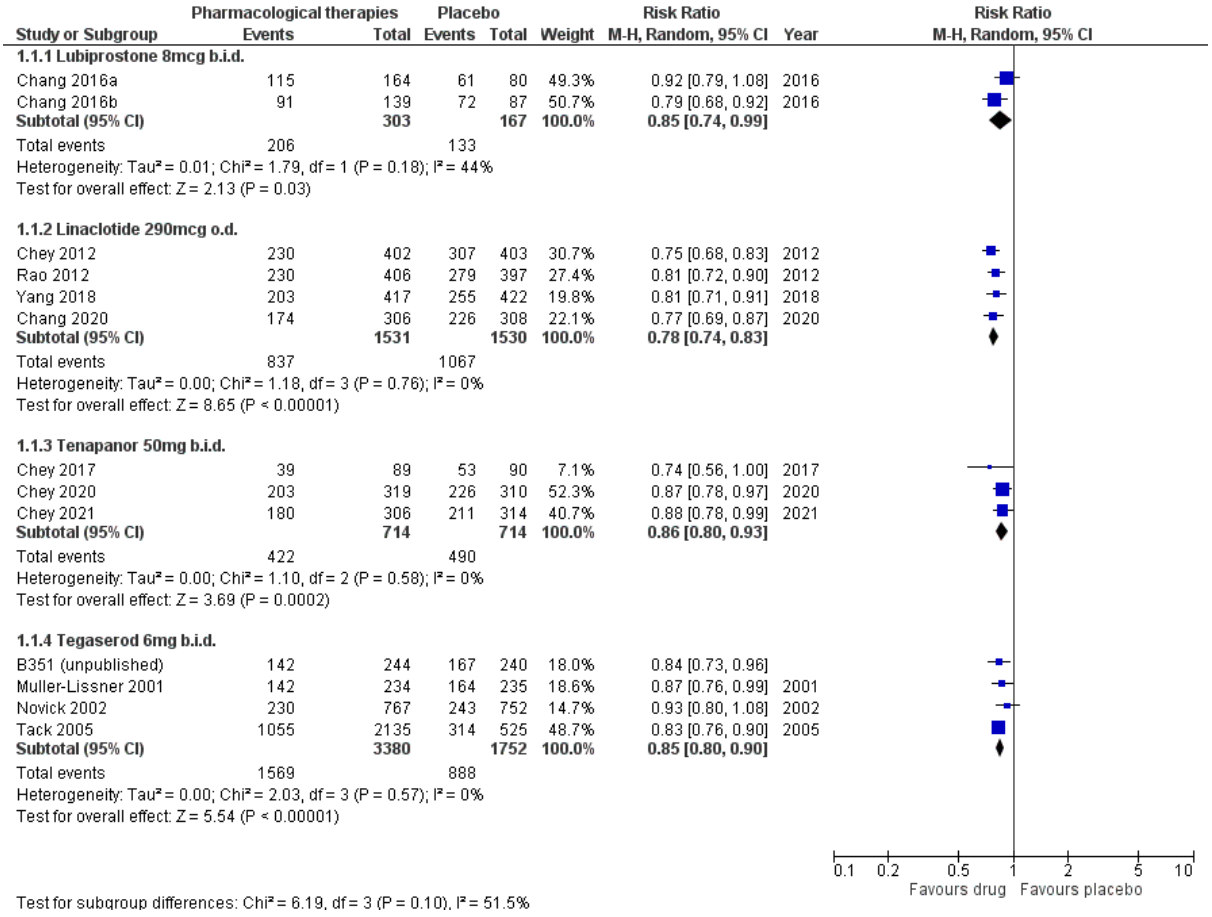
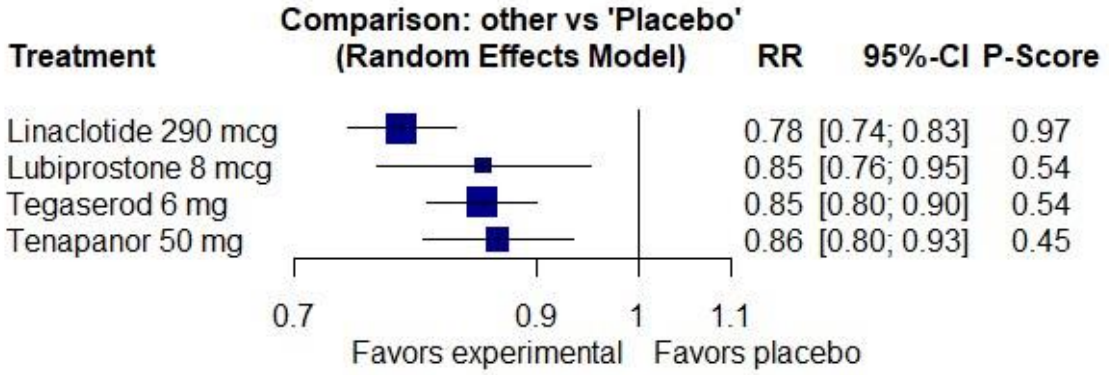


Figure 3. Forest Plot of the Indirect Evidence for Failure to Achieve an Improvement in Abdominal Bloating in IBS-C.



Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

Table 1. Characteristics of Randomised Controlled Trials of Licensed Drugs Versus Placebo Reporting on Abdominal Bloating in IBS-C.

Study	Country and Number of Centres	Diagnostic Criteria Used for IBS-C	Endpoint Used to Define Improvement in Abdominal Bloating Following Therapy	Number of Patients (% female)	Number of Patients Assigned to Active Drug, Dosage, Schedule, and Duration of Therapy
Chang 2016a [49]	USA, multiple sites	Rome II criteria	≥30% decrease in abdominal bloating score from baseline	244 (95.3)	164 patients received lubiprostone 8mcg b.d.* for 12 weeks
Chang 2016b [49]	USA, multiple sites	Rome II criteria	≥30% decrease in abdominal bloating score from baseline	226 (93.9)	139 patients received lubiprostone 8mcg b.d. for 12 weeks
Chey 2012 [50]	USA, 102 sites	Rome II criteria	≥30% decrease in abdominal bloating score from baseline for 6 of 12 weeks	805 (89.6)	402 patients received linaclotide 290mcg o.d.† for 26 weeks±
Rao 2012 [51]	USA and Canada, 118 sites	Rome II criteria	≥30% decrease in abdominal bloating score from baseline for 6 of 12 weeks	803 (90.5)	406 patients received linaclotide 290mcg o.d. for 12 weeks
Yang 2018 [52]	China, USA, Canada, Australia, and New Zealand	Rome III criteria	≥30% decrease in abdominal bloating score from baseline for 6 of 12 weeks	839 (82.0)	417 patients received linaclotide 290mcg o.d. for 12 weeks
Chang 2020 [53]	USA, 78 sites	Rome III criteria	≥30% decrease in abdominal bloating score from baseline for 6 of 12 weeks	614 (80.8)	306 patients received linaclotide 290mcg o.d. for 12 weeks

Chey 2017 [54]	USA, 79 sites	Rome III criteria	≥30% decrease in abdominal bloating score from baseline for 6 of 12 weeks	179 (86.8)	89 patients received tenapanor 50mg b.d. for 12 weeks
Chey 2020 [55]	USA, 92 sites	Rome III criteria	≥30% decrease in abdominal bloating score from baseline for 6 of 12 weeks	629 (81.4)	319 patients received tenapanor 50mg b.d. for 12 weeks
Chey 2021 [56]	USA, 92 sites	Rome III criteria	≥30% decrease in abdominal bloating score from baseline for 6 of 12 weeks	620 (82.1)	306 patients received tenapanor 50mg b.d. for 26 weeks±
Muller-Lissner 2001 [35]	Multinational, 92 sites	Rome I criteria	≥25% decrease in abdominal bloating score from baseline	484 (100)	244 patients received tegaserod 6mg b.d. for 12 weeks
B351 (unpublished) [32]	Multinational, number of sites unclear	Rome I criteria	≥25% decrease in abdominal bloating score from baseline	469 (100)	234 patients received tegaserod 6mg b.d. for 12 weeks
Novick 2002 [36]	USA, 131 sites	Rome I criteria	≥25% decrease in abdominal bloating score from baseline	1519 (100)	767 patients received tegaserod 6mg b.d. for 12 weeks
Tack 2005 [57]	Multinational, 267 sites	Rome II criteria	≥1-point decrease in abdominal bloating score from baseline	2660 (100)	2135 patients received tegaserod 6mg b.d. for 12 weeks

* b.d.; twice daily.

†o.d.; once daily.

±Data extracted at 12 weeks for this meta-analysis.

Table 2. League Table of Results for Failure to Achieve an Improvement in Abdominal Bloating in IBS-C.

Linaclotide 290mcg o.d.				
0.92 (0.82; 1.04)	**Lubiprostone 8mcg** b.d.			
0.92 (0.85; 1.00)	1.00 (0.88; 1.13)	**Tegaserod 6mg** b.d.		
0.90 (0.82; 1.00)	0.99 (0.86; 1.13)	0.98 (0.89; 1.08)	**Tenapanor 50mg** b.d.	
0.78 (0.74; 0.83)	0.85 (0.76; 0.95)	0.85 (0.80; 0.90)	0.86 (0.80; 0.93)	**Placebo**

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of indirect effects.

Boxes shaded green denote a statistically significant difference.

b.d.; twice daily.

o.d.; once daily.

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