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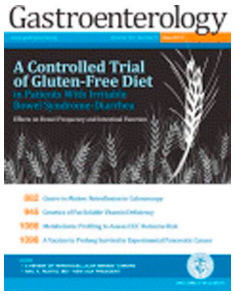

Efficacy of Secretagogues in Patients With Irritable Bowel Syndrome With Constipation: Systematic Review and Network Meta-analysis

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TITLE PAGE

Title: Efficacy of Secretagogues in Patients With Irritable Bowel Syndrome With Constipation: Systematic Review and Network Meta-analysis

Short title: Secretagogues for IBS-C: Network Meta-analysis.

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Abbreviations:

b.i.d.	twice-daily
CIC	chronic idiopathic constipation
CSBM	complete spontaneous bowel movement

CI	confidence interval
FDA	Food and Drug Administration
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with constipation
IBS-D	irritable bowel syndrome with diarrhea
MeSH	medical subject heading
o.d.	once-daily
PEG	polyethylene glycol
QALY	quality-adjusted life year
RCT	randomized controlled trial
RR	relative risk
SUCRA	surface under the cumulative ranking curve

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ABSTRACT

Background & Aims: Several secretagogues have been approved treatment of irritable bowel syndrome with constipation (IBS-C). However, their relative efficacy is unclear because there have been no head-to-head randomized controlled trials. We conducted a network meta-analysis to compare their efficacies in patients with IBS-C.

Methods: We searched MEDLINE, EMBASE, EMBASE Classic, and the Cochrane central register of controlled trials through June 2018 to identify randomized controlled trials assessing the efficacy of secretagogues in adults with IBS-C. Trials included in the analysis reported a dichotomous assessment of overall response to therapy, and data were pooled using a random effects model. Efficacy and safety of secretagogues were reported as a pooled relative risk with 95% CIs to summarize the effect of each comparison tested, and treatments were ranked according to their P-score.

Results: We identified 15 eligible randomized controlled trials of secretagogues, containing 8462 patients. Linaclotide, lubiprostone, plecanatide, and tenapanor were all superior to placebo for the treatment of IBS-C. Linaclotide (290 mcg, once daily) was ranked first in efficacy, based on the Food and Drug Administration-recommended endpoint for trials in IBS-C, the primary endpoint used in each trial, abdominal pain, and complete spontaneous bowel movements. Tenapanor (50 mg twice daily) was ranked first for reducing bloating. Total numbers of adverse events were significantly greater with linaclotide (290 mcg, once daily and 500 mcg, once daily) and plecanatide (3 mg, once daily) compared with placebo. However, 6 mg, once-daily plecanatide ranked first for safety. Diarrhea was significantly more common with all drugs, except lubiprostone (8 mcg, twice daily). Nausea was significantly more common among patients who received lubiprostone.

Conclusions: In a network analysis of randomized controlled trials of secretagogues for IBS-C, we found all drugs to be superior to placebo. Efficacy was similar among individual drugs and dosages for most endpoints. However, data were extracted at the 12-week time point, so the long term relative efficacy of these drugs is unknown.

Key words: CSBMs, RCT comparison, effectiveness, treatment response

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional bowel disorder, and affects approximately 10% of the population worldwide. [1] The cardinal symptoms are abdominal pain in association with altered stool form and/or frequency, [2] and the condition is characterized by a relapsing and remitting course. [3] Traditionally, patients are sub-grouped according to the predominant stool pattern they experience, into those who report diarrhea ≥25% of the time (IBS-D), constipation ≥25% of the time (IBS-C), or experience mixed stool pattern IBS and report both diarrhea and constipation ≥25% of the time. [2] Women with IBS are more than twice as likely to meet criteria for IBS-C than men with IBS, [4] and this sub-group make up almost one-third of patients. [1]

This classification system according to predominant stool pattern is important, because it is used to guide treatment and, increasingly, novel pharmacological therapies are directed towards either IBS-C or IBS-D. Traditionally, first-line treatment for IBS-C has included soluble fiber, such as ispaghula. [5] A previous systematic review and meta-analysis identified seven randomized controlled trials (RCTs) of ispaghula, [6] and although this was superior to placebo in terms of global symptom improvement, only one of these trials was at low risk of bias, [7] and none restricted their recruitment to patients with IBS-C. Laxatives, such as polyethylene glycol (PEG) are not recommended for IBS-C, [5] as there have been only two RCTs conducted, [8, 9] and although both trials reported a significant improvement in number of stools, there was no effect on abdominal pain scores.

In the last 10 years, several novel secretagogues have been developed for the treatment of IBS-C. Lubiprostone is a prostaglandin E_1 derivative, which activates the intestinal chloride channel type-2 on the apical surface of small intestinal enterocytes. Activation leads to chloride and water efflux into the luminal cavity. Linaclotide and plecanatide are peptides that stimulate the guanylate cyclase-C receptor, leading to electrolyte

and fluid transport into the intestinal lumen. Tenapanor is a small-molecule inhibitor of the gastrointestinal sodium-hydrogen exchanger-3, which results in increased intraluminal sodium and water excretion. Although there is evidence from high-quality RCTs that all of these therapies are effective for the treatment of IBS-C, their relative efficacy is unknown. This is because there have been no head-to-head trials of these drugs. It is unlikely that any such trials will ever be performed, as they would be expensive to conduct, because they would need huge numbers of patients in order to demonstrate superiority of one drug over another.

Network meta-analysis can circumvent this problem to some extent, allowing indirect treatment comparisons between active therapies in placebo-controlled trials, and enabling the ranking of treatments in order to inform clinical decisions. [10] Unfortunately, individual RCTs do not always use an identical design, recruit homogenous groups of patients, or assess efficacy using the same endpoints. However, in the case of IBS-C, the Food and Drug Administration (FDA) have made recommendations for the design of treatment trials, and endorsed standardized endpoints that should be used to judge the efficacy of novel therapies. We have, therefore, been able to conduct a network meta-analysis of RCTs of very similar design, using identical treatment duration and, in many instances, identical efficacy endpoints, in order to examine the relative efficacy and safety of all secretagogues tested in IBS-C, to date.

METHODS

Search Strategy and Study Selection

A search of the medical literature was conducted using MEDLINE (1947 to June 2018), EMBASE, EMBASE Classic (1947 to June 2018), and the Cochrane central register of controlled trials. We also searched clinicaltrials.gov for unpublished trials, or supplementary data for potentially eligible studies. RCTs examining the effect of secretagogues (lubiprostone, linaclotide, plecanatide, and tenapanor) in adult patients (>16 years) with IBS-C were eligible for inclusion (Supplementary Table 1). The first period of cross-over RCTs were also eligible for inclusion.

A diagnosis of IBS-C was based on either a clinician's opinion, or meeting specific diagnostic criteria, for example the Rome criteria. Studies recruiting patients with chronic idiopathic constipation (CIC), or mixed populations of patients with IBS-C or CIC, where data were not reported separately for IBS-C, were ineligible. Only RCTs that examined the efficacy of currently licensed doses of lubiprostone, linaclotide, and plecanatide or, in the case of tenapanor, the dose taken forward to phase III trials, and which compared them with each other, or with placebo, were considered eligible. A minimum treatment duration of 12 weeks was required, in line with FDA recommendations for the design of treatment trials for the functional gastrointestinal disorders. All endpoints were extracted at 12 weeks, even for RCTs that provided efficacy data at other time points. This was done in order to provide as much homogeneity as possible between individual trial results, and to avoid overestimating the efficacy of one drug relative to another, as the placebo effect tends to wane with time. [11] Studies had to report a dichotomous assessment of response to therapy. First and senior authors of studies were contacted to provide additional information on trials, where required.

The literature search was conducted independently by two investigators (CJB and ACF). Studies on IBS were identified 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). These were then combined 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,* and *tenapanor* (as free text terms).

There were no language restrictions, and abstracts identified by the initial search were evaluated independently by two investigators for eligibility. All potentially relevant papers were obtained and evaluated in detail. Foreign language papers were translated, where required. Articles were assessed independently by two investigators, using pre-designed eligibility forms, according to the pre-defined eligibility criteria. Disagreements between investigators were resolved by discussion.

Outcome Assessment

We assessed the efficacy of all drugs, compared with each other or with placebo, in IBS-C in terms of failure to respond to therapy, with the endpoints of interest used to define response reported below. Secondary outcomes included adverse events occurring as a result of therapy (overall numbers, as well as individual adverse events, including diarrhea, headache, abdominal pain, abdominal distension, or nausea).

Data Extraction

All data were extracted independently by two investigators on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes (response or no response to therapy). Some of the included eligible RCTs used

different primary endpoints. However, the majority of trials of linaclotide, plecanatide, and tenapanor adhered to the FDA-recommended endpoint for patients with IBS-C, and reported treatment efficacy according to the proportion of patients experiencing 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 RCTs of lubiprostone also applied these criteria retrospectively to a subset of patients in the two phase III studies.

In addition, due to the multitude of endpoints reported within the individual trials, we were also able to assess the efficacy of therapies according to other dichotomous endpoints to define response to treatment, including: a) the primary endpoint used in each individual RCT; b) a ≥30% improvement in abdominal pain for ≥50% of weeks (abdominal pain responder); c) an increase of ≥1 CSBMs per week from baseline for ≥50% of weeks (CSBM responder); and d) a ≥30% improvement in bloating for ≥50% of weeks (bloating responder).

For all included studies the following data were also extracted for each trial, where available: country of origin, number of centers, 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 drop-outs assumed to be treatment failures (i.e. no response to therapy), 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 performed this independently at the study level. Disagreements were resolved by discussion. The Cochrane handbook was used to assess risk of bias, [12] 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.

Data Synthesis and Statistical Analysis

A network meta-analysis was performed 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 3.4.2), and reported according to the PRISMA extension statement for network meta-analyses, [13] in order 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, [14, 15] and can also rank treatments to inform clinical decisions. [10]

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. [16] We produced a pooled relative risk (RR) with 95% confidence intervals (CIs) to summarize the effect of each comparison tested, using a random effects model as a conservative estimate. There were no direct comparisons between the active treatment groups, so we were unable to perform consistency modelling to check the correlation between direct and indirect evidence. [17]

Global statistical heterogeneity across all comparisons was assessed using the I^2 measure from the "netmeta" statistical package. The I^2 measure 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. [18] 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. [19] 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. In our main analysis we pooled data for the FDA-recommended endpoint to define treatment response in IBS-C, for all included RCTs that reported these data.

We also performed analyses to assess the overall safety of each medication, including overall numbers of adverse events, as well as occurrence of diarrhea, headache, abdominal pain, abdominal distension, or nausea. We compared the relative efficacy of therapies for all outcomes using the "mvmeta" commands in Stata, and a random effects model. We ranked the treatments according to their surface under the cumulative ranking curve (SUCRA) value. The SUCRA value is the equivalent to the P-score used in the frequentist model of our primary analyses. [19]

RESULTS

The search strategy generated 1163 citations, 75 of which appeared to be relevant to the systematic review and were retrieved for further assessment (Figure 1). Of these, 62 were excluded for various reasons, leaving a total of 13 eligible articles, reporting on 15 trials that contained a total of 8462 patients. There were three RCTs, reported in two articles, [20, 21] of lubiprostone in IBS-C, six trials of linaclotide (four of which used linaclotide 290mcg once-daily (o.d.), the licensed dose in the USA, [22-25] and two a dose of 250mcg or 500mcg o.d., the licensed doses in Japan), [26, 27] three RCTs of plecanatide, reported in two articles, [28, 29] and three RCTs of tenapanor. [30-32] A further article was also included because it provided supplementary data, reporting efficacy according to FDA-recommended endpoints for lubiprostone in the two phase III RCTs. [33] However, it should be pointed out that this article did not report data for all patients included in these two trials. This was because some of the recruited patients would not have met the updated FDA-recommended CSBM and abdominal pain thresholds for inclusion in an IBS-C treatment trial, and they were, therefore, excluded from the analysis.

Agreement between investigators for trial eligibility for the 75 articles retrieved was excellent (Kappa statistic = 0.96). Detailed characteristics of individual RCTs are provided in Table 1. Risk of bias for all included trials is reported in Supplementary Table 2. Twelve trials were at low risk of bias. [20-27 29, 30] We identified no trials making head-to-head comparisons of one drug versus another, meaning that direct evidence was only available in comparison with placebo. Active medications could, therefore, only be compared with each other using an indirect evidence meta-analysis.

Efficacy

Failure to Achieve the FDA-recommended Endpoint to Define Treatment Response

Eleven RCTs, reported in nine separate articles, [22, 23, 25, 28-33] provided dichotomous data for failure to achieve the FDA-recommended endpoint to define relief of global symptoms in IBS-C. One of these was a *post hoc* analysis of the two phase III RCTs of lubiprostone, which reported efficacy according to FDA-recommended endpoints. [33] These trials included a total of 6641 patients, 3747 of whom were randomized to active treatment, and 2894 to placebo. The network plot is provided in Supplementary Figure 1. When data were pooled there was borderline moderate global statistical heterogeneity (I^2 = 29.4%). The comparison adjusted funnel plot for publication bias, or other small study effects, showed no asymmetry around the zero line (Supplementary Figure 2). All treatments were significantly more effective than placebo, but linaclotide 290mcg o.d. was ranked as the most effective (P-score 0.91), in three RCTs (RR 0.81; 95% CI 0.76 to 0.86) (Figure 2). This means that the probability of linaclotide being the most effective when all treatments, including placebo, were compared with each other was 91%. Indirect comparison of active treatments revealed no significant differences between individual drugs and dosages. (Table 2).

Failure to Achieve the Primary Endpoint Used to Define Treatment Response in Each Trial

When dichotomous data were pooled for failure to achieve relief of global symptoms of IBS-C, according to the primary endpoint used in each of the 15 eligible trials, [20-32] there were 4846 patients randomized to active treatment and 3616 to placebo. There was no global statistical heterogeneity (I^2 = 1.8%). The comparison adjusted funnel plot for publication bias, or other small study effects, showed some asymmetry around the zero line (Supplementary Figure 3). All treatments were significantly more effective than placebo,

with the exception of linaclotide 250mcg o.d., although the latter analysis was based on only 112 patients receiving this dose in one RCT, the summary RR was similar to the other drugs, and the CIs were wide. Overall, again linaclotide 290mcg o.d. was ranked as the most effective (P-score 0.88), in four RCTs (RR 0.80; 95% CI 0.77 to 0.84) (Figure 3). On indirect comparison of active treatments, significant differences were seen with linaclotide 290mcg o.d. compared with plecanatide 3mg o.d., plecanatide 6mg o.d., and lubiprostone 8mcg twice-daily (b.i.d.), and between linaclotide 500mcg o.d. and lubiprostone 8mcg b.i.d. (Supplementary Table 3).

Failure to Achieve an Abdominal Pain Response

There were 12 trials recruiting 7302 patients, reported in 10 separate articles, [22, 23, 25-27, 29-33] that reported dichotomous data for failure to achieve an abdominal pain response. Again, one of these papers reported a *post hoc* analysis of the two phase III RCTs of lubiprostone. [33] There were 4129 patients assigned to active therapy, and 3173 allocated to placebo. When data were pooled there was no global statistical heterogeneity (I^2 = 0%). The comparison adjusted funnel plot for publication bias, or other small study effects, showed no asymmetry around the zero line (Supplementary Figure 4). All treatments were significantly more effective than placebo, with the exception of linaclotide 250mcg o.d. Again, linaclotide 290mcg o.d. was ranked as the most effective treatment (P-score 0.88), in three RCTs (RR 0.79; 95% CI 0.73 to 0.85) (Figure 4). Indirect comparison of active treatments revealed no significant differences between individual drugs and dosages. (Supplementary Table 4).

Failure to Achieve a CSBM Response

Failure to achieve a CSBM response was reported by 10 RCTs, which included 6850 patients, and were published as nine separate articles. [22, 23, 25-27, 29-32] In total, 3840 patients

were randomized to active therapy, and 3010 to placebo, and there was a high level of global statistical heterogeneity when data were pooled (I^2 = 82.0%). The comparison adjusted funnel plot for publication bias, or other small study effects, showed no asymmetry around the zero line (Supplementary Figure 5). Only linaclotide 290mcg o.d., linaclotide 500mcg o.d., and tenapanor 50mg b.i.d. were significantly more effective than placebo, with linaclotide 290mcg o.d. ranked first (P-score 0.76), in three RCTs (RR 0.76; 95% CI 0.65 to 0.88) (Figure 5). Again, indirect comparison of active treatments revealed no significant differences between individual drugs and dosages. (Supplementary Table 5).

Failure to Achieve a Bloating Response

Only five RCTs reported dichotomous data for failure to achieve a bloating response, and these were reported in four separate articles, [22, 23, 30, 33] and included 2257 patients. Again, one of these papers reported a *post hoc* analysis of both of the two phase III RCTs of lubiprostone. [33] There were 1200 patients assigned to active therapy, and 1057 to placebo. When data were pooled there was low global statistical heterogeneity (I^2 = 25.5%). There were too few studies to assess for publication bias, or other small study effects. Tenapanor 50mg b.i.d., linaclotide 290mcg o.d., and lubiprostone 8mcg b.i.d. were all more effective than placebo, with tenapanor ranked as the most effective treatment (P-score 0.79), in one RCT (RR 0.74; 95% CI 0.55 to 1.00) (Supplementary Figure 6). However, the 95% CIs were wide and touched 1, and the P-score and RR were very similar to that for linaclotide 290mcg o.d. in two trials (P-score 0.76, RR = 0.78; 95% CI 0.71 to 0.85). Given this was a secondary endpoint, with few trials reporting data, it is likely the network was underpowered to detect any differences. Indirect comparison of active treatments revealed no significant differences between individual drugs and dosages. (Supplementary Table 6).

Safety

Twelve trials, recruiting 7088 patients and reported in 10 articles, provided overall adverse events. [20-27, 29, 30] There was no global statistical heterogeneity (I^2 = 0%). The comparison adjusted funnel plot for publication bias, or other small study effects, showed no asymmetry around the zero line (Supplementary Figure 7). When comparing pooled overall adverse events, linaclotide 290mcg o.d. (four RCTs, RR = 1.12; 95% CI 1.04 to 1.21), linaclotide 500mcg o.d. (two RCTs, RR = 1.24; 95% CI 1.01 to 1.53), and plecanatide 3mg o.d. (two RCTs, RR = 1.28; 95% CI 1.05 to 1.56) were associated with a significant increase in overall adverse events, compared with placebo (Supplementary Figure 8). When ranked using a P-score, plecanatide 6mg o.d. was the best, and plecanatide 3mg o.d. the worst, in terms of overall adverse events (P-scores 0.69 and 0.23 respectively). As rates of individual adverse events were not reported separately in the plecanatide trials, other than the number of patients experiencing diarrhea, which were almost identical with both doses of plecanatide, reasons for the higher rate of overall adverse events with the 3mg o.d. dose are uncertain. Importantly, on indirect comparison there were no significant differences between plecanatide 3mg o.d. and plecanatide 6mg o.d., or any of the other active treatments or dosages, in terms of overall adverse events (Supplementary Table 7).

Adverse events leading to dropout were provided by 12 trials, reported in 10 papers. [20-27, 29, 30] Linaclotide 290mcg o.d. (four RCTs, RR = 2.72; 95% CI 1.62 to 4.57), plecanatide 6mg o.d. (two RCTs, RR = 5.37; 95% CI 1.42 to 20.4), and plecanatide 3mg o.d. (two RCTs, RR = 6.04; 95% CI 1.61 to 22.7) were all associated with significantly higher trial dropout rates due to adverse events, compared with placebo. When ranked using a P-score, lubiprostone 8mcg b.i.d. was the best, and plecanatide 3mg o.d. the worst, in terms of adverse events leading to dropout (P-scores 0.81 and 0.11 respectively). On indirect comparison of active treatments, significant differences were seen with lubiprostone 8mcg b.i.d. compared

with linaclotide 290mcg o.d., plecanatide 6mg o.d., and plecanatide 3mg o.d., as well as between linaclotide 250mcg o.d. and plecanatide 3mg o.d.

In terms of individual adverse events, rates of diarrhea were provided by 14 of the eligible trials, reported in 12 articles. [20-27, 29-32] All drugs, with the exception of lubiprostone 8mcg b.i.d., were associated with an increased risk of diarrhea and, when ranked using a P-score, lubiprostone 8mcg b.i.d. was the best, and linaclotide 500mcg o.d. the worst (P-scores 0.87 and 0.20 respectively). Indirect comparison of active treatments revealed that both placebo and lubiprostone 8mcg b.i.d. were significantly less likely to cause diarrhea than all other individual drugs, and dosages, but there were no other differences between the remaining individual drugs and dosages. There were no significant differences between any of the active therapies and placebo, in terms of incidence of abdominal pain, abdominal distension, or headache. Six RCTs, reported in five articles, [20, 21, 24, 30, 31] provided information concerning nausea. Only lubiprostone 8mcg b.i.d was associated with a significantly increased incidence of nausea, and this was the worst ranked treatment in this analysis (P-score 0.18).

DISCUSSION

This systematic review and network meta-analysis has demonstrated that all secretagogues tested in IBS-C, to date, were more effective than placebo for global symptoms. Although all drugs performed similarly, linaclotide 290mcg o.d. was ranked first in terms of efficacy for global symptoms. This was irrespective of the outcome measure used, whether it be the FDA-recommended endpoint to define relief of global symptoms in IBS-C, or the primary endpoint used to define global symptom improvement in each trial. For the latter endpoint the probability of linaclotide being superior to another competing treatment, or placebo, was 88% but this does not exceed 90% to 95%, which may be desirable according to the literature. [19] However, for the former endpoint the probability was 91%. Linaclotide 290mcg o.d. was also ranked first in terms of the effect on both abdominal pain response and CSBM response. Tenapanor 50mg b.i.d. was ranked first in terms of effect on bloating response, although confidence intervals were wide and the P-score was very similar to that for linaclotide 290mcg o.d. In our analysis that used the primary endpoint to define global symptom improvement in each trial, linaclotide 290mcg o.d. was superior to plecanatide 3mg and 6mg o.d., as well as lubiprostone 8mcg b.i.d. In terms of safety, plecanatide 6mg o.d. was the drug least likely to cause adverse events, and lubiprostone 8mcg b.i.d. was significantly less likely than all other individual drugs and dosages to cause diarrhea, but was more likely to cause nausea.

We performed a contemporaneous and exhaustive literature search, which included searching the "gray" literature and clinicaltrials.gov, allowing us to analyze data from 15 RCTs of pharmacological therapies for IBS-C, recruiting 8462 patients. The literature search, eligibility assessment, and data extraction were all undertaken independently by two reviewers. We used an intention-to-treat analysis, wherever trial reporting allowed, and pooled data with a random effects model, to provide a more conservative estimate of the

efficacy and safety of individual drugs. Finally, we translated one Japanese article, [27] attempted to contact authors of individual studies, and accessed clinicaltrials.gov in order to obtain extra information, where required.

Limitations include the fact that none of the trials were head-to-head studies of one drug versus another, which means that our analyses were based on indirect comparisons, and are not protected by randomization. This could lead to confounding due to underlying differences between individual RCTs. [34] However, as the design of the included trials was very similar, and the endpoints used and duration of follow-up identical, this issue should have been minimized. In addition, three of the RCTS were at unclear risk of bias, [28, 31, 32] and original authors did not respond to all our queries concerning individual studies. This may mean the efficacy of some pharmacological therapies in IBS-C has been overestimated. [35] We extracted data from all RCTs based on a comparatively short treatment duration of 12 weeks, and therefore the relative efficacy and safety of these drugs in the longer term are unknown. This is a potentially important clinical point, as patients often complain that they become tolerant to the effects of non-prescription laxatives over time. The vast majority of trials were conducted in North America, meaning that involved individuals may not be generalizable to patients with IBS-C in other countries. There were moderate levels of global statistical heterogeneity in the analysis using the FDA-recommended endpoint to define treatment response, and high levels of heterogeneity in the analysis for CSBM response. The comparison adjusted funnel plot for our analysis based on the primary endpoint to define global symptom improvement in each trial showed some asymmetry, suggestive of publication bias or other small study effects, although three of the trials we identified had not been published as either full papers or conference abstracts, [27, 31, 32] and were only identified during our search of clinicaltrials.gov. Finally, there were limited safety data for tenapanor, although once the two phase III RCTs are fully published, [31, 32] this is likely to change.

All of the secretagogues examined in this network meta-analysis have proved their efficacy in placebo-controlled trials in IBS-C. However, when considering the results of this study, it is important to point out some of the limitations of the original trials themselves. Firstly, as has already been alluded to, complete safety data for the two phase III RCTs of tenapanor were not available at the time this network meta-analysis was conducted. [31, 32] Secondly, all three trials of lubiprostone, and the earlier trials of linaclotide, used the less stringent Rome II criteria for IBS. Thirdly, definitions of each of the adverse events were not standardized between individual trials, as these were not the primary endpoints of interest. This has led to some debate about the relative safety of some of the drugs, in terms of their likelihood of causing diarrhea. A recent meta-analysis reported that, based on meta-regression, there were no differences in the rates of diarrhea between linaclotide and plecanatide in treatment trials in IBS-C and CIC, [36] an observation supported by our findings. However, it is important to point out that there were subtle differences in the way that diarrhea was recorded in these RCTs, [37] which mean that the data may not be comparable, even in a network meta-analysis. Fourthly, for the FDA-recommended endpoint to define treatment response in IBS-C, as well as abdominal pain and bloating response, the analyses for lubiprostone were based on a *post hoc* analysis of the two phase III trials. As a result, data from almost two-thirds of the recruited patients were unavailable, as they would not have met the updated FDA-recommended CSBM and abdominal pain thresholds for inclusion in an IBS-C treatment trial. This may have led to an overestimation of the efficacy of lubiprostone in these analyses, although excluding these RCTs from the analyses would not have led to any change in the relative efficacy of the other three drugs. Finally, given that by the time the trials of plecanatide and tenapanor were conducted both linaclotide and lubiprostone were FDA-approved for the treatment of IBS-C, it may be that patients in these more recent RCTs had already failed treatment with one, or both, of these drugs. This would imply that a more

treatment-resistant group of patients were being studied in the trials of plecanatide and tenapanor but, as the RCTs did not report the proportion of patients who had previously received treatment with either linaclotide or lubiprostone, this is speculation. Although this may partly explain why linaclotide 290mcg o.d. was ranked first in almost all efficacy analyses in the network meta-analysis, lubiprostone was FDA-approved for the treatment of IBS-C in 2008, whereas linaclotide was approved in 2012, so participants in the linaclotide trials may have failed therapy with lubiprostone prior to study entry.

The cost of all of these drugs relative to other treatments for IBS-C is also a consideration, but there have been no RCTs conducted against a less expensive, but potentially effective, comparator such as ispaghula or PEG. A recent cost-effectiveness analysis for the use of linaclotide in Scotland reported an incremental cost-effectiveness ratio of £7370 per quality-adjusted life year (QALY), versus an antidepressant, in patients with IBS-C who had already failed an antispasmodic and/or a laxative. [38] The authors reported that the likelihood that linaclotide was cost-effective at a willingness to pay of £20,000 per QALY was 73%. The choice of amitriptyline as the comparator in this analysis seems odd, given that although tricyclic antidepressants have the most evidence for their efficacy in IBS, [39] one of their side effects is constipation. Cost-effectiveness data for the other three drugs studied in this meta-analysis are lacking.

Performing a network meta-analysis of secretagogues for IBS-C could be criticized due to the absence of trials making direct comparisons. As a result, all of our conclusions were derived from data based on indirect treatment comparisons. We believe it is unlikely that pharmaceutical companies would ever conduct head-to-head RCTs of these agents, and even if such a study were to be conducted, it is likely that it would be designed as a non-inferiority trial. [40] A network meta-analysis circumvents this problem, allowing a credible ranking system of the likely efficacy and tolerability of all of the secretagogues tested in IBS-

C to be developed, even in the absence of trials making direct comparisons. The results of this study are therefore still likely to be important for both patients and policy makers, in order to help inform treatment decisions for patients with IBS-C.

In summary, although all drugs performed similarly and were superior to placebo in most of our analyses, our network meta-analysis ranked linaclotide 290mcg o.d. first in terms of efficacy profile overall, and across several different endpoints. No difference was observed between individual treatments when the FDA-recommended endpoint was used to define relief of global symptoms in IBS-C, although linaclotide 290mcg o.d. was still ranked first. However, when treatments were ranked according to the primary endpoint used to define treatment response in each trial, linaclotide 290mcg o.d. appeared superior to plecanatide 3mg and 6mg o.d., as well as lubiprostone 8mcg b.i.d. In terms of safety, plecanatide 6mg o.d. was the drug least likely to cause adverse events, and lubiprostone 8mcg b.i.d. was significantly less likely than any of the other drugs to cause diarrhea. In the absence of head-to-head trials, this information should help clinicians to make decisions as to which drug to use, based on efficacy, safety, and most troublesome symptom, when first-line therapies for IBS-C fail.

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FIGURE LEGENDS

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

Figure 2. Forest Plot of the Indirect Evidence for Failure to Achieve the FDA-recommended Endpoint to Define Treatment Response.

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.

Figure 3. Forest Plot of the Indirect Evidence for Failure to Achieve the Primary Endpoint Used to Define Treatment Response in Each Trial.

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.

Figure 4. Forest Plot of the Indirect Evidence for Failure to Achieve an Abdominal Pain Response.

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.

Figure 5. Forest Plot of the Indirect Evidence for Failure to Achieve a CSBM Response.

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 Randomized Controlled Trials of Secretagogues Versus Placebo in IBS-C.

Study	Country and Number of Centers	Diagnostic Criteria Used for IBS	Primary Endpoint Used to Define Symptom Improvement Following Therapy	Number of Patients (% female)	Number of Patients Assigned to Active Drug, Dosage, Schedule, and Duration of Therapy
Johanson 2008 [20]	USA, 19 sites	Rome II criteria	Treatment effectiveness rated as at least 'moderately effective' for all 4 weeks of the month, or 'quite a bit effective' for 2 or more of the 4 weeks of the month	100 (90.0)	52 patients received lubiprostone 8mcg b.i.d.* for 12 weeks
Drossman 2009a [21] **and Chang 2016a** [33]	USA, multiple sites	Rome II criteria	Moderate or significant relief of IBS symptoms for all 4 weeks of the month, or significant relief for 2 or more of the 4 weeks of the month for 2 out of 3 months	590 (90.0)	396 patients received lubiprostone 8mcg b.i.d. for 12 weeks
Drossman 2009b [21] **and Chang 2016b** [33]	USA, multiple sites	Rome II criteria	Moderate or significant relief of IBS symptoms for all 4 weeks of the month, or significant relief for 2 or more of the 4 weeks of the month for 2 out of 3 months	581 (90.0)	387 patients received lubiprostone 8mcg b.i.d. for 12 weeks
Johnston 2010 [24]	USA and Canada, 92 sites	Rome II criteria	≥3 CSBMs† per week and an increase of 1 CSBM per week from baseline for ≥9 of 12 weeks	170 (92.4)	85 patients received linaclotide 290mcg o.d.± for 12 weeks

Chey 2012 [22]	USA, 102 sites	Rome II criteria	≥30% improvement in abdominal pain score and an increase of ≥1 CSBM from baseline for 6 of 12 weeks	805 (89.6)	402 patients received linaclotide 290mcg o.d. for 26 weeks
Rao 2012 [23]	USA and Canada, 118 sites	Rome II criteria	≥30% improvement in abdominal pain score and an increase of ≥1 CSBM from baseline for 6 of 12 weeks	803 (90.5)	406 patients received linaclotide 290mcg o.d. for 12 weeks
Fukudo 2018 [26]	Japan, 66 sites	Rome III criteria	Global assessment of relief of IBS symptoms	331 (90.5)	112 and 107 patients received linaclotide 250mcg or 500mcg o.d. respectively for 12 weeks
Yang 2018 [25]	China, USA, Canada, Australia, and New Zealand	Rome III criteria	Considerable or complete relief of IBS symptoms for 6 of 12 weeks	839 (82.0)	406 patients received linaclotide 290mcg o.d. for 12 weeks
NCT02316899 (unpublished) [27]	Japan, 61 sites	Rome III criteria	Global assessment of relief of IBS symptoms	500 (87.8)	249 patients received linaclotide 500mcg o.d. for 12 weeks
Miner 2014 [28]	USA, 99 sites	Rome III criteria	≥30% improvement in abdominal pain score and an increase of ≥1 CSBM from baseline for 6 of 12 weeks	171 (unclear)	86 patients received plecanatide 3mg o.d. for 12 weeks

Brenner 2018a [29]	North America, 130 sites	Rome III criteria	≥30% improvement in abdominal pain score and an increase of ≥1 CSBM from baseline for 6 of 12 weeks	1054 (76.4)	351 and 349 patients received plecanatide 3mg or 6mg o.d. respectively for 12 weeks
Brenner 2018b [29]	North America, 140 sites	Rome III criteria	≥30% improvement in abdominal pain score and an increase of ≥1 CSBM from baseline for 6 of 12 weeks	1135 (71.8)	377 and 379 patients received plecanatide 3mg or 6mg o.d. respectively for 12 weeks
Chey 2017 [30]	USA, 79 sites	Rome III criteria	≥30% improvement in abdominal pain score and an increase of ≥1 CSBM from baseline for 6 of 12 weeks	178 (86.8)	89 patients received tenapanor 50mg b.i.d. for 12 weeks
NCT02621892 (unpublished) [31]	USA, 111 sites	Rome III criteria	≥30% improvement in abdominal pain score and an increase of ≥1 CSBM from baseline for 6 of 12 weeks	610 (81.4)	309 patients received tenapanor 50mg b.i.d. for 12 weeks
NCT02686138 (unpublished) [32]	USA, 117 sites	Rome III criteria	≥30% improvement in abdominal pain score and an increase of ≥1 CSBM from baseline for 6 of 12 weeks	593 (unclear)	293 patients received tenapanor 50mg b.i.d. for 26 weeks

* b.i.d.; twice-daily

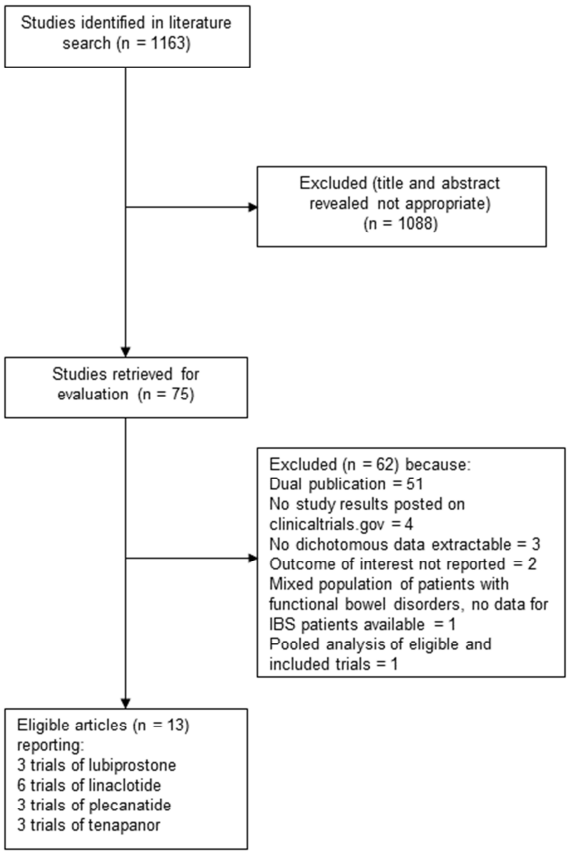
†CSBM; complete spontaneous bowel movement

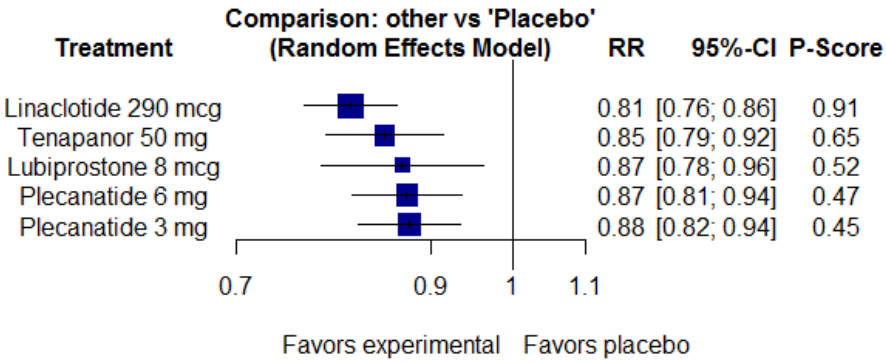
±o.d.; once-daily

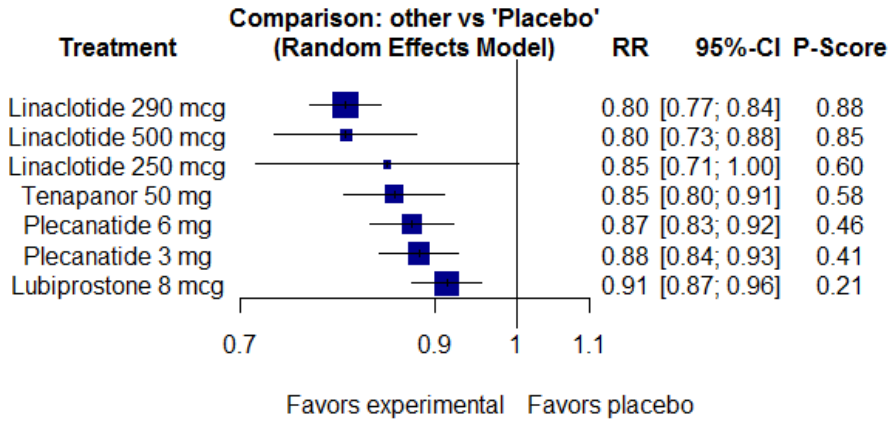
Table 2. League Table of Results for Failure to Achieve the FDA-recommended Endpoint to Define Treatment Response.

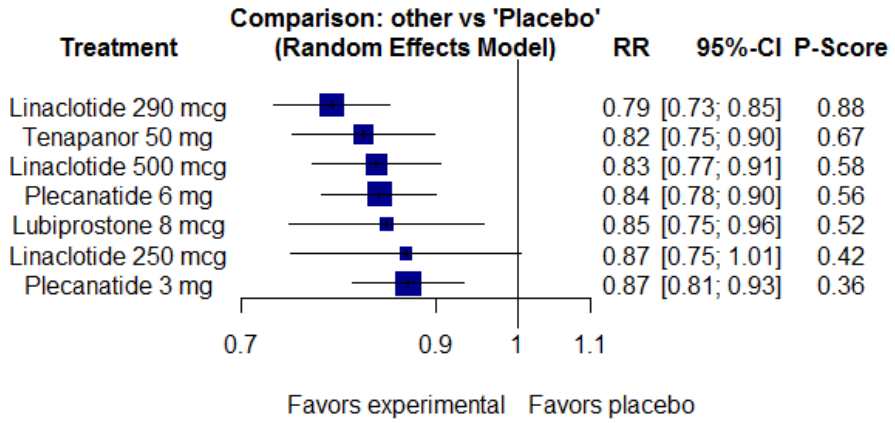
Linaclotide 290mcg o.d.					
0.96 (0.87; 1.06)	**Tenapanor 50mg b.i.d.**				
0.94 (0.83; 1.06)	0.98 (0.86; 1.11)	**Lubiprostone 8mcg b.i.d.**			
0.93 (0.85; 1.02)	0.97 (0.88; 1.08)	0.99 (0.88; 1.13)	**Plecanatide 6mg o.d.**		
0.93 (0.85; 1.01)	0.97 (0.88; 1.07)	0.99 (0.88; 1.12)	1.00 (0.91; 1.10)	**Plecanatide 3mg o.d.**	
0.81 (0.76; 0.86)	0.85 (0.79; 0.92)	0.87 (0.78; 0.96)	0.87 (0.81; 0.94)	0.88 (0.82; 0.94)	**Placebo**

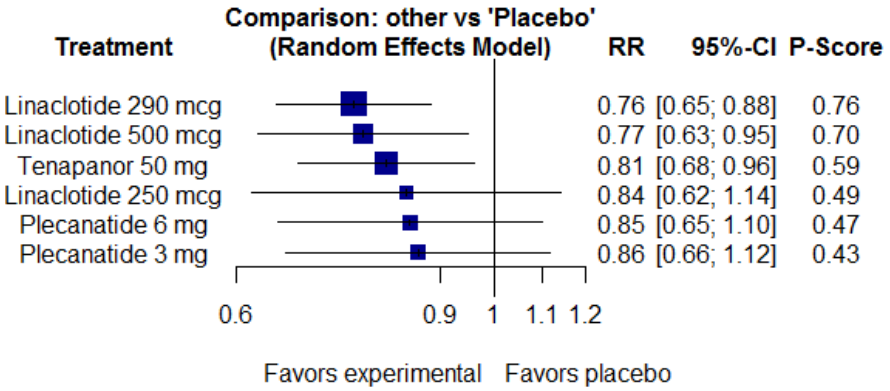
Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of indirect effects. Boxes shaded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











Supplementary Table 1. Eligibility Criteria.

Randomized controlled trials.
Adults (participants aged >16 years).
Diagnosis of IBS with constipation based on either a clinician's opinion, or meeting specific diagnostic criteria*, supplemented by negative investigations where trials deemed this necessary.
Compared lubiprostone, linaclotide, plecanatide, or tenapanor with each other, or with placebo.
Minimum treatment duration of 12 weeks.
Follow-up duration of 12 weeks.
Dichotomous assessment of response to therapy in terms of effect on global IBS symptoms following therapy†.

*Manning, Kruis score, Rome I, II, III, or IV.

†Preferably patient-reported, and according to the FDA-recommended endpoint for IBS with constipation, but if this was not available then as assessed by a physician or questionnaire data.

Supplementary Table 2. Risk of Bias of Randomized Controlled Trials of Secretagogues Versus Placebo in IBS-C.

Study	Method of Generation of Randomization Schedule Stated?	Method of Concealment of Treatment Allocation Stated?	Blinding?	No Evidence of Incomplete Outcomes Data?	No Evidence of Selective Reporting of Outcomes?
Johanson 2008 [20]	Yes	Yes	Double	Yes	Yes
Drossman 2009a [21] **and Chang 2016a** [33]	Yes	Yes	Double	Yes	Yes
Drossman 2009b [21] **and Chang 2016b** [33]	Yes	Yes	Double	Yes	Yes
Johnston 2010 [24]	Yes	Yes	Double	Yes	Yes
Chey 2012 [22]	Yes	Yes	Double	Yes	Yes
Rao 2012 [23]	Yes	Yes	Double	Yes	Yes
Fukudo 2018 [26]	Yes	Yes	Double	Yes	Yes
Yang 2018 [25]	Yes	Yes	Double	Yes	Yes
NCT02316899 (unpublished) [27]	Yes	Yes	Double	Yes	Yes
Miner 2014 [28]	No	No	Double	Yes	Yes
Brenner 2018a [29]	Yes	Yes	Double	Yes	Yes

Brenner 2018b [29]	Yes	Yes	Double	Yes	Yes
Chey 2017 [30]	Yes	Yes	Double	Yes	Yes
NCT02621892 (unpublished) [31]	No	No	Double	Yes	Yes
NCT02686138 (unpublished) [32]	No	No	Double	Yes	Yes

Supplementary Table 3. League Table of Results for Failure to Achieve the Primary Endpoint Used to Define Treatment Response in Each Trial.

Linaclotide 290mcg o.d.							
1.00 (0.90; 1.11)	**Linaclotide 500mcg o.d.**						
0.95 (0.80; 1.13)	0.95 (0.78; 1.15)	**Linaclotide 250mcg o.d.**					
0.94 (0.87; 1.02)	0.94 (0.84; 1.05)	0.99 (0.83; 1.19)	**Tenapanor 50mg b.i.d.**				
0.92 (0.86; 0.99)	0.92 (0.83; 1.02)	0.97 (0.81; 1.16)	0.98 (0.90; 1.06)	**Plecanatide 6mg o.d.**			
0.91 (0.85; 0.97)	0.91 (0.82; 1.01)	0.96 (0.80; 1.15)	0.97 (0.89; 1.05)	0.99 (0.92; 1.07)	**Plecanatide 3mg o.d.**		
0.88 (0.82; 0.94)	0.88 (0.79; 0.97)	0.93 (0.78; 1.10)	0.93 (0.86; 1.01)	0.96 (0.89; 1.03)	0.96 (0.90; 1.03)	**Lubiprostone 8mcg b.i.d.**	
0.80 (0.77;0.84)	0.80 (0.73; 0.88)	0.85 (0.71; 1.00)	0.85 (0.80; 0.91)	0.87 (0.83; 0.92)	0.88 (0.84; 0.93)	0.91 (0.87; 0.96)	**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.

Supplementary Table 4. League Table of Results for Failure to Achieve an Abdominal Pain Response.

Linaclotide 290mcg o.d.							
0.96 (0.85; 1.08)	**Tenapanor 50mg b.i.d.**						
0.94 (0.85; 1.06)	0.98 (0.87; 1.11)	**Linaclotide 500mcg o.d.**					
0.94 (0.85; 1.04)	0.98 (0.87; 1.10)	1.00 (0.89; 1.11)	**Plecanatide 6mg o.d.**				
0.93 (0.81; 1.08)	0.97 (0.83; 1.13)	0.99 (0.85; 1.15)	0.99 (0.86; 1.14)	**Lubiprostone 8mcg b.i.d.**			
0.91 (0.77; 1.07)	0.95 (0.79; 1.13)	0.96 (0.81; 1.14)	0.97 (0.82; 1.14)	0.98 (0.80; 1.18)	**Linaclotide 250mcg o.d.**		
0.91 (0.82; 1.00)	0.94 (0.84; 1.06)	0.96 (0.86; 1.07)	0.96 (0.87; 1.07)	0.97 (0.84; 1.12)	1.00 (0.85; 1.18)	**Plecanatide 3mg o.d.**	
0.79 (0.73; 0.85)	0.82 (0.75; 0.90)	0.83 (0.77; 0.91)	0.84 (0.78; 0.90)	0.85 (0.75; 0.96)	0.87 (0.75; 1.01)	0.87 (0.81;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.

Supplementary Table 5. League Table of Results for Failure to Achieve a CSBM Response.

Linaclotide 290mcg o.d.						
0.98 (0.76; 1.27)	**Linaclotide 500mcg o.d.**					
0.94 (0.74; 1.18)	0.96 (0.73; 1.25)	**Tenapanor 50mg b.i.d.**				
0.90 (0.64; 1.27)	0.92 (0.63; 1.33)	0.96 (0.68; 1.37)	**Linaclotide 250mcg o.d.**			
0.90 (0.66; 1.21)	0.91 (0.65; 1.27)	0.95 (0.70; 1.31)	0.99 (0.66; 1.49)	**Plecanatide 6mg o.d.**		
0.88 (0.65; 1.19)	0.90 (0.64; 1.25)	0.94 (0.69; 1.28)	0.98 (0.65; 1.46)	0.98 (0.68; 1.42)	**Plecanatide 3mg o.d.**	
0.76 (0.65; 0.88)	0.77 (0.63; 0.95)	0.81 (0.68; 0.96)	0.84 (0.62; 1.14)	0.85 (0.65; 1.10)	0.86 (0.66; 1.12)	**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.

Supplementary Table 6. League Table of Results for Failure to Achieve a Bloating Response.

Tenapanor 50mg b.i.d.			
0.96 (0.70; 1.31)	**Linaclotide 290mcg o.d.**		
0.87 (0.63; 1.21)	0.91 (0.78; 1.06)	**Lubiprostone 8mcg b.i.d.**	
0.74 (0.55; 1.00)	0.78 (0.71; 0.85)	0.85 (0.75; 0.96)	**Placebo**

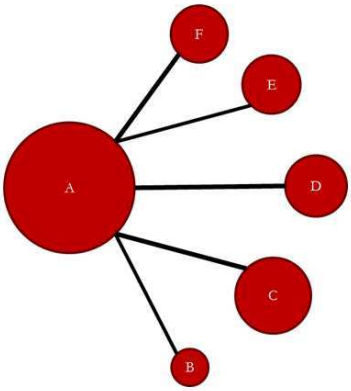
Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of indirect effects. Boxes shaded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

Supplementary Table 7. League Table of Results for Overall Adverse Events.

Placebo							
1.07 (0.86; 1.32)	**Plecanatide 6mg o.d.**						
1.12 (1.04; 1.21)	1.05 (0.84; 1.32)	**Linaclotide 290mcg o.d.**					
1.13 (0.81; 1.57)	1.06 (0.72; 1.57)	1.01 (0.72; 1.41)	**Linaclotide 250mcg o.d.**				
1.20 (0.87; 1.64)	1.12 (0.77; 1.64)	1.07 (0.77; 1.48)	1.06 (0.67; 1.67)	**Tenapanor 50mg b.i.d.**			
1.20 (0.98; 1.48)	1.13 (0.84; 1.51)	1.07 (0.86; 1.33)	1.06 (0.72; 1.57)	1.00 (0.69; 1.46)	**Lubiprostone 8mcg b.i.d.**		
1.24 (1.01; 1.53)	1.17 (0.87; 1.57)	1.11 (0.89; 1.38)	1.10 (0.74; 1.62)	1.04 (0.71; 1.52)	1.03 (0.77; 1.39)	**Linaclotide 500mcg o.d.**	
1.28 (1.05;1.56)	1.20 (0.90; 1.61)	1.14 (0.92; 1.41)	1.13 (0.77; 1.66)	1.07 (0.74; 1.56)	1.07 (0.80; 1.42)	1.03 (0.77; 1.38)	**Plecanatide 3mg o.d.**

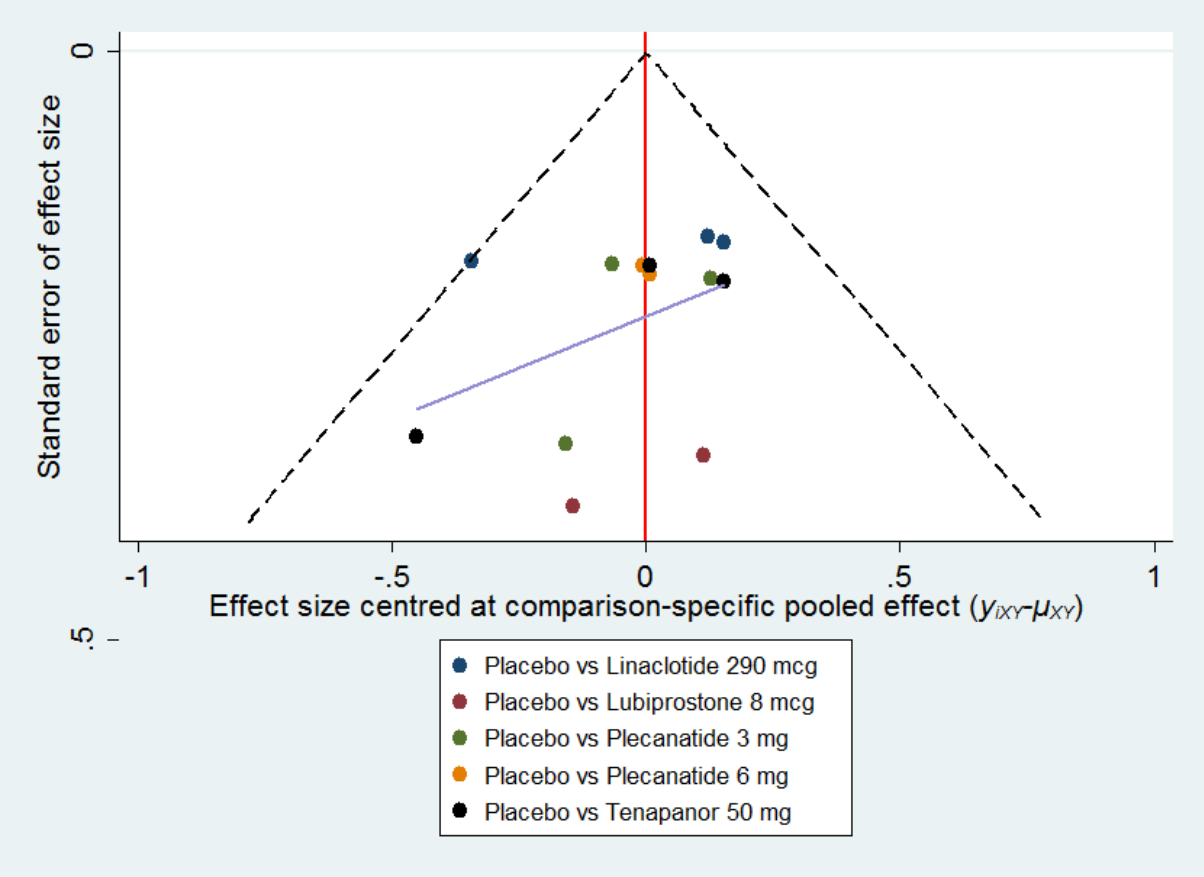
Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of indirect effects. Boxes shaded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

Supplementary Figure 1. Network Plot for Failure to Achieve the FDA-recommended Endpoint to Define Treatment Response.



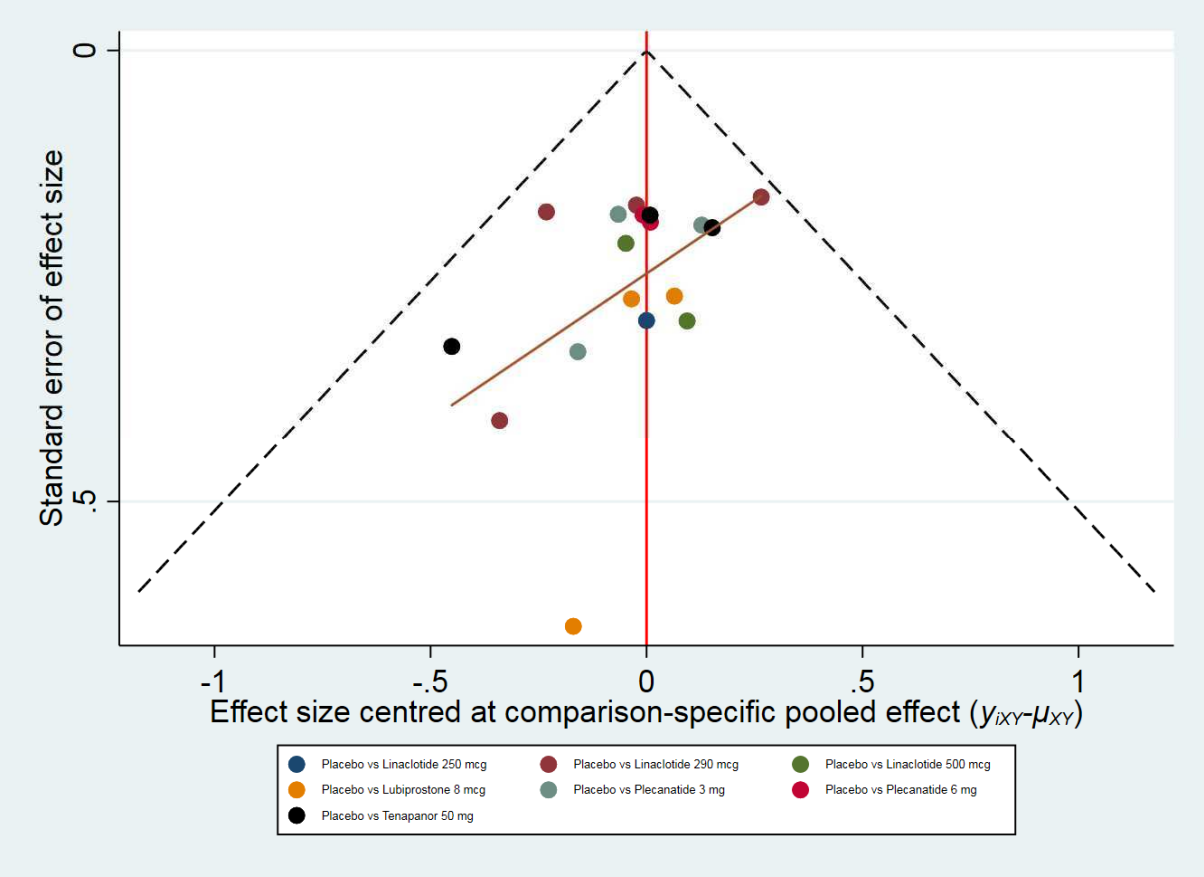
Legend	
Drug	**Abbreviation**
Placebo	A
Lubiprostone 8 mcg	B
linaclotide 290 mcg	C
Plecanatide 3 mg	D
Plecanatide 6 mg	E
Tenapanor 50 mg	F

Supplementary Figure 2. Funnel Plot for Failure to Achieve the FDA-recommended Endpoint to Define Treatment Response.



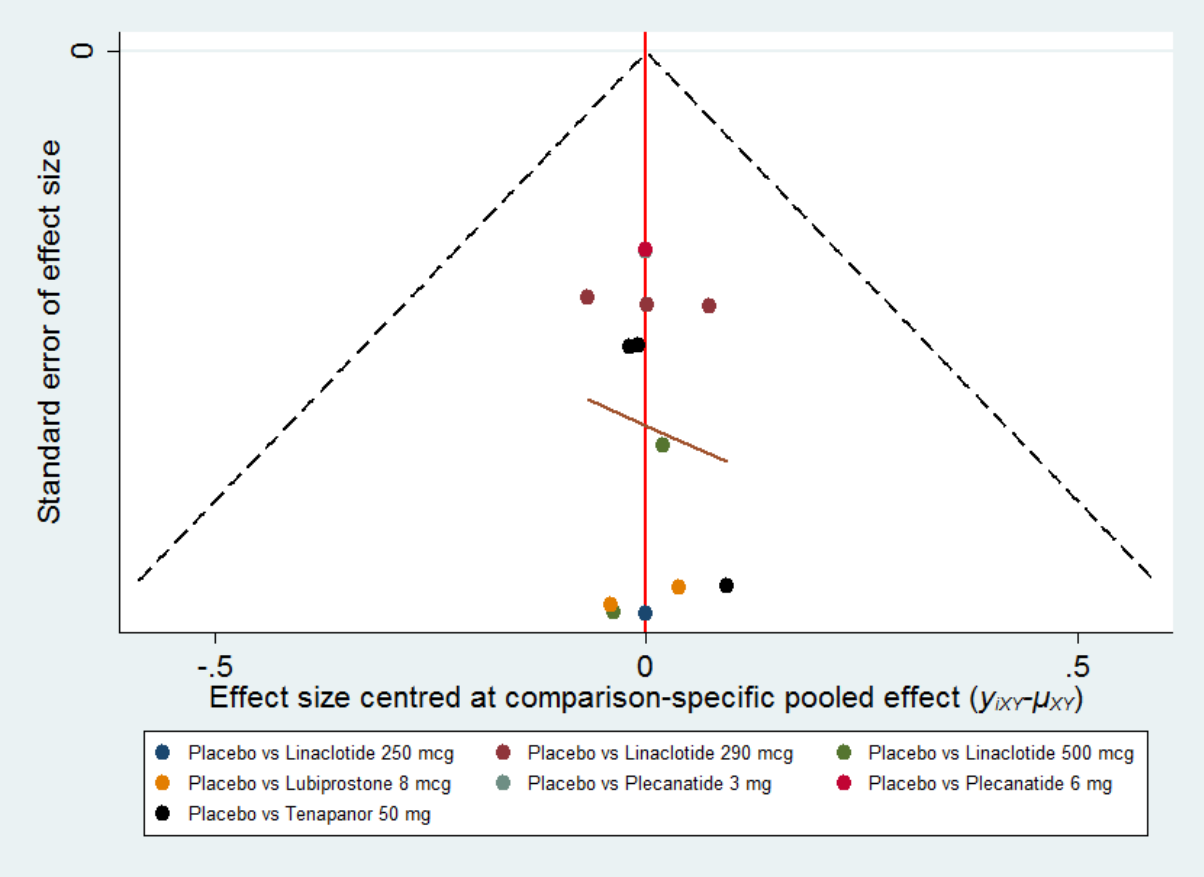
Note: The horizontal axis represents the difference between the comparison-specific and study-specific effect sizes.

Supplementary Figure 3. Funnel Plot for Failure to Achieve the Primary Endpoint Used to Define Treatment Response in Each Trial.



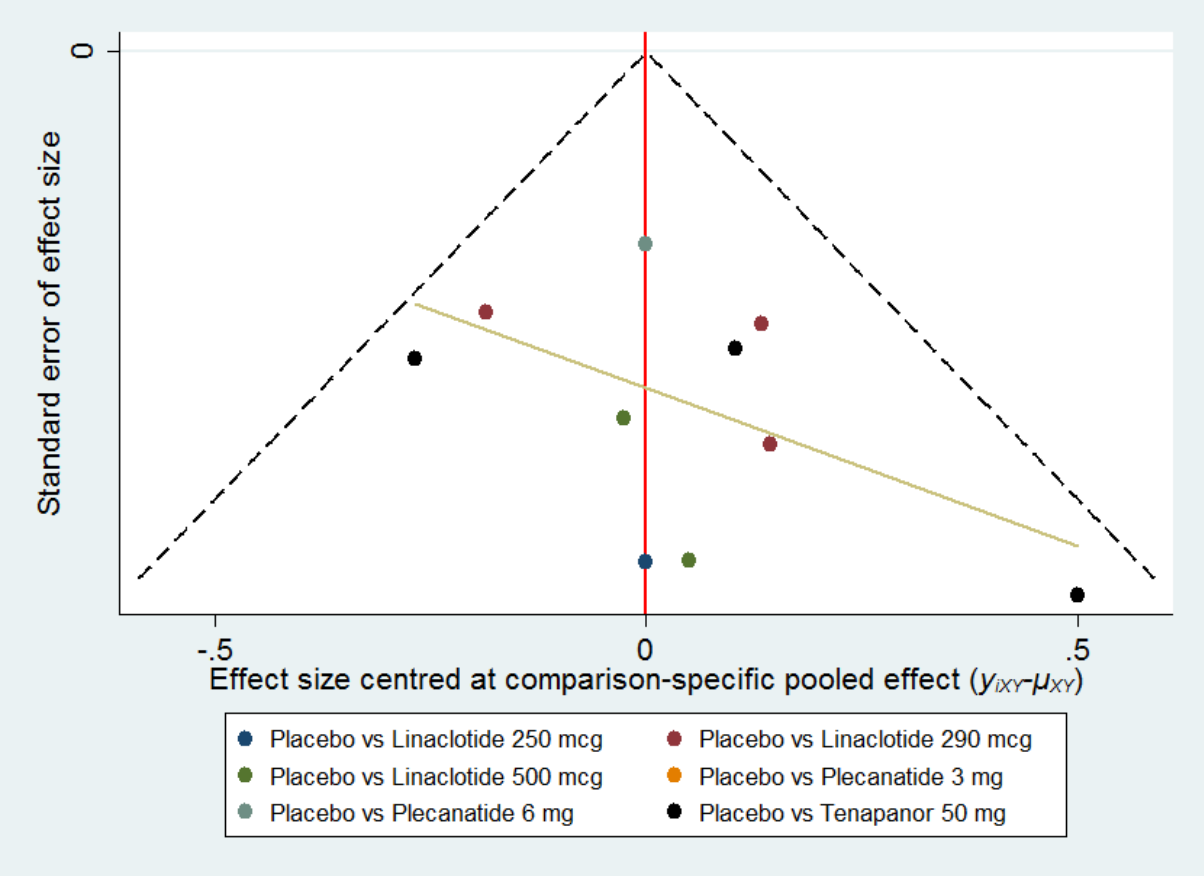
Note: The horizontal axis represents the difference between the comparison-specific and study-specific effect sizes.

Supplementary Figure 4. Funnel Plot for Failure to Achieve an Abdominal Pain Response.



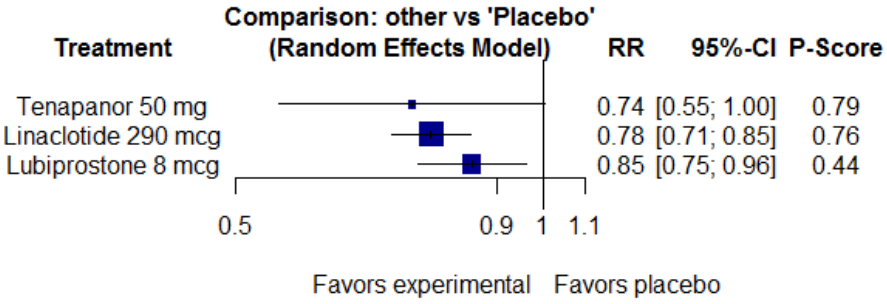
Note: The horizontal axis represents the difference between the comparison-specific and study-specific effect sizes.

Supplementary Figure 5. Funnel Plot for Failure to Achieve a CSBM Response.



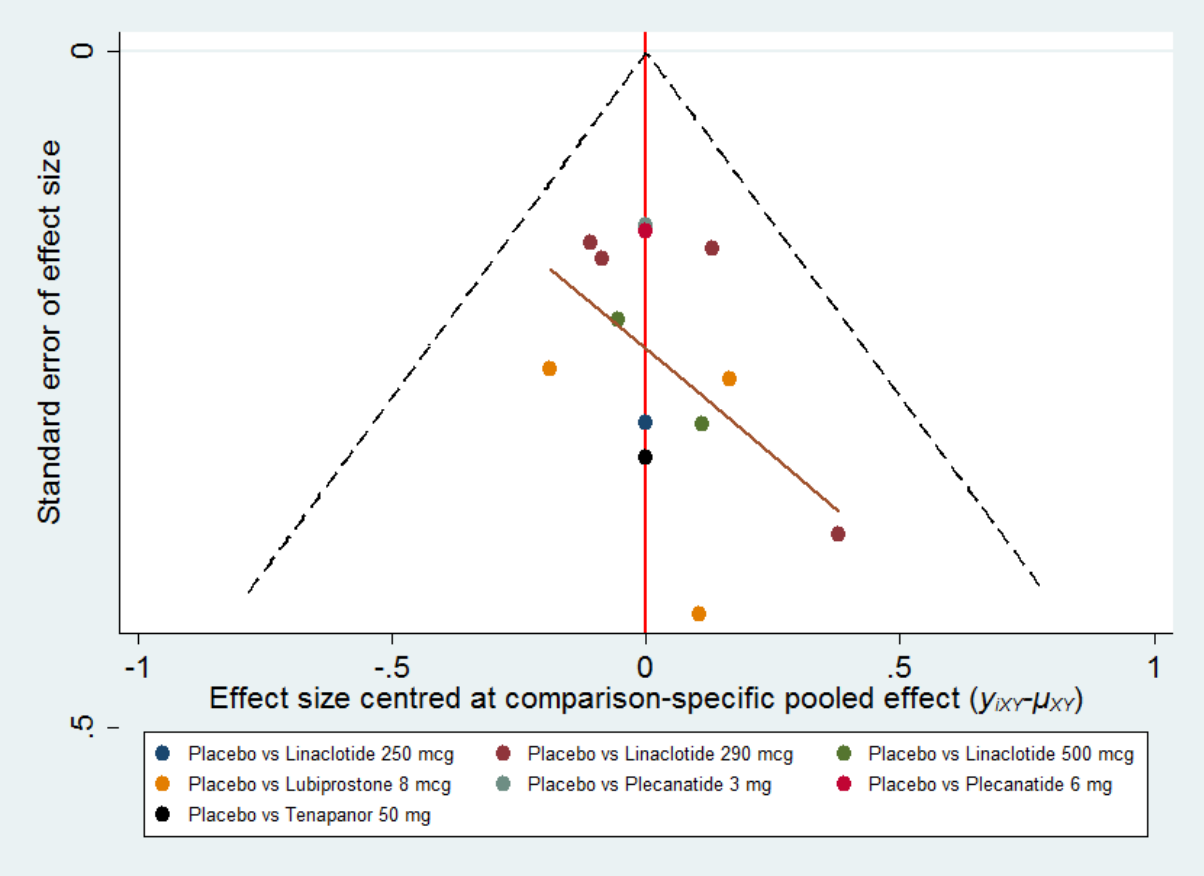
Note: The horizontal axis represents the difference between the comparison-specific and study-specific effect sizes.

Supplementary Figure 6. Forest Plot of the Indirect Evidence for Failure to Achieve a Bloating Response.



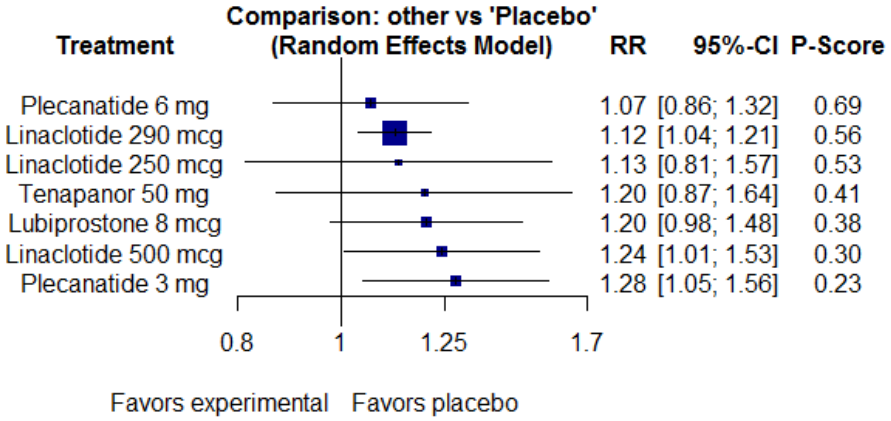
Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

Supplementary Figure 7. Funnel Plot for Overall Adverse Events.



Note: The horizontal axis represents the difference between the comparison-specific and study-specific effect sizes.

Supplementary Figure 8. Forest Plot of the Indirect Evidence for Overall Adverse Events.



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.