SYSTEMATIC REVIEW AND META-ANALYSIS

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Assessing the Efficacy and Safety of Multiple Drugs for IBS-C: A Systematic Review and Network Meta-Analysis

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ABSTRACT

Background & Aims: Intestinal secretagogues and prokinetic agents are commonly used for managing irritable bowel syndrome with constipation (IBS-C). However, no studies have provided direct head-to-head comparisons of these medications. This study aimed to evaluate the dose-stratified relationships and safety profiles of multiple agents to treat IBS-C.

Methods: We searched PubMed, Embase, Cochran Library, and Web of Science for randomized controlled trials (RCTs) from their inception until 21 November 2024. Eligible trials assessed the efficacy and safety of intestinal secretagogues or prokinetic agents in patients with IBS-C. The outcomes were abdominal symptoms, stool characteristics, and the incidence of adverse events.

Results: A total of 1,152 articles were identified, and 16 trials involving five drugs with various dosing regimens were included. Our results suggest that linaclotide (62.5 μg qd, 290 μg qd, 500 μg qd and tenapanor 50mg bid) may be superior to placebo and tenapanor (5 mg bid) in improving abdominal pain. Linaclotide (290 μg qd) was significantly more effective than placebo in alleviating abdominal cramping and increasing bowel movement frequency. Regarding safety, linaclotide (125 μg qd) was associated with a higher incidence of adverse events than both linaclotide (62.5 μg qd) and placebo. Tenapanor (50 mg bid) and linaclotide (125 μg qd) were linked to more adverse events than tenapanor (20 mg bid). Linaclotide (290 μg qd) also had a higher incidence of adverse reactions than placebo.

Conclusions: For patients with IBS-C, higher doses of linaclotide and tenapanor may provide enhanced symptom relief, but caution is warranted regarding their safety profiles.

Key words: irritable bowel syndrome with constipation – linaclotide – tenapanor -network meta-analysis.

Abbreviations: AGA: American Gastroenterological Association; CSBMs: complete spontaneous bowel movements; GC-G: guanylate cyclase-C; IBS: irritable bowel syndrome; IBS-C: IBS with constipation; SBM: spontaneous bowel movements.

INTRODUCTION

Irritable bowel syndrome (IBS) is a common chronic functional bowel disease characterized by recurrent abdominal pain, abdominal discomfort, and changes in bowel habits or fecal traits. The incidence of IBS varies by region, with a prevalence up to 20% in Western countries, higher than in some regions such as South Asia and the Middle East [1]. Irritable bowel syndrome not only imposes a significant physical and mental burden on patients [2], but also causes substantial socio-economic costs, including increased consumption of medical resources [3] and loss of productivity [4]. Irritable bowel syndrome with constipation (IBS-C), a subtype of IBS, affects a significant proportion of patients and is estimated to account for approximately 30% to 40% of all IBS cases [5].

A variety of treatments for IBS-C exist, ranging from lifestyle modifications [6] to pharmacological interventions [7]. The American Gastroenterological Association (AGA) recommends the use of linaclotide, tenapanor, plecanatide, tegaserod, lubiprostone and PEG laxatives in patients with IBS-C [8]. In terms of clinical efficacy, these drugs can be divided into intestinal secretagogues or prokinetic agents. However, selecting the most appropriate treatment in clinical practice remains challenging due to the lack of high-quality head-to-head comparative studies that directly evaluate the relative efficacy and safety of different therapies.

This study aims to bridge this knowledge gap by using a network meta-analysis to compare the clinical efficacy of multiple agents for IBS-C. The method integrates data from multiple studies, enables simultaneous analysis of multiple treatments, and provides the basis for informed treatment plans.

METHODS

Study Source

We conducted a comprehensive search of four databases: PubMed, Embase, the Cochrane Library, and Web of Science, using both keywords and Medical Subject Headings (MeSH terms) to develop search queries. Randomized controlled trials (RCTs) evaluating multiple pharmacological treatments for IBS-C were included from the inception of each database up to 21 November 2024. There were no language restrictions. In addition, we screened references from previous meta-analyses to identify eligible studies (Suplementary file). This study has been registered in the PROSPERO International Register of Prospective Systematic Reviews (registry number: CRD42024617340). As this study does not involve any patient-facing intervention or clinical data analysis that requires consent from human participants, ethical approval was not required.

Study Selection

We first removed duplicates. Two independent reviewers (L.X. and Y.F.-L.) then screened titles and abstracts to exclude studies that did not meet inclusion criteria, such as non-RCTs, irrelevant interventions, animal studies, and inconsistent outcome measurements. Subsequently, full-text reviews were conducted to determine eligibility. All differences were resolved by discussion, and unresolved issues were adjudicated by the third reviewer (H.Z.).

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) study type: randomized controlled trials (RCTs); (2) participants: patients diagnosed with IBS-C according to the Rome criteria; (3) age: adult patients (≥18 years old); (4) interventions: guanylate cyclase activators (linaclotide, plecanatide), tegaserod, prucalopride, lubiprostone, polyethylene glycol, and lactulose; control interventions: placebo, conventional treatment, no intervention, or other Western medicine monotherapy; (5) outcomes: abdominal symptoms (such as abdominal pain, abdominal discomfort), bowel movement parameters (frequency of bowel movements, stool consistency), and adverse events or side effects; (6) language: no restrictions; (7) publication type: published full-text articles. Exclusion criteria were as follows: (1) study type: non-randomized controlled trials, reviews (including systematic reviews and meta-analyses), expert opinions, editorials, and secondary analyses of randomized controlled trials; (2) participants: animal experiments or in vitro studies; patients under 18 years old; patients with other major gastrointestinal diseases, such as inflammatory bowel disease and peptic ulcer; (3) interventions: studies involving combination therapies; (4) outcome measures: studies that did not report abdominal symptoms, defecation parameters, or safety-related outcomes, or studies with incomplete data or data that could not be extracted; (5) other: republished studies - only the most complete or up-to-date version was retained; full-text articles which were not available..

Outcome Assessments

The primary outcome was abdominal pain, while secondary outcomes were abdominal discomfort, abdominal cramping, abdominal fullness, complete spontaneous bowel movements (CSBMs), spontaneous bowel movements (SBMs), stool consistency, severity of straining, and drug safety. These outcomes were evaluated at the conclusion of the treatment period. If the same outcome was reported in multiple formats, we selected the format that was most commonly presented across the included studies for our analysis. The mean difference was employed for stool frequency (CSBMs, SBMs), while severity of straining and stool consistency were represented by standardized mean differences. The incidence of abdominal symptoms and adverse reactions was expressed as an odds ratio.

Data Extraction

Data were independently extracted by two reviewers (Z.Z.-W. and Q.F.-T.) using standardized extraction forms, documenting study characteristics, participant demographics, interventions and comparators, and outcomes. Disagreements were resolved through discussion, and if consensus could not be reached, a third reviewer (H.Z.) made the final decision.

Risk of Bias Assessment

Two reviewers (M.C. and J.J.-M.) independently assessed the risk of bias using the Cochrane Risk of Bias Tool (Version 2). Risks of bias were categorized as low, some concern, or high based on randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results.

The Certainty of the Evidence

We evaluated the certainty of evidence through the GRADE approach within the minimally contextualized framework specifically developed for network meta-analyses [9]. The certainty of evidence was graded as high certainty, moderate certainty, low certainty, or very low certainty. Interventions were classified into Class 2 (most effective), Class 1 (less effective or better than least effective), and Class 0 (least effective). Experienced GRADE methodologists evaluated the data to determine the quality of the evidence and establish the strength of recommendations.

Statistical Analysis

We conducted an arm-based network meta-analysis using R version 4.4.1, employing the 'gemtc' package for analysis and Gibbs sampling via the 'rjags' package [10]. First, a Bayesian NMA model was established using the 'mtc.model' function with non-informative priors. Then, Markov Chain Monte Carlo (MCMC) sampling was performed with the following settings: four Markov chains, consistency model, random effects, 20,000 annealing, and 50,000 iterations for sampling. The deviance information criterion (DIC) and posterior residual deviance were used to assess model fit, where a posterior residual

deviance close to the number of unconstrained data points indicates a better fit [11]. Convergence of the model was evaluated using trace plots and density plots [12]. Pairwise comparisons were made to assess the mean differences for continuous outcomes and odds ratios (ORs) for binary outcomes, with results presented in forest plots and league tables. Consistency between direct and indirect evidence was evaluated using the node-splitting method [13]. We used the I^2 statistic to assess global heterogeneity. Global heterogeneity was classified as low ($I^2 < 50\%$), moderate ($50\% \leq I^2 < 75\%$), or high ($I^2 \geq 75\%$)[14]. For results displaying high heterogeneity, a leave-one-out analysis was performed to identify the individual sources of heterogeneity. We performed meta-regression analyses to assess the robustness of the findings [15]. Additionally, Surface Under the Cumulative Ranking curve (SUCRA) values were calculated to estimate the ranking of each intervention in the network, with higher SUCRA values indicating better efficacy [16]. Publication bias was evaluated using Egger's test (implemented in the 'netmeta' package in R) when there were ten or more eligible studies, where a p-value greater than 0.05 suggests no significant evidence of publication bias [17].

RESULTS

Characteristics of the Included RCTs

We retrieved 1,152 articles from four databases. After excluding 512 duplicates, we screened the titles and abstracts of the remaining articles and excluded an additional 612 papers for the following reasons: non-RCTs (n=230), not targeting IBS-C (n=226), irrelevant outcomes (n=26), non-targeted interventions (n=83), and conference abstracts (n=47). This left 28 articles for full-text review. Among them, six articles were only trial registrations, and another six articles lacked sufficient data [17]. Ultimately, 16 studies with 10,974 participants met the inclusion criteria and were analyzed. The PRISMA flow diagram for the search and selection process is shown in Fig. 1.

The characteristics of the 16 randomized controlled trials included are presented in Supplementary file. Among them, there are eight studies involving linaclotide [18, 20, 23, 24, 26-28, 30], three studies involving tegaserod [19, 21, 32], two studies involving tenapanor [25, 33], two studies involving lubiprostone [33, 39], and one study involving polyethylene glycol 3350 plus electrolytes (PEG 3350+E) [31]. The overall risk of bias assessment showed a low risk of bias in five studies (31%) [19, 23, 24, 28, 29] and some concerns of bias in eleven studies (69%) [18, 20-22, 25-27, 30-33]. A detailed assessment of the risk of bias is shown in Supplemental Figures 1-2.

Efficacy on Abdominal Pain

Nine studies [18, 23-26, 28, 31-33] reported abdominal pain at the end of treatment based on responder analysis. An abdominal pain responder was defined as a patient experiencing more than a 30% reduction in the degree of abdominal pain for at least 6 weeks out of 12 weeks of treatment. Of the nine studies, five were on linaclotide, two on tenapanor, and one each on PEG 3350+E and tegaserod. The posterior residual deviance (Dbar) was 21.98, with 24 unconstrained data points, indicating good model fitting. Trace plots and density plots indicated good convergence (Supplementary file Fig. 3a). The network diagram is shown in Fig. 2, the league Table (Fig. 3) and the forest plot (Fig. 4) show the difference in efficacy between the various treatments. The results showed that linaclotide (62.5 μg qd, 290 μg qd, 500 μg qd), and tenapanor (50 mg bid) were superior to placebo in improving abdominal pain (class 1, high certainty). Tenapanor (50 mg bid) was superior to tenapanor (5 mg bid) in improving abdominal pain (class 1, high certainty). Additionally, linaclotide (62.5 μg qd,

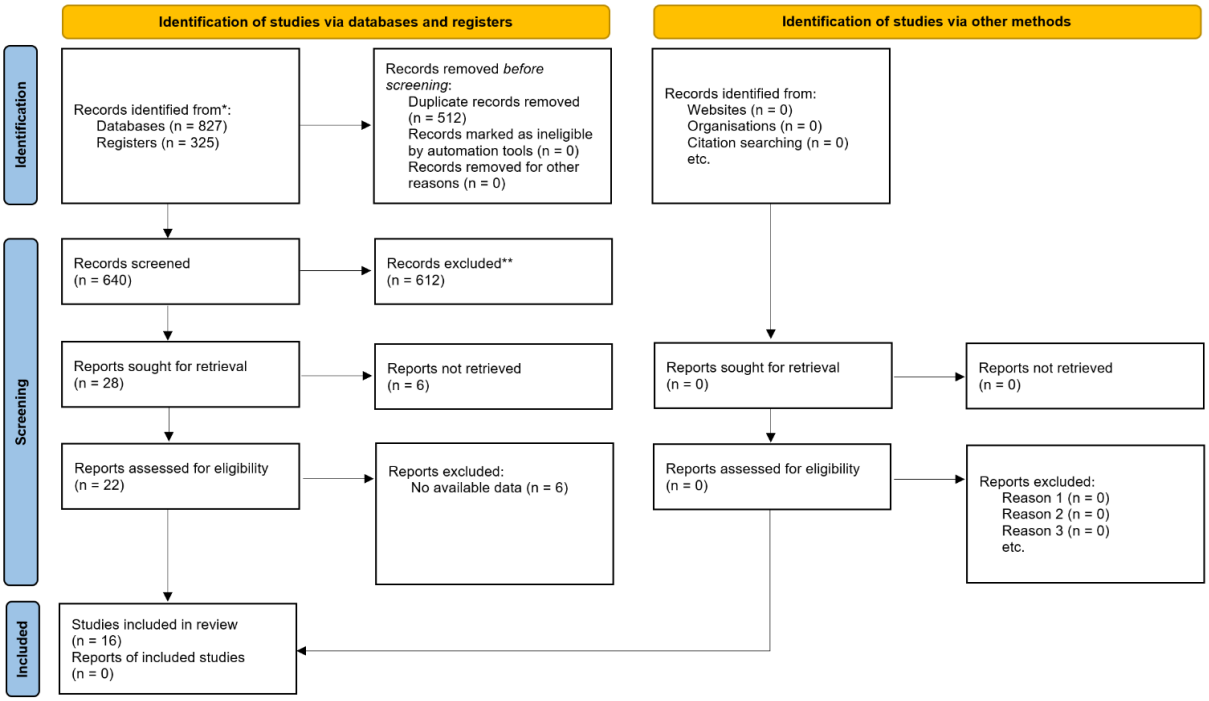

Fig. 1. PRISMA flow chart of literature search and research selection process.

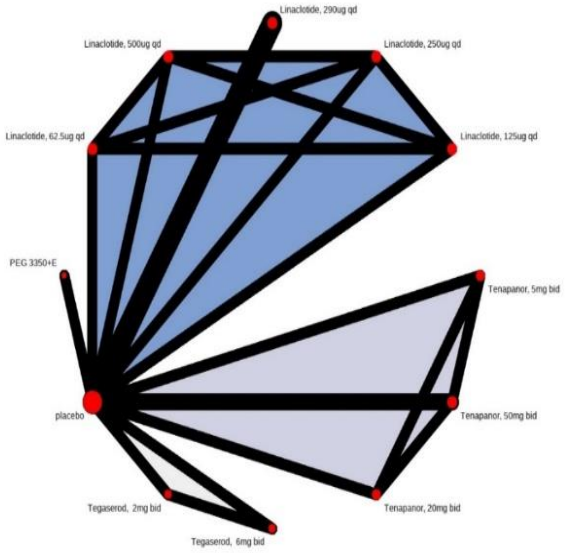

Fig. 2. Network diagram for studies on abdominal pain.

290 μg qd, 500 μg qd) were superior to tenapanor (5 mg bid) (class 1, moderate certainty). The SUCRA ranking bar chart is shown in Supplementary file, Fig. 3b. Since there were no direct comparisons between treatments, a consistency test was not required. Heterogeneity test results indicated that $I^2 = 0$. Gender, age, sample size, and treatment duration were used as covariates for regression analysis, and the results showed that $p > 0.05$. The Egger's test result indicated that $t = -0.76$ and $p = 0.46$, and the funnel plot is shown in Supplementary file, Fig. 3c.

Efficacy on Abdominal Cramping

Three studies [18, 26, 33] reported abdominal cramping at the end of treatment based on responder analysis. An abdominal cramping responder was defined as a patient experiencing more than a 30% reduction in abdominal cramping severity for at least 6 weeks out of 12 weeks of treatment. Of the three studies, two evaluated linaclotide and one evaluated tenapanor. The Dbar was 7.85, with 8 unconstrained data points, indicating good model fit. Trace plots and density plots indicated good convergence. The network diagram is shown in Supplementary file, Fig. 4a; the league table (Supplementary file, Fig. 4b) and the forest plot (Supplementary file, Fig. 4c) illustrate the differences in efficacy among the various treatments. Results showed that linaclotide (290 μg qd) was superior to placebo in improving abdominal cramping (class 1, high certainty). Heterogeneity test results indicated that $I^2 = 0$. Gender, age, sample size, and treatment duration were used as covariates in regression analysis, and the results showed that $p > 0.05$.

Efficacy on Spontaneous Bowel Movements

Four studies [24, 30, 31, 33] reported improvements in SBMs at the end of treatment. Of the four studies, two evaluated linaclotide, and one each evaluated tenapanor and PEG 3350+E. The Dbar was 10.15, with 10 unconstrained data points, indicating good model fit. Trace plots and density plots indicated good convergence. The network diagram is shown in Supplemental file, Fig. 5a; the league table (Supplementary file, Fig. 5b) and the forest plot (Supplementary file, Fig. 5c) show the difference in efficacy between the various treatments. Results showed that linaclotide (290 μg qd) was more effective than placebo in improving stool frequency (class 1, low certainty). Heterogeneity test results indicated that Global I^2: I^2.pair = 97.9%, I^2.cons = 91.7%. Gender, age, sample size, and treatment duration were used as covariates in regression analysis, and the results showed that $p > 0.05$. After conducting a sensitivity analysis using the leave-one-out method, it was found that two studies - Chang, Lin 2021 [24] and Rao, Satish SC 2020 [30] - comparing linaclotide (290 ug qd) with placebo were the main sources of heterogeneity. Specifically, when either of these two studies was excluded, network consistency improved significantly (I^2.cons=0); however, severe inconsistency persisted between this comparison and the results of other studies (I^2.pair = 100). This finding suggests that the conclusions of these two studies differ significantly, leading to a marked increase in global heterogeneity.

Safety

Thirteen studies [18-28, 31, 33] reported safety outcomes at the end of treatment: seven studies evaluated linaclotide, two each evaluated tenapanor and tegaserod, and one each evaluated PEG 3350+E and lubiprostone. The posterior residual deviance (Dbar) was 33.17, with 36 unconstrained data points, indicating good model fit. Trace plots and density plots indicated good convergence. The network diagram is shown in Supplementary file, Fig. 6a, and the forest plot (Supplementary file, Fig.6b) displays the differences in efficacy among the various regimens. Results showed that linaclotide (125 μg qd) had a higher rate of adverse reactions than linaclotide (62.5μg qd) and placebo (class 1, high certainty).

Linaclotide, 125ug qd												
1.34 (0.7, 2.61)	Linaclotide, 250ug qd											
1.4 (0.67, 2.89)	1.04 (0.49, 2.16)	Linaclotide, 290ug qd										
1.16 (0.61, 2.23)	0.86 (0.45, 1.69)	0.83 (0.39, 1.74)	Linaclotide, 500ug qd									
1.2 (0.63, 2.29)	0.9 (0.46, 1.71)	0.86 (0.41, 1.8)	1.04 (0.55, 2)	Linaclotide, 62.5ug qd								
1.94 (0.67, 5.69)	1.46 (0.51, 4.18)	1.39 (0.62, 3.14)	1.67 (0.59, 4.97)	1.61 (0.56, 4.71)	PEG 3350+E							
1.85 (0.79, 4.31)	1.38 (0.59, 3.25)	1.33 (0.78, 2.24)	1.59 (0.68, 3.81)	1.53 (0.66, 3.65)	0.95 (0.38, 2.36)	Tegaserod, 2mg bid						
1.67 (0.72, 3.92)	1.25 (0.53, 2.9)	1.19 (0.71, 2.01)	1.44 (0.61, 3.43)	1.38 (0.6, 3.27)	0.86 (0.35, 2.14)	0.9 (0.56, 1.44)	Tegaserod, 6mg bid					
2.28 (0.9, 5.78)	1.71 (0.66, 4.49)	1.64 (0.86, 3.17)	1.98 (0.78, 5.07)	1.9 (0.75, 4.85)	1.18 (0.43, 3.15)	1.23 (0.57, 2.75)	1.37 (0.63, 3.03)	Tenapanor, 20mg bid				
1.56 (0.7, 3.46)	1.17 (0.51, 2.58)	1.12 (0.73, 1.73)	1.35 (0.6, 3.01)	1.3 (0.59, 2.92)	0.8 (0.34, 1.91)	0.84 (0.46, 1.56)	0.93 (0.51, 1.72)	0.68 (0.37, 1.26)	Tenapanor, 50mg bid			
3.19 (1.25, 8.05)	2.38 (0.91, 6.12)	2.27 (1.19, 4.37)	2.76 (1.08, 7.07)	2.65 (1.04, 6.77)	1.64 (0.6, 4.38)	1.71 (0.8, 3.75)	1.91 (0.88, 4.2)	1.39 (0.71, 2.76)	2.04 (1.1, 3.77)	Tenapanor, 5mg bid		
2.47 (1.23, 4.97)	1.84 (0.9, 3.69)	1.77 (1.42, 2.21)	2.13 (1.05, 4.43)	2.05 (1.02, 4.2)	1.27 (0.58, 2.79)	1.33 (0.83, 2.17)	1.48 (0.92, 2.39)	1.08 (0.58, 1.99)	1.58 (1.09, 2.31)	0.78 (0.42, 1.43)	placebo	

Fig. 3. League table for studies on abdominal pain.

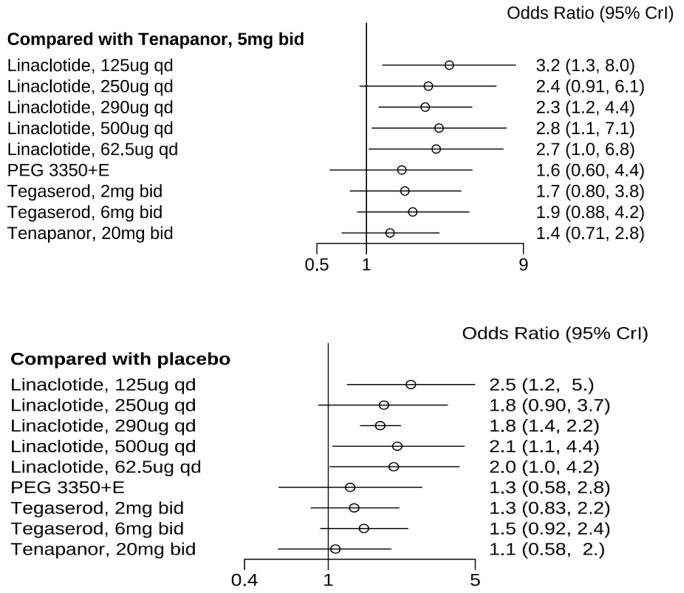

Fig. 4. Forest plots for studies on abdominal pain.

The incidence of adverse events with tenapanor (50 mg bid) (class 1, high certainty) and linaclotide (125 μg qd) (class 1, moderate certainty) was higher than that with tenapanor (20 mg bid). Linaclotide (290 μg qd) had a higher rate of adverse reactions compared to placebo (class 1, high certainty). The SUCRA ranking is presented in Supplementary file, Fig. 6c. Heterogeneity test results indicated that $I^2 = 0$. Gender, age, sample size, and treatment duration were used as covariates in regression analysis, and the results showed that $p > 0.05$. The Egger's test result indicated $t = -0.20$ and $p = 0.84$. The funnel plot is shown in Supplementary file, Fig. 6d.

Efficacy on Other Symptoms

Respondents were defined as patients who experienced a greater than 30% reduction in rating scores for more than six of the past 12 weeks. Abdominal discomfort was reported as a responder in four articles [18, 23, 26, 33], and abdominal fullness was reported as a responder in three articles [18, 26, 33]. Three studies [24, 31, 33] reported results on CSBMs using the standard mean (standard deviation) format, four studies [24, 30, 31, 33] reported on the severity of straining, and five studies [24, 29-31, 33] reported on stool consistency results. According to the above results, the degree of fit and convergence of the established Bayesian model were satisfactory, but there was no significant difference in the efficacy of each intervention regimen.

DISCUSSION

The American Gastroenterological Association recommends intestinal secretagogues and prokinetic agents for the management of IBS-C, including linaclotide, tenapanor, plecanatide, tegaserod, lubiprostone, and other agents. However, to date, there have been no direct head-to-head comparisons of these medications, which may hinder clinical decision-making. Black et al. [34] conducted a systematic review and network meta-analysis on the efficacy of secretagogues for patients with IBS-C in 2018 [34]. However, the literature included in this review comprised "a combined analysis of two phase III RCTs, post hoc analyses, and reports from drug company". Such inclusion might introduce analytical bias or compromise data independence, thereby potentially undermining the accuracy and reliability of the network meta-analysis results. Our review shares certain overlaps with the research conducted by Black et al. [34], as both assess the efficacy of intestinal secretagogues for patients with IBS-C. To ensure the accuracy and reliability of the results, we conducted a systematic literature search and applied more stringent inclusion criteria; through this process, this network meta-analysis included 16 randomized controlled trials evaluating the efficacy and safety of multiple agents at various doses for the treatment of IBS-C.

Linaclotide is a guanylate cyclase-C (GC-C) agonist that binds to GC-C receptors on the luminal surface of the proximal intestinal epithelium. This interaction increases both intracellular and extracellular cyclic guanosine monophosphate (cGMP) levels, thereby reducing the activity of pain-sensing nerve fibers and alleviating visceral pain [35]. It also enhances the secretion of chloride and bicarbonate into the intestinal lumen, which increases intestinal fluid secretion and accelerates colonic transit. Our findings suggest that multiple doses of linaclotide (e.g., 62.5 μg qd, 290 μg qd, 500 μg qd) offer advantages over placebo and a lower dose of tenapanor (5 mg bid) in improving abdominal pain. However, no significant differences were observed among these various linaclotide doses in terms of abdominal pain improvement. Notably, linaclotide (290μg qd) proved superior to placebo in relieving abdominal cramps and improving stool frequency. This outcome aligns with previous pharmacological studies on linaclotide's ability to promote intestinal secretion and accelerate intestinal transit, providing valuable reference data for clinical practice. In terms of safety, linaclotide (125 μg qd) demonstrated a higher incidence of adverse events compared to linaclotide (62.5 μg qd) and placebo, and linaclotide (290 μg qd) also showed a higher incidence of adverse events relative to placebo.

Tenapanor is a sodium/hydrogen exchanger 3 (NHE3) inhibitor that selectively blocks NHE3 in the intestinal epithelium, thereby modulating ion and water exchange, softening stools, and promoting bowel movements [36]. Our results indicate that tenapanor (50 mg bid) improves abdominal pain more effectively than tenapanor (5 mg bid) and a placebo. However, the incidence of adverse events was higher with tenapanor (50 mg bid) than with tenapanor (20 mg bid), suggesting that while increased doses of tenapanor enhance therapeutic efficacy, they also elevate the risk of adverse reactions.

In IBS-C therapy, higher doses of linaclotide and tenapanor show potential advantages in alleviating core symptoms such as abdominal pain, yet these benefits come with an increased risk of adverse reactions. Close monitoring of adverse events is warranted, particularly in patients who require a delicate balance between symptom relief and tolerability. For these individuals, careful consideration of dosage and regimen selection is essential.

The lack of significant efficacy and safety differences between multiple IBS-C treatments and placebo stood in contrast to findings reported in prior head-to-head clinical trials. This divergence implies a potential impact on the stability and credibility of the current results. One possible reason is that the network meta-analysis pooled both direct and indirect evidence from various RCTs, and this aggregated approach may have attenuated differences that were more pronounced within individual trials. Additionally, variations in sample sizes, study quality, and underlying biases could have introduced heterogeneity, ultimately diminishing the relative advantages of certain interventions over placebo.

This study has certain limitations. Firstly, the existing evidence base is limited, and no direct comparisons among multiple drugs were available. Secondly, there was variability in outcome reporting. Some studies used continuous data without providing standard deviations or 95% confidence intervals, while others employed binary "responder" definitions with inconsistent criteria. These discrepancies reduce data comparability and limit the confidence in our conclusions. Further high-quality, large-scale, and well-designed studies are needed to clarify the efficacy and safety differences across various dosing strategies.

CONCLUSIONS

For patients with IBS-C, higher doses of linaclotide and tenapanor may provide enhanced symptom relief, but caution is warranted regarding their safety profiles. This study provides a reference point for the clinical use of pharmacological agents in IBS-C, guiding clinicians to consider the severity of patient symptoms, individual patient needs, and adverse reaction tolerance when making therapeutic decisions. At the same time, future high-quality research is anticipated to offer clearer evidence-based guidance, optimizing treatment strategies for patients with IBS-C.

Conflicts of interest: None to declare.

Authors' contributions: L.X., Y.F. conducted literature screening. Z.Z., Q.F.: collected data. M.C., J.J. performed risk of bias assessment and evidenced grade evaluation for the included literature. J.J. was responsible for statistical analysis, result visualization, and initial draft writing. H.Z. was responsible for methodology design, software code development, study supervision, and manuscript editing. All authors participated in revising the manuscript critically, approved the final version to be published, and agree to be accountable for all aspects of the work.

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