INSIGHT JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY

Constipation: A Meta-Analysis

Ruth Helen
[2]Department of Medicine, Canada

[*]**Corresponding Author:**
Ruth Helen, Departments of Medicine, Canada

Received Date: 09 Feb 2026
Accepted Date: 02 Mar 2026
Published Date: 06 Mar 2026

Citation: Ruth Helen. Constipation: A Meta-Analysis. IJGH. 2026; 1: 1-4

1. Abstract

1.1. Background: Irritable Bowel Syndrome with Constipation (IBS-C) and functional constipation are frequent gastrointestinal conditions for which treatment options remain limited. This meta-analysis aimed to evaluate the effectiveness of various daily doses of oral linaclotide in treating IBS-C and chronic constipation.

1.2. Methods: A systematic literature search was conducted in May 2014. Randomized controlled trials comparing linaclotide with placebo were included. The primary outcome measured was the proportion of patients achieving at least three Complete Spontaneous Bowel Movements (CSBM) per week along with an increase of at least one CSBM from baseline. The secondary outcome focused on the occurrence of adverse events. Subgroup analysis was performed by categorizing studies into a high-dose group (290–300 mcg) and a low-dose group (145–150 mcg).

1.3. Results: Six studies involving a total of 3,654 participants met the inclusion criteria. Compared with placebo, linaclotide showed a statistically significant improvement in bowel movement frequency.

1.4. Conclusion: Linaclotide appears to be an effective therapeutic option for patients with IBS-C and chronic constipation; however, its use is associated with a higher rate of adverse effects.

2. Keywords: Linaclotide, Irritable Bowel Syndrome, Constipation, Meta-analysis

3. Abbreviations: IBS-C: Irritable Bowel Syndrome with Constipation; CSBM: Complete Spontaneous Bowel Movement; IBS: Irritable Bowel Syndrome; cGMP: Guanylate Cyclase C; DARE: Database of Abstracts of Reviews of Effects; DDW: Digestive Disease Week; ACG: American College of Gastroenterology

4. Introduction

Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder characterized by persistent abdominal discomfort or pain accompanied by changes in bowel habits without an identifiable structural cause. In North America, IBS affects approximately 10–15% of the population and is more frequently reported among younger individuals and women. Nevertheless, the condition can occur in both sexes across all age groups.

The symptoms associated with IBS can substantially impair patients' quality of life. Additionally, IBS imposes a considerable economic burden due to decreased work productivity and increased utilization of healthcare resources. It is estimated that 25–50% of referrals to gastroenterology specialists are related to IBS.

IBS is typically categorized according to predominant stool pattern: IBS with constipation (IBS-C), IBS with diarrhea, mixed IBS, and unclassified IBS. Individuals with IBS-C represent roughly one-third of IBS patients and commonly experience symptoms such as abdominal pain, bloating, infrequent bowel movements, hard stools, straining during defecation, and a sensation of incomplete evacuation.

Current pharmacological therapies for IBS-C often fail to provide satisfactory symptom relief. Lubiprostone is a relatively recent medication that has demonstrated improvement in overall IBS-C symptoms. In September 2012, linaclotide received approval from the U.S. Food and Drug Administration for the treatment of IBS-C. Linaclotide is a minimally absorbed peptide that acts on the intestinal epithelium by activating guanylate cyclase-C receptors. This activation stimulates the cystic fibrosis transmembrane conductance regulator, leading to increased secretion of chloride and bicarbonate ions into the intestinal lumen. As a result, fluid secretion into the bowel increases and intestinal transit is accelerated.

Animal studies have demonstrated that linaclotide enhances gastrointestinal motility and decreases visceral pain sensitivity. The compound's production of cGMP also appears to reduce the activation of pain-transmitting nerve fibers in the colon. Clinical studies in humans have reported improvements in colonic transit, abdominal pain, and constipation symptoms following linaclotide therapy.

The objective of the present study was to conduct a meta-analysis of available clinical trials to determine the efficacy and safety of different daily doses of oral linaclotide in patients with IBS-C and chronic constipation.

5. Methods and Materials

5.1. Literature Search

Electronic databases including MEDLINE/PubMed, Scopus, CINAHL, the Meta Register of Controlled Trials, the Database of Abstracts of Reviews of Effects (DARE), and the Cochrane Library

INSIGHT JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY

were searched in May 2014 using the keywords "linaclotide," "irritable bowel syndrome," and "constipation." Reference lists of relevant publications were manually examined to identify additional studies.

Furthermore, abstracts from the Digestive Disease Week (DDW) and the American College of Gastroenterology (ACG) conferences between 2003 and 2014 were reviewed for potentially eligible studies. All relevant publications were considered regardless of reported outcomes or document type. Citation searches in Scopus were also performed to identify newer articles citing the selected studies. Studies conducted in animals or published in languages other than English were excluded.

5.2. Study Design

Three investigators independently reviewed the titles and abstracts identified through the search process. Randomized, placebo-controlled clinical trials evaluating linaclotide for IBS-C or chronic constipation were considered eligible. Studies were included if they:

1. Examined the effects of linaclotide on IBS-C or chronic constipation symptoms.
2. Were prospective, randomized, placebo-controlled trials published in peer-reviewed journals.
3. Were conducted in human subjects.

Review articles, retrospective studies, and case reports were excluded.

5.3. Data Extraction

Two authors independently extracted relevant information from the selected studies using a standardized data collection form. Any discrepancies were resolved through discussion with a third investigator.

5.4. Outcome Assessment

The primary outcome measured was the therapeutic effectiveness of linaclotide in improving bowel movement frequency, specifically the average number of stools per week during treatment. The secondary outcome was the frequency of adverse events associated with therapy.

Subgroup analyses were performed based on dosage, dividing studies into high-dose (290–300 mcg daily) and low-dose (145–150 mcg daily) groups.

5.5. Quality Assessment

The methodological quality of each included study was evaluated using the Jadad scoring system, which assesses randomization, blinding, and description of withdrawals. Scores range from 0 to 5, with studies scoring 3 or higher considered high quality and those scoring 2 or lower considered low quality.

5.6. Statistical Analysis

Meta-analysis comparing linaclotide with placebo was performed using pooled estimates of the primary outcome (mean stool frequency per week) and the secondary outcome (adverse event rates). Odds ratios (OR) were calculated using both Mantel-Haenszel fixed-effect and DerSimonian-Laird random-effects models. A random-effects model was applied when significant heterogeneity was detected.

Statistical significance was defined as a p-value less than 0.05 or when the confidence interval did not include 1. Heterogeneity between studies was evaluated using the I^2 statistic, with values above 50% or p-values less than 0.10 considered significant. When heterogeneity was present, sensitivity analyses were conducted by excluding individual studies.

The statistical analyses were carried out using RevMan Manager version 5.2 (Cochrane Collaboration). Funnel plots were used to assess potential publication bias.

6. Results

The initial database search identified 218 articles and conference abstracts. After screening titles and abstracts, 194 records were excluded, leaving 24 articles for full-text evaluation. Eighteen of these were excluded due to being systematic reviews, duplicate publications, or lacking relevant outcomes.

Ultimately, six randomized controlled trials involving 3,654 participants satisfied the inclusion criteria and were incorporated into the meta-analysis.

These studies were conducted in the United States, with two also including participants from Canada. All were published between 2009 and 2012 in English. Five of the six trials evaluated the primary outcome of achieving at least three CSBMs per week along with an increase of at least one CSBM from baseline. All studies reported data regarding adverse events.

Reported adverse effects included diarrhea, allergic reactions, abdominal pain, abdominal distension, dyspepsia, flatulence, nausea, vomiting, proctalgia, urinary tract infection, nasopharyngitis, sinusitis, headache, and upper respiratory infection. Among these, diarrhea was the most frequently observed side effect.

All six trials were included in the high-dose subgroup analysis, while three studies contributed to the low-dose analysis.

7. Discussion

As the prevalence of IBS and chronic constipation continues to rise, effective therapeutic strategies remain limited. Previously, two medications had been approved for IBS-C management: tegaserod and lubiprostone. However, tegaserod was withdrawn from the market in 2007 due to concerns about cardiovascular adverse events, leaving lubiprostone as the only approved therapy

INSIGHT JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY

until linaclotide was introduced.

The approval of linaclotide in 2012 expanded treatment options for patients with IBS-C. Over the past several years, multiple clinical trials have evaluated linaclotide using different dosing regimens and study designs, producing varying outcomes.

The present meta-analysis combined data from six randomized trials and demonstrated that linaclotide significantly improved the primary outcome compared with placebo. However, treatment was also associated with a higher incidence of adverse events.

Both commonly used dosing regimens (145–150 mcg and 290–300 mcg daily) resulted in improved bowel movement outcomes but also increased the likelihood of side effects. Despite this increased risk, linaclotide appears to provide clinical benefit for individuals with IBS-C, particularly given the limited availability of effective treatments.

This meta-analysis has several strengths. A comprehensive literature search was performed to ensure that all relevant studies were included. Additionally, only randomized controlled trials were analyzed, which enhances the reliability of the findings. Five of the six studies successfully achieved the primary endpoint, strengthening the overall evidence. Furthermore, no evidence of publication bias was detected.

However, certain limitations should be considered. Most trials compared linaclotide only with placebo rather than other available treatments, preventing direct comparison with alternatives such as lubiprostone. Additionally, only 31% of participants achieved the primary endpoint, resulting in a relatively small proportion of successful outcomes. Many of the trials were conducted by the same research groups, which may introduce potential bias due to limited independent replication.

Another limitation is the variation in study duration, with follow-up periods ranging from two to twenty-six weeks. Differences in dosing regimens were also present; however, subgroup analyses were performed to minimize the impact of these variations. In one study by Lembo and colleagues, two parallel trials were reported within a single publication; their data were combined for simplicity in the analysis.

8. Conclusion

Linaclotide significantly increases the frequency of complete spontaneous bowel movements compared with placebo in patients with IBS-C and chronic constipation. Although treatment is associated with a higher rate of adverse events, the medication represents a reasonable therapeutic option given the limited availability of effective treatments. Future research should focus on determining optimal dosing strategies and conducting randomized controlled trials that directly compare linaclotide with other therapies such as lubiprostone.

References

1. Hahn BA, Saunders WB, Maier WC. Differences between individuals with self-reported irritable bowel syndrome (IBS) and IBS-like symptoms. Dig Dis Sci. 1997; 42: 2585-2590.
2. Drossman DA, Li Z, Andruzzi E, Temple RD, Talley NJ, Thompson WG, et al. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. Dig Dis Sci. 1993; 38: 1569-1580.
3. Talley NJ, Zinsmeister AR, Van Dyke C, Melton LJ 3rd. Epidemiology of colonic symptoms and the irritable bowel syndrome. Gastroenterology. 1991; 101: 927-934.
4. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol. 2012; 10: 712-721.
5. Lackner JM, Gudleski GD, Thakur ER, Stewart TJ, Iacobucci GJ, Spiegel BM. The impact of physical complaints, social environment, and psychological functioning on IBS patients' health perceptions: looking beyond GI symptom severity. Am J Gastroenterol. 2014; 109: 224-233.
6. Paré P, Gray J, Lam S, Balshaw R, Khorasheh S, Barbeau M, et al. Health related quality of life, work productivity, and health care resource utilization of subjects with irritable bowel syndrome: baseline results from LOGIC (Longitudinal Outcomes Study of Gastrointestinal Symptoms in Canada),a naturalistic study. Clin Ther 2006; 28: 1726–1735.
7. Everhart JE, Renault PF. Irritable bowel syndrome in office-based practice in the United States. Gastroenterology. 1991; 100: 998-1005.
8. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology 2006; 130: 1480 -1491. Austin J Gastroenterol - Volume 1 Issue 1 - 2014 ISSN : 2381-9219 | www.austinpublishinggroup.com Bechtold et al. © All rights are reserved
9. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. Gastroenterology 2002; 123: 2108 –2131.
10. Mayer EA. Clinical practice: irritable bowel syndrome. N Engl J Med 2008; 358: 1692 –1699.
11. Hulisz D. The burden of illness of irritable bowel syndrome: current challenges and hope for the future. J Manag Care Pharm 2004; 10: 299 –309.
12. Brandt LJ, Chey WD, Foxx-Orenstein AE, Schiller LR, Schoenfeld PS, Spiegel BM, et al. American College of Gastroenterology Task Force on Irritable Bowel Syndrome. An evidence-based position statement on the management of irritable bowel syndrome. Am J Gastroenterol. 2009; 104: S1–S35.
13. Hannig G, Tchernychev B, Kurtz CB, Bryant AP, Currie MG,

INSIGHT JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY

Silos-Santiago I. Guanylate cyclase-C/cGMP: an emerging pathway in the regulation of visceral pain. Front Mol Neurosci. 2014; 7: 31.

14. Bryant AP, Busby RW, Bartolini WP, Cordero EA, Hannig G, Kessler MM, et, al. Linaclotide is a potent and selective guanylate cyclase C agonist that elicits pharmacological effects locally in the gastrointestinal tract. Life Sci2010; 8: 19–20.
15. Eutamene H, Bradesi S, Larauche M, Theodorou V, Beaufrand C, Ohning G, et al. Guanylate cyclase C-mediated antinociceptive eff ects of linaclotide in rodent models of visceral pain . Neurogastroenterol Motil 2010; 22: 312–322.
16. Castro J, Martin C, Hughes P, Silos-Santiago A, Kurtz C, Blackshaw L, et al. A novel role of cyclic GMP in colonic sensory neurotransmission in healthy and TNBS-treated mice. Gastroenterology 2011; 140: S-538
17. Layer P, Stanghellini V. Review article: Linaclotide for the management of irritable bowel syndrome with constipation. Aliment PharmacolTher. 2014; 39: 371-384.
18. Johnston JM, Kurtz CB, Macdougall JE, Lavins BJ, Currie MG, Fitch DA, et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome with constipation. Gastroenterology 2010; 139:1877 –1886.
19. Andresen V, Camilleri M, Busciglio IA, Grudell A, Burton D, McKinzie S, et al. Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome . Gastroenterology 2007; 133: 761–768.
20. Jadad AR, McQuay HJ. A high-yield strategy to identify randomized controlled trials for systematic reviews. Online J Curr Clin Trials. 1993: 33.
21. Quigley EM, Tack J, Chey WD, Rao SS, Fortea J, Falques M, et al. Randomised clinical trials: linaclotide phase 3 studies in IBS-C - a prespecified further analysis based on European Medicines Agency-specified endpoints. Aliment Pharmacol Ther. 2013; 37: 49-61.
22. Johnston JM, Kurtz CB, Drossman DA, Lembo AJ, Jeglinski BI, MacDougall JE, et al. Pilot study on the effect of linaclotide in patients with chronic constipation. Am J Gastroenterol. 2009; 104: 125-132.
23. Lembo AJ, Kurtz CB, Macdougall JE, Lavins BJ, Currie MG, Fitch DA, et al. Efficacy of linaclotide for patients with chronic constipation.Gastroenterology. 2010; 138: 886-895.
24. Lembo AJ, Schneier HA, Shiff SJ, Kurtz CB, MacDougall JE, Jia XD, et al. Two randomized trials of linaclotide for chronic constipation. N Engl J Med.2011; 365: 527-536.
25. Rao S, Lembo AJ, Shiff SJ, Lavins BJ, Currie MG, Jia XD, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. Am J Gastroenterol. 2012 ; 107: 1714-1724.
26. Chey WD, Lembo AJ, Lavins BJ, Shiff SJ, Kurtz CB, Currie MG, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. Am J Gastroenterol. 2012 ; 107: 1702-1712