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Research Article

Effect of Linaclotide in the Treatment of Irritable Bowel Syndrome and Chronic Constipation: a Meta-Analysis

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Abstract

Background: Irritable Bowel Syndrome with Constipation (IBS-C) and functional constipation are common gastrointestinal disorders with limited treatment options. We performed a meta-analysis to estimate the efficacy of different daily doses of oral linaclotide in the management of IBS-C and chronic constipation.

Methods: A search was performed in May 2014. A meta-analysis was performed on randomized controlled trials comparing linaclotide versus placebo to assess the primary outcome (three or more Complete Spontaneous Bowel Movement (CSBM) per week and an increase of at least one CSBM per week from baseline) and secondary outcome (frequency of adverse events). Subgroup analysis was performed by dividing the studies into a high-dose group (290-300 mcg) and low-dose group (145-150 mcg).

Results: Six studies (N=3,654) were included. Linaclotide demonstrated a statistically significant improvement as compared to placebo (OR 3.42; 95% CI: 2.06-5.68; p<0.01) for CSBM. However, linaclotide showed a statistically significant increase in adverse events as compared to placebo (OR 1.28; 95% CI: 1.12-1.48; p<0.01). In subgroup analysis, linaclotide of 145-150 mcg and 290-300 mcg demonstrated statistically significant improvements in CSBM (OR 3.81; 95% CI: 2.55-5.70; p<0.01 and OR 3.84; 95% CI: 2.20-6.69; p<0.01, respectively) as compared to placebo. However, linaclotide of 145-150 mcg and 290-300 mcg revealed a statistically significant increase in adverse events (OR 1.39; 95% CI: 1.09-1.76; p<0.01 and OR 1.24; 95% CI: 1.07-1.45; p<0.01, respectively) as compared to placebo.

Conclusion: Linaclotide appears to be effective in the treatment of IBS-C and chronic constipation but has more adverse events.

Keywords: Linaclotide; Irritable Bowel Syndrome; Constipation; Meta-Analysis

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.

Introduction

Irritable Bowel Syndrome (IBS) is a gastrointestinal syndrome characterized by chronic abdominal pain and altered bowel habits without any other identifiable source. The prevalence of IBS in North America estimated approximately 10-15 percent [1-3], predominately in young patients and women [4]. However, IBS can affect both genders at any age.

The symptoms of IBS adversely affect patient's health-related quality of life [5]. Furthermore, a significant financial burden on society exists with IBS because of reduced work productivity and an over 50% increase in the use of health-related resources [6]. IBS also accounts for 25-50 percent of all referrals to gastroenterologists [7].

IBS is sub classified according to the predominant alteration in stool form: IBS with constipation (IBS-C), IBS with diarrhea, mixed IBS, and UN sub typed IBS [8]. IBS-C patients, accounting for up to one-third of IBS patients, complain of various symptoms including abdominal pain or discomfort, reduced stool frequency, bloating, hard stools, sensation of incomplete evacuation, and straining [9,10]. Medications targeted to treat IBS-C are often associated with patient dissatisfaction [11]. Lubiprostone is a recent medication that has been shown to improve global symptoms of IBS-C [12]. In September 2012, the FDA approved linaclotide for treatment of IBS-C. Linaclotide, a minimally absorbed peptide, binds to the intestinal epithelium, activating cystic fibrosis transmembrane conductance regulator through guanylate cyclase C (cGMP), and resulting in secretion of chloride and bicarbonate into the intestinal lumen [13,14]. Subsequently, increased luminal fluid secretion and an acceleration of intestinal transit occur [14]. In animal models, accelerated gastrointestinal transit and reduced visceral nociception were noticed with linaclotide treatment [14,15]. cGMP also reduced the firing of afferent pain fibers when applied to the colonic mucosa isolated from mice with visceral hypersensitivity [16]. In humans, linaclotide accelerated colonic transit and improved abdominal pain

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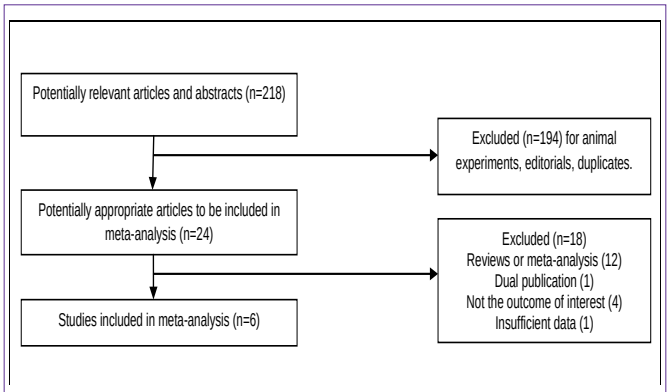


Figure 1: Identification of eligible randomized controlled trials.

and constipation associated with IBS-C [17-19].The aim of this study is to perform a meta-analysis of existing clinical trials to estimate the efficacy and safety of different daily doses of oral linaclotide in the management of IBS-C and chronic constipation.

Methods and Materials

Literature search

We searched the electronic literature from MEDLINE/Pub Med, Scopus, CINAHL, Meta Register of Controlled Trials, Database of Abstracts of Reviews of Effects (DARE), and Cochrane databases in May 2014 using the key terms *linaclotide, irritable bowel syndrome*, and *constipation*. Moreover, we conducted manual searches of reference lists from relevant papers to identify any additional articles. Additionally, all abstracts from the Digestive Disease Week (DDW) and American College of Gastroenterology (ACG) national meetings were reviewed for potentially relevant abstracts from 2003-2014. We searched all relevant articles irrespective of results or document type. We conducted reference searches in Scopus for all selected articles to identify any newer citing articles. Trials in non-English language and trials in animals were excluded.

Study design

Three investigators (DA, ME and MLB) independently reviewed the titles and abstracts of all citations identified by literature search. All randomized placebo-controlled clinical trials of linaclotide in treatment of IBS-C and chronic constipation was selected. The inclusion criteria were: (1) Studies that examine the effect of linaclotide on symptoms of IBS-C and chronic constipation, (2) studies that were prospective, randomized and placebo controlled published in peer-reviewed journals, and (3) studies in humans. Review articles, retrospective analyses and case reports were excluded.

Data extraction

Two of the authors (DA, ME) extracted data from eligible studies independently using a common data extraction form with any disagreements in the data resolved by a third party (MLB). Articles were selected if they met the inclusion criteria mentioned above.

Assessment of outcomes

The primary outcome assessed was the efficacy of linaclotide therapy in IBS-C and chronic constipation in regards to the effect on the mean number of stools per week while on treatment. The

Table 1: Characteristics of studies included in the meta-analysis. *RCT*, randomized controlled trials.

Author and year	Location	Type	No. Patients	Sex (M/F)	Mean age	Duration	Linaclotide dose	Jadad Score
[22]	U.S.	RCT	42	5/37	41.6-48.2	2 weeks	linaclotide 100 mcg daily	
							linaclotide 300 mcg mg daily	
							linaclotide 1000 mcg daily	
[18]							linaclotide 75 mcg daily	
	U.S.	RCT	419	33/386	44.4	12 weeks	linaclotide 150 mcg daily	
							linaclotide 300 mcg daily	
							linaclotide 600 mcg daily	
[23]							linaclotide 75 mcg daily	
	U.S.	RCT	307	25/282	47.3	4 weeks	linaclotide 150 mcg daily	
							linaclotide 300 mcg daily	
							linaclotide 600 mcg daily	
[24]	U.S.	RCT	1272	141/1131	47-49	12 weeks	Linaclotide 145 mcg daily	
	Canada						Linaclotide 290 mcg daily	
[25]	U.S.	RCT	800	76/724	43.3-43.7	12 weeks	Linaclotide 290 mcg daily	
	Canada							
[26]	U.S.	RCT	804	84/720	44.0-44.6	26 weeks	Linaclotide 290 mcg daily	

Table 2: Quality assessment of studies included in this meta-analysis using the Jadad score.

STUDY	STUDY DESIGN	METHOD OF RANDOMIZATION	DOUBLE-BLIND	METHOD OF DOUBLE-BLINDING	DESCRIPTION OF WITHDRAWALS	TOTAL SCORE*
[22]	1	1	1	1	1	5
[18]	1	1	1	1	1	5
[23]	1	1	1	1	1	5
[24]	1	1	1	1	1	5
[25]	1	1	1	1	1	5
[26]	1	1	1	v1	1	5

* Jadad Score: 1-5, 5 is excellent and 1 is poor.

secondary outcome included the frequency of adverse events. Subgroup analysis was also performed by dividing the studies into a high-dose group (290-300 mcg daily) and low-dose group (145-150 mcg daily).

Assessment of study quality

The quality of the studies was assessed using the Jadad scale [20]. Briefly, this scoring scale evaluates each trial according to the quality of the scientific description of the randomization method. The quality scale ranges from 0 to 5 points. Studies with a score of 2 or less were considered as poor quality studies and the ones with a score of 3 or higher were considered high quality studies [20].

Statistical analysis

A meta-analysis was performed comparing linaclotide to placebo for treatment of IBS-C and chronic constipation by calculating pooled estimates of the primary outcome of mean number of stools per week in high- and low-dose groups, and secondary outcome of frequency of adverse events using Odds Ratio (OR) with Mantel-Haenszel (fixed effect) and DerSimonian and Laird (random effects) models. Random effects model was used if statistically significant heterogeneity was noted. Statistical significance was observed if $p < 0.05$ or range in the confidence interval did not include 1. Publication bias was assessed by funnel plots. Heterogeneity among studies was assessed by calculating the I^2 measure of inconsistency, which was considered significant if $P < 0.10$ or $I^2 > 50\%$. %. If heterogeneity was statistically significant, a sensitivity analysis was performed to examine for heterogeneity when certain studies were excluded from the analysis. RevMan 5.2 (Review Manager [Computer program]. Version5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) was utilized for statistical analysis. Publication bias was assessed by funnel plots.

Results

Our initial search identified 218 articles and abstracts. Of the 218 citations identified, we excluded 194 after screening the titles and abstracts, leaving 24 articles for full-text review. Of the 24 articles selected for full review, eighteen were excluded for being systematic review articles, dual publications [21], or not having the outcome of interest. Six articles (n=3,654) ultimately met the inclusion criteria and were included in the meta-analysis [18,22-26] (Figure 1).

The six RCTs included in the meta-analysis were performed in the United States with two RCTs including patients from Canada as well [24,25]. They were published between 2009 and 2012 in English. Of the six studies, five investigated the primary outcome of having three or more Complete Spontaneous Bowel Movement (CSBM) per week and an increase of at least one CSBM per week from baseline [18,23-26], and all studies investigated the secondary outcome of frequency of adverse events. The adverse events that were identified are as follows: Diarrhea, allergic reaction, abdominal pain, abdominal distension, dyspepsia, flatulence, nausea, vomiting, proctalgia, urinary tract infection, nasopharyngitis, sinusitis, headache, and upper respiratory infection. Of the adverse effects, diarrhea was the most common. All of the studies were included in high-dose subgroup analysis, while three trials were included in the low-dose subgroup analysis [18,23,24]. Basic characteristics of the included studies are

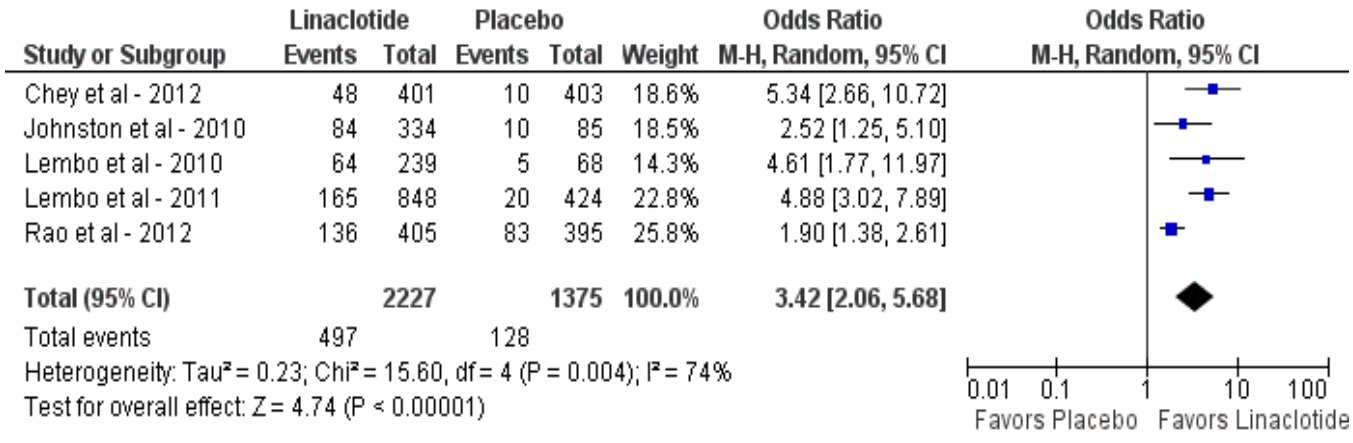


Figure 2: Forest plot demonstrating overall CSBMs for linaclotide compared to placebo.

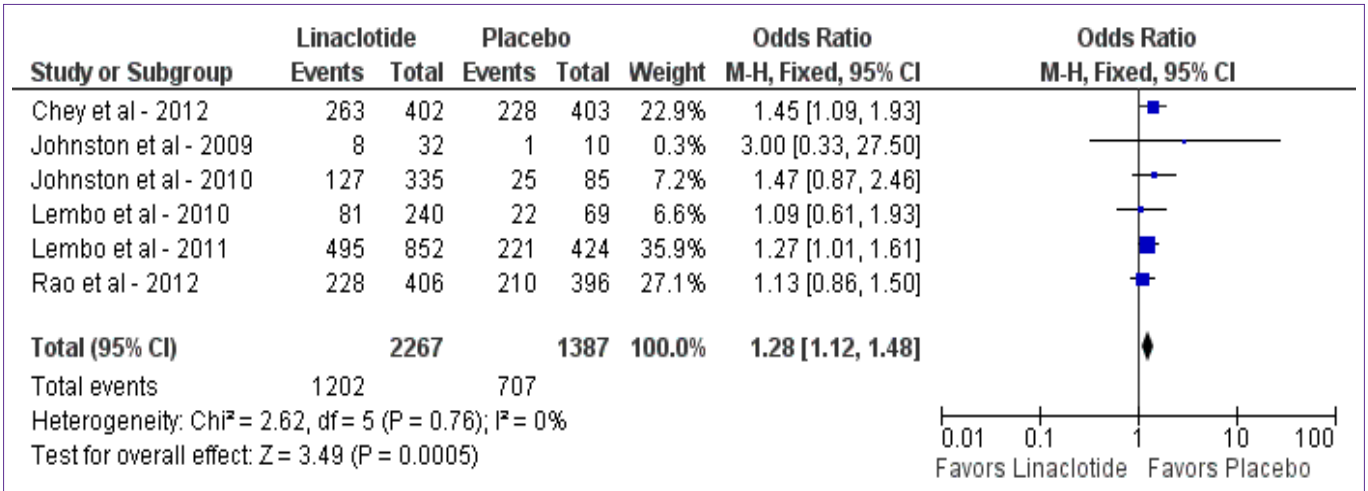
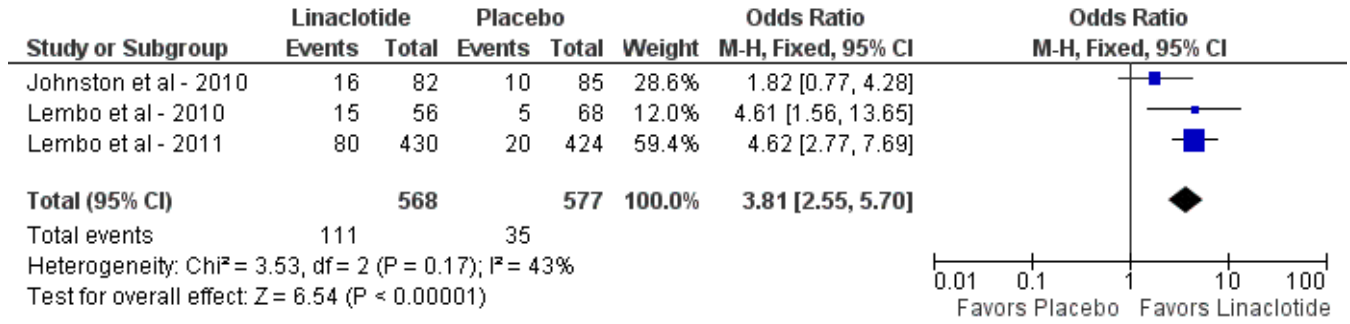
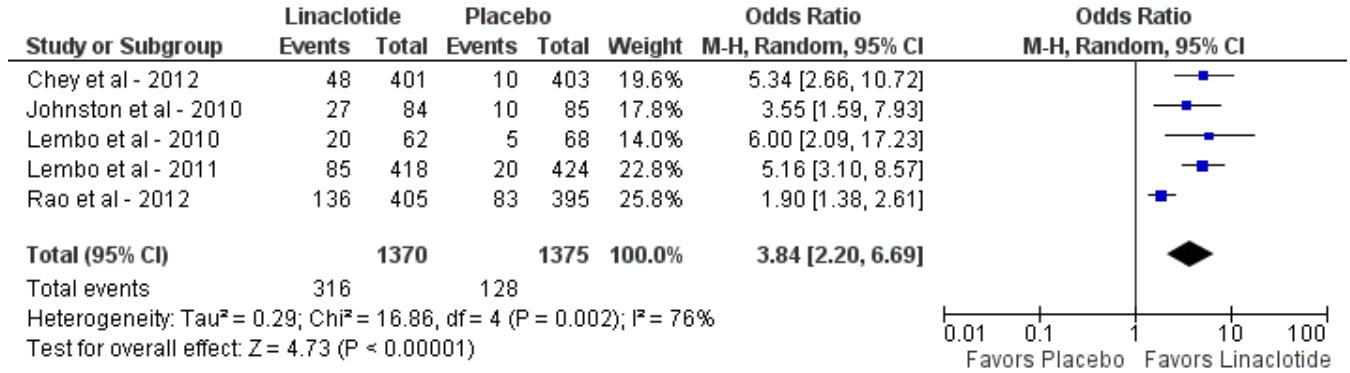


Figure 3: Forest plot demonstrating overall adverse effects for linaclotide compared to placebo.



a).



b).

Figure 4: Forest plot demonstrating CSBMs for linaclotide compared to placebo at 145-150 mcg daily (a) and 290-300 mcg daily (b).

shown in Table 1. All studies were of excellent quality based upon Jadad scores of five. Details of quality assessment are demonstrated in Table 2.

For the primary outcome of CSBM, linaclotide demonstrated a statistically significant improvement as compared to placebo (OR 3.42; 95% CI: 2.06-5.68; p<0.01). The mean percentage of patients who reached the primary endpoint was 9% in the placebo group (128 of 1,375) and 22% in the linaclotide group (497 of 2,227) (figure 2). Statistically significant heterogeneity was observed (I^2=74%, p<0.01). Upon sensitivity analysis when one study was removed [25], no heterogeneity was observed with similar results (OR 4.30; 95% CI: 3.11-5.94, p<0.01; I^2=0%, p=0.41). The pooled number of patients' needed-to-treat (NNT) with linaclotide to reach the primary end point was 8. For the secondary outcome, linaclotide showed a statistically significant increase in adverse events as compared to placebo (OR 1.28; 95% CI: 1.12-1.48; p<0.01) (figure 3).

Upon subgroup analysis, linaclotide of 145-150 mcg and 290-300 mcg daily demonstrated statistically significant improvements in CSBM (OR 3.81; 95% CI: 2.55-5.70; p<0.01; I^2=43%, p=0.17 and OR 3.84; 95% CI: 2.20-6.69; p<0.01; I^2=76%, p<0.01, respectively)

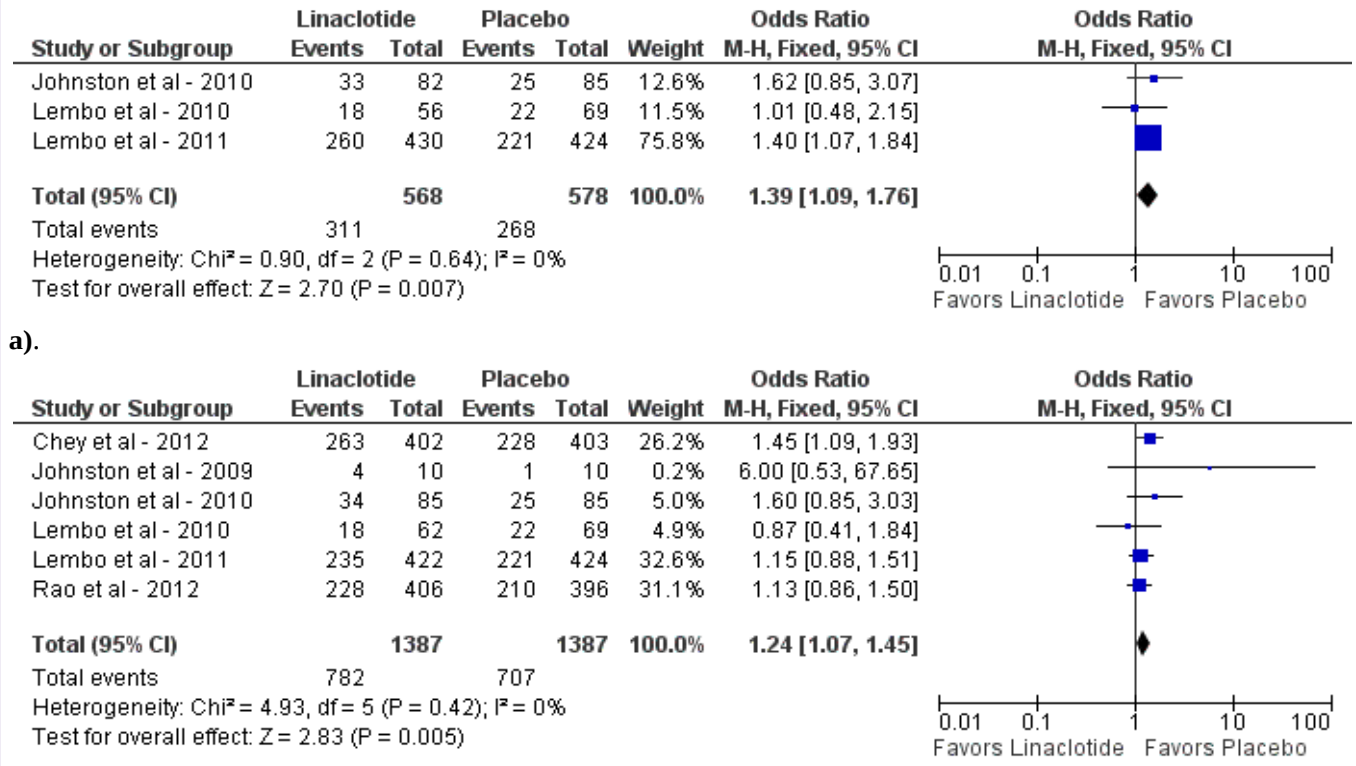


Figure 5: Forest plot demonstrating adverse effects for linaclotide compared to placebo at 145-150 mcg daily (a) and 290-300 mcg daily (b).

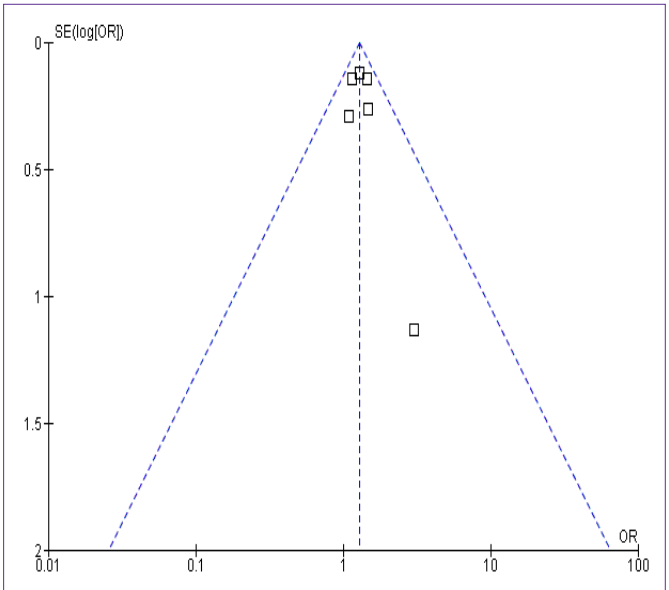


Figure 6: Funnel plot showing no publication bias.

as compared to placebo (figure 4a and b). Sensitivity analysis for 290-300 mcg daily dose for CSBM revealed similar findings after elimination of one study [25] (OR 4.93; 95% CI: 3.49-6.97; p<0.01; I^2=0%, p=0.84). However, linaclotide of 145-150 mcg and 290-300 mcg daily revealed a statistically significant increase in adverse events (OR 1.39; 95% CI: 1.09-1.76; p<0.01 and OR 1.24; 95% CI: 1.07-1.45; p<0.01, respectively) as compared to placebo. (figure 5a and b).

No publication bias was noted for all outcomes (figure 6).

Discussion

As the diagnoses of irritable bowel syndrome and chronic constipation rises, we continue to have difficulty with effective treatment and limited treatment options. Despite two previous medications being approved by the FDA for treatment of IBS-C, tegaserod and lubiprostone [12], tegaserod was removed from the market in 2007 for significant cardiovascular events [12,24], leaving patients with only one approved treatment option. In September 2012, the FDA approved linaclotide for treatment of IBS-C, essentially doubling our treatment options. Over the past six years, six studies have evaluated the use of linaclotide in this population which utilized varying doses and demonstrated varied results [18,22-26].

Our meta-analysis of these six studies demonstrated that linactolide had a statistically significant improvement in the primary outcome as compared to placebo. It also established that there was a statistically significant difference in adverse outcomes with linactolide over placebo. Both current dosing strategies of linaclotide 145-150 mcg and 290-300 mcg daily had improvements in primary outcomes as well as increased adverse effects. Although there is an increase incidence of adverse effects with treatment of linactolide, regardless of dosage, it does seem to provide benefit for patients with IBS-C, especially in the face of limited options.

The strengths of our meta-analysis are numerous. A comprehensive search was performed, allowing for the maximum number of relevant studies to be involved in the meta-analysis. All

studies used in the meta-analysis were randomized controlled trials maximizing the relevancy of the studies. Five out of the six studies reached the primary endpoint, maximizing the significance of the study. Also, no publication bias noted. However, some limitations of this meta-analysis are present. Most studies did not include other commonly used treatments for IBS-C, only placebo, so comparisons to other current options are not available such as lubiprostone, currently the only other FDA-approved medication. Of the six studies done, a total of 31% of patients reached the primary end-point, leading to a smaller number of patients maximized in the studies. Third, upon reviewing authors, most studies were conducted by the same group. This may introduce bias given lack of outside trials. However, given the limited trials on this subject, all the RCTs were included in the meta-analysis. Fourth, the RCTs varied in time for which patients were followed, ranging from two weeks to 26 weeks. Fifth, doses in the RCTs varied slightly. To minimize its affect, our subgroup analysis pooled ranges, 145-150 mcg and 290-300 mcg. Finally, in Lembo et al, two parallel trials were presented with similar design and presented in one manuscript. For simplicity, the two trials data were combined into one.

Conclusion

Linactolide use results in significant improvement in complete spontaneous bowel movements per week when compared to placebo. Although there is increase in adverse events with use of linactolide, it seems reasonable to consider it an effective treatment for IBS-C especially in the setting of minimal effective treatments available for patients. In the future there needs to be further research into dosing effectiveness as well as RCT comparing linactolide and lubiprostone.

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