REVIEW

Linaclotide: A New Option for the Treatment of Irritable Bowel Syndrome with Constipation and Chronic Idiopathic Constipation in Adults

Colleen H. Parker[1], Yuhong Yuan[2] and Louis Wing Cheong Liu[1]

[1]Department of Medicine, University of Toronto, Toronto, Ontario, Canada. [2]Department of Medicine, McMaster University, Hamilton, Ontario, Canada. Corresponding author email: louis.liu@uhn.ca

Abstract: Chronic idiopathic constipation (CC) and irritable bowel syndrome with predominant constipation (IBS-C) are the 2 most common conditions among functional gastrointestinal disorders. Despite current multiple therapeutic options, treatment remains challenging and dissatisfactory to many patients. Linaclotide is a novel therapeutic agent, which is a guanylate cyclase receptor agonist that stimulates water secretion from the intestinal epithelium by promoting chloride and bicarbonate efflux into the lumen through activation of the cystic fibrosis transmembrane conductance regulator. Clinical trials have demonstrated that linaclotide is effective, safe and well tolerated in patients with CC and IBS-C. This review article highlights the mechanism of action of linaclotide, reviews published literature based on a search of databases, including MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL), up to February 2013, and compares its utility with other currently available agents.

Keywords: constipation, irritable bowel syndrome, linaclotide, clinical trial, mechanism of action

This article is available from http://www.la-press.com.

Introduction

Chronic idiopathic constipation (CC) and irritable bowel syndrome with predominant constipation (IBS-C) are common conditions in North America and are often difficult to effectively treat. The prevalence of CC has been estimated to be approximately 14%, with higher rates in females, older patients and in patients of lower socioeconomic status.[1] The prevalence of IBS is approximately 11% with IBS-C comprising 22% to 35% of these individuals.[2] In addition, IBS is the most common functional gastrointestinal disorder worldwide.[3] These conditions have a negative impact on quality of life and a high resource demand on health care systems.[1,4]

Based on the Rome III diagnostic criteria, the presence of abdominal pain and discomfort and their association with the bowel movement is the defining feature that distinguishes IBS-C from CC. Current treatment options for the management of constipation, including diet and lifestyle modification, the use of fiber, laxatives, and more recently, the serotonin receptor agonist prucalopride and the chloride channel activator lubiprostone, do not directly ameliorate abdominal pain.[5,6] Antispasmodics, tricyclic anti-depressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have been shown to reduce abdominal pain and improve global IBS symptoms.[7] However, the anti-cholinergic property of these drugs can worsen constipation. Despite multiple treatment options, CC and IBS-C remain difficult to manage in some patients. A single agent that improves abdominal pain and discomfort as well as constipation in patients with IBS-C is not available. This remains an unmet need in the treatment of IBS-C.

Linaclotide is a guanylate cyclase C (GC-C) receptor agonist that acts locally in the gastrointestinal tract as a secretagogue. It has been found to improve colonic transit times and complete spontaneous bowel movements in patients with CC and IBS-C. In addition, it has also been shown to improve functional abdominal symptoms, such as pain, discomfort and bloating, which are major symptomatic complaints of patients with CC and IBS-C. Linaclotide represents a novel therapeutic modality for managing patients with these conditions, which are often difficult to treat. This review article highlights the molecular mechanisms, efficacy, and safety of linaclotide in the treatment of patients with CC and IBS-C.

Mechanism of Action

Linaclotide is a GC-C receptor agonist that shares its mechanism of action with the endogenous molecules guanylin and uroguanylin, and with bacterial heat stable enterotoxins. Guanylin and uroguanylin, produced by enterocytes in the duodenum and colon, are responsible for the regulation of water and electrolyte secretion in the gastrointestinal tract by binding GC-C on the luminal surface of epithelial cells. This activates the cyclic 3',5'-monophosphate (cGMP) signaling pathway,[8] which in turn activates the cGMP-dependent protein kinase II (PKG II).[9,10] PKG II activates the cystic fibrosis transmembrane conductance regulator (CFTR) that increases chloride and bicarbonate secretion from the epithelial cell[10] (Fig. 1). This subsequently promotes sodium excretion and water diffusion from the cell into the intestinal lumen, thus decreasing colonic transit time.[10] Heat stable enterotoxins produced by *Escherichia coli* act on the same pathway to cause diarrhea in an infected host.[11] In an in vitro study, linaclotide was found to inhibit the ability of bacterial heat stable enterotoxin to bind to GC-C, confirming that GC-C is the molecular target of linaclotide.[12]

Linaclotide has also been shown to exhibit antinociceptive properties. This is an additional benefit in the treatment of IBS-C where visceral hyperalgesia is a major component of the pathophysiology of the condition. In 2 rodent models of non-inflammatory visceral pain (the acute partial restraint stress-induced colonic hypersensitivity model[13] and the acute water avoidance stress model[13]), linaclotide significantly decreases colonic hypersensitivity as measured by a decrease in the number of colonic contractions detected by EMG in response to colorectal distension. A similar response was demonstrated in the trinitrobenzene sulfonic acid (TNBS) induced inflammatory rodent model of visceral hyperalgesia.[13] Using this model in wild type compared to GC-C receptor null mice, it was shown that linaclotide reduced colonic hypersensitivity in the wild type mice alone. This suggests that the antinociceptive property of linaclotide is mediated through the activation of the GC-C receptor.[13] Although the exact molecular mechanism of linaclotide's antinociceptive property has yet to be fully described, initial in vitro data suggest that extracellular cGMP (as produced through activation of GC-C) is able to reduce the sensitivity of colonic nociceptors to mechanical stimuli[10,14,15] (Fig. 1).
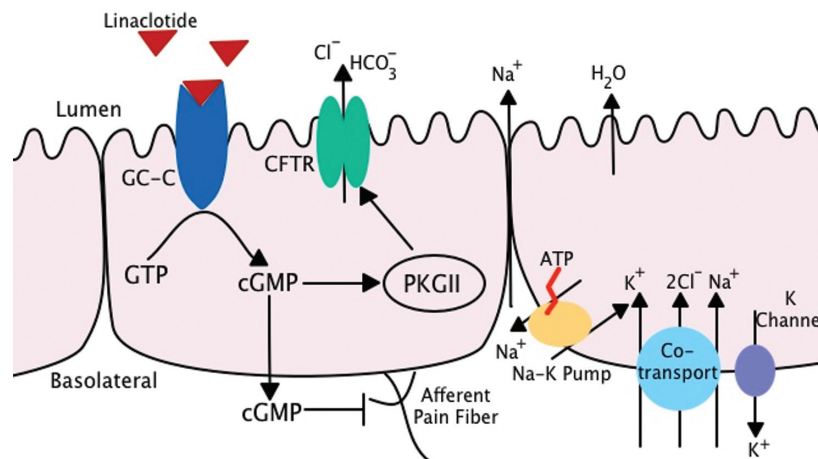
Figure 1. Mechanism of Action of Linaclotide. Linaclotide binds to the guanylate cyclase C (GC-C) receptor on the luminal side of intestinal epithelial cells, causing activation of the intracellular cyclic 3',5'-monophosphate (cGMP) pathway.[8] Subsequently, the cGMP-dependent protein kinase II (PKG II) is activated which phosphorylates and activates the cystic fibrosis transmembrane conductance regulator (CFTR).[9,10] This leads to chloride (Cl⁻) and bicarbonate (HCO_3^-) secretion from the cell, promoting excretion of sodium (Na⁺) from the basolateral cell membrane through tight junctions into the lumen and diffusion of water (H_2O) out of cells.[10,42] Furthermore, the activation of GC-C and production of cGMP appear to modulate the sensitivity of nociceptors to mechanical stimuli. The exact molecular mechanism of this anti-nociceptive effect of linaclotide has yet to be elucidated. Initial in vitro studies suggest it is an effect of extracellular cGMP on nociceptors found on colonic afferent pain fibers.[10,14,15]
Abbreviations: ATP, adenosine triphosphate; K⁺, potassium.

Pharmacodynamics and Pharmacokinetics

Linaclotide binds to GC-C with high affinity in a pH-independent manner (K_i: 1.23–1.64 nM).[16] Linaclotide increases water secretion in surgically ligated rodent small intestine, particularly in the duodenum and jejunum.[16] In vitro studies demonstrated that the increase in cGMP stimulated by linaclotide occurred in a concentration dependent manner. The concentration of linaclotide to produce 50% of the maximal effect (EC_{50}) was 8 to 10 fold more potent than either guanylin or uroguanylin with an EC_{50} of 99 nM.[16]

Linaclotide is a 14 amino acid peptide that is homologous in structure to the bacterial heat stable enterotoxins. It contains 3 disulfide bonds that stabilize its molecular structure to resist degradation and enhance its ability to bind to the GC-C receptors.[17] Linaclotide acts locally within the intestine. In rodent studies, it has been shown that linaclotide is only minimally absorbed through the gastrointestinal tract with an oral bioavailability of only 0.1%.[16] In a clinical trial, the serum levels of linaclotide and its metabolite in patients who had received the drug were negligible.[18]

In the intestinal lumen, linaclotide is modified by carboxypeptidase A that removes the carboxy terminal tyrosine residue to produce a 13 amino acid biologically active peptide with an increased protease resistance.[19] The half-life of the parent peptide is approximately 3 minutes while the half-life of the active metabolite is approximately 10 minutes within the intestine.[17] Reduction of the 3 disulfide bonds by the glutathione reductase system within the intestinal lumen is required for proteolytic degradation of linaclotide and its metabolite. These amino acids are absorbed by the intestinal epithelium.[19]

Clinical Studies and Efficacy
Search strategy

A comprehensive literature search was conducted to identify all published human clinical studies. Abstract data were excluded and only completed studies that underwent the full, rigorous peer-review process were included. Databases were searched, including MEDLINE, and EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL), up to February 2013. Search terms, both free text and medical subject headings (MeSH), included "linaclotide" or "Linzess" or "guanylate cyclase" combined with "constipation" or "irritable bowel symptom" or "IBS" or "irritable colon". Variations of the root word were also searched alone or in combination. A recursive search of the bibliographies of all relevant papers was also conducted. No restrictions were placed on the language of publication when searching the electronic databases.

Chronic idiopathic constipation

A 2-week phase IIa study, which randomly assigned 42 patients with CC (defined as less than three spontaneous bowel movements (SBMs) per week and at least one of: hard stools, straining or incomplete elimination) to linaclotide 100, 300 or 1000 μg versus placebo, demonstrated an improvement in CC symptoms.[20] For 7 days prior to treatment, during treatment, and for 8 days after treatment, patients reported on bowel habits such as frequency, consistency, straining, sensation of incomplete elimination and abdominal discomfort. It was shown that linaclotide 100 μg significantly increased bowel movement frequency ($p = 0.047$), and linaclotide 1000 μg significantly improved stool consistency ($p = 0.014$; Table 1). Though not statistically significant, there was a trend that demonstrated improvement in abdominal discomfort, severity of constipation and subjective constipation symptoms.

In another randomized double-blind phase IIa study, 310 patients with CC were treated with 75, 150, 300 or 600 μg of linaclotide or placebo for 4 weeks.[21] The primary endpoint was an improvement in the weekly SBM rate. There was a significant increase in the weekly number of SBMs from baseline at all doses of linaclotide compared to placebo (Table 1). This study also demonstrated that linaclotide significantly improved bloating, abdominal discomfort, global measurements of constipation, treatment satisfaction, and quality of life (PAC-QOL) compared to placebo.

Two phase III double-blind, randomized, placebo controlled trials (RCTs) (trials 303 and 01) were performed to evaluate the efficacy and safety of 145 μg and 290 μg of linaclotide daily over a 12 week period in a total of 1276 patients with CC.[22] In trial 303 (n = 642), 433 patients who received linaclotide were subsequently randomized to an additional 4 weeks with either the same dose of linaclotide or placebo, and those patients who received placebo (n = 209) were subsequently treated with 290 μg of linaclotide. In trials 303 and 01, patients who received 145 μg and 290 μg of linaclotide were more likely to achieve the primary endpoint (3 or more complete spontaneous bowel movements (CSBMs) per week and an increase of at least one CSBM for 9 of the 12 weeks treatment period) as compared with placebo ($p < 0.001$ for all treatment groups versus placebo, Table 1). The differences in treatment response between the 2 linaclotide groups were not significant (trial 303, $p = 0.63$; trial 01, $p = 0.19$). Secondary endpoints, including stool consistency, straining, abdominal discomfort, bloating, severity of constipation, relief of constipation, satisfaction with the treatment and continuation of the treatment, demonstrated statistically significant improvement in both trials at both doses compared to placebo.

Irritable bowel syndrome with predominant constipation

A randomized, double-blind phase IIa clinical trial involving 36 females with IBS-C, based on Rome II criteria, demonstrated that 1000 μg of linaclotide significantly accelerated ascending colonic transit time and, subsequently, had the ability to alter bowel function.[23] Patients were randomized to receive either 100 μg or 1000 μg of linaclotide or placebo for 5 days. The primary endpoint was the effect of linaclotide on gastrointestinal transit time as measured using a scintographic method involving a radiolabeled meal and hourly abdominal scans. Study subjects also self-reported bowel movement frequency, stool consistency using the Bristol Stool Form Scale (BSFS), ease of stool passage, and the ability to completely evacuate stool. Linaclotide 1000 μg significantly accelerated ascending colonic transit time compared to placebo (7.79 ± 1.74 hours (h) versus (vs) 19.96 ± 2.03 h, $p = 0.004$) and decreased the overall colonic transit time assessed by geometric center at 48 hours (4.0 ± 0.21 vs 2.9 ± 0.27, $p = 0.01$). A significant difference, however, was not seen in the colonic transit at 24 hours of treatment (Table 2). It was also shown that there were significant differences with both doses of linaclotide compared to placebo in terms of stool frequency ($p = 0.037$), stool consistency ($p < 0.001$), ability to pass stool ($p < 0.001$), and time to first bowel movement ($p = 0.013$).

In a subsequent phase IIb study, 420 patients with IBS-C were randomized to receive 75 μg, 150 μg, 300 μg or 600 μg of linaclotide or placebo over 12 weeks[24]. There was a significant improvement in the primary endpoint, change in the number of weekly CSBMs compared to baseline, at all doses of linaclotide compared to placebo (Table 2, $p < 0.01$ for all doses). This study further demonstrated that all test doses of linaclotide improved stool consistency

Table 1. Summary of clinical studies of linaclotide in the treatment of chronic constipation.

Authors	Study design	Country, study period	Diagnostic criteria	Treatment, sample size	Primary endpoints	Secondary endpoints	Efficacy (primary endpoints)	Adverse events (AE)
Lembo 2011	Pooled data from two phase III double blind RCT (Trial 303 and Trial 01). 2 weeks baseline, 12 weeks treatment. Trial 303 included a 4-week period of randomized withdrawal (RW) at the conclusion of the 12-week treatment period	204 centers in the United States and 8 in Canada, August 2008–August 2009	Modified Rome II and an average ≤6 SBMs per week and ≤3 CSBMs per week during the 14-day baseline period	Linaclotide 145 µg (n = 217 + 213) or 290 µg (n = 216 202) vs placebo (n = 209 + 215) od	≥3 CSBMs/week and an increase of ≥1 CSBMs/week from baseline during at least 9 of the 12 weeks	Stool frequency, stool consistency, severity of straining, abdominal discomfort, bloating, and constipation severity. Constipation relief, satisfaction with treatment, the likelihood of treatment continuation, and health-related quality of life.	Trials 303 and 01: linaclotide 145 µg—21.2% and 16.0%; linaclotide 290 µg—19.4% and 21.3%; placebo—3.3% and 6.0% (P < 0.01)	Linaclotide 145, 290 µg vs placebo: any AE (n = 1276), 60.5%, 55.7%, vs 52.1%; Discontinued treatment due to AE, 7.9%, 7.3% vs 4.2%. Discontinuation due to diarrhea, 4.7%, 3.8% vs 0.5%; SAE, 1.4%, 2.6% vs 2.1%.
Lembo 2010	Phase IIb dose-range double-blind RCT. 2 weeks baseline, 4 weeks treatment	57 centers in the United States, November 2006–December 2007	Modified Rome II	Linaclotide 75 µg (n = 59), 150 µg (n = 56), 300 µg (n = 62), and 600 µg (n = 62) vs placebo (n = 68), od	Change in mean weekly SBM frequency from the 14-day pre-treatment baseline period to the 4-week treatment period	Daily assessments of other bowel habits (CSBM frequency, stool consistency, straining) and abdominal symptoms (discomfort and bloating), global assessments (constipation severity, adequate and global relief of constipation, treatment satisfaction), and the Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaire.	Increases in weekly SBMs from baseline were 2.6, 3.3, 3.6, and 4.3 for linaclotide 75, 150, 300, and 600 µg, respectively, vs 1.5 for placebo (P ≤ 0.05)	Any AE (n = 309): linaclotide 33.8% (81/240: 21/59, 18/56, 18/62, and 24/63 in 75 µg, 150 µg, 300 µg and 600 µg, respectively) vs placebo 31.9% (22/69). Patients discontinued treatment due to AE: 2.9% in linaclotide vs 2.9% in placebo. SAE: 2 patients all in placebo group (fracture, pneumonia and atrial fibrillation).

(Continued)

Table 1. (*Continued*)

Authors	Study design	Country, study period	Diagnostic criteria	Treatment, sample size	Primary endpoints	Secondary endpoints	Efficacy (primary endpoints)	Adverse events (AE)
Johnston 2009	Phase IIa Double-blind RCT 7 days baseline, 14 day treatment.	14 centers in the United States, March 2006–August 2006	Modified Rome II	Linaclotide 100 µg (n = 12), 300 µg (n = 10), or 1,000 µg (n = 10) od vs placebo (n = 10) for 2 weeks	Daily bowel habits: stool frequency, consistency, straining, and completeness of evacuation	Subjective patient-reported outcomes: abdominal discomfort, severity of constipation and overall relief were evaluated weekly.	All doses of linaclotide produced a numerically greater improvement over the baseline in SBM frequency, CSBM, stool consistency, and straining vs placebo. Significant differences were seen in linaclotide 100 µg vs placebo for change of SMBs and linaclotide 1000 µg vs placebo for stool consistency (p < 0.05).	Total AE = 13/42, all mild or moderate. GI adverse event: Linaclotide 25% (8/32; 3/12, 4/10 and 1/10 in 100 µg, 300µg and 1000µg, respectively), vs placebo 10% (1/10). Patients discontinued treatment due to AE: 2 in linaclotide 100 µg (rash, diarrhea). GI AEs linaclotide 19.6% vs placebo 13.0%. No SAE.

Modified Rome II criteria: <3 SBMs per week and ≥1 of the symptoms during >25% of bowel movements for ≥12 weeks in the preceding 12 months: straining, hard or lumpy stools, and a sense of incomplete evacuation.

Abbreviations: AE, adverse events; CSBM, complete spontaneous bowel movement; SAEs, serious adverse events; SBM, spontaneous bowel movement; p value, placebo compared with linaclotide groups.

($p < 0.001$), need to strain ($p < 0.001$) and abdominal pain within the first week of treatment ($p < 0.05$) compared to placebo. Furthermore, within the first week, there was an improvement in abdominal discomfort (at doses 150 µg and above), and bloating (at all doses except 150 µg). This study also demonstrated significant improvement at all doses of linaclotide in IBS and constipation severity, and in relief of IBS symptoms.

Two phase III RCTs have been published demonstrating that linaclotide improves abdominal pain and bowel function in patients with IBS-C. Rao et al randomized 800 patients to receive either 290 µg of linaclotide daily or placebo for 12 weeks.[25] This was followed by a randomized withdrawal period where patients who received linaclotide were again randomized to treatment or placebo and those who received placebo to 290 µg of linaclotide for 4 weeks. The primary endpoints were: 1) improvement by more than 30% in abdominal pain scores (referred to as abdominal pain) and an increase of at least 1 CSBM per week above baseline for at least 6 of 12 weeks of treatment (the FDA recommended endpoint for IBS-C trials); 2) at least a 30% improvement in abdominal pain for 9 of 12 weeks of treatment; 3) having at least 3 CSBMs per week with an improvement of 1 or more above baseline for at least 9 of 12 weeks; 4) and a combination of the last 2 endpoints. The number needed to treat (NNT) to achieve the FDA recommended endpoint was 8 (Table 2; 33.6% in the linaclotide group, 21% in placebo, $p < 0.0001$). Linaclotide significantly improved abdominal pain (NNT = 13.8, $p = 0.0262$), and increased the number of subjects who achieved at least 3 CSBMs per week with an improvement of 1 or more above baseline for at least 9 of 12 weeks (NNT = 7.6, $p < 0.0001$) and the combined endpoint (NNT 14.2, $p = 0.0004$) compared to the placebo group. Linaclotide was found to be superior to placebo in all of the secondary endpoints, including an improvement in abdominal pain, abdominal discomfort, bloating, stool frequency and consistency, the need to strain, cramping, fullness, severity of IBS symptoms and constipation, the degree and adequacy of relief from IBS symptoms and patient satisfaction ($p < 0.0001$). It also illustrated that those who remained on linaclotide during the withdrawal period continued to demonstrate benefit from treatment, while those that were randomized to receive placebo during the same time period had a return of IBS-C symptoms.

Another phase III RC randomized 804 patients to receive 290 µg of linaclotide or placebo daily for a 26-week treatment period.[18] This study had the same primary and secondary endpoints as the trial outlined above by Rao et al.[25] It was found that 33.7% of treated patients achieved the FDA recommended endpoint compared to 13.9% in the placebo treated group ($p < 0.0001$) with a NNT of 5.1 (Table 2). Abdominal pain improved in 38.9% of treated patients in 20 of 26 weeks compared to 19.6% in the placebo group (NNT = 5.2, $p < 0.0001$). Three or more CSBMs with an improvement of 1 or more above baseline was achieved in 18.1% of treated patients for at least 20 of 26 weeks compared to 5.0% in the placebo group ($p < 0.0001$). The combined endpoint was found in 12.7% of treated patients versus 3.0% in the placebo-group ($p < 0.0001$). As in the previous study, linaclotide was superior to placebo in all of the secondary endpoints at 26 weeks ($p < 0.0001$). A pooled analysis of the 2 phase III IBS-C RCT trials,[18,25] which specially evaluated the European Medicines Agency (EMA) specified endpoints, demonstrated that linaclotide significantly improved abdominal pain/discomfort and the degree of relief in IBS symptoms compared with placebo over 12 and 26 weeks[26] (Table 2).

Tolerability and Safety

The most common adverse event reported in all clinical trials is the development of diarrhea (Tables 1 and 2). In all of the phase III clinical trials in patients with CC and IBS-C, there were no statistically significant differences seen for treatment emerging adverse events between the linaclotide group and the placebo, except in the Chey et al trial[18] in IBS-C patients (65.4% in linaclotide group vs 56.6% in the placebo group, $p < 0.05$). Subsequent post-hoc analyses combining the Rao and Chey trials did not show any significance.[26] The phase III trials in patients with CC showed that 16% of patients receiving linaclotide 145 µg and 14.2% of patients receiving linaclotide 290 µg developed diarrhea compared to 4.7% in the placebo control group.[22] In the IBS-C phase III trials, the incidence of diarrhea occurred in approximately 1-in-5 patients, with a number needed to harm (NNH) of 5.8–6.5.[25] Increase in flatulence (4.9% vs 1.5%, $p = 0.0084$), and abdominal pain (5.4% vs 2.5%, $p = 0.0462$) were also higher in the linaclotide treated group versus the placebo.[25] Patients required

Table 2. Summary of clinical studies of linaclotide in the treatment of irritable bowel syndrome with constipation.

Authors	Study design	Country, study period	Diagnostic criteria	Treatment, sample size	Primary endpoints	Secondary endpoints	Efficacy (primary endpoints)	Adverse events (AE)	Note
Quigley 2013	Pooled data of two Phase III double-blind RCTs (Trial 31, NCT00948818 and Trial 302, NCT00938717)	United States and Canada, multicentre, July 2009–September 2010	Modified Rome II criteria, mean daily abdominal pain score of ≥3.0 NRS during the previous 2 weeks	Trial 31: linaclotide 290 μg od (n = 405) vs placebo (n = 395) for 12 weeks; Trial 302: linaclotide 290 μg od (n = 401) vs placebo (n = 403) for 26 weeks	(i) 12-week abdominal pain/ discomfort responders: ≥30% reduction in mean abdominal pain and/or discomfort score, with neither worsening from baseline, for ≥6 weeks; (ii) 12-week IBS degree-of-relief responders: symptoms 'considerably' or 'completely' relieved for ≥6 weeks	(i) 26-week abdominal pain/discomfort responders and 26-week IBS degree-of-relief responders (responders for ≥13 out of 26 weeks treatment); (ii) the IBS-QoL and EQ-5D instruments; (iii) Other symptoms–stool frequency, stool consistency, severity of straining and abdominal bloating	(i) 12-week abdominal pain/discomfort responders: linaclotide vs placebo, Trial 31: 54.8% vs 41.8%; Trial 302: 54.1% vs 38.5%; P < 0.001 (ii) 12-week IBS degree-of-relief responders, Trial 31: 37.0% vs 18.5%; Trial 302: 39.4% vs 16.6%; P < 0.0001	Details reported in Rao 2012 and Chey 2012 (n = 1607). Linaclotide vs placebo: overall AE incidence: 56% vs 53%. Diarrhea: Trial 31: 19.5% vs 3.5%; Trial 302: 19.7% vs 2.5% (Discontinued treatment due to diarrhea 5.7% vs 0.3% and 4.5% vs 0.2%, respectively). SAEs: <2% in both groups (none related to diarrhea).	Based on data from Chey 2012, Rao 2012, but this pooled analysis reported EMA endpoints
Rao 2012	Phase III double-blind RCT	118 centers (111 in the United States, 7 in Canada) from July 2009–July 2010	Modified Rome II criteria, ≥12 weeks of the year with abdominal pain or abdominal discomfort that had ≥2 of 3 pre-defined features, and <3 SBMs per week, ≥1 additional bowel symptom, and NRS ≥ 3 for daily abdominal pain at its worst, with average <3 CSBMs per week and ≤5 SBMs per week during the 14 days before randomization	linaclotide 290 μg od (n = 405) vs placebo (n = 395) for 12 weeks; followed by a 4-week randomized withdrawal (RW) period	FDA end point responder: ≥30% improvement in average daily worst NRS and increase ≥1 CSBM from baseline in the same week for at least week 9 of the 12 weeks (i) ≥30% decrease in abdominal pain, (ii) ≥3 CSBMs and an increase of ≥1 CSBM from baseline, and (iii) combined responder: a patient who met criteria for both i and ii in the same week.	12-week change from baseline in abdominal pain, abdominal discomfort, abdominal bloating, stool frequency (CSBM and SBM weekly rates), stool consistency (BSFS), and severity of straining; abdominal pain and CSBM responders; 12-week change from baseline in abdominal fullness and abdominal cramping, IBS symptom severity, constipation severity, adequate relief of IBS-C symptoms, degree of relief of IBS symptoms, and treatment satisfaction. Adverse events were monitored	(i) FDA endpoint: linaclotide vs placebo: 33.6% vs 21.0%, OR 1.9 (1.4, 2.7), P < 0.0001, NNT 8.0 (5.4, 15.5); for at least 9/12 (ii) ≥30% decrease in worst abdominal pain 34.3% vs 27.1%, OR 1.4 (1.0, 1.9), P = 0.03, NNT 13.8 (7.4, 116.1); (iii) ≥3 CSBMs and an increase of ≥1 CSBM 19.5% vs 6.3%, OR 3.7 (2.3, 5.9), P < 0.0001, NNT 7.6 (5.6, 11.6); (iv) combined responder 12.1% vs 5.1%, OR 2.6 (1.5, 4.5), P=0.0004, NNT 14.2 (9.2, 31.3)	Linaclotide vs placebo (n = 802): Treatment-emergent AE: 56.2% (228/406) vs 53.0% (210/396); p = 0.39; Diarrhea 19.5% vs 3.5%; p < 0.0001; (discontinued treatment due to diarrhea: 5.7% vs 0.3%); Discontinued treatment due to AE: 5.7% vs 0.3%; SAE: 0.5% (1 asthma, 1 pericardial effusion and pericarditis) vs 0.5% (1 chronic cholecystitis, 1 duodenitis, gastroenteritis, hiatal hernia, esophagitis, renal cyst, and urinary tract infection)	Trial 31, NCT00948818
Chey 2012	Phase III double-blind RCT	102 centers in the United States, July 2009–September 2010	Modified Rome II criteria, ≥12 weeks of the year with abdominal pain or abdominal discomfort that had ≥2 of 3 pre-defined features, and <3 SBMs	linaclotide 290 μg od (n = 401) vs placebo (n = 403) for 26 weeks	Same as Rao 2012	Same as Rao 2012	(i) FDA endpoint: linaclotide vs placebo: 33.7% vs 13.9%, NNT 5.1 (3.9, 7.1) at weeks 1–12, 32.4% vs 13.2%, NNT 5.2 (4.0, 7.3) at weeks 1–26, for at least	Linaclotide vs placebo (n = 805): Treatment-emergent AE: 65.4% (263/03) vs 56.6% (228/402); p < 0.05; Diarrhea 19.7% vs 2.5%; p < 0.0001 (discontinued	Trial 302, NCT00938717

Study	Study design	Setting/date	Criteria	Intervention	Outcomes assessed	Results	Adverse events	Trial ID
			perweek, ≥1 additional bowel symptom, and NRS ≥3 for daily abdominal pain at its worst, with average <3 CSBMs per week and ≤5 SBMs per week			9/12, at weeks 1–26, (ii) ≥30% decrease in average daily worst abdominal pain 36.9% vs 17.4%; NNT 5.1 (3.9, 7.4); (iii) ≥3 CSBMs and an increase of ≥1 CSBM,15.7% vs 3.5%, NNT 8.2 (6.2, 12.1); (iv) combined responder 12.0% vs 2.5%, NNT 10.5 (7.7, 16.8), $P < 0.0001$ in all analysis	treatment due to diarrhea: 4.5% vs 0.2%); Discontinued treatment due to AE 10.2% vs 2.5%; SAE: 1.0% (rotator cuff syndrome, appendicitis, cystopexy, and Hodgkin's disease, 1 each) vs 1.7%. SAE: none.	NCT00460811
Johnston 2010	Phase IIb, double-blind RCT	92 centers in the United States and Canada, March 2007–February 2008	Rome II criteria, and <3 SBMs per week and ≥1 of the 3 pre-defined symptoms for ≥12 weeks in 12 months; a mean score ≥2.0 (in a 5 point scale) for daily assessment of nonmenstrual abdominal pain or abdominal discomfort, and a mean of <3 CSBMs and ≤6 SBMs per week in the previous 2 weeks of randomization	linaclotide 75 µg (n = 79), 150 µg (n = 82), 300 µg (n = 84) or 600 µg (n = 89) od vs placebo (n = 85) for 12 weeks	Increase in weekly CSBM during the 12-week treatment period from baseline "75% CSBM responder" (a patient for 75% of the treatment weeks, had a weekly CSBM ≥3 and an increase ≥1); increased in SBM, Daily bowel movement and abdominal symptoms assessment; weekly assessments of adequate relief of IBS symptoms, global relief of IBS, IBS symptom severity, and constipation severity; at the end of trial, IBS-SSS and IBS-QOL, overall satisfaction with the study medication to relieve IBS were assessed	Linaclotide 75, 150, 300, 600 µg vs placebo: Increase in weekly CSBM: 2.90, 2.49, 3.61, and 2.68 vs 1.01 ($p < 0.01$).	Linaclotide 75, 150, 300, 600 µg vs placebo: (N = 420): Diarrhea 11.4%, 12.2%, 16.5%, 18.0% vs 1.2%. Discontinued treatment due to diarrhea: 2, 4, 1, 6 vs 0; discontinued treatment due to AE: 4, 6, 3, 10 vs 2. SAE: one in linaclotide 300 µg (fecal impaction)	
Andresen 2007	Phase IIa, repeat-dose study, RCT	USA, single center	Rome II criteria	linaclotide, 100 µg (n = 12) and 1000 µg (n = 12) od vs placebo (n = 12)	Effect of linaclotide on GI transit: ascending colon emptying half-time (AC t 1/2) and the overall colonic transit defined by geometric centre at 24 hours (GC 24). Further assessments, GC at 48 hours, gastric emptying t 1/2, and colonic filling at 6 hours.	AC t 1/2 (hr) = 7.79 ± 1.74 for 1000 µg, 11.42 ± 2.39 for 100 µg vs 16.96 ± 2.03 for placebo, P = 0.015). GC24 post-treatment c.f. baseline, = 2.3 ± 0.13 vs 1.9 ± 0.08 for 1000 µg, 2.1 ± 0.12 vs 1.9 ± 0.08 for 100 µg, 2.0 ± 0.14 vs 1.8 ± 0.08 for placebo.	Linaclotide 100, 1000 µg vs placebo, with AE*, p = 0.68; overall GI AE, p = 0.11; headache 5, 3 vs 2; loose stools: 2, 3 vs 0; Discontinued treatment due to AE: No. SAE: No.	

*Some patients reported more than 1 adverse events.

Abbreviations: AE, adverse events; BSFS, Bristol Stool Form Scale; CSBM, complete spontaneous bowel movement; EMA, European Medicines Agency; EQ-5D, EuroQol-5 Dimensions; IBS-QoL, Irritable Bowel Syndrome-Quality of Life; IBS-SSS: IBS symptom severity scale; NRS, 11-point numerical rating scale; SBMs, spontaneous bowel movements.

to discontinue the study drug due to diarrhea was seen in 4.5–5.7% in the linaclotide group compared to 0.2–0.3% in the placebo group. There was no significant difference between the groups in terms of serious adverse events. In all phase III trials, there was no difference between the treatment and placebo groups in terms of laboratory investigations, electrocardiogram changes or vital signs.[18,22,25]

Place of Linaclotide in Therapy of CC and IBS-C

The initial non-pharmacological treatment in patients with CC and IBS-C is lifestyle and diet modification. Although regular physical activity has not been consistently shown to improve stool frequency, it has been found to improve quality of life and the severity of constipation in patients with CC[27,28] and the symptom severity scores of IBS patients.[29] Psyllium has been shown to be moderately effective in improving constipation but it does not improve overall symptoms of IBS.[30] Osmotic and stimulant laxatives are effective in improving stool frequency. A recent meta-analysis, including 5 double-blind RCTs using osmotic laxatives (1 used lactulose and 4 used polyethylene glycol) and 2 double-blind RCTs using stimulant laxatives (1 used bisacodyl and 1 used sodium picosulfate), showed that both osmotic and stimulant laxatives improve constipation with a NNT equal to 3.[31] However, none of these agents improve functional abdominal symptoms. Although the use of osmotic laxatives is recommended by the American College of Gastroenterology (ACG)[7] and the UK National Institute of Health and Clinical Excellence (NICE) in the treatment of constipation associated with IBS, NICE discourages the use of lactulose because it may exacerbate IBS symptoms.[32] The common side effects of laxatives, such as abdominal pain, bloating, flatulence and diarrhea, limit their uses.

Lubiprostone has been approved in the United States for the treatment of CC and IBS-C. It is a bicyclic fatty acid that activates the apical membrane chloride channel in the intestinal epithelium to stimulate intestinal fluid secretion. The NNT of lubiprostone to improve constipation was shown in a meta-analysis, including 3 RCTs, to be 4.[31] In an extension study, following 522 IBS-C patients up to 52 weeks, diarrhea and nausea were found in 11% of patients.[33]

Serotonergic (5-HT4) receptor agonists have been shown to be effective in the treatment of patients with CC and IBS-C. Cisapride and tegaserod were 2 previously widely used prokinetics. Due to their cardio-toxicity, both cisapride and tegaserod have been withdrawn from the market. A new 5-HT4 agonist, prucalopride, has shown to be effective in the treatment of CC with a NNT of 6.[31] Based on pharmacokinetic and pharmacodynamics, as well as clinical trial data, including trials in the elderly with cardiac co-morbidities,[34,35] prucalopride has been shown to be well tolerated and safe without any significant cardiovascular side effects. In addition, 3 double-blind, placebo controlled RCTs[36–38] have demonstrated that not only does prucalopride improve constipation, it also improves patients' QoL and constipation symptoms, particularly abdominal discomfort, bloating and pain.[39] Nevertheless, currently, prucalopride has only been approved for the treatment of CC and not for IBS-C.

TCAs and SSRIs are recommended by the ACG to treat abdominal pain in patients with IBS.[7] A systematic review has shown that TCAs and SSRIs improve global IBS symptoms and abdominal pain.[40] However, a meta-analysis, including 5 RCTs of SSRIs, demonstrated that SSRIs do not significantly improve abdominal pain or IBS symptoms.[41] Furthermore, the anticholinergic side effects of TCAs and SSRIs limit their tolerability.

Linaclotide offers a novel therapeutic option for the treatment of CC and IBS-C. Its visceral hyperalgesia modulatory effect makes it an exciting single agent to be used in patients with IBS-C. Recently, linaclotide has been approved by the FDA to treat CC and IBS-C and by the EMA to treat IBS-C. In Germany, linaclotide (290 µg) is indicated for the symptomatic treatment of moderate to severe IBS-C in adults. In the United States, it is approved to use in adults for the treatment of IBS-C (290 µg) and CC (145 µg). There has been no clinical trial comparing linaclotide to lubiprostone or prucalopride in patients with CC or IBS-C. Its place in the pharmacological treatment algorithm in these functional GI disorders will depend on the local availability of these various agents, as well as the cost of linaclotide and coverages by public and private programs. In the treatment of CC, it is reasonable to consider linaclotide only after patients cannot be adequately treated by fiber supplementation

and osmotic laxatives in the treatment pyramid.[5] In patients with IBS-C, particularly those predominantly suffering from abdominal discomfort and pain, it is sensible to consider using linaclotide earlier in the treatment algorithm, even before laxatives.

Conclusion

Linaclotide represents an exciting novel therapeutic option for the treatment of CC and IBS-C. Clinical trials demonstrated that linaclotide is well tolerated and improves bowel function in addition to offering symptomatic relief, which other therapies often fail to provide, in patients with CC and IBS-C. Now that linaclotide has been approved by the FDA and EMA, further studies (e.g. direct comparative RCTs to established therapies and cost-effective decision models) and consensus expert working groups to determine its place in treatment algorithms will help in further optimizing the management paradigm for these functional GI disorders.

Author Contributions

All three authors contributed to the first draft and jointly developed and approved the final manuscript.

Funding

Competing Interests

In the past 48 months, Dr. Louis Liu has served on the advisory board for Janssen Pharmaceuticals, Nycomed Canada, Takeda Canada Inc, Abbott Canada and Forrest Laboratory Canada, Inc. and on the speaker bureau for Janssen Pharmaceuticals. Dr. Yuhong Yuan and Colleen Parker disclose no potential conflicts of interest.

Disclosures and Ethics

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the authors were invited to submit this paper.

References

1. Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. *Am J Gastroenterol*. 2011;106(9):1582–1591.
2. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol*. 2012;10(7):712–721.
3. Corazziari E. Definition and epidemiology of functional gastrointestinal disorders. *Best Pract Res Clin Gastroenterol*. 2004;18(4):613–631.
4. Saito YA, Schoenfeld P, Locke GR 3rd. The epidemiology of irritable bowel syndrome in North America: a systematic review. *Am J Gastroenterol*. 2002;97(8):1910–1915.
5. Liu LW. Chronic constipation: current treatment options. *Can J Gastroenterol*. 2011;25 Suppl B:22B–28B.
6. Acosta RD, Cash BD. Existing and emerging therapies for irritable bowel syndrome. *Expert Opin Emerg Drugs*. 2011;16(2):389–402.
7. Brandt LJ, Chey WD, Foxx–Orenstein AE, et al. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol*. 2009;104 Suppl 1:S1–35.
8. Field M, Graf LHJ, Laird WJ, Smith PL. Heat-stable enterotoxin of Escherichia coli: in vitro effects on guanylate cyclase activity, cyclic GMP concentration, and ion transport in small intestine. *Proc Natl Acad Sci U S A*. 1978;75(6):2800–2804.
9. Schlossmann J, Feil R, Hofmann F. Insights into cGMP signalling derived from cGMP kinase knockout mice. *Front Biosci*. 2005;10:1279–1289.
10. Brierley SM. Guanylate cyclase-C receptor activation: unexpected biology. *Curr Opin Pharmacol*. 2012;12(6):632–640.
11. Schulz S, Green CK, Yuen PS, Garbers DL. Guanylyl cyclase is a heat-stable enterotoxin receptor. *Cell*. 1990;63(5):941–948.
12. Bryant AP, Busby RW, Bartolini WP, et al. Linaclotide is a potent and selective guanylate cyclase C agonist that elicits pharmacological effects locally in the gastrointestinal tract. *Life Sci*. 2010;86(19–20):760–765.
13. Eutamene H, Bradesi S, Larauche M, et al. Guanylate cyclase C-mediated antinociceptive effects of linaclotide in rodent models of visceral pain. *Neurogastroenterol Motil*. 2010;22(3):312–320.
14. Castro J, Harrington AM, Hughes PA, et al. Mechanism of action for linaclotide induced abdominal pain relief. *Gastroenterology*. 2012;142(5):S-699.
15. Castro J, Martin C, Hughes PA, et al. A novel role of cyclic GMP in colonic sensory neurotransmission in healthy and TNBS-treated mice. *Gastroenterology*. 2011;140(5) Suppl 1:S–538.
16. Busby RW, Bryant AP, Bartolini WP, et al. Linaclotide, through activation of guanylate cyclase C, acts locally in the gastrointestinal tract to elicit enhanced intestinal secretion and transit. *Eur J Pharmacol*. 2010;649(1–3):328–335.
17. Bharucha AE, Waldman SA. Taking a lesson from microbial diarrhea genesis in the management of chronic constipation. *Gastroenterology*. 2010;138(3):813–817.
18. Chey WD, Lembo AJ, Lavins BJ, 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(11):1702–1712.
19. Busby RW, Kessler MM, Bartolini WP, et al. Pharmacological properties, metabolism and disposition of linaclotide, a novel therapeutic peptide approved for the treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation. *J Pharmacol Exp Ther*. 2013;344(1):196–206.
20. Johnston JM, Kurtz CB, Drossman DA, et al. Pilot study on the effect of linaclotide in patients with chronic constipation. *Am J Gastroenterol*. 2009;104(1):125–132.

21. Lembo AJ, Kurtz CB, Macdougall JE, et al. Efficacy of linaclotide for patients with chronic constipation. *Gastroenterology*. 2010;138(3):886–895.

22. Lembo AJ, Schneier HA, Shiff SJ, et al. Two randomized trials of linaclotide for chronic constipation. *N Engl J Med*. 2011;365(6):527–536.

23. Andresen V, Camilleri M, Busciglio IA, et al. Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. *Gastroenterology*. 2007;133(3):761–768.

24. Johnston JM, Kurtz CB, Macdougall JE, 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(6):1877–1886.

25. Rao S, Lembo AJ, Shiff SJ, 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(11):1714–1724.

26. Quigley EM, Tack J, Chey WD, et al. Randomized 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(1):49–61.

27. Tuteja AK, Talley NJ, Joos SK, Woehl JV, Hickam DH. Is constipation associated with decreased physical activity in normally active subjects? *Am J Gastroenterol*. 2005;100(1):124–129.

28. Daley AJ, Grimmett C, Roberts L, et al. The effects of exercise upon symptoms and quality of life in patients diagnosed with irritable bowel syndrome: a randomised controlled trial. *Int J Sports Med*. 2008;29(9):778–782.

29. Johannesson E, Simren M, Strid H, Bajor A, Sadik R. Physical activity improves symptoms in irritable bowel syndrome: a randomized controlled trial. *Am J Gastroenterol*. 2011;106(5):915–922.

30. Pare P, Bridges R, Champion MC, et al. Recommendations on chronic constipation (including constipation associated with irritable bowel syndrome) treatment. *Can J Gastroenterol*. 2007;21 Suppl B:3B–22B.

31. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. *Gut*. 2011;60(2):209–218.

32. National Insitiute for Health Care Excellence (NICE). Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care. 2008; London: Royal College of Nursing (UK); Available at guidance.nice.org.uk/cg61 Accessed June 14th, 2013.

33. Chey WD, Drossman DA, Johanson JF, Scott C, Panas RM, Ueno R. Safety and patient outcomes with lubiprostone for up to 52 weeks in patients with irritable bowel syndrome with constipation. *Aliment Pharmacol Ther*. 2012;35(5):587–599.

34. Muller-Lissner S, Rykx A, Kerstens R, Vandeplassche L. A double-blind, placebo-controlled study of prucalopride in elderly patients with chronic constipation. *Neurogastroenterol Motil*. 2010;22(9):991–998.

35. Camilleri M, Beyens G, Kerstens R, Robinson P, Vandeplassche L. Safety assessment of prucalopride in elderly patients with constipation: a double-blind, placebo-controlled study. *Neurogastroenterol Motil*. 2009;21(12):1256–1263.

36. Camilleri M, Kerstens R, Rykx A, Vandeplassche L. A placebo-controlled trial of prucalopride for severe chronic constipation. *N Engl J Med*. 2008; 358(22):2344–2354.

37. Quigley EM, Vandeplassche L, Kerstens R, Ausma J. Clinical trial: the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation—a 12-week, randomized, double-blind, placebo-controlled study. *Aliment Pharmacol Ther*. 2009;29(3):315–328.

38. Tack J, van Outryve M, Beyens G, Kerstens R, Vandeplassche L. Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives. *Gut*. 2009;58(3):357–365.

39. Kerstens R, Vandeplassche L, Dubois D, Wouters L. Response of chronic constipation symptoms to prucalopride treatment and relationship with patient satisfaction. *Gut*. 2011;60 (Suppl 1):A159.

40. Ford AC, Vandvik PO. Irritable bowel syndrome. *Clin Evid (Online)*. 2010; pii: 0410.

41. Rahimi R SN, Nikfar S, Abdollahi M. Selective serotonin reuptake inhibitors for the management of irritable bowel syndrome: a meta-analysis of randomized controlled trials. *Archives of Medical Sciences*. 2008;4(1):71–76.

42. Smith ME, Morton DG. *The Digestive System, Second Edition*. New York, NY: Churchill Livingstone, Elsevier; 2010.