The management of constipation-related functional gastrointestinal disorder (constipation-predominant irritable bowel syndrome)

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The terminology constipation-related functional gastrointestinal disorders was applied to embrace two conditions – constipation-predominant irritable bowel syndrome (IBS-C) and chronic constipation – because of the similarity in the etiology between the two conditions. The cardinal symptoms of IBS-C are abdominal pain or discomfort associated with constipation. The current symptom-based Rome III criteria are used to confirm the diagnosis. Many patients with IBS-C initially treat their symptoms with lifestyle modifications and exclusion diets, together with treatment of symptoms such as constipation by using fiber supplements, over-the-counter laxatives, or probiotics. Less commonly, the patients may also undergo various forms of psychotherapy. Despite these therapeutic modalities, many IBS patients are disappointed with their symptomatic response. There are several drugs that are being proposed for its treatment in the future, one of which is linaclotide, a 14-amino acid synthetic peptide that improves stool frequency and consistency and intestinal transit. Four-week treatment with *Bifidobacterium lactis* showed superior results when compared with placebo in decreasing the abdominal distention and improving orocecal and colonic transit.

Keywords:
constipation-predominant irritable bowel syndrome, management, diagnosis, treatment instead of management

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Introduction

The terminology constipation-related functional gastrointestinal (GI) disorders was applied to embrace two conditions – constipation-predominant irritable bowel syndrome (IBS-C) and chronic constipation (CC) – because of the similarity in the etiology between the two conditions as seen by the common underlying causes and presenting symptoms between IBS-C and CC. Moreover, the vast majority of published literature treats each IBS-C and CC case as a separate condition.

Shared factors between constipation-predominant irritable bowel syndrome and chronic constipation

Decreased bowel motility

Several studies have documented decreased rectal, colonic, and small bowel motility in IBS-C [1]. These abnormalities are best described in the subset of CC identified as colonic inertia, a condition recognized by a slow colon transit time [2].

Pelvic floor dysfunction

Pelvic floor dysfunction is described as the inability to organize the sequence of events that result in the normal evacuation of stool. This involves the inability to contract abdominal wall musculature, impaired relaxation of puborectalis muscle, defective rectal contraction, paradoxical anal contraction, and/or defective anal relaxation [3].

Although recently recognized as a contributor to symptoms in a subset of IBS-C [4], this mechanism has also been identified as a primary etiology of symptoms in a subset of patients with CC [5].

Visceral hypersensitivity

Visceral hypersensitivity, representing a lower pain threshold of the digestive tract, is not only a well-defined pathophysiologic mechanism underlying IBS-C but is also proposed by others to be a biomarker of the condition [6–8].

Psychological stress

Psychological stress may be responsible for the development of symptoms in IBS-C [9] and may worsen symptoms. In contrast, psychological stress has a smaller role in CC but may promote dyssynergic defecation in some cases [3].

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Altered bowel flora

There is emerging proof to propose a role for altered bowel flora in the occurrence of symptoms of IBS-C, and possibly CC [10].

Diet

The strong association between a low-fiber diet and CC is better described in CC than in IBS-C [11].

It is essential to be aware that none of these individual pathophysiologic mechanisms are universally documented in either IBS-C or CC.

Constipation-predominant irritable bowel syndrome

Constipation-predominant irritable bowel syndrome to irritable bowel syndrome (IBS) subgroups

Patients with IBS are subtyped according to bowel symptoms into those with predominant constipation (IBS-C), those with predominant diarrhea (IBS-D), or those with a mixture of both symptoms (IBS-M) [12–14]. The definition of IBS has progressed over time; at present it is based on symptom-based criteria, such as Rome III, and the accurate use of preferred diagnostic tests to exclude organic disease [15,16].

Epidemiology and demographic

The incidence of IBS relies upon the diagnostic criteria used and the characteristics of the studied population (primary care or specialty clinic). The epidemiology of IBS in North America was studied in 2002, before the introduction of Rome II criteria, and ranged from 3 to 20% [17]. A recent study carried out in the USA and Canada, using the Rome criteria, reported that the prevalence of IBS was 5–12% according to age [18]. Using the Rome III criteria, the incidence of IBS has been estimated to range from 10 to 18% in the general population of western countries [19,20], where there is also a female predominance [17,21–23]. In contrast, a female predominance has not been consistently documented in Asia. Broadly IBS is more likely to affect younger persons, although individuals of all ages can suffer from this condition [17,21–23]. In general, the prevalence of IBS has shown similarity between the White and the Black population; however, there are some data proposing that it may be lower in Hispanics than in non-Hispanic Whites in the USA [24].

IBS is a chronic condition; in about half of the patients symptoms are relatively stable over time. Moreover, a significant proportion of patients with IBS will experience a more dynamic clinical course with improvement or change in their symptoms seen when followed up for a prolonged period of time. Patients with IBS can be affected physically, psychologically, socially, and economically [14]. Mental symptoms are associated with disturbance in sexuality, mood, and anxiety [25]. Although in addition to the physical criteria used to evaluate the IBS health-related quality of life (e.g. stool frequency, stool characteristics), global symptom severity should be addressed, including psychological status and symptom-related fears, which might lead to a low health-related quality of life score [26].

Clinical features of irritable bowel syndrome with predominant constipation

The cardinal symptoms of IBS-C are abdominal pain or discomfort associated with constipation. The current symptom-based (Rome III) criteria [14] consist of recurrent abdominal pain or discomfort for at least 3 days a month in the last 3 months, which is associated with 2 or more of the following:

(1) Improvement with defecation.
(2) Change in the frequency of stool.
(3) Change in the appearance of stool.
(4) Supportive symptoms such as abnormal stool frequency (<3/week), abnormal stool form (lumpy hard), straining, urgency, a feeling of incomplete evacuation, or passing mucus or gas.

These criteria should be fulfilled for at least 3 months with symptom onset at least 6 months before diagnosis. The cardinal symptom of IBS is always abdominal pain associated with changing bowel function. However, bloating is most common, especially in women, and is documented by a third of patients and considered an essential reason for consulting a physician. Moreover bloating is associated with decreased energy, poor quality of life, and excessive use of medications [27].

Comorbidities in patients with constipation-predominant irritable bowel syndrome

Patients also complained of a wide range of non-GI symptoms such as headache (23–45%), back pain (27–81%), fatigue (36–63%), myalgia (29–36%), dyspareunia (9–42%), urinary frequency (21–61%), and dizziness (11–27%) (Table 1).

Deficiency of biomarkers makes the diagnosis of IBS-C greatly reliant on the fulfillment of symptom-based criteria (Rome III). However, overlap with other functional disorders such as CC and functional dyspepsia may occur [14,28,29]. In addition, organic diseases can present with symptoms similar to those of IBS-C, which can lead to more tests, increasing costs,

Table 1 Comorbidities in patients with constipationpredominant irritable bowel syndrome

Disorders	% Prevalence of IBS in patients with the disorder	% Prevalence of disorder in patients with IBS
GI		
Gastrointestinal reflux disease	47	46.5
Functional dyspepsia	28–47	28–57
Other somatic disorders		
Fibromyalgia	32–77	28–65
Chronic fatigue syndrome	35–92	14
Chronic pelvic pain	29–79	35
Tembromandibular joint pain	64	16
Interstitial cystitis	30.2	–

GI, gastrointestinal.

but without diagnostic yields such as complete blood count and full metabolic panel [16].

The specificity of the Rome criteria was raised when alarm symptoms manifested along with the GI symptoms [30,31]. On average, patients with IBS documented at least 1.65 red flag symptoms such as blood passing per rectum, unintentional weight loss, iron deficiency anemia, nocturnal symptoms, or a significant change in symptoms after a stable pattern over several years [32]; such patients may require further investigation. A family history of colorectal cancer, inflammatory bowel disease, or celiac sprue is also considered an alarm feature. Unfortunately, the discriminatory value of these alarm symptoms is discouraged. Colonoscopy is indicated in patients with late-onset symptoms [33,34], and in patients older than 50 years with new symptoms. Testing is needed in patients who have not shown an improvement despite symptom-based treatment.

The current management and therapies

Many patients with IBS-C initially treat their symptoms with lifestyle modifications such as exercise and exclusion diets together with treatment of symptoms such as constipation with fiber supplements, over-the-counter laxatives, or probiotics. Less commonly, they may also undergo various forms of psychotherapy such as relaxation, stress management, cognitive behavior therapy, and hypnosis. Despite these forms of therapy, many IBS patients are disappointed with their symptomatic response. The traditional approach to therapy in IBS-C patients has extensively depended on a patient's predominant or most bothersome symptom – for example, laxatives for constipation and smooth-muscle relaxants for abdominal pain. However, this approach has its limitations and is typically without impact on the natural history of the disorder [35]. The interpretation of the response to any treatment is complicated and there is a powerful placebo effect (up to 46%) during the first few weeks of therapy [34].

In clinical practice, the principle of treating patients with IBS-C are as follows: the most evidence-based treatment for patients with IBS are those that control function of bowel. Patients with IBS-C with delayed transit usually have greater distension and bloating compared with those with normal transit. Drugs that stimulate transit can be expected to improve this problem.

Secretagogues increase small bowel and colonic transit and relieve abdominal symptoms and bowel dysfunction.

Despite meta-analyses of the benefit of use of antidepressants in IBS, evidence from pharmacodynamic and clinical trials is limited in IBS-C.

Probiotics contribute to relieving bloating, flatulence, and possibly pain in IBS, but more research is needed.

Bulking agents

Soluble fiber such as psyllium (12–20 g/day) is considered the first-line treatment for constipation associated with IBS-C. Despite its extensive use in clinical practice, evidence on the role of bulking agents in IBS is limited [34,36]. However, many researchers have reported that insoluble fiber (bran) can aggravate symptoms such as bloating [37]. The effect of fiber supplementation in clinical trials has been assessed in many systematic reviews with somewhat differing conclusions.

Osmotic and stimulant laxatives

Osmotic laxatives are often the alternative first-line therapy for IBS-C. A study has evaluated the effect of polyethylene glycol in 27 postpubertal adolescents with IBS-C, and has found that it accelerates the number of bowel movements per week without any effect on abdominal pain intensity [38]. Despite a deficiency of proof, stimulant laxatives are frequently prescribed by clinicians as a treatment for IBS-C. Although these agents increase the colonic transit, it is unknown whether stimulants offer any benefits for abdominal pain in IBS-C patients.

Antispasmodics

The cardinal features of IBS are abdominal pain or discomfort, which are thought to be symptoms related to alterations in the intestinal or colonic smooth-muscle

motility and/or visceral hypersensitivity. Because of their effects on smooth-muscle contractile activity, antispasmodics are a therapeutic modality for the symptoms of IBS-C [38]. Moreover, the liability of these agents to promote constipation makes them relatively contraindicated in patients with IBS-C [39].

Prokinetic agents

Serotonergic agents

Tegaserod was the only 5-HT4 receptor agonist available for the treatment of women with IBS-C from 2002, and its withdrawal from the market in 2009 due to unexplained raised the incidence of cardiovascular and cerebrovascular events in the treatment group in comparison with the placebo group.

Intestinal secretagogues

Lubiprostone is an activator of a chloride channel with FDA approval for the management of IBS-C. Lubiprostone is available as an 8-μg, twice-daily, oral treatment for women with IBS-C. It is an oral bicyclic fatty acid (FA) derivative of prostaglandin E1 that specially activates the chloride channel (type 2) located in the apical membrane of human intestinal epithelial cells, thereby increasing chloride-rich fluid secretion into the GI tract. Activation of the chloride channel increased passive paracellular movement of sodium and water and a resultant net increase in fluid secretion into the intestine lumen [40], softening of feces, and increase in stool biomass with secondary effects on peristalsis and transit [41,42]. The most frequent treatment-related side effects were nausea (8%), diarrhea (6%), and abdominal pain (5%). In addition to these side effects, dyspnea has been occasionally reported. However, the mechanism of dyspnea is uncertain, but it typically occurs within 30–60 min of taking the first dose and is generally improved in a few hours' time. Occasionally, dyspnea returns with subsequent dosing. Lubiprostone has a pregnancy category C rating because of the increased fetal demise observed in guinea pig research.

Low-dose antidepressants

Antidepressants (tricyclic antidepressants or selective serotonin reuptake inhibitors) can be indicated in cases with abdominal pain that does not respond to medication primarily aimed at improving bowel function. Antidepressants were found to be adequate for the global symptoms of IBS in a recent meta-analysis. Few studies of antidepressants have focused on IBS-C patients. One randomized, controlled trial involving 44 patients with IBS-C reported that the selective serotonin reuptake inhibitor fluoxetine improved global and individual symptoms [43]. It is essential to keep in mind that tricyclic agents can aggravate constipation-related complaints because of their anticholinergic properties.

A future therapy for constipation-predominant irritable bowel syndrome

Linaclotide is a 14-amino acid synthetic peptide that specifically binds to and activates guanylate cyclase C receptor on the luminal surface of the intestinal epithelium, resulting in production of cyclic guanosine monophosphate [44]. Intracellular cyclic guanosine monophosphate results in activation of the cystic fibrosis transmembrane regulator leading to increased active secretion of chloride and passive paracellular movement of sodium and water into the intestinal lumen leading to improvement of stool frequency, consistency, and intestinal transit. Linaclotide is orally administered and minimally absorbed. All primary and secondary endpoints were achieved and efficacy was maintained for 26 weeks [45]. Combining the phase 3 data showed improved quality of life, as measured by the IBS-QOL scale, in seven of eight domains in the patients treated with linaclotide [46].

There was no evidence of rebound or worsening of abdominal pain or bowel symptoms during the randomized withdrawal period [47]. Linaclotide was commonly well tolerated. The most common adverse effect was diarrhea (4 vs. 0.2% for linaclotide and placebo, respectively) [45].

Bile acid modulators

Bile acids can produce alteration in intestinal and colonic motility and secretion. Recent research has investigated the role of specific bile acid analogs or drugs that alter bile acid reabsorption as innovative therapies for IBS-C. Many studies have evaluated the effects of chenodeoxycholic acid on colonic transit, and clinical parameters in female patients with IBS-C were recently reported. Chenodeoxycholic acid significantly increases overall colonic transit and improves clinical outcomes in IBS patients, including stool frequency and stool consistency, and facilitates the passage of stool. Its most frequent side effect was abdominal cramping/pain, which was documented by over 40% of patients compared with none in the placebo group [48].

Complementary and alternative medicines

In general, there is a deficiency of extensive, high-quality studies supporting the efficacy of complementary and alternative medicines therapies for IBS-C. A single-center, randomized, double-blind trial on 34 women with IBS-C compared the probiotic

Bifidobacterium lactis with placebo [49], in this study 4 weeks of *B. lactis* (125 g of yogurt containing *B. lactis* ingested daily) treatment gave superior results to placebo in decreasing abdominal distention and improving orocecal and colonic transit.

A Cochrane review of herbal medicines (e.g. Padma Lax) for use in the treatment of IBS-C. Many well-designed clinical studies showed improvement of IBS symptoms [50]. It has been proposed that a combination of certain herbs may act in a coordinated manner on serotonin and acetylcholine receptors in isolated human intestine, but this requires further investigation.

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Conflicts of interest
There are no conflicts of interest.

References

1 Quigley EM. Disturbances of motility and visceral hypersensitivity in irritable bowel syndrome: biological markers or epiphenomenon. Gastroenterol Clin North Am 2005; 34:221-233, vi.

2 Stivland T, Camilleri M, Vassallo M, Proano M, Rath D, Brown M, *et al*. Scintigraphic measurement of regional gut transit in idiopathic constipation. Gastroenterology 1991; 101:107-115.

3 Rao SS, Welcher KD, Leistikow JS. Obstructive defecation: a failure of rectoanal coordination. Am J Gastroenterol 1998; 93:1042-1050.

4 Prott G, Shim L, Hansen R, Kellow J, Malcolm A. Relationships between pelvic floor symptoms and function in irritable bowel syndrome. Neurogastroenterol Motil 2010; 22:764-769.

5 Lembo A, Camilleri M. Chronic constipation. N Engl J Med 2003; 349: 1360-1368.

6 Mertz H, Naliboff B, Munakata J, Niazi N, Mayer EA. Altered rectal perception is a biological marker of patients with irritable bowel syndrome. Gastroenterology 1995; 109:40-52.

7 Bouin M, Plourde V, Boivin M, Riberdy M, Lupien F, Laganière M, *et al*. Rectal distention testing in patients with irritable bowel syndrome: sensitivity, specificity, and predictive values of pain sensory thresholds. Gastroenterology 2002; 122:1771-1777.

8 Lawal A, Kern M, Sidhu H, Hofmann C, Shaker R. Novel evidence for hypersensitivity of visceral sensory neural circuitry in irritable bowel syndrome patients. Gastroenterology 2006; 130:26-33.

9 O'Malley D, Quigley EM, Dinan TG, Cryan JF. Do interactions between stress and immune responses lead to symptom exacerbations in irritable bowel syndrome? Brain Behav Immun 2011; 25:1333-1341.

10 Attaluri A, Jackson M, Valestin J, Rao SS. Methanogenic flora is associated with altered colonic transit but not stool characteristics in constipation without IBS. Am J Gastroenterol 2010; 105:1407-1411.

11 Trowell H. Definition of dietary fiber and hypotheses that it is a protective factor in certain diseases. Am J Clin Nutr 1976; 29:417-427.

12 Longstreth GF. Definition and classification of irritable bowel syndrome: current consensus and controversies. Gastroenterol Clin North Am 2005; 34:173-187.

13 Thompson WG. Irritable bowel syndrome: pathogenesis and management. Lancet 1993; 341:1569-1572.

14 Longstreth GF, Thompson WG, Chey WD, *et al*. Functional bowel disorders. In: Drossman DA, editor. Rome III: the functional gastrointestinal disorders. 3rd ed. McLean, VA: Dagnon Associates; 2006. 491.

15 Longstreth GF, Thompson WG, Chey WD, *et al*. Functional bowel disorders. Gastroenterology 2006b; 130:1480-1491.

16 Furman DL, Cash BD. The role of diagnostic testing in irritable bowel syndrome. Gastroenterol Clin North Am 2011; 40:105-119.

17 Saito YA, Schoenfeld P, Locke GR III. The epidemiology of irritable bowel syndrome in North America: a systematic review. Am J Gastroenterol 2002; 97:1910-1915.

18 Talley NJ, O'Keefe EA, Zinsmeister AR, Melton LJ III. Prevalence of gastrointestinal symptoms in the elderly: a population-based study. Gastroenterology 1992; 102:895-901.

19 Jung HK, Halder S, McNally M, Locke GR III, Schleck CD, Zinsmeister AR, Talley NJ. Overlap of gastro-oesophageal reflux disease and irritable bowel syndrome: prevalence and risk factors in the general population. Aliment Pharmacol Ther 2007; 26:453-461.

20 Olafsdottir LB, Gudjonsson H, Jonsdottir HH, Thjodleifsson B. Stability of the irritable bowel syndrome and subgroups as measured by three diagnostic criteria – a 10-year follow-up study. Aliment Pharmacol Ther 2010; 32:670-680.

21 Andrews EB, Eaton SC, Hollis KA, Hopkins JS, Ameen V, Hamm LR, *et al*. Prevalence and demographics of irritable bowel syndrome: results from a large web-based survey. Aliment Pharmacol Ther 2005; 22:935-942.

22 Hungin AP, Chang L, Locke GR, Dennis EH, Barghout V. Irritable bowel syndrome in the United States: prevalence, symptom patterns and impact. Aliment Pharmacol Ther 2005; 21:1365-1375.

23 Minocha A, Johnson WD, Abell TL, Wigington WC. Prevalence, sociodemography, and quality of life of older versus younger patients with irritable bowel syndrome: a population-based study. Dig Dis Sci 2006; 51:446-453.

24 Talley N. Irritable bowel syndrome [chapter 118]. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger and Fordtran's gastrointestinal and liver disease. 9th ed. St. Louis, MO: W.B. Saunders; 2010, Chap 118.

25 Spiegel BM, Gralnek IM, Bolus R, Chang L, Dulai GS, Mayer EA, Naliboff B. Clinical determinants of health-related quality of life in patients with irritable bowel syndrome. Arch Intern Med 2004; 164:1773-1780.

26 Agarwal N, Spiegel BM. The effect of irritable bowel syndrome on health-related quality of life and health care expenditures. Gastroenterol Clin North Am 2011; 40:11-19.

27 Ringel Y, Williams RE, Kalilani L, Cook SF. Prevalence, characteristics, and impact of bloating symptoms in patients with irritable bowel syndrome. Clin Gastroenterol Hepatol 2009; 7:68-72.

28 Thompson WG, Creed FH, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA. Functional bowel disease and functional abdominal pain. Gastroenterol Int 1992; 5:75-91.

29 Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. Gut 1999; 45(Suppl 2):II43-II47.

30 Ford AC, Talley NJ, Veldhuyzen van Zanten SJ, Vakil NB, Simel DL, Moayyedi P. Will the history and physical examination help establish that irritable bowel syndrome is causing this patient's lower gastrointestinal tract symptoms? JAMA 2008; 300:1793-1805.

31 Jellema P, van der Windt DA, Schellevis FG, van der Horst HE. Systematic review: accuracy of symptom-based criteria for diagnosis of irritable bowel syndrome in primary care. Aliment Pharmacol Ther 2009; 30:695-706.

32 Whitehead WE, Palsson OS, Feld AD, Levy RL, Von Korff M, Turner MJ, Drossman DA. Utility of red flag symptom exclusions in the diagnosis of irritable bowel syndrome. Aliment Pharmacol Ther 2006; 24:137-146.

33 Spiegel BM, DeRosa VP, Gralnek IM, Wang V, Dulai GS. Testing for celiac sprue in irritable bowel syndrome with predominant diarrhea: a cost-effectiveness analysis. Gastroenterology 2004; 126:1721-1732.

34 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(Suppl 1):S1-35.

35 Camilleri M, Andresen V. Current and novel therapeutic options for irritable bowel syndrome management. Dig Liver Dis 2009; 41:854-862.

36 Ford AC, Talley NJ, Spiegel BM, Foxx-Orenstein AE, Schiller L, Quigley EM, Moayyedi P. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. BMJ 2008; 337:a2313.

37 Miller V, Lea R, Agrawal A, Whorwell PJ. Bran and irritable bowel syndrome: the primary-care perspective. Dig Liver Dis 2006; 38:737-740.

38 Whitehead WE, Holtkotter B, Enck P, Hoelzl R, Holmes KD, Anthony J, *et al*. Tolerance for rectosigmoid distention in irritable bowel syndrome. Gastroenterology 1990; 98(Pt 1):1187-1192.

39 Saad RJ. Peripherally acting therapies for the treatment of irritable bowel syndrome. Gastroenterol Clin North Am 2011; 40:163-182.

40 Cuppoletti J, Malinowska DH, Tewari KP, Li QJ, Sherry AM, Patchen ML, Ueno R. SPI-0211 activates T84 cell chloride transport and recombinant human ClC-2 chloride currents. Am J Physiol Cell Physiol 2004; 287:C1173-C1183.

41 Lang L. The Food and Drug Administration approves lubiprostone for irritable bowel syndrome with constipation. Gastroenterology 2008; 135:7.

42 Owen RT. Lubiprostone – a novel treatment for irritable bowel syndrome with constipation. Drugs Today (Barc) 2008; 44:645-652.

43 Vahedi H, Merat S, Rashidioon A, Ghoddoosi A, Malekzadeh R. The effect of fluoxetine in patients with pain and constipation-predominant irritable bowel syndrome: a double-blind randomized-controlled study. Aliment Pharmacol Ther 2005; 22:381-385.

44 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 Sci 2010; 86:760-765.

45 Chey W, Lembo A, MacDougall JE, Lavins BJ, Schneier H, Johnston JM, *et al*. Efficacy and safety of once-daily linaclotide administered orally for 26 weeks in patients with IBS-C: results from a randomized, double-blind, placebo-controlled phase 3 trial. Gastroenterology 2011a; 140:S135.

46 Carson R, Tourkodimitris S, Lewis BE, *et al*. Effect of linaclotide on quality of life in adults with irritable bowel syndrome with constipation: pooled results from two randomized, double-blind, placebo-controlled phase 3 trials. Gastroenterology 2011;140(5 suppl 1):S51.

47 Rao S, Lembo A, Shiff SJ, Shi K, Johnston JM, Schneier H. Efficacy and safety of once daily linaclotide in patients with irritable bowel syndrome with constipation: a 12-week, randomized, double-blind, placebo-controlled phase 3 trial followed by a 4-week randomized withdrawal period. Gastroenterology 2011; 140:S138.

48 Rao AS, Wong BS, Camilleri M, Odunsi-Shiyanbade ST, McKinzie S, Ryks M, *et al*. Chenodeoxycholate in females with irritable bowel syndrome-constipation: a pharmacodynamic and pharmacogenetic analysis. Gastroenterology 2010; 139:1549-1558. 1558.e1

49 Agrawal A, Houghton LA, Morris J, Reilly B, Guyonnet D, Goupil Feuillerat N, *et al*. Clinical trial: the effects of a fermented milk product containing Bifidobacterium lactis DN-173 010 on abdominal distension and gastrointestinal transit in irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2009; 29:104-114.

50 Lui J, Yang M, Liu Y, Wei M, Grimsgaard S. Herbal medicines for treatment of irritable bowel syndrome. Cochrane Database Syst Rev 2006; 1:CD004116.