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

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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].
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
Patient-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,
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.

### Table 1 Comorbidities in patients with constipation-predominant irritable bowel syndrome

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

GI, gastrointestinal.

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**

Linacotide 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. Linacotide 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 linacotide [46].

There was no evidence of rebound or worsening of abdominal pain or bowel symptoms during the randomized withdrawal period [47]. Linacotide was commonly well tolerated. The most common adverse effect was diarrhea (4 vs. 0.2% for linacotide 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 oroecal 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.

**References**

11. Longstreth GF. De
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