Irritable Bowel Syndrome: Current Approach to Symptoms, Evaluation, and Treatment

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Irritable bowel syndrome (IBS) is a common functional gastrointestinal (GI) disorder. It has a very high prevalence, estimated to be 10% to 20% in the general population [1]. IBS accounts for significant health care costs with annual direct and indirect costs estimated at $1.35 billion and at least $200 million, respectively [2]. IBS patients use more health care services than the general population, even for non–GI-related concerns [3,4].

This article provides clinicians with a current, concise, and evidence-based review of the symptoms, diagnostic evaluation, and treatment of IBS. A clear understanding of recommended diagnostic and therapeutic approaches leads to greater patient satisfaction and reduced health care costs.

CLINICAL FEATURES OF IRRITABLE BOWEL SYMPTOME

Gastrointestinal Symptoms

The main symptom of IBS is chronic or recurrent abdominal pain or discomfort associated with altered bowel habits. The new Rome III criteria for the diagnosis of IBS were published in 2006 and are listed in Box 1 [1]. The following are not part of the diagnostic criteria but are considered supportive symptoms: abnormal stool frequency (<3 bowel movements per week or >3 bowel movements per day); abnormal stool form (lumpy-hard stool or loose-watery stool); defecation; straining; urgency; a feeling of incomplete evacuation; and passing mucus and bloating.

The previous Rome II classification of IBS subtype was based on a combination of symptoms including stool frequency and form, and defecation-related symptoms. This classification was suboptimal because it was not evidence-based and because there was inconsistency with regard to the correct subclassification of patients with frequent hard stools or infrequent watery stools. Furthermore, cluster analysis and symptom studies have shown that stool
frequency is within normal range for most IBS patients [1]. Based on more recently published studies characterizing the bowel habits of the IBS subgroups [5–7], stool form was found to be the best predictor of predominant bowel habit in IBS. Furthermore, stool form is a better reflection of intestinal transit time. For these reasons, stool form rather than frequency determines classification according to Rome III. The subtype classification is illustrated in Fig. 1.

The category of alternating IBS (IBS-A) should be reserved for patients with bowel habits that have changed over time (eg, weeks to months). Patients with both diarrhea and constipation that may alternate within hours or days were classified as IBS-A according to Rome II, but should now be referred to as IBS-M. The prevalence of IBS-D, IBS-C, and IBS-M are similar, but IBS-M is the subtype most frequently encountered in primary care. Patients change

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**Box 1: The symptom-based Rome III criteria for the diagnosis of IBS**

These criteria should be filled for the last 3 months with symptom onset at least 6 months before diagnosis.

Recurrent abdominal pain or discomfort\(^a\) at least 3 days per month in the last 3 months that is associated with two or more of the following:

- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form (appearance) of stool

\(^a\)Discomfort means an uncomfortable sensation not described as pain.

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**Fig. 1.** The Rome III classification for subtyping IBS by bowel habit predominance. Patients are classified as IBS with constipation (IBS-C) if ≥25% of stools are hard or lumpy and <25% are loose ( mushy) or watery. IBS with diarrhea (IBS-D) describes patients with ≥25% of stools loose or watery and <25% hard or lumpy. Mixed IBS (IBS-M) describes patients with ≥25% of stools hard and lumpy and ≥25% of stools loose or watery. IBS patients are unsubtyped (IBS-U) if not enough stools are abnormal to meet criteria for any other subtype.
subtypes frequently, with 29% moving from IBS-C to IBS-D within 1 year [8]. Because of this symptom instability, the terms “IBS with diarrhea” and “IBS with constipation” are preferred over the previously used terms of “diarrhea- and constipation-predominant IBS” [8].

IBS-C and IBS-D patients have different symptom profiles, with IBS-C patients reporting more overall symptoms (both lower and upper abdominal pain) and particularly bloating [9]. Symptoms of IBS and functional dyspepsia overlap significantly and respond similarly to treatment. It has been argued that they are different manifestations of one condition [10].

**Extraintestinal Symptoms and Comorbid Disorders**

IBS patients make more health care visits and incur more health care costs than non-IBS patients. More than half of additional visits and additional costs are for non-GI concerns [11]. Non-GI symptoms that are more common in IBS than controls include the following (prevalence): headache (23%–45%); back pain (27%–81%); fatigue (36%–63%); myalgia (29%–36%); dyspareunia (9%–42%); urinary frequency (21%–61%) and other urinary symptoms; and dizziness (11%–27%) [11]. IBS patients with comorbid somatic disorders (eg, fibromyalgia) report more severe IBS symptoms and lower health-related quality of life (HRQOL) [11]. Common comorbid GI and other somatic disorders are listed in Table 1.

Although it seems that these comorbid disorders and IBS may have distinct contributing factors to their pathophysiology, there are common themes that are mostly related to psychologic symptoms and stress reactivity [11]. Stress is defined as acute threats to the homeostasis of an organism, be they real (physical) or perceived (psychologic). Sustained, threatening life events (psychosocial stressors) predict symptom exacerbation in established IBS patients [12–14], and the development of IBS symptoms in asymptomatic individuals following a gastroenteric infection (postinfectious IBS) [13,15]. Stress-induced changes in pain modulation (hyperalgesia) and cognitive processes (hypervigilance toward viscerosomatic stimuli) may play a key role in the pain and discomfort characteristic of these disorders. Although these mechanisms may be shared, they may be more specifically related to one particular stimulus depending on the condition. For example, IBS patients may have developed persistent symptom-specific anxiety from previously threatening visceral stimuli (eg, food or GI infection), whereas fibromyalgia patients have symptom-specific anxiety to somatic stimuli (eg, muscle injury). These threatening events, which are attached to their symptoms, may be involved in the development of anticipatory or anxiety-related responses [16] related to symptom recurrence. Symptom-specific anxiety can amplify the perception of visceral and somatic afferent input to the brain, thereby contributing to pain-related symptoms. A recently developed reliable, validated scale called the Visceral Sensitivity Index measures GI-specific anxiety (ie, fear of visceral sensations) and may be useful for clinical assessment, treatment outcome studies, and mechanistic studies of the role of anxiety in IBS presentation [17]. In addition,
a path analysis demonstrated that GI-specific anxiety mediates the relationship between general psychologic distress measures and GI symptom severity. The Visceral Sensitivity Index was related to GI, but not non-GI, symptom severity [18].

There is a higher prevalence of psychiatric disorders in the IBS population than in controls. This is true in the community (prevalence of 18%) [19]; in clinics (prevalence of 40%–60%) [20]; and in referral centers (prevalence with lifetime history of 94%) [19]. Although comorbidity is highest in the health care-seeking population, the prevalence in IBS nonpatients (ie, individuals who have not sought health care for their IBS symptoms) is greater than that seen in the general population, which suggests that psychiatric disorders influence health care seeking, but are not the primary cause. Somatization disorder deserves special mention. The diagnostic criteria for somatization disorder, a psychiatric disorder that is characterized by multiple medically unexplained symptoms, include a history of multiple pain symptoms; GI symptoms; sexual dysfunction or pain; and pseudoneurologic symptoms, such as weakness or urinary retention [21]. There is a high degree of overlap between IBS and somatization disorder, and patients with IBS who meet criteria for somatization disorder have more psychiatric comorbidity, more severe symptoms, and are less responsive to treatment [22]. Although IBS patients with somatization disorder do not have increased numbers of health care visits compared with IBS, they do incur more expenditures, which suggests both that somatization disorder is an important factor in health care use by IBS patients and that increased health care use may be mediated by physicians [23].

**Symptom Severity**

There are no consensus criteria that have been established to determine severity of IBS. This is caused in part by the large number of factors that influence

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**Table 1**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>% Prevalence of IBS in patients with the disorder</th>
<th>% Prevalence of the disorder in patients with IBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroesophageal 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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>32–77</td>
<td>28–65</td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
<td>35–92</td>
<td>14a</td>
</tr>
<tr>
<td>Chronic pelvic pain</td>
<td>29–79</td>
<td>35a</td>
</tr>
<tr>
<td>Temporomandibular joint disorder</td>
<td>64a</td>
<td>16a</td>
</tr>
<tr>
<td>Intestinal cystitis</td>
<td>30.2a</td>
<td>—</td>
</tr>
</tbody>
</table>

*Based on results of only one study [11].*
severity and the wide gap between patient and physician perceptions of severity. Current research suggests that a multidimensional view of illness severity is more useful than one that is based on GI symptom intensity. Factors that are important to consider when assessing severity are HRQOL, psychosocial factors, health care use behaviors, disability, and the overall degree to which the illness affects the patient’s life [24,25]. A preliminary report identified several predictors for patient-assessed “overall severity of GI symptoms” [26]. The predictors included multiple symptoms, such as ratings of abdominal pain and discomfort (pain, bloating); defecation-related symptoms (straining, urgency); and illness-related anxiety (“something serious is wrong with my body”). More recent epidemiologic data suggest a prevalence of severe or very severe IBS ranging from 3% to 69%, which is higher than previously thought [24].

Gender Differences
Gender differences in IBS are difficult to measure because most research participants are female; however, differences have been shown both in prominent symptoms and in the response to treatment. Although in the community the ratio of women to men with IBS is estimated to be 2:1, this difference is even greater in the health care–seeking population, with women leading men by an estimated ratio of 2 to 4:1 [27]. A recently published study, however, found equal prevalence of men and women with IBS in newly developing Asian countries [28]. Compared with men with IBS, women with IBS report greater overall IBS symptom severity, intensity of abdominal pain and bloating, impact of symptoms on daily life, and lower HRQOL [29,30]. It is not known, however, if this is caused by differences in the sensation of pain, cognitive response to pain, or reporting bias [27]. Women also report more extraintestinal symptoms, such as nausea, urinary urgency, and dyspareunia, and are more likely to report symptoms of constipation and bloating [31–35].

Symptoms in women vary according to the menstrual cycle, with increased reporting of GI symptoms in the late luteal and menses phases when compared with the midfollicular phase [36]. In particular, women report looser stools and more GI symptoms just before and during menses and rectal sensitivity has been shown to be greater in women with IBS in menses compared with women with IBS in other phases of the menstrual cycle [37].

With regard to gender differences in IBS treatment, serotonergic agents, such as the 5-hydroxytryptamine (HT)₃ antagonist alosetron, seem to have a more robust effect in women with IBS-D than in men [38,39]. This difference could be related to small sample sizes, differences in drug metabolism, or the interaction between serotonin and estrogen [27] but is likely related to a combination of gender-based differences in peripheral and central mechanisms.

DIAGNOSTIC EVALUATION OF IRRITABLE BOWEL SYNDROME
The diagnosis of IBS is symptom-based because there are not yet diagnostic biomarkers for IBS. The symptom-based Rome III criteria had a sensitivity of 0.707 and a specificity of 0.878 in the validation sample of 328 patients.
who had received a clinical diagnosis of IBS [40]. Although the presence of “red flag” or alarm signs and symptoms may indicate a need for further diagnostic work-up, it is not recommended that patients with red flag symptoms be excluded from the diagnosis of IBS. On average, IBS patients report the presence of at least 1.65 red flag symptoms [41]. Nocturnal symptoms (40%) and onset over the age of 50 (32%) were most common alarm signs. Alarm signs and symptoms include the following:

- Age ≥50
- Unintentional weight loss
- Family history of GI malignancy
- Severe unrelenting large-volume diarrhea
- Fevers, chills, recent travel to endemic region
- Nocturnal symptoms
- Hematochezia
- Relevant findings on physical examination (arthritis, skin lesions, lymphadenopathy, abdominal mass)

Historically, IBS has been a diagnosis of exclusion, but current best evidence suggests that a battery of diagnostic tests is not necessary because the prevalence of organic disease is not increased in the population with symptoms of IBS without alarm features, and the positive predictive value of such tests remains small [42,43]. Diagnostic tests are likely unnecessary, including blood tests, stool tests, lactulose breath tests, abdominal imaging, and colonic imaging; however, further research on the use of diagnostic testing is warranted. Diagnostic tests may reveal incidental findings or findings that are not related to the symptoms of IBS. Additionally, a negative finding on colonoscopy is not associated with an increased sense of reassurance in patients with IBS [44]. There are several scenarios in which diagnostic testing is recommended: (1) stool ova and parasite testing for patients who have recently traveled to endemic regions or for immunocompromised individuals, (2) colonoscopy in patients over 50 years of age for colon cancer screening, and (3) testing in patients who have not improved despite symptom-based treatment. There is good evidence that serologic testing for celiac disease followed by endoscopic biopsy confirmation of positive results is a cost-effective strategy in North American IBS-D patients [45].

Small bowel bacterial overgrowth has been theorized to play a role in the symptoms of IBS. Although some studies have shown an increased prevalence of small bowel bacterial overgrowth in IBS as diagnosed by a lactulose breath test [46,47], the use of this diagnostic tool is limited by the lack of evidence that treatment of small bowel bacterial overgrowth with antibiotics leads to long-term abatement of IBS symptoms.

Testing for lactase deficiency is not generally recommended because true lactose malabsorption is not well-correlated with reported lactose intolerance [48] and because lactose restriction has not been shown to improve IBS symptoms [49,50]. This is likely because lactose intolerance coexists with IBS but is not the predominant cause of symptoms.
TREATMENT

Patient-Centered Care

A good health care provider–patient relationship is the cornerstone of effective care of IBS. The quality of this relationship has been shown to improve patient outcomes [51]. Elements of a good provider-patient relationship include a non-judgmental patient-centered interview, a careful and cost-effective evaluation, inquiry into the patient’s understanding of the illness, patient education, and involvement of the patient in treatment decisions [6]. Because IBS is a chronic disease, it is important to assess specific reasons for the current visit, which may differ among patients (eg, concern about cancer, worsening pain, lack of response to treatment, and so forth) [52]. An intrinsic part of the clinical assessment is the psychosocial interview, which is usually quite relevant in IBS patients. Because IBS patients may have stress-related symptoms or comorbid psychologic symptoms, the psychosocial interview may uncover previously unexpressed associated symptoms and concerns that could be contributing to the patient’s illness severity, daily functioning, and health-related outcome. Addressing psychosocial factors may improve health status and treatment response [53].

Diet

Many patients report an inconsistent symptom response to certain foods, and a 1- to 2-week food and symptom diary can aid in careful analysis of potential food triggers. Although most patients cannot completely control symptoms through diet alterations alone, diet-related exacerbations may be minimized. Common food triggers include high-fat foods, raw fruits and vegetables, and caffeinated beverages.

There is some evidence that the symptoms of IBS are related to a visceral hypersensitivity to low-grade immune reactivity that does not cause symptoms in the general population. A group in the United Kingdom conducted a randomized controlled trial of food elimination based on IgG levels. IBS patients were given either a list of foods to which they had increased levels of IgG or a sham diet of similar foods to eliminate. Twenty-eight percent of patients adhering to the true diet had global improvement of symptoms versus 16.7% on sham diets. This difference was statistically significant and corresponds to a number-needed-to-treat of 9. A larger percentage of patients who fully adhered to the diet had improved symptoms (54% versus 15% of strict adherers to the sham diet), corresponding to a number-needed-to-treat of 2.5. Additionally, resumption of the regular diet caused a worsening of symptoms in a greater percentage of those following the true diet than the control diet. There was not a significant effect on HRQOL. It has been suggested, however, that the effect seen in this study was a result of diet alone regardless of IgG levels. IgG levels have not been shown to be predictive of food intolerance and a large percentage of patients in the true diet treatment group eliminated milk and wheat, which are known to affect symptoms in IBS [54,55]. Modification of diet may affect symptoms regardless of whether or not there is true food intolerance.
Pharmacologic Agents
In 2002, the American College of Gastroenterology (ACG) Functional Gastrointestinal Disorders Task Force published a comprehensive systematic review on the treatment of IBS [56]. In a subsequent publication in 2005, Schoenfeld [57] updated and expanded on the ACG’s review. The section of this article focusing on pharmacologic treatment summarizes these findings, taking into account high-quality trials that have since been published (Table 2).

Bulking Agents
Bulking agents include psyllium, methylcellulose, corn fiber, calcium polycarbophil, and ispaghula husk. Fiber supplementation has often been used as initial management of IBS; however, the ACG Functional Gastrointestinal Disorders Task Force evaluated randomized, placebo-controlled treatment trials for IBS and found that none of the trials of bulking agents were of high quality [56]. A meta-analysis showed a small, but significant improvement with soluble fiber (psyllium, ispaghula, calcium polycarbophil), but not with insoluble fiber (corn, wheat bran) [58]. This meta-analysis is limited by the inclusion of results from divergent studies and the extrapolation of end points [57]. Fiber may increase stool frequency in IBS-C, but it is not clear whether this is well-correlated with relief of pain or other symptoms. Additionally, bulking agents in quantities that are therapeutic can cause adverse effects including bloating and abdominal pain and discomfort, and it may be helpful to recommend a gradual initiation of the dose to minimize side effects, particularly in those who have relatively little fiber in their diets or those with predominant bloating [57].

Antidiarrheal Agents
The use of antidiarrheal agents has shown no benefit for global IBS symptoms or abdominal pain [56,57]. Loperamide seems to be effective at prolonging intestinal transit time and improving stool consistency in IBS-D. These agents may be very useful in some IBS-D patients to manage stool urgency, frequency, and fecal incontinence. They can be used on a more regular basis in patients with more frequent symptoms or on an as-needed basis. It is often useful for patients to use antidiarrheals prophylactically before leaving the house, a long car trip, a meal, or a stressful event. This can decrease both the diarrhea and the anticipatory stress often felt by patients before a known symptom trigger.

Laxatives
Osmotic laxatives are available over the counter and are widely used in the treatment of IBS-C and chronic constipation. Although no randomized, controlled studies have shown efficacy of laxatives in IBS, they may be useful in treating the constipation symptoms in those with IBS-C. Osmotic laxatives, such as polyethylene glycol or magnesium-containing products, are generally safe and well tolerated. Polyethylene glycol can be easily titrated by the patient, allowing adjustment in stool frequency and consistency as symptoms vary.
<table>
<thead>
<tr>
<th>Table 2</th>
<th>Agents available to treat irritable bowel syndrome by predominant symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Constipation</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Drug class</strong></td>
<td><strong>Generic name</strong></td>
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<tr>
<td>Bulking agents</td>
<td>Psyllium</td>
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<tr>
<td></td>
<td>Methylcellulose</td>
</tr>
<tr>
<td></td>
<td>Polycarbophil</td>
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<td>Laxatives</td>
<td>Osmotic</td>
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<tr>
<td></td>
<td>Stimulants</td>
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<td></td>
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</tr>
<tr>
<td>Emollients</td>
<td>Docusates</td>
</tr>
<tr>
<td>5-HT4 agonist</td>
<td>Tegaserod</td>
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<tr>
<td><strong>Diarrhea</strong></td>
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<td><strong>Drug class</strong></td>
<td><strong>Generic name</strong></td>
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<td>Antidiarrheals</td>
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<tr>
<td>Binding agents</td>
<td>Diphenoxylate</td>
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<tr>
<td>5-HT3 antagonist</td>
<td>Cholestyramine</td>
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<tr>
<td></td>
<td>Alaseteron</td>
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<tr>
<td>Tricyclic antidepressants</td>
<td>Amitriptyline</td>
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<td></td>
<td>Doxepin</td>
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### Table 2 (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>Imipramine</td>
<td>10–150 mg qhs</td>
<td>Most empiric evidence for efficacy. Less sedation and constipation</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>25–100 mg qhs</td>
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</tr>
<tr>
<td>Trimipramine</td>
<td>10–150 mg qhs</td>
<td></td>
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<tr>
<td>Desipramine</td>
<td>10–150 mg qhs</td>
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</tr>
<tr>
<td>Nortriptyline</td>
<td>10–150 mg qhs</td>
<td>Least sedating</td>
</tr>
</tbody>
</table>

**Pain/Bloating**

<table>
<thead>
<tr>
<th>Antispasmodics</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyoscamine sulfate</td>
<td>0.125 mg sl/po qid prn, 0.375 mg po bid</td>
<td></td>
</tr>
<tr>
<td>Dicyclomine</td>
<td>10 mg po bid</td>
<td></td>
</tr>
<tr>
<td>Propantheline hydrochloride</td>
<td>15 mg tid a.c. and 30 mg qhs</td>
<td></td>
</tr>
<tr>
<td>Clidinium + chlordiazepoxide</td>
<td>5–10 mg tid–qid</td>
<td></td>
</tr>
<tr>
<td>Hyoscamine + scopolamine + atropine + phenobarbital</td>
<td>1–2 tablets tid–qid</td>
<td></td>
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</tbody>
</table>

**TCAs**

<table>
<thead>
<tr>
<th>Fluoxetine</th>
<th>10–40 mg qd</th>
<th>Long half-life; less withdrawal effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>20 mg qd</td>
<td>Less side effects and drug interactions</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20–50 mg qd</td>
<td>Short half-life; more likely withdrawal effects. Greater anticholinergic effect; use in IBS-D</td>
</tr>
</tbody>
</table>

| Sertraline            | 25–100 mg qd               | Requires dose ranging                                                |
| Escitalopram          | 10 mg qd                    | Less side effects and drug interactions                              |

**SNRIs**

| Venlafaxine           | 37.5–75 mg bid–tid          | FDA approved for depression and diabetic neuropathy. Unlabeled uses include chronic pain syndromes, fibromyalgia, stress incontinence. Ongoing open labeled trial for IBS. |
| Duloxetine            | 40–60 mg qd                 |                                                                       |

**5-HT₄ agonist**

| Tegaserod             | See above                   |                                                                       |

**Antibiotics**

| Rifaximin             | 400 mg tid                  |                                                                       |

**Probiotics**

| Bifidobacterium infantis | 1 tablet qd |                                                                       |
| VSL # 3                | 1 packet bid    |                                                                       |

**Abbreviations:** a.c., before meals; bid, twice daily; g, grams; mg, milligrams; oz, ounces; qd, daily; qhs, at night; qid, four times daily; Tbsp, tablespoon; tid, three times daily; tspn, teaspoon.
Lactulose and sorbitol may also increase stool frequency, but are often associated with the side effects of bloating or cramping in IBS patients. Stimulant laxatives, such as senna, cascara, or bisacodyl, are useful on an intermittent basis for refractory constipation, although frequently cause cramping, loose stools, and urgency.

Antispasmodics

Antispasmodics work either by a direct effect on intestinal smooth muscle (e.g., mebeverine, pinaverine) or by their anticholinergic or antimuscarinic properties (e.g., dicyclomine, hyoscyamine). A meta-analysis evaluated 23 randomized clinical trials (RCTs) and reported a significantly higher global improvement with drug versus placebo (56% versus 38%) and a greater pain improvement (53% versus 41%) [59]. The ACG systematic review, however, evaluated 18 English-language RCTs assessing the efficacy of antispasmodic agents [56]. This review concluded that there is little evidence for the efficacy of antispasmodics for global relief of IBS symptoms [57]. Most of these studies have short duration, small sample sizes, and suboptimal quality. Of three higher-quality RCTs [60–62], only one showed a significant difference between placebo and treatment (dicyclomine), but this was using a dose high enough to cause 15% of the treatment group to withdraw from the study because of adverse effects compared with no withdrawals in the placebo group [62]. Side effects of these agents include dry mouth, constipation, urinary retention, and visual disturbances.

Serotonergic Agonist or Antagonists

Tegaserod

Tegaserod is a selective 5-HT4 partial agonist that stimulates gut transit and may also have an effect on visceral sensation [63,64]. Tegaserod was approved by the Food and Drug Administration (FDA) for the treatment of IBS-C in women and more recently has been approved for the treatment of chronic constipation in men and women under the age of 65. On March 30, 2007, however, Novartis Pharmaceuticals suspended marketing of Zelnorm (tegaserod) because of important safety information. This suspension occurred at the request of the FDA because of the incidence of cardiovascular ischemic events being significantly higher with Zelnorm treatment than with placebo treatment (13 per 11,614 [0.11%] with Zelnorm and 1 per 7031 [0.01%] with placebo [P = .024]).

Several large and well-designed trials have shown tegaserod to be more effective than placebo in improving symptoms of IBS-C [65–68]. More recent studies have shown that tegaserod remains as effective with repeated use (after a treatment-free interval) as it is in initial therapy, and there is no rebound effect (worsening of symptoms after treatment withdrawal) [69,70]. In addition to improving IBS-C symptoms, tegaserod has been proved to improve outcomes related to productivity and work impairment [71].

Alosetron

Alosetron is a 5-HT3 receptor antagonist that is currently available under a restricted use program and is approved only for women with severe IBS-D who
have failed conventional therapy. This restriction is because of the occurrence of GI-related adverse events including ischemic colitis and serious complications of severe constipation. These events occurred at a rate of 1.1 per 1000 patient years for ischemic colitis and 0.66 per 1000 patient years for serious complications of constipation [72]. A recent systematic review concluded that there is a significantly increased rate of ischemic colitis among alosetron-using patients compared with placebo-using patients (0.15% versus 0.0%), but no significant difference in the rate of serious complications of constipation. All of the alosetron-using patients with ischemic colitis had a reversible colopathy without long-term sequelae and most cases occurred within the first month of treatment [73]. The restriction notwithstanding, alosetron has been proved efficacious in seven placebo-controlled trials with over 3000 patients with nonconstipation IBS. Five of the seven studies showed relief of abdominal pain or discomfort and two showed relief of urgency [72]. There is a recently published placebo-controlled long-term study that demonstrated significant efficacy of alosetron compared with placebo over a treatment period of 48 weeks [74]. Alosetron is not FDA-approved for the treatment of IBS-D in men, but one trial did show an increased rate of relief from symptoms during 8 weeks of treatment with 1 mg alosetron twice a day (53%) compared with placebo (40%) [39]. Alosetron significantly reduced stool consistency scores indicating more formed stools; however, no significant effects of alosetron were seen with regard to the other secondary symptom end points.

Antidepressants

Tricyclic antidepressants

The rationale of using antidepressants in IBS is that these agents may alter pain perception by a central modulation of visceral afferents, treat comorbid psychologic symptoms, and alter GI transit. Different classes of antidepressants likely act by different combinations of mechanisms. Tricyclic antidepressants are the best studied, and are often used at low doses, because their major impact in IBS may be more associated with an analgesic effect rather than treatment of psychologic symptoms. A systematic review found that none of the seven randomized placebo-controlled trials evaluating the effect of tricyclic antidepressants in the treatment of IBS were of high quality because of relatively small sample sizes and poorly defined primary and secondary end points [56]. A large randomized 12-week placebo-controlled trial, which evaluated the efficacy of desipramine in treating moderate to severe functional bowel disorders, conducted by Drossman and colleagues [75], however, was published subsequent to the systematic review. Desipramine was shown to have statistically significant benefit over placebo in the per protocol analysis, which included only those patients who completed treatment (responder rate 73% versus 49%), but not in the intention-to-treat analysis. The lack of benefit in the intention-to-treat analysis may have been related to a significant drop out rate primarily because of symptom side effects. This study also found that the patients most likely to improve with desipramine were patients with
IBS-D, no depression, and mild to moderate symptoms. The most common side effects associated with tricyclic antidepressants include dry mouth, constipation, and drowsiness. Often initiating the drug at the lowest available dose and increasing it gradually can minimize adverse events while trying to achieve a therapeutic effect (e.g., starting dose of 10 mg at bedtime and increasing up to 75 mg if needed). In patients who have coexistent sleep disturbances, amitriptyline may be a good choice because it has a greater sedative effect caused by its more potent antihistaminic effects. Desipramine and nortriptyline are less sedating. If a tricyclic antidepressant is used in IBS-C, desipramine should be considered because it has less anticholinergic effects and is less constipating than the other tricyclic antidepressants.

**Selective serotonin reuptake inhibitors**

Selective serotonin reuptake inhibitors are commonly used to treat IBS even though there have been relatively few placebo-controlled trials. Preliminary evidence suggests that selective serotonin reuptake inhibitors have an effect on overall HRQOL, symptom frequency, and abdominal pain, and these effects seem to be independent of effects on mood. A RCT of paroxetine in IBS patients who failed therapy with a high-fiber diet showed a greater increase in overall well-being with paroxetine than placebo [76]. This was true for depressed and nondepressed participants [76]. Fluoxetine was evaluated in 44 patients with IBS-C and was more effective than placebo in decreasing the frequency of symptoms including abdominal discomfort and bloating and increasing frequency of bowel movements and improving consistency of stool [77]. A controlled crossover study of citalopram in 23 nondepressed IBS patients showed an improvement in abdominal pain, bloating, and overall well-being [78]. There is more evidence for the efficacy of tricyclic antidepressants as analgesics, but tricyclic antidepressants are not as well tolerated as selective serotonin reuptake inhibitors. Large, high-quality trials are needed to evaluate the effectiveness of selective serotonin reuptake inhibitors in IBS; however, in patients with severe IBS, treatment with selective serotonin reuptake inhibitors may be helpful and has been shown to be cost-effective when compared with routine care [79]. Combined serotonin-norepinephrine reuptake inhibitors, such as venlafaxine and duloxetine, may have possible beneficial effects in IBS but further studies are needed.

**Antibiotics**

Small bowel bacterial overgrowth has been theorized to play a role in IBS and is supported by an abnormal lactulose breath test in most IBS patients [46,47]. Rifaximin is an antibiotic that has very low systemic absorption and broad-spectrum activity against gram-positive and gram-negative aerobes and anaerobes. In a randomized, double-blind placebo-controlled trial, 400 mg of rifaximin given three times per day for 10 days was superior to placebo in improving global symptoms (mean improvement of 36.4% versus 21%) and bloating (but not abdominal pain, diarrhea, or constipation). The effects were present throughout the 10-week follow-up of the study. Although difficult to evaluate in a small
sample (N = 87), adverse effects were uncommon and included nausea and abdominal pain [80]. Future studies including an ongoing multicenter RCT will likely provide more information on the efficacy of this antibiotic treatment in IBS.

**Probiotics**

Probiotics are hypothesized to work by several mechanisms. These include a shift from a proinflammatory to an anti-inflammatory cytokine profile, the reduction of bile acid delivery to the colon, and alteration of motility [81]. A trial of probiotics comparing either *Bifidobacterium infantis* (*B infantis*) or *Lactobacillus salivarius* with placebo in 75 patients with IBS over a 12-week treatment period showed a significant reduction in abdominal pain and discomfort, bloating, and difficulty with bowel movements with *B infantis* but not with *L salivarius* [82]. IBS patients were found to have a decreased blood interleukin-10/interleukin-12 ratio indicative of a proinflammatory, Th-1 state. Normalization of this ratio occurred in patients who received *B infantis* but not in those taking *L salivarius* or placebo. A larger study (N = 362) from the same group further evaluated *B infantis* in a capsule formulation in women with IBS seen in a primary care setting. A dose of 1 × 10^8 colony-forming units given once a day over 4 weeks significantly reduced specific symptoms of IBS and global assessment compared with placebo or lower doses of *B infantis*. A higher dose of *B infantis* was not observed to be beneficial, but this may have been caused by problems with dissolution of the capsule [83].

Data from placebo-controlled trials also exists for VSL# 3, a probiotic that is a combination of three species of *Bifidobacteria*, four species of *Lactobacilli*, and *Streptococcus salivarius* ssp. *thermophilus*. VSL#3 decreased flatulence but did not show clinical efficacy for overall relief of IBS symptoms [84,85]. Another probiotic mixture (*Lactobacillus rhamnosus* GG, *L rhamnosis* LC705, *Bifidobacterium breve* Bb99, and *Propionibacterium freudenreichii* ssp. *shermanii* JS) was effective in reducing IBS symptoms overall, but when the effect on individuals symptoms was analyzed, there was only a statistically significant reduction of borborygmi, and HRQOL was not significantly improved [86].

**Novel Drugs in Development for Irritable Bowel Syndrome**

There are a number of drugs in various phases of drug development that are being studied for the treatment of IBS. Many of these agents have novel mechanisms of action. Drugs undergoing phase III clinical trials for IBS include the chloride channel activator lubiprostone and the 5-HT₄ agonist–5-HT₃ antagonist renzapride. Lubiprostone is a FDA-approved treatment of chronic constipation in men and women that was demonstrated to be efficacious at a dose of 24 μg twice daily in improving stool frequency, stool form, and straining [87,88]. Renzapride improved stool consistency and frequency in IBS-C patients but provided no overall relief of abdominal pain and discomfort [89]. Camilleri and colleagues [90] reported that renzapride was associated with an improvement in bowel function scores and a significant linear dose response for colon transit in 48 IBS-C patients, but there was no significant effect on
gastric emptying and small intestinal transit. Acceleration of colon transit positively correlated with improvements in ease of passage and stool form but not with stool frequency. Tack and colleagues [91] recently showed that a dose of 2 mg twice daily reduced overall colonic transit time and in the cecum–ascending colon and descending colon. Other drugs in various stages of development for IBS include a CRF₁ antagonist; neurokinin antagonists; guanylate cyclase-C agonist (linaclotide); 2,3-benzodiazepine (dextofisopam); kappa opioid antagonist (asimadoline); serotonin noradrenergic reuptake inhibitor ( duloxetine); novel serotonergic agents; and opioid receptor agents.

Nonpharmacologic Agents

There are several psychologic treatments for which there is convincing evidence of efficacy. Cognitive-behavioral therapy is a short-term, goal-oriented form of psychotherapy that focuses on the role that thoughts play in determining behaviors and emotional responses. In IBS, the overall negative effect of symptoms may be increased by such thoughts as “there is something wrong with my body” or “what will people think if I go to the bathroom again?” [92] Cognitive-behavioral therapy helps patients to identify these thoughts as they occur and to find alternative, more constructive ways to view the situation. It also helps people become aware of and be more in control of their own autonomic physiology. Cognitive-behavioral therapy was more effective than patient education in terms of global well-being and satisfaction with treatment and no different than desipramine in one randomized controlled trial [75]. In another high-quality study, cognitive-behavioral therapy was shown to improve symptoms but was no different than standard care or relaxation therapy [93].

Gut-directed hypnotherapy is another area in which there has been substantial research. Gut-directed hypnotherapy is hypnosis that is directed toward relaxation and control of intestinal motility by repeated suggestion of control over symptoms followed by ego-strengthening [94]. It is difficult to compare studies, because they have used different controls and end points and because hypnosis is highly operator-sensitive. Yet, many have reported positive results, and a recent systematic review [95] concluded that the evidence suggests that hypnotherapy is effective, but warned that the studies were conducted in referral centers and the subjects for the most part had refractory IBS of a long duration, and so the results may not apply to all clinic settings [95].

Complementary and Alternative Medicine

Because even the most effective treatments for IBS do not help all patients, many turn to complementary and alternative medicine in search of other treatment options. Furthermore, many patients prefer complementary and alternative medicine treatments because they view them as natural and time-tested. In addition, complementary and alternative medicine treatments often provide a more holistic approach and meaningful clinician-patient relationship than western medicine. It is important for clinicians to have an understanding of these treatments and whether there is any evidence for their efficacy.
Acupuncture has been a popular therapy for IBS patients. Despite the fact that theory predicts effectiveness of a treatment modulating ascending pain stimuli, it has not been well-studied and conclusions across studies are difficult to make because of nonstandardized experimental and placebo treatment modalities. The authors of a recent Cochrane review concluded that acupuncture was likely no better than sham acupuncture, but may have been better than other controls; however, more research is required to make any recommendations because of the heterogeneity of the studies [96].

Herbal medicine is another area of complementary and alternative medicine in which patients express interest. Theoretically, this is more amenable to rigorous randomized and controlled study designs, but few high-quality studies have been published. The best evidence is for Chinese herbal medicine. Bensoussan and colleagues [97] showed an improvement in symptoms and global scores over placebo for patients treated either with standard or individualized Chinese herbal medicine. Only those who received individualized Chinese herbal medicine treatment maintained a more sustained relief of their IBS symptoms. Peppermint oil has smooth muscle relaxant effects and there is some evidence that it may improve symptoms [98]. Other alternative or herbal medicines that have been studied are extract of artichoke [99], carmit [100], the herbal mixture STW 5 [101], and melatonin [102,103].

SUMMARY
IBS is a prevalent and heterogeneous disorder and patient care should be focused on reducing costs and improving patient satisfaction and HRQOL. The cultivation of a trusting and cooperative clinician-patient relationship reduces the ordering of unnecessary diagnostic tests and facilitates a collaborative effort of patient and clinician to find the treatment that provides the most relief of symptoms, and the greatest management of their illness and improvement of HRQOL.

References


