Current Diagnostic Strategies and Pharmacologic Treatment Options for Irritable Bowel Syndrome

by Anthony J. Lembo

The pathophysiologic mechanisms underlying irritable bowel syndrome (IBS) may involve altered small bowel motility, visceral hypersensitivity, and immune activation in the gastrointestinal tract. These mechanisms are not mutually exclusive and may vary among individuals, leading to a complex heterogeneity of symptoms that can make accurate diagnosis and optimal management of IBS challenging. Because no known biochemical markers identify IBS, diagnosis is determined by symptom-based criteria. These criteria have proven beneficial for clinical research purposes, but validation in clinical practice is limited. Current approaches to treatment of IBS include symptom-based pharmacologic interventions as well as therapies that target putative underlying mechanisms. However, few therapeutic agents have been rigorously evaluated in high-quality clinical trials. Furthermore, clinical studies of IBS therapies have a high placebo response rate, making conclusions about treatment efficacy difficult. Given these challenging issues, current diagnostic strategies and optimal treatment options for individuals with IBS are discussed.

KEY WORDS: Rome criteria, Manning criteria, antispasmodics, antidepressants, serotonin-modifying agents, antibiotics

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal (GI) disorder with an estimated prevalence of up to 20% in the United States (1).

Although few individuals with IBS seek medical treatment for their symptoms (1), IBS is the most frequent diagnosis made by gastroenterologists (2). Individuals with IBS have reduced health-related quality of life, substantially decreased work productivity, and an increased number of missed workdays compared with healthy individuals (3). Furthermore, the economic
burden of IBS in the United States is estimated to be in excess of $1.6 billion per year in direct medical costs (4).

Irritable bowel syndrome is characterized by abdominal pain and discomfort associated with altered bowel habits, which can vary from constipation to diarrhea or can alternate between periods of both symptoms (5). Additional symptoms of IBS may include abdominal bloating, flatulence, and sensation of incomplete evacuation. Putative underlying mechanisms contributing to the pathophysiology of IBS include altered intestinal motility, abnormal visceral perception, psychological distress, and environmental triggers within the intestinal lumen (e.g., food allergens) (1). These physiologic mechanisms can result from disruption of the GI tract due to infection, dietary or lifestyle changes, or psychologic stress (6). Additionally, pathophysiologic mechanisms contributing to IBS are not mutually exclusive, and specific GI dysfunction may vary among patients.

Currently, there are no known biochemical markers for identifying individuals with IBS. Thus, IBS diagnosis is determined by symptom-based criteria (e.g., Manning [7], Rome I [8], Rome II [5], Rome III [9]) and exclusion of other organic or functional conditions that may have similar clinical presentations (1,6,10). Screening studies, including blood chemistry and stool examination, and testing for celiac disease have been recommended (6,10). In the absence of “red flag” symptoms (e.g., weight loss, bloody stool, family history of colon cancer) additional testing may not be necessary (6,10). However, evaluation with flexible sigmoidoscopy, barium enema, or colonoscopy may be appropriate for some patients (1,6).

Current pharmacologic treatment of IBS is based on the predominant clinical symptoms. Only a limited number of therapeutic agents have been rigorously evaluated in randomized, controlled trials. Furthermore, the mean placebo response rate in clinical studies involving patients with IBS is approximately 40%, which is among the highest placebo rates reported from all randomized controlled trials conducted (11,12). A 2005 meta-analysis of 45 randomized, controlled trials that evaluated this high placebo response rate reported that inclusion of more stringent diagnostic criteria and an increased number of doctors’ visits during the trials correlated with a lower placebo response rate (11). Further understanding of factors that can impact the placebo response rate in IBS trials will allow the design of future clinical studies to minimize the placebo effect (11,12). In summary, the complexity of IBS pathology makes accurate diagnosis and optimal management of this disorder challenging, and continued efforts to evaluate therapeutic interventions in well-designed clinical studies are necessary.

**APPROACHES TO DIAGNOSING IBS**

Because no accurate diagnostic test is currently available to positively identify IBS, diagnosis is primarily based on symptom-based criteria (e.g., Manning [7], Rome I [8], and Rome II [5]; Table 1) (13). The Rome III criteria, which were introduced in 2006, differ from the Rome II criteria by requiring the presence of clinical symptoms for at least 6 months and active symptoms for the last 3 months (9). In contrast, the Rome II criteria only require clinical symptoms to be present within the year prior to diagnosis. The diagnosis of IBS varies depending on which criteria are used. In a clinical study of 100 patients, 73% met the Rome II criteria, 82% met the Rome I criteria (p < 0.05 vs Rome II), and 94% met the Manning criteria (p < 0.01 vs Rome II) for IBS (14).

Symptom-based criteria for the diagnosis of IBS are useful not only in clinical research but also in clinical practice. For example, a retrospective study showed that the Rome I criteria, in combination with the exclusion of red flag symptoms, had a sensitivity of 65%, a specificity of 100%, and a positive predictive value of 100% in establishing the diagnosis of IBS in an outpatient GI clinic (15). Additionally, symptoms of IBS fluctuate over time. For example, in a follow-up to a 2001 population-based survey (N = 697), 52% of patients who met Rome II criteria for IBS in the 2001 survey no longer met the same criteria in 2004 (16). Interestingly, 82% of patients in the follow-up survey who no longer met the Rome II criteria for IBS had failed to meet the requirement for the presence of abdominal pain for at least 12 weeks in the prior year. However, 45% of these individuals reported at least two symptoms that fulfilled the Rome II criteria for IBS (16).
Some research suggests that extensive diagnostic testing may not be required to exclude organic disease prior to making a diagnosis of IBS. A meta-analysis of six studies found that the probability of inflammatory bowel disease, colorectal cancer, or infectious diarrhea prior to diagnostic testing for organic GI disease (e.g., endoscopy, ultrasonography, blood chemistry tests) was <1% in patients who satisfied symptom-based criteria for IBS (10). The authors of the meta-analysis concluded that these tests were not beneficial in excluding a diagnosis of IBS. Similarly, a systematic chart review (N = 1,434) evaluated the utility of incorporating red flag symptoms into diagnostic criteria for IBS and reported that the positive predictive value of these symptoms for identifying organic disease was only 7%–9% (17). These findings suggest that red flag symptoms may identify patients who require more extensive evaluation but would not likely improve the sensitivity of Rome II criteria for diagnosing IBS.

**CURRENT PHARMACOLOGIC TREATMENT OPTIONS FOR IBS**

Current treatment for IBS depends on an individual’s predominant clinical symptoms, and available pharmacologic IBS therapies include bulking agents, laxatives, antidiarrheals, antispasmodics, antidepressants, antiinflammatory agents, 5-hydroxytryptamine (5-HT) modifying drugs, antibiotics, and probiotics. Until recently, the American Gastroenterological Association considered the majority of randomized, controlled trials of potential IBS therapies to be flawed and of poor quality (18). A 2001 assessment of controlled clinical IBS trials identified only six of 45 trials that
met the following criteria: an adequate description of the randomization procedure, double blinding, and a description of patient withdrawals and dropouts during the study (19). However, in the last several years there has been a substantial improvement in the quality of studies of new IBS treatments, and several therapies have demonstrated clinical efficacy in patients with IBS (20). Additionally, several emerging therapies are currently in clinical development for the treatment of IBS (Table 2).

### Bulking Agents

Bulking agents (e.g., psyllium, wheat bran, corn fiber) are thought to increase stool frequency and facilitate stool passage through acceleration of colonic transit (21). While advice to increase dietary fiber intake is given to up to 36% of patients with IBS (22), the benefits of fiber in the treatment of global symptoms of IBS are questionable. A 2004 meta-analysis evaluated the efficacy of soluble and insoluble fibers in the treatment of IBS (22). Of 17 trials analyzed (N = 1,363), 12 reported an overall improvement in IBS symptoms, but there was no evidence of benefit in patients with abdominal pain. Additionally, soluble and insoluble fiber may affect global IBS symptoms differently. Soluble fiber modestly improved global symptoms of IBS (relative risk, 1.55; 95% confidence interval [CI], 1.35–1.78) but not symptoms of abdominal pain or bloating, while insoluble fiber was comparable to placebo and slightly worsened global symptoms of IBS (relative risk, 0.89; 95% CI, 0.72–1.11) (22). A 2005 meta-analysis of 11 clinical trials that evaluated the efficacy of bulking agents in the treatment of IBS

### Table 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic class</th>
<th>Stage of development</th>
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<tbody>
<tr>
<td><strong>Bacterial flora modifiers</strong></td>
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<tr>
<td>Rifaximin</td>
<td>Nonsystemic antibiotic</td>
<td>Phase 2 (IBS-D/IBS-A)</td>
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<tr>
<td><em>Bacillus clausii</em> spores</td>
<td>Probiotic</td>
<td>Phase 4 (SIBO)</td>
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<td><strong>Receptor agonists and antagonists</strong></td>
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<tr>
<td>GW876008</td>
<td>CRF1 receptor antagonist</td>
<td>Phase 2</td>
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<tr>
<td>Asimadoline</td>
<td>Kappa-opioid receptor agonist</td>
<td>Phase 2b</td>
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<tr>
<td>NK modulators</td>
<td>NK-1, NK-2, and NK-3 receptor antagonists</td>
<td>Various stages of development</td>
</tr>
<tr>
<td>Talnetant</td>
<td>NK-3 antagonist</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Dextofisopam</td>
<td>2,3 Benzodiazepine receptor agonist</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Alpha-2 adrenergic receptor agonist</td>
<td>Phase 2/3</td>
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<tr>
<td>Renzapride</td>
<td>5-HT&lt;sub&gt;4&lt;/sub&gt; receptor agonist/5-HT&lt;sub&gt;3&lt;/sub&gt; receptor antagonist</td>
<td>Phase 3 (IBS-C)</td>
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<tr>
<td>DDP225</td>
<td>5-HT&lt;sub&gt;3&lt;/sub&gt; receptor antagonist</td>
<td>Phase 2 (IBS-D)</td>
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<tr>
<td>Linaclotide acetate</td>
<td>Guanylate cyclase-C receptor agonist</td>
<td>Phase 2 (IBS-C)</td>
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<td><strong>Channel activators</strong></td>
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<tr>
<td>Lubiprostone</td>
<td>Chloride channel activator</td>
<td>Phase 3 (IBS-C)</td>
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5-HT = 5-hydroxytryptamine; CRF = corticotropin releasing factor; IBS = irritable bowel syndrome; IBS-A = alternating-form IBS; IBS-C = constipation-predominant IBS; IBS-D = diarrhea-predominant IBS; NK = neurokinin; SIBO = small intestinal bacterial overgrowth.
found similar results (23). The most common adverse event associated with the use of bulking agents is increased gas, which can exacerbate bloating and abdominal discomfort in patients with IBS (24).

**Laxatives**

Stimulant laxatives (e.g., bisacodyl, senna extract) or osmotic laxatives (e.g., lactulose, sorbitol) are often administered to treat constipation, especially in patients who fail treatment with dietary fiber supplements (24). However, the efficacy of stimulant and osmotic laxatives in IBS has not been evaluated in randomized clinical trials. Additionally, these agents are associated with adverse events such as abdominal pain and severe diarrhea.

**Antidiarrheals**

Antidiarrheals are often administered to slow intestinal transit and enhance intestinal water absorption, resulting in decreased stool frequency and increased stool consistency (20,21). In four placebo-controlled clinical trials, the opioid agonist loperamide 2–12 mg/day for 3–13 weeks reduced stool frequency and increased stool consistency versus placebo (25–28). However, loperamide was not more effective in relieving IBS symptoms of abdominal pain or abdominal distention, and therefore, it is unlikely to be effective in relieving global IBS symptoms.

**Antispasmodics**

Antispasmodics (e.g., anticholinergics, smooth muscle relaxants, calcium-channel blockers) relieve abdominal pain through inhibition of contractile intestinal smooth muscle activity (21). Early controlled trials reported the efficacy of anticholinergics (e.g., dicyclomine, hyoscyamine) versus placebo; however, the studies evaluated small patient populations and did not apply standard criteria for identifying individuals with IBS (29,30). A 2001 meta-analysis identified 23 randomized clinical trials (N = 1,888) that reported superiority of select smooth muscle relaxants (e.g., mebeverine, cimetropium, hyoscine) versus placebo for global improvement of IBS symptoms (p < 0.001) and for percentage improvement in pain (p < 0.001) (31). To date, no antispasmodic has been approved by the US Food and Drug Administration (FDA) for the treatment of IBS (18). Adverse events commonly associated with antispasmodics include dry mouth, constipation, urinary retention, and vision impairment (24).

**Antidepressants**

Tricyclic antidepressants (TCAs; e.g., desipramine, amitriptyline, doxepin) are often prescribed to individuals with IBS and other pain-related disorders such as migraine, fibromyalgia, interstitial cystitis, and neuropathic pain. Three recent meta-analyses evaluated the effects of TCAs on functional GI symptoms (21,23,24,32). Two of these meta-analyses concluded that TCAs were beneficial (21,32), while one concluded that they were not superior to placebo (23). One meta-analysis evaluated 11 studies published between 1966 and 1988 and found a significant improvement of global symptoms of IBS with TCA therapy (32). However, a 2005 meta-analysis evaluated global symptom improvement from only four of these clinical trials, due to use of more restrictive inclusion criteria based on quality of study, and reported that TCAs were comparable to placebo for global symptom improvement in patients with IBS (pooled relative risk, 1.16; 95% CI, 0.78–1.73) (23). The most common adverse events associated with TCAs include dry mouth, dizziness, and constipation (24).

The role of other antidepressants in the treatment of IBS has not been well established. Recent studies with selective serotonin reuptake inhibitors (e.g., paroxetine, fluoxetine, citalopram) indicate that they may have a role in treating both depressed and non-depressed patients with IBS (33–36). The role of emerging monoamine reuptake inhibitors in IBS therapy has also not been established.

**5-Hydroxytryptamine Modifying Agents**

The neurotransmitter serotonin (5-HT) affects GI motility, secretion, and sensation and is hypothesized to be a key contributor to IBS pathophysiology (21). Antagonism of 5-HT3 receptors may result in reduced visceral pain, slowed colonic transit, and increased
small intestinal absorption (37). Two meta-analyses of placebo-controlled, randomized clinical trials reported that the efficacy of the selective 5-HT\textsubscript{3} receptor antagonist alosetron was superior to placebo in providing relief from abdominal pain and in improving the frequency, consistency, and urgency of bowel movements in adult female patients with diarrhea-predominant IBS (21,38). However, alosetron was withdrawn from the US market due to serious drug-related adverse events, including severe constipation, ischemic colitis, and bowel perforation and was only reapproved by the FDA in 2002 for women with severe IBS who fail to respond to other therapies (39).

Activation of 5-HT\textsubscript{4} receptors results in release of neurotransmitters that regulate the peristaltic reflex. Tegaserod has been evaluated in several large, double-blind, controlled trials employing Rome criteria for the diagnosis of IBS and is indicated in the United States for the treatment of constipation-predominant IBS (IBS-C) in adult females. Interestingly, the indication of tegaserod for females only is based on the lack of male patients enrolled in these pivotal clinical studies, rather than a lack of efficacy (21,40). A 2004 meta-analysis reported that tegaserod 4 mg or 12 mg daily for 12 weeks improved global symptoms of IBS and increased stool frequency in individuals with IBS-C (41). Another meta-analysis found similar results, reporting that tegaserod 12 mg daily significantly improved constipation, abdominal pain, bloating, and overall relief of global symptoms of IBS (95% CI, 1.2–1.5) (21). However, the mean difference between placebo and tegaserod for symptom relief was only 10%–15% due to the high placebo rate reported in these studies, a common occurrence in IBS clinical trials (11,12,21). Although tegaserod has demonstrated efficacy in clinical trials for IBS, this agent was removed from the market in the United States in 2007 due to safety concerns (42).

Antibiotics and Probiotics

An emerging hypothesis suggests that small intestinal bacterial overgrowth (SIBO) might explain the complexity of IBS pathophysiology (43). An abnormal breath test result serves as a diagnostic marker for SIBO and has been reported in 65%–84% of patients with IBS (44–47). Furthermore, approximately 92% of patients with IBS complain of abdominal bloating and pain, a finding possibly explained by abnormal fermentation characteristic of SIBO (43).

Results from clinical studies demonstrate that antibiotic treatment can reduce or eliminate SIBO and improve IBS symptoms (44,45,47–51). In a double-blind randomized study (N = 111), the systemic antibiotic neomycin 1 g/day for 10 days significantly improved IBS symptom scores in Rome I–positive patients with IBS versus placebo (p < 0.05) (45). Similar findings were reported in a subanalysis of this study that evaluated the efficacy of neomycin versus placebo in individuals with IBS-C (n = 39) (48).

The nonsystemic antibiotic rifaximin, which has low (<0.4%) systemic absorption following oral administration, has also been evaluated clinically for the treatment of IBS (49–51). A randomized, double-blind, parallel-group study assessed the efficacy of rifaximin 1,200 mg/day for 10 days in patients who met Rome I criteria for IBS (48). Rifaximin significantly improved global symptoms of IBS (p = 0.02) and bloating (p = 0.01) versus placebo at 10 weeks after discontinuation of rifaximin therapy. The long-term benefits of rifaximin have also been reported in other studies of functional GI disorders (50,51). Additionally, treatment with rifaximin has been associated with a placebo-like tolerability profile in multiple studies (49,51).

Regarding probiotic therapy, authors of a systematic review reported that the utility of probiotics in the treatment of IBS symptoms is limited and concluded that there is not enough clinical evidence to recommend the administration of probiotics for the treatment of IBS (20).

CONCLUSIONS

The continually evolving pathophysiology of IBS makes appropriate diagnosis and treatment challenging. Symptom-based criteria are often used to diagnose IBS; however, a large number of individuals suffer from multiple symptoms consistent with IBS but do not meet the currently accepted symptom-based diagnostic criteria. Thus, the future approach to the diagnosis of IBS should involve broader criteria to provide individuals with IBS or IBS-like symptoms a more
valid, durable diagnosis and to prevent individuals who may have IBS from being misdiagnosed as not having IBS. Application of the new Rome III criteria in diagnosing IBS may achieve this goal.

Currently, the primary goal of therapy is targeted management of specific IBS clinical symptoms. Although effective therapies for IBS remain limited, the outlook is promising. New agents, such as nontoxic antibiotics, chloride channel activators, and various receptor agonists and antagonists, in clinical development may provide additional treatment options. Further investigations in high-quality clinical studies are warranted to establish the role of these and other emerging therapies for the treatment of IBS.

References