

## REVIEW ARTICLE

## DRUG THERAPY

Alastair J.J. Wood, M.D., *Editor*

## Irritable Bowel Syndrome

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**I**RRITABLE BOWEL SYNDROME, A COMMON DISORDER IN WHICH BOWEL habits are altered in association with abdominal pain or discomfort, has a prevalence of 12 percent among adults in the United States and a similar prevalence worldwide.<sup>1</sup> By definition, no mechanical, biochemical, or overt inflammatory condition explains the symptoms. Validated, symptom-based criteria for the diagnosis of irritable bowel syndrome are highly predictive in the absence of alarming symptoms such as weight loss, fever, and intestinal bleeding.<sup>2-4</sup> The pain or discomfort experienced by patients with irritable bowel syndrome often leads to health care use and a decreased quality of life.<sup>5-7</sup> Diarrhea is a symptom that often leads to medical consultation,<sup>5</sup> since it can be inconvenient and, if associated with urgency, may be accompanied by fecal incontinence, an altered lifestyle (owing to frequent trips to the bathroom), and anxiety. Constipation may be associated with bloating, discomfort, and an altered body image. The quality of life was reported as impaired in people with irritable bowel syndrome who sought medical care but only marginally reduced in those who did not seek medical care.<sup>8,9</sup> The therapeutic goal is both a reduction in the severity and frequency of symptoms and an overall improvement in the quality of life.

The age at onset of irritable bowel syndrome varies, but the incidence appears to increase during adolescence and peaks in the third and fourth decades of life. An onset after the age of 50 years is unusual. Women have a higher prevalence of symptoms than men (2:1 ratio). Patients seen in clinics, particularly those who are referred for irritable bowel syndrome, appear to have a high frequency of psychosocial stress or dysfunction associated with the condition. However, persons with irritable bowel syndrome who do not seek medical care have no more psychological symptoms than unaffected controls.<sup>5,10</sup> Since psychosocial stress appears to predict both the use of health care and the persistence of symptoms, the patient's social history is relevant to therapy, and clinicians should attempt to determine what has triggered each consultation.<sup>11</sup>

## PATHOPHYSIOLOGY

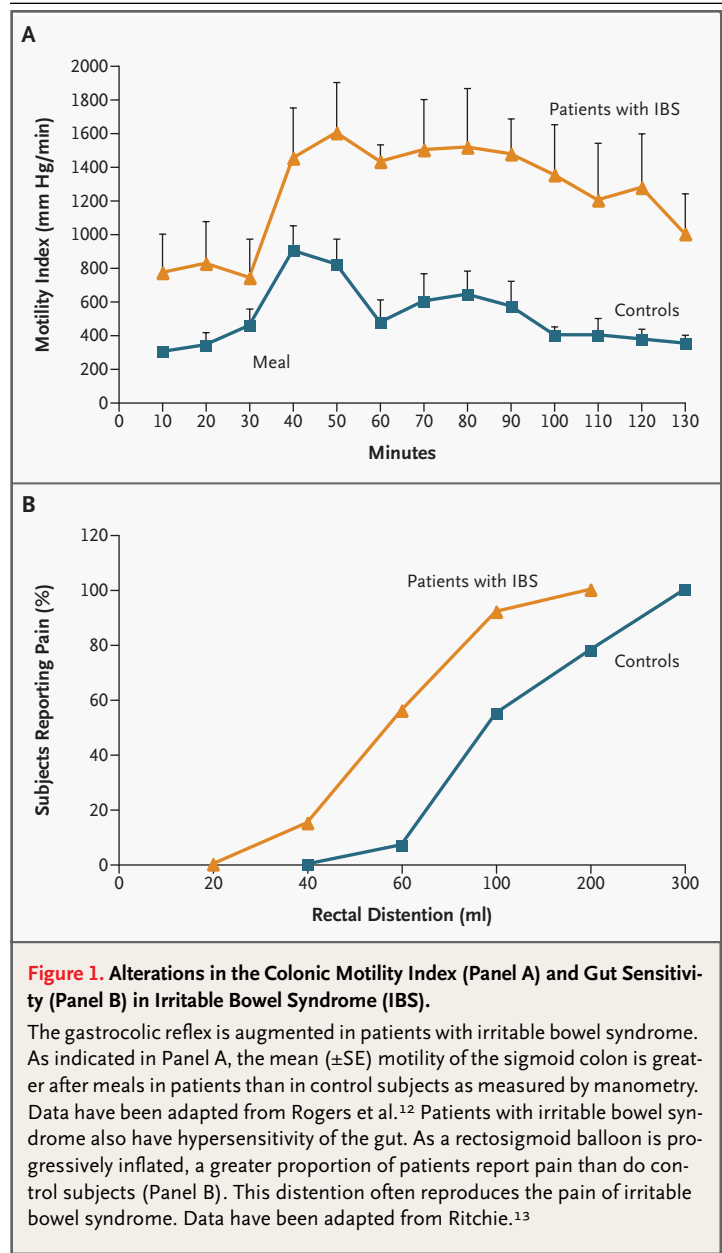
The cause of irritable bowel syndrome is unknown, though associated pathophysiology includes altered gastrointestinal motility and increased gut sensitivity (Fig. 1). Some studies,<sup>12,14</sup> but not all,<sup>15</sup> reported increased small-bowel and colonic contractions temporally associated with abdominal pain. Heightened sensitivity to visceral distention, particularly that which is perceived as noxious, has been described in numerous studies.<sup>13,16</sup> Interplay between motor and sensory dysfunction appears to explain the symptoms of irritable bowel syndrome. The gastrointestinal effects of stress in animals and humans include increased small-bowel and colonic motility and increased visceral sensitivity.<sup>17,18</sup> These effects appear to be exaggerated in patients with irritable bowel syndrome, as well as in animals previously sensitized by either visceral inflammation or psychological trauma.<sup>19-21</sup>

Patients with irritable bowel syndrome have been reported to have an increased colonic motor response to corticotropin-releasing factor, a stress hormone, consistent with the occurrence of an increased gastrointestinal stress response.<sup>22</sup> The gastrointestinal sensory-motor dysfunction in irritable bowel syndrome is consistent with an up-regulation in neural processing between the gut and the brain, termed the “brain-gut axis.” Indeed, therapies for irritable bowel syndrome are generally directed at gastrointestinal motor, gastrointestinal sensory, or central nervous system processing.

NONPHARMACOLOGIC THERAPIES

Nonpharmacologic therapies alone are adequate for many patients and should accompany pharmacologic therapy, when it is administered. A firm diagnosis of irritable bowel syndrome based on validated symptom criteria,<sup>2,3</sup> the absence of alarming symptoms, and a normal physical examination, coupled with limited relevant diagnostic testing, is reassuring to patients. Identification of psychosocial stressors that trigger or maintain symptoms should lead to supportive advice and lifestyle modification, which often reduces the number of visits to physicians.<sup>23</sup> Patients generally seek dietary advice, but specific diets or elimination diets have not been proven effective. Some studies indicate that elimination diets followed by sequential reintroduction of specific foods can be useful, though in these studies, patients and investigators were not blinded to the excluded foods. Furthermore, when no offending foods were identified during the reintroduction phase of the diet, most patients nevertheless did well.<sup>24</sup>

A reasonable approach to nonpharmacologic management includes avoidance of dietary excesses, caffeine, and dietary triggers the patient suspects of leading to symptoms. Moderation in fat intake is reasonable, since lipids amplify gut sensations and motor reflexes — effects that may be heightened in patients with irritable bowel syndrome.<sup>25</sup> Patients with diarrhea as the predominant symptom may have lactose intolerance or excess fruit or sorbitol intake that may exacerbate symptoms. Patients in whom constipation predominates may have inadequate fiber intake as a contributing factor. In patients with symptoms of bloating or flatulence, avoiding beans, cabbage, and uncooked broccoli and cauliflower may help. Exercise has been associated with improved outcomes in uncontrolled



**Figure 1. Alterations in the Colonic Motility Index (Panel A) and Gut Sensitivity (Panel B) in Irritable Bowel Syndrome (IBS).**

The gastrocolic reflex is augmented in patients with irritable bowel syndrome. As indicated in Panel A, the mean ( $\pm$ SE) motility of the sigmoid colon is greater after meals in patients than in control subjects as measured by manometry. Data have been adapted from Rogers et al.<sup>12</sup> Patients with irritable bowel syndrome also have hypersensitivity of the gut. As a rectosigmoid balloon is progressively inflated, a greater proportion of patients report pain than do control subjects (Panel B). This distention often reproduces the pain of irritable bowel syndrome. Data have been adapted from Ritchie.<sup>13</sup>

studies and is reasonable as a general recommendation.<sup>26</sup>

**THE PLACEBO EFFECT AND IRRITABLE BOWEL SYNDROME**

Symptoms of irritable bowel syndrome may respond to placebos, as reported by 20 percent to more than 50 percent of patients in some trials.<sup>27,28</sup> A salutary placebo effect appears to last at least three months.<sup>27,28</sup> As a result, the findings of any stud-

ies of therapy for irritable bowel syndrome that are not randomized, blinded, and placebo-controlled are difficult to interpret. In clinical practice, the placebo effect makes short-term effects of therapeutic trials difficult to interpret as well.

#### FIBER SUPPLEMENTS

Oral fiber supplementation has been widely recommended as therapy for irritable bowel syndrome, though supporting data are lacking. Fiber is indigestible plant carbohydrate (primarily cellulose, hemicellulose pectins, and lignins) that colonic bacteria metabolize into gas, fluid, and short-chain fatty acids. Fiber supplementation results in softer, wetter, bulkier stool, which can promote colonic peristalsis and ease defecation. Fiber accelerates stool transit in both control subjects and patients with irritable bowel syndrome and chronic constipation.<sup>29</sup> Controlled trials suggest that fiber supplements are effective for the constipation symptoms of irritable bowel syndrome, but not for pain or diarrhea.<sup>30-32</sup> In fact, many patients who take fiber, particularly those with diarrhea-predominant irritable bowel syndrome, have worsening of symptoms.<sup>32,33</sup> Since fiber may take one to three days to traverse the gut, symptoms of constipation may get worse before they improve. Patients should be advised of this possibility, and gradual introduction of fiber may be tried.

#### PSYCHOTHERAPY

Psychosocial stressors are important triggers for the symptoms of irritable bowel syndrome, and patients who seek a consultation for irritable bowel syndrome have a greater prevalence of psychological diagnoses than those who do not seek medical care. Thus, psychotherapy is expected to be useful. A variety of psychotherapy techniques, including cognitive behavioral therapy (directed at maladaptive perceptions of illness and behavior), dynamic psychotherapy (directed at interpersonal problems), relaxation therapy, and hypnotherapy, alone or in combination, are reportedly effective for symptoms.<sup>34-39</sup> A review of psychological treatments for irritable bowel syndrome identified 12 randomized, controlled trials in which the level of symptoms was the primary outcome<sup>38</sup>; 8 of these reported positive responses to psychotherapy. Two studies indicated that the marked improvement in symptoms during initial psychotherapy lasted for up to one year.<sup>34,36</sup> Diarrhea and pain appear to respond to psychotherapy, whereas constipation does not.

Patients with anxiety or depression appear to have a better outcome in response to psychotherapy than do patients without these conditions.<sup>34</sup>

It is difficult to blind patients to psychotherapy treatment; none of the published trials of psychotherapy are double-blind or placebo-controlled. In most trials patients are not representative of those seen in general practice but, rather, are identified in tertiary practices and are willing to enroll in therapy. Furthermore, psychotherapy requires a skilled practitioner, so results from selected centers may not be reproduced in general practice. Despite these caveats, psychotherapy is considered useful for selected patients with irritable bowel syndrome, particularly those who have relatively severe or refractory symptoms or prominent psychosocial issues.

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#### NONSPECIFIC BOWEL-DIRECTED THERAPY

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Initial therapy for irritable bowel syndrome should include measures to reduce specific symptoms related to constipation and diarrhea. Often in patients with constipation, regular passage of stool will reduce pain and bloating. Although antidiarrheal agents do not reduce the pain of irritable bowel syndrome, they can improve the quality of life if they decrease stool urgency and frequency.

#### TREATMENT OF CONSTIPATION

Constipation is a nonspecific symptom reported by patients who have slow transit of the colon, impaired defecation and straining, or a sensitive colon that causes a bloated feeling and a desire to defecate without result.<sup>40,41</sup> Fiber supplements such as psyllium seed, methylcellulose, and polycarbophil relieve constipation by accelerating stool transit and facilitating defecation. Fiber is unlikely to offer relief for bloating in patients with normal stool frequency. Fiber is also less likely to work for constipation in those with very slow colonic transit (e.g., more than five days between movements). In this situation, long-term use of an osmotic laxative is effective and safe. Magnesium salts, phosphate salts, and polyethylene glycol-based laxatives are effective when taken on a scheduled basis or as needed, and tachyphylaxis is rare.<sup>42,43</sup> Nonabsorbed carbohydrate laxatives such as sorbitol and lactulose are effective but expensive and can promote the formation of gas, which many patients find uncomfortable and difficult to expel.<sup>25,42</sup> Stimulant cathartics such as bisacodyl and senna are more likely than

other agents to cause cramping and are associated with both tachyphylaxis and dependency. In animal models, cathartics induce swelling and fragmentation of enteric neurons.<sup>44</sup> For these reasons, long-term use of stimulant cathartics should be avoided.

**ANTI-DIARRHEAL AGENTS**

The opiate and opioid analogues diphenoxylate-atropine and loperamide stimulate receptors in the enteric nervous system that inhibit peristalsis and fluid secretion. Loperamide has demonstrated efficacy against diarrhea, but not pain, in patients with irritable bowel syndrome.<sup>45</sup> Medications of the same class, such as diphenoxylate-atropine, would be expected to have similar efficacy. Loperamide may be preferable for long-term use because it is available without prescription, does not have an anticholinergic component, and does not induce euphoria at any dose. These agents can be used as needed or according to a schedule. A bile-acid binder such as cholestyramine may be added empirically to control refractory diarrhea. A night-time dose of a bile-acid binder is often very effective after cholecystectomy in patients with diarrhea-predominant irritable bowel syndrome.<sup>46</sup>

SPECIFIC THERAPIES

**ANTISPASMODIC AGENTS**

Antispasmodic agents relax the smooth muscle of the gut or reduce its contractility. Anticholinergic agents, calcium-channel blockers, and opiate antagonists may all act as antispasmodics, though only anticholinergic agents are approved for this indication in the United States (Table 1). Patients with irritable bowel syndrome typically have augmented colonic motility in response to meals (gastrocolic reflex), which can be associated with diarrhea and cramps<sup>47</sup> (Fig. 1A). Anticholinergic agents can reduce this excessive postprandial contractility.<sup>48</sup> The literature regarding various antispasmodic drugs for the treatment of irritable bowel syndrome is large; however, many trials lacked appropriate blinding, had small numbers of patients, were of short duration, and used unclear criteria to define a clinical response.

On balance, data from randomized trials indicate that antispasmodic agents decrease global symptoms and reduce pain. This effect is reviewed in two recent meta-analyses, which suggest that although these agents decrease pain, they have no effect on symptoms of diarrhea and constipation.<sup>49,50</sup> The

**Table 1. Antispasmodic Agents.**

Generic Name (Common Brand Name)	Dose
<b>Single agents</b>	
Belladonna	0.3–1.2 mg 4 times daily
Hyoscyamine (Levsin)	0.125–0.25 mg 4 times daily
Clidinium bromide	2.5–5.0 mg 4 times daily
Glycopyrrolate (Robinul)	1–2 mg 3 times daily
Dicyclomine (Bentyl)	10–20 mg 4 times daily
Mebeverine*	135–200 mg 3 times daily
Otilonium bromide*	20 mg 3 times daily
Cimetropium*	50 mg 3 times daily
<b>Combined sedative and antispasmodic agents</b>	
Clidinium and chlordiazepoxide (Librax)	2.5 mg and 5 mg 4 times daily or as needed
Butabarbital and belladonna (Butibel)	15 mg and 15 mg 4 times daily or as needed
Hyoscyamine, atropine, and phenobarbital (Donnatal)	0.1 mg, 0.02 mg, and 16 mg 4 times daily or as needed

\* This agent is not available in the United States.

odds ratio for global improvement with antispasmodic agents, as compared with a placebo, exceeds 2.0 on the basis of these two meta-analyses (Table 2), but this apparent beneficial effect may be overestimated, since a trial indicates that the serotonin-3-receptor antagonist alosetron (discussed below) is more effective than an antispasmodic agent, even though the odds ratio for global improvement with alosetron therapy is only 1.7.<sup>56</sup>

The heterogeneity of older studies and publication bias may lead to an overstatement of the effectiveness of antispasmodic medications. The antispasmodic agents available in the United States (Table 1) may not be the most efficacious; however, there are data to support the use of dicyclomine and hyoscyamine.<sup>57</sup> In practice, antispasmodic agents taken 30 minutes before meals can substantially inhibit the gastro-colic reflex, reducing postprandial urgency and cramps. Fast-acting sublingual antispasmodic agents are available that are appropriate for use on an as-needed basis. Long-acting forms are also available. Common but generally mild and rapidly reversible side effects of anticholinergic antispasmodic agents include dry mouth, blurred vision, fatigue, and urinary hesitancy. Narrow-angle glaucoma and urinary retention are contraindications. These drugs can be administered as needed for cramps, before meals that are expected to cause

**Table 2. Drug Therapy for Irritable Bowel Syndrome.**

Variable	Antispasmodic Agents*	Tricyclic Antidepressants*	Serotonin-4- Receptor Agonist†	Serotonin-3- Receptor Antagonist‡
Odds ratio for benefit	2.1	4.2	1.5	1.7§
Absolute increase in response rate over placebo (%)	22	33	9.3	13.2
No. needed to treat to benefit 1 patient	4.5	3.2	10.7	7.6

\* The results are from a meta-analysis of various trials and compounds.<sup>49,50,51</sup>

† The results are for constipation associated with irritable bowel syndrome and are from high-quality trials involving a single agent and a uniform design.<sup>28,52,53</sup>

‡ The results are for diarrhea associated with irritable bowel syndrome and are from high-quality trials involving a single agent and a uniform design.<sup>54,55</sup>

§ A direct comparison showed that this agent was superior to an antispasmodic agent.<sup>56</sup>

symptoms, or when postprandial symptoms would be relatively inconvenient. Because of the safety, low cost, and utility of antispasmodic agents given on an as-needed basis, these drugs are generally tried first if reassurance and nonspecific therapies fail to control symptoms.

Several formulations have combined benzodiazepine or barbiturate sedatives with anticholinergic drugs. Data from small studies support the efficacy of phenobarbital and belladonna in combination.<sup>58-60</sup> The combination compounds have a rationale for use and an extensive history. Anxiety increases intestinal motility as part of the stress response, and this response can be blunted by benzodiazepines.<sup>61</sup> Sedatives may reduce the central nervous system component of intestinal contractions, whereas antispasmodic agents reduce the intestinal motor response. The risk of dependency or recreational use of the anxiolytic component is very low, since the anticholinergic component causes unpleasant side effects in higher doses. Side effects include those of anticholinergic components and sedation related to anxiolytic agents. The use of alcohol and other sedatives must be avoided if these drugs are taken. Driving and other activities requiring an alert state should be avoided until patients determine whether they can tolerate these drugs. These agents are best used as needed for more severe episodic symptoms when anticholinergic agents alone have failed.

#### TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants in low doses appear effective for irritable bowel syndrome and for a variety of other painful conditions, including migraine, neuropathic pain, pain due to cancer, noncardiac

chest pain, and functional dyspepsia.<sup>62-64</sup> The underlying mechanism of the benefit is unknown, but it could be due to a reduction in the sensitivity of peripheral nerves or to alterations in the brain.<sup>65,66</sup> Although in healthy volunteers tricyclic antidepressants raise both the threshold for and tolerance of cutaneous pain,<sup>67,68</sup> these effects have not been convincingly demonstrated in the gut.<sup>67,69</sup> In functional bowel disorders, data are mixed regarding the ability of tricyclic antidepressants to alter visceral pain thresholds.<sup>70,71</sup> The antidepressant action of tricyclic antidepressants does not appear to be required for the salutary effects of these agents on the gut, since low doses are effective, benefits are seen within two weeks, patients without depression benefit, and full doses of selective serotonin-reuptake inhibitors do not provide the same benefits.<sup>64</sup> In theory, the beneficial effects of tricyclic antidepressants could be due to their anticholinergic properties; however, studies that controlled for this effect have still shown a benefit of treatment.<sup>72</sup>

A number of randomized, controlled trials have demonstrated decreased symptoms in patients taking low-dose tricyclic antidepressants such as amitriptyline, desipramine, clomipramine, doxepin, and trimipramine. A recent meta-analysis reviewed these treatments for irritable bowel syndrome and indicated an odds ratio for benefit of 4.0 as compared with placebo<sup>51</sup> (Table 2). Some studies, but not all, indicate greater benefits in patients with diarrhea-predominant irritable bowel syndrome than in those with other types.<sup>39,72,73</sup> Because side effects include constipation, anticipatory treatment of constipation is suggested if tricyclic antidepressants are used for constipation-predominant irritable bowel syndrome. Other side effects include fatigue, som-

nolence, dry mouth, and urinary retention. In antidepressant doses, tricyclic antidepressants have been associated with cardiac arrhythmia and lowered seizure thresholds. These effects appear exceedingly rare at low doses.

Tricyclic antidepressants are recommended for moderate-to-severe irritable bowel syndrome in which pain is prominent or when other therapies have failed. Tricyclic antidepressants can be combined with antispasmodic agents if either treatment has had partial success. Since somnolence may occur, the drugs should be taken at bedtime. Daily administration starting at a dose of 10 to 25 mg for any of the tricyclic antidepressants, with a gradual escalation to a dose of 25 to 100 mg, is suggested. Although benefits are often seen within a week, a four-week trial is reasonable. Tricyclic antidepressants may be continued for 6 to 12 months, after which an attempt should be made to taper the dose.

Selective serotonin-reuptake inhibitors and other newer antidepressants have been widely used to treat irritable bowel syndrome, since they lack many of the side effects of tricyclic antidepressants and have similar efficacy for depression. These agents do not have the same antinociceptive effects as tricyclic antidepressants and have yet to be proved effective for irritable bowel syndrome or any other functional gastrointestinal disorder.<sup>64</sup> Selective serotonin-reuptake inhibitors may be useful when irritable bowel syndrome is accompanied and exacerbated by a mood disorder. Although evidence to support its use is lacking, this class of drug may also be tried if a tricyclic antidepressant fails.

#### SEROTONIN-3-RECEPTOR ANTAGONISTS

Serotonin-3 receptors are also located on enteric nervous system sensory neurons.<sup>74</sup> Serotonin is released by gastrointestinal enteroendocrine cells after mucosal stimulation, diffuses to the nerve endings, and stimulates peristalsis by binding to serotonin-3 and serotonin-4 receptors located on enteric nerves.<sup>75</sup> Activated serotonin-3 receptors stimulate intestinal motility, secretion, and sensation. The motor effects of serotonin-3-receptor antagonists include a reduced rate of colonic transit, reduced gastrocolic reflex, and increased colonic compliance.<sup>76-79</sup> The antagonists appear to reduce intestinal sensitivity to distention in humans as well as in several animal models.<sup>80-82</sup> The serotonin-3-receptor antagonist alosetron increases colonic compliance in patients with irritable bowel syndrome and may reduce sensitivity to balloon distention.<sup>27,79</sup>

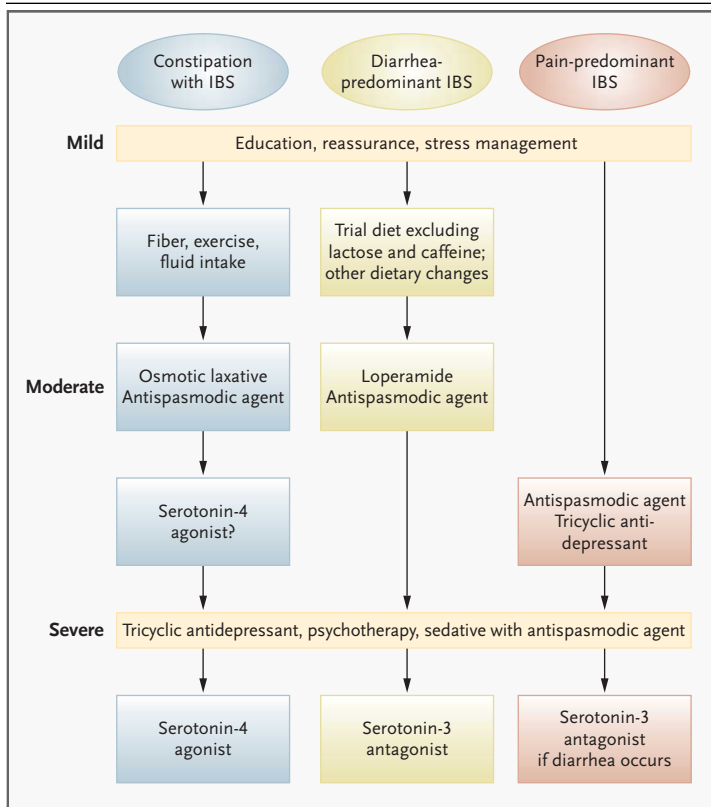
The clinical result of alosetron is a reduction in diarrhea and urgency. All these effects address the known physiological abnormalities in diarrhea-predominant irritable bowel syndrome.

In two large, randomized, double-blind, placebo-controlled trials, alosetron (1 mg twice daily) was beneficial in women with irritable bowel syndrome who did not have constipation.<sup>54,55</sup> An earlier dose-finding study indicated that a dosage of 1 mg twice daily was most effective and that its benefits were restricted to women. A response was reported in 43 percent of subjects in one study (an absolute increase of 17 percent, as compared with the rate in the placebo group;  $P < 0.001$ ) and 41 percent in the other (an absolute increase of 12 percent, as compared with the rate in the placebo group;  $P < 0.05$ ). The use of alosetron is associated with improved quality of life, as compared with placebo, in the dietary, social, and physical domains.<sup>83</sup> Constipation was a side effect in 25 to 30 percent of subjects, explaining, in part, the 10 percent dropout rate. Alosetron was reported to be superior to mebeverine, an antispasmodic agent, for pain associated with irritable bowel syndrome (e.g., rates of adequate pain relief were 10 to 13 percentage points higher at two and three months) in a multicenter European trial.<sup>56</sup> Although the incidence of side effects was similar in each treatment group, constipation was more common in the alosetron group (22 percent).

After the introduction of alosetron, ischemic colitis was diagnosed in approximately 1 of 700 patients who took the drug.<sup>84,85</sup> Consequently, the drug was withdrawn from the market by the manufacturer. In part as a result of lobbying by patient-advocacy groups, the Food and Drug Administration (FDA) authorized the reintroduction of alosetron in June 2002 under specific guidelines that require patients to sign a consent form and prescribing physicians to sign a certificate.<sup>86</sup> The drug again became available in late 2002. Given its known side effects, alosetron therapy should be limited to women with irritable bowel syndrome without constipation who have symptoms severe enough to justify the risk of drug-induced ischemic colitis and who have had no response to other therapy. Other drugs in this class are under development, although their safety and efficacy are unknown.

#### SEROTONIN-4-RECEPTOR AGONISTS

Tegaserod, a drug similar to the prokinetic agent cisapride, is a partial agonist of the serotonin-4 re-



**Figure 2. Treatment Strategy for Irritable Bowel Syndrome (IBS).**

Treatment is individualized on the basis of the type and severity of symptoms. When bowel-directed therapies for diarrhea or constipation are inadequate or when pain is a prominent finding, therapy with antispasmodic drugs is useful, particularly for postprandial symptoms. These agents are effective when given on an as-needed basis, allowing the patient to take an active role in management. A combined anxiolytic-antispasmodic agent is helpful for use as needed in patients with anxiety or refractory disease. Tricyclic antidepressants in a low dose are helpful for pain symptoms when antispasmodic agents fail or provide only partial relief. Tricyclic antidepressants can be combined with other agents such as antispasmodics. The prokinetic tegaserod is effective for women with constipation-predominant irritable bowel syndrome. It is a reasonable addition when fiber or laxatives and antispasmodic agents are unsuccessful. When pain is the predominant symptom, tricyclic antidepressants would appear to be preferred over tegaserod on the basis of their mechanism of action, rather than clinical data. Alosetron is helpful for women with refractory diarrhea-predominant symptoms in whom loperamide, antispasmodic agents, and tricyclic antidepressants have failed. Patients should be counseled regarding the risk of constipation and ischemic colitis with alosetron therapy. Pharmacologic therapy alone is likely to be ineffective for irritable bowel syndrome when ongoing psychosocial problems remain undetected or untreated.<sup>11</sup>

ceptor. Peristalsis is coordinated by neurons of the enteric nervous system that release other mediators after the activation of serotonin-4 receptors.<sup>87-89</sup> In healthy volunteers, 6 mg of tegaserod twice daily accelerated gastric emptying and small-bowel trans-

it.<sup>89</sup> The rate of colonic transit was slightly accelerated 48 hours after the ingestion of radiolabeled pellets, but not at 24 hours.<sup>89</sup> In patients with constipation-predominant irritable bowel syndrome, a 2-mg dose of tegaserod twice daily accelerates small-bowel transit and cecal filling but has no effect on gastric emptying or total colonic transit.<sup>90</sup>

Three large, randomized, double-blind, placebo-controlled trials of tegaserod for constipation-predominant irritable bowel syndrome indicate that it provides symptomatic benefit.<sup>28,52,53</sup> Tegaserod (6 mg twice daily — the FDA-approved dose) for three months is associated with increased response rates at one and three months, as compared with placebo, leading to reductions in the symptoms of pain and constipation. In the last month of therapy, 52 percent of patients taking tegaserod had an improvement in the global symptoms of irritable bowel syndrome — a value that was 9.3 percentage points higher than that in the placebo group.<sup>28,52,53</sup> Available studies suggest that these benefits occur in women but not men, although the studies were underpowered from a statistical viewpoint to detect sex-based differences.

Tegaserod has been approved by the FDA for use for up to 12 weeks in women with constipation-predominant irritable bowel syndrome. The side effects of tegaserod are generally mild, with diarrhea, generally brief, the most prominent (occurring in 10 percent of patients). For unclear reasons cholecystectomy was performed more frequently in patients who received tegaserod (0.17 percent) than in those given placebo (0.06 percent).<sup>91</sup> Given its cost and its relatively moderate advantages over placebo, tegaserod should be reserved for female patients with constipation-predominant irritable bowel syndrome who have no response to fiber or laxatives and antispasmodic agents.

**OTHER AGENTS**

A variety of other agents have been considered for the symptoms of irritable bowel syndrome, with some reports of benefit. Antibiotics have been suggested as a treatment for irritable bowel syndrome. Recently, small-bowel overgrowth by enteric bacteria has been cited as a cause of the symptoms.<sup>92</sup> In a subsequent randomized, double-blind trial, 111 patients with irritable bowel syndrome (84 percent with small-bowel overgrowth as suggested by the results of a lactulose hydrogen breath test) were treated with the antibiotic neomycin or placebo. The percentage of patients with at least 50 percent im-

provement in the symptoms of irritable bowel syndrome after one week of treatment was significantly greater in the neomycin group (43 percent) than the placebo group (23 percent).<sup>93</sup> However, the follow-up lasted only seven days, and the durability of such a response is unknown. Studies of methods to reduce small-bowel bacteria without antibiotics in patients with irritable bowel syndrome are warranted.

A double-blind, placebo-controlled 16-week trial of herbal therapy that used a validated survey and involved 116 patients with irritable bowel syndrome indicated that gastrointestinal symptoms improved in patients taking a mixture of herbs. Herbal mixtures individualized for each patient by Chinese medical practitioners were compared with a standardized mixture of 20 herbs and found to offer no advantage.<sup>94</sup> Whether diarrhea or constipation improved most was not reported. Herbal therapy might be useful but requires more robust data plus a determination of the substance or substances responsible for the effects.

Peppermint oil has been advocated as a treatment for irritable bowel syndrome and can be obtained without prescription. There are positive and negative data regarding its use in irritable bowel syndrome.<sup>95</sup> Peppermint oil appears to have direct relaxing effects on gastrointestinal smooth muscle, so it might act as an antispasmodic agent. Peppermint oil relaxes the lower esophageal sphincter, and heartburn related to acid reflux limits its use.

Leuprolide, a gonadotropin-releasing-hormone antagonist, may be moderately beneficial for irritable bowel syndrome in women.<sup>96,97</sup> The published trials were not blinded (owing to the presence of amenorrhea in the treatment group) and had vague entry criteria. The medical menopause this drug induces is not without risks, and leuprolide cannot be recommended for irritable bowel syndrome.

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#### FUTURE THERAPIES

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Increased understanding of neurotransmitters and hormones mediating gastrointestinal motility and

sensation will probably lead to novel treatments for irritable bowel syndrome. Compounds under investigation include cholecystokinin-A-receptor antagonists, neurokinin-1- and neurokinin-3-receptor antagonists,  $\kappa$  (peripheral) opiate agonists,  $\alpha_2$ -adrenergic agonists, and muscarinic-3-receptor antagonists. These agents may reduce the sensitivity or motility of the gut. Probiotics have also been used to alter gut flora, and preliminary data indicate that they may be beneficial in irritable bowel syndrome.<sup>98</sup>

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#### APPROACH TO TREATMENT

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Because irritable bowel syndrome is a disorder of bowel motility and sensation that is exacerbated by psychosocial stressors, treatment is most successful when a multicomponent, comprehensive approach is used (Fig. 2). It is important to explain and reassure patients about the origin of their symptoms and to let patients take an active approach to management that is overseen by their physician. Bowel-directed therapies should target specific types of gastrointestinal dysfunction, such as diarrhea or constipation, and prescription medication should be used judiciously when symptoms do not respond to nonprescription remedies or are severe. Finally, stress management or psychotherapy should be used when such measures do not adequately relieve symptoms or when psychological factors are prominent.<sup>99-102</sup> The benefits of multicomponent therapy for irritable bowel syndrome have recently been reviewed by both American and British gastroenterology societies.<sup>99,102</sup> Given the psychosocial factors involved and the limited benefits of current pharmacologic therapies, the treatment of irritable bowel syndrome requires physicians to attend to the minds as well as the bodies of their patients in order to help them find relief.

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