

## CLINICAL PRACTICE

## Irritable Bowel Syndrome

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*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

**A 28-year-old woman presents with a 7-month history of recurrent, crampy pain in the left lower abdominal quadrant, bloating with abdominal distention, and frequent, loose stools. She reports having had similar but milder symptoms since childhood. She spends long times in the bathroom because she is worried about uncontrollable discomfort and fecal soiling if she does not completely empty her bowels before leaving the house. She feels anxious and fatigued and is frustrated that her previous physician did not seem to take her distress seriously. Physical examination is unremarkable except for tenderness over the left lower quadrant. How should her case be evaluated and treated?**

## THE CLINICAL PROBLEM

Irritable bowel syndrome (IBS), characterized by chronically recurring abdominal pain or discomfort and altered bowel habits, is one of the most common syndromes seen by gastroenterologists and primary care providers, with a worldwide prevalence of 10 to 15%.<sup>1</sup> In the absence of detectable organic causes, IBS is referred to as a functional disorder, which is defined by symptom-based diagnostic criteria known as the "Rome criteria" (Table 1).<sup>2</sup>

IBS is one of several functional gastrointestinal disorders (including functional dyspepsia); these other functional disorders are frequently seen in patients with IBS,<sup>3</sup> as are other pain disorders, such as fibromyalgia, chronic pelvic pain, and interstitial cystitis.<sup>4,5</sup> Coexisting psychological conditions are also common, primarily anxiety, somatization, and symptom-related fears (e.g., "I am worried that I will have severe discomfort during the day if I don't empty my bowels completely in the morning"); these contribute to impairments in quality of life<sup>6</sup> and excessive use of health care associated with IBS.<sup>7</sup>

Symptoms characteristic of IBS are common in population-based samples of healthy persons. However, only 25 to 50% of persons with such symptoms (typically those with more frequent or severe abdominal pain) seek medical care.<sup>1</sup> Longitudinal studies suggest substantial fluctuations in symptoms over time. In a population-based longitudinal study over a period of 12 years, 55% of subjects who initially reported symptoms of IBS did not report these symptoms at the time of the final survey.<sup>3</sup> Although the IBS symptoms resolved in the majority of subjects, transitions to other complexes of gastrointestinal symptoms, such as functional dyspepsia, were also observed.

Symptoms of IBS (or other related functional gastrointestinal symptoms) frequently date back to childhood; the estimated prevalence of IBS in children is similar to that in adults.<sup>8</sup> The female-to-male ratio is 2:1 in most population-based samples and is higher among those who seek health care.<sup>4</sup> IBS-like symptoms develop in approximately 10% of adult patients after bacterial or viral enteric infections;

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**Table 1. The Rome Diagnostic Criteria for Irritable Bowel Syndrome (IBS).\***

<p>Recurrent abdominal pain or discomfort at least 3 days per month for the past 3 months, associated with two or more of the following:</p> <ul style="list-style-type: none"> <li>Improvement with defecation</li> <li>Onset associated with a change in frequency of stool</li> <li>Onset associated with a change in form (appearance) of stool</li> </ul>
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\* Data are from Longstreth et al.<sup>2</sup> Criteria must have been fulfilled for the past 3 months, with symptom onset at least 6 months before diagnosis. On the basis of the predominant bowel habit, IBS has been categorized into one of the following subgroups: IBS with diarrhea (more common in men), IBS with constipation (more common in women), and IBS with mixed bowel habits. Each group accounts for about one third of all patients. According to current diagnostic criteria, IBS must be differentiated from functional abdominal pain syndrome (in IBS, symptoms of abdominal pain are associated with alterations in bowel movements) and from chronic functional constipation and chronic functional diarrhea (in IBS, pain and discomfort are associated with altered bowel habits).

risk factors for the development of postinfectious IBS include female sex, a longer duration of gastroenteritis, and the presence of psychosocial factors (including a major life stress at the time of infection and somatization).<sup>9</sup> Both initial presentations and exacerbations of IBS symptoms are often preceded by major psychological stressors<sup>1</sup> or by physical stressors (e.g., gastrointestinal infection).<sup>9</sup>

Given the direct association between symptoms of IBS and stress, the frequent coexisting psychiatric conditions,<sup>10</sup> and the responsiveness of symptoms in many persons to therapies directed at the central nervous system, IBS is often described as a “brain–gut disorder,” although its pathophysiology remains uncertain. Alterations in gastrointestinal motility and in the balance of absorption and secretion in the intestines may underlie irregularities in bowel habits,<sup>1</sup> and these abnormalities may be mediated in part by dysregulation of the gut-based serotonin signaling system.<sup>11</sup> Increased perception of visceral stimuli may contribute to abdominal pain and discomfort.<sup>12</sup> Preliminary reports suggest that alterations in immune activation of the mucosa<sup>1,9</sup> and in intestinal microflora<sup>13</sup> may contribute to symptoms of IBS, yet a causative role remains to be established.

## STRATEGIES AND EVIDENCE

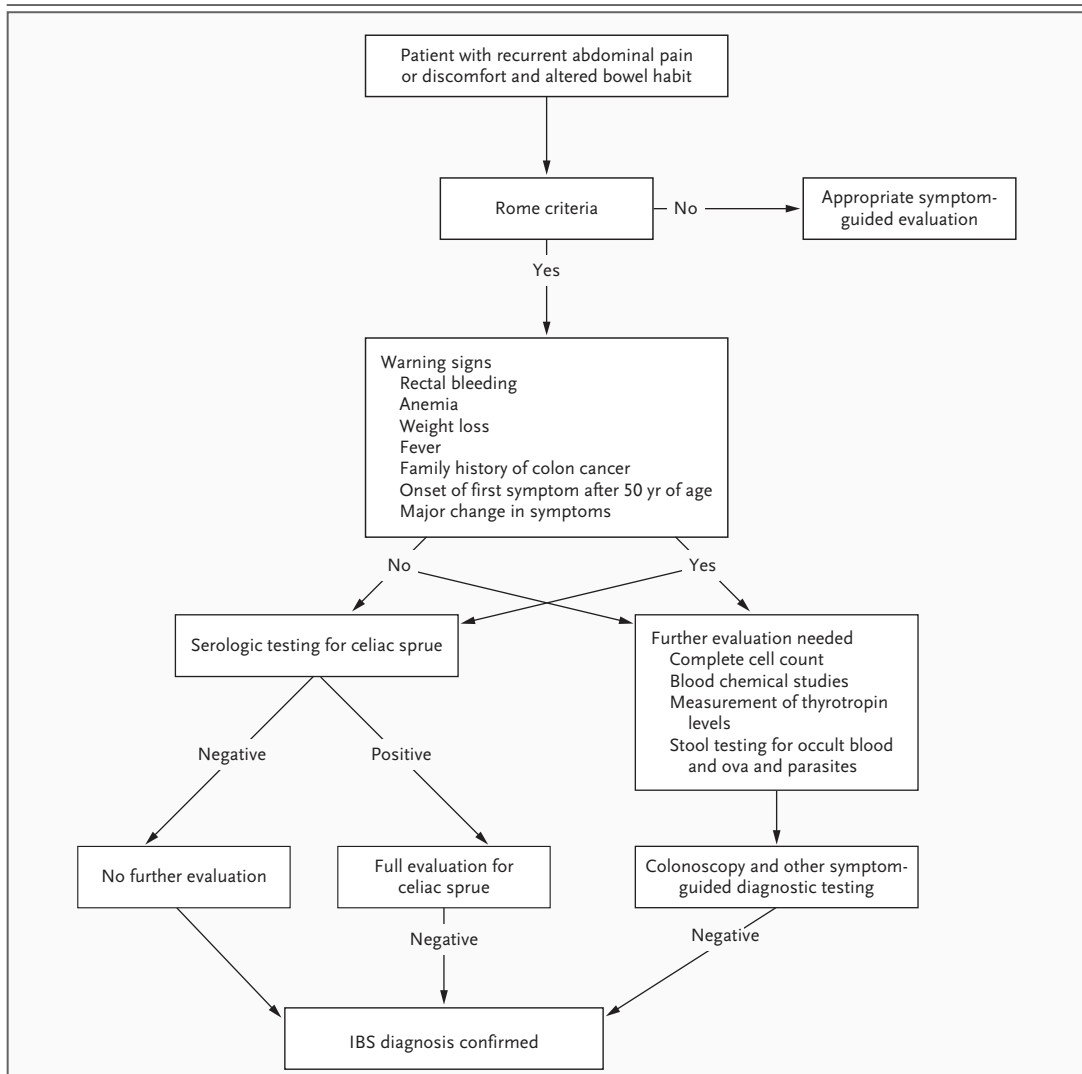
### EVALUATION

According to current clinical guidelines,<sup>1,2,14,15</sup> IBS can generally be diagnosed without additional testing beyond a careful history taking, a general physical examination, and routine laboratory studies (not including colonoscopy) in patients who have symptoms that meet the Rome criteria

(Table 1) and who do not have warning signs. These warning signs include rectal bleeding, anemia, weight loss, fever, family history of colon cancer, onset of the first symptom after 50 years of age, and a major change in symptoms. Patients should be asked about the specifics of their bowel habits and stool characteristics; on the basis of this information, they can be subclassified as having diarrhea-predominant IBS, constipation-predominant IBS, or mixed bowel habits.<sup>2</sup>

In patients who meet the Rome criteria and have no warning signs, the differential diagnosis includes celiac sprue (Fig. 1), microscopic and collagenous colitis and atypical Crohn’s disease for patients with diarrhea-predominant IBS, and chronic constipation (without pain) for those with constipation-predominant IBS. A relationship between symptoms and food intake, as well as possible triggers for the onset of symptoms (e.g., gastrointestinal infection or marked stressors) should be assessed, since this may guide treatment recommendations. In addition, attention should be paid to symptoms that suggest other functional gastrointestinal and somatic pain disorders and psychological conditions often associated with IBS.

Clinical experience suggests that accepting the patient’s symptoms and distress as real, and not simply as a manifestation of excessive worrying and somatization, and providing the patient with a plausible model of the disease (e.g., “brain–gut disorder”) facilitates the establishment of a positive patient–doctor relationship. Evidence suggests that an approach that includes acknowledging the disease, educating the patient about the disease, and reassuring the patient may improve the treatment outcome.<sup>19</sup> Physical examination frequently reveals tenderness in the left



**Figure 1. Differential Diagnosis.**

Testing for celiac sprue may be useful in patients who meet the Rome criteria<sup>16</sup> (especially in those with diarrhea-predominant IBS), in patients who have warning signs, and in populations in which the prevalence of celiac sprue is high.<sup>17</sup> If there are no warning signs, then basic blood counts, serum biochemical studies, stool testing for occult blood and ova and parasites, and measurement of thyrotropin levels are indicated only if there is a supportive clinical history.<sup>18</sup> Colonoscopy is recommended only in patients who have warning signs. However, according to screening guidelines for colon cancer, routine colonoscopy should be performed in patients at the age of 50 years or older, regardless of whether IBS symptoms are present. If there has been a major qualitative change in the pattern of chronic symptoms, a new coexisting condition should be suspected, and a more comprehensive diagnostic approach is warranted.

lower quadrant over a palpable sigmoid colon. A rectal examination is warranted to rule out rectal disease and abnormal function of the anorectal sphincter (e.g., paradoxical pelvic-floor contraction during a defecation attempt), which may contribute to symptoms of constipation.

#### PHARMACOLOGIC TREATMENT

Symptomatic treatment (usually aimed at normalizing bowel habits or decreasing abdominal pain) by a reassuring health care provider typically provides relief for patients with mild symptoms who are seen in primary care settings.<sup>20</sup> However,

the treatment of patients who have more severe symptoms remains challenging. Only a small number of pharmacologic and psychological treatments are supported by well-designed randomized, controlled trials involving patients with IBS. Treatment of IBS with currently available drugs usually is targeted to the management of individual symptoms, such as constipation, diarrhea, and abdominal pain (Table 2).

#### *Constipation*

In clinical practice, osmotic laxatives are often useful in the treatment of constipation, although they have not been studied in clinical trials specifically involving patients with IBS. Fiber and other bulking agents have also been used as initial therapy for constipation. However, the frequent side effects (in particular, an increase in bloating) and inconsistent, largely negative results of trials of dietary fiber in the treatment of IBS have decreased the use of this approach.<sup>22</sup>

Tegaserod, a partial 5-hydroxytryptamine<sub>4</sub> (5-HT<sub>4</sub>)-receptor agonist, has been shown in randomized, clinical trials to be moderately effective for global relief of symptoms in patients with IBS. In an analysis of eight randomized trials, patients assigned to tegaserod were 20% more likely to have global relief of symptoms than those assigned to placebo, with a number needed to treat of 17 to achieve clinically significant global relief. However, marketing of tegaserod was suspended in March 2007, when an analysis of the data from clinical trials identified a significant increase in the number of cardiovascular ischemic events (myocardial infarction, stroke, and unstable angina) in patients taking the drug (13 events in 11,614 patients) as compared with those receiving placebo (1 event in 7031 patients); all events occurred in patients with known cardiovascular disease, cardiovascular risk factors, or both.<sup>23</sup> In July 2007, the Food and Drug Administration (FDA) approved an investigational-new-drug program for tegaserod with access restricted to women younger than 55 years of age who have constipation-predominant IBS (or chronic constipation) without known cardiovascular problems.<sup>21</sup>

#### *Diarrhea*

Although data from randomized trials of traditional antidiarrheal agents in patients with diarrhea-predominant IBS are lacking, clinical expe-

rience indicates that these agents are generally effective. Regular use of low doses (e.g., 2 mg of loperamide every morning or twice a day) seems to be effective for the treatment of otherwise uncontrollable diarrhea and may decrease patients' anxiety about uncontrollable urgency and fecal soiling.

In large, randomized, double-blind, placebo-controlled trials involving patients with diarrhea-predominant IBS, the 5-HT<sub>3</sub>-receptor antagonist alosetron at a dose of 1 mg twice a day for 12 weeks decreased stool frequency and bowel urgency, relieved abdominal pain and discomfort, improved scores for global IBS symptoms (i.e., adequate relief of IBS symptoms), and improved health-related quality of life.<sup>24</sup> Based on phase 2 trials suggesting that efficacy might be limited to female patients, subsequent trials for FDA approval included only women, and FDA approval was limited to female patients with diarrhea-predominant IBS. A later study showed efficacy in men as well, although the indication has not been approved by the FDA.<sup>25</sup>

In pooled analyses of female patients, alosetron was associated with an odds ratio for adequate relief of pain or global relief of symptoms of 1.8 (95% confidence interval [CI], 1.6 to 2.1; number needed to treat for adequate symptom relief, 7.3). However, the FDA has restricted the use of the drug because of rare but serious adverse effects occurring in both clinical trials and post-marketing studies, including complications from constipation (ileus, bowel obstruction, fecal impaction, and perforation; combined prevalence, 0.10% in the alosetron group vs. 0.06% in the placebo group [from clinical trials dating up to 2000])<sup>26</sup> and ischemic colitis (prevalence, 0.15% in the alosetron group vs. 0.06% in the placebo group). Thus, alosetron is indicated only for women with severe diarrhea-predominant IBS who have had symptoms for at least 6 months and who have not had a response to conventional therapies (in particular, antidiarrheal agents).

#### *Abdominal Pain*

Antispasmodic agents (e.g., hyoscyamine or mebeverine) have been used for the treatment of pain in patients with IBS. However, data from high-quality randomized, controlled trials of their effectiveness in reducing pain or global symptoms are lacking.<sup>22</sup>

**Table 2. Medications Used in the Treatment of Irritable Bowel Syndrome (IBS).\***

Symptoms and Medication	Initial Dose	Target Dose	Common or Serious Side Effects	Evidence For the Symptom	FDA-Approved For the Symptom
<b>Constipation</b>					
Laxatives‡ and secretory stimulators		mg/day†			
Polyethylene glycol 3350 (Miralax, Brintree Labs)	17,000	up to 34,000, twice a day	Diarrhea, bloating, cramping	+++	-
Lactulose (Kristalose, Cumberland Pharmaceuticals)	10,000–20,000	20,000–40,000	Diarrhea, bloating, cramping	+++	-
Lubiprostone (Amitiza; Takeda, Sucampo)		24 µg, twice a day	Nausea, diarrhea, headache, abdominal pain and discomfort	+++	-
<b>Prokinetics</b>					
Tegaserod (Zelnorm, Novartis)		6, twice a day	Initial diarrhea, abdominal pain, cardiovascular ischemia (rare)	+++	Yes¶
<b>Diarrhea</b>					
Loperamide (Imodium, McNeil)	2	2–8	Constipation	+++	-
Alosetron (Lotronex, GlaxoSmithKline)¶	0.5, twice a day	up to 1, twice a day	Constipation, ischemic colitis (rare)	-	+++
<b>Bloating</b>					
<b>Antibiotics</b>					
Rifaximin (Salix)		400, three times a day	Abdominal pain, diarrhea, bad taste	-	+
<b>Probiotics**</b>					
Bifidobacterium infantis 35624 (Align, Procter & Gamble)		1 capsule per day	None	+	No
<b>Pain</b>					
<b>Tricyclic antidepressants††</b>					
Amiriptryline	10, at bedtime	10–75, at bedtime	Dry mouth, dizziness, weight gain	++	+
Desipramine	10, at bedtime	10–75, at bedtime		++	+
Selective serotonin-reuptake inhibitors‡‡			Sexual dysfunction, headache, nausea, sedation, insomnia, sweating, withdrawal symptoms	-	+
Paroxetine (Paxil CR, GlaxoSmithKline)		10–60		-	+
Citalopram (Lexapro, Forest)		5–20		+	+
Fluoxetine (Prozac, Eli Lilly)		20–40	Somnolence, dizziness, headaches, insomnia	+	-

\* This list is not exhaustive but includes major medications for which there is evidence from well-designed clinical trials of effectiveness for global IBS symptoms or for individual symptoms (e.g., constipation, diarrhea, or abdominal pain and discomfort). In the columns about evidence, + denotes some evidence from at least one controlled trial, ++ moderate evidence from several controlled trials or from meta-analysis of such trials, +++ strong evidence from well-designed, controlled clinical trials, and - no evidence. FDA denotes Food and Drug Administration.

† Dosages are in milligrams per day unless otherwise noted.

‡ A wide range of osmotic and irritant laxatives, including fiber products, are available over the counter.

§ Lubiprostone is FDA-approved for the treatment of chronic constipation.

¶ Marketing of tegaserod was suspended by the FDA in March 2007 because of rare cardiovascular side effects but is now available as part of a restricted-access program for women who have constipation-predominant IBS or chronic idiopathic constipation, without known or preexisting heart problems, that is unresponsive to other medications.<sup>21</sup>

‖ Alosetron use is restricted to women with severe diarrhea-predominant IBS, unresponsive to other medications, owing to side effects.

\*\* Many probiotics are available over the counter and are not listed. Align is a probiotic for which a beneficial effect for IBS symptoms has been shown in a high-quality, randomized, controlled trial.

†† A wide range of tricyclic antidepressants with various side effects and side-effect profiles is available. Two commonly prescribed tricyclic antidepressants are listed. The doses listed are based on clinical experience.

‡‡ Many selective serotonin-reuptake inhibitors are available. Only those that have been evaluated in IBS trials are listed. Also not listed are serotonin–norepinephrine reuptake inhibitors.

Tricyclic antidepressant medications are commonly used for IBS symptoms, often in low doses (e.g., 10 to 75 mg of amitriptyline). Hypothesized mediators of their effects include antihyperalgesia, improvement in sleep, normalization of gastrointestinal transit,<sup>27</sup> and when used at higher doses (e.g., 100 mg or more at bedtime), treatment of coexisting depression and anxiety. Despite their frequent use in practice, data on the efficacy of tricyclic antidepressants in patients with IBS are inconsistent. Two meta-analyses (including 11 randomized, controlled trials) showed that low-to-moderate doses of tricyclic antidepressants significantly reduced pain and overall symptoms in patients with IBS,<sup>1,28,29</sup> but the analyses have been criticized for the inclusion of studies that enrolled subjects with functional dyspepsia. A third meta-analysis that excluded these studies showed that tricyclic antidepressants were not superior to placebo.<sup>15</sup>

In the largest published randomized, placebo-controlled trial to date, treatment with desipramine (with an escalating dose from 50 to 150 mg) was not superior to placebo in intention-to-treat analyses. However, a secondary analysis (per protocol) limited to patients with detectable plasma levels of desipramine showed a significant benefit over placebo.<sup>30</sup> These patients presumably adhered better to the protocol. Also, given the high dose of desipramine that was studied, it is unclear whether reported improvement in IBS symptoms was secondary to treatment of coexisting depression or anxiety. Effects of tricyclic antidepressants on sensitivity to somatic pain<sup>31</sup> and sleep suggest that they may have particular benefit in patients with IBS who have widespread somatic pain or who sleep poorly, although this has not been studied explicitly.

Several small, randomized, controlled trials suggest that selective serotonin-reuptake inhibitors may have beneficial effects in patients with IBS, most commonly on measures of general well-being and, in some studies, on abdominal pain.<sup>32</sup> However, it remains unclear whether a lessening of depression or anxiety explains the benefits. Although serotonin-norepinephrine reuptake inhibitors (duloxetine and venlafaxine) have been shown to be effective in reducing pain in other chronic pain conditions, including fibromyalgia,<sup>11</sup> data from randomized, controlled trials of their role in the treatment of IBS are lacking.

There is a high prevalence of coexisting anxiety in patients with IBS. Nevertheless, benzodiazepines are not recommended for long-term therapy because of the risk of habituation and the potential for dependency.<sup>8</sup>

#### COGNITIVE-BEHAVIORAL THERAPY

Cognitive-behavioral therapy (a combination of cognitive and behavioral techniques) is the best-studied psychological treatment for IBS.<sup>15,33</sup> Cognitive techniques (typically administered in a group or an individual format in 4 to 15 sessions) are aimed at changing catastrophic or maladaptive thinking patterns underlying the perception of somatic symptoms.<sup>1,34</sup> Behavioral techniques aim to modify dysfunctional behaviors through relaxation techniques, contingency management (rewarding healthy behaviors), or assertion training. Some randomized, controlled trials have also shown reductions in IBS symptoms with the use of gut-directed hypnosis (aimed at improving gut function), which involves relaxation, change in beliefs, and self-management.<sup>33,35</sup>

Data from head-to-head comparisons of psychotherapy with pharmacotherapy for IBS or psychotherapy plus pharmacotherapy with pharmacotherapy alone are lacking. The magnitude of improvement that has been reported with psychological treatments seems to be similar to or greater than that reported with medications studied specifically for bowel symptoms in IBS, although comparisons are limited by, among other things, the lack of a true placebo control in trials of psychotherapies. In a meta-analysis of 17 randomized trials of cognitive treatments, behavioral treatments, or both for IBS (including hypnosis), as compared with control treatments (including waiting list, symptom monitoring, and usual medical treatment), those patients who were randomly assigned to cognitive-behavioral therapy were significantly more likely to have a reduction in gastrointestinal symptoms of at least 50% (odds ratio, 12; 95% CI, 6 to 260),<sup>33</sup> and the estimated number needed to treat with cognitive-behavioral therapy or hypnotherapy for one patient to have improvement was estimated to be two.<sup>33</sup>

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#### AREAS OF UNCERTAINTY

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The optimal means of treating patients with moderate or severe symptoms remains uncertain, particularly given the implementation of restrict-

ed-access programs for the newer pharmacotherapies for diarrhea-predominant IBS and constipation-predominant IBS.

Limited data from small, randomized, controlled trials have suggested benefits of nonabsorbable antibiotics<sup>36</sup> (400 mg of rifaximin three times a day), and probiotics,<sup>37,38</sup> particularly for symptoms of gas and bloating. More data are needed from larger, high-quality randomized, controlled trials that assess the effects of these and other therapies, including antidepressant agents, and provide information on factors that may predict responsiveness to these therapies. Lubiprostone (24  $\mu$ g twice a day) has been approved by the FDA for the treatment of chronic constipation and was recently shown to be effective in the treatment of constipation-predominant IBS.<sup>39</sup> The roles of this agent and other new treatments for constipation and global relief of symptoms (e.g., linaclotide<sup>40</sup>) in constipation-predominant IBS remain to be established.

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#### GUIDELINES

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Guidelines for the management of IBS have been issued by the American Gastroenterological Association,<sup>1</sup> by the American College of Gastroenterology,<sup>15</sup> by the Rome Foundation,<sup>2</sup> and by the British Society of Gastroenterology.<sup>14</sup> Because of the limited data from randomized trials involving patients with IBS, these guidelines are based largely on consensus opinion. My recommendations are generally consistent with these guidelines.

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#### SUMMARY AND RECOMMENDATIONS

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In patients such as the woman in the vignette, who present with symptoms suggestive of IBS, including chronic abdominal pain and discomfort associated with diarrhea, the first step in evaluation is a careful history taking to rule out warning signs, including unexplained weight loss and hematochezia. In the absence of any warning signs, the diagnosis usually can be made clinically without the need for further testing (Fig. 1). I would also determine whether a gastrointestinal infection or any major life event preceded the recent flare of symptoms, since these are common triggers of IBS.

Clinical experience suggests that mild symptoms may be managed effectively by symptomatic treatment of altered bowel habits (e.g., antidiarrheal agents or laxatives). I find it helpful to make it clear to the patient that I accept his or her symptoms as real and to provide a pathophysiological explanation of symptoms.

For severe diarrhea, as in the case described, I typically recommend starting a low daily dose of loperamide (2 to 4 mg every morning, noting that this can be increased if the patient has a particularly important activity), with the expectation that this treatment may also decrease anxiety about having uncontrollable bowel movements during the day. Although the data from randomized trials are conflicting with regard to the role of tricyclic antidepressant agents in patients with IBS, I would also consider this therapy (e.g., amitriptyline, starting at a dose of 10 mg at bedtime and gradually, over a period of several weeks, increasing to the maximum tolerated dose, but not higher than 75 mg at bedtime), making it clear to the patient that low-dose therapy is not aimed at altering mood but rather is aimed at reducing IBS symptoms, including abdominal pain. I would recommend participation in a cognitive-behavioral therapy program (ideally in the form of a brief, self-administered program),<sup>34</sup> although there are no data showing that the combination of cognitive-behavioral therapy and pharmacotherapy is superior to either treatment alone in cases of IBS. If symptoms failed to improve sufficiently in this patient with diarrhea, I would discuss with her the potential addition of alosetron, but with attention to its potential for rare serious adverse effects, including ischemic colitis.<sup>14</sup>

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An audio version of this article is available at [www.nejm.org](http://www.nejm.org).

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