THE CLEVELAND CLINIC FOUNDATION

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IRRITABLE BOWEL SYNDROME

IMPLICATIONS OF CURRENT EVIDENCE FOR THE PRIMARY CARE PHYSICIAN

SUPPLEMENT EDITOR:
EDY E. SOFFER, MD
THE CLEVELAND CLINIC

SUPPLEMENT 2 TO VOLUME 70
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CLEVELAND CLINIC JOURNAL OF MEDICINE

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Irritable Bowel Syndrome:
Implications of Current Evidence for the Primary Care Physician

NEW DEVELOPMENTS and evidence relating to irritable bowel syndrome (IBS) recently prompted the American College of Gastroenterology (ACG) to issue a major evidence-based position statement on the management of this prevalent disorder. Like many position statements, however, it was for the most part written by specialists for specialists.

To explore implications of the new ACG position statement from a decidedly primary care perspective, the *Cleveland Clinic Journal of Medicine* convened a case-based roundtable discussion on IBS earlier this year. Our panel of primary care physicians and gastroenterologists aimed to discuss issues in the diagnosis and pharmacologic treatment of IBS that are most relevant to primary care physicians. The roundtable began with an overview of IBS by Dr. Kevin Olden, who served on the ACG task force that developed the position statement; his overview is reflected here in a short review article that sets the stage for the roundtable transcript that follows. The figures and tables within the transcript were developed by consensus of the panel.

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Irritable bowel syndrome: An overview of diagnosis and pharmacologic treatment

Traditionally, primary care physicians and many gastroenterologists have been uncomfortable diagnosing irritable bowel syndrome (IBS), in part because we have had few treatments for IBS we could feel confident about.

Over the past half decade or so, we have begun to recognize IBS for what it is: a very common disorder with a fairly high pretest probability of being diagnosed in the right setting. During that same time, our options for treating patients diagnosed with IBS have expanded from fiber, laxatives, and magnesium hydroxide to a burgeoning group of sophisticated compounds whose full potential is only beginning to be appreciated.

This short review surveys the fundamentals of IBS, focusing on diagnosis and pharmacologic management, to set the stage for the roundtable discussion that follows.

EPIDEMIOLOGY: IBS IS COMMON

Irritable bowel syndrome is a highly prevalent disorder, affecting about 10% to 15% of North Americans. Cases are divided equally among IBS with constipation, IBS with diarrhea, and IBS alternating between diarrhea and constipation. Population-based studies in North America suggest a 2:1 female predominance.[1]

DIAGNOSIS: MOVING BEYOND EXCLUSION

In recent years, the diagnosis of IBS has shifted from one of exclusion to a "positive diagnosis." Physicians increasingly view IBS as a diagnostic possibility in itself instead of trying to evaluate for other diseases we have felt more comfortable with and confident about.

Because IBS lacks anatomic or physiologic markers, its diagnosis is presently made on clinical grounds. The foundation of a positive diagnosis of IBS consists of identifying the primary symptoms, which are:

- Abdominal pain or discomfort
- Bloating
- Constipation, diarrhea, or an alternation between both.

Alarm factors

Vigilance for alarm factors is an essential part of history-taking and the physical examination in a patient with suspected IBS. TABLE 1 lists the alarm factors that can be associated with IBS-like symptoms.[2] If one of these factors is revealed in the history or exam, it demands its own workup and exploration separate from the diagnosis of possible IBS.

Diagnostic criteria

After the primary symptoms are identified, and if no alarm factors are present, physicians can turn to one of several sets of symptom-based diagnostic criteria that have been proposed for IBS. The most recent are the Rome II criteria (TABLE 2),[3] which have been found to be reasonably sensitive and specific in diagnosing IBS.[2] From a primary care perspective, the Rome II criteria are valuable in that they represent a fairly straightforward benchmark against which physicians can match their patients and move forward with a positive presumptive diagnosis.

One point from the Rome II criteria that is worth underscoring is that symptoms need not be constant but may be intermittent.

Avoid unnecessary testing

In the absence of alarm factors, the symptoms associated with IBS can easily lead to much needless testing, resulting in unnecessary costs, inconvenience, and even suffering for the patient. Excessive testing also can raise doubt in patients' minds about the validity of an eventual IBS diagnosis.

An interesting study by Hamm et al[4] illustrates the inefficiency of the routine use of many screening tests in the evaluation of suspected IBS. These researchers retrospectively examined the yield of various screening tests in uncovering alternative diagnoses in 1,452 patients meeting Rome I criteria for IBS in two large IBS treatment trials. The tests that were assessed included endoscopy or barium enemas, thyroid function tests, fecal ova and parasite tests, and lactose hydrogen breath tests.

The researchers found the following prevalence rates of various abnormalities:

- Mucosal abnormalities, 2% (and almost exclusively benign disease, such as hemorrhoids or diverticula)
- Abnormal thyroid-stimulating hormone (TSH) level, 6%

TABLE 1

Alarm factors in the diagnosis of IBS

Weight loss, anemia, occult blood in the stool
History of travel to locations with endemic parasitic diseases
Nighttime symptoms
New onset after age 50
Family history of colon cancer, inflammatory bowel disease, or celiac disease
Arthritis or skin findings on physical examination
Signs or symptoms of malabsorption
Signs or symptoms of thyroid dysfunction

ADAPTED FROM VANNER SJ, DEPEW WT, PATERSON WG, ET AL. PREDICTIVE VALUE OF THE ROME CRITERIA FOR DIAGNOSING THE IRRITABLE BOWEL SYNDROME. AM J GASTROENTEROLOGY 1999; 94:2912–2917.

- Positive stool test, 2%
- Lactose malabsorption, 23%.

Since all of these rates were either low or comparable to the background prevalence in the general US population, we can conclude that the routine use of these screening tests in patients with suspected IBS should be scrutinized because of their low yield, added costs, and inconvenience. Moreover, in the case of lactose testing in particular, documentation of lactose deficiency seldom leads to improvement in IBS symptoms anyway.[5]

Which tests to order?

The key to appropriate testing when evaluating a patient with suspected IBS without alarm factors is astute history-taking and judicious use of the Rome criteria. A complete blood cell count and blood chemistry panel makes sense for all patients, but the erythrocyte sedimentation rate generally can be omitted from the routine workup. Testing for ova and parasites is indicated only when the patient has been in an area known to be endemic for parasites.[6,7]

Structural evaluation of the colon should be guided by the patient's age (TABLE 1) and corresponding colon cancer screening guidelines.[6,7] Routine flexible sigmoidoscopy and rectal biopsy is costly and unnecessary for most patients with presumed IBS.[8]

The evidence on testing for celiac sprue and bacterial overgrowth is more equivocal. Celiac disease can present with a wide spectrum of insidious symptoms, including diarrhea, bloating, and abdominal cramps, although it typically involves less pain than does IBS. Alarm factors are typically present in celiac disease, such as weight loss and anemia. Testing for celiac sprue may be considered in IBS patients with diarrhea, according to a new evidence-based position statement on IBS from the American College of Gastroenterology (ACG) Functional Gastrointestinal Disorders Task Force,[1] but more studies are needed to define the prevalence of celiac disease in the general North American population and in patients who meet the Rome II criteria for IBS.

Similarly, bacterial overgrowth has been documented in patients with IBS,[9] but further study of its potential association with IBS is needed before routine testing for bacterial overgrowth can be endorsed.

A final area of controversy is the value of imaging studies in the diagnosis of IBS. However, several studies have concluded that the Rome criteria are superior to abdominal ultrasound for achieving a positive diagnosis of IBS.[8,10] These studies suggest that, in the absence of alarm factors, routine use of abdominal ultrasound in patients with suspected IBS is unnecessary and adds little to the diagnosis. Moreover, ordering an ultrasound tends to increase the patient's anxiety.

We currently have no data on the use of computed tomography or other imaging studies.

Role of the psychosocial evaluation

There are no data to support the concept that IBS is caused by psychological disturbance. At the same time, psychological disturbance is seen in at least 30% of IBS patients, and at an even higher rate among referral populations. Specifically, patients with IBS have an increased likelihood of having associated (as opposed to causal) anxiety disorders and, less commonly, somatoform disorders. The anxiety disorders tend to be panic disorder, generalized anxiety disorder, or major depressive disorders, all of which are quite treatable with medications. Somatoform disorders can be more challenging.[11]

Notably, psychological disturbance has been shown to influence the patient's severity of bowel symptoms and level of disability.[12] As a result, asking patients about key symptoms of mood disorders, anxiety, and depression can be helpful, since addressing such symptoms will often improve their bowel symptoms.[7] Addressing psychological symptoms may include referral to a mental health specialist for cognitive therapy or other behavioral interventions.

Never too late to revisit the diagnosis

Once a positive presumptive diagnosis of IBS is made, it is time to devise a treatment strategy based on the predominant symptoms. However, if the patient should not respond to a trial of reasonable treatment, it is not inappropriate to reconsider the diagnosis after about 2 months, both for nonfunctional bowel disorders (eg,

inflammatory bowel disease, thyroid dysfunction) and for other functional bowel disorders (outlet constipation, functional abdominal pain, etc).

TRADITIONAL THERAPIES FOR IBS

In discussing therapies for IBS, it is helpful to understand the concept of "global symptom improvement," which is one of the points emphasized by the Rome Committee in its recommendations for the design of IBS treatment trials.[3] Essentially, global symptom improvement is the measure of whether an IBS patient ends up feeling better globally. While targeting individual IBS symptoms may be desirable, global symptom improvement is viewed as the most fundamental measure of a therapy for IBS.

The traditional therapies for IBS have included fiber and a number of symptom-based therapies, specifically anticholinergics, laxatives, antidiarrheal medications, and antispasmodics/smooth muscle relaxants (ie, dicyclomine and hyoscyamine).

However, reviews of the literature on these therapies show that there is no good evidence that they are efficacious for treating IBS.[13,14] This conclusion was echoed by the recent position statement from the ACG Functional GI Disorders Task Force, which designated none of these agents effective for relieving global IBS symptoms.[1]

Antidepressants

Antidepressant medications, particularly low-dose tricyclic antidepressants (TCAs), have traditionally been a favorite for IBS among many gastroenterologists, who have used them as second-line therapy for patients who didn't respond to the above traditional therapies. Speculation about the potential mechanism of antidepressants for IBS has ranged from their anticholinergic and antidepressant effects to pain modulation, perhaps CNS-specific pain modulation.

Jackson et al[15] conducted a good meta-analysis of trials assessing the efficacy of antidepressants, almost exclusively TCAs, for symptom improvement and pain score in patients with functional GI disorders. They concluded that antidepressants appear to be effective for these disorders, with a summary odds ratio for improvement of 4.2 (95% confidence interval, 2.3 to 7.9). An average of 3.2 patients had to be treated with antidepressants to improve one patient's symptoms. There was a strong suggestion that the efficacy was independent of the drugs' antidepressant effects, but further study is needed.

The recent ACG Functional GI Disorders Task Force[1] concluded that TCAs are not more effective than placebo at relieving global symptoms of IBS but do improve abdominal pain in IBS patients.

The literature on the use of selective serotonin reuptake inhibitors (SSRIs) for IBS is beginning to develop, but it is currently too limited to allow for any conclusions, the Task Force concluded.[1]

TABLE 2

The Rome II criteria for IBS

At least 12 weeks (which may be nonconsecutive) of abdominal discomfort or pain in the preceding 12 months with two of the following three features:

1) Relief with defecation
2) Onset associated with a change in stool frequency
3) Onset associated with a change in form (appearance) of stool

The following symptoms cumulatively support the diagnosis of IBS:

- Abnormal stool frequency (> 3 times per day or < 3 times per week)
- Abnormal stool form (lumpy/hard or loose/watery)
- Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation)
- Passage of mucus
- Bloating or feeling of abdominal distention

ADAPTED FROM THOMPSON WG, LONGSTRETH GF, DROSSMAN DA, ET AL. FUNCTIONAL BOWEL DISORDERS AND FUNCTIONAL ABDOMINAL PAIN. GUT 1999; 45(SUPPL 2):II43–II47.

IBS-SPECIFIC THERAPIES

The last few years have seen the advent of more IBS-specific medications involving the serotonin, or 5-HT, system. Members from two families of these drugs—the 5-HT_3 antagonists and the 5-HT_4 agonists—are now on the US market (TABLE 3), and more are likely to come.

Alosetron, a 5-HT_3 receptor antagonist

Alosetron (Lotronex) was the first IBS-specific therapy to be approved by the US Food and Drug Administration, but it was withdrawn from the market in late 2000, only to be reintroduced last year under a restricted prescribing program.

Alosetron is a 5-HT_3 antagonist indicated for the treatment of female IBS patients with severe diarrhea. It acts by reducing intestinal secretion, decreasing visceral afferent nerve activity (thereby decreasing IBS-related pain), and reducing intestinal motility.[16] The recent ACG Functional GI Disorders Task Force designated alosetron as more effective than placebo at reliev-

TABLE 3

Profiles of the new IBS-specific drugs

	ALOSETRON	TEGASEROD
Brand name	Lotronex	Zelnorm
Description	Selective 5-HT_3 receptor antagonist	Selective 5-HT_4 receptor partial agonist
Indication	Treatment of women with severe diarrhea-predominant IBS who have chronic (>6 months) IBS symptoms, exclusion of anatomic/biochemical abnormalities of the GI tract, and no response to conventional therapy	Short-term treatment of women with IBS whose primary bowel symptom is constipation
Dosage	1 mg orally once daily for 4 weeks,which may then be raised to 1 mg twice daily if response is inadequate and the drug is well tolerated	6 mg orally twice daily before meals for 4–6 weeks; an additional 4–6 weeks may be considered if there is response to therapy
Most common adverse effects	Constipation, abdominal discomfort/pain, nausea	Headache, diarrhea
Contraindications	• Current (or history of) constipation • History of intestinal obstruction, stricture, toxic megacolon, GI perforation, or adhesions • History of ischemic colitis, impaired intestinal circulation, thrombophlebitis, or hypercoagulable state • Current (or history of) Crohn disease or ulcerative colitis • Active (or history of) diverticulitis • Inability to understand or comply with patient–physician agreement	• Severe renal impairment • Moderate or severe hepatic impairment • History of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions

ing global IBS symptoms in these patients, based on adequate, well-designed trials.[1] Its efficacy consists specifically of relief of diarrhea, rectal urgency, and pain, although it has not been shown to improve bloating, perhaps because diarrhea-associated IBS is less likely to involve significant bloating.[17,18]

The withdrawal of alosetron from the market in late 2000 followed reports of 84 cases of ischemic colitis and 113 cases of severe constipation among 275,000 patients who received the drug. The majority of these cases required hospitalization, with 11 ischemic colitis cases and 34 severe constipation cases requiring surgery, and 2 cases of each resulting in death. Subsequent review showed that some of these patients should not have received the drug, since they did not have true diarrhea-predominant IBS, or received inappropriate doses.[19]

After the withdrawal, many patients who had benefited from alosetron lobbied for its return, prompting the FDA to authorize its recent return to the market under a restricted prescribing program. While there is no specialist qualification for prescribing alosetron, physicians must do the following in order to prescribe the drug:

- Register with the prescribing program run by the drug's marketer, GlaxoSmithKline
- Attest to their qualifications for diagnosing and treating IBS
- Agree to report any serious adverse effects to the FDA and the drug's marketer
- Sign, and have their patients sign, a consent form for the medical record
- Place special tracking stickers on all alosetron prescriptions.

Tegaserod, a 5-HT_4 receptor agonist

Tegaserod (Zelnorm) is a partial agonist of the 5-HT_4 receptor that was approved by the FDA last year for the treatment of IBS with constipation in female patients. It is the first of a new class of compounds, aminoguanidine indoles, that are very similar in structure to serotonin.[20] By acting as an agonist at the 5-HT_4 receptor, tegaserod stimulates the peristaltic reflex, reduces visceral sensitivity, and stimulates chloride secretion in the intestine.[20–23] These actions promote relief of pain and discomfort and prompt the bowel to move.

The recent ACG Functional GI Disorders Task Force designated tegaserod as more effective than placebo at relieving global IBS symptoms in female IBS patients with constipation, based on adequate, well-designed trials.[1] Tegaserod's efficacy consists

specifically of relief of abdominal pain/discomfort and bloating, as well as increasing the number of bowel movements and improving stool consistency.[24] The effect on bloating is noteworthy, since bloating can be the bane of the existence of many IBS patients with constipation.

Tegaserod's efficacy was demonstrated in trials consisting predominantly or exclusively of women, so there was insufficient statistical power to make conclusions about efficacy in men.

Tegaserod was generally well tolerated in clinical trials. The side effects reported significantly more often with it than with placebo were nonmigraine headache and, as expected from its prokinetic effect, diarrhea. A slightly higher incidence of cholecystectomies was noted with tegaserod relative to placebo in the clinical trials (0.3% vs 0.2%), but there is no evidence of a causal relationship. A recent open-label trial found that tegaserod therapy was safe and well tolerated for up to 1 year in IBS patients whose predominant symptom was constipation.[25]

Unlike its fellow 5-HT_4 receptor agonist cisapride, tegaserod has been associated with no evidence of QT interval prolongation or other cardiac abnormalities. Tegaserod has no clinically relevant drug–drug interactions.[26]

Investigational serotoninergic agents

Prucalopride is a *full* 5-HT_4 receptor agonist, in contrast to tegaserod, which exerts *partial* agonism at the 5-HT_4 receptor. Like tegaserod, prucalopride is a prokinetic, and it has shown similar clinical efficacy in relieving constipation-associated IBS. However, prucalopride has been associated with mysterious intestinal cancers in animal studies, which puts its future in doubt.

Cilansetron is, like alosetron, a 5-HT_3 receptor antagonist, and it has a similar clinical effect. To date, the only toxicity seen with its use is one possible case of drug-related ischemic colitis. Cilansetron is currently in phase III trials and may be submitted for marketing approval by the end of this year.

Beyond this there are a host of other serotoninergic drugs in earlier stages of clinical development for IBS, including the traditional 5-HT_1 agonist sumatriptan, as well as a few nonserotoninergic compounds. How well these agents will pan out is unknown, but it looks to be an exciting decade for the treatment of IBS.

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Roundtable discussion

Irritable bowel syndrome: New tools and insights for the primary care physician

It's important to establish early on whether the patient agrees with the diagnosis of IBS.
—Dr. Isaacson

CASE PRESENTATION

A 42-year-old white woman presents to her primary care physician with chronic symptoms of abdominal pain, bloating, and constipation of 6 months' duration. She has a bowel movement every other day, with straining, passing hard stool. She reports intermittent abdominal discomfort/pain and bloating almost daily, with "spasms" in the lower abdomen at the time of the bowel movement. She says the pain can be quite severe at times. Her weight fluctuates, but she has no net weight loss. There is no rectal bleeding.

She has tried fiber but stopped because it makes her bloated. She is taking paroxetine for anxiety and sumatriptan, intermittently, for migraine headaches. She was seen elsewhere and had a barium enema, which was normal. She was told to take laxatives but is reluctant to because she fears "getting used to them."

Dr. Edy Soffer—I'd like to start by asking our primary care physicians, Drs. Brunton and Isaacson, to tell us what you would do if this patient came to your office.

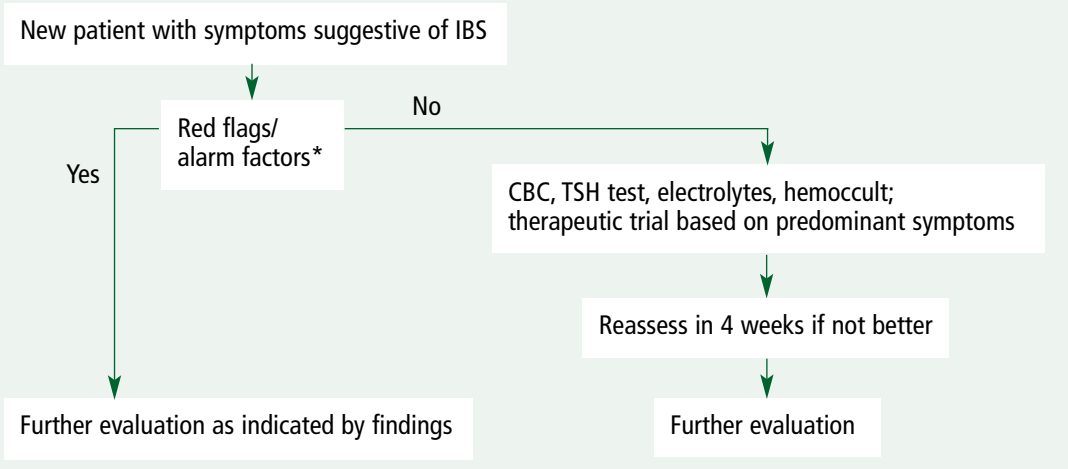
Dr. Stephen Brunton—Well, this patient has a lot of classic symptoms of irritable bowel syndrome (IBS), which would make it tempting to make a positive diagnosis of IBS after a basic history and exam, but I think there may be some insecurity issues for both the primary care clinician and the patient. Because we manage the whole patient, I think some primary care physicians may need to further rule something out rather than initially make a positive diagnosis of IBS. It also may depend on my relationship and continuity with the patient, although it sounds like I haven't seen this particular patient before. If that's the case, I'd be more likely to do at least some kind of workup before making a definitive diagnosis.

Dr. J. Harry Isaacson—I agree that the nature of the patient's relationship with the primary care physician is critical, and it has to be factored into any kind of algorithmic approach to IBS. If, based on the history, you are confident of the diagnosis and feel the symptoms are unlikely to represent something more serious, you can portray that confidence to the patient and probably not have to do much testing up front.

Also, understanding the patient's expectations up front is very important, since it can help you gauge your approach. With this patient, I could envision doing no additional evaluation other than talking to her, establishing a relationship, and maybe coming up with some change in therapy—if she is comfortable with that approach. I'd want to give her the sense that I'm going to stick with her over time, that we are going to work on this together. This approach may lower any patient demands for early and unnecessary testing. If she has very high expectations for a big evaluation, I might move up some of the testing I would normally defer, if the cost and potential for harm are relatively small.

Dr. Soffer—What about the reason why she is coming to see you right now—how much of a difference does that make? Is it because her symptoms have become unbearable? Or is her anxiety such that she just needs to know what's going on? Or did she not hit it off with the previous physician she saw? As a referral-based doctor, I generally see the patients who are uncomfortable with the diagnosis by a nonspecialist; they want that specialist "stamp of approval" that it's IBS.

Dr. Kevin Olden—Yes, and the advantage we have as referralists is that we get an outside chart with a lot of the testing already done, and that makes our job much easier in terms of what to do initially. The advantage we specialists don't have is that close ongoing relationship that many primary care doctors have with their patients. It's much less likely that our IBS patients will see us back again, because of geog-



*These include new onset after age 50, fever, weight loss, nocturnal symptoms, gastrointestinal bleeding, anemia, abnormal physical examination, and family history of inflammatory bowel disease, colon cancer, or celiac disease.
CBC = complete blood cell count; TSH = thyroid-stimulating hormone.

FIGURE 1. Diagnostic algorithm for initial evaluation of a patient with suspected IBS.

raphy or insurance or whatever else, so that puts more pressure on us to do more in our one or two office visits with the patient.

Dr. Isaacson—I think there are really two issues to clarify with this patient. First, what does she think she has? If she agrees with the diagnosis, that's one hurdle that's cleared. If she doesn't, then you have a set of challenges as the primary care physician that may include consultation to confirm the diagnosis. The second issue relates to management problems, which gets into treatment, but that usually comes after you've agreed on a diagnosis. I think it's very important to establish early on, whether you're a specialist or a primary care physician, if the patient thinks she has IBS or thinks she has something else.

Dr. Brunton—That's critical, because many patients with abdominal pain and a change in bowel habits may think they have cancer and want to ask you about it. So I'll ask up front, "Are you concerned that you have cancer?" And I can see the relief on their face, because they want to make sure you're thinking about that. Then I'll say, "Frankly, this is not a sign of cancer; here's what we look for when we think about cancer, and this is not that." Once you allay that fear, you create a much better landscape for proceeding.

Dr. Olden—Yes, that underscores the importance of asking as specifically as possible why the patient is seeing you now. I always ask, "What is your concern?" and then explore further if necessary. Some patients think that someone missed their diagnosis. Others fear that they have an ominous disease. Sometimes it's a treatment concern, where the patient just wants her symptoms to be addressed more effectively. Other times it's a quality-of-life issue, where her symptoms are well controlled but she doesn't like taking all these medicines. Or it may be a psychological issue—the patient's bowels are doing okay but she's phobic about losing control so she tracks her movements around town for bathrooms. These issues can quickly clarify both the kind and the extent of the difficulty the patient is in.

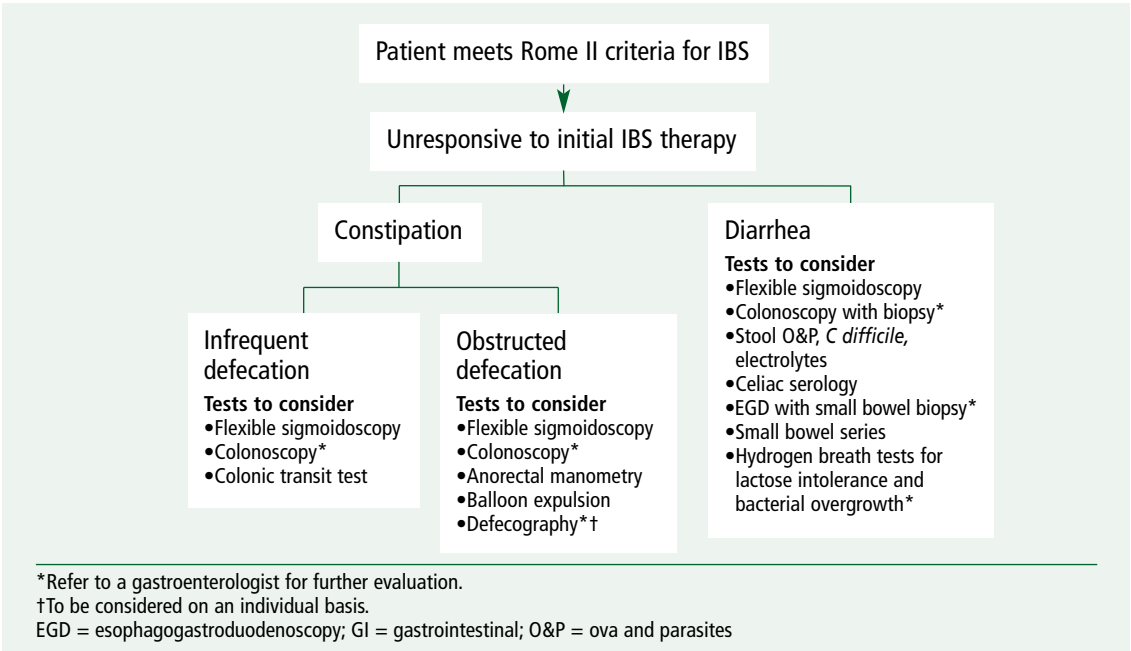
SCREENING: HOW MUCH IS ENOUGH?

Dr. Soffer—Let's change our case presentation a bit and assume you are the first physician to see this patient. Would you proceed any differently, and what tests would you do?

Dr. Olden—I see some de novo patients with IBS as well as referral patients, so I can speak to this. Obviously, I'd take a history and then do the basic studies for a de novo patient: a physical exam, a CBC, and a chemistry panel.

Once you allay the fear of cancer, you create a much better landscape for proceeding.
—Dr. Brunton

Traditionally, IBS recommendations have been by and for gastroenterologists, but it's primary care physicians who see the bulk of IBS patients.
—Dr. Soffer



*Refer to a gastroenterologist for further evaluation.
†To be considered on an individual basis.
EGD = esophagogastroduodenoscopy; GI = gastrointestinal; O&P = ova and parasites

FIGURE 2. Diagnostic algorithm for further evaluation of nonresponding patients.

But I would hit the brakes at that point, as I have cautiously become a minimalist over the last 3 years or so. I would not order any imaging, of the gallbladder or colon or otherwise, and I would not go to second-level laboratory tests, such as for celiac sprue. If the patient meets the Rome II criteria, I would treat empirically for 4 weeks, see what happens, and go from there.

This is what has worked for me, and I haven't been burned yet, but I reserve the right to go back after 4 weeks and do further investigations if either the patient or I am not a happy camper.

Dr. Isaacson—Yes, I don't think you have to rule everything else out before you make the presumptive diagnosis of IBS if the patient understands that their symptoms fit the pattern of IBS and that there will be follow-up and, if necessary, a contingency plan. The idea of a positive presumptive diagnosis is critical, because it gives us a constructive alternative to the "wastebasket" approach to IBS that most of us encountered in our training—ie, if we can't figure these symptoms out, let's put them in this wastebasket called IBS.

The thyroid-stimulating hormone (TSH) test is the one test I'd consider adding to the list Dr. Olden just outlined, since constipation and diarrhea are both manifestations of thyroid disease. When someone walks in with a 3-month history of severe constipation or diarrhea, it's hard for a primary care physician to delay doing a TSH, especially since it's easy and relatively inexpensive.

Dr. Brunton—Yes, I thought the same thing, and the TSH is actually part of our chemistry panel where I practice.

Dr. Olden—That's a very good point because you two, as primary care physicians, need to be especially oriented toward the care of the whole patient. So, while you're looking for what's causing the patient's bowel symptoms, you sure would also like to know if they have thyroid dysfunction or anemia. Within this context, doing a TSH is very reasonable and pertinent. So if you find thyroid dysfunction and treat it, even if the patient's bowel symptoms remain unchanged afterward, it is still a victory for the patient.

Dr. Soffer—Plus, we are all creatures of experience. If you missed one case of thyroid disease 10 years ago, it will cause you to always take a

TABLE 1

Further tests for evaluating patients with diarrhea and constipation

Quantitative fecal fat
This test analyzes stool collected over 72 hours, while the patient is on a high-fat diet. Stool fat content of more than 7 grams over 24 hours is considered abnormal. This test is done on an outpatient basis and is useful for diagnosing steatorrhea.

Breath tests
Breath tests measure the respiratory excretion of labeled CO_2 after oral administration and metabolism of radioactive carbon-labeled substrates (or of H_2 after administration of carbohydrates). These tests can be used to assess fat, carbohydrate, bile acid malabsorption, or bacterial overgrowth. They rely on the principle that conditions of malabsorption or the presence of bacterial overgrowth in the small bowel lead to abnormal metabolism of test nutrients in the small bowel. This, in turn, results in abnormal breath content of the gases measured.

Serologic markers for celiac disease
Antibodies against four antigens (gliadin, reticulin, endomysial, and tissue transglutaminase) are useful in the diagnosis of celiac disease. Those of the IgG subclasses are generally more sensitive, and IgA is usually more specific. Although serologic tests do not supplant small bowel biopsy in the diagnosis of celiac disease, they are useful as screening tests and for monitoring adherence to a gluten-free diet.

Colonic transit study
This test is useful in evaluating a patient with severe constipation. The patient ingests radiopaque markers while on a high-fiber diet and while abstaining from laxatives, and abdominal radiographs are taken after a number of days. Several variations exist, but all consist of giving markers and counting the remaining number in the colon. An excess number of markers indicates the presence of colonic inertia, or slow-transit constipation. The distinction between this condition and functional constipation is important since colectomy is considered only for slow-transit constipation.

Anorectal manometry
This test measures the strength of the anal sphincters, rectal sensation, and recto-anal coordination and reflex activity. It is done on an outpatient basis by transanal insertion of a catheter with pressure sensors and an attached balloon. It helps to determine the presence of obstructed defecation and to exclude Hirschsprung disease.

Defecography
This is a technique in which barium, thickened to a consistency that approximates stool, is introduced into the rectum. Fluoroscopy is then used to monitor evacuation of barium during attempted defecation. While defecography can be used to evaluate functional problems, such as obstructed defecation, it is particularly helpful in assessing the presence and functional severity of structural abnormalities such as rectocele or intussusception. It is done by radiologists on an outpatient basis.

TSH for the rest of your career. This is not likely to be changed by future recommendations.

Dr. Bo Shen—What about tests like a screening flexible sigmoidoscopy or a screening colonoscopy? Are these tests that you would be comfortable doing yourself before referring the patient to a gastroenterologist?

Dr. Brunton—I wouldn't order those tests early on in a patient like this because we have the luxury of trying some therapeutic approaches and seeing how the patient fares. In this way, the therapeutic trial can serve as an additional test to perhaps reinforce whether the diagnosis was correct. In any case, this patient has a pretty good history; I'm not really worried about colon cancer because there is no bleeding and she's only 42. Down the line, if there is no response after 4 weeks of reasonable therapy, I would assess further, and colonoscopy would probably be among the things I'd consider then.

Dr. Isaacson—I think there's a misperception among primary care physicians that you have to do some testing beyond blood work in order to establish the diagnosis of IBS. There's a tendency to not want to miss something, so you get a sigmoidoscopy or an ultrasound, which I think crosses the threshold into invasive, unnecessary, and expensive care, unless an alarm factor is present. What I like about the American College of Gastroenterology's new

position statement on IBS is that it empowers primary care physicians not to have to do any imaging or endoscopy or ultrasonography to make a presumptive diagnosis.

Dr. Soffer—Your comment points out how much the traditional IBS recommendations have been by and for gastroenterologists. Although primary care physicians see the bulk of IBS patients, your concerns have not been adequately addressed.

Dr. Olden—Yes, we as gastroenterologists have done an inadequate job of adapting the IBS data to the primary care perspective, as I'm learning this morning, and that's important because we inhabit two different worlds in terms of patient management. Primary care doctors have the advantage of ongoing, longitudinal care, but at the same time you have the dilemma of the de novo patient, where the differential diagnosis is wide open. You also have pretest probability more on your side because IBS is pretty common.

We need to thoroughly screen for *all* the medicines patients are taking, since many common agents can cause diarrhea or constipation.
—Dr. Shen

Dr. Soffer—The Rome criteria are a good example of how gastroenterologists are not sensitive enough to the realities of primary care. A study was done to assess how well primary care physicians know the Rome criteria, and the results were absolutely dismal. But for that matter, I don't know how well most gastroenterologists really know the Rome criteria. But I think the recent ACG Task Force did a nice job of simplifying these criteria for practical clinical purposes.

OTHER KEY CONSIDERATIONS IN THE EVALUATION

Dr. Soffer—Returning to our case, is there anything else you would want to find out about this patient, and how would you take it from here?

Dr. Shen—We need to thoroughly screen for *all* the medicines patients are taking, especially for de novo patients. That includes over-the-counter drugs and alternative therapies, since many of these can cause diarrhea or constipation (TABLE 2). For example, nonprescription NSAIDs can cause either diarrhea or constipation, antacids may cause bloating, and, in our case presentation, the paroxetine that the patient is taking could cause constipation.

Dr. Isaacson—Also, we don't have this patient's lab work, so obviously you'd need that. Beyond that, I'd inquire about family history and, along with determining the patient's expectations, explore any psychosocial aspects, which would include asking if there has been a history of sexual abuse, especially since pain is a dominant symptom.

Dr. Olden—Yes, sexual abuse can be a key factor in IBS patients. A number of researchers have shown conclusively that there is an excess prevalence of a physical or sexual abuse history among people with functional GI disorders. When pain, particularly pelvic pain, is a predominant symptom in an IBS patient, that's a huge red flag for a potential abuse history.

Now, is abuse etiologic in IBS? Probably not. It probably represents tremendous damage to the patient's emotional integrity and coping ability, so that their IBS becomes more intrusive and troublesome. But it is a critical area to explore because abuse histories are associated with a great deal of depression, somatoform disorders, and anxiety, and these things need to be treated.

Dr. Isaacson—Of course, asking about abuse is more difficult than other areas of the history, but I think it can be really fruitful in terms of forming a good relationship with the patient and making them realize that you understand their predicament.

Dr. Olden—Absolutely, and the abuse literature clearly supports that. It also shows that patients see this as an appropriate area for physicians to ask about.

How do you broach the subject? I bring up the epidemiologic reason for asking—"Not uncommonly, people with your set of symptoms report physical or sexual abuse; is that an issue for you?" That way, they know why I'm asking. Then I gauge their reaction: if they say yes in a reasonably unemotional way, I will explore it further; if it's clearly overwhelming for them, I will close the book and maybe try to gently reopen it over time.

Dr. Soffer—What do you recommend for those of us who don't have your background in psychiatric subcare?

Dr. Olden—I'd suggest partnering with someone in the mental health community. It can be a psychiatrist, a PhD psychologist, the nurse practitioner in your office, a counselor—it matters less where the referral goes than the fact that it is brought up and goes somewhere. So it's reasonable for the abuse issues to be taken care of elsewhere, but this is going to be more and more of a primary care issue as new generations of physicians come along.

Dr. Brunton—To return to what else we'd need to know from the patient evaluation…this isn't specific to this case presentation, but I'd like to raise the issue of the elderly person with constipation, which opens up a whole other process. In the elderly, we generally don't think "irritable bowel"—we may just think "old bowel." The elderly patient with IBS-like symptoms also makes you think about colon cancer or metastatic ovarian cancer, and it raises things like laxative abuse and other issues.

Dr. Isaacson—Yes, if a person hasn't had a pattern of these symptoms, and suddenly they appear at age 72, the first thing I'm thinking of is not IBS.

Dr. Olden—Absolutely, and this was touched on in the ACG position statement, but it was not emphasized enough. Certainly, anyone age 50 or older with new-onset symptoms suggestive of IBS absolutely demands a more aggressive workup than what we've discussed, and IBS definitely becomes a diagnosis of exclusion in these patients.

WHEN TO REFER

Dr. Soffer—Let's talk a bit about when to refer to a gastroenterologist. Under what type of scenario would you refer?

Dr. Isaacson—I think there are two scenarios: when I am unclear about the diagnosis, and when there are management problems. The first scenario would often involve a patient who has unmet expectations, who may not buy into the diagnosis and wants a specialist to confirm it. Also, if a patient hasn't responded to initial therapy, I may want the diagnosis confirmed.

The second scenario relates to management problems, when the patient and I are comfortable with the diagnosis but the patient is not improving after trying a few therapies. In this scenario, I'd want to see if there was something else we could try and want to get a fresh take on the case.

Dr. Brunton—For me, it would often be to reaffirm a suspected diagnosis. I think there is still a real concern among primary care physicians about possibly missing something. And while we can sit here and say IBS should be a positive diagnosis that we can all make, in the real world it isn't always so clear-cut and there are a lot of competing priorities. Plus, a lot of us don't have open access to colonoscopy or all the procedures in the possible workup, so that's another factor. And there are always the patients who fear that they have something

TABLE 2

Common agents associated with constipation or diarrhea

AGENTS ASSOCIATED WITH CONSTIPATION	AGENTS ASSOCIATED WITH DIARRHEA
Analgesics	Laxatives • Stimulant (senna, bisacodyl, castor oil) • Osmotic (magnesium-containing agents) • Nonabsorbable carbohydrates (sorbitol, lactulose)
Anticholinergics • Antidepressants • Smooth muscle relaxants • Antipsychotics	Prokinetics (metoclopramide, tegaserod)
Cation-containing agents • Iron supplements • Aluminum (antacids, sucralfate)	Proton pump inhibitors
Opiates	Antacids (magnesium-containing agents)
Calcium channel blockers	Antibiotics
	Nonsteroidal anti-inflammatory drugs
	Antineoplastics
	Antiarrhythmics
	Antihypertensives
	Chronic alcohol ingestion

more serious than IBS, and they aren't going to be happy without that specialist consult.

Dr. Isaacson—I'd be more apt to get a specialist consult for an IBS patient with diarrhea because I think the evaluation is a little more subtle and complex for diarrhea than for constipation. One thing I picked up from the new ACG position statement on IBS was the potential role for celiac sprue testing in IBS patients with diarrhea. I haven't paid enough attention to the sprue issue, and I worry about microscopic colitis in patients with diarrhea, so these things would push me toward a consult.

Dr. Soffer—Yes, the diarrhea cases have a wider differential diagnosis. With regard to celiac sprue, you may want to look into that in certain populations with diarrheal diseases, but you should still be selective since testing for it will generate a number of false-positives, which then generate more unnecessary testing. If I see someone of, say, Irish ethnicity with typical symptoms of IBS with diarrhea, I may test for celiac sprue, but I'm unlikely to do so for ethnic groups where celiac disease is very uncommon.

When pelvic pain is a predominant symptom, that's a huge red flag for a potential abuse history.
—Dr. Olden

TREATMENT: GENERAL ISSUES AND APPROACH

Dr. Soffer—Shall we move on to treatment now? Again, let me start by posing the first question to our primary care panelists: How would you direct the treatment of the patient in our case presentation?

Dr. Brunton—Well, she has tried fiber and stopped. I would want to know exactly how she tried it. Did she go up to 50 grams, or what? I usually start patients slower and get them used to it. I'd want to try it that way if that's not how she tried it, since it's not going to hurt unless she has some real issues with that.

Obviously, a patient like this is a great patient for tegaserod, since tegaserod has the indication of IBS with constipation and this patient's symptoms have been chronic and sound pretty substantial. Would I start tegaserod straight off? I think there would be some financial issues: Does she have insurance? Can she afford it? Also, she's someone for whom an antispasmodic like hyoscyamine might be tried, because of her spasms during bowel movements. But I would be very comfortable putting a patient like this on tegaserod, probably very early on in the process.

Dr. Isaacson—I would sit down with this patient and explain that there are a lot of treatment avenues we haven't approached yet. I would discuss them and ask her to participate in the decision. If she says the constipation and the pain are just unbearable, it's going to push me toward more aggressive therapy at an earlier stage. If she seems reassured, I'd lay out the range of options and ask what sounds good to her. Depending on the lead she gives me, I could be comfortable reintroducing fiber in a different way, or trying something else for the spasm, or maybe withdrawing the paroxetine if she suggests it may not be helping her anxiety enough.

Dr. Brunton—But her symptoms have been presented as pretty significant and chronic, so I'd perhaps consider her case as more "moderate to severe" from the start.

Dr. Isaacson—Then you can tell her that if her symptoms are more severe we have some really good options available now that have been well studied. One of the things I learned from the new ACG position statement is that there have been some very good studies done with these newer agents for IBS.

In any case, I think that showing some optimism and willingness to partner with the patient is very therapeutic in and of itself in many cases.

Dr. Olden—I agree. We tend, as researchers, to minimize the doctor–patient relationship, positive transference, or whatever you wish to call it, and its ability to improve patients' outcomes. I think it's a tremendous variable in many disorders, IBS being just one of them. I will tell patients straight up, "I'm going to hang in there with you. It may take a while, but there is a general tendency to get better. We may try a lot of drugs, and many of them might not work, but we'll work through this." That alone can get their anxiety down and let them see some light at the end of the tunnel.

TABLE 3

Selected drug therapies for IBS

PREDOMINANT IBS SYMPTOM	DRUG CLASS AND SPECIFIC AGENTS	USUAL ADULT DOSAGE
Diarrhea	**Opioid μ-receptor agonists**	
	Loperamide (Imodium and others)	2–4 mg up to four times daily, as needed
	Diphenoxylate (Lomotil and others)	5 mg four times daily, as needed
	Smooth muscle relaxants	
	Dicyclomine (Bentyl and others)	20 mg four times daily initially, then up to 40 mg four times daily
	Hyoscyamine (Levsin and others)	0.125 mg sublingually three times daily as needed, or 0.375 mg orally twice daily
	Tricyclic antidepressants	
	Amitriptyline (Elavil and others)	10–100 mg at bedtime
	Desipramine (Norpramin and others)	10–150 mg at bedtime
	Selective 5-HT_3 receptor antagonist	
	Alosetron (Lotronex)*	1 mg once daily for 4 weeks; may increase to 1 mg twice daily for 4 weeks
Constipation	**Bulking agents**	
	Psyllium (Metamucil and others)	20 g/day, divided, with >250 mL water
	Polycarbophil (Konsyl Fiber and others)	1–6 g/day, divided, with >250 mL water
	Methylcellulose (Citrucel and others)	3–6 g/day, divided, with >250 mL water
	Nonabsorbable carbohydrates	
	Lactulose (Kristalose and others)	15–60 mL/day, divided
	Sorbitol	120 mL of 25% solution
	Osmotic laxatives	
	Magnesium hydroxide (Milk of Magnesia)	1–2 oz/day
	Polyethylene glycol solution (MiraLax)	1 dose (17 g in glass of water) once or twice daily
	Selective 5-HT_4 receptor antagonist	
	Tegaserod (Zelnorm)	6 mg twice daily for 4–12 weeks

* Physicians must enroll in a special risk-management program to prescribe this drug.

Dr. Brunton—This gets at the role of the placebo effect in IBS. Part of the issue in most conditions involving chronic pain or similarly debilitating symptoms is that patients can come to feel that the pain controls them. Anything you can do or give to make them feel they are taking steps to overcome that control can be quite empowering.

If you look at some of the IBS treatment studies, you see some very large placebo response rates. I think this substantial placebo effect may be at work with some of the traditional IBS therapies that lack supportive clinical trial data, perhaps along with the natural tendency for symptoms to wax and wane. For instance, if half of my patients will do well with fiber, and that costs only pennies, I'll certainly try that. Why shouldn't I try that and then, for those who don't do as well, go on to a more clinically supported drug? Is it good science? No, but it's a "less is more" practical solution that seems to work to a certain extent, and many clinicians do this in the real world.

Dr. Soffer—You raise an important issue. If fiber is safe (except for the bloating) and it's going to give X% of patients some benefit, I would feel comfortable trying that initially, as long as I'm not harming the patient.

This touches on my one concern about the new position statement from the ACG, which is, to the credit of all the ACG Task

Force members, the most critical and evidence-based approach to IBS I've seen. When you look at the position statement, there isn't much room to recommend, say, loperamide because there's no global improvement in IBS symptoms. But if I give loperamide I can perhaps improve diarrhea, and I can do so very cheaply and very safely, and I think that's something, even if it's not global symptom improvement. Dr. Olden, as a Task Force member, do you think the Task Force might have been a little bit too academic?

Dr. Olden—You make an excellent point. Take fiber, for instance. There is a large literature criticizing the efficacy of fiber, but in the real world we all prescribe fiber, both for IBS and for non-IBS conditions. Fiber supplementation is a key element of improving or preventing a lot of medical conditions, and it is so cheap and nontoxic that there is essentially no downside to using it, and I do it all the time. So the threshold is so low, and when this is combined with a good doctor–patient relationship, you may get a certain "bang for your buck" that you won't get from a randomized controlled trial.

Showing some optimism and willingness to partner with the patient can be very therapeutic in and of itself.
—Dr. Isaacson

Dr. Isaacson—I agree, and I have a couple of related points. I like to identify what the patient's main symptoms are, define an endpoint, try a treatment for 4 to 8 weeks, and see how it works. I try to choose an objective endpoint, such as some specific measure of pain or whether the patient can do things now that they couldn't before. If the treatment hasn't worked well enough, we can try something else.

Also, if I'm unclear about where to go with the treatment and if the patient is not terribly distressed, I may just have them monitor their symptoms for a while. This can help establish my relationship with the patient and clarify how to treat if we should need to. Sometimes, if the patient's distress is not great, they may be satisfied with just understanding their disease. Not everyone has to come away with a medication.

FACTORING IN DEPRESSIVE DISORDERS

Dr. Soffer—Let's return to our case presentation. Let me propose switching our patient from her current SSRI, paroxetine, to another SSRI, say, sertraline, which has diarrhea as a side effect, plus a potential effect on pain. Let's say we consider this along with giving her fiber again or an inexpensive laxative. What do you think of this approach?

Dr. Olden—It depends on how the patient comes to me. If she comes, like this patient, on stable SSRI treatment for anxiety or depression, I am reluctant to fool with that because while the new SSRI may have a better bowel effect, I could turn her depressive illness on its ear and really interfere with her treating physician's plan. If she comes to me not already on an antidepressant, it's a different ballgame and I feel very empowered to start and then change antidepressants as needed, for either depressive or bowel symptoms.

Dr. Soffer—I'm with you. If I wanted to make a change of the antidepressant, I'd only do so through her original prescribing doctor. But in a de novo patient, because I've had a pretty good experience with antidepressants for pain, I might try this because if she does not respond to this combination, the next option is a 5-HT_4 agonist, which can address both the bowel symptoms and the pain.

Dr. Brunton—Are you suggesting, then, Dr. Soffer, that you would use tegaserod second-line?

Dr. Soffer—That depends. Let's say I've got an IBS patient who comes in with anxiety but who I don't think needs to see a psychiatrist because I feel my experience is sufficient to treat her. I would want to give her something for her anxiety and something for constipation. Remember, we are talking about someone for whom anxiety is an issue. If anxiety were not an issue, I wouldn't start with that approach.

Dr. Olden—The flip side to that question is to suppose the patient isn't depressed or anxious. Do we start with an antidepressant or do we move right to the new disease-specific agents for IBS? I would go to the new disease-specific agent, absent depression or anxiety, because frankly it is about the same price and you are getting a more specific drug. With the patient

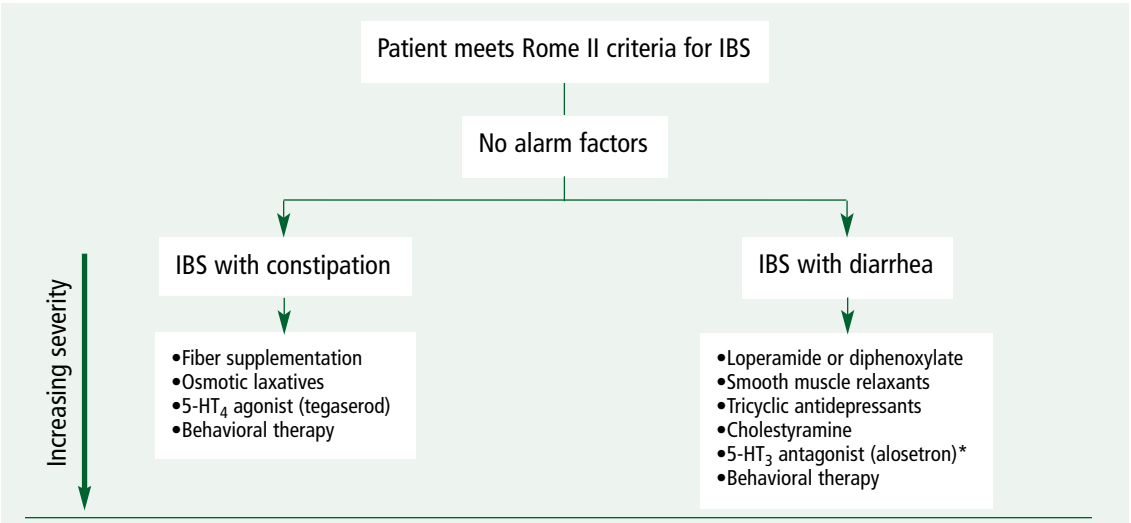


FIGURE 3. Symptom-oriented treatment of IBS.

in our case presentation, I think you have to use both. I'd keep her on paroxetine or its equivalent, and I would probably add tegaserod to her regimen.

SAFETY AND THE SEROTONIN SYSTEM

Dr. Soffer—Are there any issues with the sumatriptan our patient is taking, which is a 5-HT_1 agonist? Given that paroxetine and tegaserod both act on the serotonin system as well, how many serotonin agonists or antagonists can I give to one patient?

Dr. Olden—That's a very relevant question. Serotoninergic syndrome is a very serious disease that we created by developing new treatments. It resembles malignant hyperthermia with hyperpyrexia, delirium, arrhythmias, and rhabdomyolysis. It's still an epidemiologic work in progress, but it is seen in people who are taking multiple psychiatric drugs, mainly monoamine oxidase inhibitors or dopaminergic antagonists plus a serotoninergic-reactive antidepressant.

There has been no association between serotoninergic syndrome and the concomitant use of an SSRI and a 5-HT_1 agonist like sumatriptan. Likewise, to date there has been no interaction shown between SSRIs and tegaserod or between the 5-HT_1 agonists and tegaserod. So it's a pretty clean story. Serotoninergic syndrome is seen mainly in psychiatric settings among patients who are on big-time psychiatric drugs, but it's something we need to be continually aware of.

Dr. Shen—A lot of patients with IBS have migraines. Is there any concern that starting tegaserod in this patient from our case presentation might exacerbate her migraines, since headache may be seen with tegaserod?

Dr. Olden—No, at least not based on the evidence we have. While there was an increased incidence of headache with tegaserod compared with placebo in the phase II and III trials, there was no increase in migraine headaches. As we understand it, migraine seems to be a 5-HT_1 phenomenon, so you wouldn't expect a 5-HT_4 agonist like tegaserod to exacerbate migraine, because of its specificity.

COMFORT LEVELS WITH THE NEWER AGENTS

Dr. Soffer—What's your sense of how comfortable physicians are, particularly primary care physicians, prescribing the new IBS drugs, alosetron and tegaserod? We have not yet started with the new prescribing program for alosetron at the Cleveland Clinic, and I wonder how many general practitioners will be comfortable with that elaborate system, as opposed to just turning to specialists to prescribe alosetron.

The new position statement from the ACG is the most critical and evidence-based approach to IBS I've seen.
—Dr. Soffer

Dr. Olden—Well, I've taken on the alosetron prescribing at Mayo Clinic Scottsdale, and at just a week into the drug's return to the market, the line was getting long already. Most physicians are not doing it—I'm the only member of my gastroenterology division who wants to handle prescribing it. I think that's because the prescribing program is seen as burdensome. In fact, though, it's really not as burdensome as it sounds. Everything you need is in a three-ring binder: you just go through the forms with the patient, and everything stays in the binder. The drug's manufacturer has done a really good job of making the system nonburdensome, but it *is* a system nonetheless.

Beyond that is what I call the "Lotronex legacy," and it's been a real problem, because for all of alosetron's wonderful effects, its safety issues have created some real reluctance in some quarters that is hard to get past. With any new drug, the safety story is at least as important as the efficacy story. Physicians start wondering, "What will be the next surprise with alosetron?" It can even translate into "What will be the surprise with tegaserod?" even though that's a completely different molecule with a different effect. Tegaserod, so far, seems to be pretty clean. But the serotoninergic playing field has been contaminated a bit, so to speak.

IBS has a greater impact on patients' quality of life than many other chronic diseases that we treat without hesitation.
—Dr. Brunton

Dr. Isaacson—I agree that you're not going to get past that very easily with alosetron. One of the rules of thumb for a primary care physician is that you don't want to be the first or the last to prescribe a new effective agent. Many of us in primary care will wait a bit to see how the specialists use a medicine and define the risks a little better before we get involved. Besides, a patient would have to have pretty severe diarrhea to be a candidate for alosetron, and that's just the kind of patient I'd be more apt to refer.

Dr. Brunton—What's unfortunate is that if a lot of gastroenterologists remain reluctant to prescribe alosetron, because of either the hassle factor or the comfort factor, that has big implications for the doctor–patient relationship. If I refer my patient to a gastroenterologist, and he then refers them to another gastroenterologist because he's not prescribing alosetron, I risk losing contact with my patient and losing my leverage as the patient's advocate. That may induce me to get some comfort about using alosetron myself more quickly than I would have otherwise.

On a separate note, Dr. Olden, I was looking at the numbers you presented on the rates of ischemic colitis with alosetron use, and they seem very similar to the background prevalence of ischemic colitis.

Dr. Olden—Yes, but it was not so much the numbers as the epidemiology: many of those cases of ischemic colitis with alosetron were in young people with intact circulatory systems, not in elderly people with heart failure. That's what makes it ominous.

Dr. Soffer—What about tegaserod and the other 5-HT_4 agonists that may be coming? Do primary care physicians feel comfortable using tegaserod at this point?

Dr. Brunton—Right now, I don't see a lot of it being used by primary care doctors. After all, it's a new class of drugs, and there's the Lotronex legacy that we discussed. But as there's more education, particularly from our own primary care educators, I think you'll see more confidence and comfort in using it.

Also, the whole IBS playing field is still very confused. If alosetron had been around longer initially, there would have been a lot more education and awareness-raising about IBS, but that didn't happen because alosetron was withdrawn so soon.

Dr. Isaacson—I think the fact that IBS is not a life-threatening illness is a contributing factor as well. Physicians are generally less likely to prescribe a "risky" drug for a benign condition.

Dr. Olden—Yes, but the patients would vigorously rebut the notion that IBS is a benign illness, which they did when they organized to get alosetron back on the market. No one is going to die of IBS, but a large minority of IBS patients can't function because of it.

Dr. Brunton—Absolutely, and quality-of-life studies show that IBS has a greater impact on patients' lives than many other chronic diseases that we treat without hesitation. I think

TABLE 4

Answers to common primary care questions about IBS

What are the criteria for diagnosis of IBS?
While IBS is still considered a disorder characterized by the absence of biochemical and structural markers, it is important to make a positive diagnosis. Such a diagnosis is based on the presence of appropriate symptoms in the absence of alarm symptoms and signs. Various sets of symptom-based criteria have been developed, including the Manning criteria (1978) and the ROME II criteria (1999), which are the most commonly used (see TABLE 2 on page **S5**).

How much workup should I do in the absence of alarm symptoms?
The approach to each patient should be individualized. However, to avoid unnecessary and costly testing, the diagnosis should be made by identifying a symptom complex compatible with IBS and then using prudent, albeit not exhaustive, testing to make a positive diagnosis. Routine use of flexible sigmoidoscopy, colonoscopy, barium enema, and other imaging studies is not recommended. This is because, in the absence of alarm signs or symptoms, the pretest probability of abnormal organic disorders in patients with IBS symptoms is low. Patients with IBS do not appear to have an increased likelihood of most organic disease compared with the general population. Initial evaluation with low-cost tests such as a CBC, electrolytes, a thyroid-stimulating hormone test, and hemoccult is appropriate. A trial of symptom-oriented therapy is recommended. If the patient does not respond to this therapeutic trial, further evaluation, including invasive testing, may be indicated (FIGURES 1, 2).

When is endoscopy or sigmoidoscopy indicated?
Patients with alarm factors or "red flags," such as weight loss, anemia, gastrointestinal bleeding, and nocturnal symptoms, warrant endoscopic evaluation. Also, patients who do not respond to a therapeutic trial of symptom-oriented agents should undergo further evaluation, including flexible sigmoidoscopy or colonoscopy. In patients older than 50 or with a family history of colon cancer (especially a first-degree relative who had colon cancer before age 50), colonoscopy is indicated for the dual purpose of screening and evaluation of symptoms suggestive of IBS.

When should I look for celiac disease, and what is the best testing strategy?
A recent study reported that approximately 5% of patients with IBS symptoms had celiac disease, compared with a prevalence of less than 1% in a control population. The prevalence of celiac disease varies widely and depends on ethnic origin. Therefore, routine screening of all IBS patients for celiac disease with serology or endoscopy and small bowel mucosal biopsy is not indicated. However, for a patient with a family history of celiac disease or with a higher-risk ethnic background, such as Irish or Italian, screening may be considered, particularly if the patient has diarrhea.

Screening for celiac disease uses serologic tests for the assay of antibodies against four antigens (gliadin, reticulin, endomysium, and tissue transglutaminase). A single assay for antiendomysial antibody and, recently, tissue transglutaminase antibody is currently used for screening. The gold standard for diagnosing celiac disease remains small bowel mucosal biopsy, which should be done to confirm the diagnosis when serology is positive.

When should I refer an IBS patient to a gastroenterologist?
The purposes of referral may vary. In some cases, referral to a gastroenterologist serves to confirm the diagnosis of IBS, especially for patients who are apprehensive about their symptoms. Other times primary care physicians refer patients for more specialized tests (TABLE 1), particularly those who do not respond to therapy (FIGURE 2). Patients with IBS symptoms who do not respond to standard therapy and continue to have troubling symptoms should undergo further evaluation, usually by a gastroenterologist. Finally, patients with alarm factors or "red flags" need referral to exclude organic diseases such as gastrointestinal neoplasms, inflammatory bowel disease, infectious diarrhea, or malabsorption.

it's not that IBS doesn't have a significant impact but that we traditionally haven't felt we had good therapies for it, so we haven't asked about it. And patients don't necessarily bring it up; if they've had it for some time, they may just think that's how their gut works.

Dr. Isaacson—I agree. When I feel I have something to treat a condition with if I uncover it, I am more apt to look for it.

Dr. Olden—Yes, and that's positive, although it can have a downside, as when alosetron first came out. Because it was "the first drug for IBS," every patient who had a tummy pain had it dispensed, and that led to a lot of inappropriate prescribing.

Dr. Brunton—What strikes me about this whole quality-of-life issue in IBS is that it seems to be most dramatic in the diarrhea-pre-

dominant form. After all, patients with that symptom pattern are obsessed with always knowing where the nearest bathroom is. But it seems like the form that alternates between diarrhea and constipation is also very limiting and confusing. What is the role of tegaserod or alosetron in the alternating form of IBS?

Dr. Olden—That's an important question, but one that hasn't yet been adequately addressed in clinical trials.

Dr. Shen—While we're talking about uses outside of FDA-approved indications, what about the use of tegaserod in males? We don't have any data, right? And how long can we treat with tegaserod, since its approval was based on 12-week studies?

The ischemic colitis seen with alosetron was ominous because many cases were in young people with intact circulatory systems.
—Dr. Olden

Dr. Olden—No one is eager to venture too quickly outside of FDA-approved labeling, particularly for this condition, given the Lotronex legacy. Length of treatment is less problematic since no drug gets approved beyond the length of the trials submitted for its approval. Data on length of treatment will expand as the postmarketing data come in, and there appear to be no safety issues regarding longer treatment, so I feel comfortable prescribing beyond 12 weeks if needed.

Use in males is a bit of a different question. Based on the evidence available to me, I don't think there is any safety issue with using tegaserod in males, but I reserve the right to be proven wrong. Having said that, because of my desire to protect this drug, the one drug for IBS that I have unencumbered access to, I am encouraging physicians in general not to use it in males. At the same time, because I am a specialist in IBS and because I know this drug very well, I am prescribing it myself to selected male patients.

Now, after I made this intellectual decision, I of course checked with our legal department. They said I was well within the standard of practice as long as I documented in the chart that the patient had given informed consent after I explained that it's an off-label use, why I was doing it, and the risks and benefits involved.

Dr. Soffer—Yes, agreeing to it on an individual basis is the key. But for a while, I think, only a very select group of physicians will prescribe tegaserod for males.

Well, I think we have covered drug treatment issues pretty well. Dr. Olden, would you like to close with a word about behavioral therapy for IBS, since that is an interest of yours?

Dr. Olden—As you know, the ACG Functional GI Disorders Task Force went no further than to say that behavioral therapy appears to be superior to placebo at relieving individual IBS symptoms. That was less of an endorsement than some might have expected, but it was based on a review from a few years ago, and some of the more recent trials of behavioral therapy are more positive.

Briefly, I think behavioral therapy is a tidal wave that's going to wash over the island of IBS therapy, but it's going to take a while. In general, the behavioral therapy literature is expanding and maturing in an impressive way. The biggest challenge is marrying up the discipline of medicine with the discipline of behavioral therapy. That means getting the behavioral folks talking to us so that we're as familiar with them as with surgeons and radiologists. And it will mean gaining a more sophisticated understanding of how behavioral therapy can complement the evolving medical therapy we are offering to our IBS patients.