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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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