



# Irritable Bowel Syndrome: Pathophysiology and Goals of Therapy

Moderated by **Mark Pimentel, MD<sup>1</sup>**

Discussants: **Brooks Cash, MD<sup>2</sup>; Anthony Lembo, MD<sup>3</sup>; Phil Schoenfeld, MD<sup>4</sup>**

**DR. PIMENTEL:** I'm Mark Pimentel, Director of GI Motility at Cedars-Sinai Medical Center in Los Angeles. I am joined today by Brooks Cash from the Walter Reed National Military Medical Center in Bethesda, Maryland; Anthony Lembo, Director of the GI Motility Laboratory at Beth Israel Deaconess Medical Center, Division of Gastroenterology; and Associate Professor of Medicine at Harvard Medical School in Boston, Massachusetts; and Phil Schoenfeld, Associate Professor of Medicine and Director of the GI Epidemiology Training Program at the University of Michigan School of Medicine in Ann Arbor. Our topic for this roundtable is irritable bowel syndrome

(IBS), a condition for which we've recently observed many exciting developments, as recent as in the last week. To begin, I'd like to ask Dr. Lembo to discuss the prevalence of IBS in the general population and by sex.

**DR. LEMBO:** IBS is a very common disorder, with an estimated prevalence of 10% to 15% in the general population of the United States. At least some of the variation in IBS prevalence is due to the use of different criteria in its diagnosis, as well as differences in the populations examined and the specific questions used to elicit information from them when estimating its prevalence. Generally, women tend to complain of IBS symptoms twice as often as men do, and a greater number of relatively younger adults present with IBS symptoms compared to older adults.

**DR. PIMENTEL:** Some say that, in India, for example, the prevalence of IBS is not as high, while others say that more men than women have IBS in some developing countries. Do you think that

these differences between developed and developing nations can be attributed to a relative lack of research on IBS in developing countries?

**DR. SCHOENFELD:** Yes. Differences in the prevalence of IBS among countries most likely reflect differences in the way studies are designed. Additionally, health care-seeking behaviors may differ across cultures, which may influence the reporting of the data regarding the prevalence of these disorders in men and women. For example, epidemiologic data indicate that women are more likely than men to seek health care in the United States.

**DR. PIMENTEL:** Quality of life is a particular consideration with this disease. How does IBS compare to other disease states, such as diabetes and heart disease, in this respect?

**DR. CASH:** IBS has been shown to have a significant negative impact on the quality of life, with some data suggesting that the quality-of-life impairment of IBS patients

## ABSTRACT

The discussion focused primarily on: 1) The major symptoms and prevalence of irritable bowel syndrome (IBS); 2) the criteria for the diagnosis of IBS; 3) the major categories of IBS; 4) the pathophysiology of and mechanisms hypothesized to underlie IBS; 5) the impact of IBS on the quality of life; 6) the relationship between IBS and other gastrointestinal disorders; 7) indications for further testing of IBS patients; and 8) current and future treatments for IBS and their efficacy. *Med Roundtable Gen Med Ed.* 2014;1(3):248-256.

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is similar to that of patients on chronic renal dialysis or those with major depression. Patients with IBS are known to have additional non-gastrointestinal (GI)-associated somatic complaints such as fibromyalgia or interstitial cystitis symptoms that lower their health-related quality of life. In fact, a recent review of articles published over the last decade identified 31 comorbid conditions and 24 concomitant symptoms only in patients with IBS with constipation (IBS-C). The most common comorbid conditions identified in this review included functional dyspepsia, depression, small intestinal bacterial overgrowth, food intolerances, and urinary disorders.<sup>1</sup>

**DR. PIMENTEL:**

One thing that I notice—and talk to my patients about—is the lack of attention to IBS compared to Crohn's disease and other GI disorders. While I wouldn't wish Crohn's disease on anybody, its course is very predictable. Every day, Crohn's disease patients wake up in the morning, and have 6 bowel movements; they know what their day is going to be like and can plan accordingly. IBS patients do not have such certainty; they don't know whether they're going to have a bowel movement and, if so, if it's going to be diarrhea. They don't even know if they're going to be doubled over in pain during a meeting in the middle of the day. The unpredictability of IBS and its symptoms really affect the quality of life more than we give it credit

for, in comparison to diseases that may have a greater impression on the doctor because they are associated with inflammation. Dr. Lembo, do you think that we are expending enough effort to demonstrate the importance of IBS to the medical community?

**DR. LEMBO:** I think we need to do a better job because, as we all know from our patients, the impact of IBS on quality of life can be significant. Studies have shown that patients with IBS have quality-of-life scores similar to or worse than patients with congestive heart disease and dialysis-dependent kidney failure.<sup>2</sup>

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**Mark Pimentel**

I agree that the lack of predictability of bowel function and the severity of abdominal pain are big factors in lowering an IBS patient's quality of life. In this respect, IBS patients certainly differ from patients with other GI disorders such as celiac disease, for whom pain may not be a predominant feature. Patients with IBS also often find bloating to be quite difficult to deal with, not only because of the associated discomfort but also because of its effect on their appearance. Therefore, I think there are multiple factors reducing IBS

patients' quality of life, including the lack of predictability of bowel movements, abdominal pain, and bloating.

**DR. PIMENTEL:** That segues us into diagnosis. We've developed these criteria, and we've subcategorized IBS into diarrhea, constipation, and mixed forms of IBS. Dr. Cash, can you take us through these criteria and explain why, based upon them, we've developed these different categories of IBS?

**DR. CASH:** A number of different criteria have been devised to try and help diagnose, and then subsequently categorize IBS. One

reason for their development is that there is no biomarker for IBS diagnosis; it's almost entirely a clinically based, symptom-based diagnosis.

After the development of the first set of criteria, referred to as the Manning criteria,<sup>3</sup> the Rome

Committee on Functional and GI Disorders issued several iterations of its own set of criteria, the most current of which is the Rome III criteria.<sup>4</sup> One reason for the development of these criteria was to categorize patients with IBS symptoms into similar groups to encourage research so that, for example, researchers conducting a therapeutic study of an agent for IBS could identify patients with similar symptoms for enrollment in a study.

The Rome III criteria established 3 major categories and 1 somewhat

minor category of IBS: (1) IBS-C, (2) IBS with diarrhea (IBS-D), (3) mixed-bowel habit IBS, and (4) unsubtyped IBS (IBS-U). These criteria are based on the predominant stool form, and patients with IBS-D have soft, mushy, or loose, watery stool at least 25% of the time and don't have constipated, hard, or scybalous-type stool more than 25% of the time.

On the other end of the spectrum, patients with IBS-C have a constipated form of stool at least 25% of the time and do not have diarrhea more than 25% of the time. The mixed pattern is somewhere in between, and IBS-U doesn't necessarily fit any of those categories.

The Rome criteria were developed for application in clinical research, but many clinicians have applied them to their clinical practice. The diag-

nosis of IBS is based on, at least with the current Rome III criteria, the presence of at least 2 of the 3 major features associated with the abdominal pain or discomfort attributed to alternations in bowel habits.

The first is that patients have some relief with regards to their abdominal pain or discomfort with defecation, either completely or partially. The second is that the abdominal pain or discomfort should be associated with a change in the form of the stool. The third feature is that the abdominal pain or discomfort should be associated with a change in the frequency of the stool. Not all patients presenting with those

symptoms will be diagnosed with IBS, including a small number who fulfill the criteria for diagnosis of organic disease. Many clinicians still consider IBS a diagnosis of exclusion for explaining GI symptoms, despite good evidence of the validity of the Rome criteria in the absence of alarming features.

**DR. PIMENTEL:** How good are these criteria, Dr. Lembo? Can they be used clinically and/or are they sufficiently reliable to negate the need for testing?

**DR. LEMBO:** It's hard to answer how good these criteria are because it's a consensus definition. As Dr. Cash

such as bloating and incomplete evacuation. However, the Rome criteria are fairly reliable for the diagnosis of IBS in the average patient presenting with symptoms and no alarming features such as rectal bleeding, low weight, family history of colon cancer, or inflammatory bowel disease.

**DR. PIMENTEL:** Considering the prevalence of and diagnostic criteria for IBS together, there is a good chance that patients presenting with diarrhea have IBS, owing to the high prevalence of the disease alone. Dr. Schoenfeld, as the probability of patients having IBS pretest is so high, how do we decide on whom to perform colonoscopy? On whom do we perform triage or something more intensive?

**DR. SCHOENFELD:** Based on my experience, I try to scope patients presenting with

danger signs. I think our primary care colleagues should keep that in mind. If a patient has gross hematochezia, unexplained weight loss, and/or a family history of Crohn's disease or colon cancer, I would proceed with a colonoscopy and recommend that a complete blood count and erythrocyte sedimentation rate be checked when these patients present in the primary care setting. If a patient is anemic or has a very high erythrocyte sedimentation rate, which may occur in Crohn's disease or ulcerative colitis, I also recommend a colonoscopy.

In the absence of danger signs, the likelihood of finding that an-

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**Brooks Cash**

mentioned, the reason for devising them was to have some uniformity for both clinical as well as research purposes. To that extent, I think they serve an important purpose, but as they're not based on a pathophysiological mechanism, they overlap with the criteria for other diseases.

**DR. PIMENTEL:** Do we need testing? One of the other things that was mentioned, bloating, is a missing piece of the Rome criteria, which is also a problem that all 4 of us have discussed.

**DR. LEMBO:** The Rome criteria do not include some of the common symptoms seen in IBS patients,

other disorder is the cause of these symptoms is very low: less than 1%.<sup>5</sup> If a patient has had a prolonged bout of severe diarrhea, I may perform a colonoscopy in the absence of danger signs to obtain biopsies to rule out microscopic colitis; however, this is unnecessary for the vast majority of patients.

I routinely screen patients presenting with diarrhea and bloating for celiac disease, which, depending on the patient's ethnicity, may be responsible for 1% or more of the patients presenting with these symptoms.

**DR. PIMENTEL:**

Dr. Cash, I think that less than 1% of patients in your recent study of IBS had celiac disease.<sup>5</sup> Not to refute Dr. Schoenfeld, but I suppose the proportion depends upon the study and how intensively you look for celiac disease or which tests you use. Any thoughts on that?

**DR. SCHOENFELD:** How much lower than 1% was it?

**DR. CASH:** It was 0.6%, so the prevalence was about 0.4% in our study. This is a controversial area because we're talking about a very prevalent condition in IBS and the need to use expensive tests to exclude rare conditions, particularly endoscopies and biopsies. Even a celiac panel can become expensive. There are differing data with regard to celiac disease, and as Dr. Schoenfeld mentioned, the

likelihood of finding celiac disease depends on the pretest probability and the threshold for screening used, which depends on the prevalence of that disease in your patient population.

If I were evaluating an African-American patient, or perhaps even an Asian patient, with IBS-like symptoms, IBS-D especially, I'm much less likely to be worried about celiac disease than if I were evaluating a Caucasian of European descent, who has a higher pretest probability of having celiac disease.

patients with nonconstipated IBS. This finding leads to the consideration that what we're seeing in some patients are clinical manifestations of gluten sensitivity that could be addressed by dietary modifications. Regarding colonoscopy, I completely agree with Dr. Schoenfeld. I typically perform invasive testing such as colonoscopy in IBS-D patients, specifically to rule out macroscopic or microscopic colitis.

There is very little evidence, and actually evidence contradicting, that patients with IBS-C without danger signs have increased risk of organic disease. In contrast, in our study we found an increased prevalence of microscopic colitis in patients with IBS-D, especially middle-aged women with pure IBS-D.<sup>6</sup>

**DR. PIMENTEL:**

Let's move on to pathophysiology, on which

increasing data are being collected. We need to discuss the brain-gut axis, a classic description of an early pathophysiologic mechanism that could be responsible for IBS; postinfectious IBS; the bacteriology of the gut; the role of serotonin; and gut inflammation.

Regarding the brain-gut axis, we often think of IBS as some derangement of sensations to the gut manifesting as abdominal pain, possibly driven by peripheral or central mechanisms or perceptions. Dr. Lembo, as you've done a lot of work in this area, can you explain this concept?

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**Anthony Lembo**

As was mentioned, we recently published the results of a study evaluating this issue in patients from the University of Michigan and several military treatment facilities who presented with nonconstipated IBS as compared to healthy controls undergoing routine colon cancer screening colonoscopies. We found a very similar prevalence of biopsy-proven celiac disease in those 2 populations, namely 0.4%.<sup>5</sup>

We also found a numerically superior, but not statistically significant, increase in the levels of some celiac disease antibodies in

**DR. LEMBO:** IBS is the result of a complex interaction between psychosocial and physiologic factors via the brain-gut axis. Early life factors such as family attitudes toward illness, major loss, abuse history, and genetic predisposition may influence psychosocial development (eg, psychological state, coping skills, ability to seek social support, and susceptibility to life stress) and/or gut dysfunction (eg, gut dysmotility or hypersensitivity). Although these factors are closely interrelated, the importance of any one factor in the generation of IBS symptoms varies greatly among individuals.

Therefore, the symptoms and behaviors of IBS patients may differ significantly. For example, a patient with altered bowel function without psychological disturbance and with good coping skills

and social support may not seek medical care, whereas a patient with similar bowel dysfunction but with psychosocial disturbance, poor coping skills, and a high level of stress may frequently seek medical care and generally have a poorer outcome, which, in turn, will affect the severity of the disorder.

**DR. LEMBO:** I think of this concept as a complex interaction between psychosocial and physiological factors via the brain-gut axis. Psychological factors (eg, stress, anxiety, and social support) can alter gut functioning (eg, motility and sensation), which can lead to symptoms of IBS. This process can occur in reverse too, ie, chronic

bowel symptoms can have a significant psychological impact. The importance of any one factor in the generation of IBS symptoms can vary significantly among patients, and the symptoms and behaviors of patients with IBS will thus vary significantly.

**DR. PIMENTEL:** Serotonin is another aspect. Serotonin is the master molecule of neurotransmission of the gut—95% of serotonin is present in the gut and 5%, in the brain. We considered it a “magic molecule” around the time alosetron, and then tegaserod, came onto the market. Although both

for the gut.” It controls motility as well as visceral sensitivity in the gut. By visceral sensitivity, I mean the patient’s experience of cramping, bloating, or distention in the gut.

Serotonin could certainly play an important role in some patients with IBS. Tegaserod, which was previously available for IBS-C, stimulated a serotonin receptor, whereas alosetron, which was previously available for IBS-D, blocked a serotonin receptor. However, neither drug was universally effective in treating IBS-C or IBS-D symptoms. Again, I think that reflects the

complexity of factors that impact GI motility. As we’ll discuss further, there is no one-size-fits-all approach for IBS treatment.

**DR. PIMENTEL:** Dr. Cash and I have collaborated with some military

research facilities that are studying postinfectious IBS, as this aspect of IBS has had very important effects on our troops.<sup>7</sup> One important thing that we’ve learned is that patients with postinfectious IBS do not comprise as small a proportion of IBS patients as we had once thought.

**DR. CASH:** Absolutely. I think it’s becoming increasingly more important for us to ask our patients about postinfectious IBS. This concept is exactly what it sounds like; after contracting a GI and experiencing the typical symptoms of gastroenteritis, patients with postinfectious IBS subsequently experience persistent IBS-like symptoms that can last for variable periods of time.

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**Phil Schoenfeld**

went out of the US market, we expected a resurgence in their use.

Prucalopride, a new serotonin agent with a good reputation that was developed in Europe, appears promising. It has been available in Europe for 3 years, just got approved in Canada, and Shire just licensed the rights for it for the United States, so it will be introduced in our regions soon. Are we going to see a resurgence of serotonin-based products? Can you explain the serotonin concept regarding IBS?

**DR. SCHOENFELD:** Serotonin is the most common neurotransmitter in the enteric nervous system, which is referred to as “a second brain

While we originally thought that postinfectious IBS developed only after bacterial gastroenteritis, we now know that it can develop after viral gastroenteritis. Increasing data from our military research are suggesting that personnel who contract infectious gastroenteritis while they are deployed are more likely to develop postinfectious IBS than those who do not contract infectious gastroenteritis, and some molecular data suggest a pathophysiology for postinfectious IBS.<sup>7</sup>

We're finding an increase in the numbers of inflammatory cells around enteric neurons and numbers of mast cells, especially activated or de-granulating mast cells around enteric neurons. Unfortunately, the clinical importance of these findings in deciding whether to treat postinfectious IBS patients any differently from other IBS patients remains unclear.

**DR. PIMENTEL:** Of all the diseases for which study of gut microflora has inspired tremendous international interest, including diabetes and obesity, IBS was one of the first for which we began to consider that derangements in gut bacteria could be contributing to, for example, bloating, which is one of the symptoms that is difficult to treat.

Fermentation in the gut is generally what causes, or is at least a major contributor to, gas, bloating, and distention.<sup>8</sup> Some of our research has shown that gut flora are deranged in IBS, and that perhaps, the small bowel plays a large role and contains too many bacteria, otherwise known as bacterial overgrowth.<sup>9,10</sup> Our findings, which have since been confirmed by other researchers, have affected the treatments that are provided, including antibiotics.<sup>11</sup> A particularly interesting indication

of the emerging data is that food poisoning, or postinfectious IBS, triggers a cascade that leads to bacterial buildup in the small bowel or bacterial overgrowth, and maybe those 2 occurrences are connected in some way. The details of the relationship are currently being researched upon.

It's a very interesting time in IBS research, and I think that we'll uncover many novel pathophysiological mechanisms in the next few years. Regarding treatment, I'm excited by the approval of a new drug just last week. Traditionally, we categorize IBS into IBS-D or IBS-C. For IBS-D, we have 3 major therapeutic options: the antidepressants alosetron and rifaximin, of which alosetron is more difficult to obtain, and the tricyclic antidepressants (TCAs). Dr. Lembo, can you tell us whether the TCAs are approved by the Food and Drug Administration (FDA) for the treatment of IBS, explain the mechanism by which they affect IBS-D, and describe patients' experiences with them?

**DR. LEMBO:** The exact mechanism is not known, but it is thought to involve the blocking of the presynaptic reuptake of the neurotransmitters serotonin, norepinephrine, and, to a lesser extent, dopamine, which play a role in the endogenous pain inhibitory system. TCAs have been around for more than 30 to 40 years. Many TCAs have effects on the muscarinic, histaminic, and adrenergic receptors that can, especially in the elderly, lead to side effects such as sedation, blurred vision, urinary retention, and memory dysfunction. Because many TCAs cause constipation, I generally limit my use of them to IBS-D. It is important to remember that the effects of antidepressants in IBS appear to be independent of their effects on depression or anxiety.

In my experience, TCAs work best for abdominal pain at doses between 10 and 50 mg; occasionally, we'll administer 75 mg or 100 mg. The largest study completed to date was with desipramine with doses higher than I generally recommend to my patients.<sup>12</sup> Patients who completed that study and were taking medication regularly experienced significant improvement in symptoms, although it should be noted that the intent-to-treat analysis indicated no significant improvement, and many patients experienced side effects.

Although there are fewer data for the selective serotonin reuptake inhibitor and the serotonin-norepinephrine reuptake inhibitors in IBS, some of the data available show improvement in overall symptoms and overall IBS severity, but less of an improvement for abdominal pain.

**DR. SCHOENFELD:** When I'm consulting with my primary care colleagues about patients with IBS-D symptoms, I find it appropriate to use an antidiarrheal agent such as loperamide, which has been shown to improve stool frequency and stool consistency in these patients in randomized controlled trials (RCTs). Patients may start at only one 2-mg tablet per day and then titrate up or down depending on the frequency and severity of diarrhea symptoms. With respect to antispasmodics, I specifically note that anticholinergic agents such as dicyclomine (eg, Bentyl®) and hyoscyamine (eg, Levsin®) have not demonstrated superiority to placebo in well-designed RCTs, although anecdotal data suggest that using Levsin® at doses of 0.125 mg to 0.375 mg as an on-demand agent for cramping may be helpful.<sup>13</sup>

I certainly encourage the use of TCAs for patients with IBS-D symptoms for the reasons Dr. Lembo mentioned. However, as higher doses of TCAs may lead to more side effects, I frequently recommend nortriptyline at a dose of 10 to 25 mg as an initial dose, which, based on my clinical experience, has a more tolerable side-effect profile.

**DR. CASH:** I think Dr. Schoenfeld's comments are right on the mark in terms of reasonable practice and exactly reflect my practice with regard to the antidiarrheals.

It's interesting that many patients who are referred by my primary care colleagues, or even my gastroenterology colleagues, come to me on TCAs, antispasmodics, and other agents that don't have a very strong evidence base, even though the TCAs got a reasonably good rating from the American College of Gastroenterology in their last set of guidelines.

The antidepressant data for TCAs, selective serotonin reuptake inhibitors, and nonselective serotonin reuptake inhibitors are derived from very small studies that are quite heterogeneous in terms of the patients included as well as the outcomes evaluated. So, many patients are being treated with popular therapies that have the poorest evidence base.

**DR. PIMENTEL:** I think that all the data collected from all the antidepressant studies together would not equate to the data collected from 1 clinical trial for lubiprostone, tegaserod, or alosetron. It's remarkable that we can make such broad conclusions regarding the antidepressants with such few data. Although I think that Dr. Lembo is right that these pa-

tients may respond due to the anticholinergic effects, these effects can go the other direction, leading to constipation and other side effects.

Speaking of constipation, alosetron is the prototypical constipation-causing drug, but it has a very powerful and definitive effect on IBS-D. Dr. Schoenfeld, could you comment on that?

**DR. SCHOENFELD:** Primary care physicians probably should avoid prescribing alosetron. If a patient has severe IBS-D and conventional therapies have failed, I would refer the patient to a gastroenterologist to discuss the risks and benefits of alosetron.

Although alosetron has been shown to be beneficial in well-designed RCTs, a very small number of patients, in the order of 1 of the more than 500 treated with alosetron per year, will develop ischemic colitis, and that's why great caution should be exercised when using it.<sup>13</sup>

**DR. PIMENTEL:** The next drug is rifaximin, whose activity is based on a gut microbial theory that IBS is caused by a disturbance of the small bowel or enteric microbes.

In large-scale RCTs, rifaximin has been shown to not only be effective but also have features unique among the agents used to treat IBS. One feature is that it provides a lasting benefit, as evidenced by the fact that many patients in the RCTs who had taken it for only 10 to 14 days were still experiencing benefits 3 months later. Another feature is its ability to improve global symptoms as well as the specific symptom of bloating, which, as I've mentioned earlier, seems to be one of the symptoms most refractory

to many IBS therapies. Rifaximin has been approved by the FDA for traveler's diarrhea and hepatic encephalopathy, but not yet for IBS. Nevertheless, it's being used quite commonly in the community for IBS, and many primary care physicians have been wanting to try it.

Moving on to IBS-C, I'm seeing a resurgence in the use of lubiprostone, which has been on the market for some time, which may be in anticipation of the release of linaclotide, another secretagogue. I think maybe there is a better understanding of their mechanism. Can you comment on that, Dr. Cash?

**DR. CASH:** Some have suggested that lubiprostone fits into a new category of laxatives termed secretagogues. Lubiprostone is a chloride channel activator that opens up chloride-type 2 channels in the gut, which are located throughout the GI tract but most densely in the small bowel. When you open up these chloride channels, you allow chloride to enter the small bowel. Sodium follows to maintain electrical neutrality, and fluid follows to maintain osmotic neutrality. It is believed that this agent works by distending the bowel, increasing the fluid content of the stool, and possibly increasing its motility as a result of these mechanisms.

A unique mechanism hypothesized to underlie lubiprostone's action is inherent to prostones. Namely, lubiprostone is a prostaglandin derivative, and several studies that have shown that prostones, lubiprostone in particular, can help restore tight junctions between enterocytes when they're damaged in animal models. Whether this mechanism plays a role in the improvement of IBS symptoms with lubiprostone is unclear, but

Phase 3 clinical trials have shown that it is superior to placebo for overall IBS-C improvement.

**DR. PIMENTEL:** Linaclotide, a second secretagogue with which Dr. Lembo's performed some trial work,<sup>14</sup> just got approved last week. Turning back to lubiprostone, earlier this year, Dr. Lembo and I published our finding that, because lubiprostone is a diarrheogenic drug, diarrhea is a side effect, but not a major one, in contrast to its benefits. As lubiprostone is not a potent diarrheogenic drug, and linaclotide is a little more potent, linaclotide may be more efficacious as well.

**DR. LEMBO:** Linaclotide, as you stated, was recently approved by the FDA for both IBS-C and chronic constipation. Its doses for IBS-C and chronic constipation approved for adult men and women are 290 µg/day and 145 µg/day, respectively. It's important to note that there is a box warning. Linaclotide is contraindicated in young children aged between 0 and 6 years and not recommended for children aged between 6 and 17 years.

Linaclotide is a 14 amino-acid peptide that is minimally absorbed from the GI tract. It activates the guanylate cyclase-C receptors located on the epithelial cells in the lumen of the small bowel and colon, causing an increase in cyclic guanosine monophosphate, which has been shown in animal models to reduce visceral pain and firing of visceral afferent nerve fibers. This increase in cyclic guanosine monophosphate in turn activates the cystic fibrosis transmembrane regulator, which increases the release of chloride and bicarbonate into the lumen of the GI tract.

As Dr. Pimentel stated, in clinical trials, linaclotide was shown to

be effective in improving IBS-C symptoms, including abdominal pain and bowel function. Approximately 5% of patients withdrew from Phase 3 clinical trials due to diarrhea, which was the most common side effect associated with linaclotide.

**DR. PIMENTEL:** Dr. Schoenfeld, Michigan appears to be the fermentable oligo-, di- and mono-saccharides, and polyols (FODMAP) capital of the United States. I think primary care physicians are seeing many IBS patients who are making varied changes to their diet. Can you comment on what they're doing when they come to your office and what you might advise them?

**DR. SCHOENFELD:** First, many patients with IBS can identify foods that seem to trigger their symptoms. Again, according to

### COMPOUNDS DISCUSSED:

alosetron, *Bifidobacterium infantis*, desipramine, dicyclomine, hyoscyamine, linaclotide, loperamide, lubiprostone, nonselective serotonin reuptake inhibitors, nortriptyline, prostones, prucalopride, rifaximin, secretagogues, selective serotonin reuptake inhibitors, tegaserod, tricyclic antidepressants

anecdotal data and common sense, you should ask your patients with IBS if they can identify these foods and encourage them to avoid them.

Because symptoms of lactose intolerance can mimic IBS, I routinely advise patients to avoid lactose-containing products for 2 to 3 weeks to assess its impact on their symptoms. For patients with severe IBS, we advise the FODMAP diet,

## Clinical Implications

- ▶ Irritable bowel syndrome (IBS) is a very common disorder, with an estimated prevalence of 10% to 15% in the general population of the United States.
- ▶ Due to its unpredictability and the variation in its symptomatology, IBS has a significant impact on quality of life.
- ▶ There is no biomarker for IBS, so diagnosis is almost entirely symptom based, and the criteria for diagnosis tend to vary.
- ▶ IBS is generally divided into the 3 major categories and 1 minor category of (1) IBS with constipation (IBS-C), (2) IBS with diarrhea (IBS-D), (3) mixed-bowel habit IBS, and (4) unsubtyped IBS (IBS-U).
- ▶ The need for testing and subsequent treatment of IBS patients depends on the presenting symptoms and the presence of any danger signs.
- ▶ Several new promising pharmacological agents have recently been approved or are undergoing review for the treatment of IBS.

which limits gluten intake and eliminates most cruciferous vegetables such as Brussel sprouts, cabbage, asparagus, and other green vegetables, in addition to foods that have a high fructose-to-glucose ratio, including certain fruits.

Since the FODMAP diet is very restrictive, we usually advise it only for patients with severe symptoms, and we only initiate it after the patient has had a 1-hour consultation with a nutritionist. Second, I encourage moderate cardiovascular exercise, as a previous RCT demonstrated improvement in overall IBS symptoms in patients who get this

exercise 3 times a week compared to patients who do not exercise.<sup>15</sup>

Many patients usually try probiotics, which are available as supplements without a prescription. I would like to simply state that the only probiotic that has demonstrated efficacy in appropriately designed RCTs is Align<sup>®</sup>, which is a specific strain of *Bifidobacterium infantis*, but caution that the improvement demonstrated with Align<sup>®</sup> was relatively moderate. Again, use the American College of Gastroenterology Evidence-Based Position Statement on Management of IBS as a reference.<sup>13</sup>

**DR. PIMENTEL:** The widespread use of probiotics in the community is interesting. I think primary care physicians probably see probiotic use by their patients, and many are passionate about it, although the data regarding efficacy are modest. We just published an article about probiotics in the Gut Microbe supplement of the *American Journal of Gastroenterology*.<sup>16</sup> In this supplement, we review the breadth of information on probiotics. The interest in probiotics has run a little ahead of the science, but the science is catching up. I believe that probiotics will have a role in the future, but it will be more complex than initially thought.

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