Chronic Constipation and Constipation Predominant Irritable Bowel Syndrome: Fostering a Patient-Centric Model of Care

Dr. Schiller: Hello. I'm Larry Schiller, Professor of Medicine at Texas A&M College of Medicine and Head of the GI Training Program at Baylor University Medical Center in Dallas. I'm pleased to welcome you today to a symposium on *Chronic Constipation and Constipation-Predominant Irritable Bowel Syndrome: Fostering a Patient-Centric Model of Care.* Joining me today are 2 experts in the areas of irritable bowel syndrome (IBS) and chronic constipation. First, Brian Lacy is Section Chief of Gastroenterology and Hepatology and Professor of Medicine at Geisel School of Medicine at Dartmouth Hitchcock Medical Center in New Hampshire. Brian, welcome.

Dr. Lacy: Welcome, everybody, and thank you for attending this conference.

Dr. Schiller: And also with us today is Dr. Brooks Cash who’s Professor of Medicine in the Division of Gastroenterology at the University of South Alabama in Mobile, Alabama. Brooks, welcome.

Dr. Cash: Thank you very much. It’s a pleasure to be with you all and I want to thank everybody for listening in today.

Dr. Schiller: We’re going to start off our symposium by talking about the
impact of IBS and chronic constipation on patients with these problems. The burdens of IBS and chronic constipation are fairly substantial. These are common diseases. The prevalence has been estimated at 10% to 15%, roughly 1 out of every 8 adults in the United States. It’s one and a half times more prevalent in women than men; it’s more commonly diagnosed in younger patients and more common in lower socioeconomic groups. It produces annual direct medical costs of up to $10 billion and indirect costs due to loss of work time and activities of an additional $20 billion. The greater health care costs involve increased outpatient visits, hospitalizations, prescriptions, lab tests, and radiologic procedures. So this truly is a problem that impacts on our society in general. The increased health care costs and effect on quality of life is substantial. The quality of life overall is quite dramatic in patients who have IBS with an overall quality of life reduction as well as issues related to eating, a sensation of dysphoria, and interference with daily activities. As IBS symptoms become more severe, the increase in health care costs becomes substantial.

Chronic constipation is also a major issue for many patients. The overall incidence of constipation amounts to up to 17% over 12 years. So 1 out of 6 people have problems with constipation at some point in that time period. Many of these patients use laxatives. Over-the-counter laxative use is almost a billion dollars annually. Prescriptions are also written frequently for these patients, and it’s said that there are more
prescriptions written for laxatives than birth control or antihypertensives. There are millions of physician visits, many hospitalizations, and it costs roughly $3000 per patient to evaluate them with diagnostic tests. Many patients with chronic constipation suffer with impairment of their daily activities at work, reduction in productivity, and missing days from school or work. Enjoyment of life, recreational activities, mood, normal work and mobility, are also compromised by what, to many of us on the health care provider side, are thought of to be a relatively minor problem. It’s just constipation is a common thought amongst providers. But it is very serious for those patients who suffer with it.

An important feature to keep in mind is the definition for IBS and chronic constipation. IBS is a syndrome. It’s a collection of signs and symptoms. And these signs generally revolve around abdominal pain, which can be anywhere in the abdomen and are characteristically relieved by defecation. The pain in IBS is particular in that it is associated with a change in stool frequency or form so that we see IBS patients who have excess frequency, more than 2 bowel movements per day, and those with infrequency, less than 3 bowel movements per week. And these form the basis for our phenotyping of IBS between those who have IBS with diarrhea and those who have IBS with constipation. Altered stool form is also something that accompanies the pain in IBS. Stools can range from lumpy to loose and anywhere in between. And this
too is a feature that is particular to those patients with IBS. There are many causes of abdominal pain, but there are only a few causes of pain that has this sort of relation to bowel frequency or form. We tend to subtype IBS by the predominant stool pattern. So we recognize IBS with constipation, IBS with diarrhea, and IBS with mixed or alternating stool characteristics. The definitions depend on the frequency with which one has altered stool form. So those people with IBS with constipation have hard or lumpy stools more than 25% of the time; whereas those with IBS with diarrhea have loose or watery stools more than 25% of the time. These divisions are somewhat arbitrary but when they’re applied to groups of patients one sees the fact that these patients vary from group to group over time. Just because you start off with IBS with diarrhea does not mean that you’ll always have that particular phenotype.

One of the big advances in the field of functional bowel disease is the development of the Rome criteria. These are consensus criteria by experts in the field originally designed for research purposes, but I think they have a good role to play in the clinic too because—if your patient would be defined by these criteria—they’ll be like other patients with IBS who are recognized in the literature with these same symptoms. The more your patient is atypical for the criteria the less likely they are to behave like other patients with IBS in the literature. The most recent iteration of the Rome III criteria for IBS shows that patients have to have recurrent abdominal pain or discomfort that’s been chronic. It has to be
present at least 3 days per month for the last 3 months and associated with improvement with defecation; the onset of the pain is associated with a change in the frequency of stool, or the onset is associated with a change in the form of the stool. So 2 of those 3 characteristics, along with the abdominal pain, make for a diagnosis of IBS. It’s important to recognize that this is a chronic illness. Patients may have this sort of pattern for only a week or 2 but should not be diagnosed as having IBS until sufficient time has gone by to establish this bowel pattern. One of the important things to keep in mind is that if someone meets the criteria it’s very unlikely that they have some other diagnosis. There are very few conditions that have this particular combination of abdominal pain and altered stool habit, so it’s not necessary to do extensive diagnostic testing initially in patients who meet the criteria unless they have some alarm feature present such as bleeding or weight loss. A somewhat simpler definition was used by the American College of Gastroenterology (ACG) Task Force when this task force did a literature review on IBS. The diagnosis was made somewhat simpler in order to encompass literature that predated the Rome criteria. And so the ACG definition was abdominal discomfort associated with altered bowel habits, without all of the particular duration and frequency cues.

Now let’s turn to the definition of chronic idiopathic constipation. This is another area in which we deal with a great deal and have a feeling that we understand, but clearly the application of criteria can help us define
the population more closely. One of the initial things to consider is whether your patient has chronic or occasional constipation. Chronic constipation is defined as constipation symptoms lasting more than 6 to 12 weeks. Typically there’s no response to simple dietary or therapeutic measures and often the doctor has to help with the management of this problem. Occasional constipation, on the other hand, lasts less than 6 weeks and can often be dealt with using over-the-counter remedies that patients can start with, and pharmacologic measures are only needed if the simpler solutions do not provide relief. One of the things we have to remember about constipation is that it’s a symptom and not necessarily a disease by itself. So constipation can be a symptom of other problems, such as mechanical bowel obstruction, metabolic diseases such as diabetes, painful anorectal conditions such as a hemorrhoid or fissure, collagen vascular diseases, neurologic disease including (importantly) Parkinson’s disease, pregnancy, and also key, the use of certain medications. If one looks through the *Physician’s Desk Reference*, you find that anywhere from a third to a half of medicines list constipation as one of the top 5 gastrointestinal side effects. That having been said, sometimes constipation exists by itself. And idiopathic constipation is fairly common in our population. We divide this in terms of pathophysiology as in those patients who have slow transit constipation in which the movement of material through the colon is more sluggish than usual resulting in more complete absorption of water and salt and more complete reduction of the solids in stool by fermentation so that
less stool gets to the rectum each day. These patients often have infrequency as their major complaint. On the other hand, there are those individuals who have normal transit through the colon but have difficulties with the evacuation process. Defecation is disturbed and they have what’s described as functional outlet obstruction. This often is due to misbehavior of the pelvic floor muscles, which may contract and in essence shut the door rather than relax and open the door. These patients typically describe problems with having to strain excessively to produce a bowel movement. One of the things that is always surprising to physicians and other clinicians is that infrequency is not the most frequent symptom in patients who have chronic constipation. Ordinarily if a patient tells a doctor that they have a problem with constipation the first question back will be, “How often are you having bowel movements?” Infrequency—having fewer than 3 bowel movements per week—is less common in patients who identify themselves as having constipation and straining, having hard or lumpy stools, the sensation of incomplete emptying, inability to pass the stool, or abdominal fullness or bloating. So these other symptoms are the symptoms that we need to ask our patients about when they complain about constipation.

The Rome Committee has come up with criteria for chronic constipation as well as IBS and, again, this has to be a chronic problem and there has to be a combination of symptoms and signs. So the way that it’s structured you have to have 2 or more of the following symptoms at least
25% of the time. These include manual maneuvers (the use of your fingers to facilitate the evacuation of stool), having fewer than 3 bowel movements per week, having lumpy or hard stools, having the sensation of anorectal obstruction or blockage, having the sensation of incomplete evacuation, and having excessive straining to produce a bowel movement. In addition, loose stools are not present without laxative use, there are insufficient criteria for IBS that comes down to there being little abdominal pain, and the symptoms have been chronic. They’ve been present at least for the last 3 months with an onset at least 6 months ago. Again, these are research criteria. You can use these criteria in the clinic, although they perhaps will not meet all the specific frequency information.

How do we distinguish between those patients who have IBS with constipation and those with chronic constipation? The main feature is whether abdominal pain or discomfort is present. Remember, IBS always involves abdominal pain; whereas in chronic constipation it is not a common finding. Bloating or abdominal distension also is a bit more frequent in the IBS population than in the chronic constipation population, although it is fairly common in those as well. If one has a sense of anorectal obstruction or the need for manual maneuvers it points more to chronic constipation than to IBS. But the other features, having infrequency of defecation, having hard or lumpy stools, having to strain to evacuate, and having the feeling of incomplete evacuation are as
common in IBS with constipation as in chronic constipation.

What causes chronic idiopathic constipation? Well the short answer is that we don’t know all the details. We do divide them into 3 pathophysiologic groups. As already mentioned, there are patients who have slow transit constipation. In the past this was referred to as colonic inertia. There are also people who have defecatory disorders: the functional outlet obstruction patients who may have dyssynergia, which is the abnormal contraction of the pelvic floor muscles when they need to relax to facilitate defecation. There are patients in this group who have megarectum and inefficient evacuation of the rectum because of that. There are people with a rectocele who are able to stash extra stool in the rectum and have a difficult time emptying the rectocele. And then there are also those patients who have perineal descent, weakness of the pelvic floor muscles that allows them to cave as a person exerts more pressure to try to induce evacuation. The final group has a normal transit constipation but don’t have an obvious defecation problem and yet seems to have movement through the colon in a normal fashion. This is the group that’s most perplexing to those of us who try to explain why people have constipation, but they clearly exist and in some surveys had the more common type of constipation. Now can we distinguish between constipation subtypes? Well slow transit comes down to a couple of items in the history: the lack of an urge to move the bowels that suggests that the stool hasn’t built up in the rectum enough to trigger the sensation of
a need to evacuate and decreased stool frequency. The things that suggest defecation problems include hard stools, the presence of fecal impaction, the need for digital maneuvers that has an excellent predictive capacity for outlet problems, feelings of anal blockage, severe straining to have a bowel movement, a high anal sphincter tone at rest, either minimal or excessive perineal descent suggesting that the pelvic floor muscles are not working properly, tenderness to the puborectalis muscle on palpation, and a defect in the anterior wall of the rectum that suggests a rectocele.

Let’s turn now to a case history. She’s a 22-year-old woman who came in because of constipation. Her story is that she had bowel movements daily until 6 years ago. She developed some irregularity of defecation at that time. Of interest, she had daily bowel movements at the time of her menstrual cycle, and she had a reduced frequency of defecation after ovulation. When she first became ill she was still seeing her pediatrician, and his diagnosis was IBS and she was treated with fiber. She had modest improvement with fiber, but she became gassy and took a fiber supplement irregularly because of this. About 3 years prior to her visit she developed increasing problems with irregularity through the month and she would have fewer than 3 bowel movements per week. She had difficulty with evacuation of pebble-like stools. She needed to splint the posterior wall of her vagina with her finger to ease the evacuation of stool and she had little or no pain or discomfort. She went to the store and
started to take a bisacodyl laxative twice weekly. On physical examination she had modest abdominal distension, excellent anal sphincter tone, and no stool in the rectal vault. When one felt posteriorly where the puborectalis muscle crosses the back of the anorectal area, the muscle was tender and somewhat bulky. When she pretended to evacuate stool and would bear down, the muscle actually contracted. So let’s take a moment and think about what she might have. What’s her diagnosis? Why do we make this diagnosis? Brian, let me start with you. What diagnosis would you make in this woman?

Dr. Lacy: Great. Larry, I’d go back and the first thing I would think about is your nice discussion about whether or not she has IBS with constipation or chronic constipation. And I think a key point in her history is really the absence of abdominal pain. And so right away, although the pediatrician had diagnosed her with IBS, I don’t think I’d agree with that. And then I would start thinking about the pathophysiology of chronic idiopathic constipation, trying to decide whether she fits the category of slow transit constipation, whether or not she has a defecatory disorder, or whether or not she has normal transit constipation. And when I think about somebody who has slow transit constipation these are typically women, not men, but the story I hear typically is somebody who has a bowel movement every 2, 3, or 4 weeks and that’s not what we’re hearing from this patient, so I don’t think she has slow transit constipation. But what you so nicely highlighted in her
history was the need for manual maneuvers, and on examination she appears to have this bulky kind of tender puborectalis muscle and during simulated defecation she could not evacuate the examining finger very well. So I'm much more concerned that she has a pelvic floor disorder.

**Dr. Schiller:** Brooks, what are your thoughts about this?

**Dr. Cash:** I completely agree with Brian and I think even taking it back further with regard to the differential diagnosis in this patient the thing that I'm always thinking about when I evaluate these patients is really trying to decide whether or not they have an organic gastrointestinal disease or a functional gastrointestinal disease. And there are several points in her history that point more toward a functional gastrointestinal disease, whether it's IBS or chronic constipation. And I also agree with Brian completely in that I much more favor chronic idiopathic constipation based on exactly the points that he mentioned. But in terms of distinguishing between organic disease and functional disease there are several features that go in favor of the functional disorder. And that would be her age as well as the chronicity of her symptoms; the fact that this is not relatively new onset. This has been there for quite a few years. The periodicity with regard to her menstrual cycles, especially when her symptoms first started, also raises the specter of functionality with regard to her complaints. So again I would completely agree with Brian. I
favor an evaluation leaning toward a defecatory disorder and alteration of
the diagnosis to chronic idiopathic constipation at this point.

Dr. Schiller: All right. Well, Brooks, why don’t you go ahead and tell us a
little bit more about the pathophysiology and symptoms that these
patients have.

Dr. Cash: Well thank you, I’d be happy to. I’ll preface this by saying that
Larry has already discussed a bit about the pathophysiology especially
with regard to chronic idiopathic constipation. And what I’m going to
discuss are some of the emerging theories behind the pathophysiology
and symptom development in patients with IBS with constipation and
chronic idiopathic constipation. Several of the concepts that I’m going to
discuss have not really evolved into things that we can test for at this
point; however, several other things that I will discuss are now becoming
more mainstream in terms of testing for and then subsequently treating
for when we discover the particular pathophysiology. The other thing that
I do want to mention at the outset is that there is likely not a single
cause for IBS or chronic idiopathic constipation. And you’ve already
heard about that in the introductory comments by Larry. This is a
collection of symptoms and, as such, there are multiple different causes
as well as multiple different approaches to treatment. And you’ll hear
about that more later on from Brian.
So, with that introduction, let’s just first talk about the concept of visceral hypersensitivity in patients with functional gastrointestinal disorders. We tend to think of the pathophysiology of these disorders as being really a triad, which is altered sensation, altered secretion, and altered motility. And so we’ll discuss the concept of altered sensation first with regard to functional GI disorders, and IBS in particular because remember that is the condition when we’re trying to distinguish between IBS with constipation or chronic constipation. The IBS patients are the ones that are typically coming in complaining of abdominal pain or discomfort as a primary symptom. So the concept of visceral hypersensitivity is not a new one. A simplistic way of describing this is that patients with visceral hypersensitivity have a greater sensitivity to visceral stimuli than patients who don’t have that condition. So if you take a balloon, for instance, and put it into a body orifice of a patient with visceral hypersensitivity and blow it up to a certain volume those patients are going to say, “Ouch,” at a lower volume than patients who don’t have visceral hypersensitivity. And this has been a frequent and reproducible finding in research studies, especially involving patients with all of the various subtypes of IBS. And it does tend to be organ-specific, but it can be pan-intestinal as well. And we’ve seen similar findings in patients with other functional disorders, such as functional dyspepsia. It can be made worse by certain foods, for instance, lipids or fatty foods, fried foods; and our patients will often come in having self-identified certain food triggers with regard to their gastrointestinal
symptoms. And that may be because of this concept of visceral hypersensitivity. It can also be influenced by cognitive and psychological factors such as emotional arousal, vigilance or somatization, or perhaps even depressive syndromes—and can also be modified by gender as well as immune factors and various hormones and peptides. And there’s actually been some fascinating research showing that there are specific gender differences with regard to how the different sexes process visceral stimuli in terms of the different pain sensing areas and processing areas in both the enteric nervous system as well as the central nervous system.

Now in terms of motility issues we tend to think of IBS and chronic constipation as large intestinal diseases. But I think it’s important for us to realize that there can be dysmotility in the small intestine, especially in patients with IBS symptoms. There can be impaired segmental gas handling throughout the small intestine; there are differences in some patients with regard to some of the contractile forces and typical patterns with regard to motility, especially high-amplitude propagated contractions in the right side of the colon. There have been some studies that have shown that the so-called migrating motor complex or housekeeping motility waves have been disordered in some patients with IBS. This is not a universal finding in all patients with IBS, and this also is one of those series of tests that really hasn’t made its way to the mainstream. Much of these data and evidence comes from tertiary care facilities and is not something that a general gastroenterologist or primary care physician is going to have available to them, but it certainly
does lend some credence with regard to perhaps a subtle organic basis to some of these so-called functional GI disorders and that there are true and measurable alterations in gut motility.

Just like there are disorders of small intestinal motility, there also can be large intestinal motility disorders. And this is actually where more evidence has been derived with regard to IBS as well as chronic idiopathic constipation. And some of the motility abnormalities are similar to what have been observed in the small intestine. And that is altered numbers, both amplitude as well as frequency of high-amplitude propagated contractions. We see alterations depending upon the predominant stool pattern of patients with IBS. Those high-amplitude contractions are increased in patients with IBS with diarrhea and have been noted to be decreased in some patients with IBS with constipation. There can also be rectal compliance and tone alterations in patients with IBS of the various subtypes and altered transit over on the left side of the colon as well. So do realize that there have been a multitude of studies that have shown altered motility patterns associated with IBS. And I also want to stress that this is in some patients with IBS. This is not absolutely a universal finding and is not a disease-defining abnormality. And as such, we don’t use these types of tests routinely in our clinical practice.

In terms of functional constipation, we see a similar story with regard to
alterations both in colon and in anorectal motility, tone, and sensation. And there have been numerous studies that have shown altered transit, altered motility, and altered sensation throughout the colorectum in patients with functional constipation.

One of the more exciting and evolving areas of pathophysiology and etiology with regard to IBS especially but also chronic constipation has been investigations into the microbiota of the human GI tract. I think it’s important for us to realize that this is a very complex system that’s comprised of up to $10^{14}$ bacterial cells, the majority of which are not even culturable. We have actually now sequenced the human microbiome and are now trying to figure out how we can alter that or coapt that to the benefit of our patients with regard to the use of antibiotics perhaps or probiotics or perhaps even prebiotics to foster the development of more favorable microbiota environments for patients. The microbiota is vital for the development of the host immune system. It has a number of functions, one of which is as a barrier against various pathogens. It also helps to break down and digest and subsequently absorb various vitamins and essential nutrients. And it appears to be capable of signaling enterochromaffin cells, which are some of the most important cells in the gut with regard to viscera-sensitive motor and sensation functions. And so there appears to be some form of communication among the microbiota and the enteric nervous system and motor cells of the gut that may, in fact, have some etiology and basis with regard to
gastrointestinal symptoms, especially in our patients with functional GI disorders. And we have some evidence to support that. One of the key concepts with regard to the human microbiome is the concept of small intestinal bacterial overgrowth or dysbiosis being associated with IBS. And it’s felt that perhaps alterations in the microbiome may be responsible for the very high frequency of symptoms such as bloating or gas that these patients experience. And we heard a little bit about gassiness associated with fiber therapy in our case that Larry presented. This study actually looked at a number of different ways of diagnosing bacterial overgrowth. The easiest way that we most commonly use in clinical practice is what’s called a breath test. And we can do this with a glucose substrate or perhaps even a lactulose substrate and basically have patients ingest these sugars and then measure the hydrogen and methane that are produced by the gastrointestinal bacteria in the patients’ expired breath. If we see certain features such as early peaks of hydrogen or methane within a certain time period, we can diagnose those patients with small intestinal bacterial overgrowth. This group looked at breath tests but they also looked at the gold standard test for diagnosing small intestinal bacterial overgrowth, which is small intestinal aspirate and the culture of that aspirate. What they found was that there really didn’t appear—at least in their experience—to be remarkable differences with regard to breath testing in IBS patients versus controls; however, when you look at the culture data you can see that clearly there does appear to be an alteration with regard to enteric bacteria in the jejunal
aspirate in patients with IBS. So, while these patients didn’t necessarily meet the strictest criteria for small intestinal bacterial overgrowth, there did seem to be evidence of a dysregulation or disproportionate concentration of enteric pathogens in the proximal small bowel.

If we look at other areas of emerging pathophysiology and etiology evidence, one of the other hot areas in the last several years has been the concept of a very subtle inflammatory infiltrate or perhaps even mast cell activation in patients with IBS. And what was found by these investigators is that mast cells in the jejunum in IBS patients appeared to be at a higher density and also appeared to be in a more activated state than in patients who didn’t have IBS, suggesting that there may be an inflammatory component very subtle to these patients’ symptoms. These were patients with IBS with diarrhea, and we need to keep that in mind as well. There did appear to be—at least in these patients with IBS and diarrhea—some evidence that mast cells may be playing a role with regard to these symptoms or there may be a relationship there. Whether or not it’s causal still remains to be proven.

Finally, another evolving theory with regard to etiology is the interaction of neurohormones. In this case what we’re discussing is corticotropin-releasing hormone. And corticotropin-releasing hormone has been associated with depression and some neuropsychiatric abnormalities. It’s also been shown, at least in this investigation, to have a modifying role
with regard to mast cell excitability and release, as well as stabilization. These investigators looked at colonic biopsies from 39 healthy subjects, and they did mucosal permeability testing and found that corticotropin-releasing hormone affected mucosal permeability and actually served to stabilize mast cells as well. So there’s some evidence that this could be playing a role with regard to some of the symptoms that our IBS patients suffer.

There’s been a lot of interest in looking at genetics as a possible etiology for the functional GI disorders, especially IBS. And there have been some IBS phenotypes that have been shown to have some genetic basis with regard to response to various therapies and perhaps even familial clustering. So, while this is not true for every patient with IBS or functional constipation, for some patients there may be a genetic component. In other patients, as you’ve already heard, there may be a learned component or a behavioral component to their symptoms. So again this is a very complex set of symptoms that these patients suffer from without one single etiology, but we are learning that it’s a very fascinating and complicated field with regard to trying to tease out the different causes or potential causes.

One of the things that a lot of this etiologic work has done in determining some of the various pathophysiologic bases for IBS and chronic constipation is it’s allowed us to identify certain target therapies. Some of
the emerging therapies for IBS include agents that work both in the peripheral nervous and enteric nervous systems, including antidepressants and serotonin modulators, as well as CRF antagonists and NK antagonists. In terms of peripherally acting agents, we actually now have available chloride channel modulators of several different types, opioid receptor modulators, which have really found a lot of their use in opioid-induced constipation, but there are also some of these agents now being investigated for IBS. Antibiotic use has now come to the fore especially in patients with functional bloating or a prominent bloating component to their IBS symptoms. And then probiotics and prebiotics as I mentioned at the outset when I was discussing the microbiome have also become really commonplace therapies for IBS. And some patients have really been able to help improve their quality of life and decrease their symptoms tremendously. One of the things that I would underscore with regard to that, it’s often a trial and error process of some of these various medications and approaches.

Let’s move back to our patient. So what should we do next? Well we have a number of different options, and I’ll go ahead and turn this over to Larry and ask him where he thinks the next step ought to go with our patient.

Dr. Schiller: Well I certainly think that if you look at patients who have constipation the vast majority of them will respond to relatively simple
things. So I think it’s always useful after one has carefully considered all the different possibilities to try a sort of routine management with simple laxatives like polyethylene glycol or perhaps some of the other bulking agents that we use for improving stool volume and seeing if that makes a difference. Now Jane had tried that. She had been put on a fiber supplement, but it wasn’t very effective for her. It made her gassy. Fiber is carbohydrate that none of us can absorb in the small intestine; it all gets ferried down to the colon and the bacteria there are very efficient at fermenting it. It’s been calculated that for every teaspoonful of carbohydrate that gets down to the colon you can make a liter of gas. And about half of that gas can be absorbed through the mucosa of the gut and exhaled in the breath but about half of it has to find its way out through the anus. And that can result in a fair amount of bloating and discomfort for people. So fiber isn’t always the solution. I think it’s a good place to start in people, and I think in Jane’s case it was fine to give that a try but if you try and it doesn’t work it’s time to move on to something else. When you have someone who has these pelvic floor problems, I think it is useful to try and investigate them further because we have some treatments that can be helpful in dealing with the problem of dyssynergia, particularly biofeedback training, but before you can undertake that you need to understand the pathophysiology and what’s working and what’s not down there. So I think there is a value to some of the diagnostic testing that we do.
Dr. Cash: Thank you, Larry. The other thing that I think we ought to keep in mind with regard to these patients, especially when we’re thinking about pelvic floor dysfunction, is trying to understand why they may have developed pelvic floor dysfunction. We actually did that in this case, and we found that the patient was quite concerned that she could have cancer or inflammatory bowel disease. And while we spent quite a bit of time saying how that’s unlikely in this young patient it’s still a real concern that we need to address and help her understand. And we may need to do some diagnostic testing to help reassure her with regard to that. But even taking this a step farther—when we actually ask about when the patient links her symptoms to her emotional state—we find that when she feels sad and anxious her symptoms seem to come to the fore with a significant impact on her personal and professional life. She’s had to cancel numerous social engagements and actually even avoided intimacy with her partner. And on further questioning, she admits to some sexual abuse episodes in her late teens. And that can be a red flag for pelvic floor dyssynergy. We have done some diagnostic tests in this patient to address some of her fears but also to reassure ourselves as well that we’re not missing any organic disease. She had normal complete blood count, thyroid function studies, and celiac antibodies. A colonic marker study was done that did show retention of markers in the sigmoid colon and rectum after 5 days. She had a balloon expulsion test, which is a test for pelvic floor dysfunction, and this was found to be abnormal. And then she proceeded to anorectal manometry, which is the
current gold standard diagnostic test for pelvic floor dysfunction, and that showed normal rectal sensation and compliance with an increased external anal sphincter contraction with straining, which is again entirely consistent with that subtype of chronic constipation. So it appears that we’re honing in on her diagnosis.

So with that let’s go ahead and segue over to discuss the treatment options for IBS with constipation and chronic constipation, and I’ll turn it over to Brian Lacy.

**Dr. Lacy:** Great. Thank you very much, Brooks. Patients and clinicians have a number of treatment options available to treat the multiple symptoms of constipation. Treatment options include over-the-counter agents as well as prescription medications. And over the next few minutes I’ll review the data supporting the use of these medications using an evidence-based approach.

Stool softeners are classified as emollients. They may also add up to 3% of additional water weight to stool. They are commonly used by patients, because they are readily available and oftentimes recommended by clinicians because they are safe and inexpensive. However, there are very little data to support their use. In fact, there are only 4 studies published to date, and only 3 were considered of high quality. Generally stool softeners are thought to be less effective than psyllium and no better
than placebo. Bulking agents are generally fiber products. Fiber is classified as either soluble or insoluble depending on its interaction with water. Psyllium is a classic soluble fiber while bran is insoluble. Although commonly used, only 10 clinical trials have been performed in patients with chronic constipation, and most of these trials were suboptimal in design due to a short duration of the study. Many were less than 2 weeks or had a very small sample size of patients included in the study. Nevertheless, if a patient has symptoms of constipation, a trial of fiber is reasonable given its safety and low cost. Patients should be started slowly to prevent excessive bloating. Note that if somebody is already on a normal or high-fiber diet, meaning more than 25 grams of fiber per day, adding more fiber will not improve their symptoms and likely will just make gas and bloating worse.

What about stimulant laxatives? These have been used for decades. They appear to induce fluid and electrolyte secretion by the colon and also induce peristalsis in the colon. Although there are a number of misconceptions about stimulant laxatives, the most common of which is that they are either addictive or that they injure the enteric nervous system, we now recognize that stimulant laxatives are generally quite safe. There are 4 randomized controlled trials involving either senna or bisacodyl. Effects were modest at best, which led to a grade B recommendation. Grade A, as you know, is the highest level of recommendation. These agents are not approved for long-term use and
most clinicians recommend them only for PRN use due to their potential side effects, typically including significant cramping and urgency. Data supporting the use of osmotic laxatives are much better than what we have seen for stool softeners and fiber products. Eleven trials have been performed to date; 8 were placebo controlled and 6 were of high quality based on sample size, trial design, and length of study. Based on improvement in overall symptoms of constipation, osmotic laxatives—and this really means polyethylene glycol—were given a grade A recommendation. At present these agents are not approved for long-term use for the treatment of chronic constipation. Note that many patients treated with lactulose have significant bloating and can’t tolerate it. Also keep in mind that patients treated with milk of magnesia, be very careful with those with renal insufficiency. And that received only a grade B recommendation.

Now what about lubiprostone? This was approved in 2006 for the treatment of chronic constipation. It’s classified as a chloride channel activator and stimulates the type 2 chloride channel in the GI tract. By doing so, chloride is secreted followed by sodium to maintain isoelectric balance, and then this is then followed by water. Each trial was randomized, double blinded, and placebo controlled. There were approximately 240 patients enrolled in each of these 2 pivotal studies with most of these patients being women. In both of these studies, lubiprostone at 24 micrograms twice daily significantly improved
symptoms of constipation. The primary endpoint was spontaneous bowel movement. Symptoms improved within the first week and symptom improvement was maintained during the 4-week study. When the medication was stopped, symptoms of constipation did not significantly worsen, meaning there was no rebound effect.

Linaclotide is a guanylate cyclase C activator, and we’ll call that a GCC activator. And by stimulating the GCC receptor linaclotide a cascade of events is initiated including the production of cyclic GMP within the cells and stimulating the cystic fibrosis transmembrane receptor. That being said, this increases fluid secretion into the GI tract that improves symptoms of constipation. This slide demonstrates the 2 large pivotal studies that led to the approval of linaclotide for the treatment of both men and women with chronic constipation, and in these 2 studies patients were randomized to either placebo or to 1 of 2 doses of linaclotide. Patients treated with the active medication had a significant improvement in constipation symptoms, and these benefits persisted throughout the 12-week study period.

Pucaloprider is a serotonin receptor agonist. More specifically, prucalopride stimulates the serotonin type 4 receptor and by doing so increases gastrointestinal transit. It is approved for the treatment of chronic constipation in Europe but is not FDA approved or available for use in the United States. Two large multicenter, randomized, double-
blind studies were conducted over 12 weeks using the primary endpoint of complete spontaneous bowel movements. Patients randomized to placebo did not do as well in terms of complete spontaneous bowel movements over the study period compared to patients randomized to either prucalopride at 2 or 4 milligrams. Time will tell as to whether or not prucalopride will become available in the United States.

Elobixibat is a novel agent currently under development for the treatment of chronic constipation and possibly IBS with constipation. Elobixibat inhibits the bile acid transporter. As such, it increases the flow of bile into the colon, which can then stimulate colonic transit and colonic movement. The largest study published to date involves 190 patients enrolled in a double-blind, randomized, placebo-controlled trial lasting 8 weeks. All patients met Rome III criteria for chronic constipation and the key endpoints were changes in either spontaneous bowel movements (SBM) or complete spontaneous bowel movements (CSBM). Compared to placebo, patients randomized to either the 10-milligram dose or the 15-milligram dose of elobixibat, which was given once daily, did significantly better with regard to both spontaneous bowel movements or complete spontaneous bowel movements. Future studies are currently underway in the United States to determine whether this is safe and efficacious in larger numbers of patients.

Let’s shift gears and focus on treatment options for IBS with chronic
constipation. And the treatment options, whether involving lifestyle modifications or over-the-counter agents, are compared and contrasted with prescription medications. In clinic, one question that typically comes up is what’s the association between diet and IBS? A very nice study published by Albina Halpert from Boston looked at over 1200 patients with IBS, recognizing that many of these patients believe there’s a significant association with diet, stating that avoiding fat or by adding fiber or by avoiding milk products made some of their symptoms better. Many IBS patients are concerned that they have a food allergy, but food allergies are actually uncommon, affecting less than 3% of the population. Lactose intolerance is a little bit more common in IBS patients with a prevalence of about 35% to 38%. Although many patients are quite concerned that their symptoms represent a true wheat allergy, this is actually not common, with the prevalence in the United States of about 0.41%. However, many patients with IBS seem to be a little bit sensitive to gluten and that may be because of the fructan component. Finally, many patients who have lactose intolerance and IBS are also fructose intolerant.

Looking at bulking agents for IBS with constipation (IBS-C), there are more studies performed in this patient population than in chronic constipation. And this slide illustrates that fiber may improve IBS-C symptoms in some patients. Overall, the difference between fiber products and placebo was 48% to 43%, leading to a number needed to
treat of 11. You’ll see that ispaghula actually did better overall; however, one important point there is that bran did not improve IBS-C symptoms and actually worsened symptoms in many patients, especially that of bloating.

What about polyethylene glycol (PEG)? PEG is commonly used to treat symptoms of constipation, but does it help IBS patients? Well, we didn’t have much data until recently, and this study showed that patients who received PEG had an improvement in spontaneous bowel movements. However, pain associated with their IBS did not improve, and remember that pain is one of the most common reasons that patients with IBS come to clinic.

So, let’s now look at the data for lubiprostone in IBS-C patients. As we’ve mentioned already lubiprostone activates type 2 chloride channels in the GI tract. And it is FDA approved for the treatment of women with IBS and constipation. And this study shows data from two large prospective, randomized, double-blind, placebo-controlled studies showing that patients randomized to lubiprostone did significantly better in terms of their overall IBS-C symptoms than those randomized to placebo. The dose recommended by the FDA is 8 micrograms twice daily.

As we mentioned earlier, linaclotide stimulates guanylate cyclase receptors. This study focused on both men and women with IBS-C
symptoms who met Rome III criteria. This initial part of the study was a 12-week study. This is a double-blind, randomized, placebo-controlled study. Patients randomized to 290 micrograms of linaclotide once daily had a significant improvement in their symptoms. The primary endpoint was complete spontaneous bowel movements. They noticed an improvement in their symptoms within the first week. This was maintained over the full 12-week period. When they stopped the drug you can see that symptoms relapsed because they had a drop in their CSBM. This is in contrast to patients randomized to placebo who had a slight improvement in CSBMs—that’s the placebo effect; however, at week 12 when they were transitioned to linaclotide, they had a significant improvement in their CSBMs.

What about antispasmodics for IBS? These are commonly used again mostly for the treatment of pain or bloating in IBS. Although multiple studies have been performed, unfortunately, most of these agents are not available in the United States. Meta-analyses have been performed showing that many patients improve with the use of antispasmodics; however, some patients develop tachyphylaxis with long-term use.

What about the use of a tricyclic antidepressant or SSRI for the treatment of IBS symptoms? Multiple studies have been performed to date looking at tricyclic antidepressants (TCAs) for the treatment of IBS. And generally the meta-analysis favors treatment for this primarily for
symptoms of visceral pain—the nice concept of visceral hypersensitivity already discussed by Brooks and Larry. Only 5 studies have been performed for SSRIs. The data are less robust. Data are sometimes in conflict but, overall, SSRIs seem to help. But, at least in my practice, I believe it tends to help more with coexisting symptoms of anxiety or depression and less for the visceral pain.

With that in mind, let’s go back to our case and as mentioned earlier, the SITZMARKS® study was consistent with outlet obstruction, not colonic inertia. The anorectal motility study and the abnormal balloon expulsion test confirms the symptoms and the physical exam findings that this patient likely has pelvic floor dyssynergia. As Brooks earlier noted there was a warning sign there about the history of abuse and certainly that’s something that needs to be addressed at the time of our office visit. Our office visit would be the perfect opportunity to educate the patient and explain the etiology and physiology of pelvic floor dyssynergia. Different treatment options should be explained to the patient, whether that’s physical therapy at home, seeing a physical therapist, or possibly using a suppository or enema. The need to address the history of prior abuse is really critical in this patient, and she should be referred to either a psychiatrist or a knowledgeable behavioral therapist. And this patient then, because of her symptoms, was referred to a physical therapy retraining program for exercises, biofeedback, and relaxation techniques.
Dr. Cash: Well thanks, I’m going to jump in here and talk just a little bit about patient-centered care. As we’ve really tried to emphasize during the program, these functional gastrointestinal disorders are disorders that can cause a tremendous impact on our patients’ quality of life. And as you’ve probably heard throughout the discussions there are multiple areas where simply talking to the patient and really developing a patient-centered environment and approach may be actually beneficial.

So with that in mind I’m going to talk about a couple of recommendations that have been put forward. The first set of recommendations was actually published in the *Journal of Gastroenterology*. This is from the *American Gastroenterological Association Guidelines on Irritable Bowel Syndrome* that were published in 2000. And these are some of the important questions to ask our patients. The first would be just asking them why they came to see you and what their concerns are. Often these patients will have an agenda or some fears that they may be reticent to voice. And we tried to highlight that in the case that we presented where our young patient was actually concerned that she had an organic disease such as cancer or inflammatory bowel disease. Finding out the chronicity of the symptoms is critical with regard to finding the right diagnosis according to the Rome criteria with regard to the chronicity requirements, finding out just how limited the patients are. So how does their constipation limit their daily activities and what are their most distressing symptoms that may
help develop both their diagnostic approach as well as your therapeutic approach? How much fiber are they taking and are they experiencing any side effects? Also what laxatives have our patients tried? Are they currently using laxatives? How often? And at what dose? Have they used enemas or suppositories? And are they using any herbal medications or teas? And that’s especially important not only for gauging our patient’s approach and views on complementary and alternative medicine, but also from a safety issue because there have been multiple reports of hepatotoxicity from some of these therapies as they are poorly regulated and not terribly well understood. Other questions to ask are how often do the patients have bowel movements? How often are they experiencing bowel movements and what is the quality of that bowel movement? Are they feeling completely evacuated? Are they straining? How long are they straining for? How long are they actually sitting on the toilet for? Do they get that urge to defecate? Are there relevant life events such as abuse, loss, or grief to try and determine if there are psychological comorbidities that may be at play. And, finally, asking patients if they’re using recreational drugs or other agents and delving into their social lives and habits, can be very important.

Dr. Doug Drossman is really one of the leaders in the field of functional gastrointestinal disorders and one of the major leaders in the Rome Committee on Functional GI Disorders. He has a series of what we’ll call “Ten Commandments,” and I’m just going to read through these very
briefly. Number 1, obtain the history through a non-directive, non-judgmental patient-centered interview. Number 2, conduct a careful examination and cost-efficient investigation. Number 3, determine how much the patient understands about the illness and his or her concerns. Number 4, provide a thorough explanation of the disorder that takes into consideration the patient’s beliefs. Number 5, identify and respond realistically to the patient’s expectations for improvement in their symptoms. Number 6, when possible provide a link between stressors and symptoms that are consistent with the patient’s beliefs. Number 7, set consistent limits. Number 8, involve the patient in treatment. Number 9, make recommendations consistent with the patient’s interests. And number 10, establish a long-term relationship with a primary care clinician.

There are other considerations from a patient-centered approach with regard to these functional GI disorders, and those would include things like allowing enough time for a visit. These patients are not going to be well served with a 5- or 10-minute evaluation. Using physician extenders can be very helpful in the evaluation of these patients. Setting an agenda with the patient at the start of the visit for future visits as well as the subsequent evaluation and possibly even the therapeutic approach that may be embarked upon as we move forward with these patients. Avoid those doorknob moments or those “Oh by the way ...” moments and really sit down and take the time to engage with your patients, look them
in the eyes and empathize with them. Make it clear that you understand and can commiserate with regard to the symptoms, as well as to make an effort to understand just how limited they may be with regard to their GI symptoms. And finally, arrange appropriate follow-up and interaction after the initial visit. Larry, do you have any other thoughts with regard to other considerations?

Dr. Schiller: Well I think that we need to really get back to the idea of the patient-physician relationship being a relationship. That’s a 2-way street. Doctors are teachers by definition and physicians need to provide a clear explanation about the nature of the illness, the treatment goals and options, and self-management strategies; how the patient can avoid problems by looking for triggers that seem to bring out symptoms. On the other hand, patients need to develop adaptive coping skill and the doctor can help with this to some extent. They can’t be passive. It’s not just taking pills that’s important when you’re dealing with these kinds of functional problems. It’s interesting, studies that have looked at how you can interact with patients show that just giving people advice about their diet, exercise needs, stress, and medication alleviated IBS symptoms in more than 80% of the patients. So that’s as good as or better than many of the medicines that we use. It’s not just being a drug dispenser; you need to be a doctor and interact with the patient and try and find out what’s going on. We think about the patient-clinician encounter from the patient perspective; they’re coming to you to talk about what are frankly
embarrassing symptoms for many people. Often if you are short with them and don’t give them enough time to explain their problem and show some empathy with it, they feel that you’re not validating their problem and you’re not understanding their symptoms well. And this is a major cause for patient dissatisfaction. I see a number of patients who’ve been to other physicians before, and this is what bothers them. They’re very appreciative of the time that you take. But it does take time and you don’t want to minimize things for the patients, even though you may feel that constipation isn’t the most health-threatening problem that the person has. They may feel differently about it. And after all, they’re taking the time to come to you to discuss it and find out about it, so don’t minimize what they think is an important problem. Patients with IBS really want you to listen. This may vary with their cultural backgrounds, but you need to be sensitive to their concerns and answer their questions.

The education aspect is very important. Many of them feel that they have some other problem and that needs to be addressed in one way or another. And reassurance is very important and very much a part of the management. You need to make the diagnosis be a positive diagnosis, not just we’ve looked for everything and can’t find anything. You must have IBS—which is often how it’s been presented in the past. You need to celebrate symptom improvement with the patients. Even small steps go toward improving the overall patient experience. So encourage positive
attitudes in your patients, but keep your expectations realistic. Don’t promise them a normal lifestyle if you can’t deliver. And you need to reassure the patient that these are common conditions; that you have some expertise in dealing with them because you see them often; that the course is benign and they don’t turn into cancer; they’re likely to have exacerbations as life goes by, and they’ll have a variable impact. Even though a cure is unlikely, proper management can alleviate many of the symptoms and make life worthwhile again.

If you look at their primary care physicians and poll them they’re perceptive; 55% to 71% of the primary care doctors identified stress or anxiety as a trigger for IBS symptoms. And many people feel it’s a nervous complaint, but even if you feel that way, you need to deal with the problem and try to help the person manage their nerves better. So that this is an area in which we’re continuing to evolve and learn more about the disorder, as you’ve heard today. And I think you have to keep up with things and inform your patient about these new developments as they come to pass.

**Dr. Cash:** Okay, well thank you very much. And I’m going to turn it over to Brian and Larry to just finish us out with regard to the treatment approach and then let’s close out with our case history.

**Dr. Lacy:** Great, Brooks. Thank you very much. The pyramid approach
demonstrates a couple of key points here. The first key point that you’ve seen today is that we don’t have an algorithm for the treatment of IBS. One does not exist because there’s no treatment algorithm that fits all IBS patients. And as already alluded to by both Brooks and Larry, the first thing is to really listen to patients, identify their goals, understand their concerns, and then formulate a treatment plan that’s really patient-specific. So for those patients with more mild symptoms—and that will be the majority of patients in primary care—those where symptoms are not disabling, not affecting them on a daily basis. If you educate the patient, if you reassure, if you tell them that this diagnosis is actually quite common, they’re not all alone, if you change some parts of their diet, if they get some exercise, they sleep better, many of those patients do dramatically better. And that may be all you need. And all you really need to do is listen, validate, and understand those patients. Some patients have more moderate symptoms, or maybe it’s starting to affect them on a near daily basis, they’re missing school, they’re missing work. Those patients may need those same bits of advice we just discussed, but they may also need something else. And that may be more involved pharmacologic therapy, more involved dietary therapy, maybe a visit to a behavioral therapist. Again, it’s very individualized. Severe patients are typically those seen at academic centers; they may have seen several physicians. Those patients oftentimes have significant coexisting psychological distress, they’re very anxious, they’re very depressed, they somaticize, they catastrophize. And those patients likely will have failed
the simple things we’ve just discussed, frequently require medical therapy for their IBS symptoms, and frequently require therapy for their psychological symptoms as well. So the key point I think here is one size does not fit all, and just learn to individualize treatment.

**Dr. Lacy:** So let’s now go back to the case and think about Jane. And Jane returns for follow-up six months later. Her symptoms improved after physical therapy retraining for about 3 months. Stool frequency decreased from 6 times a week to 2 times a week, but now she’s straining again and the stool form has changed. On examination she now has hard stool in the rectal vault. The puborectalis appears more normal and the pelvic floor seems to work a little bit better with simulated defecation. But going through her history a little bit more carefully you learn that fiber supplement was stopped about 2 months ago, and she had stopped her biofeedback because she was doing so well. At present she’s consuming a low-fiber diet because she had read on the internet that too much fiber could cause gas, and so she wanted to reduce gas and bloating. But, as already discussed, by doing so it seems like there’s a correlation with a change in stool consistency with these hard stools. So the goal at that visit was to focus again about diet, introducing some more natural fiber and also a low dose of polyethylene glycol was reinstituted and physical therapy training and retraining was advised as well.
Dr. Schiller: Well let’s turn now to some of the frequently asked questions about IBS and chronic constipation. And since we mentioned with Jane that her diet is an issue, I think certainly the question that patients ask most often and many physicians ask is about diet. So, Brooks, why don’t you tell us a little bit about what kind of diets you recommend for patients who have IBS with constipation and chronic constipation?

Dr. Cash: Sure. I’d be happy to. Thank you. Brian already alluded to it as did you, the first hallmark of therapy in terms of dietary therapy for these patients is to try and get them to increase their fiber if they can tolerate that. So I frequently will do that if patients have not tried that before they’ve gotten to me.

Dr. Schiller: What kind of fiber do you recommend?

Dr. Cash: I typically recommend a semi-synthetic fiber, so something like calcium polycarbophil, because I believe that is associated with less bloating; it also comes in a tablet form that a lot of patients prefer over mixing up a powder and drinking that, which they often perceive as gritty and unpleasant. That’s my preferred fiber. But I think any type of non-crude fiber. So avoiding the bran type fibers and moving more toward the soluble fibers like psyllium or as I mentioned calcium polycarbophil I think is the way to go in these patients.
Schiller: How about other aspects of the diet?

Cash: Especially in those patients with bloating, there’s been a huge move toward using what’s called the FODMAPs diet, which stands for Fermentable Oligo-saccharides, Disaccharides, Mono-saccharides and Polyols. And this really got its major push from investigators in Australia. This is a diet that consists of decreased doses or amounts of poorly absorbed carbohydrates, such as fructose and fructans; and raffinose, which is found in many vegetables and cruciferous vegetables in particular; but also involves decreasing the amount of wheat and gluten products. And, you know, one of the big crazes right now in terms of the lay population but also even the medical population is to advise gluten-free diets. I’m somewhat cautious on that but I find that many patients with IBS in general, especially bloating, can improve if they can decrease the amount of poorly absorbed carbohydrates such as wheat and lactose from their diet. That’s not specifically a treatment that I give to IBS-C but can benefit those patients, but it also can have some benefit in patients with IBS-D or IBS with a mixed bowel pattern.

Dr. Schiller: Now, Brian, the other question that I get asked all the time, often by patients and frequently by consulting doctors, is about probiotic therapy. That seems to be all the rage too. What can you say about that?

Dr. Lacy: Yeah, probiotics are a very controversial subject only because
they are widely available, they’re fairly inexpensive, and the misconception out there is that probiotics will cure all of your GI ills. But that’s really not the case. There are some good data showing that one probiotic in particular, *Bifidobacterium infantis*, seems to be pretty good at improving some IBS with diarrhea symptoms and some bloating symptoms. But we really don’t have great data on probiotics using any prospective, randomized, controlled study for patients with either chronic constipation or IBS with constipation. That being said, some patients like to try them. I think it’s not unreasonable, keeping in mind, though, that there’s not great data and also keeping in mind that about 50% of probiotics are really dead on arrival and probably won’t help any type of IBS patient.

**Dr. Schiller:** Well the last question I’d like to tackle is about psychological therapies for these patients. Many of these individuals have psychological issues, although we certainly don’t believe that’s the cause of all their problems. And I’m curious, Brooks, as to how you incorporate that into your management of these patients?

**Dr. Cash:** I think that’s a great question and it’s a great point to make. And while it’s not the majority of patients that I will embark on psychological therapies with, it’s certainly still a fair amount. And the way I like to do that is through a multimodal or multidisciplinary approach. And we actually have a clinical psychologist that works with
us that we refer our patients to. I'll typically try the pharmaceutical approaches and lifestyle approaches, but when I am able to develop that excellent rapport and relationship with patients, if I do find that there appears to be some psychological comorbidity at play with regard to symptom generation or impact, then I have a very low threshold to refer those patients for psychotherapeutic counseling. And typically it is more of a cognitive behavioral approach—developing coping mechanisms as opposed to a desire to put them on neuropsychiatric medications. So I really try and focus on that behavioral approach and coping mechanisms to help them deal with their life stressors as well as their gastrointestinal symptoms. And I've been very happy and impressed with that line of therapy in the select patients that I send for that therapy.

Dr. Schiller: Well thanks, Brooks. I’d like to thank Brooks and Brian for their expert opinions. I hope the audience has gained a great deal of knowledge about these conditions and how to manage them, and particularly given some thought to this patient-centric model of care that I think can really help many of these patients with functional problems. Thanks very much for tuning in.