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https://reachmd.com/programs/cme/in-your-waiting-room-the-virtual-ibs-c-patient-clinical-experience/14955/

Released: 03/27/2023
Valid until: 03/27/2024
Time needed to complete: 30 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

In Your Waiting Room: The Virtual IBS-C Patient Clinical Experience

Announcer:
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[CHAPTER 1]

Dr. Brenner:
Despite advances in the treatment of irritable bowel syndrome with constipation, or IBS-C, there remains an unmet need for patients who are not experiencing adequate relief from their current therapies. Today, we'll meet 3 different patients and hear their stories. This will help us better understand the complexity of IBS-C and the nuances of management options in each situation.

This is CME on ReachMD, and I'm Dr. Darren Brenner.

Dr. Cash:
And I'm Dr. Brooks Cash.

Dr. Brenner:
Today we're meeting Mara, Sara, and Josephine, who are already in our waiting room, and we'll hear more about their IBS journeys. Let's begin with Mara, who has been experiencing recurrent abdominal pain and constipation associated with concurrent urinary symptoms.

Mara:
Hi, Doctor, I'm here because I've been experiencing some weird symptoms on and off for the past year. Every now and then, my stomach starts cramping on me, the pain stops me in my tracks and sometimes brings me to tears. I've tried over-the-counter pain meds and using a heating pad, but they don't seem to help much. Eventually, the pain just goes away, but there's no rhyme or reason why or when the pain will happen or how long it will last. Oh, and I also get this feeling like my stomach is full and bloated. When I have these symptoms, I also have an urge to have a bowel movement. But when trying to go to the bathroom, no matter how hard I strain, either nothing comes out or I just pass hard pellets. I've also noticed that when I'm backed up, I have difficulty urinating. This resolves when I finally have a good bowel movement. Between these episodes, I'm completely fine and I have no symptoms. I try to work out regularly and eat healthy in general. I hope you can help me understand what's happening to me. I'm really afraid something bad might be going on.

Dr. Brenner:
So, Dr. Cash, based on what Mara just shared with us, do you think she's experiencing IBS-C? And can you also give us an overview of the pathophysiology of this disease?

Dr. Cash:
I do think she's suffering from IBS with constipation. So I think it's important for us to really go over the definitions of these conditions.

The 2 things that I would be thinking about in her case would be is this irritable bowel syndrome with constipation, or is this chronic idiopathic constipation? And we use these definitions that are clinical definitions and criteria based on symptoms from the Rome committee on functional GI disorders or disorders of gut-brain interaction. The thing that I would stress is that these are very similar conditions. Irritable bowel syndrome with constipation is broadly defined as abdominal pain associated with disordered defecation. And patients can have diarrhea, constipation, or a mixture of the 2. And it's really based on the frequency of those abnormal bowel habits. We use what's called the 25% rule; constipation more than 25% of the time with less than 25% diarrhea, that's IBS with constipation.

Now, chronic constipation has the exact same symptoms. And there's really 6 primary symptoms. Patients should endorse at least 2 of the symptoms, and they should have symptoms for at least 12 weeks in duration. And these symptoms are straining at bowel movements, a sense of incomplete evacuation, a feeling of obstruction, having to use manual maneuvers to facilitate defecation, hard and lumpy stools, and finally, less than 3 spontaneous bowel movements per week – that's a bowel movement without the use of a laxative.

So those are the questions that I will go through and ask patients about and try to untie and figure out whether or not they've got IBS with constipation or CIC, or chronic idiopathic constipation. The pragmatic answer with regards to those is, it's really the abdominal pain that's driving these diagnoses. They're very similar; we work them up the same; we treat them largely the same. The recommended evaluation for these patients is very simple. It's a CBC to make sure they're not anemic, and a thyroid function study to make sure that they're not hypothyroid.

Now in terms of other symptoms, we talked about abdominal pain, we talked about the constipation symptoms, bloating is another symptom that we need to ask our patients about. It's not part of the criteria, but nearly 90% of patients with these conditions suffer from bloating, and it's a very bothersome symptom. And in our patient's case, we see that she's also got urinary symptoms. Urinary symptoms do seem to travel with constipation symptoms. And so asking about urinary hesitancy or dysuria or frequency, urge incontinence is very important as well, because these do seem to tie in, likely because of crosstalk between those pelvic nerves that can be disordered.

Finally, let's talk about pathophysiology. The macro picture with regards to pathophysiology for these conditions, is disorders of motility, secretion, and in the case of irritable bowel syndrome, sensation, or what we call visceral hypersensitivity. We don't know what causes those macro changes. And we end up treating those macro changes with our therapies, our over-the-counter therapies and our prescription therapies. There is evidence to support a wide variety of different potential mechanisms behind the pathophysiology. Food-related sensitivities, emotional or psychological issues, infection, perhaps the immune system, impaired barrier with regards to the gastrointestinal mucosa and translocation of bacteria, perhaps microinflammation. And that's one of the reasons why there's not a single diagnostic test for these conditions. We have to use clinical criteria to make these diagnoses.

Now as we saw on our patient, this is a really impactful condition. Significantly impacts quality of life, lost productivity, curtailed social activities. There's a huge cost in terms of direct medical care. And nearly twice the cost of direct medical care can be attributed to indirect medical care, the cost of missing work and being less productive because you're at the doctor's office or because you've got symptoms that are prohibiting you from doing those activities of daily living or your job.

So these are really impactful conditions, the prevalence somewhere between about 4% to 10% depending on which criteria you look at. So I think those are really the major points that I would want to convey with regards to the pathophysiology and the epidemiology of irritable bowel syndrome with constipation.

Dr. Brenner:
Absolutely.

Dr. Cash:
So I'm going to ask you a question. Now, how does making a definitive diagnosis or producing a definitive diagnosis help a patient like Mara?

Dr. Brenner:
Yeah, I think to your point, you know, you just mentioned, this is a common disorder. Think about that, 4% to 10% of the population. And I think a lot of times we hear that irritable bowel syndrome is a nuisance disorder, or it's not bothersome, just to learn to live with it. But like you mentioned, I mean, this leads to a secondary anxiety, depression, significant reductions in quality of life, social stigmata, people tell us they don't leave their homes, they're not able to go to work. So I always tell my patients the faster we can make an accurate diagnosis, the sooner we can get to treatment and really improve the symptom profiles that they're experiencing.

And one of the things that I always find concerning is how long it takes us to get there. I mean, when we look at the literature, it says, 4 to 5 years, see 4 to 5 practitioners, up to three-quarters of all people suffering from irritable bowel syndrome in the United States have

yet to be diagnosed. And yet, when we look at guidelines, the guidelines are pretty finite: make this a positive diagnostic strategy, get to the diagnosis quickly. And we know that the patients meet those Rome criteria you mentioned, without a few alarm signs or symptoms, the predictive value of the criteria is as high as 97% to 98%. So what that really tells us as practitioners is, we don't need to do a lot of diagnostic testing, we don't need colonoscopies, CAT scans, blood tests, stool studies, et cetera. Just make the diagnosis and start to treat these individuals.

And the nice thing now is that in 2023, we really have good therapies that treat the global or totality of the IBS symptoms that these patients experience.

So, Dr. Cash, if there was one key takeaway message you want to leave our listeners with, with regards to diagnosing IBS-C and its related symptoms, what would that be?

Dr. Cash:
Well, I think the one key message that I would convey, it really ties into what you said. It's a relatively simple diagnosis, and if we are aware of those criteria, we're aware of the symptoms and the impact that these symptoms cause our patients, and we convey that to our patients, and the questions that we ask and the information that we're soliciting from them, I think it conveys to them that we, A, know what they're experiencing. We also are familiar with the condition. And hopefully that really gives them confidence that we're familiar with how we can best treat this condition. And it is a relatively simple diagnosis. We do obviously have to keep a broader differential in mind always, but as you mentioned, when patients come in meeting these symptom-based criteria and they don't have alarm features, using a positive diagnosis is the way to go.

Dr. Brenner:
Well, thanks, Dr. Cash.

In the next 2 chapters, we'll be hearing from Sara and Josephine, and we'll dive deeper into our discussion on irritable bowel syndrome with constipation.

[CHAPTER 2]

Dr. Cash:
Welcome back. In the first chapter, we covered the underlying mechanisms of irritable bowel syndrome with constipation and the impact on our patients' quality of life. Now let's dive a little deeper into how to treat patients with this disease.

Let's see who's next in our waiting room. This is Sara, who was referred by her primary care physician due to worsening abdominal symptoms.

Sara:
Hi, Doctor. I'm here today because I've been having stomach problems for the past couple of years. Well, what happens is that I get this incredible pain in my abdomen along with really bad bloating. I try to relieve it by going to the bathroom, but I find myself straining really hard without passing anything. I feel like I need to have a bowel movement, but I just can't, and it's just getting worse. This constipated feeling on top of my pain makes me very frustrated, and I just can't figure out why this keeps happening to me. I try to avoid eating anything that might upset my stomach. And I've tried using stool softeners to help me go to the bathroom, but they don't always work, and the symptoms keep coming back. I've tried various laxatives from the pharmacy, but nothing seems to work. I even had a colonoscopy last year that was normal except for some hemorrhoids. Yesterday I ate some cheese which is normally fine. Literally 5 minutes after, I started having this incredible stomach pain and I felt really bloated. I tried increasing the fiber in my diet and drinking more water, but that just made me more bloated. Yesterday I was awake at 4 o'clock in the morning and I couldn't go back to sleep until noon. It's really difficult to live my life like that, and I'm hoping you can help me, Doctor.

Dr. Cash:
So, Dr. Brenner, based on what we just heard, it sounds like Sara is experiencing IBS with constipation, without much help from her over-the-counter [OTC] options that she's tried. Can you give us an overview on why OTCs may not be beneficial for this patient and what other initial therapies we should consider for our patients with IBS with constipation?

Dr. Brenner:
Yes, I think Sara has done what a lot of our patients do when they get these symptoms. They start with the over-the-counters, fiber, water, maybe some of the standard laxatives. And part of the problem we have is when they come to talk to us, we don't have a lot of evidence. There aren't a lot of clinical trials looking at using over-the-counter therapies for irritable bowel syndrome with constipation.

Now, there is one, PEG3350; there are a few trials that have looked at that. And unfortunately, what we see is while this is a very good medication for what I like to define as the constipation symptoms of IBS-C, the frequency, the harder stools, the strain, and the

incomplete evacuation, and the medication does improve those symptoms, at the heart of it, the over-the-counters don't improve the abdominal symptoms: the pain, the bloating she mentioned, which is very, very common in these patients. That just general sensation of discomfort. And we have to remember that when it comes to irritable bowel syndrome, the sine qua non is that pain piece, right? If you don't have pain or discomfort, you don't have irritable bowel syndrome, and the OTCs just don't get there.

In fact, some of the guidelines, even the international guidelines coming out of the United States, Europe, Mexico, are now recommending against the over-the-counter therapies because they do not improve the global symptoms; they do not get those abdominal symptoms.

Now, that's not to say there aren't over-the-counter or healthy interventions that you can try or that we can try for these types of patients. Exercise, it's been shown over and over again, if anybody comes in and says, "Doctor, should I be exercising for my irritable bowel?" invariably, the answer is, "Yes." Diet. She didn't respond to fiber. Fiber made her worse. But it's important for us to realize that there are many different types of fiber. And when we think about using fiber for irritable bowel syndrome, we want to recommend soluble, viscous or gelling, or poorly fermentable, ie, ispaghula or corn husk, what we find in psyllium; that's been shown to be effective.

And then there are dietary changes, the Modified National Institutes of Health Care and Excellence Guidelines from Europe and then low FODMAP [fermentable oligo-, di-, and monosaccharides and polyols] diets. Historically, I've always thought of the low FODMAP diet as been more beneficial for IBS-D [IBS with diarrhea] as opposed to constipation, but there is some data suggesting it improves constipation. Although anecdotally from my experience, I do get improvement in the abdominal symptoms from the low FODMAP diet, but haven't found that it's really effective for constipation. And that may be that, with constipation, there's more than meets the eye and there can be more than just IBS-C.

So when somebody like Sara comes into my office, we talk about these sorts of things. We talk about reducing stress, getting more sleep, those can be factors that exacerbate symptoms. And then when those don't work, we start thinking about more pharmacologic agents.

So, Dr. Cash, can you tell us a little bit more about the pharmacologic therapies that IBS-C patients can try?

Dr. Cash:
Sure. Now, there's a number of different pharmacologic therapies that are available, and most of these cause secretion of fluid into the GI tract. So I'm going to start with actually some of the over-the-counter therapies. You mentioned fiber. The way fiber works is that it holds on to fluid in the GI tract. It also creates a bit of a viscous mucilage that helps ease the passage of stool. It's not a prokinetic per se. And you alluded to the fact that it can increase bloating, and that's its major side effect. You know, fiber and lifestyle modifications, as you alluded to, are always the first-line therapies that we try to endorse for our patients.

We also have osmotic laxatives, and those also can help the symptoms of constipation. And there are first-line therapies for chronic constipation, you know, a condition where patients don't have as much pain. They're reasonable to use for irritable bowel syndrome with constipation, but they may be incomplete in terms of improving those pain syndromes as well as the totality of symptoms.

Stool softeners are frequently used, docusate-type products. I find that these really don't have much of an evidence base for irritable bowel syndrome with constipation. It's a similar story, as with the other OTCs; they don't seem to help pain very much. They really, I think, have a place for the acute therapy of occasional constipation, not so much chronic constipation.

And then, you know stimulant laxatives and some of the other over-the-counter therapies can also help constipation, but sometimes they can actually cause more crampy abdominal pain and worsen patients' symptoms.

So that moves us to the pharmacologic therapies. And I alluded to the fact that most of these agents work by bringing fluid or trapping fluid in the GI tract. We'll start with the chloride channel activators, lubiprostone. That's an agent that activates chloride channels in the gut, primarily in the small intestine, and causes the secretion of chloride into the gastrointestinal lumen; sodium wants to follow, so now you've created this osmotic gradient, and water remains in the gut.

We also have guanylate cyclase-C receptor [GCC] agonists, and there's 2: linaclotide and plecanatide. These both work through a very similar mechanism of action. They bind to a specific receptor called the GCC receptor, and they cause active secretion of chloride and bicarb as well as sodium into the gut, and fluid. Now, in terms of tolerability and evidence, all of these agents have been shown to be effective for not only chronic constipation, but also irritable bowel syndrome with constipation with improvement in constipation symptoms, but also abdominal pain and a composite definition of IBS response.

There are some potential adverse effects with lubiprostone. You can have diarrhea, and you can also experience nausea if taken on an empty stomach. It does seem to be dose related. There are several doses available. The dose for irritable bowel syndrome with constipation is 8 mcg twice a day. The dose for chronic idiopathic constipation, 24 mcg twice a day. It's important to tell our patients to

take this medicine with food.

Now with regards to the linaclotide and plecanatide, linaclotide comes in 3 doses: 72 mcg once daily, 145 mcg once daily – both of those are for chronic idiopathic constipation – and then the 290-mcg dose once daily for irritable bowel syndrome with constipation. The major adverse event that's seen with linaclotide is bothersome diarrhea. Most patients in the clinical trials who experienced this did not stop therapy. And it can be a very effective therapy for some of our patients.

Plecanatide is similar. The difference between these 2 agents is it's thought that plecanatide has more binding activity in the small intestine where the pH is a little bit lower than the colon. And it's thought that perhaps that may mitigate some of the diarrhea side effects, but we do see diarrhea in patients who take plecanatide. The dose for both chronic idiopathic constipation and irritable bowel syndrome with constipation are the same. And that's 3 mg once daily. Again, can be effective for some of our patients.

So that's really what we've been utilizing in terms of pharmacologic therapy and prescription therapy for patients with IBS-C. But there are some newer approaches to treating IBS-C. Dr. Brenner, can you give us some insight on the new class of IBS therapies, the NHE3 inhibitor?

Dr. Brenner:
Yeah, so this is to your point, a new class of therapy. The sodium/hydrogen ion exchange subtype 3 channel, not receptors – like the drugs you mentioned bind to receptors – but channel inhibitors. And it's important to note that this is a different molecule, because what I hear from a lot of people in practice is, "Oh, this is just the next PPI [proton pump inhibitor]," meaning that it's the next secretagogue after the ones you mentioned: lubiprostone, linaclotide, plecanatide. But it really has a different mechanism of action. And when I talk to my patients, I really call it a "retainagogue," because it blocks this sodium ion channel and thus keeps sodium in the lumen. Like you mentioned, where you have sodium, you have an osmotic gradient so water is not reabsorbed, but maintains in the lumen.

Now, why is this important? Because when we talk about therapeutics and how we treat patients with IBS, we want to talk about biologic plausibility, right, how can this work? Well, we know for retaining water in the lumen, we're going to take hard stool and make it softer. We know that we're going to distend the intestinal lumen which is going to increase peristalsis. And the faster that things go through the GI tract, the softer they come out the other end. So that explains how it can help for the constipatory symptoms. The abdominal symptoms is even more unique and intriguing because the way this potentially reduces visceral hyperalgesia, or increased pain, is completely different from its predecessors.

So there are a couple of preclinical models that have shown a few different mechanisms of action. One, it seems to close tight junctions. And we know we hear a lot of people talk about leaky gut. And what I really think they mean is microbiota immune-based interactions which activate neuronal signals along that gut-brain inner axis, thus the disorders of gut-brain interaction. And by blocking or closing these junctions, we're reducing these interactions and reducing that pain component.

The drug also seems to antagonize what we call TRPV1 or red hot chili pepper or capsaicin receptors, which again are hyperalgesic pain-inducing receptors. And by blocking them, that reduces pain as well.

So we're talking about a new therapeutic molecule that has a completely different mechanism of action from its predecessors, and thus may improve IBS-C symptoms for a different segment of the population of individuals that suffer from this disorder.

Dr. Cash:
Thanks, Dr. Brenner.

Now, in our final chapter, we'll be hearing from Josephine about her experience with IBS-C progression.

[CHAPTER 3]

Dr. Brenner:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Darren Brenner, and here with me today is Dr. Brooks Cash. We're reviewing a series of IBS-C clinical cases that practitioners commonly encounter in their day-to-day practices.

Welcome back. In Chapter 2, we reviewed a variety of treatments for IBS-C and weighed the pros and cons of classes in individual therapies. Now in Chapter 3, we're going to discuss the efficacy of these treatment options and what this may mean for our patients.

Let's see the last patient in our waiting room. Josephine was diagnosed 5 years ago with IBS-C. At different times in the past, she has been managed with lubiprostone, plecanatide, dicyclomine, and linaclotide. But she's back in the office today because her symptoms have worsened.

Josephine:

Hi, Doctor, I really hope that you can help me. I'm sick and tired of my gut symptoms. I've been diagnosed with irritable bowel syndrome for almost 5 years now. My previous doctor, who recently moved out of town, helped me keep my pain reasonably under control for the most part, using a couple of meds and a dairy-free diet, but things have been slowly getting worse. For the last year, I've been on a few medications that made me nauseated or were too strong, and I got diarrhea. I get this horrendous pain in my stomach more frequently. And my constipation seems to be getting more persistent and severe. I'm also having a lot more bloating, to the point where I look pregnant sometimes. I can't wear my normal clothes, and I'm missing more and more days of work. I just don't know what else can be done.

Dr. Brenner:
So, Dr. Cash, based on what we heard from Josephine, it sounds like her symptoms are not well controlled with her current drug regimen. For the past year, she has been on plecanatide, dicyclomine, lubiprostone made her nauseated, and linaclotide was too strong and she got diarrhea. What treatment approach would you recommend next? And how would you discuss this with your patients like Josephine?

Dr. Cash:
Well, that's a great question. Now Josephine is on the more refractory side. She's tried multiple therapies, including over-the-counter therapies and prescription therapies, and we alluded to the efficacy and the adverse events of those therapies in Chapter 2.

So I'm going to start broadening my differential with Josephine. And one of the things that I would think about in her case is, as a patient with chronic constipation – just the symptom of chronic constipation, regardless of whether it fits into that criteria for IBS with constipation or chronic idiopathic constipation – I'm going to start thinking about pelvic floor dysfunction. This is a common disorder. Somewhere between about 20% to 30% of patients with the symptom of chronic constipation suffer from pelvic floor dysfunction. Now, it's not something we look for right off the bat in many cases because it's not more than 50%. This is a disorder of defecation. It's the muscles of the anorectum and the pelvic floor in terms of their coordination to have an effective bowel movement. And the way that we diagnose this is any number of different tests. We can do what's called anorectal manometry. That's a balloon with pressure transducers that we insert in the rectum. We ask patients to make some maneuvers, and we can see how well they coordinate those muscles. We can also do imaging. We can do old-fashioned defecography, which is rarely done these days, or a functional MRI test. And finally, there's a simple test called a balloon expulsion test where we can also place another balloon in the rectum. We give patients some privacy; we ask them to evacuate that balloon. If they can't do it within 2 minutes, it's considered an abnormal test suggestive of pelvic floor dysfunction. We treat it with pelvic floor therapy. And what I found is that this is often a cause for refractory symptoms. That's really the only signal that I found, and based on my review of the literature, that's the symptom that seems to predict for this, when patients don't respond to different laxative therapies. So I'm going to think about that, and I'm going talk to Josephine about that; we'll talk about the diagnostic tests involved.

The other things that I would think about would be GYN issues. I would want to make sure that she's up to date with her GYN exams, perhaps even consider a pelvic ultrasound. That's low yield. I would make sure that she's had the recommended tests that we do recommend for irritable bowel syndrome with constipation, which is generally a CBC [complete blood count], primarily to look for anemia, and also thyroid function testing.

And then finally, we'd discuss colonoscopy. Now constipation is not an indication for colonoscopy in a young patient who has not reached colon cancer screening age of 45 or older who doesn't have a family history of colon cancer or colon polyps. And it really has low yield. It's not recommended in our guidelines, but we often will see these patients, they've had 1, 2, or even 3 colonoscopies because of their constipation symptoms. We should not expect to find much in terms of a putative cause for constipation symptoms by doing a colonoscopy.

Some patients, however, are going to be reassured by that colonoscopy, and I think that's where we really get into that patient-centered care. For somebody with irritable bowel syndrome with constipation who's suffering from abdominal pain, a colonoscopy is reasonable but low yield. And in Josephine's case, I probably wouldn't go there, and I'd tell her why. But if she really pushed me to do it, I would consider doing that but not expect much to come from that.

So I think that really highlights the importance of shared decision-making in these patients.

Now, it's exciting to see emerging agents with the potential to ease some of the treatment burden when it comes to IBS with constipation. Dr. Brenner, can you put the safety and efficacy of the NHE3s into context for us so that we can better understand how they might fit into our treatment armamentarium?

Dr. Brenner:
Yes. So I think, when we lose, is kind of the way I like to talk about this, and now we have multiple therapeutics that we talked about –

lubiprostone, linaclotide, plecanatide, and now tenapanor – that have all been FDA-approved for treating irritable bowel syndrome with constipation in adults. And they've all proven to be effective and safe. So the question becomes, which one do you use for second, third, and fourth, right? And for those, it's difficult, because we don't have any head-to-head trials looking at it. And if we look at the actual data, when we look at meta-analyses, the answer is really, you're never going to be wrong, right? None of these therapeutics have been shown to be more or less effective than the others.

So for me, then, it comes down to what I like to call my 4 Cs. The first 2, I think, as practitioners, we're all really well aware of, which is cost and coverage. If you can't get it, you can't use it, so we have to be able to actually get it in the hands of our patients so they can see if it can be effective. Compliance, not so much an issue with these medications. They're all pretty easy to take. But then there's the comfort factor, which is the fourth C. And that's not only from our perspective as practitioners, but also our patients. Are they going to be comfortable taking these medications? And I will tell you that a lot of my patients first look at the side effect profiles. What might this do to me? And we look at some of these medications, as you mentioned earlier, lubiprostone stands out as potentially causing nausea. And when I talk about these therapeutics, I mention the nausea, I mention the diarrhea, and the constipated patients always come back and say, "Oh, I'll be thrilled with diarrhea." Now sometimes they don't know what they're getting into when they say that, but we get their point: "I'd much rather have diarrhea, or loose or softer stools, than nausea." And many of the patients come in and they already have nausea at baseline from their constipation. So that helps me choose a little bit.

And when we look at the other 3 medications, linaclotide, plecanatide, and tenapanor, they don't have as much of that emetic type of effect, or at least inducing that symptom of nausea. So we talk about diarrhea. And the diarrhea rates are across the spectrum. Again, we know that diarrhea is very subjective. Some of my patients come in and say, "I have one soft bowel movement a day," and define that as diarrhea. And some of these patients come in and it seems like the drug made them develop an inflammatory bowel disease, and they're having 20 bowel movements a day. So it's really important to ask the patient what they mean.

Now, when it comes to the newer therapeutic, like tenapanor, the diarrhea rates are about 16%, but severe diarrhea much lower, really less than about, I want to say, 2% to 3%. And again, they tolerate this medication very, very well. One of the benefits of this medication, and we know from clinical trials, TEMPO-1 and TEMPO-2, which were 12- and 26-week trials, and I love seeing 6-month data, is that this drug is very effective. We see improvements in abdominal symptoms, including pain, bloating, discomfort, and bowel movements, significant increases in complete spontaneous bowel movements, which means that the patient is completely evacuating by the end of the first week. And these responses are maintained throughout all 12 and 26 weeks of these trials, respectively.

Now, why is that important to somebody like me, and more so to the patient? Because we're talking about a chronic incurable disorder. And so I really don't care if you get a benefit at weeks 1, 2, and 3, I want to see what's going on months afterwards. And we can tell our patients, "You're going to probably respond quickly if the drug works, and it's going to maintainthat response." And the side effect profile is very good. So when I look at compliance and comfort from a patient standpoint, and the efficacy of the therapeutic, tenapanor really checks all those boxes for me as well.

So, Dr. Cash, on that note, do you have any major takeaways for our audience with regards to this conversation this morning?

Dr. Cash:
You know, as we talked about, we often will start with over-the-counter therapies, not as great an evidence base, but they can be effective in some patients. When those are unsatisfactory to our patients, then we generally move on to our prescription therapies.

The thing that I would want to really convey in terms of our takeaway is that we've got a lot of new therapies over the last decade or 2, and really over the last 5 years, that have come to the fore that we can now use their evidence based in terms of showing improvement in multiple symptoms, as well as the overall symptoms of IBS with constipation.

Dr. Brenner:
Unfortunately, that's all the time we have today. So I want to thank our audience for listening in and thank you, Dr. Cash, for joining me and sharing all of your valuable insights. It was great speaking with you today.

Dr. Cash:
Thank you, Dr. Brenner.

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