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Irritable Bowel Syndrome: Clarifying the Vagaries and Improving Patient Care in Women

Announcer:
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Dr. Brooks Cash:
Well, welcome to Women's Health 2024, Beyond the Annual Visit. Today we're going to be talking about irritable bowel syndrome, clarifying the vagaries and improving patient care in women. I'm Brooks Cash. I am the Dan and Lillie Sterling Professor of Medicine at McGovern Medical School. I'm also chief of the Division of Gastroenterology, Hepatology, and Nutrition at the University of Texas Health Science Center. And I am joined by my esteemed colleague, Kavita Kongara, who's the motility clinical chair at United Digestive, Georgia Physician executive committee member at United Digestive, and a physician with the Atlanta Gastroenterology Associates in Atlanta, Georgia. Thanks for joining me, Kavita.

Dr. Kavita Kongara:
Thank you for having me, Brooks.

Dr. Brooks Cash:
Here are our disclosure slides for your review and here are our learning objectives. I'm going to turn it over to Kavita to take over from here.

Dr. Kavita Kongara:
Thank you Brooks. So in general, when we want to talk about a condition, it's important to understand the definition, and Rome IV criteria is really a research tool, but it is helpful to look at the overall definition of what you would think of for one with IBS. So here we're talking about recurrent abdominal pain on average of 1 day a week over the last 3 months associated with at least 2 of the following criteria. So this would be issues related to defecation, changes in stool with the frequency. And when we talk about constipation, generally we think 3 times a week or less and maybe in diarrhea 3 times a week or more. So it's a change in frequency. And then finally a change in the form of stools. So typically loose stools, hard stools, that kind of thing. And you will see a Bristol stool chart, which is very helpful along that route.

So a combination of sort of discomfort and pain with changes in bowel is what defines IBS. The prevalence in the US is anywhere from 7% to 16%, as high as 20% in some studies. That's about 35 million Americans impacted, which really parallels the incidence of GERD. It's more prevalent in women, in this country at least, in patients seeking care. And you typically think of it in individuals that are under the age of 50. So if you have someone who's a lot older and you're thinking IBS, you want to think other things first. The direct medical cost of this condition exceeds $1 billion. In terms of the burden that IBS has on the healthcare system, it's substantial. There's impaired health status that restricts activity for several days per year, about 73 days and up to 38% of patients report having contemplated suicide as a result of their symptoms. And generally we see an average of at least one and a half missed days of school or work and 8 days of

lost productivity every month. And this is not including absenteeism where someone's there but not really producing to their maximal ability because of how they feel due to the condition.

In terms of subtypes, we will hit on this again, but generally we think about IBS diarrhea or IBS constipation and there are patients with IBS mixed. In terms of distribution, we typically see more patients that are female with IBS constipation over male. In IBS-D it's surprisingly more men that might have this, and in mixed it's about equal.

The big burden of this condition is quality of life. And because of symptoms, this nicely shows all the different things that patients have to avoid. On the left you see that often they'll avoid any situation where they don't know for sure there's a bathroom. Also, they change their plans based on if they can hit the bathroom during the day. They're afraid to leave the house. It affects their personal relationships. In terms of overall leisure, patients really are very nervous to travel and fly, especially with IBS diarrhea. They don't really enjoy the activities when they're out, and often they don't feel they're reaching their full potential at work in other events because of this. So it affects their day-to-day and their quality of life. Over 50% of patients said their symptoms feel that they are not normal; they're not like themselves; they're not like other people; they're self-conscious. And so a huge burden that they carry when their condition is not treated adequately.

I'm going to turn this over now back to Brooks.

Dr. Brooks Cash:
Thanks, Kavita, for that great introduction. We're talking about IBS like it's a singular disease, and that's often the way that we teach our trainees about IBS and the way we talk to our patients about IBS. And I really want to try to convince you that IBS is not a singular disease. It really is a syndrome of symptoms and there are multiple causes of irritable bowel syndrome. What we're showing on this slide is just a few that have been identified over the last 30 to 40 years. Now I tend to think of 3 macro disturbances in patients with irritable bowel syndrome. There's altered motility, there's altered gastrointestinal secretion of fluid, and there's visceral hypersensitivity or altered perception from enteric neurons. Now those are the macro disturbances that lead to the symptoms that Kavita talked about in the Rome criteria and those clinical symptoms that patients with IBS share.

However, the causes of those macro disturbances remain unknown. We do know that some patients have psychological drivers or stressors that seem to augment their symptoms. I try not to tell patients that I believe that their symptoms are psychologically driven because they're rarely the cause of their motility disturbances or altered secretion, but they can certainly augment symptoms. We do know that patients can have altered enteric neuronal firing. We often will see this in patients who've had inflammation of some sort, say, from a gastroenteritis episode. There can be a dysbiosis or frank small intestinal bacterial overgrowth through a change in the microbiome of the small bowel. We do see patients who have dietary drivers, often food intolerances or food sensitivities, they notice that they get postprandial symptoms. Sometimes they have the insight to identify certain types of foods, oftentimes they don't. They also have a disturbed brain-gut axis.

And that actually is what we've termed these conditions recently. We've moved away from the term functional GI disorders and now we're calling irritable bowel syndrome and similar disorders, disorders of gut-brain interaction. And we are gaining additional insight into the potential causes. However, we still don't have great diagnostic assays or tests to actually rule in IBS. So it's often a rule-out scenario when we do diagnostic testing. Now if we look at the patient journey, a lot of this has to do with – this is the biopsychosocial model. A lot of this has to do with psychosocial factors and early life events, but there's also a physiologic basis, and you see the motility, sensation, secretion, the response to food as well, the disordered gut-brain axis resulting in increased healthcare resource utilization because of these impactful symptoms of abdominal pain and disordered bowel habits. These can all be playing a role.

There are various places where we can intervene with different therapies, both gut directed as well as directed towards the central nervous system and perception with this biopsychosocial model.

Now you heard Kavita allude to the Bristol stool form scale earlier, and that's what's shown over on the left of this slide. This is a validated scale of stool form that correlates with the amount of water in the stool. Most humans defecate about a hundred ccs of water in their stool per day or when they have bowel movements. Type 1 and type 2 stools are associated with constipation. Types 3 through 5 are considered within the normal range. And types 6 and 7 are consistent with diarrhea. So constipation and diarrhea, especially diarrhea, are defined by stool form. Constipation has other features that define it in terms of the ease or difficulty of defecation as well as the completeness of defecation.

I want you to look at the right for a moment. These terms that we use, IBS with constipation or IBS-C, IBS-D, which is IBS with diarrhea, and there's also a mixed IBS that Kavita alluded to, these are really defined by the presence of abdominal pain, as she mentioned, with disorder defecation. There are 2 corollary disorders of gut-brain interaction, functional diarrhea and functional constipation. These patients have the exact same disordered defecation, but they don't complain predominantly of abdominal pain. I think that this is a very

blurred line. We've got research that shows that, in fact, some of the same patients that I see at different points in time may be labeled as either functional constipation, at a different point in time they may qualify as having irritable bowel syndrome with constipation because of the presence of abdominal pain. So the point here is don't get too locked in to these diagnoses. They are very semantic and imply that IBS patients have pain

Now how do we diagnose this? Well, we should do a good history and physical. This is really the key to making a positive diagnosis of irritable bowel syndrome. History-wise, we want to make sure that we assess how long the patients have had their symptoms? What are the potential triggers? Do they have any alarm features? And what we mean by that is hematochezia, unintentional weight loss, a family history of organic gastrointestinal disease, worsening symptoms despite over-the-counter therapies or perhaps nocturnal diarrhea in the case of patients who we think may have IBS with diarrhea, those sorts of alarm features. And we may do a more directed diagnostic evaluation in those patients. Are there any new medications? What is our patient's diet? And bowel habit diaries can be very helpful.

We want to look for comorbid conditions. There are some that travel with irritable bowel syndrome, very sematic conditions, such as fibromyalgia, interstitial cystitis, or irritable bladder, migraine headaches, and chronic pain syndrome. We see this in an increased frequency in patients with irritable bowel syndrome and it may relate to that visceral hypersensitivity. And then a good physical exam. In patients with constipation or diarrhea, a rectal exam is recommended. That can help us assess rectal tone, especially if patients complain of incontinence, and in the case of constipation, we can get an idea of pelvic floor dysfunction. But we also want to examine the abdomen. All too often we'll see patients who have chronic abdominal wall pain who present with these types of symptoms and they end up getting unnecessary procedures and diagnostic tests. And we want to feel for masses. Especially in women as they age, we want to think ovarian cancer as a possible cause for some of these symptoms as well.

So in terms of diagnostic testing, the patients who have diarrhea as a component of their IBS are going to require more diagnostic testing because the differential simply is larger for patients with diarrhea. What's recommended in current guidelines is to get a CBC in everybody to make sure that they're not anemic. Also to make sure that they're consistent or compliant with their age-appropriate colon cancer screening. Remember that's age 45 for average-risk adults in the United States. Now if we look at patients who have either IBS-M or IBS-D, we want to exclude inflammatory conditions, and we generally do that with a C-reactive protein as well as a fecal calprotectin, a very sensitive test for colonic inflammation. We also recommend ruling out celiac disease, and the best test to do that with is a tissue transglutaminase, and that is an IgA subtype antibody. So we often will get a serum IgA to make sure that we don't miss this in patients who have a selective IgA deficiency, which is a relatively common normal variant, about 4% of the population.

I mentioned stool diarrhea, especially in patients with more variable stool habits. Patients with IBS-M have diarrhea and constipation at least 25% of the time with their abnormal bowel habits. Patients with IBS with diarrhea have diarrhea 25% of the time, at least, with their abnormal bowel habits and constipation less than 25% of the time. And then the converse is true for patients with IBS with constipation.

There are some other tests that are recommended in some guidelines. *Giardia* antigen assay. *Giardia* is a relatively uncommon parasite, but it is the most common parasite in the United States. And if you have the wherewithal to test for fecal bile acids, that's also a potential cause of diarrhea. For IBS-C, there's really not a lot of recommended diagnostic testings beyond the CBC and colon cancer screening. And when patients fail to respond to therapy, then we start doing some more directed testing, especially looking at colonic transit and pelvic floor function.

So I'm going to turn this back over to Kavita and she's going to walk us through a case.

Dr. Kavita Kongara:
All right. Thanks, Brooks, for that comprehensive discussion.

So now let's go to clinic. Let's go to our practice and talk about someone that we typically see, and this could have been any one of my patients last week. So a 25-year-old woman who came to me with persistent abdominal pain, also constipation and bloating. That's one of the most difficult symptoms to treat, but that's part of this symptomatology, and this is not new. This has been ongoing for 4+ years. And as Brooks alluded to, in IBS constipation, there was minimal testing needed really. So she had a CBC to prove she wasn't anemic. She had thyroid tests, which is important to pick up. And really when you see someone like that, they've had basic labs, they're without alarm features, then you're thinking already in your mind, well, could this be IBS constipation? I mean she has the pain part so that would fit.

Well, then you look at what has she done. So she's tried diet; she's tried exercise; she drinks plenty of fluids. All these things are important. Lifestyle modifications, very important in treating bowel conditions. She's done that. She tried over-the-counter laxatives, and most commonly that would be a PEG solution, PEG powder that she makes into a solution. And she's done that and said, hmm, really hasn't helped my overall symptoms. Fiber therapy, the goal is about 25 to 35 g in the US diet, which most people don't do, but she actually tried to do this. That hasn't changed things. And the persistence of the pain and bloating were very bothersome. There's no

rectal bleeding. Again, the labs are normal. Physical exam was within normal limits. The digital rectal exam was normal. So at this point that is a very reasonable thought process to say, wow, am I thinking this is IBS-C? Could I be right? She's tried some things, what do we do? So that's the kind of the case scenario I want to set up. Should be something we see, all of us, every day.

And let's talk about where we go from here. So as I mentioned, you want to exclude any kind of organic disease, if there's abnormalities, if they're anemic, they're bleeding family history, of course you want to rule that out. You want to establish a rapport with the patient. You want to educate, reassure, and also set some reasonable limits. And I think in all the decades I've been practicing with all the areas in GI, IBS tends to be one of the more challenging in the sense that that relationship in that first visit that you build with the patient can make a huge difference. And so absolutely spend some time getting to know the patient, having that honest discussion and educating them about this condition and let them know what you're thinking this might be.

Then you want to categorize in your mind the subtypes. So as Brooks had shown with the Bristol stool form, that makes it very easy. I actually have Bristol stool scale posters in every exam room, and it is very eye-opening for the patient, and they really understand that, wow, having those small type 1, type 2 rabbit small pellets and pebbles, even if I go every day, that's probably not normal. That's constipation. Helps define sort what we're looking at, objectify what's coming in, what's coming out. So that's super helpful. And then there's nothing wrong with talking about first-line therapies. As gastroenterologists, a lot of patients have already tried these when they come see us. But it is important to quickly just go over lifestyle dietary modifications, what OTC things have they done, and then talk about the bothersome symptoms. And after this lecture today, hopefully you'll have some tools in your toolbox because we're going to talk about the FDA-approved prescription therapies, if they're needed. And then I think Brooks at the end will touch on some of the newer psychological therapies and off-label treatments that might be tried as well in particular patients.

In terms of their lifestyle modifications, what does that mean? Simple recommendations. I mean, these days when everyone is on a computer and at their desk and we're not getting a lot of exercise, a 20-minute walk, just starting there. When you move, I always tell patients, your colon moves. So getting up, moving around, it helps the body, helps the mind. That's a necessity. Avoiding constipation meds, meaning constipating drugs. So patients do take medications that constipate. A lot of them put themselves on iron because they're tired, not because they're needing to take iron but just because they did and then they're constipated. So a lot of them are popping tons for different symptoms and that can be constipating.

So it's perfectly fine to take some fiber to help with constipation, but don't be surprised if their overall bloating and cramping and overall pain may not be improved. And the American College of Gastro said, look, it is okay to try it, but you may not get that global relief. You might get some relief more typically if they have chronic idiopathic constipation. I don't always find that relief for the more difficult-to-treat IBS constipation patients. However, it's a low cost. There's very few side effects. And so for other reasons, psyllium may be a reasonable first-line therapy, especially if they're not getting that fiber in their diet. They've been around for over 20 years and over the counter for that long. They improve stool frequency and consistency but they don't reliably improve - again, we're talking about IBS tonight, not chronic constipation. So in terms of that abdominal pain or bloating symptom, they don't often, despite evacuation, relieve that, those symptoms, and that's what we refer to as global symptoms of IBS, some of the more difficult-to-treat symptoms. ACG does recommend PEG. But overall, looking at studies and quality of the studies and the numbers of patients enrolled and these strict criteria used, they recommended against using PEG alone for global symptoms of IBS. And that's what I keep kind of alluding to is they may help some, reasonable to try, especially for mild symptoms, but don't be surprised if you're seeing the patient back because they have residual symptoms. And stimulants, they've been out for a long, long time. I mean we use them, honestly, as sometimes part of our bowel preps, but those are not ideal. They can cause cramping. They sometimes can give you the desired effect of evacuation, but often with many side effects. So they're not typically our go-to or long-term treatment. And there's no long-term trials or data. So the American College of Gastro does not make a recommendation for IBS with stimulants and there's really no randomized studies. We typically prefer osmotic medications if we're going to have them try OTCs, and that includes PEG and magnesium-based products.

This is a nice table that shows the FDA-approved medications for IBS constipation. And tonight we're talking about IBS. So I'm not going to go into too much detail about prucalopride, which is a medication mentioned in this chart because that is FD-approved for chronic idiopathic constipation, not for IBS with constipation. One could argue they're cousins of one another, treated similarly. But for the sake of tonight's talk, we are going to talk about the ones that are FDA-approved. This is a nice summary of all of them, and I'm going to go into each one now, briefly, so that you have an understanding of, again, these tools in your tool chest.

So lubiprostone was the first medication that came out a while ago. It's been a couple decades now. This is approved for women over the age of 18 for both IBS-C and chronic idiopathic constipation and also for opioid-induced constipation and for noncancer-related pain medication use. The dosing is 8 µg twice a day or for IBS or for the other 2 indications, 24 µg twice a day. It can be taken with food, which actually helps with some of the nausea, which I'll show you in terms of the side effect profile that patients can get. And the way that this medication works, I mean patients often will tell you, well, how is it different than a PEG, and how does it actually work in terms

of helping my overall symptoms?

So I think a brief sentence or 2, just understanding the mechanism and explain that to the patient, often really is helpful. So this works on – there are chloride channels in our intestine. This is the chloride 2 channel. It stimulates sodium efflux into the lumen, and then the sodium kind of goes through these paracellular pathways. And because sodium goes in, then water follows. And so you've got water in the lumen, you've got these hard stools that are now more liquidy and softer, and that, then, accelerates transit. So I like to tell the patient this in a very brief, concise way to say the osmotic laxatives that are over the counter kind of bring in water by osmosis, but these work on specific receptors in the intestine to target your IBS.

And in terms of the data, these were phase 3 trials, 12 weeks that looked at patients who took lubiprostone 8 µg twice a day versus placebo. And at the time they looked at the spontaneous bowel movement and abdominal pain response. And at 12 weeks you can see a statistically significant difference between the patients that were given lubiprostone versus placebo. And this is a long-term condition. They also looked at an extension study, which you see on the graph at the right. These patients were defined as monthly responders if they had moderate relief of their symptoms for 4 out of the 4 weeks. So all 4 out of the 4, so every month, or significant relief for 2 out of the 4 weeks. So this was, again, exciting because it was the first FDA-approved medication for IBS with constipation and did have good long-term data in terms of having several months of extended use.

What is the side effect? Because besides patients asking, well, how does this work and how is it different than what I'm doing now, they will absolutely ask what are the side effects? What do I have to watch for? And I make it very clear for these patients, no matter what medication you use, that you may have diarrhea. Anything you take over the counter or with this typically causes an increased diarrhea rate over anything else like placebo or anything else you've tried. And that is very important to educate them so that they know, when they're starting the medications, when to take it. If they're on a commute, maybe not pop a pill before I get in the car before they know when the diarrhea might hit if they have it. You want to prepare them for success and be honest and tell them that these side effects may occur so that they can work with the medication. So in this trial diarrhea was shown, you can see on the table on the left with IBS-C and CIC over placebo, but nausea is notable as well.

And I remember when the medication first came out, patients were taking the medication at any time twice a day. And once we found out that the nausea rates were higher, especially in the chronic idiopathic constipation trial, taking it with food was very helpful. So again, we educate ourselves as to the side effects and we tell the patients, and then that really helps them tolerate the medication if this is the right medication for them. So diarrhea, nausea, and then you see the other side effects listed.

Let's go on to the next kid on the block that came out, which is linaclotide. This is approved for adults 18 and older at the dose for IBS of 290 µg a day, which is the higher dose. And then for chronic idiopathic constipation, there are 2 dosages as well, 145 and 72. What was fairly exciting, I don't treat children, I'm an adult gastroenterologist, but for the pediatric gastros out there, this is the only medication that I know of as of now to have an approval for ages 6 to 17 for functional constipation. So the dose there is 72 µg a day, just good to know that. And then patients would take it a half hour, typically, before the first meal of the day, once a day. The reason being if they took it with a meal, you get that gastrocolic reflex that tends to make people go anyway. And then if there's some diarrhea associated with this product, then you might just increase the diarrhea side effects. So we typically say half hour before your first meal of the day, and it's contraindicated in anyone under 2.

In terms of mechanism of action here, you can see this diagram on the right. So this binds and activates the GC-C receptor, and this receptor in our intestine leads to an increase in cyclic GMP, both intracellular and extracellular. So intracellularly you could see, through the CFTR, this sort of results in chloride secretion into the lumen followed by bicarb into the lumen. And then you have the fluid that follows. So that accelerates transit. And extracellularly, there is evidence in animal models that the increased cyclic GMP can decrease afferent firing of visceral nerve pathway. So that decreases pain. Because you want to see more liquid bowel movements through this mechanism, but you also want to see an improvement in pain. So that is the mechanism there.

And in terms of the trial here, the efficacy was established in 3 randomized controlled trials with the primary endpoint or success being defined in this trial as a 30% or more reduction of the worst abdominal pain score and an increase in one complete spontaneous bowel movement, both for 6 or more of the 12 weeks that was studied. And you can see there's a statistically significant difference in the purple bar, which is linaclotide over placebo. And this was, I believe, the first trial to change that definition of spontaneous bowel movement to complete spontaneous bowel movement.

And that is important, that's remarkable, because what that means to my patient is I go and I'm done, it's complete. I do not have to keep going back 2, 3, 4 times to get the stools out. So that definition by the FDA has actually increased, I guess, the bar in terms of what patients had to define to actually respond. So that was a more rigorous endpoint. And the side effects, as predicted, there's diarrhea rates in both the IBS and the CIC trials. You can see that with linaclotide over placebo, and many of these patients start off with less

than 1 or 2 movements per week. So again, super important to be very clear on this and say, look, the diarrhea rates are higher, efficacy is good, as stated, but this is something I want you to know. And they are prepared, and then it is not catching them by surprise. And you can see some of the other side effects listed.

Then to compete, came on the block, plecanatide. And this is approved for adults over 18. This is dosed once a day as well. Three mg once a day, contraindicating kids. And this can be taken with or without food. And this is sort of a unique nuance on the last medication. It's an analog of naturally occurring uroguanylin by, like, 1 amino acid. They changed it, and that protein works in a pH-dependent manner throughout the intestinal tract starting from the stomach on through the colon. So the idea is it's a nuance where typically you have more secretion of water where you want it and less secretion of water theoretically in the colon. So with that diagram on the right, plecanatide also, through that specific uroguanylin protein, works through the GC-C agonist and activates the CFTR. You get chloride and water in the lumen and then you get moister, softer stools and also you get decrease in pain firing. But again, slight nuance on the mechanism here.

This is the data in terms of the studies with plecanatide in phase 3. So Study 1 and Study 2, you see here the overall responder was defined similarly to the last trial as a 30% or more reduction in abdominal pain plus an increase in one or more complete spontaneous bowel movement from baseline in the same week for 6 of 12 weeks. So very stringent kind of criteria. They had to have what you want patients to tell you they're better with, not just I'm going more, Doc, but I'm also having improvement in pain in the data. So this was significant in both trials. And this is sort of interesting amongst side effects listed in trials. This was it. More than what occurred in any other trial, it was just diarrhea. And so you can see placebo versus plecanatide, and I of course still tell my patient that this potentially can happen, but quite remarkable that that is the only notable side effect with this product in the studies that were conducted.

Finally, the newest kid on the block tenapanor, this kind of changed things up a bit. So this is approved for adults 18 and older. It's dosed 50 mg twice a day, not for children, and you take it immediately before the first meal of the day and before dinner. And what I meant by this change things up is the mechanism of action is different. This works on a different receptor. The first 3 that I mentioned, we think of them as secretagogues, because through one receptor or the other, you saw that they increased fluid secretion, and that's how they worked on similar receptors. Here, this is the first-in-class medication that works on the sodium/hydrogen isoform 3 exchanger inhibitor. And basically, that is a receptor that, ultimately, the way the medication binds to it leads to decreasing sodium absorption. And if the sodium absorption is decreased, you have more sodium in the lumen and thereby – guess what? – water follows. And so you have more fluidity to the stool and you have softer stools. It also works, that's the first mechanism, by blocking that dietary sodium absorption. So you have this fluid stool, but the second mechanism, that decreases intestinal permeability, and the third is that it decreases visceral hypersensitivity. So it's sort of a triple-action new mechanism first in class for a different type of option for these patients.

And these are the trials. So there's T3MPO-1 and 2 published in our American Journal of Gastro. And both studies showed that the patients did respond. This was approved in 2019 with the definition of response being greater than or equal to 30% reduction in worst abdominal pain as well as an improvement in one or more complete spontaneous bowel movements, both in the same week for the 12 weeks of the trial. So pretty rigid, again, criteria. And you can see the response for, on the left, the combined response. And then on the right you can see the tables for the bars for abdominal pain, which is statistically significant as well as separately complete spontaneous bowel movement. This, again, side effect is diarrhea as well as some of the other side effects listed. And just a reminder, again, this is just for adults, not for children.

That sort of concludes our options for the secretagogues and the retainagogue, which was tenapanor, that we talked about. And I kind of bring it back to our case now that we kind of have heard about the prescription options and also the other things that you would've already tried, the dietary and the OTCs. We go back to our 25-year-old who has persistent abdominal pain, constipation, bloating over the last several years. Well, now we're armed to help her, right? So you have lots of options here. She typically didn't respond to OTCs, had persistent bloating and cramping. I would probably dive in, honestly, to one of the secretagogues. So either linaclotide, plecanatide, or tenapanor. And for realities of practice and what's approved, typically, we might do linaclotide with the different options of dosing and adjust as needed, and hopefully this will be better for her to help with her global symptoms, and that's typically how I'd approach this.

So with that I am going to turn this over to the other side, which is IBS-D. Brooks, back to you.

Dr. Brooks Cash:
All right, thanks Kavita. So yeah, we'll talk about the other extreme of IBS and that's IBS with diarrhea.

Now I've got another case for you. This is Roberta. She's a 45-year-old woman who's been diagnosed with IBS with diarrhea. You can see her medical background. She has an elevated BMI. She was diagnosed about 2 years ago by her primary care provider, but she never followed up with regards to her IBS with diarrhea. She has had a long history, 10 years of abdominal pain and diarrhea. She doesn't have any known gastrointestinal disease, she's never had any surgeries, and she doesn't have any alarm features. So no GI

symptoms that would make us think that she has something else going on, and she doesn't drink any alcohol, in terms of her social background.

She describes her symptoms as having basically consisting of 3 to 4 loose stools per day. She describes around 50% of them being Bristol stool form type 6 or 7. She does not have nocturnal diarrhea. She's not been recently traveling. She doesn't have fevers that would make us think of infection. She has occasionally had incontinence. That's an important question to ask. Patients aren't typically going to volunteer that information, and she has urge incontinence, which simply means that she can't make it to the toilet in time. That's different than passive incontinence. She's tried probiotics as well as antispasmodic therapies. She self-medicates with loperamide, which is available over the counter, and she does take some lorazepam to help her sleep and actually says that she has a little bit of improvement in her symptoms. So we've got a lot of therapies that we can try with her. Now I've put little asterisks by the therapies that are FDA-approved, and you can see among this entire list there's 3 medicines that are approved for IBS with diarrhea by the FDA.

A lot more therapies available. Now our patient's already tried probiotics. Generally we will try modulation of gut flora with different diet and we often will do a low-FODMAP diet. Bile acid agents or bile acid-binding agents for bile acid diarrhea can be tried. We'll talk a little bit about that. She's tried antispasmodics. I'll give you some data on that. And then we've got serotonin antagonists, which slow motility, as well as opioid receptor modulators. Recognize that loperamide is an opioid receptor modulator; it's over the counter. We also have some prescription availability or agents available in that group. And then neuromodulation, what we mean by this is really low-dose antidepressant therapies in the form of tricyclic antidepressants, and there's some others that can be used as well as behavioral therapy.

So let's talk about diet. This is always one of the first-line recommendations. Same thing for IBS with constipation. We recommend, and you heard Kavita talk about, fiber and PEG increasing exercise, changing the diets. Same thing applies for patients with diarrhea. One thing we've recognized over the last decade or so is that FODMAPs, which stands for fermentable, oligosaccharides, disaccharides, monosaccharides and polyols, it's a bit of a mouthful, can contribute to gastrointestinal symptoms. These are basically poorly digested sugars and carbohydrates for the most part. And you can see fructose, raffinose, sorbitol, which is in sugar-free products, and fructans, high amounts of fructans in wheat, rye, as well as things like onions, leaks, and zucchini. It's really common to get a patient tell you that they don't tolerate onions and they take onions and they get diarrhea and bloating and abdominal discomfort. There's lots of theories as to why these foods cause these symptoms in patients. We don't know exactly why. Some of it may be enzyme deficiencies with regards to some of the disaccharidases, the enzymes that break down sugars like lactose and sucrose. Some of it may be bacterial fermentation. But the bottom line is, and this is some theories behind where these symptoms may come from, these foods induce luminal changes which then result in changes in motility as well as sensation and can produce IBS symptoms. And when you reduce these foods in the diet, it's been shown in multiple studies both within as well as outside the US that IBS symptoms can get better.

Now it's important to use a skilled dietician to do this. It's not fair to patients to just tell them to try a low-FODMAP diet because they won't do it the right way. And actually we run the risk of engendering eating disorders. So it starts with a motivated patient, that's really key of any dietary therapy, and you do a highly restrictive diet for about 4 to six 6, taking out as many culprit foods in the different FODMAP groups as possible. And then if patients get better, you gradually reintroduce foods containing individual FODMAPs over time. If they don't respond and don't get better to the highly restrictive 4- to 6-week trial, then you're done with a FODMAP diet. They can return to their previous diet and you look in other directions in terms of treatment, and then you gradually should personalize this. This is not meant to be a highly restrictive diet forever. So it's meant to be modified and personalized as we move forward.

Probiotics, lots of controversy. Our 2 major societies, the AGA and the ACG, both recommend against probiotics for irritable bowel syndrome with constipation or diarrhea. Lots of our patients are going to try probiotics. Some of them will say that they feel better on them, and I never argue with them with regards to that. There is some data to support the use of probiotics, especially for symptoms like bloating in IBS with diarrhea, but they don't seem to affect stool form or abdominal pain dramatically. And that's why our societies don't recommend them. They're not thought to be harmful, but they're also probably not terribly useful.

Same thing for antispasmodics with one exception, and I would highlight peppermint oil. This is a really simple antispasmodic and that's exactly what it is. It's a calcium channel blocker because the primary ingredient is L-menthol. There are multiple meta-analyses involving about a thousand patients with irritable bowel syndrome symptoms that continue to show global improvement in IBS symptoms, especially with abdominal pain. Now they really don't change stool form, so you're not going to change somebody's diarrhea to a solid stool or constipation to a softer stool. So I really reserve this for patients who have abdominal pain. I have them use it as needed. I prefer to use the triple-coated preparation that's available over the counter. This way patients don't get the side effect of GERD or dyspepsia as often. And that's shown some promise in clinical trials. It's ideal to use an enterically coated preparation. So patients will often tell you they drink peppermint tea or they have peppermint capsules. Really you want to use enterically coated peppermint. You want deliver this to the small bowel because that seems to be where it's most active and where this pain is originating.

Let's talk about the 3 FDA-approved therapies. Rifaximin is the first. This is a poorly absorbed antibiotic. Now this doesn't kill a lot of bacteria, but it seems to change the behavior and the replication of gram-negative and anaerobic bacteria. It is approved for IBS with diarrhea. There's been 3 randomized controlled trials with nearly 4,000 patients in these trials. The nice thing about this is that it's a nonabsorbed medication, so its adverse events are similar to placebo, and you can see in the TARGET 1 and TARGET 2 pivotal trials that not only adequate relief of global IBS symptoms was achieved at about 10% greater rates than placebo, but adequate relief of bloating was also achieved. So those are the cardinal symptoms that I target with rifaximin.

Now there's a third trial that looked at repeat treatment. One of the things that we notice with rifaximin is that when we treat patients, if they improve with their IBS with diarrhea symptoms, it's not uncommon, in fact, about two thirds will gradually have recurrent symptoms. And this was a re-treatment trial which showed that when you re-treat people with rifaximin, and the dose is 550 milligrams TID for 2 weeks, that they tend to respond again. Remember, we haven't done anything about the motility disturbances and so these patients can redevelop a dysbiosis or perhaps even bacterial overgrowth. And so that's the rationale for treating. Again, they used up to 2 repeat treatments in this study and that's what the label will include. But I generally will treat patients whenever they say that they need to be re-treated. When they have recurrent symptoms, they tend not to be as severe as they were prior to the successful rifaximin treatment.

Now if we look at adverse events, as I mentioned, this is a very well-tolerated medication. The side effect profile is essentially equivalent to placebo. And so that's a nice aspect of this medication.

Next, we'll move to something called eluxadoline. Now this is an opioid modulator. It actually is a receptor agonist at the mu- and kappa-opioid receptors, and it's an antagonist at the delta-opioid receptor. Now remember, the mu receptor is the same receptor that loperamide and diphenoxylate work on. It slows motility. It's also the same receptor that is involved in analgesia in patients taking narcotics for chronic abdominal pain or other forms of pain. So 2 randomized controlled trials with eluxadoline, about 2,400 patients roughly. And what you see here, they looked at 2 different doses, a 75 mg dose as well as a 100 mg BID dose. That's the standard dose.

They did show statistically significant differences in the composite endpoint responder, which is an improvement in abdominal pain. At the same time, patients had an improvement in their diarrhea. Now there are some adverse events that you need to be aware of. Constipation with this medication was an adverse event. There were some rare cases of sphincter Oddi spasm and pancreatitis. It's particularly important to not use this medication in patients who don't have a gallbladder. Every patient that had sphincter Oddi spasm, and there were 8 out of the clinical trials, did not have a gallbladder. And that's been identified as a risk factor for that symptom and that condition. With regards to the pancreatitis, it's a lot less clear. There were only a few cases of pancreatitis. They may have been related to the effects of this opioid agonism on the opioid receptor with the sphincter of Oddi, but some of the patients were heavy or binge alcohol users and that may have also contributed to their pancreatitis. So it is in the label recommended that you do not use this medication in patients with heavy alcohol use.

Now there's another randomized controlled trial. This is actually a phase 4 trial. So this is done after this drug was approved. This is a study that was done in patients who had previously tried loperamide and not had adequate relief. This is called the RELIEF trial. These patients were randomized to placebo or eluxadoline. They had a slightly more stringent endpoint definition, which was a 40% improvement in abdominal pain at the same time that patients had improvement in their diarrhea. And you can see that they did hit that statistically significant difference compared to placebo for the composite endpoint that I just mentioned as well as stool consistency and abdominal pain. So even if you have patients who failed loperamide or not responded adequately to loperamide, which should not be expected to improve global symptoms because it doesn't seem to do much for pain, this isn't a reasonable option to use for those patients.

I mentioned the dose is 100 mg twice a day. There is a lower dose that can be used in certain patients, and you can see those criteria listed there. And I also mentioned the cholecystectomy or absence of a gallbladder contraindication. And really you just don't want to use this medication in anybody with a history of pancreatic biliary disease. Also, it's not been studied in patients with severe liver impairment, and you shouldn't use it in patients who drink more than 3 alcoholic beverages a day.

This is a busy slide, and I just want to highlight that we do think, and some experts believe, that bile acid diarrhea may be present in up to 50% of patients with IBS with diarrhea. Now there's no strong, strong data to corroborate those numbers, but we do find in some studies that there does seem to be an increased prevalence of bile in the stool or increased prevalence of bile acid diarrhea. Now we don't have any specific therapies for that, but we often will use bile acid sequestrants. This can theoretically slow diarrhea. We use this for chronic functional diarrhea a lot. We do not know whether or not these therapies improve abdominal pain. At least initial studies that have been done, and they're all very small and quite anecdotal, have not shown a dramatic pain relief effect with bile acid sequestrants. But if patients are really bothered by frequent loose stools with urgency, this may be an option for them. Remember, you do need to be careful with other medicines and separate other medicines from bile acid sequestrants to avoid them binding those medications.

What about neuromodulators? Well, antidepressants can work in IBS. We call these neuromodulators when we discuss this with patients, but I also tell them that they are antidepressants. The best data supports the use of tricyclic antidepressants.

SSRIs do not seem to help as much with irritable bowel syndrome. In fact, they tend to be agitating and can worsen abdominal pain as well as diarrhea. So the best data supports low doses of tricyclics 10 mg, 25 mg, perhaps going as high as 75, maybe every once in a while 100 mg. By that time you start to get some side effects. So most people are going to respond to 25 to 75 mg QHS if they're going to respond to these medications. And we use these medications primarily to target abdominal pain. And this has been shown in other pain conditions such as the ones I mentioned earlier, fibromyalgia, chronic pain syndromes, migraine headaches. These help patients with chronic pain or chronic somatic symptoms. They really don't do a lot at the doses we use in terms of motility or constipate people, but you do need to be aware of those potential side effects. But start low, titrate slowly, about every 4 weeks or so is what I use in my practice before I even titrate to the next dose. And I usually will stop at about 75 mg with these medicines.

There's a recent very nice study that was published in *The Lancet* looking at tricyclic antidepressants in primary care. This is a study of patients with irritable bowel syndrome in the UK. They use low-dose amitriptyline versus placebo. And as you can see from the scores here on the right, that patients had a statistically significant improvement in their IBS symptom severity scores when they were placed on low-dose amitriptyline, and they were allowed to self-titrate to some degree, compared to placebo. They actually did not show an improvement in patients' mental health parameters, which is at those doses you wouldn't expect any. But their primary improvement was in their global IBS symptoms and probably deriving mostly from their improvement in abdominal pain. And this was an actually 6-month-long study. So it's a nice, durable, long study that is really the most sizable and well-done study of TCAs in this patient population.

Now we also have behavioral therapies that we can use. And what I mean by these are things like gut-directed hypnotherapy, cognitive behavioral therapy, mindfulness meditation, and relaxation training. And there is abundant data to support the use of these approaches in patients with bothersome IBS symptoms. Not only IBS with diarrhea, but also IBS-M as well as IBS with constipation. The hard thing is to find a clinician, a psychologist who's got the appropriate training to provide this, but they do exist and you can go to the Rome Foundation website to look for these types of therapists and find them in your area, hopefully. So I do encourage you to think about this. We don't offer this typically first line, but a patient's got to be properly motivated and have appropriate insight. But as I tell my patients, the mind can augment the gastrointestinal symptoms that you experience, and if we can get some control over our response to our symptoms, we can often suppress and minimize those symptoms.

So as we talk about our case, we'll bring this back. We've diagnosed her with IBS with diarrhea and we can treat her with any of those therapies we talked about. I would generally treat her with empiric rifaximin because it's a 2-week course, if we can get it approved by insurance. It's a very safe therapy. If it works, that's wonderful. If it doesn't work, we can move on to something else. She does have some urge incontinence, so I would have a low threshold, because she does still have her gallbladder, to put her on eluxadoline if the rifaximin didn't work. And then we can go on down the list with these various therapies. She may not want to do that. We may have issues getting those medications and having that list at hand for other things that we can try, I think, can be helpful.

What we've tried to highlight today for you is that IBS is a common chronic disorder of gut-brain interaction, and it's really a syndrome of symptoms with multiple diverse etiologies. We diagnose IBS in a positive fashion, incorporating those Rome criteria that we went through, a thorough history and physical exam, and limited diagnostic testing based on the absence of alarm features and our clinical suspicions. And then we went through a lot of the treatments for irritable bowel syndrome, including diet, lifestyle modifications, as well as over-the-counter therapies. And then the prescription therapies for IBS with constipation as well as IBS with diarrhea. And these therapies are quite appropriate. In fact, this entire approach is quite appropriate to initiate in primary care. Primary care actually sees more IBS patients than gastroenterology. Yes, it's a high percentage of our patients, but we tend to see the referral cases of these patients. Our primary care colleagues are on the frontline of taking care of these patients. So it's absolutely appropriate, just like treating patients with gastroesophageal reflux disease and other common GI disorders. And then certainly don't hesitate to refer these patients to specialty care if they have severe or refractory symptoms.

So I want to thank my cohost, Dr. Kavita Kongara, and I look forward to engaging with you all, and I know she does as well, in the question and answer session.

Kavita, do you have any last comments that you'd like to make?

Dr. Kavita Kongara:
I sure do. First of all, I want to thank you, my esteemed professor, friend, and colleague for inviting me to do this. I agree with everything that Dr. Cash had said. I had a hybrid career with academia for the first decade and saw some of these very complex patients and now in private practice for almost 15 years. We all see, this is my point. So I saw it in academia; I see it in private practice. You see all levels of these patients. Being female, I probably see a lot more than some of my colleagues because a lot of women in this country that seek

care are very frustrated and they want a diagnosis and they seek another female. But the bottom line, I will tell you, is it is challenging, but we have so many more options now as opposed to when Brooks and I probably started 20+ years ago.

There are options for both IBS diarrhea for both IBS constipation. So not every patient is going to need a medication. There are different pieces of this puzzle to solve and there are predominant symptoms in one over the other. It's a syndrome as he talked about, but there are tools in our tool chest. They are complex and sometimes challenging patients and it takes relationships. But we have the tools. So don't be afraid, just be confident in your diagnosis. When you think it's IBS, guess what? You're probably right and go ahead and treat the patient. You will have the most grateful patients out there in terms of improving their overall quality of life. And so it's not just quantity of life, but quality of life. And this is one of those conditions. So don't be afraid to make the diagnosis, use those tools in your tool chest. But Brooks and I and our colleagues are here if you need us after that point in some of the more difficult or refractory cases.

So thank you for inviting me again, Brooks. It's an honor to be here, and I look forward to some of the questions in theQ&A session as well.

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