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Chairperson's Perspective: Innovative Approaches to IBS-C: Personalized Treatment for Better Outcomes

Announcer:
Welcome to CME on ReachMD. This activity, titled “Chairperson's Perspective: Innovative Approaches to IBS-C: Personalized Treatment for Better Outcomes” is provided by Prova Education.

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Dr. Brenner:
This is CME on ReachMD, and I'm Dr. Darren Brenner, professor of medicine and surgery in the Northwestern University Feinberg School of Medicine at Northwestern Memorial Hospital in Chicago, Illinois. Today, I'll be highlighting the key messages presented at a satellite symposium by Prova Education at a recent meeting in San Diego, California.

Now I think a good place to start is with defining irritable bowel syndrome. I think most of us know that IBS is a disorder of gut-brain interaction characterized by chronic abdominal pain associated with alterations in bowel habits. It's, in fact, one of the most commonly diagnosed GI conditions, and almost a third of all GI referrals are for irritable bowel syndrome. It's important to note, however, that the vast majority of practitioners still consider irritable bowel syndrome a diagnosis of exclusion, despite the fact that both the American College of Gastroenterology and the American Gastroenterological Association recommend a positive diagnostic strategy for making a diagnosis of IBS, which means limited to no diagnostic testing. Because studies have shown that all the superfluous testing has resulted in nothing more than billions of dollars of wasted expenditures, not improving symptoms or quality of life in individuals with irritable bowel syndrome.

This is a common disorder. If we use strict Rome-based criteria, IBS impacts about 1 out of 25 Americans on a daily basis. But the reality of the situation is that the Rome criteria were homogenized for international clinical research studies. If we relax the criteria a little bit, we actually find that IBS is diagnosed in about 1 out of every 10 individuals, with the 3 major subtypes—IBS-D, IBS-C, and IBS-M—accounting for about a third, a third, and a third of the population.

So today we're focusing more so on irritable bowel syndrome with constipation, or IBS-C. And to make that diagnosis, patients have to have, more than 25% of the time, a hard or lumpy stool, or a Bristol type 1 or 2 stool more than 1/4 of the time, and a loose, mushy, or watery stool, or a Bristol 6 or 7 stool, less than 25%. So you can see that this is really based on stool texture.

Now the hard part about irritable bowel syndrome is that this is not a one-size-fits-all disorder. There are multiple different pathogenic mechanisms that result in the characteristic IBS symptoms that we see day to day in clinical practice, and this slide just highlights a few of the ones that we have identified.

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Now when we look at treatments of IBS, specifically pharmaceuticals, we see, and we'll see later, that the numbers needed to treat to an improve an IBS patient usually ranges between 8 to 12, and that's because in 2025 we're targeting the global symptom profile of IBS. And that's great, because we can finally do that, as opposed to targeting 1 symptom. But if we want to practice more precise medicine, as it relates to IBS, then what we have to do is identify the underlying causes, like the ones here, come up with accurate diagnostic tests for identifying the cause, and then target our treatments to the cause, not to the symptoms themselves, and we'll see those numbers needed to treat reduce.

Why do we want to get there and get there quickly? Why do we want a positive diagnostic strategy? Because IBS has a major impact on quality of life. This is an older study. It goes back about a decade. This was the IBS in America study. It asked patients, how are your symptoms impacting you? And when we look at IBS-C patients, three-quarters of them say that they are frustrated with their symptoms. Almost a third feel depressed because of their symptoms. And when we look at this compared to other disorders, patients with irritable bowel syndrome say the quality of life impact is as bad as having end-stage renal disease on dialysis or New York Heart III or IV stage heart failure. In fact, if we go back a decade, my colleague Doug Drossman did a study on 2,000 people with IBS around the world. And Doug asked these patients, “If I could cure you of your IBS symptoms on the spot, would you be willing to give up part of your life?” And invariably, people said yes. As a matter of fact, the average person said they would give up a quarter of their life left, which averaged out to 15 years, for a cure for IBS on the spot. So that shows us the burden of illness that is irritable bowel syndrome and why we have to come up with better treatments.

Now I think a lot of us begin with dietary modification. This is important because the societies recommend them, the data supports it, and if you ask IBS patients whether or not you think foods are triggers for your symptoms, more than 80% of individuals will say yes. If you ask gastroenterologists, “Do you think diet changes can be as good if not better than pharmaceutical management?” they'll say yes as well. And there are lots of diets that have shown efficacy for treating irritable bowel syndrome. Probably the most robust data is for the low FODMAP diet. And historically, we thought about this being effective for IBS-D or IBS-M, but there is now data showing that it's really subtype agnostic, and the low FODMAP diet can be useful in IBS-C. But we talk about the restrictions, and many people don't want to eliminate as many of the foods as they have to. We don't have to do that. Now we talk about a FODMAP-like diet, where all we restrict are fructans and galacto-oligosaccharides. And data from the University of Michigan, at least pilot data, has shown this can potentially be as effective as the full low FODMAP diet. There's also data for fiber, gluten-free diets, low carbohydrate diets, and the Mediterranean diets. So that's nice, because it is not a one-size-fits-all process.

But we also have to remember that everybody is different. And when we talk about treating irritable bowel syndrome, it really comes down to shared decision-making.

And I will tell you there are 2 types of people out there, those that live to eat and those that eat to live. And I'm a live-to-eater. So if I had irritable bowel syndrome, I’d tell you definitively, “I don't want you to change my diet. I’d like to look at something different.” So we have to discuss with our patients all the potential therapeutics that can be useful for treating irritable bowel syndrome, or specifically here, IBS-C.

So when we think about treating patients with irritable bowel syndrome, we talk about the criteria from Rome III, IV, or everything before. There's one major take-home message, knowing that we have had more than 4 decades of criteria for irritable bowel syndrome, and that is that the sine qua non set of symptoms are abdominal pain or discomfort. Now if you look at the criteria for Rome IV, you see pain. If you look at the criteria for Rome III, you see pain and discomfort. And that's because, as I said before, the criteria are homogenized for international use, and more than half of the languages around the world do not have a definition for discomfort. But I'll tell you, in the United States, when I see patients with IBS, they don't complain of sharp, stabbing pains; they talk about bloating, distension, fullness, the blahs, “I don't feel good after eating.” And all these, in a clinical setting, should be considered a part of that IBS spectrum.

Now why am I focusing on pain and discomfort? Because we're talking about, again, a disorder that has visceral symptoms, these types of symptoms, and bowel symptoms. And if we look at the therapies that are out there for treating IBS, a take-home message is that none of the over-the-counter therapies, with the exception of soluble fiber, have ever been shown to improve abdominal symptoms like pain, discomfort, and bloating. In fact, in clinical trials for IBS, some of the over-the-counter therapies have actually made them worse. So if we're looking at treatments to get the totality of IBS symptoms, and we know that's what our patients want, because when we do patient-reported outcome studies, they say, “Treat my abdominal symptoms and my bowel symptoms at the same time,” then we're really looking at the FDA-approved therapeutics.

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And for IBS-C, there are 4 FDA-approved therapies that break down into 2 separate categories: the secretagogues, including the ClC-2 channel agonist lubiprostone, the GCC receptor agonists linaclotide and plecanatide, and now the first-in-class sodium and hydrogen subtype 3 exchanger inhibitor, tenapanor. Now you'll see that the last is noted as a retainagogue, and that's because it has a completely different mechanism of action from its predecessors, the secretagogues, and I'm going to explain why that's important moving forward. And a take-home message here is this – in clinical practice, I hear this all the time – tenapanor is just a fourth-in-class, secretagogue. It is not. And we will talk about the differences in the mechanisms of action.

So how do secretagogues work? Exactly as the name implies. These particular therapeutics bind to receptors in the GI tract. They lead to the secretion of negatively charged ions like chloride or bicarbonate. Because you've created a negative gradient in the intestinal lumen, sodium follows to neutralize the negative charges, and all of a sudden, you have a concentration of sodium chloride or sodium bicarbonate in the intestinal lumen, and that's salt. So you've created an osmotic gradient, and where you have an osmotic gradient, water follows. Now we talk about the biological plausibility of therapeutics for treating IBS. Well, let's think about this. I add water to a hard stool. What does that do? It softens it. And by adding water to the intestinal lumen, I stretch the walls of the lumen, which increases peristalsis, and that improves stool texture as well.

Now when it comes to actually improving the abdominal or visceral sensory symptoms of IBS, here's where things differ. For lubiprostone, there have been a few different trials trying to elucidate the mechanism that improves pain, and they have not come to fruition. We don't know how lubiprostone improves pain. For the GCC receptor agonists, the increase in intracellular cyclic GMP crosses the basolateral membrane and reduces the firing of pain neurons in the sumucosal space, at least based on preclinical and animal models. So we understand that mechanism of action.

But when we look at the data, and granted, this is a little bit of comparing apples to oranges, because there were different endpoints in the lubiprostone trials compared to the linaclotide and plecanatide, what we see is, overall, all these therapeutics work significantly better than placebo, and as I mentioned earlier, with a number needed to treat between 8 and 12.

So let's talk about the new kid on the block, tenapanor. Why do we call it a retainagogue? Because this does not work on a receptor, it works on an exchanger, and it blocks the resorption of sodium and water from the intestinal lumen, ie, these are retained in the intestinal lumen; they are not secreted from the cells. And again, if we have more water in the lumen, the stools are softer, it accelerates transit. We understand that mechanism of action. But where I think the real bang for the buck comes from with tenapanor is on its mechanism of action for pain, discomfort, and bloating. Because we know that a decent percentage of individuals with irritable bowel syndrome have evidence of intestinal or increased intestinal permeability, so there's loss of that barrier function by the loss of tight junctions in between the cells. Now why is that important? Because it allows the microenvironment of the intestinal lumen to interact with the submucosal space.

And what's in the submucosal space are our inflammatory cells. So you get activation of these inflammatory cells, which send signals up the gut-brain axis. That's why these are disorders of gut-brain interaction. And what the brain sends back are signals that say, ouch, ouch, pain, visceral hypersensitivity, increase or decrease secretion and motility. And what tenapanor has been shown to do in preclinical and animal models is close these tight junctions and improve barrier function, thus reducing the symptoms of IBS-C.

Another mechanism is that they also antagonize TRPV1 receptors in the GI tract, and these are hyperalgesic receptors. So by blocking these, you're reducing pain as well. So again, not a fourth-in-class secretagogue, a retainagogue.

And when you look at the data from T3MPO-1 and T3MPO-2, this used the identical endpoint as linaclotide and plecanatide trials, the FDA's endpoint, a 30% reduction in pain, increase of at least 1 complete spontaneous bowel movement a week for 6 out of 12 weeks of the trials. Here we see, again, tenapanor significantly improved symptoms compared to placebo, with a delta of 10 and a number needed to treat of 10.

The question that always comes up in clinical practice is, "If I use one of these therapeutics and it doesn't work, ie, if I use a secretagogue and I want to switch to a retainagogue, is it going to be effective?" And the answer, based on this data from Eric Shah's lab at the University of Michigan, is yes. In people that had previously tried secretagogues, 42% of these individuals responded, compared to 18% in the placebo group. And interestingly, if you look at the group that had already tried secretagogues versus the treatment-naïve patients, numerically, those that had failed secretagogues did better.

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Now the other question always comes up is, “Well, if I fail one secretagogue, can I try another?” And there's data being presented at Digestive Disease Week this year from Greg Sayuk’s lab in St. Louis that says, yes, if you fail a secretagogue and you want to try another one, it can be effective. So we now have data validating that we can move within classes or between classes for treating patients with IBS-C that fail initial therapies.

So how do we know which is best? Well, the honest answer is we don't. On the left is data from a network meta-analysis from Alex Ford’s lab. And what this shows us is that all the therapeutics we've already discussed are better than placebo, but if you look at the confidence intervals, neither of them, or none of them, are better than all of the others. So when it comes to how I treat this with shared decision-making, it comes down to the 4 C’s. Cost. If your patient can’t afford it, they're not going to get it. Coverage. If the insurance company is not going to cover it, they're not going to get it either. Comfort, from the practitioner standpoint and the patient standpoint on the efficacy, safety, and tolerability of the therapeutic. And then compliance: “How many pills do I have to take a day? And am I willing to do that?” That plays a major role in our decision analysis.

But probably the most important thing here is the practitioner-patient relationship. This is not a disorder that's all in patients’ heads. These are not patients that are crazy. IBS is seeped in biological causes and mechanisms. So if we validate our patients’ symptoms, we have empathy for our patients, then the symptoms of healthcare-seeking are reduced, and the patients buy in to the treatment process.

So what is the best treatment process? Integrated or multidisciplinary care, mixing in dietary strategies, like we talked about, with bringing gut behavioral therapies, potentially pharmaceutical interventions, and as long as the patient is involved in the process, the outcomes are always better. In fact, there's data to show that if we use integrative care, as opposed to just a single modality, symptoms, quality of life both significantly improve, as do health expenditures and costs as well.

So at the end of the day, what can I tell you about our symposium? I can tell you that irritable bowel syndrome is a heterogeneous disorder that should be treated as such. There are multiple pharma and non-pharma interventions for treating IBS-C, but the choice of treatment can be difficult because there are no head-to-head studies. All the therapies outperform placebo and all improve global and individual IBS symptoms. Don't forget my 4 C’s, but remember that a better understanding of the pathophysiology of IBS-C will improve in precision treatments and outcomes. Until then, the integrative model works best and most importantly, be a patient advocate and not a pessimist.

Well, thank you very much for joining me, but our time is up. This has been CME on ReachMD.

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