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Mechanism Matters: Retainagogues in IBS-C Care

Announcer:
You're listening to *GI Insights* on ReachMD. This episode is sponsored by Ardelyx. Here's your host, Dr. Brian McDonough.

Dr. McDonough:
Welcome to *GI Insights* on ReachMD. I'm Dr. Brian McDonough, and joining me to discuss the role of retainagogues in the management of irritable bowel syndrome with constipation, or IBS-C, is Dr. Darren Brenner. He's a Professor of Medicine and Surgery and Director of the Neurogastromotility and Interdisciplinary Bowel Dysfunction programs at Northwestern University Feinberg School of Medicine in Chicago.

Dr. Brenner, it's great to have you here today.

Dr. Brenner:
Thanks for having me, Dr. McDonough. It's a pleasure.

Dr. McDonough:
Starting off with some background, Dr. Brenner, how do you typically approach treatment selection for IBS-C, and how does mechanism of action factor into your decision making?

Dr. Brenner:
I think that's a really good point. I really think, as we look at treating irritable bowel syndrome in 2026, that it's a multidisciplinary type of intervention. And in many cases, pharmaceuticals will be involved. And there are two classes of FDA-approved therapeutics. One is known as secretagogues, which include medications like lubiprostone, linaclotide, and plecanatide.

And now, there's a new class of therapeutics known as the retainagogues, with a first-in-class therapeutic known as tenapanor. I have some subtle ways that I think about differentiating what I want to use in my patients, but if we're going to be honest to the practitioners listening to this conversation, it really comes down to the four Cs, if we're going talk about anything first.

And the first two are the most obvious: cost and coverage. If it's too expensive, the patient's not going to pick it up. And if it's not covered by the insurance company, they're probably not going to be able to afford it, and they're not going to use it.

From a practitioner standpoint, I care more about the next two. Comfort--comfort from the patient's standpoint in taking the therapeutic in terms of its efficacy, safety, and tolerability, and comfort from the practitioner's standpoint in terms of whether they want to be able to use the medication. And then compliance--is it the type of therapy that a patient's going to use on a regular basis, or are they going to skip doses because it is too difficult to use? These are the things that I take into account.

After that, I like to look at some of the differences in the mechanisms of action--understanding the process and how these medications can work. But even now, when we think about using these therapeutics, part of where we lag is understanding how to define the underlying causes of the given individual's IBS-C symptoms. So, very often, it is trial and error, and I try to explain that to my patients. I've got a litany of therapeutics that we can try, but what we're going to use first, second, or third may not work best for you. So give me a little bit of time, understand the process, and hopefully, we'll come up with something that is very, very beneficial.

I'll be honest, in clinical practice, I do walk through--because there are four major FDA-approved therapeutics--each of the drugs, what they do, and how they work, and then it's a shared decision-making process with respects to which ones we want to try and give first and foremost. But, again, realistically, as I said earlier, it does in many cases come down to what the insurance company's willing to give for a first-line intervention for these patients.

Dr. McDonough:
Let's dig into that a little more. Can you walk us through the key mechanistic differences between secretagogues and retainagogues for IBS-C?

Dr. Brenner:
Sure. As I just mentioned, there are three major FDA-approved secretagogues. The first that was approved was lubiprostone. This is a chloride channel activator. You get secretion of negative ions into the intestinal lumen to maintain electrolytes or isoelectric neutrality. Sodium follows, you develop sodium chloride, and this is salt. It creates an osmotic gradient, and then there is secretion of water into the intestinal lumen.

Well, we want to talk about biological plausibility, right? So if you have something like constipation--hard stools in the intestine of lumen--and you add water, you're going to take something that's hard and make it softer. Also, the more water you add to the intestinal lumen, the more you're going to stretch the lumen, and that's going to increase peristalsis. And we know that the faster things go through the GI tract, the softer they come out the other end. So we understand the mechanism of action for lubiprostone.

Then there's linaclotide and plecanatide, which are GC-C receptor agonists. They hit CFTR receptors and do the same thing: lead to the secretion of electrolytes into the intestinal lumen, and sodium follows. Now, interestingly, clinical trials have tried to identify how these therapeutics improve the abdominal symptoms: pain, discomfort, bloating, and distension, and for lubiprostone, we don't know. The studies have been negative. For linaclotide and plecanatide, we know that there's actually a chemical made in the cells called cyclic GMP that can actually cross through the cell into the submucosal space and reduce the firing of pain neurons in the submucosal. So this is how some of the secretagogues work.

With tenapanor, however, we have categorized it as a first-in-class retainagogue. It is a sodium hydrogen exchanger, and by blocking the re-uptake of sodium from the intestinal lumen, we retain sodium. And by retaining sodium, we also retain water in the intestinal lumen. Thus, there's a similarity in the mechanism of action. From that standpoint, you're adding water, increasing peristalsis, and accelerating stool transit through the GI tract. But where I think tenapanor really differentiates itself from its predecessors is how it works for pain, because we know a significant percentage of individuals with irritable bowel syndrome develop their pain or visceral hypersensitivity due to the loss of the intestinal epithelial barrier.

There are tight junctions that keep these cells connected. And when you lose these tight junctions, which has been found in many patients with IBS, it opens the intraluminal space to the submucosal space, and you've got organisms in your intestinal lumen that can secrete inflammatory markers. Now, when the cells are tight, those markers can't go anywhere. It's like playing tennis against the wall. The markers just bounce off the wall of the intestinal epithelium, and they can't get in that submucosal space. But when you lose that barrier, then those inflammatory markers can get into the submucosal space and activate the pain neurons. So the pain neuron sends signals to the brain, which is why IBS is known as a disorder of gut-brain interaction. If the brain gets the signal, it sends the ouch signal back down, and you get visceral hypersensitivity.

Now, what does tenapanor do? In preclinical and animal models, tenapanor has shown to close tight junctions and improve the intestinal epithelial barrier, thus mitigating this mechanism for pain. But they also antagonize what we call TRPV1 receptors in the GI tract. And TRPV1 receptors are hyperalgesic receptors. So by antagonizing these receptors, you're also reducing that pain that comes along with visceral hypersensitivity and, in other cases, allodynia. So we understand the mechanism of this drug. It's a completely different mechanism, and I stress that, because in clinical practice, here's what I always hear: tenapanor is a fourth-in-class secretagogue. That couldn't be farther from the truth. It has a completely different mechanism of action.

Dr. McDonough:
Now, from a clinical perspective, how do these mechanistic differences translate into real world patient outcomes or experiences?

Dr. Brenner:
And that's what we need to figure out. The reality of the situation is, there are no head-to-head clinical trials comparing these therapeutics, and the vast majority of the newer therapeutics have been assessed using the same clinical endpoint with very similar responses to therapy, with numbers needed to treat that usually fall within the seven to 10 point range.

The reason why that occurs is because, again, we devise these drugs that are very good at treating symptoms, but they're not targeting the underlying mechanism of action. So we see that range between seven and 10 because we can treat the global symptom profile, but we're not treating the underlying cause. And with respects to IBS-C compared to IBS-D, we lag at identifying the underlying causes for these symptoms. So we can't target them directly. So it can make it very, very difficult.

Dr. McDonough:

For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Brian McDonough. I'm speaking with Dr. Darren Brenner about the role of mechanism of action in IBS-C therapeutics.

So, Dr. Brenner, I'd like to zero in on the retainagogues for a moment. In the Phase 3 T3MPO-1 and T3MPO-2 trials, tenapanor showed significantly higher rates of the combined endpoint, defined as at least 30 percent reduction in abdominal pain and an increase of at least one complete spontaneous bowel movement per week compared with placebo. It also demonstrated improvements in stool frequency and consistency. At the same time, diarrhea was the most common adverse event and led to discontinuation in a subset of patients.

With all of that being said, how do you think about tenapanor when making treatment decisions?

Dr. Brenner:
I think it's an excellent potential first-line agent for treating irritable bowel signal with constipation, especially because we do understand the mechanism of action and how it works. I do think it's more beneficial in some cases for the abdominal symptom component: pain, discomfort, and bloating.

You alluded to the fact that it met the FDA's endpoint for clinical response, and to that, I respond--and I know this is going to be taken as a curt response--but my response is, who cares?

I will tell you that I have never had a patient come back to my clinical practice where I have asked them, have you had a 30 percent reduction in your pain and an increase of at least one complete spontaneous bowel movement a week during the same week for six out of 12 weeks since I last saw you? No, that's not where we go. We want to look at specific symptoms.

So the more important data is actually in the secondary endpoints. And what the secondary endpoints show is this: you can reduce abdominal pain by about 50 percent with this therapeutic from baseline. You can reduce bloating by about 50 percent from baseline.

Astonishingly, in these clinical trials, the average individual that enrolled in these studies was having one good bowel movement every 10 weeks. So I ask our audience to think about that: one good bowel movement every two and a half months. By the end of the third or fourth week of treatment, the average individual in these trials was having three-plus good bowel movements a week. So having three bowel movements a week where they are saying, I've had complete evacuation of my stools, is an improvement of about 32 to 33 times baseline.

The other thing the studies show is a hundred percent of people who enrolled in these studies at baseline had moderate-to-severe pain. At the end of the studies, 62 percent of these patients had mild pain or no pain whatsoever, and, in fact, almost a third of these patients had no pain.

Those are the data points that I care about. How long is it going to take to work from a pain and bowel standpoint? One fill? Can you really make clinically meaningful improvements--50 percent improvements in pain and bloating? Absolutely. An increase in complete spontaneous bowel movements by 32 times? A hundred percent. A third of patients in the trial are no longer with pain.

Those are endpoints that I can look at and I can discuss with a patient which drives their thought processes towards considering using this medication to treat their IBS-C symptoms.

Dr. McDonough:
So if a patient isn't responding adequately to one of these therapies, how do you approach the decision to switch mechanisms rather than stay within the same class? And what role, if any, does timing play in that decision?

Dr. Brenner:
It really is about shared decision-making when it comes to this process. With many of these therapeutics, they can be increased in terms of their dosages, and there is data to support that increasing the dose can improve symptoms. So some practitioners will increase the dose of the medication the patient's on, other ones will change within a class, and some will switch to another class. And really, I can't argue as a practitioner that any of those decision analyses are wrong, because there's data to support all of them. At the end of the day, it is a conversation with the patient.

But my most important point here is this: you want to make sure that the patient has given the therapeutic an ample chance to work. And what I mean is this: we see patients all the time in our clinical practice who come in and say, I tried that and it failed. And the next question we ask is, how long did you try it? And the individual says, I gave it one or two doses. That is not an adequate amount of time to consider changing that therapeutic. That is not a treatment failure. It's a failure in the response, because we have not given the drug enough time to become effective in the GI tract.

But really, we want to talk about these things with our patients. If I see a patient who says, I'm on a therapeutic and it causes severe

diarrhea, then I may want to go to a different mechanism of action. If I see a patient who comes in and says, my bowel habits are better, but I haven't gotten what I wanted out of the abdominal symptom component--the pain and bloating--that may shift me in another direction as well. But at the end of the day, I will tell you that I have never made a unilateral decision. This has always been a discussion between me and my patients, because what we know is that compliance and outcomes are always better, especially with disorders of gut-brain interaction, if the patient is playing an active role in her or his care.

Dr. McDonough:
Before we wrap up our discussion, Dr. Brenner, let's look ahead. How do you see the role of retainagogues evolving in IBS-C treatment algorithms?

Dr. Brenner:
I think it has a big role. If you look at the older studies--the IBS in America studies, the Burden IBS-C studies--they tell us definitively when we ask patients. The secretagogues are great drugs. I'm not taking anything away from them. The data is valid. I use them every day. But these surveys have told us that the patients want and need more. They're not getting everybody better. And when that occurs, we have to have a different mechanism to look at.

And again, this new class--and tenapanor, the first-in-class retainagogue--provides another mechanism that was not assessed in these earlier patient-reported outcome studies that may be advantageous to our patients. And we can't forget that when we're thinking about our patients and we're thinking about whether or not we want to offer new opportunities and treatments to improve their symptoms and quality of life.

Dr. McDonough:
As those final thoughts bring us to the end of today's program, I want to thank my guest, Dr. Darren Brenner, for joining me to discuss why mechanism of action matters in the management of irritable bowel syndrome with constipation. Dr. Brenner, thanks for joining us today.

Dr. Brenner:
Thanks so much for having me. It's been my pleasure.

Announcer:
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