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Examining IBS-C Therapies: A Look at Mechanism, Efficacy, and Safety Profiles

Announcer:
You're listening to *GI Insights* on ReachMD, and this episode is sponsored by Ardelyx Incorporated. And now, here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
Welcome to *GI Insights* on ReachMD. I'm your host, Dr. Jennifer Caudle, and joining me to discuss different treatment options for irritable bowel syndrome with constipation, or IBS-C for short, is Dr. Kyle Staller. He's the Director of the Gastrointestinal Motility Laboratory at Mass General and an Associate Professor of Medicine at Harvard Medical School. Dr. Staller, it's great to have you here today.

Dr. Staller:
Thank you so much for having me, Dr. Caudle.

Dr. Caudle:
So to start us off, Dr. Staller, what does the therapeutic landscape for IBS-C currently look like? And what factors help guide your treatment selection for each patient?

Dr. Staller:
Well, the average patient meets their potential therapeutic options in the drugstore aisle. There's a lot of over-the-counter laxatives that many patients will encounter. Those are things they often try before they even show up in a doctor's office. Once they get to the doctor's office, there are a variety of agents that are approved by the FDA, including secretagogues, retainagogues, and prokinetic agents for chronic constipation. Things that are out there may have different labels, but a lot of times, when it comes to something for IBS-C and something for chronic constipation or chronic idiopathic constipation, we really don't make much of a differentiation between those when it comes to taking care of our patient. The FDA certainly does, though.

Dr. Caudle:
So if we zero in on secretagogues like linaclotide and plecanatide, how do you assess their efficacy and tolerability in clinical practice? And what patient profiles might benefit most from these agents?

Dr. Staller:
Well, linaclotide and plecanatide are really the first prescription drugs that many patients will see. Linaclotide has been around for a long time, and both have a very similar mechanism of action where they draw water into the small intestinal lumen and that then causes contractions or peristalsis, which then speeds up bowel movement frequency, softens consistency, etc. They also decrease abdominal pain.

Now, in truth, there's not a lot of comparative data to look at one drug versus another, and that goes across the classes and within the classes as well. So in many cases, it's what drug we can get into our patient's hands, which is the one that we pick first. And then we have to try other mechanisms of actions or other different drugs to find the best efficacy for our patient.

So in general, when we're thinking of these drugs, we're thinking efficacy from a perspective of improving bowel movement frequency, consistency, making the bowel movements more soft, decreasing abdominal pain—which, of course, is a key differentiator of IBS and a key definer of IBS—and then finally, avoiding side effects. And for the most part, the big side effect that we see with any of these agents

is diarrhea. And diarrhea, of course, can be short-lived or long-lasting, but certainly something that our patients don't want to have. So when we're thinking about which patient, it's a little bit of trial and error, frankly.

Dr. Caudle:
Now, with the availability of 5-HT4 agonists like prucalopride, how do these serotonergic agents compare to secretagogues in terms of symptom relief, safety, and long-term use?

Dr. Staller:
Again, in terms of comparative data, we don't have anything that's directly comparing any of these drugs, both within class and between classes, to one another. In general, we get about a similar efficacy when we think of a bigger population. But in clinical practice—in my experience and certainly many of my peers—a lot of these drugs work very specifically: one drug will work for one patient and then for the next patient, it won't work, and vice versa. And so often, as I said, it can be a little bit of trial and error. Now, prucalopride, as you said, is a 5-HT4 agonist. It's specifically approved for chronic idiopathic constipation as opposed to IBS-C. Yet at the same time, as I said, we tend to blur that distinction between the two when we're taking care of patients. So I find the 5-HT4 agonist prucalopride to be very effective for our patients, no more so than any of the other drugs that are out there. It does have somewhat of a different safety profile. Specifically, diarrhea is always a possibility, as I mentioned, with these drugs, but some patients can develop a headache with these agents as well. It tends to be a very small percentage of people, and it tends to go away within a self-limited amount of time. But it's something to think about; if you develop a headache, I say to my patients, it's not you, it's me.

Dr. Caudle:
And for those of you who are just tuning in, you're listening to *GI Insights* on ReachMD. I'm your host, Dr. Jennifer Caudle, and I'm speaking with Dr. Kyle Staller about various treatment options for IBS-C.

So, Dr. Staller, if we focus next on tenapanor, which is a sodium hydrogen exchanger 3 inhibitor, how does its mechanism differ from other IBS-C treatments? And what advantages and challenges do you see with its use?

Dr. Staller:
I think tenapanor is the newest kid on the block. As you said, mechanism of action is inhibiting a certain sodium hydrogen exchanger 3. What that does is it prevents sodium from being absorbed in the small intestine. And when sodium is not absorbed in the small intestine, water tends to hang around with it, and as a result, you have more water in the lumen of the small intestine. That stretches the wall of the small intestines, causes peristalsis and contractions, and increases frequency and bowel movement frequency as well.

Interestingly, there's some data that shows that there are some other mechanisms that may not be expected. So these tight junctions between cells in the small intestine may get tighter. They become less permeable with exposure to tenapanor. And also, there may be a 'turning down the volume' on some visceral pain sensations. And that's something that's very important when we think about our IBS patients who are often bothered, not just by constipation, but by abdominal pain as well. So we have this mixed mechanism of action, but primarily, we're retaining, right? It's a retainagogue; we're retaining sodium that's increasing bowel movement frequency.

Now, do we know whether it's different, specifically in terms of efficacy compared to these other drugs? We don't. But we do know that it's different. And so I think it can be important for patients to have another option out there. And as I said, many individual patients will respond preferentially to one mechanism of action or another mechanism of action, and so often we have to cycle through these to find it. So tenapanor is a welcome addition because, again, it's another thing that we have to offer our patients who are suffering so much.

Dr. Caudle:
Now, despite promising clinical trial data, what barriers exist in the widespread adoption of newer IBS-C therapies? And how can we address them?

Dr. Staller:
I think one of the biggest barriers is just the fact that many people are not aware of what's out there. As I said, the average patient interacts with medication when it comes to constipation in the aisle of their local drugstore. And interestingly, all of those agents that are available are going to speed up the bowels and they're going to soften bowels, and that, to some extent, is important to patients. But what none of these agents do is address abdominal pain. So all of the FDA-approved treatments specifically for IBS-C—so that includes linaclotide, plecanatide, tenapanor, and lubiprostone in certain populations—actually do have an impact on abdominal pain, which is important. So many patients have already tried things. They may feel like they've given up because before you even have a chance to try anything, they've tried things as well.

But even our providers aren't aware of all the various medications that are out there; they sort of say, okay, we're going to try one medication—the one that they are most familiar with and that they're most comfortable with. And then when that doesn't work, they

maybe throw up our hands and say, “Okay, there's not much more we can do for you.” So I think in the landscape of IBS-C, it's important for providers to know that there are multiple mechanisms of actions that are available. And if one mechanism of action—the one that maybe you're most familiar with—is not working, feel free to jump to another mechanism of action, knowing that the clinical trials really analyze these big patient datasets and look at big macro trends. But in the micro trend side, individual patients will respond differently to different drugs, even within the same class. So just think about other options, and then furthermore, warn your patients that there may be a trial-and-error period. We can be an expert in IBS-C, but we still don't know which drug is right for which person without trying it on that person.

Dr. Caudle:
That's great advice. And as we approach the end of our program, Dr. Staller, do you have any final takeaways you'd like to share?

Dr. Staller:
I think the takeaway that I would say is that we should be taking care of our patients with IBS-C and offering them treatments. I think far too often gastroenterologists and other providers are telling their patients, “Well, you have IBS-C, it's not going to kill you. You sort of just have to live with it.” And they’re right, it won't kill you, but it is going to have a big impact on your quality of life. And I think that's a reason why we should be offering medications to our patients—other things aside from medications as well—but certainly taking an active role in their treatment.

Dr. Caudle:
Well, with those wonderful insights, I'd like to thank my guest, Dr. Kyle Staller, for joining me to discuss the different treatment classes available for patients with irritable bowel syndrome with constipation. Dr. Staller, it was great having you on the program.

Dr. Staller:
Thank you so much for having me, Dr. Caudle, I appreciate it.

Announcer:
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