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Mechanisms of Action in IBS-C Therapies: Secretagogues and Serotonergic Agents

Announcer:

You're listening to *GI Insights* on ReachMD, and this episode is sponsored by Ardelyx Inc. 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 mechanisms behind novel therapies for irritable bowel syndrome with constipation, or IBS-C for short, is Dr. Chethan Ramprasad, a gastroenterologist at Harvard Medical Faculty Physicians at Beth Israel Deaconess Medical Center. Dr. Ramprasad, it's great to have you here today.

Dr. Ramprasad:

Thank you, Dr. McDonough. Glad to be here.

Dr. McDonough:

To start us off, Dr. Ramprasad, what does the therapeutic landscape for IBS-C currently look like?

Dr. Ramprasad:

It's an exciting time to be a practicing gastroenterologist, particularly for IBS. There are a lot of new classes of medications coming onto the market; some of them have been on the market for a few years. And although there's new technology and therapeutics, I always like to talk to my patients about some of the basics with nutrition and hydration and having good exercise. But certainly, in IBS with constipation, there are some new medications, and some of them have a little bit more marketability now, given some recent results.

Dr. McDonough:

Now, looking more closely at novel mechanisms of action, I'd like to zero in on secretagogues. How do they work to alleviate constipation?

Dr. Ramprasad:

Secretagogues are a class of medications that we've had for some time. And when we talk about secretagogues, we're talking about medications for IBS that bring fluid content into the lumen of the colon. So, we're looking at mechanisms that work specifically on chloride channels and on guanylate cyclase, and they're bringing in fluid into the lumen. They're helping patients with spontaneous bowel movements, increased stool frequency, and less pain and bloating. And so these are really helpful medications. They've been around for some time, but certainly, the ability to prescribe them and for patients to know about them is increasing.

Dr. McDonough:

And what can you tell us about the efficacy and safety of secretagogues?

Dr. Ramprasad:

The secretagogues that I think of mostly are lubiprostone, linaclotide, and plecanatide, and these are pulling the fluid into the lumen. And when I think about efficacy of these, these are efficacious medications. They are helping patients usually within a few weeks when they're on a medication. And I always tell my patients that it may not be an immediate fix. It may not be a medicine I'm giving you where on day one, all of your constipation symptoms will get better immediately. So I tell them to be patient. It's important to realize that they're looking for progress week-to-week or month-to-month rather than just overnight. So I ask them to take a medication and, oftentimes, be aware that there are some side effects, mostly diarrhea, with secretagogues that may get better over weeks to months. But by telling them to expect a little bit of that side effect, or maybe even just a transition from their state of being constipated to having more

spontaneous bowel movements—to at least expect that there's a change in that way is really helpful for them to understand the ultimate efficacy of what they're taking.

Dr. McDonough:

For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Brian McDonough, and I'm speaking with Dr. Chethan Ramprasad about the mechanisms behind novel IBS-C therapies.

So, now that we've discussed secretagogues, let's shift to serotonergic agents. Dr. Ramprasad, can you tell us how they work?

Dr. Ramprasad:

Serotonergic medications are working on serotonin. And what I explain to my patients is that we think of serotonin as mostly in the brain—we think about mood regulation with serotonin and reward pathways. But more than 70 to 80 percent of serotonin is actually in the gut.

So serotonergic agents are working specifically on serotonin receptors in the gut to help overall motility of the colon. Prucalopride is used very often for constipation, but it could also be used for gastroparesis, and it works specifically on the serotonin receptors.

Dr. McDonough:

And what do we know about the efficacy and safety of these agents?

Dr. Ramprasad:

Yeah. I think of both secretagogues and serotonergic agents as efficacious. For serotonergic agents, we're primarily looking at prucalopride, which is an efficacious medicine. It's really helpful for constipation and IBS and also could be helpful for gastroparesis. It can certainly help in constipation, and the data does not show a lot of big differences between these two classes of medications. Both of them can be efficacious. But tegaserod, which is an example of a serotonergic agent, was pulled off the market in a lot of ways because of its side effect profile, particularly ischemia and some cardiac side effects.

Dr. McDonough:

As we approach the end of the program, Dr. Ramprasad, how might the novel mechanisms of secretagogues and serotonergic agents lead to tangible benefits for patients with IBS-C?

Dr. Ramprasad:

These are examples of medicines that certainly help with daily bowel movements, spontaneous bowel movements, improved abdominal pain, and improved symptoms like bloating, so they're really important for the landscape of therapeutics.

I also think it's really important to discuss with each patient the importance of nutrition, hydration, and pelvic floor therapy. A lot of my patients get better with these prescription medicines, but I really have to coach them through a holistic approach. If their mental health is not in the right space, and they're constipated, a prescription medicine that's a secretagogue or a serotonergic agent may help. But there's still contributing factors, like not eating enough fiber, not eating fruits and vegetables, or eating a lot of processed foods. That's not going to be fixed just with a prescription medicine.

So I think about things all together. But that being said, there's many different types of medicines that would be helpful, and we've talked about a few of them here: secretagogues and serotonergic agents.

Dr. McDonough:

Well, given those impacts, I want to thank my guest, Dr. Chethan Ramprasad, for joining me to talk about how novel therapies work to treat patients with IBS-C. Dr. Ramprasad, it was great having you on the program.

Dr. Ramprasad:

Thank you so much for having me.

Announcer:

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