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The Pharmacological Perspective: Treatment Options & the 2020 IBS Guidelines

Dr. Nandi:
On this episode of GI Insights at ReachMD, we are welcoming back to the show Dr. Brian Lacy, who is a renowned gastroenterologist at the Mayo Clinic, Jacksonville, and, of course, the co-editor-in-chief of the American Journal of Gastroenterology. Dr. Lacy, welcome back to the program.

Dr. Lacy:
Well, thank you so much for asking me to come back. We had such a great discussion before, and I'm excited to hear more interesting questions today.

Dr. Nandi:
Now, Dr. Lacy, no doubt, phenotypic characterization of IBS really helps clinicians in directing what medications are gonna be appropriate for their patients. I think it was really thought-provoking that the guidelines showed that there was really low quality of evidence for polyethylene glycol, right? Low risk, but one of the most commonly recommended constipation medicines that we use, and yet the evidence for some of our pharmacologic therapies, such as chloride channel activators and G. cyclase activators, are high quality of evidence. So, how and when should we use polyethylene glycol, if at all, and when would you position the other agents in choosing the right treatment for IBS-C?

Dr. Lacy:
Okay. So this is great because polyethylene glycol has been around for about 30 years, right? We know it's generally very safe, and it's effective for many patients with constipation symptoms. So why, then, would we say this isn't a great drug for IBS? Remember, IBS is a constellation of symptoms, and the two most bothersome symptoms to patients are abdominal pain and bloating. Bowel habits always come in number three. So although polyethylene glycol may help constipation, it does nothing for pain, and it does nothing for bloating, and there are two small studies in IBS patients, showing that yes, it helped constipation, but did nothing for bloating or pain, thus you need to add on a second, or even a third medication. For chronic constipation, Miralax is quite reasonable. I use it in my practice, but I don't use it to treat the global symptoms of IBS. And so, that means that, you know, if you see somebody with IBS symptoms and they've failed Miralax because they've probably already tried it over-the-counter, then start to do something else. Don't just reinvent the wheel and tell them more fiber, or more Miralax. They've probably already done that. Let's go on to something new, and fortunately, we have some great alternatives right now. Dr. Nandi, you already mentioned, we have lubiprostone, a chloride channel activator. It's been around for almost 20 years now. It's very safe and can improve global IBS symptoms. We have two guanylate cyclase activators, they're actually fairly similar, linaclotide, a 14 amino acid short peptide, and we have plecanatide, which is 16 amino acids. These act on the GCC, guanylate cyclase receptors and they stimulate motility through the GI tract, but they also increase cyclic GMP levels, and they help visceral pain. So those can be very effective agents as well, and it's great that we now have this, kind of broadening armamentarium for your patient. We don't have a validated treatment algorithm, however, so I can't tell you that if you fail Miralax as an outpatient usually, do you go to lubiprostone first, or linaclotide first, or plecanatide. Oftentimes, that depends upon the patient's values and their understanding, also sometimes, to be honest, the patient's insurance company.

Dr. Nandi:
Yeah, that's a very practical, honestly. And I think, you know, every patient is so unique. We need to tailor the therapy, but probably the highlight of this discussion is choosing a treatment that not only gets some motility going, but treats the visceral pain, and that's not what polyethylene glycol does, but our other agents. You know, you men, we have also had another agent, tegaserod, which was only on the market for five years, before being pulled in 2007 due to one study suggesting an increased risk of cardiovascular events. But then, it

was re-approved in 2019 by the FDA, when more U.S.-based studies did not see such a signal. How should clinicians utilize tegaserod, now that it's back on the market? Are there any particular cardiovascular risk factors that we should be aware of when prescribing it?

Dr. Lacy:
Wonderful. So I think for many of your listeners who might be a little bit older, that means we remember this long-storied history. It came out in 2002 to high acclaim, was very effective for treating IBS and CIC, chronic idiopathic constipation symptoms, but then voluntarily withdrawn in 2007, due to some concerns about cardiovascular events. It was re-approved by the FDA in 2019. Tegaserod is six milligrams, twice daily, and it's re-approved for women only though. That's important, women under the age of 65 without known cardiovascular risk factors. We've actually recently submitted an article looking at 18,000 patients treated with tegaserod and focusing on women. And what we found is that if you follow the FDA guidelines, meaning you're under 65 and you have one or fewer cardiovascular risk factors, the classic ones, a known prior event, you're obese, you're a smoker, have elevated blood pressure. If you have one or fewer, you can safely use tegaserod, and tegaserod, by acting on the serotonin signal system, significantly improves gut motility, gut sensation, and was really very effective at treating IBS symptoms. But I think the teaching points here are women under 65 with one or fewer cardiovascular risk factors and I would not use that upfront. I would probably use linaclotide or plecanatide first and then I would use this if that failed, or lubiprostone as well, of course.

Dr. Nandi:
For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Neil Nandi, and today I'm speaking with Dr. Brian Lacy about the ACG's hot off the press, 2020 IBS Clinical Guideline.

So that's really helpful. We talked about IBS-C now, and that was, you know, a nice kind of summary of the available agents. I want to shift gears to IBS-D. The guidelines discourage bile acid sequestrants and encourage the therapeutic use of rifaximin with a moderate quality of evidence, so I won't debate that. I think that's pretty well established. But notably 5HT3 antagonists, Alosetron had a low quality of evidence, but still evidence, and mixed opioid agonist/antagonists, like eluxadoline, with moderate-quality evidence, were endorsed. Can you give us some guidance on how you choose these agents for what type of IBS-D patient?

Dr. Lacy:
Yeah, great question. So, again, there's not a validated algorithm, but let me give you kind of my personal approach, that certainly if I see somebody, they meet criteria for IBS with diarrhea. Let's assume they first fail a low FODMAP diet, that's reasonable. They have probably failed loperamide. We don't even recommend loperamide, although it helps diarrhea, remember? It does nothing for pain or bloating, the number one and number two symptoms. Then, if somebody is a little bit more bloating-predominant or diarrhea-predominant, in terms of the most bothersome symptom, I would choose rifaximin, because I think it's very safe and efficacious. However, if they either fail that, or their symptoms are more pain-predominant, then I'm gonna choose probably eluxadoline, and eluxadoline is 75 or 100 milligrams, once or twice a day, and we have good data showing that even for patients with IBS-D symptoms who failed loperamide over the counter, they will respond to eluxadoline, so that's a reasonable treatment option. Alosetron is a 5HT3, or serotonin type 3 antagonist. We have very good data, studied in over 85 publications and eight large, randomized controlled studies, showing that in women, and remember for our listeners, Alosetron is approved just for women, is significantly beneficial for IBS-D symptoms. And the recommendations are for women who have failed standard therapy. What's standard therapy? That means you failed diet and/or Immodium. The FDA is a little vague about that. It comes as either a 0.5 or 1 milligram dose. I think it could be very effective, and when used in the right person, a woman, with IBS-D symptoms, it's very safe. And it does help those symptoms of pain and bloating and urgency, so I think that can be a very valuable medication.

Dr. Nandi:
That's really great. I have one more question to ask you. I would be amiss if I didn't ask, the role of probiotics. The AGA released a probiotic guideline last summer, of 2020. Is there any role, in your review of the literature, for probiotics in the management of IBS?

Dr. Lacy:
Yeah, so we could either spend two minutes or twenty minutes. So, probiotics are a pretty controversial topic, right? So, remember what is the definition of a probiotic? The probiotic is defined as a live bacteria, designed to promote good intestinal health, kind of whatever that means. It's kind of vague, right? So here's the problem: think about what we're asking patients to do, to take a capsule, a single capsule. That's gonna change four pounds of bacteria in your colon. To me, conceptually, I have trouble wrapping my head around that. There are some other issues, too. Most probiotics have never been tested, and as you know, there is a neat study, published a couple years ago. Somebody went to the pharmacy, they bought about 85 different probiotics over the counter. Most are dead on arrival. Beyond that, most have never been tested. We really only have data for about two, and we're not even sure that most get through the stomach and the small bowel to the colon. So, do they work? The answer is maybe, and I'm gonna say that again, maybe they work. A couple years ago, we published a big study. We did a metanalysis of 37 studies involving probiotics in IBS patients

only. What were the final results? Probiotics are barely better than placebo, and if your listeners decide to recommend them or use them on their own, generally a combination probiotic is better than a single probiotic. But are they magical? Absolutely not, and don't forget, for many patients, probiotics worsen bloating, a predominant symptom.

Dr. Nandi:
Dr. Lacy, thank you so much for coming back to the show and sharing those wonderful insights. We really appreciate the time and education that you've provided today.

Dr. Lacy:
Well, what an honor to be online with you and your listeners today. This is a great discussion. I hope that your listeners find some valuable teaching points for their patients in clinic.

Dr. Nandi:
No doubt they absolutely will. For ReachMD, I'm Dr. Neil Nandi. To access this episode, and others from GI Insights, please visit reachmd.com/giinsights, where you can be part of the knowledge. Thanks for listening.