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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

The Role of Neuromodulators in Treating IBS

Dr. Buch:
Welcome to *GI Insights* on ReachMD. I'm Dr. Peter Buch. And today we are joined by Dr. Douglass Drossman, who will be discussing his article, "Central Neuromodulators in Irritable Bowel Syndrome: Why, How, and When," which was published in *The American Journal of Gastroenterology* in 2024. Dr. Drossman is the President of the Drossman Center for Education and Practice of Psychosocial Care and Drossman Consulting. He is also Professor Emeritus of Medicine and Psychiatry at the University of North Carolina School of Medicine. Welcome back to the program, Dr. Drossman.

Dr. Drossman:
Thanks for having me again.

Dr. Buch:
It's absolutely a pleasure. So let's get started. Dr. Drossman, to start us off, can you explain how neuromodulators play a role in irritable bowel syndrome?

Dr. Drossman:
Sure. And before I answer that directly, maybe the term neuromodulators is not familiar to people. But this was a term that we decided to use to replace the older terms of antipsychotics, antidepressants, and antianxiety medications because that has a psychiatric stigma, and we're talking about using these for GI symptoms, like pain or bowel dysfunction. So neuromodulators is a more proper term because we're treating disorders of the brain-gut axis, which we call irritable bowel syndrome.

So to answer your question, it plays a role in modulating or normalizing the dysregulation of these symptoms. Patients with irritable bowel are characterized by having abdominal pain, and that's associated with change in bowel habit: diarrhea, constipation, or both, maybe abdominal bloating, some nausea. And these medications act on those brain-gut pathways to normalize it, so that's how we're using it for IBS and many other functional GI, which we now call disorders of gut-brain interaction.

Dr. Buch:
Great. And as a follow-up to that, Dr. Drossman, what percentage of all patients with irritable bowel syndrome might have relief when using neuromodulators?

Dr. Drossman:
50 to 60 percent, I would say.

Dr. Buch:
Perfect. And, Dr. Drossman, I'd like to dig deeper into the use of specific medications, and specifically, when should we be using tricyclic antidepressants in treating irritable bowel syndrome?

Dr. Drossman:
Tricyclic antidepressants like amitriptyline, desipramine, and imipramine are medications that have been around a very long time, and the research is now showing that it works very well. There was a study that came out a year ago by Alex Ford showing that low-dose tricyclics—amitriptyline, 10 to 30 mg a day, which is a low dose when you consider it could be 200 mg to treat depression in psychiatry—so these lower doses can relieve abdominal pain and bowel dysregulation, and it was found to be significantly beneficial in a cohort of about 300 patients being treated in primary care. So tricyclic antidepressants are the first choice, but there are other antidepressants I tend to favor. The SNRIs—we're going to talk about that a little bit later—but I would say it's one of the first things you would consider

using for mild to moderate IBS.

Dr. Buch:
Moving on from there, how about selective serotonin uptake inhibitors or serotonin and norepinephrine reuptake inhibitors? When should they be used to treat irritable bowel syndrome?

Dr. Drossman:
Well, the selective serotonin reuptake inhibitors, rarely. Most people are very surprised when I say that. But in order to get benefit for pain, which is the keynote symptom of IBS, you need to use medications that act on norepinephrine and serotonin receptors. Serotonin reuptake inhibitors are purely serotonergic. There's no norepinephrine benefit. Tricyclics are serotonin and norepinephrine, as are serotonin and norepinephrine reuptake inhibitors, or SNRIs. So you can use tricyclics or SNRIs for IBS, particularly to treat the pain. The tricyclics do have additional receptors like antimuscarinic and anticholinergic that can give you constipation, so if the patient has a lot of constipation, I would choose the SNRI, which only works on the serotonin and the norepinephrine.

Now, the SSRIs are frequently used, but they don't help pain. The reason why they're sometimes used is, in part, because doctors don't know any different. That's why I would refer you to the article, which explains it in more detail. But it also can reduce anxiety. And patients with IBS can get flaring of their symptoms with anxiety, and so it can work to help reduce the anxiety, which can help the symptoms, but a direct effect on the pain is not seen. The SNRIs can be helpful for the pain and also can be used if they have diarrhea or constipation.

Dr. Buch:
So, just clarifying a little bit, would we ever use SNRIs for pain as primary medication in patients with irritable bowel, or would we always go with the tricyclics first?

Dr. Drossman:
I use the SNRIs first, and here's why. Most of the studies have been done with tricyclics, but in the real world, the tricyclics, especially in higher doses, have side effects because they have anticholinergic and antimuscarinic activities. Older patients can get orthostatic dizziness, they can get dry mouth like an antihistamine, they can get blurry vision, and they can get cardiac effects like tachyarrhythmias in the higher doses, whereas the SNRIs don't do that. So tricyclics have all the studies and all the data. Very few studies have been done with the SNRI. But in the real world, more and more of us are using the SNRIs because they give you the benefit of treating the pain with the serotonin and the norepinephrine, just like tricyclics, but don't have the action on the antimuscarinic, anticholinergic, and antihistaminic pathways, which cause the side effects with higher doses of tricyclics.

Dr. Buch:
Thank you very much for that wonderful insight. For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Douglass Drossman about his research into central neuromodulators and irritable bowel syndrome.

So moving ahead, Dr. Drossman, when should we consider atypical antipsychotic agents in irritable bowel syndrome? And what are your concerns in using these medications?

Dr. Drossman:
So we've done a study looking at an antipsychotic called quetiapine. We use that when we're not getting adequate benefit. In our study, we took patients who were on either a tricyclic or an SNRI for a month, and if they weren't responding, we added Seroquel, or quetiapine, an antipsychotic, and 50 percent got better, so it had an added effect on monotherapy. Now, again, the term antipsychotic—we call them atypical neuromodulators, rather than antipsychotics, because of the stigma that's associated with that. And it's important to remember that these agents—we're using them at one-tenth the dose that's used in psychiatry. So if someone has schizophrenia or bipolar disorder, you might use 800 mg of Seroquel. We would use 25 to 50 mg to treat for these GI disorders. Olanzapine is another. You might use 20 mg in psychiatry, but we use 2.5 to 5 mg, much lower doses.

The side effects are of some concern in higher doses. Most of the studies showing side effects are in the psychiatric patients on these huge doses. What are they? Well, they can get weight gain. They get sedation—they get very sleepy. And in primary care, a lot of doctors prescribe these agents at bedtime because it normalizes sleep architecture as opposed to Ambien and some of the other hypnotics. It improves REM sleep, and it causes less sleep fragmentation, because with irritable bowel, these patients do get sleep fragmentation and reduced REM sleep, and this normalizes that. Many patients with the functional GI disorders and also GERD have sleep disturbance, so Seroquel or olanzapine (Zyprexa) can be used for that.

We did a survey of gastroenterologists and asked them about their comfort level of these medications. Well, it's no surprise the tricyclics they felt the most comfortable with; the SSRIs, about similar comfort; the SNRIs not so much; and the antipsychotics they didn't feel

comfortable with. However, the side effect profile is very low in the doses we're using and in the side effects that occur. With young women, especially in higher doses, we have to watch out for the weight gain. They won't want to go on it. But in general, it's a pretty safe medication.

Dr. Buch:
Thank you for that insight. To close us out, Dr. Drossman, when and how should we be implementing augmentation therapy to treat irritable bowel syndrome?

Dr. Drossman:
Actually, using the antipsychotic or atypical neuromodulator is an example of augmentation. There are a couple of reasons why we would use augmentation. The first is if we're getting no benefit from the first-line treatment, whether it's a TCA or an SNRI. If they're getting no benefit, then we could look at one or two other options in a similar class of antidepressant, and if it doesn't work, we can add it. Another reason we would do it is if they're getting side effects even at low doses. And so augmentation means adding a second agent. If they're not showing benefit or they're getting side effects, then what you do there is drop the dose. So if you're using 50 mg of amitriptyline and they're getting a lot of side effects, you could drop it to 25 mg and add Seroquel or olanzapine in low dose. And by using two drugs, you're acting on different receptors, and the likelihood of side effects are less because the doses are lower. Other augmentation treatments you can use are the delta ligand agents, like gabapentin has been used, or Lyrica, pregabalin. You can use peripheral neuromodulators like linaclotide, which can act on treating pain, but it's not a central neuromodulator like this. And then behavioral treatment—hypnosis or cognitive behavioral therapy—are two other treatments that are very valuable in augmenting or enhancing the benefit of monotherapy.

Dr. Buch:
Thank you for that insight. I'd like to thank our guest, Dr. Drossman, for his insights into the role of neuromodulators in treating irritable bowel syndrome.

Dr. Drossman:
Thank you.

Dr. Buch:
Dr. Drossman, it was a pleasure working with you today. For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in the series, visit *GI Insights* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening, and looking forward to learning with you next time.