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## How Neuromodulators Can Treat Functional GI Disorders

Dr. Buch:

Neuromodulators, such as antidepressants and antipsychotics, are frequently used to treat functional gastrointestinal disorders which are recognized as disorders of gut-brain interaction. However, this treatment method is not well understood by many gastroenterologists, which is why today, we're going to be clearing up some of the confusion surrounding neuromodulators and their role in functional gastrointestinal disorders.

Welcome to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and joining me today in this discussion is Dr. Douglas Drossman, president of the Rome Foundation, which recently came out with a report focusing on neuromodulators and functional gastrointestinal disorders. Dr. Drossman, welcome to the program.

Dr. Drossman:

Thank you, glad to be here.

Dr. Buch:

To start us off, Dr. Drossman, what are your goals when establishing a therapeutic relationship with a patient who has irritable bowel syndrome, or IBS?

Dr. Drossman:

Well, therapeutic relationship—and again, this applies to IBS or any GI disorder—is one which we are often calling patient-centered care, which came from the Institute of Medicine about 20 years ago that changed the paradigm that we're not just telling the patient what we want, but we're working with the patient in a partnership way, so we provide the guidance, we give them the recommendations, and in doing so, they can make choices. To me, that's patient-centered care or a therapeutic relationship. And the goal of doing that is that we can get better outcomes and better adherence to medication because patients who are making the decisions themselves are engaged and involved in the treatment. So, if I say to a patient, "You need to take this medication," they may take it and not tell you they have concerns about it, but if I say, "Here are some options; Here are the pros and cons; Tell me what you prefer," then they are engaging, so the goal of the therapeutic relationship is to improve your outcome.

The other part is communication. Patients who are in a therapeutic relationship, which means that they are trusting the doctor and sharing in ideas, is much more willing to disclose meaningful information. You know, there is a concept in psychology that they call a social response set. Doctor is way up here, and the patient is down here, and the patient doesn't want to say anything that would annoy or disagree with the doctor, so they answer questions the way they think the doctor wants. Well, we even the playing field with a therapeutic relationship by giving them the option to voice their view.

Dr. Buch:

And why is it so important to establish that relationship with our patients, Dr. Drossman?

Dr. Drossman:

Well, first of all, you get more meaningful information. The patient gives you more information that can help with diagnosis, you have a greater likelihood that you're going to effect a better treatment because the patient has voiced their willingness to go on the medication, and there are some other subtleties that when you have a good relationship with a patient, they like you, and doctors like patients who like them.

Dr. Buch:

So, once we've established that relationship, when should we choose antispasmodics and when should we choose neuromodulators to

treat IBS?

Dr. Drossman:

Yeah, that's a good question, and I like to think about treating IBS in terms of 2 factors. One is the nature of the symptoms, the quality, and the other is the severity of the symptoms, the intensity. So, when we make decisions about medications, if they have diarrhea-predominant or constipation-predominant, we choose certain medications, so we use secretagogues for constipation, and we might use 5-HT<sub>4</sub> blockers—5-HT<sub>3</sub> blockers for diarrhea.

But severity is talking about the intensity of the pain and the discomfort, and an antispasmodic is more for the milder form. You know, we can look at these conditions on a continuum of severity. You have someone with occasional symptoms after a meal, before an exam, during menstrual cycle, and then it goes away, and then you can get the kind that we see in referral practice where the pain is there all the time and it's severe. It's not even related to eating or bowel movement. The more severe, the more you're likely to use a neuromodulator, whereas if it's an intermittent, worse with eating, you might be inclined to use an antispasmodic, and that's where the research was. The original work on antispasmodic is it reduced the gastrocolic response, the motility, the increased motor response after a meal, and so, if there is value in the antispasmodics, it's going to be intermittently, perhaps, in relation to a meal or when you have a bad episode, whereas with the neuromodulators, you're having a more persistent pattern.

And by the way, thank you for saying neuromodulators. You know, the Rome Foundation has made an effort to change the terminology from antidepressants and antipsychotics to neuromodulators. The reason why is very clear. These drugs were developed in the '50s and '60s, and they were targeted towards psychiatric patients, but the same drugs work in GI as raising sensation threshold, affecting motility and the like, and so we're borrowing from these drugs. Just like aspirin can treat pain, it can also prevent a heart attack, and these neuromodulators treat psychiatric disorders, but that's not what we're doing here. We're treating pain and we're treating motility, and if they have a comorbid disorder, well, that's helpful too, but the reason to do that is to avoid that stigmatization of patients saying, "You know, I'm not crazy. Why am I taking this antidepressant?"

Dr. Buch:

For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and today I'm speaking with Dr. Douglas Drossman about the role of neuromodulators in the treatment of functional gastrointestinal disorders.

So, Dr. Drossman, when you're selecting a drug class to treat patients with IBS, how do you decide among TCAs, SSRIs, SNRIs, etc.?

Dr. Drossman:

So, if we go with the idea of neuromodulators, even before that we have what we call central neuromodulators that are working in the brain and the brain-gut axis, and those are the ones you've just mentioned, and we also have peripheral neuromodulators, ones that work in the enteric nervous system, like linaclotide or the secretagogues or gabapentin or any of the agents that work to affect pain or motility in the peripheral tract, so it's a good way to harmonize it.

Now, getting back to the central, you do have anti-anxiety agents, antidepressants, and even antipsychotics. What you highlighted are the first line of treatment, which are the antidepressants. And you're right, there are TCAs, which are called tricyclic antidepressants, and that group is particularly helpful for treating IBS where there is pain and diarrhea. The tricyclics have serotonergic and norepinephrine activity. Norepinephrine slows down the bowel. Serotonin activates the bowel. So, when you have diarrhea, you would be more inclined to use a tricyclic, and you can use that in doses anywhere from 25 mg to 75 mg, and what you'll find is an improvement in pain anywhere 4 to 6 weeks and possibly reduction in the diarrhea within several days to a week.

Now, the side effect problem is that these are what we call dirty drugs because they have antihistaminic effect and acetylcholine effect, so in high doses you have to watch out for dizziness, orthostatic dizziness, dry mouth, blurry vision, sicca syndrome and tachycardia, so we try to stay with lower doses. If you have to go to higher doses, just be sure that the patient can tolerate it.

Now, there is a little extra credit here. The so-called tertiary amines, which are amitriptyline and doxepin, have more of these anticholinergic effects. The secondary amines, like desipramine and nortriptyline, don't have as much side effects, so you can get away with higher doses of desipramine and nortriptyline without all the other side effects I mentioned.

Now, moving forward, the new kid on the block—well, not so new but had been around about 10 years, but we're using it more and more—is the SNRIs. The SNRIs act like the tricyclics because they have serotonin and norepinephrine for pain, but they have less effect in terms of the acetylcholine or the histamine effect, and they have less effect on the diarrhea, so the SNRIs you can push to higher doses and get pain benefit. The main side effect of an SNRI would be nausea, and if they have that, you can take it with a meal, and sometimes that helps it as well.

Now, the SSRIs, serotonin reuptake inhibitors, are another class of antidepressants that are helpful for depression and anxiety, but they

are really not targeted for pain, and so we don't really use them in GI for abdominal pain because they don't have noradrenergic activity. We can use it if the patient has a lot of anxiety or is highly depressed and we think that's contributing to the pain, but it's not working directly on the pain. The only exception to that is the data showing that esophageal chest pain has in several trials shown benefit with SSRIs, but most of the other GI pains—abdominal pain, biliary pain, levator syndrome—all of those won't respond to an SSRI.

Dr. Buch:

And if we switch gears a bit, can you tell us about your experience with virtual therapies?

Dr. Drossman:

Well, it is the world right now. I know in my own practice I went through 4 months of all telemedicine, and that was very hard. My patients are often very complicated, and I need to see them in person, but you can do it. You can do it through telemedicine. What I can do with telemedicine is I can share the screen and show them some slides, which helps me to teach the patient about the value. You know, when you're prescribing neuromodulators, it's all about getting them to recognize why it's being used, that it's not for a psychiatric problem, that it's for the management of the pain or their IBS per se, so, if I can show them the physiology, that does help. I still would prefer to do it face-to-face.

Dr. Buch:

Lastly, Dr. Drossman, if you had one call to action to give your colleagues, what would that be?

Dr. Drossman:

I think that would be learn about patient-centered care, learn about active listening to the patient, and engaging in dialogue in a collaborative way.

Dr. Buch:

Well, that's all the time we have for today, but I want to thank Dr. Douglas Drossman for joining me to discuss the roles of neuromodulators in IBS and other disorders of gut-brain interaction. Dr. Drossman, it was great speaking with you today.

Dr. Drossman:

Thanks for having me.

Dr. Buch:

For ReachMD, I'm Dr. Peter Buch. To access this episode and others from this series, visit [ReachMD.com/GIInsights](https://ReachMD.com/GIInsights) where you can Be Part of the Knowledge. Thanks for listening.