#334 IBS, Functional Dyspepsia, and Cyclic Vomiting: Disorders of Gut Brain Interaction (DGBI)

Understand the conditions, set goals, fear diagnosis no more!

[The Curbsiders Internal Medicine Podcast theme]

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[music]
Matt: Welcome back to the Curbsiders. I'm Dr. Matthew Frank Watto. Here with my very good friend, Dr. Paul Nelson Williams. Hi, Paul. How you doing, tonight?

Paul: [laughs] I've been downgraded from great, but other than that, I'm doing okay. How are you?

Matt: You're still great. Great, very good. To me, same thing. I didn't mean to downgrade you.

Paul: Sure. [crosstalk]

Matt: Tonight, on the show, Paul, we're talking about disorders of the gut-brain axis, which I think we're pronouncing dig-buh.

Paul: [laughs]

Matt: We'll see if it catches on. Well, of course, what we mean by this IBS, functional dyspepsia, and cyclic vomiting syndrome. Our guest is the great Dr. Xiao Jing (Iris) Wang. She's back for a third time on the show and in just a moment, I'll tell you a little bit more, give a little more of a teaser but first, Paul, what is it that we do on the Curbsiders?

Paul: Sure. Just in case, the audience doesn't know at this point, we are the Internal Medicine Podcast. We use expert interviews to bring you clinical pearls and practice changing knowledge. And Matt, why don't you, I was going to say, finish that tease, but that feels a real gross sentence. So, why don't you finish-telling the audience what we talked about and who we talked to?

Matt: [laughs]

Paul: -telling the audience what we talked about and who we talked to?

Matt: Well, we go through three cases and we talk all about these disorders of the gut-brain axis. Particularly, we talk about how to approach them in a very patient centered way, which is what I most appreciated about this because oftentimes these patients are stigmatized or I guess told they just have anxiety and that's really not it. So, Dr. Wang did a great job of really telling us how she counsels patients and giving us just a wide range of therapeutic options for functional dyspepsia, for IBS, and for cyclic vomiting. We did talk about some of the diagnostics which really, Paul, there's not as much diagnostics here. It's a pretty minimal diagnostic, most of it can be done in primary care.

Paul: Right. And in keeping with the theme, it's really talking and listening to the patient because we talk a lot about letting the patient's symptom presentation guide what your therapeutics look like. It's not algorithmic, it's not cookbook medicine, you actually have to listen and listen to what symptoms are most bothersome and that will guide your treatment all the time. So, really fascinating and helpful stuff.

Matt: Our guest, Dr. Xiao Jing (Iris) Wang, she is a clinical gastroenterologist with a passion for teaching. While she's a general gastroenterologist, her clinical and research interests are in functional GI disorders or disorders of the gut-brain axis. She's currently an Assistant Professor at the Mayo Clinic.
in Rochester, Minnesota during the week and an amateur baker during the weekends. Paul, do you have a pun?

**Paul**: I do not.

**Matt**: Okay. All right. Before we get to the interview, a reminder that this and most episodes are available for free CME for all healthcare professionals through VCU Health at curbsiders.vcuhealth.org. So, now without further ado, let's get to it.

Iris, so good to have you back. The audience probably knows you by now. I feel maybe we just need to officially bring you into the team, but remind them in case they haven't heard you before or they forget, remind them and tell them one hobby or interests outside of medicine.

**Iris**: You got to be careful where you invite me to be part of the team.

**Paul**: [laughs]

**Iris**: I will totally take you up on that offer.

**Paul**: [laughs]

**Iris**: My name is Xiao Jing (Iris) Wang. I am an Assistant Professor in the division of gastroenterology at Mayo Clinic in Rochester, Minnesota. My clinical duties are general gastroenterologist, but my clinical niche and research interests are in disorders of the gut-brain axis and I'm so excited to be talking to you guys about that today. Hobby wise, I am still an amateur baker, but I am producing many more carbs every weekend as we speak.

**Matt**: Good for you. Good for you. Stressful times you know?

**Iris**: Carbs make the world go around.

**Paul**: You had shared an anecdote with us before we started recording about karaoke. I'm going to change up my usual question and actually ask, what's your go-to karaoke song is and if you don't have one, now's the time to make one up. So, I'm going to ask you to commit to your go-to karaoke song.

**Iris**: Do you really think that I would have invited you to karaoke without a song for every specific occasion depending on who I'm karaokeing with?

**Paul**: [laughs] You get one.

**Iris**: Flo Rida, Club Can't Handle Me.

**Matt**: Wow.
Paul: It's a solid choice. All right.

Iris: Mm-hmm.

Paul: That was what I was going to guess, actually.

Matt: [laughs]

Iris: [laughs] Thank you.

Matt: Paul, dare I ask your-- What is your karaoke go to song?

Paul: Bon Jovi's, Dead or Alive. I feel I don't know why you wouldn't.

Matt: [laughs]

Iris: Solid choice.

Paul: Yeah. Thank you.

Matt: It used to be Total Eclipse of the Heart, but I think now that's played out. With that, that for me--
[crosstalk]

Iris: Also, really long.

Matt: But so fun, so fun.

Iris: Sure.

Matt: Well, Elena couldn't be here tonight. Our great super producer, Dr. Elena Gibson, who really put this thing together couldn't be here, because of clinical duties. She did want to send in a pic of the week. So, she said, "This week, I will recommend the documentary, Searching for Sugar Man, a story of the life and work of the 1970s artist, Rodriguez and she also recommends listening to the Rodriguez' albums. I can only imagine I've never heard of this, Paul. It's probably something hip because it's Elena and I will check it out and be a cooler person for it, what do you think?

Paul: I think you'd like it. It's actually really great documentary. It's a movie I have seen. So, it can't be that hip, but I liked the one.

Matt: I would put you and Elena in the category. Most of your picks of the week, I've never heard of it, so you're making me more cultured by hearing them. Well, Iris, we have a lot to get to tonight. So, I think we're just going to jump right into a case from Kashlak Memorial and of course, the great Dr. Paul Williams, he will take us there.
Paul: Yeah, of course. Let's talk about Ms. Floyd first. Ms. Floyd is a 32-year-old. She has no significant past medical history. She's coming to you with ongoing episodes of epigastric pain and nausea for the past year. Her symptoms are frequently worsened by eating, but exacerbating foods are not consistent. She describes one normal bowel movement most days and has no dysphagia, no weight loss, no heartburn symptoms. She has tried calcium carbonate and bismuth at home intermittently and without improvement. The workup so far by her excellent primary care doctor has included a negative stool H. pylori antigen, a normal CBC, a normal CMP and Ms. Floyd is beginning to become frustrated regarding the lack of an explanation for her symptoms thus far. So, astute listeners will know the title the episode and know that we're hitting into discussion of-- maybe this is my first question. What are we calling what we're talking about tonight? I've heard there's functional disorders, now, there's disorders of the gut-brain axis, which we're going to with dipigabah, is that how the gastroenterologist abbreviate it?

Matt: Yeah. What's the cool way to pronounce it as well?

Paul: What are we calling it this time?

Iris: I think it's still a tongue twister that I often get incorrect. But the official name for these disorders is "disorders of the gut-brain axis," which I may have called interaction before. But there is an interaction there. But the official name is "disorders of the gut-brain axis." Also, before we get too far ahead of ourselves, I have thought about my pick of the week for two months. So, you have to let me give it.

Matt: Oh, I'm so sorry. How rude of me? All right, let's hear it.

Iris: This is the most important part of this for me.

Matt: [laughs]

Iris: I have to recommend this video game called It Takes Two. It came out on PS5 and it's very on theme with what we're talking about because it is a two-player cooperative game, and talks about therapy, and it's about this couple that's about to get divorced, and then they're forced into this situation where they play through a cooperative game in order to figure out where they went wrong. The graphics are amazing. The play is actually very balanced between the two players. If you have any marital issues, even minor ones, oh, this is the place to go to solve them, so high recommend, also, awesome-

Matt: Wow.

Iris: -minigames throughout, I have to get that out.

Matt: I never heard of that.

Iris: [laughs]

Matt: Paul, you're the gamer. You're the gamer on the show. Have you heard of this?
Paul: I have. I unfortunately don't have friends with which I could play it but it's [crosstalk] good thing.

Matt: [laughs] I'll come over, Paul.

Iris: Matt, step up.

Paul: [laughs] We'll work on our relationship together, it'll be perfect.

Matt: Yeah. The show has created a major rift between me and Paul, we really need this game. So, thank you, Iris.

Paul: [crosstalk] We wouldn't talk without the show, so it's probably helping us. [laughs]

Iris: Okay. Back to business. I'm sorry.

Matt: Yeah.

Iris: Disorders to the gut-brain axis, so these were formerly known as functional GI disorders. But then the title functional has become very burdened with bias. There's this move to rebrand these disorders, because we now know a little bit more about why they happen the way they happen. It does have to do with the interaction between the nervous system in the gut and the nervous system in the brain. But the formal definition is that these are disorders that are characterized by symptom clusters with limited findings on structural abnormalities on diagnostic testing. And that symptom cluster is going to be really important as we keep talking. Pathophysiology, we think is a combination of altered motility, visceral hypersensitivity, a change in the epithelial barrier of the gut, mucosal immune dysfunction, microbiome disturbance or/and gut central nervous system neural processing. That's a lot of stuff. But it's really important to remember that these all interplay to produce the symptoms in these patients.

That was a lot. That's really not how I tell my patients about them. When I talk to my patients about one of these disorders, I tell them, "Look, there's nothing that looks wrong on our testing, but that doesn't mean things are working correctly." While we're getting better at testing for function or motility, testing for sensation, for hypersensitivity, for microbiome, all of that is far behind in terms of clinical relevance. Just because the testing is normal that just means we're not using or we don't have the right test right now to diagnose you. That doesn't mean nothing is wrong with you. I do have to qualify that you want to say that, you are ruling out the structural things that will kill them. So, you want to make sure you're allaying their fears, but validating the symptoms and the impact that these symptoms are having on their lives.

Matt: This just reminds me, we talked about long COVID recently and it was the same thing. We often the testing is negative, you don't find anything, but that doesn't mean there's nothing wrong. Some of the other disorders on the show that we've talked about, any chronic pain syndrome or fatigue, there's just like we don't have necessarily diagnostic tests and a lot of the times, you're just working with the patient and trying a lot of things. So, I imagine that's going to have some of the model here. By the time,
patients get to you, they've probably been pretty demoralized, I imagine, because you're pretty up there on the specialist's chain. They might have even seen another GI before they get to you, right?

Iris: Yeah, absolutely. And actually, as a fellow these patients cause a lot of anxiety. In preparing for talking to everyone about these disorders, I've been thinking a lot and reflecting a lot about why these patients cause anxiety for providers? Because we can deny that all we want and say that there's bias, but it's true that we see a patient who has bloating, chronic pain, nausea, vomiting, diarrhea, and we turn up our hackles. I think a couple of reasons that I've come up with, at least, that pertain to me is that, these diseases aren't diseases that we are taught a lot throughout training.

Part of is because they don't kill patients and that's one of the good things about them. But because they don't kill patients, they also don't show up on board exams, because they don't tend to put patients in the hospital as we go through residency training and were mostly inpatient based in our heavy clinical learning and education, we don't learn about these patients. We see them as, "Oh, these disorders don't fit an inpatient diagnosis." So, they don't have to be worried about right now while my COPD patient is crashing.

A lot of the times, they're not necessarily an inpatient priority and so, we don't learn about that. Perhaps, we don't have the same heuristics that we use for a lot of our other conditions. What I mean by that is, when you see a patient with sepsis, heart rate increases, blood pressure decreases, you've been trained and taught to recognize that as sepsis and you have an algorithm in your mind that you can automatically go down to say, "Okay, bolus fluids. Check for an infection. Let's get source control, let's start antibiotics while we do that." Those are now mental shortcuts because as inpatient providers, and residents, and inpatient services, we do that a lot.

Similarly with outpatient disorders, we have the central criteria. When we have a sore throat patient come in, we can have a mental anchoring for that disorder. These patients don't fit in neat boxes. We don't often have those heuristics and those boxes and algorithms to go down. That's what I want to make sure everyone has tonight is that, we can have those. We can understand these disorders a little bit better. We do see patterns in these patients. So, when you do see those patterns, let me tell you, let us share with you what the algorithms are for you to go down, so that it becomes a little less anxiety provoking.

Matt: And what we're going to do tonight audience, the first case here we're going to talk about functional dyspepsia, the second case we're going to talk about more of the irritable bowel syndrome, and then finally we're going to talk about a case of somebody who has recurring episodes of vomiting. And hopefully, we will give you some tips, some diagnostics that you can do, and then how you can talk to patients, and how you can think about approaching the treatment for that. So, Iris, this first case here, this person is a 32-year-old. They're having epigastric pain, nausea, negative H. Pylori test. Where do we go from here, how do you think about the initial workup?

Iris: Yeah. Let's talk a little bit about functional dyspepsia, because we can put that label on, but actually, it's helpful to further subdivide that label of functional dyspepsia into the two Rome IV subclasses. All of the criteria we're going to use today are based on Rome IV criteria. Before we go into
that, most of them you have to fulfill the criteria for at least three months with symptom onset at least six months prior to diagnosis. That's blanket across all Rome disorders.

For functional dyspepsia, you have to have one or more of either bothersome postprandial fullness, bothersome early satiation, bothersome epigastric pain, bothersome epigastric burning, and no evidence of structural disease including upper endoscopy to explain the symptoms. That doesn't mean everybody needs an upper endoscopy, but we will get there in just a second. We can break down functional dyspepsia into what's called postprandial distress syndrome or epigastric pain syndrome. These are excellently named. One of them, you get postprandial distress. You have to have the pain after you eat usually severe enough to impact usual activities. The other one, you have epigastric pain.

The other thing about postprandial distress syndrome is bothersome early satiation. I love asking this question to all of my trainees on rounds. So, the difference between early satiety and early satiation is something that I don't think I learned until I was a fellow.

**Matt:** Paul knows, right, Paul?

**Paul:** I, no. No, I didn't know satiation was a word until about five minutes ago.

**Matt:** [laughs]

**Iris:** Yeah, I learned it in fellowship. Actually, a lot of what we consider satiety and call satiety is actually satiation. Early satiation means that a patient eats a smaller amount of food and feels full. When we talk about heart failure symptoms of, "Oh, are you eating a small sized meal and getting full," that's actually early satiation. That is not early satiety. Early satiety means that you are actually full for longer. This is important because we can correlate that sometimes not 100%. But in my mind, expert opinion, not guideline based, early satiation makes me think that the stomach is not able to stretch as wide as it used to, or that there's something preventing it, or bothering it when it's doing what's called accommodation, which is increasing its size in order to accommodate that food bolus. I just defined a word using the same word, but you're with me.

**Matt:** [laughs]

**Iris:** But we can test for that and that's different from gastric emptying where a delay in gastric emptying could cause early satiety, where you eat and then you're just full for a really long time because the food's sitting there and not leaving. Why is this important? It's because functional dyspepsia and gastroparesis overlap a little bit in terms of symptoms. And sometimes, the only defining characteristic is this normal gastric emptying study. But part of that is because gastric accommodation testing is not widely available. When we actually do that testing, we can see abnormalities in one, in both, or a combination of that. So, I like to characterize the difference in those two terms mostly because it helps us understand gastric function. So, this then becomes-- [crosstalk]

**Matt:** I just want to make sure-- Can I try to summarize to make sure I got it? Satiety, they are full longer and that's more of a gastroparesis feature because the foods just sitting there, it's not getting
pushed through, the stomach's paralyzed, that's my simplified. And then satiation, they're full earlier in
the eating process but they don't necessarily stay full longer than usual, but they just get full really
quickly.

**Iris:** Yeah. Absolutely.

**Matt:** And that's more of a functional dyspepsia symptom.

**Iris:** Symptom because we can't measure accommodation very well yet.

**Matt:** Mm-hmm. Okay.

**Iris:** We can-- [crosstalk]

**Paul:** There's not some sort of swallowable balloon test? This seems improbable to me. [crosstalk]
inflating in body parts, this feels it should be it.

**Iris:** That's how we used to do it. We used to have patients swallow a balloon, and then we would fill up
this balloon, and it was a barrel stat, and you could actually measure the volume of the balloon. Now, I
can go on a very big tangent here, but I won't. But now, we do-- [crosstalk]

**Matt:** We don't have time-- [laughs].

**Iris:** Yeah. Now, we do it with a nuclear medicine test and we can actually see the size of the stomach
change. I'm hopefully going to make some improvement in that even with some clinical trials, fingers
crossed coming down the line. But back to postprandial distress syndrome. The other side of functional
dyspepsia is epigastric pain syndrome, which is bothersome either epigastric pain or burning that's
severe enough to impact your usual activities that doesn't usually get induced by a meal and these two
overlaps, right? But the reason why it's important to distinguish whether food is related or not is
because we go down different treatment algorithms when we can make that distinction.

**Matt:** Yeah. And of course, we'll have a figure that after-- for the audience, by the time they're hearing
this, we'll have a figure that lays these out. There're some great algorithms that have been out there in
the guidelines. There was a lancet paper I saw that had a nice figure as well. We'll have sources for you
for that. Well, so, what would be the diagnostic workup? H. pylori I think is part of it. We've already done
one of the steps and what will we do next if that H. pylori test is negative and do we have enough
information here about Ms. Floyd, our 32-year-old with epigastric pain to say, if they're more of the
epigastric or the postprandial flavor, which one would you think from this? We said the symptoms are
frequently worsened by eating. I can't really pick any specific foods. The pains in the epigastrium and
those were the main symptoms. They've tried some calcium carbonate and bismuth.

**Iris:** Yeah. Everybody gets H. pylori testing. Absolutely true. The caveat there being how you do that H.
pylori testing. As long as they're young and they have no alarm symptoms, we recommend noninvasive
HP testing. Stool antigen is just fine. If there are any alarm features or they're over the age of 65, we do that H. pylori testing with an upper endoscopy. So, that's that difference. I think-- [crosstalk]

**Matt:** And that's because they're more likely to have malignancy or something serious if they're older, right?

**Iris:** Correct and more important for us to assess for that. This 32-year-old woman with no significant past medical history, I would label as postprandial distress syndrome because most of her symptoms are going to be worsened by eating, it looks like. It doesn't matter that the exacerbating food is not consistent. This is an analogy I like to use for a lot of my patients. I tell them that it's not the food that's the problem. It's the vessel. It's the stomach, it's the lining. This is really important because a lot of these disorders of the gut-brain axis, patients attribute to food. Because often they're related to when they eat and patients get so frustrated by not being able to identify which food is doing it. Even worse, when they can identify specific foods and start eliminating them.

We run this risk of patients doing their own elimination diets and ending up on super restrictive diets with a fear of reintroduction and eating. We can get into that a little bit later if we want to, but suffice it to say that we have to reiterate that it's a function of how the stomach and intestines are working, it's not the food. That's the problem here. I think that another thought in these functional dyspepsia patients, too, is if there is a component of gastroparesis of nausea, vomiting with these. It doesn't imply in our case, but a gastric emptying study can be considered. If they're not quite fitting in a-- oh, it's pain, bloating after a small amount of food, but instead they're also having vomiting, they're also having regurgitation or bringing up undigested food, something like that is when I would trigger a gastric emptying study.

**Matt:** Iris, we've talked about with our patient here, we think maybe it's more of a postprandial flavor. We've done our H. pylori testing, they're younger than 60, so, they don't need to proceed right to endoscopy. What would be the next step? Are you going to do a therapeutic trial here or would you do more diagnostics? What will be the next step and how would you talk to the patient about that?

**Iris:** For this patient, I would go down a treatment algorithm for functional dyspepsia without any more testing. I would reassure her that I'm fairly confident that this is the disorder that she has that the H. pylori testing was really the only thing that's indicated from our large trials. I would start with a PPI trial. Always a reasonable place to start four weeks or so is generally what I give it in terms of time and standard dose. Once daily PPI for most of them. H2 blockers can be considered as well. And actually, H2 blockers have been shown to decrease hypersensitivity in the bowels. For the upper GI tract, they're actually a pretty reasonable option as well and they can have that extra benefit over a PPI, when we're talking about things like functional heartburn.

**Matt:** Yeah.

**Paul:** Are you counseled to give those? I know, PPI or H2s are often used as on-demand therapies in terms of-- for patients with these symptoms. Do they take them routinely or what does that empiric treatment start with?
**Iris:** I would actually have them take it nightly if I'm trying to use it as empiric treatment for a hypersensitivity condition. Yep.

**Paul:** Great. Thanks.

**Iris:** Short of the PPI, there are other pharmacologic and nonpharmacologic treatment options that I use depending on the severity of symptoms and patient preference in addition to any other comorbidities and medications that they're already on. This is where that really taking a good history. I try to focus on, what is the most bothersome problem for the patient in this situation and I tried to target my therapy to that issue. Starting with the non-pharmacologics, peppermint oil and caraway oil have both this formulation called FDgard has been shown in trials to be pretty good. But even the peppermint oil itself has had some good data for improvement of functional dyspepsia and it does that by a mechanism of decreasing that hypersensitivity and as an anti-spasmodic.

The caveat here is, while you can get peppermint in many formulations, [giggles] the biggest thing I tell my patient is, "Please don't drink essential oil," because they could potentially find it and it's peppermint extract.

**Matt:** and **Paul:** [laughs]

**Iris:** But it's formulated for your diffuser. That is poisonous and they should not do that. For older patients, who may not want to take a medication, I actually have them try peppermint tea and sometimes that peppermint tea might be enough if their symptoms are relatively mild. Now, peppermint by itself can actually cause relaxation of your GE junction. It will actually worsen reflux potentially, which is why all the formulated peppermint supplements on the market are enteric coated, so that they don't release until they hit the stomach and are a little bit further along. So, your formulaic options are enteric-coated peppermint, FDgard, and also IBgard, both of which are available over the counter.

**Matt:** Those are peppermint ones. The caraway oil, is there any specific name that that might go by people might see it at?

**Iris:** FDgard and IBgard are both formulated with both and yeah.

**Matt:** Oh, they have peppermint and caraway,

**Iris:** FDgard, at least has both, I think IBgard has as well. Now, caraway oil for the right patient, you can actually just have them take the seeds, and brew it into a tea, and drink it that way. And so, that's an option too, for patients who really want to try it, but don't necessarily want to pay for it or don't have access to it. [laughs]

**Matt:** Paul, you-- [crosstalk]
Paul: It sounds awful. You must be in dire straits if you’re drinking steeped caraway seeds than just have-- [crosstalk]

Matt: [laughs]

Iris: Well, so, Paul, that's a really great point, because these patients are in dire straits. This is the whole point is that many of them are coming to us with, "I've tried this, and that, and the other thing, and give me something." This is where our empathy really comes into play because they are willing to try these things. This is usually really impacting their lives with no benefit from any of the other things they've tried.

Matt: Would you also tell someone with the postprandial distress or epigastric pain syndrome, any just blanket lifestyle things that you would tell these people to do? Because we've talked about some medical foods, I guess, and we've talked about PPIs and H2, but H2 blockers, what else might you do?

Iris: There's more pharmacologic stuff and then there're dietary changes. Let me talk about the dietary changes since you asked. If you're thinking about satiation as a mechanism, it's that their stomachs aren't stretching potentially or that the stretching itself is what's causing their symptoms. Having them eat smaller meals, so that they're not pushing their stomach to the limit that it has to go and avoiding things that would potentially slow down their stomach, so, things that are really high in fat, for example or high in fiber may irritate things in the stomach.

Other things I would absolutely tell them to avoid would be NSAIDs, every GI doctor will tell you to avoid NSAIDs, coffee, alcohol, smoking. The evidence for that is pretty weak, but you can't really go wrong telling someone to avoid [laughs] smoking and alcohol.

Matt: Yeah, but coffee, Iris, you're really watching out, Paul--

Paul: Yeah. This is the-- [crosstalk]

Matt: [laughs]

Iris: Weak evidence, weak evidence. Going [giggles] the other end of that spectrum, what other pharmacologic medications what I actually write a prescription for? This is where it matters, whether they have postprandial distress syndrome or if they have epigastric pain syndrome. The PDS folks, buspirone is actually the medication that is recommended. What buspirone does is it's marketed as an anxiolytic, but it has a lovely smooth muscle relaxation effect. It can actually help that stomach stretch.

This is my disclaimer. Every time I write one of these medications for patient I will tell them, "When you read the label for this, you will see that it is written for anti-anxiety. I am not treating you for anxiety. I am not telling you that this is related to your anxiety." Because by the time they come to me, they have heard that somewhere before. I'm very clear with them that I do not think this is in your head that buspirone has clinical trial data for the treatment of functional dyspepsia. If they look like they don't believe me, I pull out the paper for them. I have all these papers on file, because some patients just
don't. They think that I'm just trying to sell them an anxiolytic, because I still don't believe their gastric symptoms. So, I will pull out a paper for functional-- [crosstalk] [laughs]

Matt: You should put QR codes on the wall with all your common papers and just have them take a picture, if you want to be hit.

Iris: I have them in an EndNote library. That's about as hip as I can get.

Matt: Okay.

Iris: [laughs]

Paul: [laughs] Because it's really nothing hipper than an EndNote library, for sure.

Iris: I've plugged a PS5 at the beginning of the show, how hip can I get?

Paul: That's [crosstalk]

Matt: Yeah.

Iris: For buspirone, I have my patients generally start at five milligrams at night. I'll titrate them up to 15 milligrams t.i.d. before meals. It's about 30 minutes before they eat. However, I want to make sure that they're not having sedation effects from that medication because it is a little bit of an anxiolytic. For the ones who know, who understand that anxiety does play a role, it doesn't cause these conditions, but it can certainly worsen a lot of that hypersensitivity. Those are the ones I tell, "Hey, this is going to be good for your anxiety as well." But in the patients, who are not ready to make that connection, I separate it very clearly. Because that is why I'm using it. It's not because of the anxiety.

For the epigastric pain syndrome, we think that the main pathologic abnormality instead of maybe an accommodation or gastric function issue is that visceral hypersensitivity that they are too aware of what is happening in their stomach lining and that's how I explain it to patients. It's that, "You didn't use to feel this. You don't have to feel this, but you are." One of my colleagues online had actually given this really great analogy of, "Your body was sending an alarm that there's a fire." I can tell you now from looking at your labs, looking at the testing be it H. pylori or endoscopy that there is no fire. Now, we have to help your body turn off the alarm. That's what the TCA is doing. It's turning off the alarm. TCAs have a good proven efficacy for pain control in all of the disorders of the gut-brain axis and SSRIs, we use them, but the data is not as robust as it is for the TCAs.

Matt: Let me try and recap if there's no other agents for this. We started off with a PPI trial four weeks or so, or you can also give an H2 and that was a once daily PPI or you could do H2 blocker nightly, and then we could also recommend maybe try peppermint oil or tea, or caraway oil or tea. Paul, he really wants to try this caraway tea. Dietary changes for smaller meals avoid high fat, high fiber, because that slows stomach emptying and of course, NSAIDs, smoking, they're bad for the stomach. If that's not working, we might think about buspirone as a muscle relaxant for people, who have the postprandial
distress and for patients with epigastric pain since there is more visceral hypersensitivity, we might use TCAs which have better evidence then you said SSRIs.

Iris: Yeah.

Matt: Okay.

Iris: There are some new drugs that are being developed. One of them that I do want to mention is called Vonoprazan. It's a potassium competitive acid blocker in trials in Japan.

Matt: We talk about that on the H. Pylori.

Iris: Yeah. With the [crosstalk]

Matt: Because it's an H. Pylori.

Iris: Yeah. And so, hopefully that will give us a new option, when some people don't metabolize the PPIs very well. Some other medications coming out in Japan called Acotiamide and it basically is altering your gastric function. But they don't know how it's working in humans. It just works. We've got some trials as well that are again, fingers crossed, we're going to be able to start a clinical trial here too, for some other competitive receptors. But basically they're all targeting either gastric function or hypersensitivity.

Paul: Matt, as you're going through the pathway, I'm reminded of our Peabody award-winning cough episode with Brad Hayward, this feels a lot like the same thing, where I think probably, it's helpful to counsel patients upfront. Listen, this might take some time for us to actually get you feeling better addressing your issue. I believe that you're having symptoms. We'll go through things and we will work through this together, but this might take some effort. I imagine there has to be some upfront counseling as it sounds like there's a little bit in terms of trial and error as to what approaches you're using and what's going to be effective for specific patients.

Iris: Absolutely.

Matt: Paul, if you'll remember the Thelma & Louise GIF-

Paul: [laughs]

Matt: -that I put into a PowerPoint. Iris, if you have ever seen this? It's Thelma & Louise. They're sitting in a convertible, and it just shows them like class pants and drive off a cliff together. I was like, "Yeah, treating chronic cough is like a Thelma & Louise thing," where you're just like to the patient, "I'm in this with you till the end. Let's go." It might be a wild ride because you might try so many different steps and treatments, and eventually there're invasive procedures, and this sounds like a similar thing. Do a lot of these patients end up getting EGD with a chronic cough, bronchoscopy was one of the final pathways of it.
Paul: The terminal pathway.

Iris: I think a lot of them do end up getting EGD when they're not responding to some of these lower therapies. But I would say that the way to the society guideline and overall guidance on these disorders is to use that positive diagnosis. I have seen this before. For better or for worse, I've seen other patients who are going through what you are going through. This is called functional dyspepsia. If you don't believe me, I will pull up the Rome IV diagnostic criteria and go over it with you. This is how we treat it. For certain patients, I will go through-- We think this is what's going on. We think it's a hypersensitivity. This is why I'm using these medications. This is the rationale behind why I chose this for you. This is what you should look for. I think that a lot of this--

It's the other reason for anxiety, because it takes time, it takes you having to sit down, and look a patient in the eye, and make this treatment plan with them, and often we don't have that time. But I think it's important that you don't necessarily feel that anxiety or show it because the more rushed you are, the more you drive up your patient's anxiety. The more they feel you are on their team, the more willing they are to give these medications a try, and not seek that second opinion, and not force that upper endoscopy when it's not needed.

The other thing too is this idea of positive diagnosis. You want to introduce these disorders early. When you have this pattern in a patient where you read the patient history and you're suspecting a disorder of gut-brain axis, I tell them, "I will send you for X, Y, and Z testing. H. pylori, routine labs, if they're over 55, I'll send you for the upper endoscopy. However, if this comes back positive you fit the category of these disorders and I'm fairly certain this is what you will have." So, that it's not a-- "Oh, hey, the testing came back negative. So, it's probably this." I bring it to them upfront before I do the testing that, "This is a likely diagnosis for you and there's nothing wrong with that diagnosis. But if this is the path and everything else comes back negative, I have a diagnosis for you and I have a treatment plan that we will go down to not be disappointed if the EGD is negative." Yeah.

Matt: What strikes me about this is there's very little testing. It's H. pylori, some therapeutic trials, and they may have an endoscopy at some point. But it's not a huge amount of testing here.

Iris: Yeah. Plus or minus like a gastric emptying in a patient who's very, very persistent or has that right profile where they could potentially have it, yeah.

Matt: Right. Paul, how do you think things ended for Ms. Floyd? Do you want to wrap it up for us? What do we do for her postprandial distress?

Paul: Yeah. No, I'm happy to report. We stopped at the caraway tea shockingly. She had some tea that tasted like toast and her symptoms relieved magically overnight. So, we cracked the case wide open. She's doing great now. [unintelligible [00:40:03] up in this way.

Matt: [laughs]
Paul: All right. We’re going to move on to Ms. Cruz now. This is a much shorter case. I guess, maybe, because we have presumptive diagnosis, but Ms. Cruz is a 40-year-old female. She's coming to us with a past medical history significant for gastroenteritis about six months ago, who is now presenting with recurrent loose bowel movements and abdominal pain. Right out the gate just given that very brief and abbreviated history, Iris, does that trigger any thoughts or any presumptive diagnosis that we start chasing down?

Iris: Well, given the theme of the episode, I'm going to go with IBS and I'm going to go with postinfectious IBS. Let's talk a little bit about IBS. I know you guys covered this on a prior episode fairly extensively. So, we'll go through that--

Matt: It was so long ago. It needs an update.

Iris: [giggles] Rome IV criteria for irritable bowel syndrome. It's recurrent abdominal pain on average at least one day a week in the last three months associated with two or more of either relation to defecation, so associated with the change in frequency of stool, or associated with the change in form, or appearance of stool. And of course, with all Rome criteria filled for the last three months, symptom onset at least six months prior to diagnosis. This is actually getting called into question a little bit in the irritable bowel syndrome diagnosis because the last this like time lag makes it necessary that patients have to wait this long before they receive an IBS diagnosis.

And often, we already know it's IBS. It's a little bit of a minutiae if you will, but the societies are moving towards saying, "You don't need to wait three months necessarily to make an IBS diagnosis in the right patient." That way, drugs can be covered, patients can undergo less testing, and they can get treatment a little bit faster. So, it's just something to be aware of.

Matt: We have done episodes recently with you talking about diarrhea, talking about constipation and Elena made these great figures that-- Walk us through what kind of workup you might do for someone with chronic constipation or chronic diarrhea? When you're thinking about this diagnosis here what is the minimal testing that someone needs to have done that you would recommend? And of course, we can post these figures that I'm referring to in the show notes.

Iris: Absolutely. The societies have been really good about putting out guidelines for this testing, so that we can follow an algorithmic approach and that we can really minimize unnecessary testing. Again, positive test strategy, Mrs. Cruz, I'm going to send you for these tests because these are common conditions that may mimic what you have. However, what you have really sounds to me like it's postinfectious IBS, and if the testing comes back negative, which it's very possible it will, we will go down that algorithm, and we will still get you the treatment that you need.

IBS diarrhea subtype, the testing that is recommended is to rule out celiac disease with serologies. Noninvasive testing, fecal calprotectin to rule out inflammatory bowel disease. If that's not available, consider a CRP. But the fecal testing is actually pretty good to identify IBD versus IBS. If available, either a calprotectin or fecal lactoferrin is what is recommended. The pathogen testing is not recommended, but in the cases of these postinfectious or in patients with high risk, I will test them for
either C. diff, or Giardia, or both. For Giardia, the risk is frequent hiking, where they're drinking stream water. If their water source, if their primary water source is well water, I will test them for Giardia as well or if they have other risk for outbreak like a family member had it or something like that.

Other things to think about, when at the primary care level, I think that is really, really appropriate testing and it's okay to stop there. At the GI level. If a lot of our empiric stuff is not working, we'll think about doing a flexible sigmoidoscopy and taking random colon biopsies for microscopic colitis. It always sounds terrible when I call them random biopsies. I'm aware of this term, but it just means that you're not targeting anything that looks abnormal and that there's no quadrants or anything like that.

Then we do bile acid testing for bile acid malabsorption and that's generally a 48-hour stool collection. High-risk patients for this include those who have abnormal bile acid circulation. Anyone who's had ileal disease for any reason, if they had Crohn's disease and they had their ileum taken out or an extensive appendectomy, anyone who has had their gallbladder out, and that diarrhea never got better they're at risk for bile acid malabsorption. But a large percentage of our IBD patients have this as well and it's important to know because they respond to different treatments, right?

Matt: You've told us, it was less than 100 centimeters above.

Iris: Yep.

Matt: They overproduce bile acids. So, they might actually just be producing so much that they can't reabsorb them all.

Iris: Absolutely. If they have lost their terminal ileum then they can't recycle and recapture those bile acids as effectively. The other thing that always comes up is SIBO. The small intestinal bacterial overgrowth for any reason, if they had Crohn's disease and they had their ileum taken out or an extensive appendectomy, anyone who has had their gallbladder out, and that diarrhea never got better they're at risk for bile acid malabsorption. But a large percentage of our IBD patients have this as well and it's important to know because they respond to different treatments, right?

For IBS-C, testing becomes a lot more easier. We do the GI digital rectal exam, or an anorectal manometry, or both. And then if they are above the age of 45 and have not had colorectal cancer screening, new age 45, that's when we do the colonoscopy. But that's for colorectal cancer screening. That's not for the constipation workup. Basically, we're just trying to catch them while we will screen you.

Matt: Yeah.

Iris: But important to note that that's why, because insurance will cover one of those and potentially put the patient responsible for a cost if you're doing this for diagnostic purpose. So, know that we're not doing it for diagnosis. It's for screening.
**Matt:** Yeah. Last time, when we talked to you about constipation, we looked for secondary causes, medications, and things like that, any red flags. And then we did a trial of laxatives. If that didn't work, they're getting the manometry, and the advanced rectal exam, and-- Yeah, the manometry, the balloon expulsion. If we don't find anything with the pelvic floor dysfunction testing, which is the manometry and such, then we might do these transit tests for slow transit constipation. If there's no slow transit, then they're like, "Okay, this is probably IBS-C." But I imagine most patients don't even get that far or need to get that far.

**Iris:** The transit testing doesn't happen very often and I think there was actually a listener question. I think somebody had posted this on Twitter. I think it was Katie Donlevy. The question was like, "When do we do the slow transit constipation testing?" Because the testing is so onerous and it doesn't necessarily change your management, I actually will treat my patients when they sound like IBS-C. When they have that pain component, I will treat them down the IBS-C algorithm. When I think about transit testing is really when those laxatives aren't working as well as I think they should, and they're not getting a response, and there's no pelvic floor dysfunction, and somewhere the rest of their history is more consistent with some neuromuscular disorder as opposed to a central sensitization flavor.

It's unfair for me to say, because I see these patients day in and day out. I'm developing these kinds of protocols, and algorithms, and patient imprints. But if my patient has fibromyalgia, chronic fatigue, migraine, and these other central sensitization conditions that are known to be traveling with IBS, I'm not going to put them through slow transit constipation testing.

**Paul:** You've mentioned all this in terms of framing it as being that as a positive diagnosis and we expect the testing to come back relatively reassuring. Similar to the dyspepsia question, how are you explaining what's going on to patients? When you're talking to patients about, obviously, they're worried about the worst and I think always cancer is a huge concern, especially, imagine with the constipation. But how are you framing the discussion about the background pathophysiology?

**Iris:** Depending on a little bit on what is their predominant symptom, so, let's talk about if the predominant problem is pain is this visceral hypersensitivity that they are just feeling their colons move. And often, that is what they're feeling in irritable bowel syndrome, because it's their colons pushing that bowel movement along or trying to push the bowel movement along unsuccessfully. I talk to them, depending on patient level, I will pick and choose my spiel. But I'll tell them that the CNS, upper brain and the enteric nervous system develop together embryologically. They used to be one nervous system and then they separated. This is really important because they still respond to the same exact neural modulators. This is why we use them. It's not to treat anxiety, it's not to treat depression, it's to treat the gut nervous system itself because it responds to the same stuff.

I tell them about how that visceral hypersensitivity can develop from a number of reasons. One of them being, the postinfectious IBS is a really good example for how to start is when they have an infection, a lot of things in their bodies become abnormal. One is the microbiome. The good bacteria get wiped out along with the bad bacteria or there's this dysbiosis where the bad bacteria grow back and the good ones don't. That can cause an increase in sensitization of their bowels. So, that basically they had this
fire, we will go back to the fire example. When they were infected, but the infection has gone, the fire has been cleared. Now, you just have to turn off the fire alarm. The fire alarm is basically stuck on.

When I talk to patients about this, I try to gauge where they are and I meet them there. I'll just give you a couple of examples of the analogies that I'll use to explain this to a patient. Sometimes, I'll start with how the nervous systems are related. I'll tell them that the enteric nervous system and the central nervous system were one nervous system embryologically. And then, as we develop, they migrated apart. But that's why they respond to the same neurotransmitters and that's why the neuromodulators that we use to treat anxiety and depression also work in the gut. Here's why I'll reiterate that I am using this to treat gut disorder and not to treat anything in the brain.

The other thing that sometimes I'll use is that role of the parasympathetic nervous system, which I think we've talked about in the constipation episode, where heightened sympathetic nervous system activation can drive gut function to slow or stop. But really, when it comes to disorders of the gut-brain interaction, we're talking a lot of hypersensitivity, so that the gut is again feeling things that it's really not meant to be feeling and how do we get that to calm down. So, we talked about that fire alarm. The fire alarm was set off either by something like an infection, or a cold, or a course of antibiotics even though there was necessarily, either the fire is already gone or there was no fire to begin with and we just have to turn that alarm off.

Sometimes, I'll talk to them about, "Well, yes, we don't see a cancer, but you feel there's something bothering you." Well, folks, who have phantom limb syndrome, they don't have an arm, but they can still feel arm pain. That's how our central nervous system is wired. Sometimes, often, I'll give them an example, especially in chronic constipation, where I know that they have stool sitting in their bowels irritating the lining. I'll tell them that if I take my intact skin and I rub it over, and over, and over, and, over, and over again, well, eventually it's going to turn red. And then if I keep doing that, it's going to get rugged raw and there was nothing wrong with it. But now, the sensation has changed and it's hypersensitive. If there was an insult like an infection, I'll tell them, "Well, we cut your arm open, and then didn't quite allow it to heal, and it's just still being irritated."

When we talk about more of a central sensitization when the IBS comes along and it frequently comes along with things like fibromyalgia and chronic fatigue, then I give them more of a talk about central sensitization and what does that mean? Well, that means that the pain receptors that were carrying bowel function, or pain from the back, or even from fatigue, now, instead of these thin pain fibers have been activated so many times that your body thinks that this pain signal is really, really important, so, now, it's become a myelinated superhighway. We have evidence that this happens. The MRI findings of chronic pain patients light up differently than patients who don't have chronic pain. So, I try to take that science and what I know about the pathophysiologies of these conditions and make it relevant to a patient's experience depending on how they're experiencing it. Does that help or is that too scattered?

Matt: I don't think it's scattered.

Paul: [crosstalk] that's great.
Matt: I think it's a hard condition to explain and it's nice to have some answer, as far as the actual pathophysiology of this. Especially, better than as we've already said multiple times on this. Don't just tell the patient, "This is your anxiety. Here's an anxiety medicine," which is I think happens way too often.

Iris: Often. It's not necessarily that right. "Oh, the testing came back negative. There's nothing wrong with you, but the algorithm says to try this medicine." And then patients see that it's an antidepressant and they get that wrong message because it wasn't conveyed or explained why they weren't getting this medicine, and so they don't take it. So, often, it's well meaning.

Matt: And I think we should move on to talking a little bit about the treatment and whether it's IBS-C, IBS-D or mixed type. What's your spiel about treatment? We can go through the pharmacologic and nonpharmacologic and we do have some listener questions about some of the nonpharmacologic stuff as well.

Iris: Maybe I'll go over the guideline-based stuff pretty quickly and also, you guys talked about this in a prior episode. FODMAP diet is a big question. Always a very limited trial with a nutritionist if possible. But only six weeks and they have to start reintroducing, otherwise they're risking micronutrient deficiencies, but they're also risking persistent food intolerance. That's something that I think we could talk about more, but doesn't get talked about enough. If there's significant cramping pain, I will reach for an antispasmodic. But the guidelines do not recommend for an antispasmodic for global IBS symptoms. There's just not enough data to support their use overall.

Aggressive constipation management, the guidelines recommend lubiprostone, linaclotide, plecanatide, tegaserod, and we can give the doses, and what these are in the show notes, I'm sure. Peppermint supplementation has some good evidence for IBS as well. That's that same medication we were just talking about for functional dyspepsia. Prescription laxatives are recommended for your constipation like we talked about and rifaximin is recommended for IBS-D. However, I'm sure their ID doctors, who would skewer me if I'm recommending this. It is still an antibiotic and I actually do try not to use it, if possible, one because it's so difficult to get covered for most patients. I'm already talking to a patient about dysbiosis. I think that their microbiome was disrupted. And now, I'm going to give them unless I really, truly think that they have SIBO, and they need that treatment to limit their flora. I try not to use that antibiotic, but it is recommended in the guidelines. So, expert deviation if you will.

Otherwise, for IBS-D, alosetron is a new recommended medication. It's a serotonin antagonist for IBS-D in women. And then eluxadoline is still available, but know that you shouldn't use that medication if a patient doesn't have a gallbladder. It is contraindicated in that situation. The TCAs have pretty good efficacy for global IBS symptoms, but I will mention that, because we talked about central sensitization coming as a package for a lot of these patients. They often come with the comorbidities of anxiety and depression. They're already on something for either anxiety or depression. In those cases, I will always leave it to their treating psychiatrist or their primary care physician, who's managing that other medication. I will not add on a TCA.

Paul: Iris, before since TCAs have come up now twice, can I just ask--
Paul: In the absence of a reason to not prescribe one, do you prefer amitriptyline or nortriptyline, or what does that look like practically speaking for you?

Iris: I like to reach for nortriptyline. I also like the desipramine mostly because amitriptyline can be a little bit constipating for patients. So, I don't want to send, especially, if I'm trying to treat constipation, I'm not using a constipating medication but nortriptyline and desipramine seems to have better profiles for that.

Matt: And audience, I know we have some geriatricians listening. One of whom I have office hours with. Antispasmodics and the TCAs, be careful. If you got a 75-year-old, please, that's all I'll say. But Iris, do you have favorites out of these? You gave us a ton of options here. Antispasmodics, aggressive constipation, peppermint, you said alosetron, maybe elux--

Iris: Elux--.

Matt: Eluxadoline and then the TCAs, in primary care, what do you think we should be reaching for? Probably, I'm not going to be able to get my hands on some of the newer fancier ones. What do you think we'd have most success with and we should be comfortable reaching for?

Iris: Just on the topic of geriatrics medicine, the other thing about these medications and TCAs and this whole central sensitization issue, it's not just overlapping mood disorders. It's also chemical sensitivities. Often, I hear from patients that they do not tolerate the TCAs or SSRIs because they end up with side effects. That's also another caveat that while they are good, they're often difficult to tolerate for patients. What are my favorites? I will use the secretagogues. I know we talked about my constipation plan. That is always where I start. I try to aggressively manage their constipation. In trials, that hasn't necessarily shown improvement in the pain component, but I think improving the bowel movement is the key to reversing some of this hypersensitivity, if I think that that's where it started. I will aggressively manage constipation, if it's there.

For diarrhea and so from a primary care standpoint, it's very reasonable. I've seen a lot of primary carers for some of these secretagogues, either lubiprostone or even linaclotide seems to be a pretty popular choice. And unfortunately, often, it's dictated by insurance. It's like, "Which one insurance will cover before I'm allowed to try the next one?" We could rage about this for a very long time. So, I will use that. We had talked about probiotics a little bit, too and we could talk about it more, because I think there was a question about it.
**Matt:** There was a question from Twitter and I believe it was John Damianos and he asked about probiotics and then another listener on Instagram was asking about the microbiome and its relation to this. So, I think these two questions, do you talk about that with your patients and do we have anything there that you're recommending?

**Iris:** I talk about it a lot. I talk about how the microbiome plays a role in both microscopic inflammation, which we know exists at the tissue level of IBS. We have good data showing mass cell activation, increased neurons, etc., etc. We know there's some sensitization happening at the nerves and we know that with certain microbiome compositions that that's more likely or less likely. There's proinflammatory gut bacteria and then anti-inflammatory gut bacteria. We know that it's better when the ratio is better for the anti-inflammatory folks. What we don't know is how to make that happen. That's where I leave it with patients. I'll tell them that we have evidence that this matters, which is why I'm not going to give you a fifth course of antibiotics, because I want to preserve what you have, which is also why, if you limit food for a really long time, the bacteria that help you digest certain products are going to not be fed. It just to simplify that and so, you'll be less likely to tolerate that in the future, which helps patients stop doing this like, "I will avoid all things that make me feel bad," especially when everything makes them feel bad. Getting a little off topic.

I help them to understand that the microbiome does play a really important role and then I tell them, unfortunately, I have really no good way of fixing that right now. There has been some talk about stool transplant to fix it, but that is not recommended at this time. One, because it's relatively invasive and two, there is a risk that you'll get some infection from that stool, even though, that risk is incredibly small. When you're using it to treat something like IBS, where the risk of mortality from the disease itself is low, you can't take that risk.

Then we're left with probiotics. There's a couple of probiotics out there that do have some reasonable data. VSL#3 being one of the few that have clinical trial tests. But the problem with a lot of these disorders and with probiotics is how heterogeneous everything is. Your meta-analysis data is unable to be pulled, because you're essentially using different drugs, but calling it all the same. The probiotic formulations being used are so different that they don't pull very well. You don't really know what's working and what's not and there's no FDA approval for most of these. So, you don't know what's actually in them.

I will tell patients just like the prior speaker you had, I will say, "If the probiotics are helping you, fine. All it's hurting is your pocketbook. If you want to give it a try even, fine." I would recommend, you can give VSL#3 a try or I'll tell them that their specific strains that have some good data and to look for those if they're going to buy a supplement. I'll talk to them about natural forming probiotics. So, fermented foods, for example, yogurt with live active cultures has some data that it helps and then things like kombucha, like kafir, data is very limited, but as long as it doesn't hurt it's not unreasonable. And sourdough is my favorite.

**Matt:** Paul, you can keep drinking your kombucha.

**Paul:** Oh, thank God.
Matt: [laughs] Well, so, with our patient here, let's go back to our patient. We've given just a huge amount of options for IBS here. And Paul, that always makes me think that, as we said at the beginning, this is one of these just like another Thelma & Louise type thing, where you're just going to try a lot of things. I do find that patients often— You just give them a lot of options, you empower them, and if they're motivated and you work with them, see them frequently, those figure things out that that help get themselves better. I don't know that I can take credit for the IBS patients that seem to be doing well. I'm not sure if you have that experience, Paul, with your IBS patients.

Paul: It can go either way. I'd be much more [unintelligible [01:04:58] Iris’ experience. but I feel if you give too many options all at the same time, they're like, "You're the doctor. You tell me what to do." So, I think you have to give, at least, some initial framework and wait for them to select. I think that's probably the most helpful way to empower them without overwhelming them, because there's a lot of choices here.

Iris: Yeah. Let me throw a couple more in the mix. We just talked about some of our patients have chemical sensitivities. They don't want medications. They don't like taking medications, they'd rather go a natural path. Let's talk a little bit about CBT. Because among all of the options, guideline recommended CBT has excellent data. A number needed to treat a four. So, gut-directed psychotherapy. This is very different than CBT or cognitive behavior therapy for something like anxiety, something like depression. These are specific psychotherapists who are trained specially in gastrointestinal psychotherapy and so, they'll apply symptom-specific management and treatment options. It's a short-term eight-to-12-week treatment period. Number needed to treat is four. Similar in efficacy to a TCA with no side effect. However, no side effect. The caveat is access. The caveat is patient time, and provider availability, as well as insurance coverage.

The other treatment, which is, of course, near and dear to my heart in this category is gut-directed hypnotherapy.

Matt: Yes.

Iris: That's got the same number needed to treat NNT of 4 with very minimal side effects. With the hypnotherapy protocols, we do a seven-session protocol over the course of 12 weeks. They take about 20 to 30 minutes each. I usually see a patient for about 40 minutes because we talk about how they've been, we do brief after, and it's an option now, because availability is limited. Both of those options are now becoming increasingly digitized and so, there are more and more apps coming on the market to improve access to CBT and hypnotherapy for gut specific disorders. And so, that's going to be really exciting I think for patients and providers alike.

Matt: And for functional dyspepsia, the NNT that you're giving was that for functional dyspepsia, cyclic vomiting, and IBS or just IBS?

Iris: It's for IBS.
Matt: Okay.

Iris: That was where that study was done.

Matt: Got it.

Iris: But what it's really targeting is the visceral sensitivity. That's a common thread in all of these conditions. Functional dyspepsia, specific hypnotherapy protocols are actually in development. One of the hypnotherapy folks has developed a digitized version of that as well. Hopefully, we're going to be able to run that through a clinical trial soon and be able to provide that for folks to listen to on their own time, which would be really, really helpful, I think.

Paul: Very cool.

Matt: I think we've ran through a lot of options here and we definitely want to get onto cyclic vomiting, because the audience was excited to hear about that. I know Paul and I are too, because I don't know much about that. One of the things I think we didn't mention, yet. Do you have a favorite anti-diarrheal for patients with IBS-D that you recommend? Is it loperamide or the combination medicine that I only know the brand name for atropine, whatever? What do you like to use for that?

Iris: I do like to start with loperamide. It's just easy, it's usually easier for patients to get. I really don't like dealing with insurance companies to be very honest with you. But the difference that I'll do with the loperamide is that, I'll tell patients to schedule it. Often, they'll tell me, it didn't work. That's because they're taking it according to the package instruction of, "Take one after diarrhea starts and then thereafter." But I'll let them know that this is their pathophysiology and it's the difference between trying to keep a horse in the barn and then trying to rein in a horse after it's already out of the barn. So, scheduling the loperamide tends to be better than trying to chase the diarrhea after it's already out, when it's a chronic issue.

Matt: She just said, she is in diarrhea, Paul. It's late at night. I'm having trouble keeping a straight face.

Iris: Why I'd need to? There is no need to keep a straight face.

Matt: We're having fun. We're talking about poo. Iris, is bismuth also something that you find for these patients as maybe a second line or just loperamide is generally sufficient?

Iris: I try really, really hard to diagnose them with something else to be honest with you. Bile acid malabsorption and then I'm giving them cholestyramine if they have microscopic colitis. Actually, I will use bismuth for that. That is actually one of the frontline treatments. Otherwise, I will try bismuth, but often, I'm not finding a lot of success with it and patients, they just really don't like it. It just doesn't taste great.

Matt: Okay.
Iris: And so, I can't force them to keep trying it.

Matt: Well, lucky for our patient here. We'll wrap up this case. Ms. Cruz, she was in the area, she was lucky enough to have you as her physician. She had some hypnotherapy and just felt better after that and symptoms are managed. Maybe she's using some peppermint now and again, and with this gastroenteritis, the people that have the postinfectious type, does that tend to go away as opposed to somebody who has more of an idiopathic cause of it?

Iris: I think they're more likely to resolve and it's about 30% of them will respond completely. They will resolve spontaneously. 30% will need some therapy to help and 30% persist.

Matt: Okay. So, let's get on to the final case here, cyclic vomiting. Paul, did you want to take that one?

Paul: I mean, you probably gave out the diagnosis, but I suppose I can at least read it to get us there. We'll talk about Mr. Banks. He can't be 27 years old and gentleman, so just male with a past medical history significant for generalized anxiety disorder on citalopram presenting to your clinic as a referral from the emergency department. After presenting with recurrent nausea, vomiting episodes requiring IV medications to alleviate emesis over the past year. He does not drink alcohol, he really smokes cannabis. The symptoms of nausea, emesis, and abdominal pain lasts for about five days, and they recur every few months. Hot showers do seem to alleviate the symptoms, however.

Already, Matt's steered us straight into the oncoming traffic of cyclic vomiting syndrome. There is this hot shower, they once looked at a joint and now, so, we have to assume that it's cannabis-associated hyperemesis. Could you talk us through the two diagnoses, and how they're related, and how they're different? Because I feel they're often talked about as if they're the same thing and it sounds as if maybe they're not.

Iris: Absolutely. I feel at one point in time, I didn't even realize that cyclic vomiting syndrome was a separate condition. I thought everything was related to the cannabis and it's really not. Cyclic vomiting has a Rome IV criteria. At least, three discrete episodes in the prior two years, two episodes in the past six months occurring at least one week apart, but the kicker here is absence of vomiting between episodes and other milder symptoms can be present. So, they don't have to feel their best, but they're not vomiting between episodes. This is very different than patients with functional nausea and vomiting, where they feel sick almost all the time. These patients in between episodes feel fine, and they think that their disorder is gone, and then all of a sudden, hits again. The other big component of CVS or cyclic vomiting syndrome is this family or personal history of migraines. Sometimes, they're actually compared to abdominal migraines, because even though, it's called cyclic vomiting syndrome, it can come with abdominal pain.

The other important thing to note here is both cyclic vomiting syndrome and cannabis hyperemesis syndrome can have relief from hot showers. You cannot diagnose cannabis hyperemesis just from the hot shower alleviating the symptom. Otherwise, the cannabis hyperemesis really-- You have to have used cannabis for a prerequisite for the suspicion. But what we're finding is, it's actually quite prolonged use. Usually, it's not the occasional or rare cannabis user who's developing cannabis hyperemesis, just
the chronic users who smoke a significant amount over time and on a regular basis, who are developing this problem.

But to keep things really confusing for everyone, patients with cyclic vomiting syndrome tend to present relatively young and they know that cannabis helps prevent the nausea. Then they start using the cannabis, because they were previously nauseous and then it becomes a cycle of you really have to dig back into that history to say, "Well, when did that nausea actually start," so that you're not just labeling them with cannabis hyperemesis when they were actually using the cannabis to try to treat this underlying disorder, but now, the two have gotten all mixed up.

**Matt:** I thought they were totally separate things. I didn't really realize. But I have seen patients, where you're not sure if it's the fact that they're smoking every day that came first or the nausea and vomiting came first and in some cases, a couple patients that I'm thinking up from the past few years, they couldn't even really tell me clearly which came first. At that point, they felt that they had to smoke to try to help with their nausea.

**Iris:** Yeah. And sometimes, I will tell them, "I know you've heard this that you have to quit the marijuana. Listen, I'm not blaming it on the marijuana, but I will tell you that it is not helping that it helped in the beginning, but now, you are almost dependent on it to treat the symptom and we have to take it away." But that's asking someone to stop smoking. You can't just take it away. You have to help support them while you're trying to get them off their other treatment option, basically.

**Matt:** I always thought it was maybe a month off, but I was reading maybe even six months you have to take to tell them to stop. For someone with a daily habit, that can be pretty tough.

**Iris:** There's no consensus guideline on how long you have to tell them to stop. I will tell them that it can be months and I think six months is not unreasonable. I have sometimes used and this is a weird. I wish Elena were here. [laughs] I use relationship breakup guidelines. How long does it take you to get over a relationship? Well, at least, half the time you spent in the relationships. [laughs] Well, I use the same principle. If you've been smoking marijuana for a decade, this is not going away in two months. You have to be clear for a little bit longer. But that's a wishy-washy kind of [unintelligible [01:16:31] counseling.

**Matt:** I like it though.

**Iris:** There's no guideline. [laughs]

**Matt:** That's good.

**Iris:** [laughs] Paul is not amused.

**Matt:** That's expert opinion, if I've ever heard it, Paul.
Paul: No, that's terrific. I'm just thinking because I feel like I don't know, when we were coming up in training a million years ago, when we're doing therapeutic leeches and trepanning and stuff, that was just when they were started talking about this cannabinoid-associated hyperemesis. And then as soon as everyone heard about it, they became so excited to diagnose people with it. But I just wonder how many patients were misdiagnosed with that just because you had--

Marijuana use is so prevalent. You hear some vague history of marijuana use and they have these recurrent episodes of vomiting. I just wonder how many patients unfortunately got saddled with a diagnosis just because it's appealing and you also get to maybe a little bit of moralism on top of it, too, that this is anything new that we're talking about, but just spit balling here.

Iris: No, but it can be definitely stigmatizing and this also plays into how you counsel a patient and how you approach a patient with this, because they already know. They've heard this. They've heard that you're just going to blame the weed and not treat them. It's really important to make that alliance to say, "I'm here to help you, whether or not marijuana was the reason." On the flipside, ED visits for nausea and vomiting in Colorado have doubled since marijuana was legalized.

Paul: Oh, interesting.

Iris: There is certainly something there, but how many patients are misdiagnosed? I don't know. Because they are a very similar population. It's young patients, who are probably also in the time of their lives, where they're experimenting with things because they weren't big nerds like me.

Paul: [laughs]

Matt: Iris, we had a listener from, I believe, this is Instagram. Seema Jaga, who asked about like, "What are the most common etiologies for hyperemesis?" They see this a lot in inpatient side of things? We talked about the differential. Is it cyclic vomiting, is it cannabis? But what else do you think about for these patients? What's the diagnostic workup or framework for this?

Iris: Oh, gosh. Vomiting, it's one of those diagnoses that give me heart palpitations. Because nausea as a symptom, we can talk about that probably for another hour. There're so many other things that could be, especially, when it's bad enough to get someone admitted to a hospital. For me, I always try to rule out not GI. Is there some brain etiology that you have to worry about? Is the patient pregnant? Do we have some other electrolyte abnormalities or disturbances? I don't know if we have time to talk about all of this. But for me, the pathophysiology of nausea, we think about smooth muscle distension, like, which piece of smooth muscle in your internal organs is being distended right now? Any of them will cause nausea. That's why gall stones cause nausea, that's why when you have kidney stones, you get nausea, that's why gastroparesis gives you nausea. So, the differential is so broad that it is really hard to give a-- I don't have my heuristic algorithm necessarily, unless I see a patient.

Matt: That's probably why these patients end up getting CAT scans.

Iris: Yeah. GI consults.
Matt: Yeah. CAT scans and GI consults. I guess, the first time someone presents with this, if it's intractable nausea and vomiting, most of these patients are going to get imaging and oftentimes, they might get an endoscopy. What else do you think of, does gastroparesis overlap with this? Is that something that people confuse for this? We've talked about that overlapping with functional dyspepsia.

Iris: Yeah, it certainly can. Nausea and vomiting in the setting of eating, I think it's always reasonable to do a gastric emptying study, but that's an outpatient workup. It's generally relatively uncommon for that to suddenly appear as intractable nausea and vomiting. Nausea and vomiting as a symptom, you have to think about like, "Is this acute, is it chronic, is it a change, or is this something insidious, does it come with pain, does it come with other symptoms, is it morning, is it postprandial, is it recurrence or is it cyclic?" So, there's a lot of history that goes into trying to work up the nausea.

Matt: Okay.

Iris: I'm trying to get myself invited back, apparently.

Matt: Okay. We might have to do it a nausea episode to follow up. Somebody mentioned and are there action plans that are created for these patients? This was on Twitter. Pat Reeves was mentioning a "It CVSA online, a cyclic vomiting syndrome action plan online," which is a non-profit that exists I had never heard of.

Iris: I actually looked at that action plan and it's beautiful. I love it. I'm going to start using it. I usually draw it out for my patients in chicken scratch. This is beautiful. That goes into a little bit about cyclic vomiting syndrome and how it presents. We actually think about cyclic vomiting syndrome in phases. There're four different phases of CVS. Phase 1 is the inner episode time, when the patients are feeling really, really well. Phase 2 is prodrome where they usually can feel that vomiting is about to start or that nausea is about to start. Phase 3 is the actual episode of intractable nausea and vomiting and Phase 4 is the recovery period when they're settling out.

This might sound very familiar to a lot of folks, because this is how migraines are thought about. And this goes into why cyclic vomiting syndrome is-- Sometimes, it tends to calm with folks who have this history of migraine headaches either in themselves or their family. We actually treat it very similarly. In the Inter Episode Phase or Phase 1, our goal is to prevent an episode from happening. We can actually use migraine prophylaxis to do this, including amitriptyline, propranolol, and even cyproheptadine, which is a really good medication for nausea of all ideologies.

In the prodromal phase, our thought is to stop the episode before it happens. Things like lorazepam, this is when you're doing the sublingual Zofran, analgesics, and a triptan can sometimes help, especially, if there's a headache component to that prodrome. You're actually doing very similar things to migraine prevention. During an episode, often, patients with cyclic vomiting and CH cannabis hyperemesis as well, don't respond very well to our routine antiemetics but IV Zofran can help-- Oh, sorry, IV ondansetron. Lorazepam has been used for these episodes, as well as chlorpromazine, diphenhydramine, etc. These are usually being given not necessarily PO, so sublingual, IV, PR rectal,
because patients are having trouble keeping the medication down. So, if you're making them swallow a pill it's not going to work as well.

Sometimes, patients take sedatives so that they're asleep just like in migraine headaches until the episode passes and then they recover. Sometimes, if it's bad enough that they're hospitalized, we're using IV proton pump inhibitors, we're using IV fluids to try to get them through that acute episode. Some evidence for haloperidol as well as like a second-line medication.

Matt: Right. Prochlorperazine, haloperidol, these anti-psychotics seem to have some nausea benefit, the earlier generation ones anyway.

Iris: Yeah, absolutely.

Matt: Paul, are you raising your hand to ask a question or--?

Paul: I'm just scratching my forehead but thanks for-- [crosstalk]

Matt: Just scratching your forehead. Audience, Paul's scratching his forehead. Sorry for the interruption.

Paul: [laughs]

Matt: Well, there're a lot of options here. I think probably people are very comfortable with ondansetron, but I think sometimes people forget that these other things like you mentioned antihistamines, and we talked to anti-psychotics, benzos, and those can all have the antiemetic properties, and then you mentioned because there's some migraine overlap that triptans can also be used. And probably, intranasal or subcu, if they're vomiting, they're just going to vomit up if you give them the tablets.

Iris: The triptans are really good for aborting the episodes and so you want to do it when they're having their prodrome and not when they're already vomiting. Then your options are a little bit more wide. If you can prevent that episode from happening, which is why you have the action plan, so that if you're giving patients these four different medication options, you want them very clear like, "This is when you use this, this is when you use that. When you feel your prodrome coming on, you reach for this."

There are other heavy duty antiemetics, like aprepitant, that have been used in severe cases. The aprepitant is a medication that has been approved for chemotherapy-induced nausea and vomiting. But sometimes, one of the only things that will work PO for these patients with severe vomiting and so, we apply for insurance exceptions and we try to provide patients with a way to stay out of the emergency department.

Matt: I feel that the patients with this condition they definitely get stigmatized when they're admitted recurrently, the hospital starts to know them, and sometimes, when they have a heavy pain component, and they're getting IV pain medications, plus all these other IV medications for, I feel these patients
have a tough time. As far as just counseling or nonpharmacologic, do you have any tips for the audience if they're working as a hospitalist in seeing a lot of these patients?

**Iris:** I think that if they have cyclic vomiting syndrome, there is no cannabis involved, often it's a little easier because there isn't that stigma associated. And then even though they're all the same patient population, people feel bad, and then take care of them, and it's not such a problem. When they come in with a lot of pain, certainly, but I think that making sure that they have a good outpatient provider, who they have a therapeutic relationship with and then if they come in with a good plan, I think it's easier for everybody involved to say, "Hey, this is what my outpatient provider and I came up with." It's like patients who have a pain contract. "This is what works for me. I'm not trying to ask for more." But to make sure that the patients know what's safe for them and to develop that relationship with an outpatient provider, so that they have a plan, whether it's inpatient or outpatient, and a person to call and notes to refer back to help anchor their diagnosis.

When cannabis is involved, I think it becomes a lot more complicated because there is a lot of bias. I think working with patients to help them understand that this is beyond the marijuana use, that this is a condition that you are suffering. But like it or not, the cannabis is playing a role. You're not telling them this while they're acutely vomiting. They're not going to listen. This is not helpful information. You treat them, you take care of the patient as they need to be taken care of and then when they're in that recovery phase and ready to leave is when I would sit down and have that conversation and say, "This isn't good for you. You can't keep coming back like this. I know how hard it is to ask you to just quit this and keep being without a crutch that you have been using. So, let's figure out a way to almost do the same as addiction management to try to get them off cannabis."

**Matt:** And these patients, they're feeling okay between episodes, but if they're having frequent episodes, what we talked about so far, they might be on a beta blocker like propranolol or TCAs to try to prevent, and then they may have something like lorazepam or a triptan in the prodrome phase to try to abort something before it gets out of hand. But then if they're admitted, they're going to be getting all these IV antiemetics and maybe pain medication as well. Anything else that you think is important for the audience to know about the treatment? I think we need to start to wrap up here. This has been great, covered a ton of ground and this cyclic vomiting stuff is very new ground for me, so I really appreciate that.

**Iris:** I think there was a question that had come up. If patients aren't able to discontinue the cannabis, like, what do you do? You can't just keep telling them over and over without another option. Haldol has been tried in the trials to treat the patients through the cannabis use and that has been helpful and then we just treat them cyclic vomiting. We give them the same plan, we try to teach them about the phases, and try to help them get through the episodes while cutting back. Because cutting back is still better than continuing. And eventually, you may be able to get them to cut back to a point where they can stop. But unfortunately, they have to be completely off for you to be able to tell whether this is going to resolve completely or whether there's going to be an underlying cyclic vomiting syndrome component in which case we treat. Yeah, trials for that also in development, not by me, but other people.

**Matt:** We will be in just a couple of weeks here recording a cannabis episode and-
Iris: Awesome.

Matt: -talking a little bit about cannabis use disorder. I'm not sure how much we'll be able to give solutions, because from my pre-reading, they've tried a lot of different things. But so far, it's a lot of just hypothesis generating stuff, not necessarily any slam dunk for treating it other than like CBT and--

Iris: Hypnotherapy.

Matt: Hypnotherapy, we'll send them to you for hypnotherapy.

Iris: I can't do that.

Matt: Yeah. [laughs] Well, with our patient here, Mr. Banks, we bring him into the hospital and get him through it with all this cocktail of medicines that you told us about and then we develop a nice action plan and make sure we hand off to Dr. Paul Williams, who is a fantastic primary care doctor and very good at rapport building.

Paul: That's what I do. It's who I am.

Matt: [laughs] Iris, if you had to give the audience some take-home points for, what has been a whirlwind tour of disorders of the gut-brain axis? How are we pronouncing that, Paul?

Paul: Different way each time. I try not to, I think is the answer.

Matt: Dig-buh.

Iris: It's better than the other one.

Paul: [crosstalk] and this is why. Thank you for illustrating my point.

Matt: [laughs] Okay. Iris, take home points whenever you're ready.

Iris: Yeah. I would start with, when you see one of these patients, take a deep breath, check your assumptions at the door. These are not psychosomatic or conversion disorders patients are suffering, and they need you to listen, and if you listen, those patterns will emerge, and it will be easier to identify one of these disorders in a positive light as opposed to rolling out. Be positive and be confident in your positive diagnosis. You don't have to be a workup for exclusion. But even if you do undertake a workup, bring up this concept early, so that it doesn't come up as an afterthought or as a nothing else is wrong, so it must be this diagnosis.

Remember that the placebo effect is super high in these disorders and that CBT works. But both of those things, the patient following through and the placebo effect are predicated on their confidence in you as their ally and in your diagnosis that this is what they have. Explaining why you are sending a
patient for this or why you are prescribing for this disorder is so key and really helps it work. These are heterogeneous disorders. The treatment is not going to be a one size fits all, but certain symptoms will really respond to certain treatments better and so your good history is a key.

The last thing that we really didn't quite mention, but we've touched upon is that these are multidisciplinary managements. You want to get your dietician involved, a psychologist involved, and really have a team approach for managing these patients. Use the Rome IV, if you need the actual diagnostic criteria. [laughs]

**Matt:** Anything that you wanted to plug before we fade into the outro? Any resources, courses for becoming a hypnotherapist, anything like that?

**Iris:** Yeah. A couple of things. So, Rome has a psycho-gastroenterology section with an excellent website that has a find a provider option by zip code. That's where I send a lot of my patients to find a psychologist to help them with CBT. Digital therapeutics are really going to be a game changer. Watch for them coming onto the market. They're actually getting FDA approval now as therapeutic options. And then the last website that I'll mention is asch.net. A-S-C-H dotnet. This is the accrediting society for hypnotherapy training. They will only train licensed providers. So. you cannot be average random person off the street who wants to do show hypnosis. They will not train you. But also, on that website is a find-a-provider option, so that you can help send your patients to those appropriate resources and you can cut this last part if you want, but my children's book needs a publisher. [laughs]

**Matt:** We will not cut that.

**Paul:** Nope. This is a place for self-promotion.

**Matt:** That is staying in there. [laughs]

**Paul:** We're expecting a percentage.

**Matt and Iris:** [laugh].

**Matt:** All right. I'm going to stop the recording.

**Paul:** This has been another episode of the Curbsiders bringing you a little knowledge food for your brain hole.

**Matt:** Yummy.

**Paul:** No, just like old times. Get your show notes at thecurbsiders.com and while you're there, sign up for our mailing list to get our weekly show notes in your inbox, plus twice each month you'll get our new Curbsiders Digest recapping the latest practice changing articles, guidelines, and news in Internal Medicine.
Matt: And we’re committed to high value practice changing knowledge and to do that, we need your feedback. So, please subscribe, rate, and review the show on Apple Podcasts or contact us at the curbsiders@gmail.com. A reminder that this and most episodes are available through VCU Health at curbsiders.vcuhealth.org. And a special thanks to our writer and producer for this episode, who we sorely missed tonight. Dr. Elena Gibson and to our whole team. Beth 'Garbs' Garbitelli, still our executive producer, Paul for a little while before we have to let her go off to residency. Elizabeth Proto runs our social media, Tima Karginov does the website, and this episode was edited and produced with help from the team at Pod Paste. And finally, Paul, Stewart Brigham composed our theme music. So, with all that, until next time, I've been Dr. Matthew Frank Watto.

Paul: And as always, I remain Dr. Paul Nelson Williams. Thank you and goodbye.