Revisiting IBS: Recrafting the Diagnosis for More Timely Treatment and Patient-Centered Care

CMEO Podcast Transcript

William Chey:

Welcome, everybody. We're actually around the corner in terms of Digestive Disease Week (DDW). Can you believe it? It just seems like it just started and it's almost over. It's been a great meeting, so much energy at this particular meeting. I've been really struck by how enthusiastic and excited everybody is. I guess we haven't gotten a chance to see each other in a couple of years, but it's great to see all of you here tonight, so thanks for coming out. Welcome to our program "Revisiting Irritable Bowel Syndrome (IBS): Recrafting the Diagnosis for More Timely Treatment and Patient Centered Care." Today's program is sponsored by educational grants from AbbVie Inc. and Ironwood Pharmaceuticals, Inc. As I mentioned, my name's William Chey. I'm a Professor of Gastroenterology (GI) and Nutrition Sciences, and also the Chief of GI and Hepatology at the University of Michigan in Ann Arbor. I'm delighted to be joined today by two very distinguished colleagues, and I'll ask them to introduce themselves.

Lin Chang:

I'm Lin Chang, I'm a Professor of Medicine. I'm also Vice-Chief of the Vatche & Tamar Manoukian Division of Digestive Diseases at the University of California Los Angeles (UCLA).

Amy Ladewski:

Hi, there. My name is Amy Ladewski. I'm a physician assistant and I have a background as a registered dietician. I work in the Digestive Health Center at Northwestern Memorial Hospital in Chicago. It's a pleasure to be here and represent our advanced practice provider community.

William Chey:

Thanks, Amy. So let's get started by going over our learning objectives for today. Our first learning objective is to implement strategies, to improve diagnostic accuracy of IBS through the use of patient queries and diagnostic tools. Our second learning objective is to recognize efficacy and safety of IBS therapies to inform treatment decision-making. Our third objective is to implement approaches for patient-centered care of IBS, such as shared decision-making, education, and patient-reported outcomes.

So, the diagnostic approach for patients with IBS is an important part of our discussion today, so let's start with our first case, who's Michael R. Michael R is a 42-year-old male who reports a two-year history of recurring diarrhea with abdominal pain, worsening the past few months. An episode of food poisoning actually preceded the onset of Michael's symptoms. He has 4-6 urgent bowel movements per day, daily bloating and gassiness, and pain which improves with the bowel movement. Diarrhea improves with loperamide taken up to twice a day, but seems to worsen his problems with pain and bloating. He tried limiting dairy for two weeks, but it didn't seem to help very much with his symptoms and he has mild tenderness in the left lower quadrant on physical examination. Otherwise, his exam's normal.

William Chey:

So, Michael has a number of questions, typical questions that all of our patients ask us in clinic. Do I need a colonoscopy? What kind of tests do I need? What's causing my symptoms and what can I do for my symptoms? So, let's go to our first polling question, which laboratory study would you recommend for a patient like Michael? All right. So, this is a very enlightened audience, 81% choosing celiac serology. Amy, what do you think? Do you agree with that?

Amy Ladewski:

Yeah, I think we all recognize that his symptoms are chronic and that the abdominal pain, bloating, and diarrhea certainly could potentially be celiac disease, which we wouldn't want to miss. It's good to recognize that no one chose the erythrocyte sedimentation rate (ESR), which has less sensitivity for, if we were wanting to rule out anything like inflammatory bowel disease (IBD). He's not describing any upper abdominal pain, it's not acute, where we would be concerned for pancreatitis. He is not having any food allergy symptoms, tongue swelling, or hives to suggest that this could be a food allergy. The 14% that answered, “I don't know,” we'll have an opportunity to learn on the upcoming slides.

William Chey:

Alrighty, very good. Let's go ahead and move on. We'll start with talking about diagnosis of IBS. So Lin, why don't you go ahead and get us oriented in this discussion, talking about prevalence and burden of illness?

Lin Chang:

I'm sure most of you know that, or all of you know that, IBS is a really common condition. It has a worldwide prevalence. The prevalence can change based on the diagnostic criteria. In general, whether you're using Rome III or Rome IV diagnostic criteria, the prevalence is between 4% and 11%, and you can see this map of the different prevalences in the different areas of the world, and that's based on the Rome IV Criteria. But it is the bread and butter of GI. It's also the seventh most common diagnosis seen by primary care physicians. We have three different bowel habit subtypes: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), and IBS with mixed bowel habits (IBS-M) which is diarrhea and constipation. Two thirds of individuals with IBS symptoms experience symptoms for at least a year before they actually seek health care. Many individuals with IBS don't seek health care so it takes a while to make the diagnosis; they can have symptoms for seven years or even more. It does impact their quality of life. It can be associated with school absences and decreased work productivity.

So, this is the Rome IV Criteria for IBS. This came out in 2016. Now, the frequency of the abdominal pain is based on over 90% threshold of the U.S. general population on abdominal pain frequency. So, the criteria was designed this time, this iteration, to be more precise and specific for IBS because it's being used in clinical trials. So, the patients have to have the presence of recurrent abdominal pain at least 1 day per week in the last 3 months (because we're looking for active symptoms), associated with two or more of the three following features: related to defecation (which means the pain could get better or worse after a bowel movement), it has to be associated with a change in stool frequency, and a change in stool form. So, you just have to meet two out of the three and the criteria ask that the patients have symptoms at least 6 months ago, but they're active for the last 3 months, because we're looking for chronicity.

Lin Chang:

The IBS diarrhea subtype is all based on stool form, which we are going to go over in just a minute. So, I think we can probably show the next slide because I think that illustrates what we use in clinic and in clinical trials, which is the Bristol Stool Form scale. I'm sure many of you are familiar with this. It's on coffee mugs and t-shirts and birthday cakes, so it's something that's very, very common, but this is a nice, validated instrument because it actually correlates with gastrointestinal transit time, with colon transit time. So, we have type 1 through type 7. It's validated based on the words, the text. The pictures add some confirmation but type 1 or type 2 stools are the hard, drier stools, with associated slower transit time. So, patients with IBS constipation have at least 25% of their bowel movements, now this is without medication, are type 1 or type 2 and less than 25% are type 6 or 7, which is the loose, watery stools. That's the diarrhea-type associated with more rapid transit.

IBS diarrhea is the opposite. So at least 25% of bowel movements are loose, watery and less than 25% are the hard, dry type 1 or type 2 stools. IBS mix means that the patient will report that at least 25% of their bowel movements are type 1 or 2, and at least 25% of their bowel movements are type 6 or 7.

William Chey:

Lin, everybody likes an algorithm, right?

I think the Rome Foundation has developed some algorithms. You want to walk us through this?

Lin Chang:

Yeah, so the algorithms always start with symptoms because that's why the patient is coming into the health care professional's office. So, for the diagnostic algorithm for IBS, the patients are reporting recurrent abdominal pain that's associated with defecation and/or disorder bowel habits, so diarrhea, constipation or both. We always do a medical history, of course, which includes a psychosocial, dietary history, and medication history. We do a physical examination. It's helpful to do a digital rectal examination, even though I know in studies it's shown that health care professionals are doing it less and less. Gastroenterologists (GIs) are doing it more than the other types of health care professionals. But it's always important to ask about alarm features because the alarm features is where it helps to determine what path diagnostically you're going to take. If a patient has alarm features, which are unintentional weight loss, bloody stools, nocturnal diarrhea, or family history of celiac disease (colon cancer, inflammatory bowel disease), you're probably going to be a little more aggressive in your diagnostic workup depending on what they're reporting.

But if they don't have alarm features, which many of these patients don't, we do limited screening tests, which we'll go over in a minute, and this is supported by scientific evidence. If you find an abnormality, then you would do more specific evaluations depending on what you find. But if you don't, find anything or if they have no abnormality on this limited diagnostic testing, then you can diagnose them with IBS if they have the symptom criteria, and then you determine what bowel habit subtype based on the Bristol Stool Form scale.

Lin Chang:

So, in a very more simplified algorithm, you see their symptom presentation, you rule out alarm features, and if they're present, you do diagnostic testing based on what they're reporting so it's appropriate for what their symptoms are. Then if they don't have any alarm features, then you can do very minimal or limited diagnostic testing.

The American Gastroenterological Association (AGA), American College of Gastroenterology (ACG), and other GI societies have reviewed the literature and they have come up with their guidelines on the diagnostic testing for IBS. These two tables are really based on very recent evidence and these guidelines. So, if you see on the left side, these are the tests that were recommended. The first one is really more of an approach, that we can make a positive diagnostic strategy versus excluding multiple different diseases before we make that diagnosis of IBS. If they have the symptoms and you've done some limited testing and they're negative, you can make that positive diagnosis. Now, the IBS-with-diarrhea group has a wider differential diagnosis. So, it's been recommended to measure celiac serologies (which many of you got correct on the answer), fecal calprotectin or fecal lactoferrin, and basically looking for inflammation in the GI tract, and then a C-reactive protein, again, looking for an inflammatory condition like inflammatory bowel disease.

Now, there's a little bit of disagreement on bile acid diarrhea testing, but we know that there's about 25% in the literature of patients with chronic diarrhea or IBS with diarrhea can have bile acid diarrhea, which would be a different treatment approach. In those patients where you're suspecting it, maybe in a patient, say, who has had a cholecystectomy, you can do some testing like fecal bile acids, but you can just empirically treat them as well. If Giardia is endemic like it is in the United States, it is recommended based on the guidelines to do Giardia testing and in patients, for patients with more constipation where you're suspecting that they have pelvic floor dysfunction, they have refractory constipation symptoms, it is recommended to refer the patient to anorectal physiologic testing like anorectal manometry and balloon expulsion tests.

Now, on the right side, the red light, is where you see it's not recommended. It's not recommended to do routine stool testing unless there is something in the history that's suggesting they could have an infection, like maybe they traveled to a certain location. It is not recommended to do a routine colonoscopy under the age of 45. You would do routine colonoscopy screens, just like you do in the general population. Food allergy or food insensitivity testing currently is not recommended based on the evidence and it is also not recommended to routinely do a breath test lactulose or glucose hydrogen breath tests.

William Chey:

Amy, can you lead us through the barriers, the challenges that we all face when we're confronted with a patient with suspected IBS?

Amy Ladewski:

Of course. I think Lin already described that it takes up to 7 years, on average, for a patient to be diagnosed and confirmed to have IBS as their diagnosis. So, why is it taking that long for these patients to get diagnosed? I think one issue is initiating that conversation with the patient. It takes a lot of time to talk to the patient and get a good thorough history of their GI symptoms. As we know, a lot of providers' clinics are super busy and are not able to invest potentially the time. There's also the lack of clinician understanding of the criteria for diagnosis, which we just reviewed. So then, this diagnosis becomes this diagnosis of exclusion where patients are getting that "multimillion-dollar workup." They're getting their gallbladders removed; they're getting repeated colonoscopies; they're going to the emergency room and getting computed tomography (CT) scans because they're concerned that there is an organic underlying condition.

This apprehension is coming from the patient asking for additional testing and then the clinician not feeling confident in exactly what's going on. But remember, if we're sticking to that realm for criteria ruling out those alarming features, we can make that confident diagnosis and be able to initiate an appropriate management plan for the patient.

William Chey:

Lin, Amy alluded to this, and you talked about it too, the use of that term, "making a positive diagnosis." What do you mean by that?

Lin Chang:

Yes, there's actually studies to support this. A positive diagnostic strategy means that the patient meets the symptom-based diagnostic criteria for IBS and that you have done the limited diagnostic testing, like a complete blood count, making sure they're not anemic, the celiac serologies, fecal calprotectin. If that's negative, you can actually make that diagnosis of IBS. You don't have to do an exhaustive workup. Particularly, you might be thinking about this a little bit on the younger population, but definitely on patients without alarm features. So definitely, you can make that positive diagnostic strategy. And then, studies have shown that when health care professionals talk to patients who have these functional GI disorders like IBS or what we call now disorders of gut-brain interaction, we tend to use more vague terms. "You may have this," or, "It doesn't look like it shows that," and sometimes the patients are not really, it's not resonating, or they really aren't understanding what their actual diagnosis is.

Lin Chang:

So sometimes they leave and say, "I was never really given a diagnosis." Then they find that health care professionals, when they're seeing patients with inflammatory bowel disease or these structural or anatomic disorders, that more definitive words are used. I would encourage everyone to start, if you're confident about that diagnosis, that you use more definitive terms. It's also helpful to explain the pathophysiologic mechanisms so the patients understand why they are having symptoms. Because they'll say, "Well, all my tests are normal. Why do I have these symptoms?" It's very helpful to explain, "Well, there are studies that have shown that the colonic motility is more hyperresponsive, particularly after meals, and that's why you may have, that's why you are having (not “why you may have”)abdominal pain, loose stools, bloating after meals; that there's evidence of visceral hypersensitivity that leads to a reporting of abdominal pain, discomfort, bloating.” You really want to validate the patient's symptoms that they're real symptoms, and even though our routine testing can't measure these pathophysiologic mechanisms, they've just been studied in many, many research studies, but they do explain their symptoms.

William Chey:

Lin, I think you raised a whole bunch of really important points there, but one of the ones I think is, that really bears reemphasis is, the language that you use. Patients pick up in 2 seconds whether or not you feel confident about the diagnosis that you rendered and that influences their confidence in what you're recommending to them, both in terms of treatment and in terms of their confidence in you. So, thinking about and using language that provides your level of confidence, hopefully you feel confident about your diagnosis, is really important. Remember that exhaustive testing, as well, implies a lack of confidence in your diagnosis in addition to tremendously driving up cost. And at the end of the day, an earlier diagnosis leads to earlier treatment. I’m really struck by numerous studies, which have been alluded to, that show that patients with IBS symptoms take years to get to a diagnosis. You wonder what’s happening to those patients as they’re sort of trying to find their way in terms of understanding what their condition is.

Lin Chang:

Bill, can I add another thing? So, it’s not also just the way we talk to the patient. Doug Drossman and Johannah Ruddy wrote a book recently on gut feelings, the patient stories, and I was reading them and one struck me because the patient wrote the story of how she saw her physician looking increasingly anxious and frustrated with the repeated negative tests. The patient herself was already, I can't remember if it was a male or female patient, but remembered already feeling anxiety themselves, unsure what the diagnosis was, but actually seeing the doctor feel that way raised their anxiety more. So, they're not only listening to what we're saying, they're watching the way we're responding and the way we're handling the diagnostic approach and it affects them.

William Chey:

It raises a really interesting point. You published that study a number of years ago, you and your colleagues at UCLA, showing that patients with IBS symptoms were not necessarily reassured by a negative colonoscopy, and you wonder how much of that result was related to the actual colonoscopy being normal not being reassuring, or how much of it was related to exactly what you just alluded to, which is the way the physician communicated that result to the patient.

Lin Chang:

It's also exhausting for the doctor, and I think they feel drained when they're ordering multiple tests, they keep coming back, it's negative, they're struggling for another test. So, it's also not helpful for them. But they showed it, I remember, in a fibromyalgia study, which has some overlap with IBS, that the more tests you give, the more frustrated the patient got and the more they expected that you were missing something because they kept expecting that if we're ordering another test, we must be thinking we're missing something.

William Chey:

Right. Yeah, I mean, I think that's absolutely true. So, let's talk through a couple of special considerations in regards to this case. So, first thing is, this patient clearly identified an episode of food poisoning that preceded the onset of their symptoms. Tell us what you think about that. Would you communicate the diagnosis or does that have any implications that matter from the patient's perspective?

Lin Chang:

I think the patient always wants to know why they got the condition. So, what are the factors that increase their risk of getting that? They will understand that if they get a gastroenteritis, and even though the infection has cleared, they still have symptoms. That's a really known entity because the infection can lead to some dysregulation and gut function and brain-gut access where they have these symptoms of post-infection IBS. I think the other important point is that post-infection IBS doesn't necessarily have the same natural history as the regular IBS, where you get that, not related to an infection. So, they've had studies that have followed patients out for a long period of time and find that with time the IBS prevalence goes down.

Now, the one infection, because you can get any different type of infection and it could be associated with post-infection IBS, but what's interesting is that they showed in a study with Giardia that post-infection IBS actually lasted longer. Now, some of the other symptoms they get like chronic fatigue got better, but the IBS symptoms actually stayed longer, more prevalent than with a bacterial infection. I was thinking, "Why is that happening?" I was thinking that maybe it's because Giardia is not self-limited. You actually have to get diagnosed and get treated or bacterial infections can be self-limited. So it might be longer, they may be dealing with these off-and-on symptoms, it may take longer, and we know that the more severe and prolonged the illness is, the infection, the more likely they're going to get post-infection IBS. I have no idea if that's a reason, but I thought that was interesting.

William Chey:

Okay, so the second one is a really easy question, right? So, when do you order breath testing in small intestinal bacterial overgrowth (SIBO)? I know that at the meeting there was a whole debate on this today. Lin, give us a brief answer on what you think about this. I know that you also did a session on this just the other day as well, right?

Lin Chang:

Yes. I debated the great Mark Pemetel. It was very exciting. So, we have a little bit of a difference of opinion. What I always say to people is that you should really look at the data and you should decide yourself whether or not you want to order breath testing for SIBO. There's been ACG clinical guidelines on SIBO and also AGA clinical practice update. I would encourage people to read it. In general, for me, I don't normally order breath testing. If I'm going to treat them for their IBS symptoms, I personally think that there are patients who have, and studies have shown that, there's a negative breath test, they can still respond. So, if I'm going to treat them anyways, and if it's negative, am I going to say I'm not going to treat them? And if it's positive, I'm going to treat them anyway. So, that's for me, but I can see in some situations where you may want to do breath testing.

William Chey:

Amy, so how would your diagnostic approach change if you had a patient with more constipation related symptoms? Obviously, we talked more about the patient with predominant diarrhea, but how about the patient with constipation?

Amy Ladewski:

If a patient's coming in with constipation, I'm less concerned for more that inflammatory, really not like inflammatory bowel disease. If 15% of patients with celiac disease could present with constipation, but the guidelines currently don't really support testing for celiac disease. So, if a patient's coming in with this chronic abdominal pain associated with constipation, I think really you can focus more on starting, well, one, making sure you get a complete blood count (CBC), make sure they're not anemic. They don't need a colonoscopy unless they're due. And at that point, you really can initiate treatment for them and see how they respond. I think it's also very important that you ask those additional questions that may support an underlying pelvic floor dysfunction, like dyssynergic defecation. We also know that over 30%-50% of patients with IBS with constipation could already have that as an overlapping condition, and make that decision maybe earlier in the algorithm if you did want to do any type of pelvic floor testing, like with an anorectal manometry and balloon explosion testing to further support pelvic floor dysfunction.

William Chey:

This is a question actually online that came in and the other thing is don't forget, digital rectal examination is very helpful as a screening test for dyssynergic defecation and fecal incontinence. So, don't forget about your digital rectal exam.

Amy Ladewski:

Especially if you don't have as much access to manometry testing such as at Northwestern where we have that. Of course, a digital rectal exam should be done whether you're in a university setting or community setting.

William Chey:

All right. Let's summarize our first section here. So, most patients require limited diagnostic investigation and of course, a lack of alarm features is associated with a lower pretest probability of organic disease. Celiac serologies should be done in patients with IBS-D and IBS-M. A fecal calprotectin and/or a serum C-reactive protein (CRP) can help to rule out IBD and patients with IBS symptoms and no alarm features. Additional diagnostics can be ordered in the setting of persistent or changing symptomatology.

Okay. So before we move on to our second learning objective, let's look at another case. This case is Yvonne S, a 44-year-old female who complains of crampy abdominal discomfort most days and this has been ongoing for several years. She reports abdominal pain, which has caused her to miss part or full days of work as an event planner. She's missed more than 6 times in the past 3 months. She reports passing spontaneous bowel movements about two to three times per week and she's currently using polyethylene glycol (PEG) 17 grams twice a day, in addition to soluble fiber.

She uses dicyclomine 10 milligrams as needed for abdominal pain and without the PEG and fiber, her stool frequency is actually even worse: 1-2 times per week. In terms of a more focused history, she reports that her stools are hard, 1-2 on the Bristol Stool Form scale. She denies the use of manual maneuvers to facilitate defecation, reports straining with roughly half of her bowel movements. Past medical history is remarkable for hypertension and migraines. No family history of gastrointestinal disease or GI or ovarian malignancy. She smokes a quarter pack of cigarettes per day and has cut back recently. She underwent a colonoscopy less than two years ago, which was fortunately normal, and she also underwent a non-contrast abdominal CT scan from an emergency room visit three months ago, which actually showed moderate stool burden, but was otherwise unremarkable.

So here are some common questions that patients like Yvonne would want you to address, “What prescription medications can I try? What diet changes can I try?” Also, can she stop taking her medications, PEG and fiber, if she started on a prescription medication? So, let's go to our next audience response system (ARS) question for all of you. All right, so, 75% choosing linaclotide. Lin, can you briefly tell us whether you agree or disagree?

Lin Chang:

Yeah, I definitely agree. Linaclotide has been shown to be highly effective for symptoms, not just of constipation, but abdominal pain. That was some part of the issue. So, I definitely think at that dose, that's indicated by the U.S. Food and Drug Administration (FDA) and other regulatory agencies for IBS with constipation. So, I think it's a good choice.

William Chey:

Amy, we touched on the fact that these patients commonly want to know about non-medical treatment alternatives like diet, for example. So, can you lead us through a discussion about the low-fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet?

Amy Ladewski:

I would be happy to, and I could spend all evening talking with you about diet. What I do want to emphasize is that the low-FODMAP diet is not designed to be for all of your patients. I know dietary counseling and interventions take time, but I've seen providers just hand a patient some information on the low-FODMAP diet, but this is a very complex dietary intervention that requires detailed counseling by a dietician and a significant investment of the patient. I think it's also very important that the provider recognizes, does the patient have irritable bowel syndrome with diarrhea? Does the patient have IBS with constipation? Is there a significant abdominal bloating component? And based off of the subtype, is really where you can kind of cater the type of dietary intervention that you're going to choose for them.

Furthermore, if they have a lot of already perseveration on their diet, if they're already underweight, if they have a history of disordered eating behaviors or restrictive food intake disorder, the low-FODMAP diet may not be the appropriate choice for this patient. They also need to be in the right stage of change to be able to really invest their time into this diet.

So, what is the low-FODMAP diet? Well, it stands for fermentable, oligo-, di-, and monosaccharides and polyols, and what these are, are short chain carbohydrates that are poorly absorbed in the gut, resulting in that osmotic diarrhea, fermentation by the gut bacteria, leading to bloating, gas, abdominal symptoms.

So, for our patient that has potentially already tried a lactose-free diet or a gas-bloating diet where they've eliminated just the garlic and onions and just trying to eat more consistently and are still maybe having those symptoms and are interested in this diet, then maybe that's the right patient. So, this diet requires them to eliminate these food groups from their diet and restrict all of them for 4-6 weeks with a plan to reintroduce each type of low-FODMAP back into the diet over the upcoming 6-10 weeks, so we can see which foods of the low-FODMAP diet are actively triggering their symptoms. Then at that point, it's designed to be personalized. So, this can be a less restrictive diet that has more longevity for them because how restrictive this is, could lead to other health implications and isolation because they're not able to socialize or be able to enjoy their food.

William Chey:

Very good. Lin, we also saw from those questions that patients are oftentimes really interested in over-the-counter (OTC) medications for lots of reasons, right? So, tell us about the OTC options for patients with IBS.

Lin Chang:

Well, there's evidence that soluble fiber can be efficacious in treating IBS symptoms and there's studies where they had all different bowel habit subtypes. It's usually more recommended for the patients with IBS with constipation. Peppermint oil basically works as an antispasmodic and there's a number of studies that support its use to treating and relieving global symptoms of IBS. I think it's very useful for postprandial symptoms, just like other antispasmodics. Polyethylene glycol is I think the most commonly used over-the-counter agent for children and adults with constipation. There's not much data in IBS-C, but in general can help the constipation symptoms, of course, but hasn't been shown to reduce abdominal pain or bloating in the limited data that's available. Many patients will use probiotics, but there was an AGA guideline that was fairly recent that showed looking at the evidence for probiotics and IBS, that it's not recommended based on the available evidence. That if it's used in IBS, it should be studied in a research trial. So, in general, it's not recommended. I know patients will take it and sometimes they have some improvement, but that's based on the guidelines.

So, this is the quality of evidence for IBS with diarrhea and this table is set up for the type of medication and the AGA and the ACG guidelines. So, the AGA had pharmacotherapy for IBS guidelines in 2014. Some of the agents were just carried forward to the current guideline that's going to be published in the next month or two, and some of them are new. Antispasmodics was reviewed in 2014 and you can see the recommendation and the quality of evidence in the different columns, and then just some comments. So the AGA and ACG have a difference of opinion on recommendation. The AGA had a conditional recommendation. There's conditional and strong. Conditional means that there could be future evidence that could change the recommendation or the certainty of evidence. Strong means that it's unlikely to do that. The quality of evidence for antispasmodics is low, but the ACG felt that they had a conditional recommendation against antispasmodics. They thought that the data was older, had poorer quality.

Peppermint oil, though, was recommended by the ACG. The AGA didn't really separate out antispasmodics and peppermint oil, but there was a conditional recommendation although there is a low quality of evidence. Tricyclic antidepressants (TCAs), which we really try to use the term neuromodulators, since that's how we're using it in IBS, both the AGA and ACG recommended it, but the AGA gave it a conditional recommendation, low quality of evidence. ACG gave it a strong recommendation, moderate quality of evidence, and it's recommended to start at a lower dose and then move up the dose to the lowest, most effective dose, best tolerated dose. Bile acid sequestrants, the ACG had a conditional recommendation against using that in IBS diarrhea. The quality of evidence was very low and felt like there needed to be more rigorous randomized control trials, which is true, and that testing for bile acid diarrhea is limited, but you can think about testing or treating it if you really suspected.

William Chey:

Yeah. I think I'm going to try to put this in perspective, because Lin helped to author the AGA guidelines, I helped author the ACG guidelines. A question you might ask is, why is it that for some of these things the organizations have come to different conclusions? It's because a lot of this has to do with the philosophy of the committees going in, in terms of how the recommendations were made. So specifically, the ACG looked at it like, do these treatments offer benefits for the global symptoms, abdominal pain and altered bowel habits, for the specific subgroup of IBS for which the medication is intended? If it did not address the global symptoms, it was not recommended. That's why, for example, antispasmodics got a conditional recommendation against, is because while they help with abdominal pain, they don't consistently help with bowel habits. Bile acid sequestrants help with diarrhea, but don't necessarily help with abdominal pain.

On the other hand, the AGA took a much more practical approach, which is would you use these things related to the fact that they do offer efficacy for certain symptoms? They are relatively inexpensive and safe. So, it's actually not that these things are so different. If you read the actual texts in the guidelines, they're not actually that different, but it's the approach that each organization took to these guidelines, just to help you to put it into perspective.

Lin Chang:

I mean, I think guidelines are really important. We're both involved in guidelines, but you don't want to live and die by them. You want to still be clinically practical and look at the factors of the patient and what they've been through and decide if it's reasonable to use them in particular patients.

William Chey:

So, here's an example of what I was talking about. Loperamide, AGA made a very practical recommendation, which is a conditional recommendation, because it's reasonable to start with loperamide in your patients with IBS-D, but loperamide is unlikely to do very much for abdominal pain or urgency. So for that reason, the ACG recommended against loperamide as an evidence-based treatment for IBS-D. You can see that there was really pretty good symmetry between rifaximin, alosetron and eluxadoline.

So, let's go through some of these treatments in a little bit more detail, first talking about rifaximin. I think you all know that rifaximin is a broad spectrum, non-absorbable oral antibiotic. It's FDA-approved for patients with IBS-D in the United States at a dosage of 550 milligrams, 3 times a day for 14 days, and the FDA approval also allows for up to two retreatments in patients that develop recurrent symptoms. It improves global symptoms in patients with IBS, which is why it's been recommended by both organizations, and it also improves gas, bloating, and abdominal pain. There is some data that suggests that a positive breath test (the data right now is for allolactose, but we're actually going to be presenting some data in the near future on glucose), that a positive breath test identifies patients with IBS-D who are more likely to improve with rifaximin. Actually, the likelihood ratio is 2-3 times more likely to respond to rifaximin with a positive breath test.

William Chey:

Eluxadoline is a mixed mu kappa opioid receptor agonist, and a delta antagonist. It's FDA-approved for IBS-D at a dosage of 75 or 100 milligrams taken twice daily with meals. The most common side effect in association with eluxadoline is constipation, but the one that everybody needs to be aware of, the two, are: one, sphincter of Oddi dysfunction, and also acute pancreatitis. For this reason, although those adverse events (AEs) are quite rare, this drug is contraindicated in individuals who have previously undergone a cholecystectomy, have any history of significant biliary disease or pancreaticobiliary disease, and also those individuals who are consuming more than three alcoholic beverages per day. In those settings, you should not use eluxadoline.

Alosetron is an oftentimes overlooked but a very effective drug, a 5-HT3 receptor antagonist, FDA-approved in a pretty narrow indication; women with severe IBS-D who have failed to improve with traditional therapy. The starting dosage is 0.5 milligrams taken twice daily, and it may be increased up to 1 milligram taken twice daily.

Now, related to rare events of ischemic colitis and dose-dependent constipation, there's actually a risk evaluation and mitigation strategies (REMS) program which is necessary, if you prescribe alosetron. It's pretty simple to use, but it does require some education and also signing a consent form. Now, I'm going to turn it to Amy to talk about the data for IBS-C.

Amy Ladewski:

Thank you, Bill. So, we'll transition now to talking about the recommendations by the ACG and AGA for IBS with constipation. Again, the recommendations are based off of not only their response for the constipation, but the abdominal symptoms as well. So, when we look at the over the counters, the soluble fiber and the polyethylene glycol, maybe there is less, it may not treat all of the global symptoms compared to the FDA-approved medications we see lower. Soluble fiber, in particular psyllium, is a really great water-soluble fiber that bulks up the stool, is minimally absorbed by the gut bacteria, and can be a great place to start for patients that are looking for something more natural and over-the-counter.

Polyethylene glycol is extremely effective for constipation. We can give it to children and pregnant women, and it's very, very good at softening the stool by drawing more water in. But the reason that it got the ACG conditional recommendation against its use is: one, there's a low quality of evidence to support that it can impact and treat the global IBS symptoms, and in fact, it can actually make the bloating and abdominal symptoms worse. So, if a patient is wanting to try it, first, it's obviously very cheap, there's no harm in starting there. But if it's not treating their global symptoms of the abdominal pain, then at that point, I would recommend you transition to one of the FDA-approved therapies for IBS with constipation, which are listed here: lubiprostone, linaclotide, plecanatide, tegaserod, and tenapanor. I'll be reviewing these individually on the upcoming slides.

Amy Ladewski:

So lubiprostone, it was the first secretagogue to come out on the market around 2007. There's three secretagogues, there's the lubiprostone, the linaclotide, and the plecanatide and they are all very effective for IBS with constipation; overall very safe with minimal, if any, systemic absorption, so can be prescribed with confidence for a majority of your patients. So lubiprostone, it works by GI targeting the bicyclic functional fatty acid, and it selectively activates the type 2 chloride channels, which then enhances intestinal fluid secretion. So, there's two doses of lubiprostone; there's the 8 microgram dose and the 24 microgram dose. The 8 microgram dose is the IBS-C, FDA-approved dose, whereas the 24 microgram dose is the chronic idiopathic constipation (CIC), FDA-approved dose. It's dosed twice daily, and it's best taken with meals. It's best to take it with meals because the main side effect of lubiprostone is nausea, which can be mitigated by taking it with food. Now, for lubiprostone, for IBS in particular, it is only approved in adult women. Whereas in CIC, the 24 microgram dose is approved for adult women and adult men.

So, the second secretagogue to come on the market, I think that was around 2012, is linaclotide. It's one of two guanylate cyclase-C (GC-C) agonists, the other being plecanatide that we'll talk about next. Both of these work by targeting this GC-C receptor that then starts the cascade to release cyclic guanosine monophosphate (GMP). Cyclic GMP is supposed to release extracellularly and animal models have shown that that may reduce a visceral firing of the neurons and thus reduce abdominal pain, and that studies have shown with linaclotide use, which we'll look at the next slide a little bit more, how it can reduce those abdominal symptoms over the course of 6-8 weeks of use.

So, linaclotide for IBS with constipation is FDA-approved at the 200 microgram dose and is dosed daily. It's best to take at least 30 minutes before the first meal of the day to potentially help mitigate that primary side effect of diarrhea. Linaclotide also comes in additional doses; 72 microgram and a 145microgram, and those doses are FDA-approved for CIC. So, the main side effect is diarrhea at 20%, compared to 3% in placebo, but you will see that severe diarrhea is only 2% compared to 1% in placebo.

William Chey:

Lin, can you talk us through this? Because there's been a lot made about the role of GC-C agonists for abdominal symptoms, like abdominal pain, abdominal discomfort, bloating, and you guys published this study, which specifically addresses that. So, can you lead us through this?

Lin Chang:

Yeah. So, prior to this study, the FDA did not feel that there was any primary endpoint or patient- reported outcome measure that was developed according to proper guidance that they had for a patient-reported outcome measure. So, they have been using the interim endpoint of a reduction in abdominal pain and improvement in stool consistency or frequency, depending on what subtype you're talking about. But this took a lot of effort, as a collective effort, where IBS endpoint was determined following the FDA patient-reported outcome (PRO) guidance for IBS. This main endpoint is about, it's an abdominal score and it's a 0-10 scale, so it's 11 points, very similar to what we use for abdominal pain. And it's comprised of abdominal discomfort, abdominal bloating, and abdominal pain and they really correlate very highly together.

Lin Chang:

So, what this study shows, that linaclotide can improve the abdominal score compared to placebo, and you can see the change, the improvement of 1.9 on a scale of 0-10 versus placebo 1.2. So, it's the average of all of them. But if you look, individual abdominal discomfort to abdominal bloating and abdominal pain, linaclotide improved these symptoms, these abdominal symptoms compared to placebo in a statistically significant manner. So that's why bloating, the FDA has always said, there's no bloating endpoint that has been developed properly according to their guidance. But this is included in that type of PRO that is now, I think, accepted by the FDA. It's just a reminder that the GC-C agonists are really designed for patients that are perseverating and maybe either presenting more with bloating and less on the constipation symptoms, that these could still be a really good therapy to offer them.

So, plecanatide is the second GC-C agonist. It is a uroguanylin analogue, and so what that means is when we eat food, we stimulate uroguanylin to promote fluid secretion and secondary motility. The uroguanylin is more pH selective for the small bowel and has less affinity for the colon, and therefore, this is thought to reduce the side effect of diarrhea. As you can see for plecanatide, diarrhea rates are around 5% compared to 1%. Plecanatide comes in one dose, 3 milligrams, which makes it easier for the provider if they're questioning if their patient has IBS with constipation or CIC, and what we're learning maybe is that the two conditions are kind of along the same spectrum too. So, it's an easy medication to prescribe. Furthermore, you don't have to dose it around eating. You can take it with or without food, which makes administration of the medication a little easier for the patient.

Tenapanor has recently become FDA-approved and on the market. For some providers, they think maybe this is that fourth secretagogue, but it's actually considered its own class. It's called a sodium-hydrogen exchanger isoform type 3. So, instead of secreting fluid and electrolytes into the lumen of the bowel, it's blocking reabsorption of sodium and this secondary fluid. So, for some, it's considered a retainer of the sodium. Because it's retaining the sodium, it's best to take immediately before meals. Larger meals, you're going to have more efficacy, especially if it's a larger meal with more sodium intake. So, it's dosed, and it's only approved for IBS with constipation and not CIC. It's dosed at 50 milligrams twice a day, immediately before those meals. The data, as far as the efficacy and safety profile would be similar to the secretagogues. The most common side effect is diarrhea at 16% compared to 4% in placebo.

The last medication I'll discuss for IBS with constipation is tegaserod. It is a 5-HT4 receptor agonist. It works specifically for that type 4 serotonin receptor that lines the gut. We know there's serotonin receptors throughout our entire body, but it has affinity specifically for that type 4 serotonin receptor. You may know that there's another 5-HT4 receptor agonist as well. That's called prucalopride. That medication is only approved for CIC and thus is not part of our presentation this evening. Tegaserod had been on the market maybe 10+ years ago. Some of your older patients or older providers may recall prescribing it and the patients having a good response to it. It was taken off the market for questionable risk of cardiovascular events, but had been used in Europe, and then it was brought back and FDA-approved back in the U.S. more recently with more stringent criteria.

Lin Chang:

So, it's only approved for IBS with constipation in women and these women have to be less than 65- years-old and have no history of any cardiovascular ischemic events and not more than one cardiovascular risk factor. When you take into account this criteria, the risk for a cardiovascular event is basically zero and consistent with placebo. For tegaserod, specifically for IBS-C, it's dosed at 6 milligrams twice per day, taken at least 30 minutes before meals. The main side effect that patients can have with those 5-HG4 agonists, especially what I see in clinic is a headache. They'll describe a transient headache, that I counsel those patients can be responsive to acetaminophen. These patients may also describe some abdominal pain or diarrhea.

William Chey:

Thanks, Amy. In regards to those of us that are old enough to remember tegaserod, can you, rather than referring to us as older, maybe referring to us as more experienced?

Amy Ladewski:

Wiser. Yeah.

William Chey:

All right. So, let's go back to our case. So, Yvonne returns after trialing linaclotide 290 micrograms daily for 10 weeks and discontinuing PEG. She has not identified any food related triggers. She reports bowel movement frequency of three to four bowel movements per week. Most bowel movements are complete, and she reports significant improvement in straining. She has less bloating and pain, but still has some symptoms 1-2 days per week, especially when she's working more, or getting less sleep. She's begun avoiding all social activities outside of work, because she's worried that her symptoms will interfere with these activities and it's easier to just stay home and deal with her pain.

So, our next ARS question for everybody, what would be the next step for Yvonne? All right. Again, a very enlightened audience. Lin, you're going to lead us through the next part of this discussion. Let's move on for the sake of time here. There's been a whole bunch of questions actually coming in online about behavioral therapies. So, perfect time for us to go ahead and discuss it. What do you think?

Lin Chang:

There's been actually a couple of reviews, one that Bill coauthored, about what is now termed brain-gut behavior therapy (BGBT). That's the new term, BGBT. This first slide I think is a nice one because it's really important for all of us to realize, who is the right patient to refer for a brain-gut behavior therapy and who's inappropriate? So, if we look at the green light, yellow light, red light, I'm going to start with the green light. Who are the good candidates to refer for behavioral therapy? It's individuals who accept their diagnosis, that there's a disorder of brain-gut behavior. They understand the role of these brain-gut behavior therapies and how they can relieve their symptoms and that it's part of the integrated care. Could be combined with pharmacotherapy or diet, but it's just one of the treatments that are instituted in their management. They agree that coping could be improved. The behavior therapy is basically giving them a skill set to have greater control over their symptoms, and they have the time to invest in this. This takes time. It takes some effort, homework to improve their symptoms.

There also are patients who experience isolation, avoidance. They have significant stress or distress around their GI symptoms. They have GI symptom-related anxiety or stress. Now, potentially appropriate, that's the yellow light. People with disordered eating, motivational deficits, personality features impacting care, post-traumatic stress disorder (PTSD) or psychological comorbidities. Now, some of these patients are already saving some management that it's addressing that from a different health care professional, and they may at the same time do well with behavior therapy, but that’s really focusing, the brain-gut behavior therapy is really focusing on their GI symptoms. So, if they need behavioral therapy for non-GI symptoms, then they may either have to simultaneously get that treatment or get that treatment first and then get a brain-gut behavior therapy for their GI symptoms after.

Now, inappropriate candidates, and our GI health psychologists have definitely educated us about this, but patients with uncontrolled or severe psychopathology, active substance use, patients are overly focused on a cure and need case management services, they don't really accept or have insight on the brain-gut association with this condition, or they can't invest the time in behavior therapy. I've definitely referred patients and then they'll cancel, and they don't really keep up. Because this takes time, it's going to be multiple sessions and it takes effort.

But the nice thing about behavior therapy is it can give them this skill set that can help them long term and potentially eventually get them off pharmacotherapy or over-the-counter remedies, and that's why it's useful. It could even help their other non-GI symptoms because behavioral therapy has been effective for different conditions.

Lin Chang:

This is a nice figure because it shows along the brain-gut access that you can have these centrally-mediated processes that enhance the bothersome-ness of and amplify symptoms, maladaptive behavioral responses, overactive emotional response, stress sensitivity, and GI motor dysfunction, and leads to what you can see on the white boxes of hyperalgesia avoidance, hypervigilance, pain catastrophizing, fear of the symptoms. They're attentive, very attentive to their symptoms, very focused on it. They have more of a fight-or-flight sympathetic response and a visceral hypersensitivity. You can see that in different types of behavior therapy like gut-directed hypnotherapy, cognitive behavioral therapy (CBT), mindfulness-based stress reduction, and relaxation training. It targets the different outcomes or the characteristics that the patient reports, but you can see many of them hit multiple targets. The gut-directed hypnotherapy is really more of an acceptance, a more passive approach. The cognitive behavioral therapy is more of an active approach. It's really good for patients with catastrophizing behavior. Our GI psychologist will sometimes start hypnotherapy first and then move to cognitive behavioral therapy because it gets them in a better frame of reference to do the cognitive behavioral therapy.

William Chey:

Very good. Amy, so Lin's done a great job reviewing behavioral therapies, but we can do this with medications as well. So how about neuromodulators? What do you think?

Amy Ladewski:

Yes, I think neuromodulators certainly have a place for the right patient that you're seeing. Before, a lot of us would just be, instead of using the term neuromodulators, using the term tricyclic antidepressants, which has a negative connotation for our patients. They hear an antidepressant, "Well, I'm not using that. I'm not depressed," or, "I'm not anxious. Why do I need that medication?" Therefore, by changing and shifting the terminology to describe it as a neuromodulator, that we're focusing and honing in specifically on the pain component, those abdominal symptoms that they're describing, and that there's a lot of good data to support their use in patients with IBS and specifically those abdominal symptoms.

When we look at a large meta-analysis of 16 randomized control trials, we know that the most data are going to be on the TCAs and this can reduce those global IBS symptoms and specifically that abdominal pain. TCAs are really good for abdominal pain. They also have those anticholinergic properties. So, for a patient that has IBS with diarrhea, it may help potentially slow down some of the motility and help with some of the diarrheal component of their symptoms. Depending on the patient, there's a variety of different TCAs that you could consider for them. There are TCAs that have more anticholinergic properties like amitriptyline. Nortriptyline may have a little bit less, and then there's desipramine that may have even less as far as those sedating properties for the patient.

Amy Ladewski:

For the TCAs, if a patient's already on a mood stabilizing medication and they're stable on it, it's okay to still layer on a neuromodulator for them. It's just you would start at a low dose. For TCA, it's 10 milligrams. It's best taken before bed, again, because of the sedating side effects. In my practice we typically have them on the 10 milligrams for a couple weeks just to make sure that they tolerate it and then increase them up to the 25 milligrams. Certainly, it's very important to counsel your patient that this is not a short-term medication, that it takes commitment to the therapy and that they may not see those responses for 8-12 weeks on the therapy. So I see patients that are quick to stop it and then jump to the next one because of a quick side effect, or they don't feel like it's working.

Other neuromodulators or medications to consider to help with their IBS symptoms, there are some studies to support selective serotonin reuptake inhibitors (SSRIs), but they're not going to be as good for those abdominal symptoms. When I would choose an SSRI for a patient is when there's a significant anxiety component to their symptoms or overlapping depression, where maybe that is really what's driving their symptoms and that we need to get them on and address the anxiety component, potentially in conjunction with behavioral therapy or other types of counseling that's focused more on the anxiety piece of their global symptoms. Selective norepinephrine reuptake inhibitors (SNRIs), really we don't have good data yet to support their use, but when we look at other chronic pain conditions such as fibromyalgia, we know that duloxetine can be effective, so that's another therapy that you could consider for the right patient that may have some overlapping other chronic pain conditions.

William Chey:

Excellent. Lin, this meeting has been transformative in a way, because we've been talking more and more about digital health solutions. So, what do you think about digital health solutions? Give us some insight based on what's on the slide.

Lin Chang:

This is probably just some of the ones that are out there that we have, but what you see on the left side is symptom tracking apps. Patients can enter their daily symptoms and then you'll be able to see over time what's been happening with the symptoms, which can be very useful, especially when you're trying to institute a therapeutic intervention. It's Dieta, GI health, bowelle, and they can also share them with their health care professional as well. There's also digital therapeutic apps for these brain-gut behavior therapies. Mohana is an FDA-approved app for cognitive behavioral therapy for IBS. So, it's actually been shown in a study to be efficacious. Zemedy is another app; it's not FDA-approved. It's for cognitive behavioral therapy, it offers cognitive behavioral therapy as well.

Lin Chang:

Regulora and Nerva are gut-directed hypnotherapy apps. The Regulora was recently FDA-approved, so the FDA-approved apps will require a prescription. The other ones are not. It will come with a lower cost, but there are apps that you can download. There's also dietary resources. These are a lot of the times focused on FODMAP, but it's helpful for patients because they're not really sure if a food that they're eating is a high-FODMAP food or a low-FODMAP food. There's also the Monash FODMAP app that's been available for a long time. I like that app because it'll show the quantity. So, there could be a certain fruit or vegetable that a very low amount is a low-FODMAP, but if you raise the amount, it becomes a high-FODMAP. So, you want to take that into count on the amount that they're eating. So that's kind of nice too.

There's also additional resources. The Rome Foundation and the International Foundation for Gastrointestinal Disorders (IFFGD), these are both well known, long-standing organizations that provide education. The Rome Foundation has educational information on their website. There's a lot of books. There's also videos, and they will give videos on communication or certain particular settings, like a patient who keeps wanting a CT scan. Then how would you do that? So, it's role playing, and you could look at these short videos to try to give you some education or information that might be helpful to you as you're communicating with your patient.

The IFFGD is really focused on giving information to patients and Bill and I have been very actively involved in their publications library for all different questions. This is really using expert opinion, scientific evidence to give information to patients on many, many different topics. There's a lot of resources, also on our GI society websites, but there's a lot of resources, but these in particular use expert input and are based on scientific evidence.

William Chey:

Excellent. Let's go ahead and close the loop on our patients, Michael and Yvonne. So for Michael, he's diagnosed with IBS and diarrhea. It's likely post-infection IBS-D. He's advised to take loperamide 4 milligrams as needed instead of daily for work and social situations as it worsens his pain and bloating. He takes rifaximin 550 milligrams, 3 times a day for 14 days. There's an improvement in symptoms and no repeat courses needed, at least to the point of follow up. Stool studies are negative for bacterial infection. For Yvonne, she's diagnosed with IBS and constipation. She enjoys significant improvement with linaclotide. She's expressed interest in psychotherapy and discussed options, and she opted to try a CBT mobile application. She still would like to quit smoking but is concerned about it causing constipation. So here are our SMART goals. The specific, measurable, attainable, relevant, and timely goals for tonight's discussion.

We want to confidently diagnose IBS, utilizing symptom-based criteria like the Rome criteria and excluding red flags or alarm features and using limited diagnostic tests. We want to utilize a combination of evidence-based treatments, including over-the-counter remedies, dietary interventions and prescription medications to manage patients' overall IBS symptoms. We want to identify patients who will benefit from behavioral therapy and Lin did a nice job of summarizing the factors that predict a patient who's more likely to respond to behavioral therapy. Then finally, ask patients about their priorities of care when developing a treatment plan for IBS, so, meeting the patient halfway.

William Chey:

If you have colleagues who missed tonight's live program, this activity will be available on Gastroenterology Hub on the CME Outfitters website, which also has additional resources for both clinicians and patients. I'd like to thank my colleagues who joined me on the stage tonight, Lin, as well as Amy. I'd also like to thank CME Outfitters for their assistance in developing today's program. So I think we'll go to our Q&A session now. We have a lot of questions. So, first question, I'll ask Lin. Lin, what do you think about Colace, for IBS-C? We strategically avoided that particular medication. Do you have an opinion on Colace?

Lin Chang:

Yeah, so Colace, or docusate, has not been studied in IBS with constipation and there's also a recent review by Darren Brener and I think Satish Rao, on over-the-counter remedies for chronic idiopathic constipation. There's not really data to even study docusate in chronic idiopathic constipation. So in general, it's not recommended. I think it probably has a little effect if I'm going to say from an anecdotal standpoint, but in general, if you're going to treat constipation, there are a lot better remedies than that.

William Chey:

Yeah, I think it's useless. I wouldn't use it. That's my honest, unvarnished opinion on Colace for constipation and IBS-C. Amy, what do you think about this issue of smoking? That one particular patient, Yvonne, was worried about stopping smoking and what effect that might have on her constipation. Do you counsel folks in regards to smoking?

Amy Ladewski:

Well, when I have a patient that's smoking, certainly I look at the bigger picture. What are they struggling with as far as stopping smoking and why are they continuing to smoke? Is there a large anxiety component? Are they doing it for weight maintenance? Have they tried to quit and they can't? So, it's a conversation that I emphasize. It's obviously important for them to stop for not only their overall health, but other risk factors such as colon cancer, esophageal cancer, stomach cancer. So, when it comes to IBS, I do think it's important that they're in the right place and frame of mind to stop quitting. For our patient, it sounds like we really made a lot of progress in treating her constipation piece of her symptoms and in making progress with the abdominal symptoms. She was interested in behavioral therapy, and I think once she's able to get those additional resources and feels really good as far as her IBS control and gets a little more confidence, that that would be the appropriate time for her to stop smoking.

William Chey:

Great. Lin, an interesting question from the audience and that is about COVID and GI symptoms. I know that the Rome Foundation lecture this year was on COVID and GI symptoms and I know you moderated that. Can you provide a brief summary about what's been observed?

Lin Chang:

Yes. So, you can have GI symptoms with active COVID. I'm sorry that I can't remember the exact percentage. It was like 25%, I can't really recall. But there are a group of patients that get long-COVID symptoms, including GI symptoms. Having GI symptoms, interestingly, during COVID does not predict getting long-COVID GI symptoms. There's a lot of different data about it. I want to say that Giovanni Barbara was doing it prospectively. I think proton pump inhibitors (PPIs) and having allergies, I can't remember the other risk factors, but there may have been anxiety is a risk factor to get post-COVID IBS-like symptoms. I really think when looking at the literature that post-COVID IBS or disorders of gut-brain interaction (DGBI) is very similar to post-infection IBS. However, the post-infection IBS is really more about having GI symptoms and a gastroenteritis, where COVID is a systemic infection that can target the GI tract, but really the symptoms come from having an enhanced immune system.

So that's really what's causing the symptoms and it's not only isolated to the GI tract. I think what he found is the post-COVID IBS was about 4%, as opposed to what you see in post-infection IBS. That prevalence is more like 10% and it's probably because it's a different type of infection.

William Chey:

I think people forget that, though, is that there are papers, they're a little bit older now, showing that not only GI infections can lead to IBS. There are actually papers published showing that any systemic infection in a susceptible individual can lead to the development of IBS. I think it underscores exactly the point that you made, which is that it's certainly more likely to ramp up the gut immune system with a GI infection, but it's not the only way to ramp up the gut immune system. So, I think that's a fascinating topic actually.

Lin Chang:

Yeah. The other speaker with Sarah Ballou and she was making the point about the psychological effects and how that can influence having GI symptoms and actually recovering from COVID. It's interesting because there's some conflicting data, but it probably depends on a lot of factors, such as how much that patient is impacted emotionally, financially, by other family members, their job, school, or by educating their children. But it did show that women are more impacted than men and it might be because of what women experience that might be different than men during COVID.

William Chey:

While we're on the infection topic, there's an interesting question here. In the age of GI polymerase chain reaction (PCR) test, and pretty much everybody gets a GI PCR nowadays, we're picking up blastocystis. This is for either one of you guys, whoever feels comfortable with this. Is there any association with blastocystis and IBS?

Lin Chang:

I don't think so. I mean, in general you would think about treating it if the patient has diarrhea, right? If they have symptoms. Normally you wouldn't do that. I don't recall seeing a study with that and IBS per se.

Amy Ladewski:

Any time I've had diagnosed patients with it, they were having diarrheal symptoms and actually did respond to treatment and made significant improvements. So that's a patient, lots to follow up, and I presume is not having ongoing IBS-like symptoms but didn't have IBS symptoms for years. It was something more, I wouldn't say acute, but maybe more sub-acute presentation.

William Chey:

Yeah. I don't think we know the answer to this. I think it's reasonable to say that if you incidentally pick up blastocystis and the patient doesn't have diarrhea, you probably don't need to treat it. But on the other hand, I think it's not unreasonable to treat blastocystis in a patient that has diarrhea.

Amy Ladewski:

Maybe the treatment, that may not even have been what we were actually treating. If there was an overlapping SIBO or other, like an IBS presentation that we're treating, that they actually made improvements from the antibiotic.

William Chey:

Digital rectal examination, there's a couple questions in here about, we alluded to that, but we didn't talk about what you focus on or what you do. Lin, you want to talk us through a digital rectal examination in patients with constipation?

Lin Chang:

I know it's your favorite topic, so I will.

William Chey:

It is my favorite topic.

Lin Chang:

I know you want to hear me say it so I will. It really is important. It's particularly important in constipation and fecal incontinence. I definitely think so, but you really, I always explain what I'm going to do because I'm standing behind the patient. So, I always explain what I'm going to do, but they get on the left lateral decubitus position. You can, before you start, just have them bear down so you could get a feel for their pelvic floor movement. Sometimes their buttocks actually increase and they actually ascend, which means they're squeezing instead of relaxing. A lot of times it's hard to do because they're probably worried about passing stool or gas and then you just gently put in your finger, but I always do it on the side and then move it in rather than sticking straight in. You normally just stop for a moment where you're feeling the external anal sphincter and internal anal sphincter.

Lin Chang:

Then you put your finger all the way in and with the tip of your finger, is really feeling the puborectalis muscle, which is the muscle that starts at the pubic bone and it's a sling-like muscle that wraps around the rectum and creates this anal rectal angle about 90 degrees at rest. It's a somatic muscle so it's under our voluntary control and it's contiguous with the external anal sphincter. So you feel that, and you ask the patient first to squeeze, which they can do, and you sometimes, you have to try to get them to really focus on just squeezing their anal sphincter and not their entire body. So sometimes they need some coaching, but you're looking for the tone and the pressure with squeeze. Then you ask them to bear down, to push out, like they're sitting on a toilet evacuating, and I put my left hand on their abdomen, and I have my right finger in their rectum.

What I'm feeling on my left hand is, are they contracting their abdominal wall muscles when they're pushing out, which is the proper way to do it. Then in your finger, what you're feeling is relaxation, which is hard if you really think about it. You have to contract your abdominal muscles and relax your pelvic floor and anal sphincter muscles. In fecal incontinence, you have to squeeze your anal sphincter muscles, but you have to relax your abdominal wall muscles. So that's kind of something harder to do, so you're really looking for relaxation. If you find paradoxical pelvic floor contraction, that means they're squeezing when they're supposed to be relaxing when they're bear down. So, we call it PPFC and some patients just don't relax. Sometimes I coach them a little bit just to make sure because it's kind of hard to do that in that kind of setting.

Now, if it's normal, there's a very low likelihood that they have pelvic floor dyssynergia. If it's positive, like they contract when they're supposed to relax, that could just be because of the setting. You don't really know if they have dyssynergic defecation, but you are going to refer those patients for anorectal manometry and balloon expulsion test.

William Chey:

Yeah. I completely agree with all that. It's an interesting thing, though, because obviously if you're in a setting where you don't have anorectal manometry, I agree with you that the greatest value of digital rectal examination is in its negative predictive value. The positive predictive value is less consistent, but that said, it's not bad. So, if you're in a setting where you don't have anorectal manometry and you find obvious dyssynergy on your digital rectal examination, I think you should just refer the patient to physical therapy and biofeedback training.

Amy, you got a really interesting question here, and that is, given your background as a dietician, does that change your view or approach, do you think, in regards to when to recommend diet therapy?

Amy Ladewski:

Well, I think most patients are going to need some dietary intervention. I think most patients have already tried and attempted dietary interventions before they're seeking help, so for the majority of my patients, at the right time. Obviously getting a diagnosis and discussing treatment interventions can be quite overwhelming. There's a lot of options. It's a collaborative discussion as far as where they feel they want to start with their management plan, but at the right time, whether it's at, maybe it's not that first visit, or it might be subsequent visits if they're still having the abdominal symptoms. For example, despite treatment of the constipation or to the diarrheal piece, then I certainly want to have that conversation about diet and discuss with them their options.

Amy Ladewski:

I would say a majority, though, of patients are asking me what they've tried. "What do you think? I feel so much better on gluten-free diet. Is that fine to continue?" That's a big one. One, we don't have really good data to support the gluten-free diet in IBS and I am concerned about patients that are on a very restrictive diet when on gluten, their celiac serologies were normal. But if they, there are fructans in gluten and that's part of the low-FODMAP diet. You think of foods that have gluten and having a lot more preservatives or additives to it. So, this, overall, might be a more healthier diet and a more mindful diet. But for example, for that type of patient, I would counsel them on that and maybe focus more on a low-gluten diet instead of being extremely restrictive. So, I really cater my dietary counseling to what the patients already tried, what their health literacy is. But I would say for a majority of patients that have abdominal IBS symptoms, they've already intervened on their own, and at that point we have to work together to cater and make sure what they're doing is correct and in a healthy matter.

William Chey:

Lin, a question here has to do with, why are some of these medications only FDA-approved for women?

Lin Chang:

Well, it started with alosetron, but most IBS and constipation trials are predominantly women. So, you have a smaller number of men in these trials. Sometimes when they analyze the data, they separate the men and women, and sometimes you don't get a significant effect in men, but it could be due to the small sample size, like with alosetron. It actually worked in men in a controlled trial, but if you look at the initial data, when they first did the FDA approval, they had less men, and when they separated out by gender, it was only effective in women, not in men. So, they started realizing that IBS is a female predominant disorder and that maybe there is a differential type of treatment response between men and women. But I think the approval was really based on that there was definitive evidence that it was effective in women, statistically, but not in men. I think more and more what we're seeing as we move along is, it's really being approved in both, but predominantly more women do these trials than men.

William Chey:

Yeah. Although don't you think there is biologic plausibility that there might be differences?

Lin Chang:

Oh, definitely. In men and women?

William Chey:

Yeah.

Lin Chang:

Oh, yeah. I mean, that's one of the areas that I study. There's a lot of differences between men and women. There hasn't been as much data on treatment response, sex differences in treatment response, as there has been by looking at motility or transit or visceral hypersensitivity or brain imaging.

William Chey:

Yeah. Interesting. I'll take this next question, which is tenapanor seeking approval for hyperphosphatemia. Any need to monitor phosphate levels in patients who don't have end-stage renal disease? The answer is no. In the phase III trials, we've very closely monitored phosphate levels and other electrolyte levels, and there were no significant changes and there's no recommendation in the product insert (PI), for monitoring of phosphate or other electrolytes.

Well, we're almost out of time here. So, another question, and that is the insurance issue. There's a lot of questions about whether there are any tricks that you'd recommend to help to get insurance coverage for prescription medications. I'm going to ask both of you this and see if there are any tips. Amy, you want to go first?

Amy Ladewski:

Yeah. I mean, for most of the FDA-approved therapies for patients with private insurance, there are savings cards that you can go to their websites and have the patient fill out and present to their pharmacist for a majority of insured patients that are first being prescribed a secretagogue, for example, should be able to get it covered. Now, for the newer medications, such as the 5-HT4 agonists, for insurance to cover, typically they require trying at least one of the secretagogues and some over the counters as well, and so it may require that they've failed those in order to get it approved. So, most of the time, I start with the secretagogues, document in my note that they've failed them. before trying one of the newer medications.

For patients with Medicaid or have Medicare where they have large deductibles, a lot of the prescription drug companies offer patient assistance programs. So, I have many of my patients that qualify for that and are able to get their medications through this patient assistance program.

William Chey:

Lin, you got any comments?

Lin Chang:

Yeah, I would say that the one thing you definitely want to make sure is that you're using the right dose with the right indication, because that's the sure way of getting rejection. So, if you're going to use 290 of linaclotide, but you associate with chronic idiopathic constipation, it could get rejected. You have to associate with IBS with constipation. Rifaximin, you can't say the indication is SIBO. It's IBS with diarrhea. You just have to make sure you're matching the right medication, right dose, with right indication. Often, you do need a prior authorization, so what I've been doing in my notes is I start saying previous medications tried and what the response is. I keep the list so that when I ask the office to submit a prior authorization, then they'll see what they have tried and that makes it a lot easier.

The other thing, particularly with new drugs, there'll be certain specialty pharmacies that you can send your prescription to that are very good about trying to get that coverage and they'll even do sometimes prior authorization, so you actually fax them your last clinic note. So sometimes there are certain pharmacies that will be helpful and knowledgeable on particular agents.

William Chey:

Well, Lin and Amy, thanks so much for your participation tonight. Audience, thanks so much for coming and I hope you enjoy what there is left of DDW 2022. Thanks very much. Have a good night.

