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IBS-D: What to Do when Typical Treatment Methods Fail

Announcer:
This is CME on ReachMD. This activity, titled *IBS-D: What to Do When Typical Treatment Methods Fail*, is jointly provided by TOPEC and MedEdCom and is supported by an educational grant from Salix Pharmaceuticals, Inc.
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Here's Dr. Darren Brenner.

Dr. Brenner:
Hello, ladies and gentlemen. My name is Darren Brenner, and I'm an Associate Professor of Medicine and Surgery in the Northwestern University Feinberg School of Medicine. I direct our Neurogastro-motility and Functional Bowel programs, as well as our GI Physiology Laboratory. I am here today to discuss evidence-based approaches to the treatment of irritable bowel syndrome with diarrhea.

My goal is to provide you with some new paradigms regarding the way we think about IBS which can allow us to directly target specific underlying mechanisms of action, possibly improving our clinical outcomes.

One of my personal patients, Janice, is a 30-year-old woman who presented to my IBS clinic for a second opinion regarding potential treatment options for her irritable bowel syndrome with diarrhea, or IBS-D. She was diagnosed with IBS-D by her previous gastroenterologist after a workup that included negative serologies, including a normal CBC, comprehensive metabolic panel, thyroid and celiac testing, and a colonoscopy with biopsies, which were negative.

Her symptoms have been present for the past 5 years, and she denies having any specific precipitants. She is currently experiencing daily abdominal pain, which she describes as a pressure-fullness sensation radiating throughout her lower abdomen. It usually develops in the postprandial setting and partially improves with defecation. Janice further describes recurrent bloating and distention, noting that she can look 9 months pregnant. She is passing 3 to 4 Bristol 6 to 7 stools per day, and although she identifies mucous in her stools, she does not see blood. There are no associated alarm signs or symptoms.

Janice has tried fiber, which made her symptoms worse; loperamide, which decreased her bowel movements to 2 a day, but she experienced no other improvements; dicyclomine and hyoscyamine, which were ineffective; and avoiding dairy and gluten, which resulted in a minimal response.

So, first, let's ask ourselves: Does Janice meet criteria for irritable bowel syndrome?

Here I'm presenting you with the most up-to-date criteria used to diagnose this disorder. Currently, the Rome criteria in their fourth permutation defines IBS as a disorder of pain and altered bowel habits. Specifically, individuals must experience pain at least 1 day a week. Many patients present to our clinics with alterations in bowel habits but without the pain, and while this may represent a functional gastrointestinal disorder, this is not irritable bowel syndrome. If your patients do endorse pain, then it must be associated with at least 2 of the following: a change in visceral perception with defecation, meaning that the pain improves or worsens with a bowel movement, and/or on days that patients experience pain, this pain is associated with a change in stool frequency or texture. These symptoms have to be present in the previous 3 months with symptom onset 6 months prior to making the diagnosis. If your patients meet these criteria to be defined with IBS-D, they then have to endorse having loose, mushy or watery stools with greater than 25% of their bowel movements and hard or lumpy stools less than 25% of the time.

If your patients meet these criteria, there are a myriad of different evidence-based treatments—with

FDA-approved therapies recognized with an asterisk. So the question at this point is how to choose the correct treatment for our patients. And this is difficult because the reality is we do not have specific treatment algorithms because there have been no rigorously designed head-to-head trials comparing one treatment or intervention to another. But if we can identify a specific mechanism of action inducing a patient's IBS symptoms, that may improve our ability to appropriately treat these individuals. And more recently, there has been increased emphasis on determining underlying mechanisms of actions.

As you can see here, multiple disorders have been associated with the development of IBS symptoms, including changes in motility, secretion, and visceral perception. We have also determined that subgroups of IBS patients suffer from disorders including small intestinal bacterial overgrowth, bile acid malabsorption, and alterations in the gut microbiome. And in some of these cases, we now have ways of identifying these potential mechanisms of action.

As you can see in this meta-analysis, across a wide spectrum of breath tests and compared to age and sex-matched controls, individuals with IBS have an almost 10 time increased likelihood of developing small intestinal bacterial overgrowth, or SIBO. Thus, if we identify ways to treat SIBO or alterations in the gut microbiome, this may more accurately dictate our treatment recommendations.

For a patient with IBS symptoms and evidence of alterations in the gut microbiome, rifaximin may be an appropriate first option. Rifaximin is a non-systemically absorbed antibiotic which has been shown to inhibit bacterial transcription which may potentially inhibit bacterial growth or reduce bacterial products which can elicit IBS-D symptoms. Rifaximin has been shown in multiple rigorously designed clinical trials to be effective and safe for the treatment of IBS-D.

The data I'm presenting here comes from the TARGET 3 trial. In this study, almost 2,500 patients received the FDA-approved dose of rifaximin, 550 mg 3 times daily for 14 days in an open-label, real-world analysis. Forty-four percent of these individuals met the primary endpoint, which was a combination of a 30% reduction in abdominal pain compared to baseline associated with a 50% reduction in the number of Bristol 6 or 7 stools passed during the same week for at least 2 out of the 4 weeks subsequent to completing the course of the medication. Of the 44% of individuals who met this initial endpoint, a little bit more than a third continued to experience appropriate symptom resolution out to 5 months.

The other 59% relapsed and then entered a double-blind retreatment phase during which they received a second course of rifaximin at the same dosage, 550 mg 3 times daily, or placebo for 14 days and 10 weeks later a third course. In both instances, individuals receiving the rifaximin, again in a blinded fashion, had improved outcome. There was no evidence of bacterial resistance during these trials, and only a single case of C. difficile colitis occurred many weeks after the rifaximin was consumed and

developed in the setting of a urinary tract infection when a cephalosporin was being taken. Consequently, rifaximin appears effective for treating IBS-D, and based on its mechanism of action may be most effective for individuals with an altered gut microbiome or evidence of bacterial overgrowth.

Another example where mechanism of action may dictate treatment is in the setting of bile acid malabsorption. Now, to most of us, the common scenario we associate with bile acid-related diarrhea is in the setting of a cholecystectomy. The excess bile acids stimulate colonic motility and secretion, inducing a diarrhea state. However, up to 30% of individuals with intact gallbladders and functional diarrhea or irritable bowel syndrome with diarrhea can experience bile acid malabsorption, and newer diagnostics can now be used to detect these changes. One of these markers to measure is serum 7-alpha-hydroxy-4-cholesten-3-one, or more commonly this is known as C4. This should not be confused with the complement factor, as this C4 is a cholesteryl ester intermediate in the synthesis of bile acids from cholesterol. Thus, the greater the bile acid synthesis, the higher the serum level of C4.

In a small but unique study completed at the Mayo Clinic, a population of healthy volunteers and individuals with IBS-C and IBS-D were evaluated to see if a correlation between bile acid synthesis using C4 levels as a surrogate, stool weight, and fat concentrations could be detected. As evidenced in these box and whisker plots, individuals with IBS-D produced significantly higher levels of C4 compared to patients with IBS-C or functional constipation in healthy controls. In fact, 38% of individuals with IBS-D had evidence of elevated serum C4 levels. Furthermore, these elevations also significantly correlated with stool concentrations of bile acids, increased stool weight, and fecal fat. Thus, individuals with IBS-D had higher levels of serum C4 due to loss of bile acids in the stool, and increased stool weight related to fat malabsorption.

As C4 is a commercially available test, it can be used in individuals with IBS-D to detect bile acid malabsorption, and if bile acid malabsorption is identified, then bile acid binding agents like cholestyramine, colesevelam, or colestipol could potentially be considered as first-line treatment agents.

And that's what this study set out to prove. In this trial, individuals with IBS-D were tested for bile acid malabsorption using C4, as well as 75 selenium-labeled homocholic acid-taurine nuclear medicine studies. Overall, 19% of the individuals in this study with IBS-D had evidence of elevated C4 levels, and individuals with abnormal SeHCAT retention, which is consistent with bile acid malabsorption, were offered the bile acid binding agent colestipol in an open-label fashion for 8 weeks. The primary clinical endpoints in this study were an adequate relief assessment as well as an evaluation of overall clinical improvement using the IBS Symptom Severity Scale. Fifty-six percent of these individuals

experienced an adequate relief of their symptoms during at least 2 of the last 4 weeks of the trial, and clinically significant drops in the IBS Symptom Severity Score were detected as well. Thus, again, defining the underlying mechanism of action may lead to improved treatment decisions and outcomes.

The final mechanism of action to treatment example I'd like to discuss is the potential interplay between food and IBS symptoms, specifically the use of a low-FODMAP diet. For those of you unfamiliar with this acronym, FODMAP stands for fermentable oligo-, di-, monosaccharides and polyols. Basically, these are highly fermentable carbohydrates which can induce IBS symptoms through a myriad of mechanisms.

FODMAPs can act as direct nonabsorbable osmotic loads leading to increased fluid secretion and accelerated intestinal transit. They are converted by gut flora into gases like hydrogen, methane, and carbon dioxide, which can lead to increased abdominal discomfort, bloating, and distention—symptoms endorsed by most individuals with IBS. The gut flora can also convert these into short-chain fatty acids, which are used as nutrients for colonocytes but have the potential to change intraluminal pH and shift the gut microbiome. This is important because alterations in the gut microbiome have also been associated with induction of IBS symptoms through multiple mechanisms including activation of the mucosal immune system. Consequently, dietary modification can have direct impacts on the induction or modulation of IBS symptoms.

On the right, this data represents the largest FODMAP study in the United States to date, and in this study IBS patients were randomized to either a low-FODMAP diet or a diet based on modified NICE guideline. The primary endpoint here was a subjective assessment of adequate relief, and individuals were considered responders if they endorsed adequate relief for at least 1 of the last 2 weeks of the study. While there was a numerical increase in favor of the low-FODMAP diet, this did not reach statistical significance.

However, significant improvements were seen in abdominal pain and bloating by the end of Week 1, carrying over throughout all weeks of the study. There were also significant improvements identified in multiple quality-of-life domains.

Overall, I found that the low-FODMAP diet works most efficaciously for gut-derived symptoms, including abdominal discomfort, bloating, and distention.

So these are just a few examples how I believe identifying an underlying mechanism of action can help prognosticate responses to therapies, but that doesn't mean there aren't other good evidence-based therapies available for treating irritable bowel syndrome with diarrhea, and another one of these is eluxadoline.

Eluxadoline is a first-in-class, mixed mu-kappa-opioid receptor agonist, delta receptor antagonist, FDA approved in May 2015 for the treatment of IBS-D. Its mechanism of action is quite unique, and this combination of agonism and antagonism has been shown to reduce GI secretion and motility and pain, ultimately reversing the 2 cardinal symptoms of IBS-D.

Its efficacy has been validated in 2 large phase 3, randomized, double-blind, placebo-controlled trials. In these trials, overall responders were defined as individuals who experienced at least a 30% decrease in their worst daily pain compared to baseline levels and had a concurrent normalization of their stool texture on the same day for 50% of the trial days. At 12 weeks, significantly greater percentages of individuals receiving either 75 or 100 mg of eluxadoline twice daily experienced improvements in that endpoint compared to placebo, with a delta between the treatment groups of approximately 10 and a number needed to treat of about 10. A unique post-hoc subgroup analysis identified a subgroup of individuals who had previously received and endorsed a lack of response to loperamide and compared the outcomes of eluxadoline to placebo in this subpopulation. They found that a significantly greater percentage of patients who defined themselves as loperamide failures responded to eluxadoline compared to placebo. However, again, this was a post-hoc analysis and was not powered to accurately assess the subpopulation.

So, as a follow-up to this study, RELIEF was a prospective, multinational, multicenter, 12-week, randomized, double-blind, placebo-controlled trial comparing the effects of 100 mg of eluxadoline twice daily to placebo in individuals who had used the over-the-counter mu-opioid agonist loperamide in the previous 12 months and subjectively failed to achieve an adequate response. Similar to the data in the post-hoc analysis, patients receiving eluxadoline fared significantly better in terms of improvement in their global IBS symptoms compared to placebo. So, in multiple rigorous trials, eluxadoline appears effective for treating global IBS symptoms and effective for those not responding to loperamide.

Peppermint oil is a complementary alternative therapy, which actually has decent data supporting its ability to improve IBS symptoms. It's currently considered a first-line agent for treating IBS by the European medical agencies. Peppermint oil's active ingredient, L-menthol, has been shown to exhibit antispasmodic, anti-inflammatory, and serotonergic properties. In fact, a recent meta-analysis revealed that peppermint oil is effective in reducing global IBS symptoms and was more effective than other staples in our treatment armamentarium, including fiber, tricyclic antidepressants, and antispasmodics, with extremely low numbers needed to treat.

Cash evaluated the benefits of a concentrated, microspherical formulation of peppermint oil compared to placebo in individuals with non-constipated IBS. In this study, patients with IBS-D or -M, but predominantly IBS-D, were randomized to receive 2 capsules of this concentrated peppermint oil or

placebo 3 times a day for 4 weeks. The primary assessment was a change in the total IBS Symptom Score, or TISS. There was significantly greater reduction in the TISS score for the cohort receiving the peppermint oil versus the patients who received placebo. Furthermore, subsequent data revealed that peppermint oil may represent a beneficial on-demand treatment for IBS, as reductions in the intensity of these symptoms were reduced by as much as 40% within the first 24 hours of starting this therapy. Importantly, rates of adverse events were low and equivalent between the 2 treatment groups.

And finally, there is now a significant body of literature suggesting and validating behavioral therapies for the treatment of IBS. The two with greatest evidence base are cognitive behavioral therapy, or CBT, and hypnotherapy. Here is data from the recently published Irritable Bowel Syndrome Outcomes Study, or IBSOS. In this prospective education-controlled trial, 436 individuals with moderate to severe IBS symptoms of all subtypes were randomized to 1 of 3 cohorts: an education group, a standard CBT group, which underwent 10 therapy sessions, and a minimal-contact CBT group receiving 4 sessions of treatment. The primary endpoint was improvement in the CGII, or Clinical Global Impressions of Improvement Scale. Changes over time, specifically at Week 12, were assessed by both the patient and the gastroenterologists. Significant improvements, represented by a score of 6 or 7 on the CGII scale, were identified in a much higher percentage of the treatment population receiving standard or minimal-contact CBT compared to education, as subjectively evaluated by both patients and gastroenterologists. Numerically, a higher percentage of patients receiving the minimal-contact CBT responded compared to the standard CBT, despite receiving only 40% of active therapy time compared to the standard CBT cohort. Also, the response rates were quite similar across all 3 cohorts. This data further substantiates the benefits of CBT and suggests that patients can achieve significant clinical improvements from CBT in very short periods of time and with minimal therapist participation.

Despite all of our novel interventions, one of the key elements of this process is the development of a strong doctor-patient relationship. As I mentioned earlier, we're just beginning to scratch the surface of our understanding of the pathogenesis of IBS, and by identifying novel mechanisms of action, we will better target our therapeutic interaction. Until such time as we've elucidated these mechanisms of action and developed direct diagnostic and therapeutic tools for each of them, treating IBS will continue to remain a bit of a trial-and-error process. As such, the key to treatment is the foundation of a strong doctor-patient relationship based on mutual respect and trust. It's been shown time and time again that this strong relationship reduced doctor shopping, diagnostic testing, and increased adherence to treatment recommendations and improved outcomes.

I'd like to leave you with a few key clinical pearls. We know that IBS is a common disorder affecting 10% to 15% of the international population. The pathogenesis is heterogenous, and identification and development of diagnostic studies for underlying mechanisms of action will likely improve treatment

outcomes. Currently, treatments are based on subtype but with no specific algorithms. Our prognostic data are lacking or poor, and the decisions for treating individuals should be based on personal biases and whether or not patients are more interested in using pharmaceutical or complementary or alternative therapies.
Importantly, communicating openly with patients and allowing them to participate in the process leads to improved clinical outcomes. Thank you very much for your time.

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