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10 Recommendations for Managing CIC

Dr. Buch:
Welcome to *GI Insights* on ReachMD. I'm your host, Dr. Peter Buch. And joining me today to discuss 10 recommendations for managing chronic idiopathic constipation, or CIC, in adults that were developed by the American Gastroenterological Association and the American College of Gastroenterology is returning guest, Dr. William Chey. He's the Marvin Pollard Professor of Gastroenterology and Chief of the Department of Gastroenterology and Hepatology at the University of Michigan in Ann Arbor.

Dr. Chey, welcome back to the program.

Dr. Chey:
Thanks so much for having me again, Peter. I'm looking forward to our conversation.

Dr. Buch:
So, Dr. Chey, let's start our conversation with some discussion on these recommendations for managing CIC. Why were these joint guidelines necessary?

Dr. Chey:
Well, first off, chronic idiopathic constipation is an incredibly common and bothersome problem. Realize thatroughly 1 in 10 Americans suffer with some degree of constipation, and many of those individuals suffer with ongoing chronic issues around constipation. Remember that constipation, too, is more than just not going to the bathroom often enough. Patients that report hard or lumpy stools or a sensation of incomplete defecation or problems with chronic straining are also classified as suffering with chronic idiopathic constipation, and this guideline you're referring to represents the first joint ACG and AGA clinical practice guideline, and it, hopefully, will serve as a model for collaboration between the two organizations going forward. We felt really strongly that a unified, singular document would be more powerful not only for providers and patients but also in terms of dealing with insurance companies and third-party payers.

Dr. Buch:
That's great. And I hope the collaboration does continue. And since there are 10 recommendations, let's break them down a bit. Can you first give us an overview of what the updated guidelines say about fiber supplementation and polyethylene glycol?

Dr. Chey:
Yeah. So I think one of the real benefits of this guideline, which focuses on pharmacological therapies, is that it provides a really detailed evaluation of the over-the-counter options. Oftentimes, reviewed documents really focus on the prescription medications, and those are really important and really valuable, but the reality is the vast majority of CIC patients are never going to see a prescription medication. They're going to be managed with the over-the-counter remedies, like fiber, like polyethylene glycol. I'm sure we'll get into the other OTC remedies, like magnesium oxide, bisacodyl, and senna, which are all equally important, actually.

So first, in terms of fiber, remember that we tend to recommend 20 to 30 grams of total fiber intake per day. And I emphasize that word "total." That's not supplemental. That's total fiber per day. So when deciding on a fiber supplement or how much of a fiber supplement to give, one needs to understand, how much fiber a patient is taking on a daily basis in their regular diet. That's the first bit of advice.

Second thing is that from an evidence standpoint, the type of fiber that is most evidence-based in terms of improving symptoms in patients with CIC is psyllium and ispaghula husk, so soluble fiber, and the nice thing about psyllium and ispaghula husk is that it's a low fermentable fiber. Depending on what's living inside your GI tract, some might have some degree of fermentation of those types of fiber, but for the most part they're either nonfermentable or low fermentation fibers. And there's good evidence to show that they improve overall constipation symptoms, as well as stool frequency, stool consistency, and straining. Polyethylene glycol is probably the most evidence-based over-the-counter constipation remedy. There are actually six-month randomized controlled trials showing that polyethylene glycol improves stool frequency, stool consistency, and straining, so a very effective treatment for chronic idiopathic constipation, relatively safe at usual doses. As you push the dose up, some people can get problems with bloating, abdominal cramping, or diarrhea, but for the most part is very well tolerated.

Dr. Buch:
And what should we know about magnesium oxide, lactulose, and bisacodyl, or sodium picosulfate?

Dr. Chey:
Yeah. So I think first thing is just to recognize that they split off into two broad mechanistic categories, so osmotic laxatives, those are laxatives that create a luminal osmotic load and that osmotic gradient leads to net secretion of water and electrolytes, which would have obvious benefits to complaints of chronic constipation, and those would include polyethylene glycol, which we talked about a moment ago; magnesium oxide, which we'll talk about in a second, as well as lactulose. Those are all osmotic laxatives. And then there are the stimulant laxatives, which are thought to more directly affect the colonic smooth muscle and that way stimulate contractile activity. Those would include bisacodyl, sodium picosulfate, as well as senna.

Now this is the first guideline to recommend magnesium oxide as an evidence-based treatment option for patients with CIC, and the data or that recommendation is based upon two small randomized controlled trials that were conducted in Japan both evaluating magnesium oxide in a dose of 1.5 grams per day, so a big dose. One comparative effect in this trial comparing to senna, and that study basically found that magnesium oxide and senna were both superior to placebo in terms of improving symptoms of CIC, and then another study that just showed superiority of magnesium oxide to placebo.

In general, we recommend starting at a lower dose of magnesium oxide, say four or 500 milligrams per day with a glass of juice or water and titrating up to a maximum of 1.5 grams per day if needed. Of course, you're going to want to avoid using magnesium oxide in patients with significant renal dysfunction, and overall, in the studies, even at that higher dose, magnesium oxide was very well tolerated with a really quite low rate of developing diarrhea or other adverse events.

Sodium picosulfate and bisacodyl are biochemically related, so one is a prodrug, and the other one is the active drug, and bottom line is that those stimulate contractile activity in the colonic smooth muscle and in that way help with chronic constipation, but that mechanism also explains the main side effect related to those drugs, which is abdominal pain, which can be reported in up to 40 percent of patients taking bisacodyl or sodium picosulfate.

The senna is also a stimulative laxative, and as you escalate the dose of senna, you can start getting into problems with abdominal pain and cramping in particular.

Dr. Buch:
Thank you for that. For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. William Chey about the updated recommendations for managing chronic idiopathic constipation, or CIC.

So now that we have some insights into the first five recommendations, Dr. Chey, let's talk about lubiprostone.

Dr. Chey:
Yeah. Lubiprostone is the only drug available that is a direct CIC-2 activator, so it actually activates or opens the CIC-2 chloride channel. That leads to net secretion of chloride into the intestinal and colonic lumen. And, of course, chloride is negatively charged, so

it leads to paracellular movement of water and sodium, so there's net secretion of fluid and electrolytes, again. Lubiprostone has been shown to be of benefit in patients with chronic idiopathic constipation in four-week randomized controlled trials, so relatively short duration trials, but it's been around for a long time now, and I think all of us are very used to using lubiprostone. And, again, for a subset of CIC sufferers, it can be a very effective treatment.

Remember that there are two doses that are available in the United States, an eight microgram b.i.d. dose for patients with IBS-C and then a 24 microgram b.i.d. dose for patients with chronic idiopathic constipation. And remember that the most common side effect, adverse event, is nausea, which is dose-related, so nausea rate six to eight percent with that lower dose upwards of 30 percent with the 24 microgram dose taken twice a day, and that's the reason why we recommend that you take lubiprostone with food to try to reduce or mitigate the risk of developing nausea.

Dr. Buch:
And what are the key insights we should know about the use of linaclotide, plecanatide, and prucalopride?

Dr. Chey:
Okay, so we'll split those up a little bit because remember that linaclotide and plecanatide are GCC, guanylate cyclase-C, agonists, so they bind the GCC receptor, which leads to the production of intracellular GMP, which then opens CFTR, the cystic fibrosis transmembrane regulator, which is arguably the most robust chloride channel on the enterocyte. So again, we see net chloride secretion, passive paracellular movement of water and potassium, so you get net movement of fluid and electrolytes into the bowel lumen, which is potentially beneficial for constipation.

The other thing about GCC agonists is that cyclic GMP that's generated in the cell, as it migrates out of the cell, can inhibit firing of visceral afferent neurons, so pain pathways emanating from the gut and projecting to the brain, and that's the proposed mechanism for why linaclotide and plecanatide seem to offer benefits not only for constipation but also for abdominal pain and bloating, so-called abdominal symptoms.

Remember that for linaclotide, there are three doses available in the United States. For chronic idiopathic constipation, 72 micrograms and 145 micrograms given once a day, and for IBS-C, 290 micrograms once per day. The most common adverse event with linaclotide is diarrhea, and a key thing to remember about linaclotide—remember we said a second ago that lubiprostone you dose with food—linaclotide you dose on an empty stomach, and that's to reduce the likelihood of developing diarrhea.

Plecanatide is pretty much the same discussion. The one difference for plecanatide is you can actually dose plecanatide either with or without food.

The other drug that you mentioned, prucalopride, is a prokinetic medication, so in other words, it stimulates peristalsis within the colon—by the way, not just the colon, also the small bowel and the stomach—and in that way benefits the symptoms of chronic idiopathic constipation. This is a very well-studied drug, six phase 3 trials, actually, all showing benefits of prucalopride versus placebo in patients with CIC.

I think the big benefit for prucalopride is in patients that you think have pan-dysmotility, so patients that have upper GI symptoms, as well as lower GI symptoms. Prucalopride is an attractive option because it has pan-prokinetic properties.

Dr. Buch:
And when making a choice among these, the linaclotide, plecanatide, and prucalopride, which should we choose for patients with chronic idiopathic constipation?

Dr. Chey:
I think for patients with overlapping upper and lower symptoms prucalopride is an attractive choice. Unfortunately, in today's day and age, the reality is that insurance coverage will play a big role in terms of dictating the choice of treatment between the doc and his or her patient. There are no direct comparative effectiveness studies between the prescription medications. So as to whether to make the recommendation for one versus the other, right now, you really can't say something from an evidence-based standpoint. I think that there's data to show that each of them are efficacious versus placebo. It would be very interesting and valuable to have data looking at

comparative effectiveness, but we don't have that right now.

Dr. Buch:
Perfect. So, Dr. Chey, can you tell us why misoprostol and colchicine, used on the appropriate circumstances, were left out of the recommendations?

Dr. Chey:
Yeah, largely because there's so little data for misoprostol and colchicine. As you probably know, Peter, the misoprostol data is a very small number of patients, and it's just one or two studies. Colchicine has even less data. So there's very little data to support the use of those drugs, and frankly, given the number of much more evidence-based options, I think that those medications have really been relegated to third- or fourth-line treatment options.

Dr. Buch:
Thank you. And lastly, how do you hope clinicians use these recommendations in practice?

Dr. Chey:
I hope it serves as a touchstone to understanding, which OTC, so over-the-counter and prescription medications are evidence based, the level to which they are evidence based because we make a statement regarding a so-called PICO statement around the recommendation or suggestion of the use of medications, and we talk about the strength of recommendation and the strength of the evidence, so it really gives interested parties a deep dive into what the data is in support of the medications that we review and recommend as part of the guideline.

Dr. Buch:
What an excellent review of the updated recommendations for managing chronic idiopathic constipation. I want to thank my guest, Dr. William Chey, for an excellent discussion.

Dr. Chey, it was great speaking with you again today.

Dr. Chey:
Thanks, Peter. Always a pleasure.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit ReachMD.com/GIInsights where you can Be Part of the Knowledge. Thanks for listening.