ADVANCES IN IBS

Current Developments in the Treatment of Irritable Bowel Syndrome

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Highlights From the Joint AGA/ACG Guideline on Pharmacologic Management of Chronic Idiopathic Constipation

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G&H What was the aim of the 2023 AGA/ACG guideline on chronic idiopathic constipation?

LC The aim was to perform a systematic review and meta-analysis of pharmacologic treatments for chronic idiopathic constipation (CIC). Drug therapies for CIC have not been systematically reviewed for about 10 years. The last American Gastroenterological Association (AGA) Medical Position Statement on Constipation was published in 2013, and new medications for CIC have become available, so it was time for an update using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology. What was interesting was the American College of Gastroenterology (ACG) and AGA had wanted to develop a guideline on this topic at the same time. The ACG and AGA had not collaborated on a joint guideline before. If both major gastrointestinal (GI) organizations worked together and provided the same recommendations or suggestions, there would be no conflicting opinions between them as would be possible if they developed separate guidelines. I spoke to Dr William D. Chey who was chairing the ACG guideline on CIC, and we decided to ask both societies to consider working on this jointly, and everyone agreed.

G&H Could you provide an overview of the updated guideline on CIC?

LC Basically, the committee reviewed 10 treatments and gave each a strength of recommendation based on the level of evidence, which ranged from very low to high. Of the 10 treatments, 5 had a strong recommendation based on a moderate certainty of evidence, and 5 of them were given a conditional recommendation based on very low to low certainty of evidence. For a strong strength of recommendation, the GI society panel *recommends* this treatment. For a conditional recommendation, the GI society panel *suggests* this treatment. Of the 10 treatments, the ones with a strong recommendation with moderate certainty of evidence are polyethylene glycol plus bisacodyl and sodium picosulfate, which are grouped together because they have the same active metabolite but different hydrolysis methods, and linaclotide (Linzess, Ironwood), plecanatide (Trulance, Salix), and prucalopride (Motegrity, Takeda). The treatments given a conditional recommendation with varying certainty of evidence are fiber, magnesium oxide, lactulose, senna, and lubiprostone.

The guideline reviewed studies conducted in adults with CIC. There are not many pediatric studies available. Similar to past guidelines, the guideline statement is written in a way that recommends or suggests a treatment over not using it. For example, the recommendation on fiber says, "The panel suggests the use of fiber supplementation over management without fiber supplementation." Because each agent is usually compared with placebo, not with another agent, the statement can only recommend or suggest a treatment over not using it. The guideline also includes implementation remarks about each treatment that provide the clinician with more information on how to apply that recommendation or suggestion to clinical

practice. Obviously, multiple factors must be considered when prescribing an agent (eg, whether the patient has tried the medication before, insurance coverage, the cost, access, and availability), and the decision to prescribe does not rely on a single statement that says use it or not use it.

G&H What is an important part of the guideline for people to read?

LC As I mentioned, the new joint guideline includes implementation considerations for each of the 10 treatments. The panel tried to bring in practical information that was important in clinical practice and that a clinician could consider when implementing this treatment. The implementation considerations are not always based on hard evidence; they may be based on expert opinion and some evidence. For example, for fiber, the guidelines say, "Dietary assessment is important to determine total fiber intake from diet and supplements." A patient with CIC who does not eat that much fiber can use fiber supplementation. However, some patients consume a high-fiber diet, and a clinician must consider how more fiber will affect their CIC symptoms based on what the patient is already doing. The implementation consideration provides more nuanced information to think about that could impact the success of treatment. For a patient who does not eat a high-fiber diet, from a practical standpoint (this is not in the implementation consideration), it makes sense to start at a lower dose. Starting at 20 grams of fiber could cause patients on a low-fiber diet to be uncomfortable and have abdominal symptoms, and they could potentially discontinue the treatment right away. In these patients, I usually have them start with a lower dose, about a rounded teaspoon of psyllium, for example, then increase to 2 teaspoons after a few times to ease it in, and then increase to 1 rounded tablespoon. In addition, the guideline says that fiber supplements can be used as first-line therapy for CIC, particularly for individuals with low-fiber intake. Among the evaluated fiber supplements, only psyllium appears to be effective, with very limited and uncertain data on bran and inulin. Adequate hydration should be encouraged with the use of fiber, so patients should drink a lot of fluids, and flatulence is a commonly observed side effect with the use of fiber. These statements are helpful from a clinical standpoint and are provided for every CIC treatment.

G&H How strong is the evidence for the newer prescription options for CIC?

LC The newer prescription options such as linaclotide, plecanatide, and prucalopride were all given a strong recommendation for use based on a moderate certainty of evidence. No treatment had a high certainty of evidence. Lubiprostone has a conditional recommendation because the certainty of evidence was low, meaning that there were limited data, or the trial was of short duration. The other issue for chronic constipation, because it is a chronic condition, is that patients can have some fluctuation of symptoms over time. A trial may be 4 weeks long but patients are likely going to be on the treatment for longer. Because a trial of a drug was short in duration does not mean the drug cannot be used for a longer period. In fact, some of the implementation remarks state that although the length of the trial was, say, 4 weeks, the drug label does not state that it must be limited. The guidelines do not state a specific duration of use.

> Many clinicians may not use magnesium as an osmotic laxative.

G&H Which recommendations will have the greatest impact on GI practice now?

LC Many clinicians may not use magnesium as an osmotic laxative. Magnesium, like Milk of Magnesia, is often not used because of how it is formulated. However, there are different preparations of magnesium. Although only magnesium oxide has been studied, other preparations of magnesium may be helpful. Magnesium is used for different reasons (for leg cramps, to relax at night). From a practical standpoint, often clinicians recommend using magnesium early in the evening. However, this requires making sure patients will not have to go to the bathroom in the middle of the night, as often patients with constipation have a delayed response to a treatment. In patients without constipation, taking magnesium at a higher dose may induce a bowel movement sooner than in patients with chronic constipation. In some patients with constipation, the effect of a constipation medication could take many hours; they can take it at night to help them go to the bathroom in the morning. Although magnesium is well known, it has not been systematically reviewed and is probably not on everybody's radar screen. Another interesting fact about magnesium oxide is that it has been studied in doses up to 1500 mg. Many patients will take 200, 400, or 500 mg, not realizing that they could increase the dose, as long as they do not have kidney issues.

G&H About half of CIC patients reportedly respond to evidence-based medical therapies—why not the other half?

LC The answer is probably complex and may have something to do with the chronic constipation diagnostic criteria. Patients must have only 2 of 6 signs and symptoms for a diagnosis, so they may not have the same symptoms but could meet the criteria for functional constipation, chronic constipation, or CIC; all 3 terms refer to the same group of patients. In the general population, there is a wide range for normal bowel movement frequency, from 3 times a week to 3 times a day. Less than 3 bowel movements per week is considered abnormally low and is 1 of the 6 criteria. The 5 remaining criteria have to be present in at least 25% of bowel movements. These include straining, hard (dry or lumpy) stools, sensation of incomplete evacuation, sensation of anal rectal blockage or obstruction, and use of manual maneuvers to help facilitate defecation. Any 2 of the 6 can indicate constipation. For example, one patient can have infrequent bowel movements and straining, and another patient may have bowel movements at least 3 times a week but has hard stools and does not feel empty afterward. In addition to having different symptoms, patients may have other factors that can affect treatment response or side effect profile. A patient could have a defecation disorder (eg, dyssynergic defecation) that may not respond to laxatives. Treatment response will vary for every patient. One patient could have a quicker effect than another, and this variability can impact daily activities. Some patients have to wake up hours in advance to make sure they drink their coffee, take their medicine, and have a time for their bowels to respond. If they miss that time and hold the bowel movement, then sometimes they are unable to go. Some of the medications have side effects, so there are many patient and treatment variables. As I mentioned, there is also fluctuation in symptoms over time. Similar to heartburn, constipation is common with multiple choices for remedies, variability of response, and differing patient needs.

The algorithm, available through the AGA website, is a clinical decision support tool that incorporates the treatments measured and how they might be used in patients with an unsatisfactory response.

G&H What are some pointers on choosing between the therapies?

LC The joint committee developed an algorithm to use when managing a patient with CIC. The algorithm, available through the AGA website, is a clinical decision support tool that incorporates the treatments measured and how they might be used in patients with an unsatisfactory response. According to the algorithm, the first step is to look for alarm features to rule out a structural disease, like colon cancer, for example. For the patient who is identified as having CIC after appropriate diagnostic testing based on symptoms and evaluation confirming there are no alarm features (it is assumed that the patient met the CIC symptom-based criteria), the first-line treatment is to increase fiber. If there is an unsatisfactory response to fiber, then more than one option can be tried. Note that there is some layering in the way treatments are used; clinicians are not going to use only one, then switch. The patient will continue the fiber and first try adding an osmotic laxative, for which 3 options are provided. The committee added footnotes with more information on treatment caveats. For example, lactulose, which has been studied in 2 small trials in older adults, has been shown to improve constipation symptoms but is associated with the common side effects of gas and bloating. Many clinicians do not want to use lactulose because patients with chronic constipation already often have bloating and gas. I would not use lactulose before polyethylene glycol or one of the other medications. Sometimes an osmotic laxative may not be the right choice for someone with severe bloating.

After trying osmotic laxatives and the patient still has an unsatisfactory response, this is when to think about using another over-the-counter agent. Unlike the osmotic laxative which draws water into the bowel lumen to help move stool, the stimulant laxative stimulates the smooth muscle to bring fluid into the bowel and is a common rescue medicine in a chronic constipation trough. Regarding the stimulant laxatives, the algorithm says, "Consider adding as needed rescue or short-term therapy." Bisacodyl, for instance, is a good rescue medicine but is not advocated for long-term use. However, in the short term, a stimulant laxative may be helpful when the patient experiences short periods of increased constipation like when traveling or taking a medicine known to cause constipation. For the patient who does not respond

to osmotic laxatives, the clinician should consider the possibility of a defecatory disorder. This was not part of the guideline but is in the clinical algorithm. The clinician could also just go straight to the prescription medications for this patient and skip the stimulant laxatives. There are 2 prescription options: the secretagogues and the prokinetic agent prucalopride. Deciding on the use of a secretagogue like lubiprostone, linaclotide, or plecanatide also would depend on patient-related factors, insurance coverage, or prior use. Sometimes in patients with more refractory symptoms, prucalopride and 1 of the secretagogues are prescribed. Using treatments with 2 different mechanisms of action may increase the chance of the patient responding but this is based on anecdotal experience. Again, the clinician can add or switch therapies, as shown in the algorithm.

G&H Can you comment on some emerging evidence-based nonmedical therapies for CIC?

LC There are vibrating colon capsules on the market right now in the United States and in China that contain no active substance. The patient takes the capsule, which is of typical size, for 5 days a week at night; the patient chooses which days. The capsule is placed in a pod (connected to a cloud, which stores the capsule data) that activates the capsule prior to ingestion. The vibrating capsule will turn on around noon the next day once it is expected to be in the colon, where mechanical stimulation is thought to help the patient have bowel movements. Another option for patients is acupuncture, which was evaluated in a large, well-designed study published in *Annals of Internal Medicine* that showed the modality helped chronic constipation. There are a handful of natural laxatives that patients can try. Fruit-based laxatives (eg, 5 prunes a day, 2 kiwis a day) have been shown to be efficacious for mild constipation, probably at the level of fiber. Some people use herbal remedies, typically rhubarb root or senna, as in preparations that are used for constipation.

G&H What should a provider think about and do when medical therapies are not working?

LC My advice would be, first, to figure out whether the treatment is partially effective. If the treatment is achieving some symptom relief that is important to the patient, then find out what symptom is not addressed and target treatment to that symptom. An example is the patient taking a medication like polyethylene glycol and the recommended dose results in loose stools, but when taken at a lower dose, the stools are hard and infrequent. The patient may need to add fiber, increase the current intake of fiber, or add magnesium. If the patient reports having bowel movements but still has bloating or discomfort, then prescribing a medication known to address these symptoms, such as linaclotide or plecanatide, may help. The clinician adjusts treatment to achieve the goal that is important to the patient. My second point of advice is to evaluate the patient for a defecatory disorder, like dyssynergic defecation, because the treatment is different. The oral medications mentioned do not work as well in patients with this disorder. The underlying problem must be treated with anorectal biofeedback or pelvic floor physical therapy. If a dyssynergic defecation is suspected, clinicians should refer the patient for anorectal manometry to make sure this diagnosis is not missed.

Disclosures

Dr Chang has served as a scientific advisory board member for Ardelyx, Atmo, and Vibrant; as a consultant for Bausch Health, FoodMarble, and Trellus Health; and as a speaker for Ironwood. She has received research support from the National Institutes of Health, Arena, AnX Robotics, and Ironwood, and has stock options with FoodMarble, ModifyHealth, and Trellus Health.

Suggested Reading

Chang L, Chey WD, Imdad A, et al. American Gastroenterological Association-American College of Gastroenterology Clinical Practice Guideline: Pharmacological Management of Chronic Idiopathic Constipation. *Gastroenterology.* 2023;164(7):1086-1106.

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