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AGA-ACG Clinical Practice Guideline on Chronic Idiopathic Constipation Treatments: Parsing Benefits and Risks

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COLON

This article reviews Chang L, Chey WD, Imdad A, et al. AGA-ACG Clinical Practice Guideline: Pharmacological Management of Chronic Idiopathic Constipation. Am J Gastroenterol 2023; 118(6):936-954. doi: 10.14309/ajg.0000000000002227

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STRUCTURED ABSTRACT

Question: Which therapies are superior to placebo for chronic idiopathic constipation (CIC)?

Design: Evidence-based guidelines using GRADE methodology and Evidence-to-Decision (EtD) frameworks to assess benefits, risks, and costs, among other factors.

Patients: Patients diagnosed with CIC, although individual trials used different definitions of CIC.

Interventions/Exposure: Fiber supplements (psyllium, methylcellulose, bran, and inulin), osmotic or surfactant laxatives (polyethylene glycol [PEG], magnesium oxide, lactulose, docusate), stimulant laxatives (bisacodyl, senna, sodium picosulfate), secretagogues (lubiprostone, linaclotide, plecanatide), serotonin agonists (prucalopride). Active interventions could be compared versus placebo, no intervention or standard of

care. Studies comparing different CIC therapies without a placebo arm were excluded.

Outcome: Complete spontaneous bowel movements (CSBMs) per week, spontaneous bowel movements (SBMs) per week, responder rate (defined as $\geq$ 3 CSBMs per week and an increase from baseline of 1 CSBM per week), diarrhea (adverse event) leading to discontinuation of treatment, serious adverse events, global relief, and quality of life. CSBMs per week, SBMs per week, and adverse events leading to discontinuation of medication were chosen as critical outcomes.

Data Analysis: Meta-analysis was performed using ReviewManager software (RevMan; Cochrane Collaboration, Copenhagen, Denmark) and the Cochrane Risk of Bias tool assessed risk of biased results based on use of concealment of allocation, blinding, incomplete outcome data reporting, selective reporting, and other potential biases. GRADEpro software (McMaster University and Evidence Prime, Hamilton, ON, Canada) was used to facilitate the assessment of study design, risk of bias, imprecision, and other factors to assess certainty of evidence, which refers to the likelihood that the estimated treatment effect from meta-analysis reflects the true effect of the medication. EtD frameworks then facilitate decision-making on whether or not to provide a strong recommendation (i.e., most patients should receive the treatment) or conditional recommendation for use (i.e., different choices will be appropriate for individual patients based on their preferences and values).

Funding: None

Results: Among over the counter (OTC) agents, PEG was the only therapy to receive a strong recommendation for chronic use (Table 1). Bisacodyl/sodium picosulfate received a strong recommendation for short-term (< 4 weeks) use or as rescue therapy. Based on low or very low-quality evidence, other OTC agents, including fiber supplements—specifically psyllium—senna, magnesium oxide, and lactulose were suggested for use (i.e, conditional recommendation: different choices will be appropriate for individual patients consistent with his/her values and preferences.) Among prescription agents, linaclotide, plecanatide, and prucalopride were all strongly recommended for use after unsuccessful trials of OTC agents, based on moderate certainty of evidence about treatment effect

and risk of adverse events. Lubiprostone was suggested based on low certainty of evidence. No assessment of surfactant laxatives/stool softeners was provided.

Superior to Placebo with Strong Recommendation	Strength of Recommendation[1]	Certainty of Evidence[2]
Polyethylene Glycol	Strong	Moderate
Superior to Placebo and Use After Failing OTC Agents		
Linaclotide	Strong	Moderate
Plecanatide	Strong	Moderate
Prucalopride	Strong	Moderate

Table 1. Strongly recommended CIC therapies.
[1]Strong Recommendation: Most patients should receive the intervention.
[2]Moderate Certainty of Evidence: Moderately confident that the true effect lies close to that of the estimated effect from meta-analysis.
CIC, chronic idiopathic constipation; OTC, over the counter.

COMMENTARY

Why Is This important?

CIC is one of the most common disorders treated by gastroenterologists, but CIC guidelines from the ACG and AGA have not been updated since 2013-14.[1-2]. For the first time, magnesium oxide and prucalopride randomized control trial (RCT) data is included, and the authors emphasize that prescription therapies should only be used after OTC agents. While I agree with this approach, many CIC patients are dissatisfied with their current treatment and cycle through multiple OTC treatments before getting prescription medications and experiencing adequate symptom improvement. Utilizing these guideline recommendations, we should recognize this cycle and prescribe therapies proven to be effective, and I commend the authors for the huge effort required to produce this well-designed guideline.

Key Study Findings

PEG is superior to placebo and strongly recommended for treatment of CIC based on moderate quality evidence. Linaclotide, plecanatide, and prucalopride are all superior to placebo and strongly recommended

for treatment of CIC after OTC treatments fail based on moderate quality of evidence. Fiber supplementation, senna, and magnesium oxide were conditionally suggested for treatment of CIC based on low or very low-quality evidence.

Caution

The GRADE methodology and EtD frameworks provide transparency about how recommendations were made, although most of these data are in the supplemental information and require careful review to understand how the authors parsed benefits, risks, and costs of different therapies. Thus, the authors' subjective opinions do influence choice of critical outcomes, assessments about the strength of recommendations, and certainty of evidence.

The Methods section states that docusate, a stool softener or surfactant laxative, will be evaluated, but no recommendations or literature review is presented. Prior guidelines[3] identified small RCTs with methodologic limitations of docusate, which reported no superiority to placebo and inferiority to psyllium.

My Practice

While OTC agents, including fiber supplementation, PEG, and stimulant laxatives, should be an initial therapy for CIC, the vast majority of my patients have already tried and failed some combination of OTC agents along with diet modification prior to my evaluation. We should always remember to ask patients about what they have tried and failed in the past, focus on initiating prescription therapies, and avoid combination of OTCs in supra-therapeutic doses in these patients. Shared decision-making is also crucial. It's unhelpful to prescribe an agent that the patient cannot afford. However, if the patient has commercial insurance or Medicare Part D, then at least one effective prescription agent is usually available without prior authorization. Patient co-pays also can be minimized with coupons available online. I usually start with linaclotide or plecanatide in CIC patients who have failed to get adequate relief with PEG or other OTC agents.

Remember the basics: perform a digital rectal exam and assess for pelvic floor dysfunction based on inappropriate ascent of the pelvic floor when the patient does a Valsalva maneuver. When I suspect pelvic floor dysfunction, especially

in women who have had complicated vaginal deliveries and have failed multiple CIC therapies, I'll order anorectal manometry and defecography.

Finally, I will combine therapies in severe CIC patients, but it may be even more important to set appropriate expectations. Near-total resolution of symptoms is not the expected goal. We proactively educate our patients that getting several complete spontaneous bowel movements per week is success and to expect occasional loose stools when starting potent therapies.

For Future Research

Comparative RCTs are needed to clarify superiority amongst therapies. Properly designed RCTs of stool softeners, including docusate sodium and docusate calcium, are needed to clarify if these agents actually improve stool frequency or consistency.

Conflict of Interest

Dr. Schoenfeld reports serving on advisory boards, consultant and speakers bureau for Ironwood Pharmaceuticals, AbbVie Pharmaceuticals, and Ardelyx Pharmaceuticals, and serving as an advisory board member for Takeda Pharmaceuticals and Salix Pharmaceuticals within the past 3 years.

Note: The authors of the article published in *The American Journal of Gastroenterology* are active on social media. Tag them to discuss their work and this EBGi summary.

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