REPORT

Update on the Management of Chronic Idiopathic Constipation

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Introduction

Chronic idiopathic constipation (CIC), previously labeled as functional constipation, is a highly prevalent disorder reported to healthcare providers.[1] Symptoms of constipation can vary by patient but are observed in all age groups and patient populations across the United States, with millions of physician visits occurring annually.[2,3] CIC is a functional bowel disorder characterized by difficult, infrequent, and/or incomplete defecation. Patients with CIC should not have an underlying anatomic or structural abnormality as the cause of their symptoms.[1,4] It is recommended that patients with CIC be differentiated from patients with irritable bowel syndrome (IBS),[4] although there is significant overlap in the physiology and treatment of IBS-constipation (IBS-C) and CIC.[5-7]

An exact measure of CIC incidence and prevalence is difficult to obtain, as many published studies rely on patient self-reports, although clinical studies have assessed the epidemiology of CIC using a wide variety of questionnaires.[8] With these caveats in mind, it is estimated that approximately 35 million adult Americans have CIC, and 16 of 100 adults have symptoms of constipation.[2,9] A 2011 systematic review of studies measuring the prevalence of constipation in countries throughout the world reported a pooled prevalence of 14% for patients with the primary definition of CIC in each study.[1] CIC has a significant impact on the healthcare system, accounting for 3.92% of all ambulatory care visits in the United States in 2014.[3] Furthermore, although CIC has been found to affect all individuals in the general population, it disproportionately affects women (odds ratio [OR], 2.2 female to male ratio), the elderly (OR, 1.4), and individuals of lower socioeconomic status (OR, 1.3).[1,8,10,11] Other common risk factors of constipation include reduced caloric intake, sedentary lifestyle, decreased fiber intake, and usage of anti-inflammatory agents.[12,13]

Guidelines for the treatment of CIC are available from the American College of Gastroenterology and the Rome Foundation.[4] The management of CIC is multifaceted and focuses on empiric therapy for many patients and ruling out secondary causes of constipation in others, with the overall goal of developing an individualized treatment plan that provides multisymptom relief. The

ABSTRACT

Chronic idiopathic constipation is a functional bowel disorder characterized by difficult, infrequent, and/or incomplete defecation, affecting 35 million adult Americans, resulting in more than millions of physician visits annually. Symptoms of constipation vary from patient to patient and impact all age groups and patient populations in the United States. The definition of constipation was previously not well specified, beyond stool frequency, and has been revised to incorporate the patient perspective and experience in addition to specific criteria created by the Rome Foundation. In the absence of red-flag (alarm) symptoms, and with a normal physical (including rectal) examination, patients can initially be empirically treated for their symptoms of chronic constipation assuming adequate follow-up is arranged. Unfortunately, both patients and healthcare providers have documented unmet needs with currently available therapeutic options, thus prompting research for new agents with novel mechanisms of action that are both efficacious and safe.

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For author information and disclosures, see end of text.

purpose of this document is to review underlying mechanisms in the development of CIC and to provide an update on currently available therapeutic agents.

Normal Physiologic Function of the Colon

To fully understand the pathophysiology of CIC and its treatment, it is important to briefly review the normal physiology of the colon. A healthy colon utilizes peristalsis and mass movements (propulsive activity) to move contents through the colon, which then leads to defecation.[14] These mass movements occur primarily as a result of high amplitude propagating contractions (HAPCs) due to the contraction of colonic smooth muscle and neuronal signaling via the myenteric nerve plexus.[15,16] A healthy individual generally experiences 6 HAPCs per day on average,[17] usually after awakening and after meals. This is in contrast to those with CIC who may have fewer, shorter, or lower amplitude HAPCs.[18,19] HAPCs are considered a driving event in the normal physiology of the colon and defecation; some therapeutic agents have been shown to increase the frequency and amplitude of HAPCs, which may account for their therapeutic effects.[20,21]

Serotonin, also known as 5-hydroxytryptamine (5-HT), plays a major role in normal colon function with respect to gastrointestinal (GI) motility and sensation.[11] 5-HT is the most common neurotransmitter synthesized and released by the GI tract, primarily by enterochromaffin cells, which produce the majority of serotonin found in the body (approximately 95%).[15,16,22] Although the role of 5-HT in normal colonic activity is controversial, 5-HT does mediate peristalsis by binding to 5-HT receptors.[15] When neurotransmitters, such as acetylcholine, are released, smooth muscle contraction occurs in the GI tract on the orad side of the luminal contents and moves forward with the end goal of defecation.[23] In addition to peristalsis, the colon also is responsible for the management of intestinal fluid and electrolyte content via reabsorption (approximately 1-2 L of fluid/day). Increasing fluid content in the GI tract through the use of secretagogues is a newer therapeutic area of interest.[16]

Clinical Presentation and Diagnosis

The term constipation is used liberally, referring to multiple symptoms including hard stool, excessive straining, infrequent bowel movements, bloating, and the feeling of difficult or incomplete evacuation.[11] Due to the lack of a proper meaning of the term, there is often confusion and mischaracterization of constipation by both patients and physicians.[24] The definition of constipation has been revised in recent years to focus less on stool frequency, thereby not only addressing the patient's perspective, but to also acknowledge constipation as more of a syndrome with overlapping features.[25] For example, expert consensus from the current Rome IV criteria (**Table 1**[4]) addresses functional bowel disorders as a spectrum of GI disorders, as opposed to isolated entities.[25]

Furthermore, experts recognize that although there are specific diagnostic criteria for each functional GI disorder (eg, dyspepsia, IBS, CIC), symptoms are nonspecific and frequently overlap, making it difficult to accurately distinguish between each disorder.[25] The Rome IV criteria indicate that it is common for patients to transition between one bowel disorder, or predominant symptom, to another (eg, CIC to IBS), which may occur normally as part of the disorder, due to treatment, or a combination of the two.[25]

A survey by Johanson et al found the most frequent symptoms reported by patients with CIC to be straining (79%), hard stool (71%), abdominal discomfort (62%), bloating (57%), feelings of incomplete bowel evacuation after a bowel movement (54%), and infrequent bowel movements (57%).[26] As discussed, it is common for patients with bowel disorders to have overlapping symptoms, and CIC is commonly confused with IBS-C.[8] For example, patients with CIC may report symptoms of abdominal pain and bloating, but those symptoms typically are milder and do not predominate, as opposed to those in patients with IBS-C.[4]

The diagnosis of CIC begins with a comprehensive review of a patient's history (dietary, medical, surgical, and psychological) and a careful physical examination. This should include a digital rectal exam, which may identify pelvic floor dyssynergia in younger patients or an occult malignancy in older patients. Although CIC and IBS-C are some of the most common disorders associated with chronic constipation (CC), there are a number of secondary causes of CC (eg, medications, mechanical obstruction, metabolic disorders) (**Table 2**).[8,11,27] If a patient presents with any red-flag symptoms, such as sudden weight loss or rectal bleeding, further evaluation is necessary to rule out potentially more serious etiologies (eg, malignancy). When appropriate, practitioners can order diagnostic tests (preferably when the patient is laxative free) that assess stool frequency, daily stool

TABLE 1. Rome IV Criteria for the Diagnosis of Functional Constipation[4]

Criteria for Functional Constipation Diagnosis
Onset of constipation symptoms at least 6 months before diagnosis Below criteria met for the past 3 months
I. Two or more of the following criteria must be present: a. Straining with >25% of defecations b. Lumpy or hard stools with >25% of defecations i. Bristol stool form types 1 and 2 c. Sensation of incomplete evacuation with >25% of defecations d. Sensation of anorectal obstruction/blockage with >25% of defecations e. Manual maneuvers required with >25% of defecations i. Eg, digital evacuations, support for the pelvic floor f. Fewer than 3 spontaneous defecations per week
II. Loose stools are rare without administration of laxatives
III. Insufficient criteria for irritable bowel syndrome

Adapted from Lacy BE, Mearin F, Chang L. *Gastroenterology.* 2016;150(6):1393-1407.

weight, colonic transit, and anorectal function, to exclude other etiologies, such as slow transit constipation and pelvic floor dyssynergia.[4] In practice, it can be challenging to distinguish between IBS-C and CC or even the different types of CC based on symptoms alone; thus, additional testing may be necessary. For example, significant straining is indicative of defecatory disorders (DD) but not diagnostic. Tests such as an anorectal manometry and a balloon expulsion test may be useful to confirm a diagnosis of DD, although these tests are not always readily available.[8] In addition, the Bristol stool form scale[28] (**Figure**[4]) can be used to monitor changes in intestinal function and at the extremes of the scale,[29] it can be used as a surrogate for colonic transit.[8] Once secondary etiologies have been ruled out, the Rome IV criteria can be used to diagnose a patient with CIC.[4] The Rome IV criteria are shown in Table 1; the diagnosis requires the onset of symptoms at least 6 months before presentation, with symptoms present for the previous 3 months.[4]

There are 3 main subtypes of CC: normal-transit constipation (NTC), slow-transit constipation (STC) or "colonic inertia," and DD, such as pelvic floor dyssynergia.[8] Identifying the subtype is important, as it helps facilitate management decisions, such as medications for NTC and STC or pelvic floor therapy (physical therapy with biofeedback) for DD. In a tertiary referral practice involving approximately 1400 patients with constipation symptoms, about 5% were diagnosed with STC, 65% with NTC, and 30% with DD.[30]

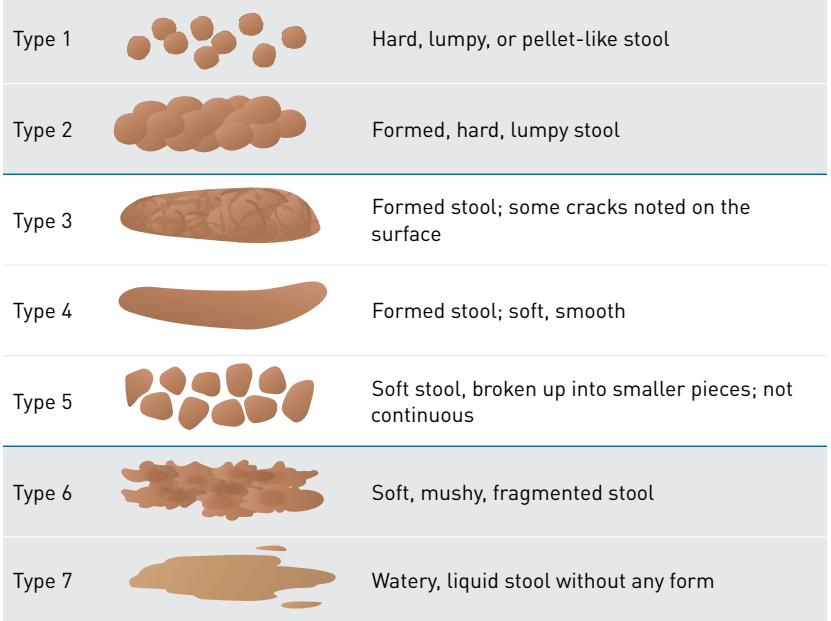
Several limitations should be highlighted concerning the 3 subtypes of CC, as there is a growing body of evidence suggesting that these subtypes are an oversimplification of the categorization of CIC.[18,24,31-33] For example, symptoms of STC and DD differentiate these 2 conditions poorly[24] and they frequently overlap.[33,34] Additionally, delayed colonic transit and DD are commonly seen among individuals with IBS.[31,32] Therefore, treatment for CIC should be individualized, taking into account prior treatments and the real possibility that CIC may be multifactorial in origin. Selection of

TABLE 2. Frequent Causes of Secondary Constipation[8,11,27]

Medication	Anticholinergics	Diphenhydramine, oxybutynin
	Antidepressants	Tricyclic antidepressants
	Antihistamines	Cetirizine, fexofenadine, loratadine
	Calcium channel blockers	Amlodipine, diltiazem, verapamil
	Diuretic	Furosemide
	Iron supplementation	Ferrous fumarate, ferrous sulfate
	NSAIDs	Aspirin, ibuprofen, naproxen
	Opioids	Hydrocodone, morphine, oxycodone
	Serotonin 5-HT_3 antagonists	Ondansetron
Mechanical obstruction	Anal fissures	
	Colon cancer	
	Strictures	
Metabolic disorders	Diabetes mellitus	
	Hypercalcemia/hypokalemia/hypomagnesemia	
	Hyperparathyroidism	
	Hypothyroidism	
	Neurological disorders	Amyloidosis, multiple sclerosis, Parkinson disease, spinal cord injury
Miscellaneous conditions	Diet	
	Eating disorders/depression	
	Immobility	
	Paraneoplastic syndromes	

5-HT indicates 5-hydroxytryptamine; NSAID, nonsteroidal anti-inflammatory drug.
Adapted from Toney RC, Wallace D, Sekhon S, Agrawal RM. *Geriatric Gastroenterology*. 2008;18:12-28; Rao SS, Rattankovit K, Patcharatrakul T. *Nat Rev Gastroenterol Hepatol*. 2016;13(5):295-305.

FIGURE. Bristol Stool Form Scale[4]



Adapted from Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology*. 2016;150(6):1393-1407.

a therapeutic agent to treat symptoms of constipation should be a joint decision between the patient and provider that takes cost, tolerability, safety, patient preference, lifestyle considerations, and other pertinent clinical information into consideration.

Management of Chronic Idiopathic Constipation

Initial treatment of CIC begins with patient education, medication review (discontinuing any agents that could slow colonic transit), and lifestyle modifications (eg, increased dietary fiber to 20-30 g/day, physical activity, and adequate hydration). In addition, it is also helpful to create a routine schedule for using the lavatory. Using a toilet that is closer to the floor or adding a device to elevate the feet can also help ease straining.[4]

Nonprescription Treatment

Bulking Laxatives

Patients with CIC are commonly initiated on fiber supplementation (maximum of 30 g/day) as empiric therapy.[4] Insoluble fiber, such as bran, has been associated with increased cramping, bloating, and flatulence, whereas soluble fiber (eg, psyllium) has been shown to provide some relief in CIC.[35] A 2011 systematic review showed that soluble fiber improved global symptoms, straining, the mean number of stools per week (3.8 on soluble fiber vs 2.9 at baseline) and stool consistency compared with placebo.[36] However, fiber supplementation must be introduced gradually with sufficient water intake to decrease unwanted GI adverse effects (AEs) (**Table 3**).[35,37,38] If a patient fails empiric fiber therapy, there are no randomized controlled trials dictating the next therapy; however, according to Lacy et al, osmotic agents are usually the next agent of choice due to their favorable safety profile, efficacy, ease of use, and low cost.[4]

Osmotic Laxatives

Osmotic laxatives, such as polyethylene glycol (PEG) and lactulose, contain poorly absorbed molecules that draw water into the intestinal lumen, thus softening stool and increasing intestinal transit.[4,35]

The efficacy of osmotic laxatives was evaluated in a meta-analysis of 6 randomized controlled trials and was found to be superior to placebo for the treatment of CIC.[39] A systematic review found that PEG was superior to both placebo and lactulose in adults and children.[40] The most common AEs for PEG include distension and diarrhea, whereas lactulose commonly causes dose-dependent abdominal cramping and bloating.[4] In April 2018, the FDA decided to remove the "Rx-only" status of PEG, thus allowing patients to purchase this agent without the need for a prescription.[41]

Stimulant Laxatives

Stimulant laxatives, such as bisacodyl, sodium picosulfate, and senna, help relieve constipation by decreasing water absorption, stimulating intestinal motility directly, and releasing prostaglandins that may indirectly accelerate intestinal transit.[4] The efficacy and safety profiles of bisacodyl[42] and sodium picosulfate[43] have been established in randomized controlled trials for patients with CIC. Senna is also frequently used in patients with CIC; however, there are currently no placebo-controlled trials that support its use for CIC. The most common AEs with the stimulant laxatives are abdominal pain and diarrhea.[38,42,43]

Prescription Treatment of Chronic Idiopathic Constipation

Both patients and healthcare providers report unmet needs with current CIC treatment options.[44] For example, 50% of patients with CIC report dissatisfaction with nonprescription laxatives due to unpredictability, bloating, poor symptom relief, or inability to improve quality of life.[26] Similarly, 78% of healthcare providers reported being unsatisfied with current prescription agents and felt there was room for improvement.[44] To address these concerns, alternative agents with novel mechanisms of action, all of which increase intestinal or colonic secretion of chloride and water, have been developed over the past 10 years (**Table 4**[45-48]). These new agents were developed to specifically address the underlying pathophysiology of CC and patient concerns.

TABLE 3. Comparison of Nonprescription Laxatives Recommended for Use by the American College of Gastroenterology (ACG)[35,37,38]

Drug Category	Generic Name	Dosage	ACG Recommendation/ Quality of Evidence for CIC	Adverse Effects
Bulking laxatives	Psyllium	Up to 30 g in 1-3 doses per day	Strong/low	Diarrhea, abdominal pain, cramping, flatulence, obstruction (with insufficient fluid intake)
Osmotic laxatives	Polyethylene glycol	17 g once daily	Strong/high	Flatulence, nausea, diarrhea
	Lactulose	15-30 mL daily	Strong/low	Flatulence, abdominal discomfort, cramping
Stimulant laxatives	Bisacodyl	5-15 mg daily	Strong/moderate	Abdominal pain/cramping, nausea, vomiting, electrolyte imbalances with prolonged use

CIC indicates chronic idiopathic constipation.
Adapted from Ford AC, Moayyedi P, Lacy BE. Task Force on the Management of Functional Bowel. *Am J Gastroenterol*. 2014;109(suppl 1):S2-S26; Thomas RH, Luthin DR. *Pharmacotherapy*. 2015;35(6):613-630.

Prosecretory Agents (Secretagogues)

Lubiprostone was the first secretagogue approved by the FDA for the treatment of CC; in 2008, it received an expanded indication for IBS-C in women.[37] Lubiprostone is a bicyclic fatty acid, derived from prostaglandin E_1, which exerts its effect via activation of type 2 chloride channels (CLC-2) on the apical membrane of epithelial cells.[8] CLC-2 activation leads to higher chloride concentrations in the intestinal fluid, which increases water secretion in the intestinal lumen, ultimately causing accelerated intestinal and colonic transit.[8,49] Lubiprostone is taken by mouth and is almost completely metabolized in the gut lumen.[50] The recommended dose of lubiprostone for the treatment of CC is 24 mcg twice daily.[48]

TABLE 4. Comparison of FDA-Approved Prescription Treatments for CIC in Adults[45-48]

Drug Category	Generic Name (Brand Name)	Dosage	Adverse Effects
Prosecretory agents	Lubiprostone (Amitiza)	24 mcg twice daily	Nausea, diarrhea, abdominal pain, abdominal distension, headache
	Linaclotide (Linzess)	72 mcg or 145 mcg once daily	Diarrhea, abdominal pain, flatulence, abdominal distension
	Plecanatide (Trulance)	3 mg once daily	Diarrhea, sinusitis, upper respiratory tract infection, abdominal distension, flatulence
Serotonergic agent	Prucalopride (Motegrity)	2 mg once daily	Headache, abdominal pain, nausea, diarrhea, abdominal distension

CIC indicates chronic idiopathic constipation.

Short-term efficacy and safety of lubiprostone were evaluated in two 4-week, phase 3, randomized, double-blind, placebo-controlled trials conducted in tandem with identical study points and designs.[51,52] The primary end point for each study was the number of patient-reported spontaneous bowel movements (SBMs) during the first week of treatment. Johanson et al showed that lubiprostone was superior to placebo at increasing stool frequency in the first week (5.69 vs 3.46; $P = .0001$), reducing straining, and improving stool consistency over all weeks ($P \leq .0003$) compared with placebo.[51] Similarly, Barish et al also increased the number of SBMs during the first week in patients treated with lubiprostone compared with placebo (5.89 vs 3.99; $P = .001$) and reported improvements over all weeks in stool consistency, straining, and constipation severity compared with placebo.[52]

The most common reasons for discontinuation were AEs in the lubiprostone arms (7.5%[51] and 12.6%,[52] respectively) and lack of efficacy in the placebo arms (1.6%[51] and 5.1%,[52] respectively). Long-term safety has also been evaluated for lubiprostone in CC in a 48-week open-label trial that included 248 patients.[53] A total of 13.3% of patients discontinued the study due to AEs including nausea (5.2%), abdominal distension (2%), headache (1.6%), abdominal pain (1.6%), diarrhea (1.2%), and vomiting (1.2%).[53] Although not studied in a prospective manner, some providers suggest either taking lubiprostone with food or reducing the dose to help alleviate symptoms of nausea, which was generally reported as mild. Lubiprostone is contraindicated in patients with a known or suspected mechanical obstruction. There are limited available data in pregnant women to indicate a drug-associated risk of adverse developmental outcomes. This medication should be used with caution in women who are breastfeeding, and breastfed infants should be monitored for diarrhea.[48]

Linaclotide was the second intestinal secretagogue approved by the FDA for adults with CIC and has a novel mechanism of action via activation of guanylate cyclase type C receptors (GC-C).[8] It is a 14-amino acid peptide that binds to and activates the GC-C receptor. When the GC-C receptor is activated, intracellular cyclic guanosine monophosphate (cGMP) is increased, which stimulates chloride secretion through the cystic fibrosis transmembrane regulator, resulting in an increase in water secretion into the intestinal lumen, accelerating intestinal transit.[8,31] The recommended dose for CIC is 72 mcg or 145 mcg once daily, by mouth, taken 30 minutes before breakfast.[9,45] Because the drug is minimally absorbed, drug interactions and renal and/or hepatic impairment are unlikely to affect the metabolism or elimination of linaclotide.[45]

Approval for linaclotide was based on 2 phase 3, randomized, double-blind, parallel-group, placebo-controlled, dual-dose, 12-week trials (Trial 303 and Trial 01) in patients with CIC (N = 1272).[54] The primary end point of the trials was 3 or more SBMs per week and a minimum increase of 1 SBM per week compared with baseline over the 12-week treatment period.[54] Patients received either 145 mcg or 290 mcg of linaclotide once daily for 12 weeks or placebo. Compared with placebo, the primary end point was met by a significant number of patients in both trials who received 145 mcg or 290 mcg of linaclotide ($P < .01$).[54]

Safety was also evaluated in both phase 3 studies, with diarrhea being the most common AE leading to discontinuation of treatment in 4.2% of linaclotide-treated patients.[54] Other AEs experienced in patients taking linaclotide (similar to placebo) included abdominal pain, flatulence, abdominal distension, upper respiratory infections, nasopharyngitis, and sinusitis.[54] Given that the 2 doses tested were equally efficacious, and the higher dose was more likely to cause diarrhea, the highest approved dose of CIC treatment is 145 mcg per day. Since the first approval, a lower dose level of 72 mcg has also been approved for a CIC indication.[55] Linaclotide has a boxed warning for use in pediatric patients aged 6 to 17 years due to reported deaths secondary to dehydration in animal studies. Its use is contraindicated in children younger than 6 years and in

patients with mechanical GI obstruction.[45] There are no adequate studies of linaclotide in pregnant women; animal fetal toxicity has occurred only at supratherapeutic doses, but trials have not been conducted in women.[45] Due to the minimal absorption of linaclotide from the GI tract, it is not expected to enter breast milk; however, data are lacking and postmarketing studies have been mandated by the FDA.[45]

Plecanatide is a synthetic analogue of the endogenous human intestinal peptide uroguanylin (16-amino acid peptide) and a new GC-C receptor agonist approved by the FDA in 2017 for the treatment of CIC in adults.[56,57] Similar to linaclotide, plecanatide agonism of the GC-C receptors expressed in the epithelial lining of the GI mucosa causes increased intestinal fluid secretion.[57] The recommended dose is 3 mg once daily, taken with or without food.[47]

A phase 3, multicenter, double-blind, placebo-controlled trial showed that plecanatide improved complete SBMs in patients with CIC.[57] It also significantly improved the frequency of SBMs versus placebo at 12 weeks (3.2 vs 1.3 per week, respectively). Patients also reported improvements in overall constipation severity, treatment satisfaction, and the patient's desire to continue treatment compared with placebo.[57]

The most common AE was diarrhea, which occurred in 1.3% (placebo), 5.9% (3-mg dose), and 5.7% (6-mg dose) of patients.[57] Less common AEs similar to placebo were sinusitis, upper respiratory tract infections, abdominal distension, flatulence, and abdominal tenderness.[47] As the drug is minimally absorbed, it is not expected to cause fetal exposure, although there are no adequate studies in pregnant women. Similarly, no lactation studies have been conducted to make a recommendation in women who are breastfeeding.[47] Plecanatide contains a boxed warning regarding risk of serious dehydration in pediatric patients younger than 6 years and is contraindicated in these patients as well as those with known or suspected mechanical GI obstruction.[47] Plecanatide should also be avoided in patients aged 6 to 18 years because safety and efficacy have not been established in this patient group.[47]

Ileal Bile Acid Inhibitors

Elobixibat (A3309) is an ileal bile acid transporter inhibitor (IBAT) and a pure enantiomer of a synthetically modified 1,5-benzothiazepine.[58] The drug exerts its novel mechanism of action by blocking the ileal absorption of bile acids, which ultimately expands the flow of bile into the colon, causing increased intestinal secretions and transit.[58] Two small phase 2 trials revealed that elobixibat accelerated colonic transit in patients with CC.[59,60] An 8-week phase 2b study in 190 patients with CC revealed a dose-dependent increase in SBMs from baseline with increases of 2.5, 4, and 5.4 in the 5-mg, 10-mg, and 15-mg groups, respectively.[59] Abdominal pain was the most common AE occurring in 10.4%, 10.6%, and 27.1% of patients treated with elobixibat in the 5-mg, 10-mg, and 15-mg groups, respectively.[59] Currently, elobixibat is not approved in the United States but has been approved in Japan based on 2 phase 3 trials.[61] Three trials were cancelled due to issues with trial drug distribution.[58]

Serotonergic Agents

There are 7 main classes of 5-HT receptor subtypes (5-HT_1-5-HT_7), with the 5-HT_3 and 5-HT_4 receptors being the most extensively studied due to their roles in sensation and motility in CIC, respectively.[15,35] The 5-HT_3 receptor is a ligand-gated ion channel and is less relevant to drugs used in treatment of constipation. The 5-HT_4 receptors are G-coupled receptors and are commonly found on smooth muscle cells, enterochromaffin cells, myenteric plexus neurons, and intrinsic pathway primary afferent neurons.[11] Agonists of these receptors increase peristalsis and proximal smooth muscle contraction (via acetylcholine and calcitonin gene-related peptide), thereby increasing motility.[11]

Cisapride was one of the first 5-HT_4 agonists to be developed (it is also a 5-HT_3 antagonist). It was originally used for the treatment of nocturnal heartburn but was also prescribed for a variety of upper GI disorders, including dyspepsia and gastroparesis.[62] Although cisapride demonstrated some efficacy in CIC, it was withdrawn from the worldwide market due to cardiac arrhythmias resulting from lack of specificity for the 5-HT_4 receptor and subsequent interactions with the human ether-a-go-go-related gene.[62]

Tegaserod was a serotonergic agent developed for the treatment of IBS-C. It is a partial agonist for the 5-HT_4 receptor and has known prokinetic effects on the GI tract.[63] It was superior to placebo for improving stool frequency and other constipation-associated symptoms.[64,65] Similar to cisapride, tegaserod was also withdrawn from the market in March 2007 due to possible concerns for cardiovascular AEs.[4] However, in July 2007, the agent was reintroduced in the United States through a treatment investigational drug protocol for IBS-C and CIC for women younger than 55 years, with no risk of certain cardiovascular events.[66,67]

In contrast, prucalopride is a highly selective 5-HT_4 agonist that has greater selectivity for the 5-HT_4 receptors compared with previously developed agents and no affinity for the delayed rectifier potassium channels in the heart that are responsible for cardiac arrhythmias.[4] Six randomized controlled trials (N = 2484) have demonstrated that significantly more patients taking prucalopride (2 mg daily for 12 weeks) compared with placebo had a mean of 3 or more SBMs per week (27.8% vs 13.2%, respectively; $P < .001$).[68,69] Response to treatment was seen rapidly (as early as 1 week) and was retained throughout the 12-week study period.

Based on these trial results, prucalopride was approved by the FDA in December 2018 for adults with CIC and is expected to be available for patient use in 2019.[70] Of note, the FDA requested 5 postmarketing studies that will evaluate the pharmacokinetics,

efficacy, and safety of prucalopride in pediatric patients aged 6 months to less than 18 years and pregnant/lactating women with CIC.[70] The approved dose is 2 mg, which is taken by mouth once daily. Prucalopride is contraindicated in patients with intestinal perforation, structural or mechanical obstruction, obstructive ileus, or severe inflammatory conditions of the intestinal tract (eg, Crohn disease and ulcerative colitis).[46] Patients who are initiated on prucalopride will need to be monitored for persistent/worsening depression and the development of suicidal thoughts and behaviors.[70] These events were reported in clinical trials; however, no causal association has been established.[70]

Overall, prucalopride was very well tolerated with mild or moderate AEs being reported in both treatment groups with no fatalities. The most common AEs (≥5%) reported in the prucalopride group were nausea, diarrhea, abdominal pain, and headache.[68,69] There were 2 cardiovascular AEs reported.[68] It was important to evaluate the safety profile of prucalopride because prior medications in this class have been associated with adverse cardiovascular events.[71] Preliminary results from a study with data available only in abstract form revealed that patients treated with prucalopride (n = 5717) showed no evidence of an overall increase in the risk of major adverse cardiovascular events compared with patients treated with PEG (n = 29,388). This study was noninterventional and included pooled analyses of data from the United Kingdom and Sweden.[71] Currently, there are insufficient data to make recommendations for use in pregnancy or lactating women; however, prucalopride is present in breast milk.[46] Prucalopride dosing will need to be adjusted in patients with severe renal impairment (CrCl <30 mL/min) and should be avoided in end-stage renal disease that requires dialysis.[46]

Conclusions

CIC is a common complaint experienced by all patient groups in the general population in the United States. Current treatment guidelines are available from the American College of Gastroenterology and the Rome IV criteria. CIC was previously characterized by reduced stool frequency but is now more appropriately characterized as a syndrome that more accurately reflects patients' experiences. Patients with CIC may have overlapping symptoms with other bowel disorders (such as dyspepsia and gastroesophageal reflux disease), which can make the diagnosis challenging. However, because CIC usually does not have a single or uniform physiologic abnormality, it can generally be treated empirically without any specialized tests (in the presence of a normal examination and the absence of red-flag symptoms). Comparative trial data for the available agents for the treatment of CIC are sparse; therefore, treatment must be selected on a patient-by-patient basis. Still, even with a variety of treatment options widely available, patients and healthcare providers alike have reported unmet clinical need or incomplete satisfaction with currently available treatment modalities. Therefore, continued research and development are necessary to provide novel therapeutic agents that are both efficacious and safe for patients with CIC. ■

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