CHRONIC CONSTIPATION: MECHANISMS OF ACTION AND EFFECTIVE TREATMENT

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ABSTRACT

This is an exciting time in the treatment of functional gastrointestinal (GI) disorders because of our rapidly evolving understanding of the mechanism of action of these illnesses and their treatment. In this article, chronic constipation (CC), which is one of the most common functional disorders of the gut, is discussed. Although not life-threatening, CC can profoundly and negatively affect quality of life and is associated with a significant economic burden of direct and indirect annual healthcare costs. In the United States alone, estimates from several years ago placed the annual cost of laxatives to treat constipation at $800 million. Possible causes of CC range from psychologic disorders to dysfunctions of GI motility, though most patients do not have an identifiable explanation for their constipation. Recent research indicates that constipation most likely results from abnormalities of myenteric neurons or pacemaker function, defects in neurotransmitters, or incoordination of the muscles of the pelvic floor or anorectum, and may be influenced by environmental factors or chronic stress. In this article, the symptoms of CC are reviewed and the safety and efficacy of traditional, novel, and emerging therapies are examined. Because of the overlap in symptoms, many of the treatments discussed in this review also apply to patients with constipation-predominant irritable bowel syndrome.

T he definition of constipation differs among individuals affected with the disorder, their physicians, and the professional medical organizations that provide guidelines for treatment. Research reveals that 50% of patients define constipation by the symptoms reported most often: infrequent, difficult, or incomplete evacuation; the passage of hard stool; or the unproductive urge to defecate. Most clinicians define constipation simply as fewer than 3 bowel movements per week, but both the Rome II Functional Gastrointestinal Disorders Coordinating Committee and the American College of Gastroenterology (ACG) Chronic Constipation (CC) Task Force have published current guidelines for diagnosis and treatment that are more specific.

Rome II criteria for CC specify that during the preceding 12 months symptoms must have occurred for at least 12 (not necessarily consecutive) weeks. In addition, more than 25% of defecations must be characterized by 2 or more of the following symptoms: lumpy or hard stools, straining, a sensation of incomplete evacuation or anorectal obstruction, the need for a manual maneuver to evacuate the rectum, and/or fewer than 3 defecations per week. It is essential that no organic disease, irritable bowel syndrome (IBS), or loose stools be present. However the ACG CC Task Force members concluded that this definition was rather onerous for primary care clinicians because many patients who self-report CC do not meet these criteria. The Task Force proposed a broader definition of the disorder that includes the most common symptoms of self-reported constipation (infrequent stools, difficult defecation [straining, incomplete evacuation, hard or lumpy stools, prolonged time for defecation], or both) and states that a combination of those symptoms should have been present for at least 3 of the prior 12 months. The ACG CC Task Force rec-
ognized that CC is associated with a significant decrease in quality of life and that, because there are no symptom-based criteria that identify subtypes of CC such as colonic inertia or defecatory disorders, those subtypes may occur concomitantly in individual patients. In its definition of CC, the Task Force also recognized that abdominal discomfort or bloating usually is minimally present in patients with CC and that the symptoms of CC often are difficult to differentiate from those of IBS.

**PATHOGENESIS AND PATHOPHYSIOLOGY**

In his article in this monograph, Dr Camilleri addresses the pathogenesis and pathophysiology of CC and IBS. In summary, the clinical causes of CC can be divided into 3 primary categories: extracolonic constipation, mechanical constipation, and functional constipation. In patients with extracolonic constipation the function of the colon and/or rectum is affected by exogenous factors such as dietary habits (eg, low fiber intake, anorexia); medications (eg, antidepressants, anticholinergics, antihypertensives, opioids, iron supplements, aluminum- or calcium-based antacids); metabolic, endocrine, neurologic, or connective-tissue disorders; or trauma such as spinal cord injury. Mechanical constipation is caused by a physical anomaly of the colon and/or rectum (ie, anal stenosis, rectal prolapse, rectocele, the colonic effects of diverticular disease). Functional constipation is classified as 1 of 3 entities: constipation-predominant IBS (C-IBS) characterized by abdominal discomfort and bloating; slow-transit constipation, in which fewer than 3 bowel movements per week are produced without either the urge to defecate or abdominal pain; or a defecatory disorder of the pelvic floor or anal sphincter, in which patients must strain excessively and may rely on manual maneuver to defecate. Within any one person slow-transit constipation, defecatory disorder, and C-IBS may coexist.

**CHRONIC CONSTIPATION: FALLACIES AND FOLKLORE**

CC is a widespread disorder of the gut that has been long misunderstood. Before various treatments are presented, it is important to briefly review the myths about constipation, which influence prescribing practices, patients' perceptions of CC, and compliance with therapy. Misconceptions about the benefits of fiber consumption and fluid intake will be discussed in the treatment section of this article.

**THE TOXIC GUT**

Many patients (and even some healthcare providers) believe that toxins produced by undigested food in the gut are systemically absorbed and produce a wide variety of adverse health-related symptoms, from lassitude to hypertension to various cancers. The need for a “daily bowel movement” is a widespread myth to which the regular use by many individuals of laxatives or cleansing techniques ranging from herbal teas to enemas can be attributed. To date, however, no single such toxin has been identified, and the prompt relief of many nonspecific symptoms of idiopathic constipation probably results from a mechanical rather than systemic effect. Another common myth states that in some individuals, CC is caused by a colon that is too long or “kinked” and that surgical intervention might be helpful. Other than for the treatment of volvulus or severe refractory colonic inertia, surgery does not play a role in the treatment of constipation, and no valid studies correlate colonic length with transit.

**THE EFFECT OF HORMONES**

Sex hormones and GI hormones have been long hypothesized to influence intestinal transit. Sex hormones do not appear to exert a major effect on bowel function during the menstrual cycle, although the looser stools often seen on the first day of menses may be related to the local action of prostaglandins produced on the first day of menstruation. However, progesterone may be responsible for the slower colonic transit that occurs during pregnancy. Xiao et al have suggested the possibility that down-regulation of contractile G proteins and up-regulation of inhibitory G proteins, likely caused by overexpression of progesterone receptors, may be a cause of slow-transit CC in women. Women with severe idiopathic constipation seem to exhibit a reduction in steroid hormones, which may result from alterations in the hepatic circulation of those hormones and/or their breakdown by the intestine. The role of GI hormones such as motilin, glucagon, and pancreatic polypeptide is less clear. Alterations in hormone levels have been found in people with severe idiopathic constipation, but the differences in primary and secondary changes in those levels must be further elucidated. In individuals without the clinical features of hypothyroidism, the role of thyroid dysfunction in CC is minimal.

**THE HAZARDS OF LONG-TERM LAXATIVE USE**

The myth that the long-term use of laxatives caus-
es enteric neuronal damage, impairs the function of the colon, and creates laxative dependency often leads patients to fear treatment with a laxative medication when it is required. Recent reviews examining this misconception and the literature that created it show that such concern is unfounded. However, laxatives can cause electrolyte disturbances and abdominal discomfort and must therefore be appropriately selected and prescribed in correct doses.

**The Increased Risk of Colorectal Cancer From Anthraquinone Use**

Also common is the misperception that anthraquinone cathartic use increases the risk of colorectal cancer. That impression results from a meta-analysis by Sonnenberg and Muller, who examined the colorectal cancer risk associated with cathartic use and constipation in 14 case-controlled studies. The analysis of those investigators revealed a statistically significant pooled odds ratio of 1.46 for cathartics and 1.48 for constipation, and their review of the data on dietary factors such as the consumption of fat, alcohol, meat, and low-residue foods revealed relative risks ranging from 2 to 4. It thus appears much more likely that the risk associated with anthraquinone laxatives reflects the effect of diet. A subsequent population-based, case-controlled investigation confirmed that constipation and not laxative use was the significant risk factor for colorectal cancer.

**Treatment**

Before treatment for constipation is initiated, the clinician must obtain the patient’s complete medical history and perform a thorough physical examination (especially important is a rectal examination to assist in excluding patients with defecatory disorders). When patients with CC present without alarm symptoms (Table 1), the recommendation from the ACG CC Task Force is to initiate empiric treatment without diagnostic testing (Grade C recommendation). The ACG CC Task Force also recently reviewed many available laxative treatments and classified those therapies as Grade A, B, or C according to the quality of the studies supporting their use. The ACG grades of laxative treatment are similar to those developed by the American College of Gastroenterology Functional Gastrointestinal Disorders Task Force on the management of IBS in North America.

ACG Grade A recommendations for the treatment of CC are based on Level I evidence, which represents data obtained from high-quality randomized controlled trials (RCTs). Grade B recommendations are based on intermediate-quality RCTs (Level II evidence), and Grade C recommendations are based on Level III-V evidence (primarily observational studies). Where applicable, the ACG grades are discussed in this article, but it is important to note that only North American literature (United States and Canada) was reviewed in determining the levels of evidence. Those grades should be used as guidelines to assist the clinician in choosing therapies for the treatment of CC but are not meant to prohibit treatment with any of the agents graded.

The goals of treatment for patients with CC, then, are to restore normal bowel function and relieve symptoms by accelerating colonic transit time, stimulating gut motility, facilitating defecation, and/or promoting secretion by the intestinal mucosa. Discussed below are treatments commonly used to do so, such as traditional therapies including lifestyle changes, laxatives and enemas, pelvic floor retraining, and surgery; novel therapies including tegaserod; and emerging therapies. Traditional and novel pharmacotherapeutic agents for the treatment of CC are listed in Table 2, and emerging therapies are featured in Table 3.

**Lifestyle Changes**

Although public perception holds that diet, fluid, and exercise influence constipation, most studies demonstrate only limited support of that view. Analysis of available data indicates that a low-fiber diet is a contributing factor to CC in only a select group of individuals. Because increasing natural fiber intake increases bloating and flatulence, patients’ acceptance of this recommendation is limited. Clinicians often rec-

<table>
<thead>
<tr>
<th>Table 1. Alarm Signs and Symptoms in Patients With Chronic Constipation*</th>
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<tr>
<td>Acute onset of constipation in older individuals</td>
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<tr>
<td>Overt or occult blood in stool</td>
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<td>Weight loss ≥10 lb</td>
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<tr>
<td>Anemia</td>
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<td>Family history of colon cancer or inflammatory bowel disease</td>
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*The list above is not all-inclusive; the suggested signs and symptoms are based on guidelines from the American College of Gastroenterology Chronic Constipation Task Force.
ommend that individuals with constipation increase their fluid intake, but studies do not demonstrate that this increases stool bulk or colon transit time,\textsuperscript{21} even if the fluids consumed are hyperosmolar.\textsuperscript{27} Only in the setting of clinical dehydration is increasing fluid intake helpful in treating CC.\textsuperscript{41} With the exception of especially vigorous activity such as marathon running,\textsuperscript{28} exercise exerts no proven benefit in ameliorating CC in young, healthy patients.\textsuperscript{21,22,24,29,30} In older adults, the cause of constipation may be multifactorial; etiologic factors include medication, diet, and inactivity. However, evidence for physical inactivity as a risk factor for CC in older persons does exist.\textsuperscript{31,32} Despite the fact that changes in lifestyle and diet have not been validated in controlled trials, those measures often are recommended as treatment for both CC and IBS before pharmacologic therapy is considered.\textsuperscript{6,33}

**LAXATIVES**

*Bulking agents*: Initial treatment for the patient with CC who seeks clinical assessment often involves the use of a bulk-forming supplement such as psyllium (ispaghula husk, Metamucil\textsuperscript{8}, Konsyl\textsuperscript{9}), calcium polycarbophil (Perdiem\textsuperscript{6}, Fiber Therapy, FiberCon\textsuperscript{10}), methylcellulose (Citrucel\textsuperscript{11}), carboxymethylcellulose, or bran. Those agents have been approved by the US Food and Drug Administration (FDA) for the treatment of occasional constipation;\textsuperscript{6,34,35} however, only psyllium has been shown to increase stool frequency.\textsuperscript{34,35}

Bulking agents retain water in and increase the solid content of the stool but, like high-fiber foods, they may produce gas and bloating. The ACG CC Task Force, citing the fact that studies often were of short duration or suboptimal design or revealed conflicting results, applied a Grade B recommendation to bulking agents for the treatment of constipation.\textsuperscript{8,36,37} These agents also

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Name</th>
<th>Brand Name</th>
<th>ACG Grade*</th>
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<tbody>
<tr>
<td><strong>Laxatives</strong></td>
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<tr>
<td><strong>Bulking agents</strong></td>
<td>Psyllium</td>
<td>Metamucil, Konsyl</td>
<td>B</td>
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<td></td>
<td>Methylcellulose</td>
<td>Citrucel</td>
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<td></td>
<td>Calcium polycarbophil</td>
<td>FiberCon, Equalactin, Perdiem Fiber Therapy</td>
<td>B</td>
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<td><strong>Stool softeners</strong></td>
<td>Docusate sodium</td>
<td>Colace</td>
<td>B</td>
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<td></td>
<td>Docusate calcium</td>
<td>Surkak</td>
<td>B</td>
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<td></td>
<td>Mineral oil</td>
<td>No brand name</td>
<td>B</td>
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<tr>
<td><strong>Osmotics</strong></td>
<td>Magnesium hydroxide</td>
<td>Milk of Magnesia</td>
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<td></td>
<td>Magnesium citrate</td>
<td>Citronia</td>
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<td></td>
<td>Sodium phosphate</td>
<td>Folic Phospho-Soda</td>
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<td></td>
<td>Lactulose</td>
<td>Cephol, Kristalone, Enulose</td>
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<td></td>
<td>Polyethelene glycol (PEG)</td>
<td>Miralax</td>
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<td>Sorbitol</td>
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<td>Mannitol</td>
<td>No brand name</td>
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<td><strong>Stimulants</strong></td>
<td>Cassara sagrada</td>
<td>Nature’s Remedy</td>
<td>B</td>
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<td></td>
<td>Senna</td>
<td>Perdiem, Senokot</td>
<td>B</td>
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<td></td>
<td>Rcinoleic acid</td>
<td>Castor oil</td>
<td>B</td>
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<td></td>
<td>Lactulose</td>
<td>Dulcolax, Correctol</td>
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<td><strong>Enemas and suppositories</strong></td>
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<td><strong>Innovative-use agents</strong></td>
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<td>Sodium phosphate</td>
<td>Visicol</td>
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<td>monobasic monohydrate</td>
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<td>and sodium phosphate</td>
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<td>dibasic anhydrous</td>
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<td>Misoprostol</td>
<td>Various brand names</td>
<td>Off-label use</td>
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<td>Bethanechol</td>
<td>Various brand names</td>
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<td>Colchicine</td>
<td>Various brand names</td>
<td>Off-label use</td>
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<tr>
<td><strong>Prokinetic agents</strong></td>
<td>Tegaserod</td>
<td>Zelnorm</td>
<td>A</td>
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<td>(5-HT\textsubscript{4} agonists)</td>
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<td><strong>Alternative treatments</strong></td>
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<tr>
<td>Herbal supplements</td>
<td>Various commercial brands</td>
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<tr>
<td>Combination laxatives</td>
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<td>lubricants (in adults)</td>
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ACG = American College of Gastroenterology; 5-HT\textsubscript{4} = 5-hydroxytryptamine.\textsuperscript{4}


1. Grade A, recommendations supported by 2 or more Level I trials without conflicting evidence from other Level I trials; Grade B, recommendations based on evidence from a single Level I trial or recommendations based on evidence from 2 or more Level I trials with conflicting evidence from other Level I trials or supported by evidence from 2 or more Level II trials; Grade C, recommendations based on Level III-V evidence. Insufficient studies available to judge safety and effectiveness.

2. Applies only to herbal laxatives; other alternative therapies have not yet been evaluated.
received a Grade B designation from the American College of Gastroenterology Functional Gastrointestinal Disorders Task Force as treatment for IBS.\textsuperscript{10} Because of flaws in study design, an accurate assessment of the efficacy of bulking agents cannot be made. In addition, adverse effects such as an increased risk of mechanical obstruction of the esophagus or colon or an anaphylactic reaction have been associated with the use of those agents.\textsuperscript{26} When bulking agents fail, stool softeners may be added or other laxatives may be used.

**Stool softeners (emollients):** Stool softeners (emollients), which are thought to be inferior to psyllium in managing the symptoms of CC,\textsuperscript{6} act primarily as detergents to soften stools. The most common agents available as stool softeners in the United States are docusate calcium (Surfak) and docusate sodium (Colace). Those medications, which are FDA approved for the treatment of occasional constipation, received a Grade B recommendation from the ACG CC Task Force.\textsuperscript{6} Mineral oil, which also exerts an emollient effect, was not evaluated by the ACG Task Force because no RCTs of that agent have been conducted in adults. RCTs in the pediatric population demonstrate that mineral oil is more effective than senna-based laxatives and less effective than osmotic laxatives in producing more frequent and softer stools as treatment for CC.\textsuperscript{5} Adverse effects of mineral oil include lipoid pneumonia, anal seepage, malabsorption of fat-soluble vitamins, and foreign-body reactions in tissue.\textsuperscript{38} The ACG CC Task Force has designated a Grade C recommendation for the use of herbal supplements (eg, aloe), lubricants (eg, mineral oil) in adult patients, or combination laxatives (eg, psyllium plus senna) because no published RCTs on the efficacy of those therapies exist in the United States in patients with CC.\textsuperscript{5}

**Osmotic laxatives:** Osmotic laxatives, which increase stool bulk and the volume of water in the small and large intestine, often require 1 to 2 days to produce a full result. Osmotics are of 3 types: saline laxatives (magnesium hydroxide [milk of magnesia], magnesium citrate, magnesium sulfate, sodium phosphate, etc), nonabsorbed sugars (solutions of lactulose [Cephulac, Kristalose\textsuperscript{6,} Enulose], sorbitol, or mannitol),\textsuperscript{39} or polyethylene glycol (PEG, MiraLax), which is a large polymer with osmotic activity. FDA approval of those agents for the treatment of CC is variable. Lactulose is approved for the treatment of constipation, but magnesium hydroxide is approved for only occasional use. PEG can be used for 2 weeks or fewer in the treatment of CC. Both PEG and lactulose received a Grade A recommendation from the ACG CC Task Force, but a Grade B recommendation was applied to magnesium hydroxide because of insufficient data on the effect of that agent in patients with CC.\textsuperscript{6} Lactulose and sorbitol have been shown to be similarly effective, but in 1 trial that compared those agents, lactulose was more likely to produce nausea.\textsuperscript{33,}\textsuperscript{39} As a treatment for constipation, PEG has been shown to be somewhat more effective than lactulose and to cause fewer adverse effects, although both agents have been reported to cause abdominal bloating, flatulence, and abdominal cramps.\textsuperscript{29} Osmotic laxatives also have been associated with multiple electrolyte abnormalities (hypermagnesemia, hyperphosphatemia, hypercalcemia, hyponatremia, hypokalemia), hypovolemia, and diarrhea,\textsuperscript{6,}\textsuperscript{26} and for those reasons may be contraindicated in patients with renal insufficiency or cardiac dysfunction.\textsuperscript{9,}\textsuperscript{29} In addition, magnesium toxicity has been associated with the use of magnesium hydroxide.\textsuperscript{38} When overused, osmotic laxatives can cause dehydration.\textsuperscript{41}

**Stimulant (irritant) laxatives:** Stimulant (irritant) laxatives, which increase the frequency of intestinal contractions, include over-the-counter remedies such as cascara sagrada (Nature’s Remedy), senna (Peridiem, Senokot), ricinoleic acid (castor oil, Castor), and derivatives of diphenylmethane (Correctol, Dulcolax).\textsuperscript{42} Those agents, which are believed to exert a direct effect on mucosal transport and motility, have been approved by the FDA for the treatment of occasional constipation,\textsuperscript{5} but insuffi-
icient evidence exists about their effectiveness in the management of CC. As a result, stimulant laxatives have received a Grade B recommendation from the ACG Task Force. Diphenylmethane derivatives include bisacodyl, picosulfate, and phenolphthalein (which has been withdrawn from the US market). Bisacodyl is a diacetic acid ester, picosulfate is a disulfuric acid semiester, and phenolphthalein consists of free diphenolic groups. The mechanism of all stimulant laxatives involves conversion to free diphenolic groups.

Phenolphthalein is no longer available in the United States because it was associated with an increased risk of carcinogenesis (an assumption that remains unproven and probably is incorrect). Bisacodyl, which is more potent than phenolphthalein, is thought to inhibit water absorption in the colon and small bowel by exerting an effect on kinases, prostaglandins, and (possibly) adenosine triphosphatase. Picosulfate, which seems to exert a direct effect on colonic bacteria, is transformed to the same active molecule as that of bisacodyl.

Stimulant laxatives exert their effect within hours after ingestion but should be taken infrequently because they can cause flatulence, abdominal pain, and metabolic disturbances and may be overused. Other adverse effects associated with stimulant-laxative use abound. Diphenylmethane derivatives can cause abdominal cramping, Stevens-Johnson syndrome, fixed drug eruptions, protein-losing enteropathy, hepatotoxicity, and reactions similar to those produced by lupus erythematosus. Long-term use of any stimulant laxative can cause diarrhea and resultant hypokalemia, hyponatremia, and dehydration, and some investigators associate radiographic changes in the colon with the use of these agents. As discussed previously, however, neurologic damage is unlikely to be caused by this class of drug.

**ENEMAS AND SUPPOSITORY**

Enemas are of different types: phosphate, mineral oil, tap water, and soap suds. The mechanism of action varies with the type of enema used. Suppositories can be osmotic (bisacodyl) or more lubricating (glycerine). Glycerine suppositories are thought to exert an osmotic effect and also may act as a local irritant. This group of agents, which was not evaluated or even mentioned by the ACG CC Task Force, is thought to be useful in the management of patients with fecal impaction of the rectosigmoid colon. Adverse effects include mechanical trauma from placement and (with phosphate enemas) hyperphosphatemia. Soap suds enemas can be severely irritating to the lining of the intestine and generally are not recommended.

**INNOVATIVE-USE AGENTS**

A variety of other agents (sodium phosphate compounds, misoprostol, bethanechol, colchicine) have been prescribed as innovative treatments for CC in certain populations. Those therapies often are limited in their application because of their unfavorable adverse effect profile. At the time of this writing, only sodium phosphate compounds remain the focus of ongoing investigation for the treatment of constipation.

**Sodium phosphate monobasic monohydrate + sodium phosphate dibasic anhydrous** A combination of low-dose sodium phosphate monobasic monohydrate plus sodium phosphate dibasic anhydrous (Visicol) was shown in an open-label, multicenter, 4-week, phase 4 study to provide relief of constipation in patients with C-IBS and CC. Benefit was achieved in subjects receiving the 4- or 8-tablet regimen of sodium phosphate as opposed to those receiving placebo. The treatment was well tolerated in general (particularly in the low-dose group) and promptly relieved constipation (usually within the first week of treatment), a benefit that persisted during the 28-day period of therapy. This combination drug currently is approved by the FDA for bowel cleansing before colonoscopy. Sodium phosphate laxatives, like osmotic laxatives, can cause electrolyte disturbances. Because of this and the fact that phosphate may be more readily absorbed than magnesium, this laxative is contraindicated in patients with renal insufficiency and cardiac dysfunction.

**Misoprostol** Because misoprostol often causes diarrhea when prescribed to treat acid peptic disorders, it has been used to treat severe constipation that is refractory to other therapy. Adverse effects (nausea, diarrhea, abdominal pain, increased risk of spontaneous abortion) have limited the use of this drug. Some studies have shown, however, that 50% of patients with severe CC benefit from treatment with misoprostol.

**Bethanechol** The cholinergic agent bethanechol increases gastric motility and tone and can improve diminished rhythmic peristalsis. Older research indicates that bethanechol 25 mg to 50 mg, when administered 3 or 4 times daily, ameliorates constipation caused by tricyclic antidepressant use. However, it also is associated with hypersalivation, nausea, vomiting, and dizziness, and those adverse effects have limited the usefulness of bethanechol.
**Colchicine.** Although the exact mechanism of action of colchicine is unknown, this agent seems to act as a mucosal toxin. It is used primarily in the treatment of acute gout and may produce diarrhea as an adverse effect. A double-blind, placebo-controlled, randomized, crossover study of colchicine was performed in a small group of patients with CC. A dose of 0.6 mg 3 times daily was used for a 4-week treatment period. Patients reported reduced transit time, an increased number of bowel movements, and no particularly adverse effects. However, colchicine can cause neutropenia, aplastic anemia, and neuromyopathy. Less severe side effects include alopecia, rash, nausea, vomiting, and abdominal pain. The use of colchicine or misoprostol is usually reserved for patients with severe constipation that is refractory to other therapy because the desired result of treatment with these agents is, in essence, an adverse reaction to the drug. Both drugs are contraindicated in pregnancy.

**Prokinetic Agents (5-HT4 Agonists)**

**Tegaserod:** Tegaserod (Zelnorm®) currently is the only 5-hydroxytryptamine4 (5-HT4) agonist approved by the FDA for the treatment of CC. A partial agonist of the 5-HT4 (serotonin) presynaptic receptors in the enteric nervous system (Figure 1), tegaserod exerts several beneficial effects in those who suffer from CC. It may decrease visceral hypersensitivity, stimulates the peristaltic reflex, increases colonic motility, and acts on intestinal chloride secretion, thus facilitating the transport of fluid into the lumen of the colon and improving stool consistency and frequency. Studies have shown that this agent also is effective in improving the frequency of complete spontaneous defecation and that it decreases straining. Approved by the FDA to treat CC in men and women younger than 65 years, tegaserod received a Grade A recommendation from the ACG CC Task Force. The American College of Gastroenterology Functional Gastrointestinal Disorders Task Force applied a Grade A recommendation to tegaserod for the treatment of C-IBS, but its use is restricted to women with that disorder.

The mechanism of action of tegaserod is limited to the periphery by a unique design: Its molecular structure replicates that of the serotonin molecule but has been altered by the addition of a hydrophilic “tail” that restricts passage across the blood-brain barrier. As an aminoguanidine indole, tegaserod does not obstruct cardiac potassium channels and is thus thought not to potentiate cardiac arrhythmia.

In a recent review of therapies for CC, Ramkumar and Rao found that Grade A evidence similar but not equivalent to that of the ACG CC Task Force grading system supported the use of tegaserod for the treatment of constipation. The grades those authors cited were based on 2 large, multinational, randomized, double-blind, placebo-controlled studies indicating that tegaserod was a safe, effective, and tolerable therapy that was superior to placebo for the treatment of CC in those under age 65. Treated subjects experienced significant improvement in the frequency of complete spontaneous bowel movements, total spontaneous bowel movements, global satisfaction with bowel habits, and straining to defecate. Mild, transient diarrhea occurred significantly more often in the tegaserod-treated group but usually resolved without additional therapy. Other reported adverse effects of treatment include headache and nausea, but in general, the safety profile of that agent is favorable. According to the results of several studies, serious sequelae were no more likely to occur with tegaserod treatment than with placebo, and tegaserod induced neither clinically relevant drug interactions nor electrocardiographic abnormalities. New prescribing recommendations from the FDA include a “precaution” stating that ischemic colitis has occurred in patients treated with this drug, but according to information gathered from clinical trials and postmarketing...
surveillance, the likelihood that tegaserod produces that adverse effect is minimal.\(^6\)\(^3\)

**EMERGING TREATMENTS**

Although safe and effective therapies do exist for the treatment of occasional constipation, the need for improvement in the treatment of CC is evident. Pharmacologic agents that increase peristalsis by their effect on serotonergic receptors are under investigation. Other receptor sites targeted pharmacologically in individuals with CC include opioid receptors and chloride channels, which work via different mechanisms. Newer pharmacotherapeutic agents effective at those receptors and the combination 5-HT\(_4\) agonist-5-HT\(_3\) antagonists renzapride and mosapride are reviewed below.

5-HT\(_4\) agonists—prucalopride: The drug prucalopride, a benzofurancarboxamide and a full agonist at 5-HT\(_4\) receptors,\(^5\)\(^2\) once was thought to be a promising agent in the treatment of CC. The results of 2 large RCTs revealed that when compared with placebo, daily doses of prucalopride 2 mg or 4 mg produced a modest benefit in patients who had characterized themselves as having “severe” or “very severe” CC. Over 12 weeks of therapy, treatment with prucalopride increased the number of complete spontaneous bowel movements from a median of 0 per week to 3 per week in 29% of study patients.\(^5\)\(^2\),\(^5\)\(^9\) However, studies of prucalopride were suspended because of concern about the development of cardiac arrhythmias in treated patients.\(^6\)\(^4\) It is unlikely that this drug will be marketed in the United States, but its development underscores the importance of the 5-HT\(_4\) receptor as a target for drug therapy.

Combination 5-HT\(_4\) agonist-5-HT\(_3\) antagonists—mosapride, renzapride: Mosapride citrate, a novel selective 5-HT\(_4\) receptor agonist-5-HT\(_3\) receptor antagonist, enables acetylcholine release from enteric cholinergic neurons but does not block potassium channels or D\(_2\) dopaminergic receptors.\(^6\)\(^6\) In a small trial of patients with Parkinson’s disease, 10 men and 4 women (mean age, 67 years) with constipation (a bowel movement fewer than 3 times per week or difficult defecation) were treated with 15 mg daily of mosapride citrate for 3 months. Treatment was well tolerated by all but 1 patient, who terminated participation in the study because of epigastric discomfort. The remaining 13 patients reported a subjective improvement in the frequency of bowel movements and difficult defecation. The investigators concluded that mosapride alleviated several symptoms of constipation in subjects with Parkinson’s disease without inducing serious adverse effects. This agent awaits further study.

Renzapride is another promising therapy that may be used for the treatment of CC and C-IBS. This agent, which functions as both a 5-HT\(_3\) antagonist and a 5-HT\(_4\) agonist, has been tested in clinical trials in men and women with C-IBS. Its presumed mechanism of action is the activation of 5-HT\(_4\) receptors in cholinergic neurons that stimulate contractions, and the 5-HT\(_3\) antagonist activity of this agent also may decrease visceral sensation. In a recent trial of its effects in patients with C-IBS, renzapride improved stool consistency and increased the frequency of bowel movements but provided no overall relief of abdominal pain and discomfort.\(^6\)\(^4\) In a randomized, double-blind, parallel-group, 2-week study of 48 patients with C-IBS and normal or slow baseline colonic transit but without pelvic outlet obstruction, renzapride was associated with an improvement in bowel function scores and accelerated colonic transit, although small-bowel transit and gastric emptying were not affected.\(^5\)\(^2\),\(^5\)\(^9\) In that study, the renzapride-treated subjects exhibited an acceleration of colonic transit and an improvement in bowel function scores, although gastric emptying and small-bowel transit were not affected. Like many evolving agents for the treatment of CC, renzapride also awaits further study.

Chloride-channel activators—lubiprostone: Lubiprostone (RU 0211) is an orally administered novel bicyclic fatty acid\(^6\)\(^4\)\(^6\)\(^5\) undergoing development for the treatment of CC, postoperative ileus, and C-IBS.\(^6\)\(^4\) By activating a chloride channel on the apical side of epithelial cells lining the gut (the driver of intestinal fluid secretion), lubiprostone increases fluid to the small intestine, which in turn increases overall fluid content in the colon (Figure 2). The greater amount of fluid in the intestine promotes spontaneous bowel movements; reduces abdominal discomfort, pain, and bloating; and softens the stool.\(^6\)\(^4\) In addition, chloride-channel activators show promise in the ability to repair mucosal barrier function following ischemic injury, an effect that appears to result from reduction in paracellular permeability via changes to the tight junction following CIC-2 channel activation.\(^6\)\(^6\),\(^6\)\(^7\)

Two phase 3, multicenter, double-blind, placebo-controlled studies have shown that lubiprostone, when compared with placebo, was significantly more effective in providing relief from the symptoms of CC (Figure 3).\(^5\)\(^6\),\(^5\)\(^7\) Both male and female patients meeting Rome II criteria for CC were included in the study. At a dose of
24 mg twice daily highly significant statistical improvements were seen, not only in the global assessments of treatment effectiveness and constipation severity but also in that patients experienced an increase in spontaneous bowel movements. Secondary measures of frequency and consistency of spontaneous bowel movements were also significantly improved. The most common adverse effects of treatment were headache, diarrhea, and nausea. Nausea occurred in approximately 30% of patients. Although more common in the treatment than the control group, the number of patients in either group who withdrew from the study because of nausea was limited. The new drug application for the use of lubiprostone in the treatment of CC, under review at the FDA at the time of this writing, includes the results of 3 long-term safety studies, 2 of which are 12-month assessments.

Peripheral opioid antagonists—methylaltrexone and alvimopan. Opioids administered as long-term analgesics for patients with cancer or during and after surgery can cause constipation or postoperative ileus. Although blocking peripheral opioid receptors in the bowel is the ideal mechanism for ameliorating opioid-induced constipation, most opioid antagonists (eg, naloxone) cross the blood-brain barrier, reverse analgesia, and result in opioid withdrawal. N-methylnaltrexone bromide (methylaltrexone), the first peripheral opioid receptor antagonist, is a quaternary derivative of naltrexone, which is a pure opioid antagonist. Because methylaltrexone does not cross the blood-brain barrier, it may block the adverse effects of opioids that are primarily mediated by peripherally located receptors and preserve centrally mediated analgesia. It is presumed to act as an antinociceptive and to disrupt the antinociceptive effects of opioids. Research indicates that in healthy individuals, intravenous or oral methylaltrexone reversed opioid-induced inhibition of bowel motility without affecting analgesia and, in patients receiving long-term opioid therapy, reduced (with minimal adverse effects) the delay in oral-cecal transit and evoked laxation in all subjects without evoking withdrawal symptoms. Other investigators suggest that subcutaneous methylaltrexone may also be useful in treating opioid-induced constipation.

Alvimopan, a novel peripherally acting mu-opioid antagonist, is currently being evaluated for the treatment of acute postoperative ileus and reversal of the delayed gastrointestinal and colonic transit caused by opioid therapy. Mu-opioid receptors are located in the enteric nervous system and on nociceptive pathways that transmit pain to the central nervous system. A study by Paulson and colleagues indicated that alvimopan reversed the opioid-induced inhibition of gastrointestinal transit without affecting analgesia. Mild to moderate adverse events, which were bowel-related, occurred during the first week of treatment, but therapy with alvimopan generally was well tolerated.

**Figure 2. The Role of Chloride Channels in Intestinal Transport**

1. As negatively charged chloride ions actively enter the lumen via chloride channels.
2. Positively charged sodium ions passively diffuse through the intracellular spaces to balance chloride.
3. Allowing water to follow passively into the lumen.

**Figure 3. Effect of Lubiprostone on Chronic Constipation**

- Onset of action was within 24 hours in the majority of subjects.
- Most common adverse events were nausea (31%), diarrhea, and headache.
- 9 subjects taking lubiprostone withdrew due to adverse events.

NONPHARMACOLOGIC TREATMENTS

Pelvic floor retraining (biofeedback): For patients with evidence of pelvic floor dysfunction (PFD), biofeedback is a behavioral approach of varying effectiveness in the treatment of CC. Via manometry or electromyography, patients with PFD learn techniques for the relaxation of the pelvic floor muscles and the anal sphincter, which enables the expulsion of stool. Although good results are obtained from biofeedback in many medical centers, the effectiveness of the training depends on the availability of qualified personnel. Success rates have varied from 48% to 75%.3,9 Anal disorders, such as fissures or a tender puborectalis muscle, also may limit participation, and patients must exhibit some degree of rectal perception to benefit from biofeedback training. The cost of the technique may also be prohibitive.32,46

Surgery: Surgery is rarely required and should be reserved only for the most refractory cases of CC. The procedure of choice is subtotal colectomy with ileorectal anastomosis (in patients with megarectum, the rectum also is removed). In some individuals, ileostomy is performed. Ten percent of patients who undergo surgery for CC experience postoperative ileus and mechanical small-bowel obstruction. Postsurgical diarrhea is common but tends to resolve over time in most cases.38,44 A limited number of patients with outlet obstruction also may require surgery to correct a large rectocele or repair rectal prolapse.84 Patients with a high rate of postoperative bowel obstruction in addition to PFD, small-bowel dysmotility, or severe abdominal pain are not candidates for the surgical treatment of CC.

Colonic electrical stimulation: Three types of colonic electrical stimulation, a non-drug treatment for CC, are currently under development. The electric stimulation of sacral nerve function is used as therapy for urinary and fecal incontinence, and patients so treated exhibited an increase in the sensory threshold for desire to defecate as well as an increase in the frequency of the sensation of the need to defecate.81 Another approach, which has been tested only in a canine model, involves using microprocessor-controlled sequential electric stimulation to induce peristalsis.82 This technique appears to be successful but awaits further study. Fajardo and colleagues demonstrated that in patients with spinal cord injury, electric stimulation of the abdominal wall muscles reduced (by half) the time necessary for a bowel movement and also decreased the time required for bowel care.83

CONCLUSION

CC and C-IBS are among the most prevalent and enduring GI diagnoses in North America. Most often identified by primary care physicians and gastroenterologists, these common disorders of the gut impose a substantial burden of healthcare costs and can negatively affect quality of life and productivity. Research has shown that nonpharmacologic and pharmacologic therapies designed to address each patient’s specific symptoms are most effective in the management of CC, the causes of which may range from abnormalities in myenteric neuron function, defects in neurotransmitters, and incoordination of pelvic-floor or anorectal muscles to environmental factors and chronic stress. A more complete understanding of those etiologic mechanisms will enable the development of a new generation of superior therapeutic agents, which even now are the subject of ongoing analysis and research.

ACKNOWLEDGEMENT

Dr Harris would like to thank Jane Vail for her assistance in the development of this manuscript.

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