Pharmacologic Management of Chronic Constipation

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KEYWORDS

• Chronic constipation • Medical management • Laxatives
• Lubiprostone • Linaclotide • Methylnaltrexone
• Alvimopan • Prucalopride

Chronic constipation (CC) affects 20% of the population,[1] has a significant effect on quality of life and use of health care resources including drug therapy,[2] and causes significant psychological distress.[3] Almost 85% of physician visits for constipation result in a prescription for laxatives,[2] and $821 million is spent annually on over-the-counter laxatives.[3]

Constipation comprises many symptoms such as hard stools, excessive straining, infrequent bowel movement, feeling of incomplete evacuation, and abdominal bloating; its treatment largely encompasses relieving these symptoms and restoring a normal bowel habit. An essential component of management of CC is identification and management of secondary causes such as drug-induced constipation, for example opioid-induced constipation or an obstructive lesion in the colon, the management of which usually results in resolution of constipation.

If excluded, primary constipation consists of 3 overlapping subtypes[3,4]: (1) slow transit constipation, characterized by prolonged transit through the colon owing to a primary dysfunction of colonic smooth muscle (myopathy) or its nerve innervations (neuropathy)—this usually requires aggressive medical management but may need surgical intervention[3]; (2) dyssynergic defecation, a disorder of impaired abdominal, rectoanal, and pelvic floor muscle coordination that requires both medical management and biofeedback treatment[3]; (3) constipation-predominant irritable bowel syndrome (IBS-C), seen in patients in whom abdominal pain or discomfort is the predominant symptom with usually normal colonic transit and pelvic floor function, and thought to be a result of an interaction of genetic, environmental, social, biologic,

Conflict of interest: None.
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Gastroenterol Clin N Am 39 (2010) 509–527
doi:10.1016/j.gtc.2010.08.001 **gastro.theclinics.com**
0889-8553/10/$ – see front matter

and psychological factors.[3] IBS-C is managed medically, using a wide variety of medications.

The treatment of constipation should be customized for each individual considering the cause of constipation, patient's age, comorbid conditions, underlying pathophysiology, and the patient's concerns and expectations. Lifestyle changes such as an adequate fluid intake, increased dietary fiber intake, regular nonstrenuous exercise, and dedicated time for passing bowel movements can be useful, but there is limited evidence to support these measures.[3] This article focuses on the pharmacologic management of constipation, not related to IBS, with special emphasis on newer agents.

PRESENT TREATMENT OPTIONS FOR CHRONIC CONSTIPATION

Several over-the-counter laxatives are available for the management of CC. However, studies using conventional laxatives were not well designed and have been summarized previously.[5–7]

Bulk (Fiber) Laxatives

Bulking agents are organic polymers that increase the weight and water-absorbent properties of stool. The efficacy and side effects of bulking agents are shown in **Table 1**.

Stool Softeners or Wetting Agents

Stool softeners are surface-acting agents that function primarily as detergents, that is, they allow water to interact more effectively with solid stool, thereby softening the stool, and include dioctyl sodium sulfosuccinate/docusate sodium (Colace) and docusate calcium (Surfak). The efficacy and side effects are shown in **Table 1**.

Stimulant Laxatives

Stimulant laxatives increase intestinal motility by stimulating the colonic myenteric plexus on their contact with the colonic mucosa, and by inhibiting water absorption. Both bisacodyl and sodium picosulfate (SPS) are prodrugs that are converted in the gut into the same active metabolite, bis-(*p*-hydroxyphenyl)-pyridyl-2-methane, which causes the desired laxative effect. There is limited evidence to support their use. In a recent 4-week, double-blind, placebo-controlled trial using SPS, there was a significant increase in number of complete spontaneous bowel movements (CSBMs) per week (SPS: 0.9 ± 0.1 to 3.4 ± 0.2; placebo: 1.1 ± 0.1 to 1.7 ± 0.1; $P<.0001$), constipation-related symptoms, and quality of life.[8] These agents have often been used as rescue therapy in many constipation and IBS-C trials, and their chronic use may induce tolerance. Abdominal discomfort and cramps are well-known side effects. Senna may cause melanosis coli or hepatotoxicity.

Osmotic Laxatives

Osmotic laxatives contain poorly absorbed ions or molecules, which create an osmotic gradient within the intestinal lumen, thereby retaining water in the lumen, leading to softer stools and improved propulsion. Polyethylene glycol (PEG) is a nonabsorbable, nonmetabolized osmotic agent. Electrolyte-free PEG has been used for the management of constipation. In 5 high-quality, placebo-controlled trials, PEG consistently increased stool frequency and improved stool consistency.[5] PEG was shown to be more effective than tegaserod, with a favorable adverse effect profile.[9] An open-labeled study of PEG, 17 g/d for 12 months, demonstrated that it was safe and