

Pharmacological Update for Chronic Constipation.

Naresh Bansal, Munish Sachdeva, Pankaj Jain, Piyush Ranjan, Anil Arora

Department of Gastroenterology and Hepatology, Sir Ganga Ram Hospital, New Delhi, India

Abstract: The management of constipation continues to evolve. Several new agents that target different mechanisms appear promising such as chloride-channel activator (lubiprostone), guanylate cyclase agonist (linaclotide), 5HT₄ agonist (prucalopride), and peripherally acting mu-opioid receptor antagonists (alvimopan and methylnaltrexone) for opioid-induced constipation. Biofeedback therapy is efficacious for treating dyssynergic defecation and fecal impaction with soiling. Multiple studies have addressed the treatment of chronic constipation in adults in general; however, less guidance is available for treating this condition. This review introduces new therapeutic options in the treatment of chronic constipation. Therefore, prucalopride and lubiprostone are discussed including their mechanisms and side effects. In addition, other substances that are currently under evaluation such as linaclotide are described, since recent results showed a significant effect in patients with constipation. Thus, after the withdrawal of tegaserod due to cardiac side effects, new potent drugs are now available for the treatment of constipation.

INTRODUCTION

Constipation is variably defined, and its diagnosis is often arbitrary. Physicians tend to consider stool frequency (<3 defecations per week)¹ whereas patients more often consider straining, stool consistency, incomplete evacuation, and nonproductive urges to have a bowel movement². A combination of objective (stool frequency, manual maneuvers needed for defecation) and subjective (straining, lumpy or hard stools, incomplete evacuation, sensation of anorectal obstruction) symptoms are used in the Rome III criteria for constipation³.

Although most studies suggest an adult prevalence for constipation of about 15%, estimates range from 2% to 27%^{2,4,5,6,7} with the variability largely explained by the definitions used and population sampled. Most epidemiologic studies demonstrate a higher prevalence of constipation and laxative use in the elderly^{7,8,9}.

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 measures¹⁰. This article focuses on the pharmacologic management of constipation, not related to IBS, with special emphasis on newer agents.

TREATMENT SUGGESTIONS

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

Medications	Mechanism of Action	Side Effects
Psyllium, calcium polycarbophi	Retaining water in stool increasing stool bulk, and improving consistency	Flatulence, bloating abdominal distension
methylcellulose	consistency	rarely, causing mechanical

Carefully increasing fiber intake from 15 to 25 g/d may be accomplished with dietary adjustments, and supplements. Although increasing water intake on its own has not been shown to improve constipation, maintaining adequate fluid intake is prudent with fiber supplementation to avoid excessive bulk, which may exacerbate CC. A well-formed, softer stool that is easier to pass is the ultimate goal.

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.

Stimulant Laxatives

Medications	Mechanism of Action	Side Effects
Docusate sodium, docusate calcium increasing stool bulk	Promoting luminal water binding by detergent-like action,	Intestinal cramping irritation of throat (liquid formulation)

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.¹¹ 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.

Medications	Mechanism of Action	Side Effects
Senna, aloe, bisacodyl, sodium picosulfate large intestinal water absorption	Increasing intestinal peristalsis by acting on myenteric nerve plexus; decreasing	Abdominal discomfort rarely electrolytes disturbance, melanosis coli

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. In 5 high quality placebo-controlled trials, PEG consistently increased stool frequency and improved stool consistency⁵. PEG was shown to be more effective than tegaserod, with a favourable adverse effect profile⁹.

It is a reasonable choice for patients not responding to fiber. As there is no clearly superior osmotic agent, the laxative should be based on relevant medical history (cardiac or renal status), possible drug interactions, cost, and side effects. The dose should be titrated to the clinical response. For chronic or more severe constipation, regular dosing is indicated.

Suppositories and Enemas

Useful for some suppositories (e.g., glycerin) help initiate or facilitate rectal evacuation. They may be used alone, in conjunction with meals (to

Medications PEG, lactulose, sorbitol, milk of magnesia, magnesium citrate	Mechanism of Action Osmotic water binding	Side Effects Bloating, flatulence, abdominal cramping in rare instances electrolytes disturbances
--	---	--

capture the gastrocolic reflex), or in conjunction with other agents. Suppositories, which usually work within minutes, may be tried as part of a behavioral program for those with obstructed defecation and in the institutionalized.

In general, enemas may be used judiciously on an as-needed basis, particularly for obstructed defecation and to avoid fecal impaction. Routine use is typically discouraged but may be necessary. Whereas tap water enemas seem safe for more regular use, electrolyte imbalances are more common with phosphate enemas. Soapsuds enemas can cause rectal mucosal damage and are not recommended.

The aforementioned approaches are usually the first-line agents used in the management of constipation, owing to their low cost and wide availability. As a general rule, patients who do not respond to fiber supplementation can be advanced to osmotic laxatives, which can be titrated to clinical response. Stimulant laxatives and prokinetic agents are typically reserved for patients with more refractory constipation.

Throughout any treatment program, one should remain vigilant of PFD, as pelvic floor rehabilitation is the treatment of choice. Surgery is rarely indicated for constipation, exclusion of PFD is essential, and outcomes in the elderly are uncertain. Fecal impaction should be cleared before instituting maintenance regimens.

However 50% of CC patients report dissatisfaction with these therapies and concerns include unpredictability (71%–75%), bloating (52%–67%), poor symptom relief (44%–50%), or inability to improve quality of life (44%–68%)¹³. Hence, several new pharmacologic classes of medications have been developed that are reviewed here.

Chloride Channel Activators

Chloride channels are voltage-gated anion channels, which allow the transport of chloride ions across cell membranes and play a critical role in fluid transport, maintenance of cell volume, and intracellular pH. Lubiprostone approved by the FDA for the treatment of chronic-idiopathic constipation, is an oral bicyclic fatty acid that selectively activates type 2 chloride channels in the apical membrane of the intestinal epithelial cells. This activity stimulates chloride secretion, along with passive secretion of sodium and water¹⁴, and is mediated by a protein kinase-A independent, as well as the cystic fibrosis transmembrane regulator (CFTR)-mediated pathway^{15,16}. The fluid-induced bowel distention secondarily induces peristalsis and causes laxation, but lubiprostone has no direct stimulatory effect on gastrointestinal smooth muscle¹⁴. Lubiprostone has a rapid onset of action with a half-life of 3 hours¹⁴. Lubiprostone, 24 mg twice a day was shown to be effective in the treatment of chronic idiopathic constipation in 2 RCTs^{17,18} as well as 3 large open-label trials¹⁹. There was a significant increase in SBM frequency, improvement of straining effort, stool consistency, constipation severity, and global satisfaction with bowel function.

Adverse Effects and Safety

Nausea (31%), diarrhea (12%), and headache (11%) were the most common side effects. Abdominal distension, pain, and flatulence occurred in more than 5% patients who received lubiprostone. No electrolyte changes were observed up to 48 weeks¹⁴.

Guanylate Cyclase C Activators

Linaclotide is a novel 14-amino-acid peptide GC-C agonist; it activates the luminal GC-C receptor on intestinal enterocytes, with an increase in intracellular as well as extracellular cGMP. The former activates CFTR, with an increase in luminal chloride and bicarbonate secretion, resulting in increased fluid secretion and acceleration of intestinal transit²⁰. The extracellular cGMP, however, helps to

ameliorate visceral hypersensitivity by a direct action on afferent nerve endings in the gut²¹.

In 2 recent phase 3 RCTs of 1200 patients, linaclotide, 150 to 300 mg/d increased the number of CSBMs per week²⁰ and improved bloating, discomfort, stool consistency, straining, and constipation severity, as well as quality of life measures.

Adverse Effects and Safety

Dose-dependent diarrhea was the most common side effect, and was usually rated mild to moderate; the rate of discontinuation from side effects was 2.4%²⁰.

Alvimopan

Alvimopan is a quaternary m-opioid receptor antagonist that exists in the zwitterions form, and this polarity restricts gastrointestinal absorption and prevents the drug from crossing the blood-brain barrier.

Several studies in opiate-induced bowel dysfunction have shown that alvimopan decreases the median time to first bowel movement, increases mean weekly bowel movements, and reduces hard stools and the need for severe straining without compromising patient analgesia²². Alvimopan is approved for the management of postoperative ileus, with a risk evaluation and mitigation strategy, that is, restricted to inpatient use only.

Adverse effects and safety

The most common side effects include nausea and vomiting²³. There was concern that alvimopan might increase cardiovascular adverse events; these were noted in patients with established coronary artery disease, but were not dose-related²².

Serotonergic Enterokinetic Agents

Serotonin (5-hydroxytryptamine; 5-HT) is produced from gastrointestinal mucosal enterochromaffin (EC) cells. The 5-HT₄ receptors are G-protein coupled receptors found on smooth muscle cells, EC cells, myenteric plexus neurons, and they alter gut motility. Activation of these receptors augments peristalsis by stimulating secondary messengers (acetylcholine and calcitonin gene-related peptide), enhancing proximal smooth muscle contraction, and relaxing distal smooth muscles resulting in effective peristalsis²⁴.

These receptors also modulate cyclic adenosine monophosphate-mediated chloride secretion and visceral sensitivity²⁴. Antagonism of 5-HT₃ receptors decreases postprandial colonic motility and delays colonic transit²⁴. 5-HT₄ Receptor Agonists

Three 5-HT₄ receptor agonists have been tested for constipation: tegaserod, substituted benzamides (eg, cisapride, mosapride) and prucalopride.

Tegaserod is a selective 5-HT₄ agonist. Several RCTs have shown that tegaserod is effective in the treatment of CC, by improving bowel motility per week, decreasing training, bloating, and abdominal distension, at doses of 2 to 6 mg twice a day, orally²⁵.

Common side effects included transient diarrhea, abdominal pain, headache, and nasopharyngitis. Because of a numerically higher incidence of ischemic cardiovascular adverse events, tegaserod was withdrawn in March 2007. At present, tegaserod is available only on a restricted basis for use in IBS-C and CC in women younger than 55 years who are not at risk for cardiovascular events.

Prucalopride, is a highly selective, high-affinity 5-HT₄ receptor agonist, with minimal activity at other 5-HT receptors.²⁶ Prucalopride has a 90% bioavailability after oral ingestion, with a half-life of 24 to 30 hours. Three large phase 3 RCTs have

demonstrated efficacy in relieving all aspects of constipation^{27,28}. The drug is well tolerated; the most common side effects are headache, nausea, abdominal pain, and diarrhea. Of importance, no clinical cardiovascular side effects have been noted.

Neurotrophin-3

Neurotrophin-3 (NT-3) belongs to a family of protein growth factors, neurotrophins that play an important role in the development and maintenance of the central, peripheral, autonomic, and enteric nervous systems. A multicenter RCT showed that NT-3, at a dose of 9 mg subcutaneously 3 times per week, significantly increased SBMs, softened stool and ease of passage, improved constipation-related symptoms, and decreased colonic transit time²⁹. The drug can be administered only by a subcutaneous injection. Minor injection site reactions (approximately 33%) were the most common adverse events. After 4 weeks of therapy, approximately 50% of patients developed anti-NT3 antibodies.

Motilin Agonists

Motilin is a 22-amino-acid peptide, secreted from EC cells, that stimulates gut motility through activation of a G-protein-coupled motilin receptor found in the enteric nervous system and intestinal smooth muscle³⁰. Recently a nonantibiotic, orally active motilin agonist, Mitemincal, has been developed and is in phase 2 trials for IBS and gastroparesis, and is also being considered for CC³¹.

Probiotics And Prebiotics

Probiotics are defined as live organisms that when ingested in adequate amounts exert a health benefit to the host (eg, lactic acid bacteria, Lactobacillus species, and nonpathogenic yeasts). Prebiotics are defined as nondigestible, but fermentable, foods that beneficially affect the host by selectively stimulating the growth and activity of one species or a limited number of species of bacteria in the colon. Synbiotics are defined as a combination of a probiotic and a prebiotic, aiming to increase the survival and activity of proven probiotics in vivo and stimulating indigenous bifidobacteria and lactobacilli. Data on their effect on CC are lacking. Bifidobacterium animalis has been shown to accelerate colonic transit in healthy individuals and patients with IBS, suggesting a direct effect on colonic motility. Two RCTs have shown a positive benefit for the probiotics Lactobacillus casei and Bifidobacterium lactis DN-173,010³²

Botulinum Toxin

Clostridium botulinum toxin type A (Botox), a potent neurotoxin that inhibits presynaptic release of acetylcholine, has been injected intramuscularly into the puborectalis muscle to treat defecatory disorders. Preliminary data suggest that botulinum toxin may be effective for treating patients with defecatory disorders in which spastic pelvic floor dysfunction causes outlet delay, including those who also have Parkinson's disease. One study showed that 19 of 24 patients reported improvement in symptoms and physiologic measurements of pelvic floor function at two months. Controlled trials have not yet been performed, however, and this approach is not recommended in lieu of biofeedback, for which clinical experience is greater.

SUMMARY

CC is a common problem and is variably defined, has a significant impact on quality of life and the use of health care resources. A careful history, medication assessment, and physical examination are helpful in obtaining relevant clues that help direct management. Physiologic

categorization of the cause leading to patient presentation improves management outcomes, realizing that many causes can be present in one patient, and many factors influence the clinical presentation of an older patient. Emerging therapies, such as sacral nerve stimulation, botulinum toxin injection for PFD, alteration of the bacterial milieu, and several novel medications may play more of a role in the future management of CC.

KEY POINTS

- Lifestyle modifications that promote regular bowel habits should be encouraged
- Increased dietary fiber may be used initially, followed by an osmotic laxative if there is no response; stimulant laxatives may be used on a short-term basis.
- Polyethylene glycol [PEG-3350] is safe for relief of medication-induced and chronic constipation.
- Lubiprostone activates intraluminal CIC2 channels to promote secretion; it is approved for the treatment of chronic idiopathic constipation and constipation-predominant irritable bowel syndrome
- Methylnaltrexone may be used to treat opioid-induced constipation
- Surgery should be considered only after all medical therapies have failed.

Biofeedback, if available, should be considered first-line therapy in patients with pelvic floor dysfunction

REFERENCES

1. Drossman DA, Sandler RS, McKee DC, et al. Bowel patterns among subjects not seeking health care. Use of a questionnaire to identify a population with bowel dysfunction. *Gastroenterology* 1982;83:529-34.
2. Pare P, Ferruzzi S, Thompson WG, et al. An epidemiological survey of constipation in Canada: definitions, rates, demographics, and predictors of health care seeking. *Am J Gastroenterol* 2001;96:3130-7.
3. Longstreth GF. Functional bowel disorders: functional constipation. In: Drossman DA, editor. *The functional gastrointestinal disorders*. 3rd edition. Lawrence (KS): Allen Press, Inc 2006:515-23.
4. Stewart WF, Liberman JN, Sandler RS, et al. Epidemiology of constipation (EPOC) study in the United States: relation of clinical subtypes to sociodemographic features. *Am J Gastroenterol* 1999;94:3530-40.
5. Sonnenberg A, Koch TR. Physician visits in the United States for constipation: 1958 to 1986. *Dig Dis Sci* 1989;34:606-11.
6. Higgins PD, Johanson JF. Epidemiology of constipation in North America: a systematic review. *Am J Gastroenterol* 2004;99:750-9.
7. Johanson JF, Sonnenberg A, Koch TR. Clinical epidemiology of chronic constipation. *J Clin Gastroenterol* 1989;11:525-36.
8. Talley NJ, Fleming KC, Evans JM, et al. Constipation in an elderly community: a study of prevalence and potential risk factors. *Am J Gastroenterol* 1996;91:19-25.
9. Crane SJ, Talley NJ. Chronic gastrointestinal symptoms in the elderly. *Clin Geriatr Med* 2007;23:721-34.
10. Rao SS. Constipation: evaluation and treatment of colonic and anorectal motility disorders. *Gastroenterol Clin North Am* 2007;36:687-711.
11. Mueller-Lissner S, Kamm MA, Wald A, et al. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of sodium picosulfate in patients with chronic constipation. *Am J Gastroenterol* 2010;105:897-903.
12. Lacy BE, Levy LC. Lubiprostone: a novel treatment for chronic constipation. *Clin Interv Aging* 2008;3:357-64.
13. MacDonald KD, McKenzie KR, Henderson MJ, et al. Lubiprostone activates non-CFTR-dependent respiratory epithelial chloride secretion in cystic fibrosis mice. *Am J Physiol Lung Cell Mol Physiol* 2008;295:L933-40.
14. Bjévids MJ, Bot AG, Escher JC, et al. Activation of intestinal Cl secretion by lubiprostone requires the cystic fibrosis transmembrane conductance regulator. *Gastroenterology* 2009;137:976-85.
15. Johanson JF, Morton D, Geenen J, et al. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. *Am J Gastroenterol* 2008;103:170-7.
16. Barish CF, Drossman D, Johanson JF, et al. Efficacy and safety of lubiprostone in patients with chronic constipation. *Dig Dis Sci* 2010;55:1090-7.
17. Johanson JF, Panas R, Holland PC, et al. Long-term efficacy of lubiprostone for the treatment of chronic constipation. *Gastroenterology* 2006;130:A317.
18. Lembo A, Schneider H, Lavins BJ, et al. Efficacy and safety of once daily linaclotide administered orally for 12-weeks in patients with chronic constipation: results from 2 randomized, double-blind, placebo-controlled phase 3 trials. *Gastroenterology* 2010;138:S53-4.
19. Bueno C, Beaufraud C, Mahajan-Miklos S. Anti-nociceptive actions of MD-1100, a novel therapeutic agent for C-IBS, in animal models of visceral pain. *Am J Gastroenterol* 2004;99:A283.
20. Bream-Rouwenhorst HR, Cantrell MA. Alvimopan for postoperative ileus. *Am J Health Syst Pharm* 2009;66:1267-77.
21. McNicol ED, Boyce D, Schumann R, et al. Mu-opioid antagonists for opioid-induced bowel dysfunction. *Cochrane Database Syst Rev* 2008;2:CD006632.
22. Cash BD, Chey WD. Review article: the role of serotonergic agents in the treatment of patients with primary chronic constipation. *Aliment Pharmacol Ther* 2005;22:1047-60.
23. Johanson JF, Wald A, Tougas G, et al. Effect of tegaserod in chronic constipation: a randomized, double-blind, controlled trial. *Clin Gastroenterol Hepatol* 2004;2:796-805.
24. Camilleri M, DeTeeren A. Prucalopride for constipation. *Expert Opin Pharmacother* 2010;11:451-61.
25. Camilleri M, Kerstens R, Rykx A, et al. A placebo-controlled trial of prucalopride for severe chronic constipation. *N Engl J Med* 2008;358:2344-54.
26. Quigley EM, Vandeplassche L, Kerstens R, et al. Clinical trial: the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation—a 12-week, randomized, double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2009;29:315-28.
27. Parkman HP, Rao SS, Reynolds JC, et al. Functional Constipation Study Investigators. Neurotrophin-3 improves functional constipation. *Am J Gastroenterol* 2003;98:1338-47.
28. Feighner SD, Tan CP, McKee KK, et al. Receptor for motilin identified in the human gastrointestinal system. *Science* 1999;284:2184-8.
29. Peters TL. GM-611 (Chugai Pharmaceutical). *Curr Opin Investig Drugs* 2001;2:555.
30. Emmanuel AV, Tack J, Quigley EM, et al. Pharmacological management of constipation. *Neurogastroenterol Motil* 2009;21:41-54.