

Treatment of Chronic Constipation: Prescription Medications and Surgical Therapies

Zilla H. Hussain, MD, Kelly Everhart, BS, and Brian E. Lacy, PhD, MD

Dr Hussain is a gastroenterology fellow, Ms Everhart is a medical student, and Dr Lacy is a professor of medicine and chief of the Section of Gastroenterology and Hepatology at the Geisel School of Medicine at Dartmouth and the Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire.

Address correspondence to:
Dr Zilla H. Hussain
Dartmouth-Hitchcock Medical Center
Section of Gastroenterology and
Hepatology
One Medical Center Drive
Lebanon, NH 03756
Tel: 603-650-5215
Fax: 603-650-5225
E-mail: zilla.h.hussain@hitchcock.org

Abstract: Constipation is a highly prevalent disorder that affects people regardless of age, race, gender, or socioeconomic status. For many patients, constipation is a chronic condition that reduces quality of life. Chronic constipation also imposes a significant economic burden on the health care system. The treatment of constipation remains problematic for both patients and providers for a variety of reasons, including a lack of specificity of symptoms, an inconsistent relationship between underlying pathophysiology and symptom generation, and different and unpredictable patient responses to medications. A large number of over-the-counter agents are used to treat symptoms of constipation, although many of these agents are not effective, and data to support their use are limited and generally of poor quality. Patients referred for consultation typically have failed therapy with over-the-counter agents and require prescription medications or possibly even surgical therapy. This article discusses medical treatments and surgical options for chronic idiopathic constipation.

Chronic idiopathic constipation is a highly prevalent disorder that affects approximately 14% of the US adult population.¹ Although generally considered a benign process by many health care providers, chronic idiopathic constipation has a significant impact on the health care system with regard to both increased costs and reduced quality of life.^{2,3} Symptoms of constipation vary from person to person. In a survey evaluating 557 subjects with chronic constipation, most (79%) respondents reported straining, 71% hard stool, 62% abdominal discomfort, 57% bloating, and 54% a feeling of incomplete evacuation after defecation; infrequent bowel movements were reported by 57%.⁴ These multiple symptoms have changed the definition of constipation, de-emphasizing decreased stool frequency as the sole descriptor of constipation. The Rome III criteria for functional constipation, which are frequently used to identify patients with chronic idiopathic constipation, are shown in Table 1.⁵ The American Gastroenterological Association recently published guidelines on the diagnosis and treatment of

Keywords

Chronic constipation, tegaserod, linaclotide, lubiprostone, bile acid-modifying agents, chenodeoxycholic acid, sacral nerve stimulation

Table 1. Rome III Criteria for Functional Constipation

Two or more of the following symptoms for 3 months or longer, with onset at least 6 months prior to diagnosis, and symptoms present at least 25% of the time:

- Straining
- Hard stools or scybala
- Sensation of incomplete evacuation
- Sense of anorectal obstruction/blockade
- Manual maneuvers (digital disimpaction)
- Fewer than 3 bowel movements per week

In addition, patients cannot meet criteria for inflammatory bowel disease.

Adapted from O'Keefe EA, Talley NJ, Zinsmeister AR, Jacobsen SJ. Bowel disorders impair functional status and quality of life in the elderly: a population-based study. *J Gerontol A Biol Sci Med Sci.* 1995;50(4):M184-M189.

constipation; the criteria for these guidelines are listed in Table 2 for comparison.⁶ These guidelines classify patients into 1 of 3 groups (normal-transit constipation, pelvic floor dysfunction, and slow-transit constipation) based on results of anorectal testing and assessments of colonic transit. Unfortunately, tests to evaluate anorectal and colonic function are not widely available everywhere, which can make accurate diagnosis of the subtypes of chronic idiopathic constipation difficult in rural and underserved areas.

The effective treatment of chronic idiopathic constipation remains problematic for a number of reasons. First, symptoms do not accurately reflect the underlying pathophysiology. Second, symptoms are a poor predictor of responsiveness to medications. Third, patients with similar symptoms often respond differently to the same medication. Fourth, patients may have overlapping processes that cause constipation symptoms (ie, chronic constipation and overlapping pelvic floor dysfunction) and so may require 2 different therapeutic interventions. Finally, no medication is uniformly effective in all patients with constipation. Given the complexity of this disorder, the goal of this article is to review the available prescription medications (Table 3) and surgical treatment options for chronic constipation in an evidence-based approach.

Literature Search

The published literature included in the PubMed, Ovid MEDLINE, and EMBASE databases was searched. For PubMed (1966-July 2014), Ovid MEDLINE (1966-July 2014), and EMBASE (1980-July 2014), the search terms *constipation*, *chronic constipation*, and *functional constipation* (English language) were combined with other search terms, some of which were drugs/medications (*osmotic agents*, *polyethylene glycol*, *bile acid*, *chenodeoxycholic acid*, *A3309*, *tegaserod*, *prucalopride*, *velusetrag*, *lubiprostone*, *linaclotide*, *plecanatide*, *surgery*, *sacral nerve stimulation*,

Table 2. American Gastroenterological Association Criteria for Chronic Constipation

Patients should be classified via anorectal testing and assessments of colonic transit into 1 of 3 groups:

- Normal-transit constipation
- Pelvic floor dysfunction (defecatory disorders)
- Slow-transit constipation

Adapted from Bharucha AE, Dorn SD, Lembo A, Pressman A. American Gastroenterological Association medical position statement on constipation. *Gastroenterology.* 2013;144(1):211-217.

Table 3. Prescription Pharmacologic Treatments for Constipation

- Osmotic agents
- Serotonin agonists (tegaserod, prucalopride, and velusetrag)
- Secretagogues (lubiprostone, linaclotide, and plecanatide)
- Bile acid-modifying agents (chenodeoxycholate and elobixibat)

and *colonic resection*). The results were then further refined by limiting them to include only human trials, fully published manuscripts, randomized clinical trials, and English language papers. Results published only in abstract form were generally not included unless they were felt to be of significant clinical interest. References within studies that met the selection criteria were manually searched for other potentially relevant studies.

Medications

Polyethylene Glycol

Osmotic laxatives contain poorly absorbed substances that serve as osmotic agents, drawing water into the intestinal lumen and holding it there. Although some osmotic laxatives, such as milk of magnesia and polyethylene glycol (PEG), are sold over the counter, many patients still obtain PEG with a prescription, so its mention here is warranted. PEG is a nonabsorbable and nonmetabolized polymer that is formulated either with or without electrolytes. A systematic review found evidence that PEG effectively improves stool frequency and consistency.⁷ A multicenter, double-blind, placebo-controlled trial evaluated the therapeutic effect of daily doses of PEG in the treatment of chronic constipation (n=48).⁸ In comparison with placebo, PEG solution induced a statistically significant increase in weekly bowel frequency at 4 weeks and at the end of the 8-week study (4.8±2.3 for PEG vs 2.8±1.6 for placebo; $P<.002$) and significant decreases in straining at defecation ($P<.01$), stool hardness ($P<.02$), and use of laxatives ($P<.03$). Another double-blind, placebo-controlled study measured the long-term therapeutic effectiveness, safety, and tolerability of low daily doses of isosmotic PEG.⁹ Successful treatment of constipation,

according to the primary efficacy variable, was defined as the relief of constipation symptoms included in the modified Rome criteria. This endpoint was reported by a significantly ($P < .001$) higher number of patients treated with PEG than of patients given placebo over a 6-month treatment period. Numerous other randomized, controlled trials have shown similar effectiveness.^{10,11} PEG was well tolerated, and side effects of abdominal cramping, flatulence, and nausea were rare. Trials have also been conducted comparing PEG with other laxatives. PEG is more effective than lactulose¹¹ at increasing stool frequency, and another trial showed PEG to be more effective than tegaserod (Zelnorm, Novartis).¹² Although PEG is commonly used in the treatment of chronic constipation, it is approved by the US Food and Drug Administration (FDA) only for the treatment of acute constipation.

Serotonin Receptor Agonists

Tegaserod Tegaserod is worth a brief mention here because it is the only serotonin (5-HT₄) receptor agonist approved by the FDA (in 2004) for the treatment of chronic idiopathic constipation. However, tegaserod was removed from the North American market in March 2007 because of concerns about potential adverse cardiovascular events,¹³ although a follow-up study in which an insurance claims database was used showed no relationship between tegaserod use and cardiovascular side effects.¹⁴ Tegaserod may have relieved symptoms of constipation because it accelerates both orocecal transit time and proximal colonic filling at 6 hours.¹⁵ The FDA approval was based on the results of 2 large studies considered to be of high quality because they were prospective, placebo-controlled, randomized, double-blind, multicenter studies with a duration of 12 weeks and with well-defined primary and secondary endpoints.^{16,17}

Prucalopride Prucalopride (Resolor, Shire) is a 5-HT₄ agonist currently approved for the treatment of chronic constipation in Europe, but it is not yet approved by the FDA for use in the United States. Prucalopride, a selective dihydrobenzofurancarboxamide derivative, binds with high affinity to the 5-HT₄ receptor (Figure 1). The drug is well absorbed (oral bioavailability estimated at 90%), most is eliminated in the urine (60%-70%), the pharmacokinetic profile is not altered by food, and it has negligible activity in the human ether-a-go-go potassium channel.^{18,19}

The efficacy and safety of prucalopride for the treatment of chronic constipation have been evaluated in 3 large studies that were essentially identical in design—multicenter, randomized, double-blind, placebo-controlled, parallel-group studies conducted over 12 weeks.²⁰⁻²² Patients were randomized to once-daily prucalopride (2 or

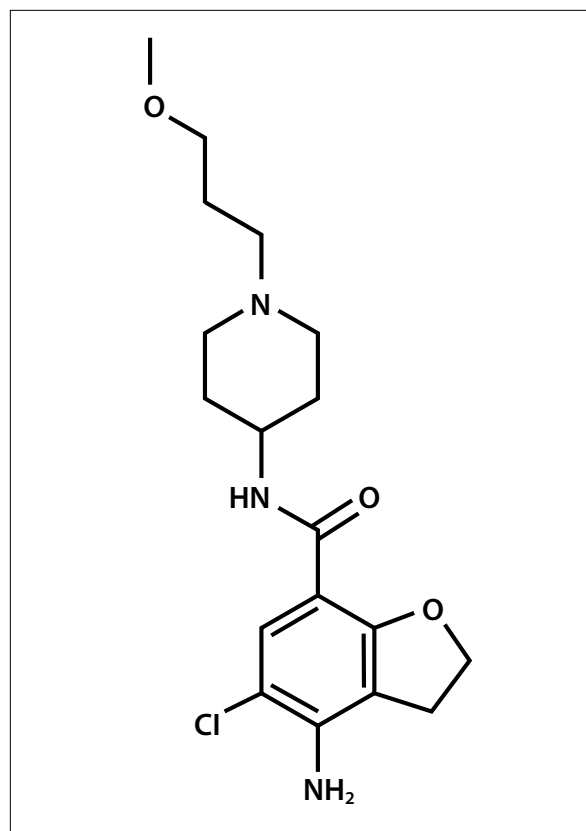


Figure 1. The structure of prucalopride.

4 mg) or placebo after symptoms had been measured for 2 weeks. The primary efficacy endpoint was the proportion of patients having 3 or more complete spontaneous bowel movements (CSBMs) per week, averaged over the 12-week period, in an intention-to-treat analysis. In the first study, 620 patients were randomized (88% women; mean age, 48 years). The primary endpoint (≥ 3 CSBMs per week) was reached by 31% of those on 2 mg of prucalopride, 28% of those on 4 mg, and 12% of those on placebo ($P < .001$ for both study groups).²⁰ The second study included 720 patients (mean age, 48.1 years) with a mean duration of constipation of approximately 18 years.²¹ Patients treated with prucalopride (both the 2- and 4-mg doses) were more likely to meet the primary endpoint than were patients given placebo ($P < .01$ and $P < .001$, respectively), and these patients also reported an improvement in several secondary endpoints, including the percentage of bowel movements with normal consistency ($P < .05$ for both groups) and the percentage of bowel movements not associated with straining ($P < .01$ for both groups). In the third study, which involved 651 patients (mean age, 47.9 years), 23.9% and 23.5% of the patients treated with prucalopride met the primary endpoint in comparison with those given placebo ($P < .01$ for both groups).²² In terms of serious adverse events, no deaths were reported in any of the trials.

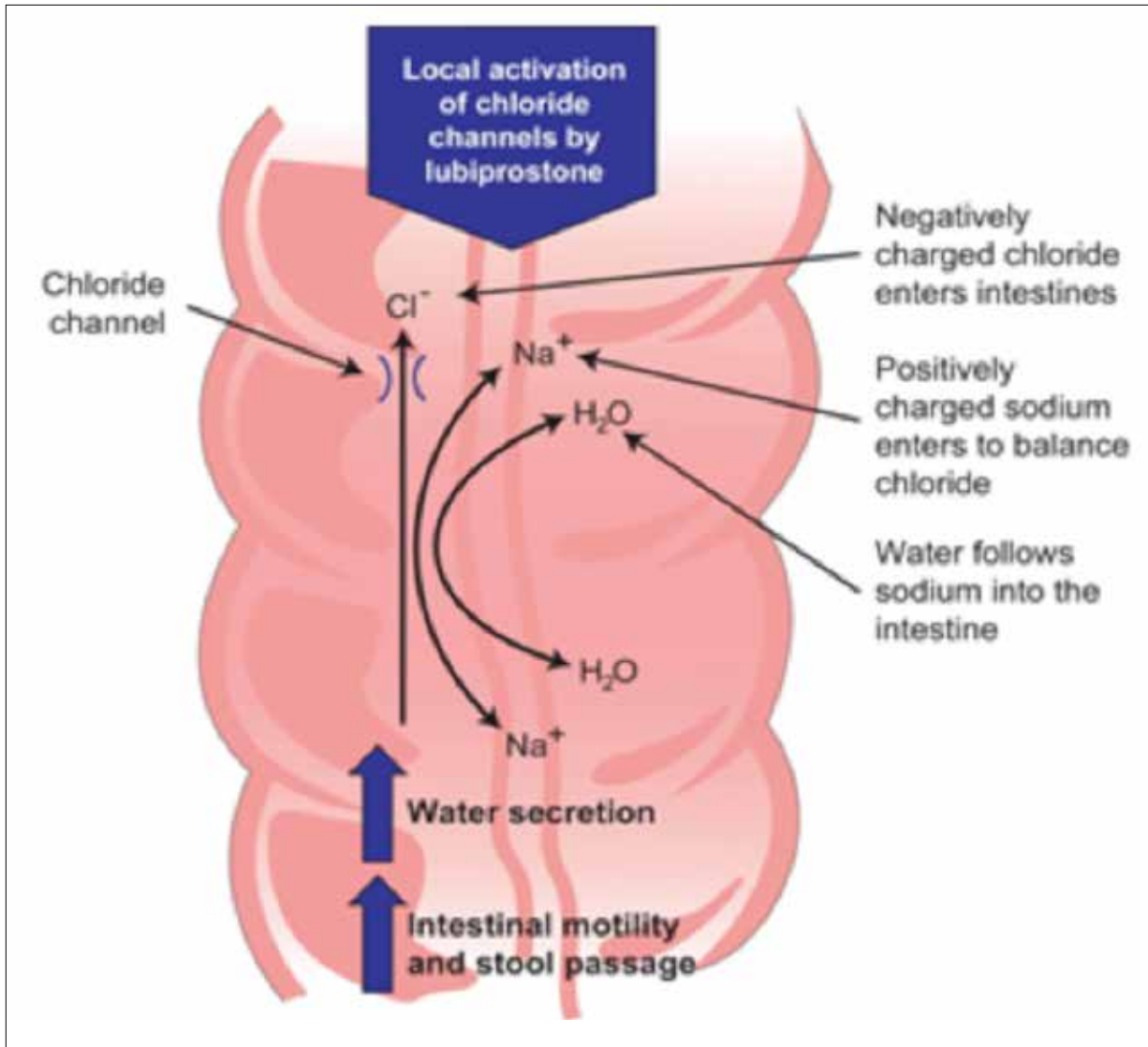


Figure 2. The mechanism of action of lubiprostone.

No clinically significant differences were found in serum chemistries, electrocardiographic data, urinalysis results, or hematologic data. No patient in the placebo group stopped the medication because of diarrhea, although 1.5% to 4.4% of the patients on prucalopride discontinued the medication because of diarrhea (2- and 4-mg doses, respectively). Adverse events leading to discontinuation consisted primarily of headache, nausea, diarrhea, and abdominal pain and usually occurred within the first few days of treatment. It is worth noting that based on the balance between efficacy and adverse events, the 2-mg but not the 4-mg dose was brought to market.

Velusetrag Velusetrag is another highly selective 5-HT₄ agonist with no apparent effect on human ether-a-go-go-related potassium channels.²³ The effects of velusetrag on gastroin-

testinal transit were evaluated in a dose-ranging study of 60 healthy volunteers.²⁴ Single doses of velusetrag (30 and 50 mg), but not placebo, accelerated colonic transit, as measured by colonic filling at 6 hours ($P < .038$) and geometric center at 24 hours ($P < .001$). A phase 2B dose-ranging study compared the effects of velusetrag (15, 30, or 50 mg) with placebo over 4 weeks in 401 adults (mean age, 45.1 years; 92% women) who had chronic constipation.²⁵ The authors reported that all doses of velusetrag improved stool frequency and stool consistency and decreased straining compared with placebo ($P < .01$ -.0001). Diarrhea occurred in 11% to 15% of the patients treated with velusetrag vs 1% of those randomized to placebo. Large randomized, placebo-controlled trials will be required to confirm these results and determine whether velusetrag is a viable treatment option for patients with chronic constipation.

Secretagogues

Lubiprostone Lubiprostone (Amitiza, Sucampo/Takeda) is classified as a prostone, a bicyclic fatty acid compound derived from a metabolite of prostaglandin E₁ (Figure 2).²⁶ Lubiprostone accelerates intestinal and colonic transit, purportedly by activating ClC-2 chloride channels on the apical membrane of epithelial cells.²⁷⁻²⁹ Activation of ClC-2 chloride channels causes an efflux of chloride into the lumen of the gastrointestinal tract; this is followed by the efflux of sodium and then water in order to maintain both isoelectric and isotonic equilibrium. Several studies have postulated that the actions of lubiprostone may not be entirely due to activation of the ClC-2 chloride channel. Bassil and colleagues found that lubiprostone induced the contraction of rat and human stomach longitudinal muscle,³⁰ whereas other researchers demonstrated that lubiprostone increased the contractility of circular but not longitudinal smooth muscle through a prostaglandin E receptor 1 pathway.³¹ T84 cell monolayer cultures were used to demonstrate that lubiprostone stimulates the secretion of intestinal fluid via prostanoid receptor signaling (EP₄ receptors),³² whereas other researchers found that lubiprostone can activate the cystic fibrosis transmembrane regulator (CFTR) via the EP₄ receptor.³³

Lubiprostone was approved for the treatment of chronic constipation in 2006 based in part on the results of 2 separate phase 3 multicenter trials performed after an initial dose-ranging study.³⁴⁻³⁶ Patients were classified as having symptoms of chronic constipation based on modified Rome II criteria.³⁴ The first study involved 242 subjects (mean age, 48.6 years; 90% women; >84% white) from 20 centers across the United States.³⁵ Patients were randomized to twice-daily lubiprostone (24 µg) or placebo taken with food after a 2-week baseline period. Prescription and over-the-counter constipation remedies were prohibited during the washout and study periods, although bisacodyl suppositories or sodium phosphate enemas were available as "rescue" therapy for those subjects without a bowel movement for 3 or more consecutive days. Compared with the patients given placebo, the treatment group had more spontaneous bowel movements (SBMs) during week 1 (5.7 vs 3.5; $P=.0001$), and the effect was sustained during each of the subsequent weeks of the study. A larger percentage of the patients on lubiprostone had an SBM within 24 hours (56.7% vs 36.9%; $P=.0024$) and within 48 hours (80.0% vs 60.7%; $P=.0013$). The percentages of patients who needed rescue medications were similar in the 2 groups at baseline, but the percentage had decreased in the lubiprostone group by the end of the study period (35.6% vs 50.8%; $P=.0357$). The symptom scores of the patients on lubiprostone were significantly improved compared with those of the patients on placebo for weeks 1 through 4 in regard to stool consistency ($P<.0001$), strain-

ing ($P\leq.0001$), and severity of constipation ($P\leq.0003$). Abdominal bloating was decreased by lubiprostone compared with placebo during weeks 1 and 2 ($P\leq.031$), and the scores for abdominal discomfort were significantly improved for weeks 2 through 4 ($P\leq.045$). At least 1 adverse event was reported by 70% of the subjects on lubiprostone, compared with 50.8% of the patients on placebo ($P=.0026$). The most common treatment-related adverse event was nausea, occurring in 31.7% of the lubiprostone group and 3.3% of the placebo group ($P<.001$). Because of nausea, 5% of patients withdrew from the study.

The second phase 3 trial included 237 subjects (mean age, 45.8 years; 88% women).³⁶ The patients on lubiprostone experienced a significant increase in the weekly frequency of bowel movements (5.9 vs 4.00; $P<.0001$). As in the previously described studies, the patients on lubiprostone reported improvements in subjective measures of constipation, and more patients in the lubiprostone group than in the placebo group had a SBM within the first 24 hours (61% vs 31%; $P<.0001$). Nausea, headache, and diarrhea were again the most commonly reported adverse events. Mild to moderate nausea occurred more frequently in the lubiprostone-treated group than in the placebo group in the second study (21% vs 4.2%; P value not reported). No serious adverse events were reported; 15 patients on lubiprostone withdrew from the second trial.

The long-term safety and efficacy of lubiprostone were evaluated in a prospective, open-label study of 248 patients treated with 24 µg of lubiprostone twice daily for 48 weeks (modified Rome II criteria; mean age, 51 years; 84% women)³⁷; 127 patients (51%) completed the trial. Nausea (19.8% of participants) and diarrhea (9.7%) were the 2 most common adverse events, and these were categorized as either mild or moderate. A total of 33 patients (13.3%) withdrew from the study; nausea was the most common reason (5.2%), followed by abdominal distension (2%), headache and abdominal pain (1.6% each), and diarrhea (1.2%). No clinically significant changes were noted in body weight, vital signs, physical examination findings, urinalysis results, electrolyte levels, liver function test results, or complete blood cell counts. One serious adverse event was considered to be possibly related to medication use; a normal pregnancy resulted in a baby with 2 clubfeet. It should be noted that lubiprostone is not available in Europe.

Linacotide Linacotide (Linzess, Forest Laboratories and Ironwood Pharmaceuticals) is a 14-amino acid peptide that stimulates intestinal guanylate cyclase type C (GC-C) receptors (Figure 3).³⁸ Linacotide is acid stable and protease resistant. It is minimally absorbed and undetectable in the systemic circulation at therapeutic doses. Linacotide mimics the action of endogenous guanylin (15 amino

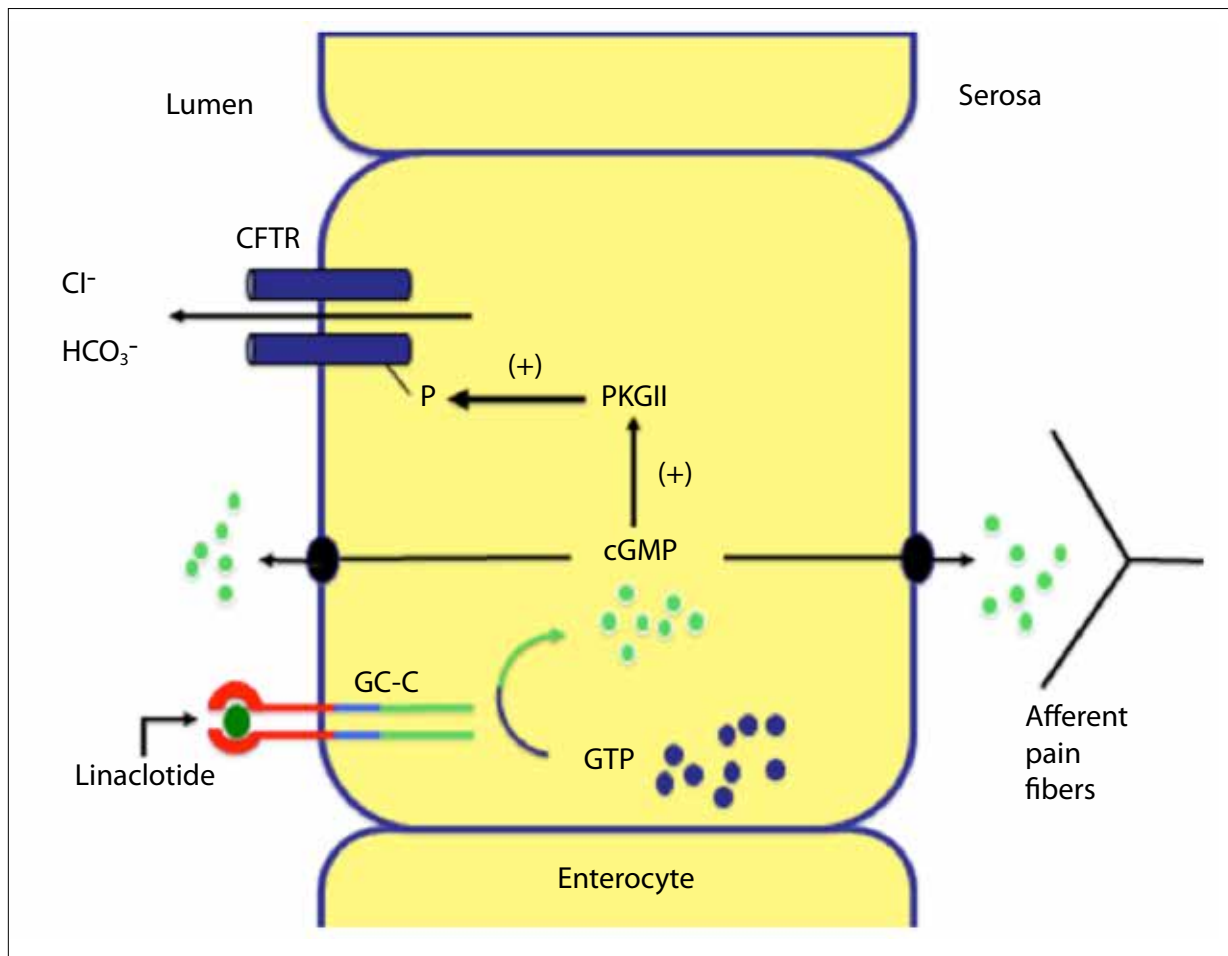


Figure 3. The mechanism of action of linaclotide.

CFTR, cystic fibrosis transmembrane receptor; cGMP, cyclic guanosine monophosphate; GC-C, guanylate cyclase type C; GTP, guanosine triphosphate; PKG, protein kinase G.

acids) and uroguanylin (16 amino acids), both of which activate the GC-C receptor.^{39,40} GC-C is expressed at high levels in the small intestine and colon, but at low levels in the stomach. The activation of GC-C stimulates the production of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate, which then increases the flow of electrolytes (HCO₃⁻ and Cl⁻) and water into the lumen of the gastrointestinal tract (Figure 3).⁴¹ The result is an increase in gastrointestinal transit.⁴² In addition, stimulation of the GC-C receptor on intestinal epithelial cells and the release of cGMP into the serosa reduce visceral hyperalgesia.⁴³

The safety and efficacy of linaclotide in chronic constipation were evaluated over 12 weeks in 2 large parallel, randomized, placebo-controlled, double-blind trials involving 1272 patients taking 2 different doses (145 and 290 µg).⁴⁴ Trial 01 included 630 patients, and trial 303 included 642 patients (median age, 48 years; 89% female). The primary endpoint of both trials was defined a priori as a composite endpoint of 3 or more CSBMs per

week and an increase of at least 1 CSBM per week from baseline for at least 9 of the 12 weeks. Secondary endpoints included measurements of stool frequency, stool consistency, severity of straining, abdominal discomfort, bloating, and overall severity of constipation. The authors reported that once-daily linaclotide produced early and sustained decreases in bowel and abdominal symptoms and increases in SBMs and CSBMs within the first week of treatment. For the 12-week study period, the primary endpoint (12-week CSBM overall response for ≥9 of 12 weeks) was met in both trial 01 (16.0% and 21.3% vs 6.0% for placebo; $P=.0012$ and $P<.0001$) and trial 303 (21.2% and 19.4% vs 3.3% for placebo; $P<.0001$). These benefits remained when the data were pooled and analyzed for weeks 1 through 12. Secondary endpoints with linaclotide, including CSBMs per week, SBMs per week, stool consistency, straining, severity of constipation, abdominal discomfort, and bloating, were superior to those with placebo, and the differences were statistically significant in both studies for each dose of linaclotide.

Trial 303 included a randomized 4-week withdrawal study involving 538 of the 642 patients. The patients initially treated with linaclotide either continued linaclotide or were switched to placebo, while the placebo patients were switched to 290 µg of linaclotide. The CSBM rates for the patients initially treated with linaclotide and re-randomized to placebo decreased to the CSBM rates for placebo during the study, while the CSBM rates of the patients maintained on linaclotide were sustained (complete data not provided). The CSBM rates of the placebo patients later allocated to linaclotide increased to levels seen during the primary treatment period (complete data not available). A rebound effect, characterized by a worsening of constipation symptoms, was not seen following the cessation of linaclotide. A significant treatment effect on chronic constipation, bowel and abdominal symptoms, and global assessments was found (*r* values of 0.51-0.60, 0.46-0.59, and 0.44-0.59, respectively). The authors reported 1 death in this study, which was caused by an overdose of fentanyl and was not thought to be related to the study drug. Adverse events occurred in 2.1% of the patients treated with placebo and in 1.4% and 2.6% of those treated with linaclotide (145- and 290-µg doses, respectively). The rates of discontinuation due to adverse events were 4.2% in the patients treated with placebo, 7.9% in the patients treated with 145 µg of linaclotide, and 7.3% in those treated with 290 µg of linaclotide. Discontinuation of the study medication and adverse events were primarily related to gastrointestinal problems, and the most common gastrointestinal adverse events were diarrhea, flatulence, and abdominal pain. No clinically significant differences were found among the 3 groups with regard to electrocardiographic results, vital signs, blood chemistries, urinalysis results, or hematologic findings.

Plecanatide Plecanatide (Synergy Pharmaceuticals) is a 16-amino acid GC-C agonist that is structurally and functionally nearly identical to the human hormone uroguanylin.⁴⁵ As with linaclotide, the binding of plecanatide to transmembrane enteric receptors stimulates the increased production of intracellular cGMP, which activates the CFTR and increases the secretion of fluid and ions into the gastrointestinal lumen. A large multicenter trial to evaluate the safety and efficacy of plecanatide in 951 patients with chronic constipation was completed in 2012; the full data are awaiting release.⁴⁶ Study participants were randomized into 4 study arms in which varying doses of plecanatide (0.3, 1.0, and 3.0 mg) were compared with placebo during a 12-week period. A statistically significant improvement in the number of CSBMs was noted for all doses of plecanatide compared with placebo; the greatest improvement was observed with the 3-mg dose of plecanatide. More than half of the

patients in the arm given 3 mg of plecanatide experienced an increase of at least 1 CSBM per week relative to baseline (52.3% vs 36.8% for placebo; $P<.001$). The most common adverse event reported was diarrhea (9.7% for 3 mg of plecanatide vs 1.3% for placebo).

Newer Agents: Bile Acid–Modifying Agents

Bile acids induce diarrhea by increasing colonic fluid and electrolyte secretion and stimulating colonic propulsion.^{47,48} Elobixibat (Ajinomoto Pharmaceuticals) is a novel oral agent that inhibits the ileal bile acid transporter and consequently increases the flow of bile into the colon. In a randomized, placebo-controlled, dose-escalating study (0.1, 0.3, 1, 3, and 10 mg daily) of 30 patients (mean age, 61.5 years; 76% women) with chronic constipation, the 2 highest doses of elobixibat accelerated colonic transit.⁴⁹ In a double-blind, placebo-controlled study of 36 women with chronic constipation, 14 days of treatment with 20 mg of elobixibat improved colonic transit at 24 hours and improved stool consistency.⁵⁰ Colonic transit at 48 hours was accelerated with both a 15- and a 20-mg dose compared with placebo ($P=.002$ and $P<.001$, respectively). Patients reported improvements in stool consistency and straining. Gastric emptying in patients treated with elobixibat appeared to be slightly delayed compared with gastric emptying in those given placebo, although this difference was not statistically significant.

The largest study of elobixibat published to date enrolled 190 patients (mean age, 48 years; 90% women) in a randomized, double-blind, placebo-controlled, 8-week trial at 45 US sites.⁵¹ Patients met modified Rome III criteria for chronic constipation; the primary endpoint was the change in SBM frequency during week 1 compared with baseline. Patients were randomized to 1 of 4 oral daily treatment groups (placebo or a 5-, 10-, or 15-mg dose of elobixibat). The authors reported a significant improvement in the number of SBMs (the primary endpoint) in the 10-mg (4.0 SBMs) and 15-mg (5.4 SBMs) treatment groups ($P<.002$ and $P<.001$, respectively) compared with the placebo group (1.7 SBMs). Significantly more of the patients treated with elobixibat (either 10 or 15 mg) than of the patients given placebo reported a SBM within 24 hours of taking their first dose of medication ($P=.012$). Secondary endpoints, including decrease in straining, improvement in stool consistency, and increases in CSBMs and stool frequency at week 8, were all better in the 10- and 15-mg groups in comparison with the placebo group, and the differences were statistically significant. Adverse events were reported by 54% of patients and severe adverse events by 7%. The most common were abdominal pain and diarrhea, and these were dose-related. The study medication was discontinued by 15% of the patients (6 in the placebo group and 23 in the elobixibat groups). In most cases, discontinu-

ation was because of abdominal pain and diarrhea. Total cholesterol levels dropped in the 10- and 15-mg treatment groups. Further trials are warranted to determine whether the reported efficacy can be maintained over a prolonged period of time and whether adverse events are short-lived and/or tolerable.

Surgical Options

Sacral Nerve Stimulation

The first report of electrical stimulation to improve colonic motility was published in 1995.⁵² Since then, sacral nerve stimulation (SNS) has been shown to induce pancolonic antegrade propagating sequences and increase stool frequency both in patients with slow-transit constipation and in those with normal-transit constipation resistant to standard therapy (ie, the “difficult” patients with constipation). SNS is a minimally invasive surgical option for patients with chronic constipation secondary to colonic inertia, rectal hyposensitivity, or obstructed defecation when symptoms remain refractory to more than 12 months of medical and behavioral management.⁵³ Eligible patients undergo a 2- to 3-week peripheral nerve evaluation, in which a temporary lead stimulates afferent outflow from S3; a significant clinical response to electrical stimulation is an indication for the permanent implantation of a SNS device (Figure 4).

Mechanistically, SNS appears to lower the threshold of maximum tolerated volume in the rectal vault,⁵⁴ and it has been shown to induce pancolonic antegrade propagating sequences at suprasensory thresholds and to increase stool frequency both in patients with slow-transit constipation and in those with normal-transit constipation resistant to standard therapy.⁵⁵ Notably, Kamm and colleagues demonstrated normalization of the whole-gut transit time 6 months following permanent device implantation at a subsensory threshold of stimulation.⁵⁶

In a review of 13 studies describing the results of SNS for chronic constipation, Thomas and colleagues reported successful test stimulation in 42% to 100% of patients.⁵⁷ Of the 13 studies reviewed, the largest successful response to permanent SNS device implantation was reported by Kamm and colleagues. In this multicenter prospective study, 45 of 62 patients (89% women) noted a 50% decrease in symptoms during a 3-week peripheral nerve evaluation, which qualified them for chronic stimulation. Of these patients, 39 (87%) reported a significant increase in stool frequency, decrease in straining, and improvement in ease of evacuation and in half of the 8 domains of the 36-Item Short Form Health Survey (SF-36) during a median follow-up period of 28 months.⁵⁶

In 2012, Govaert and colleagues reviewed data gathered from 2 prospective studies performed at 2 ter-

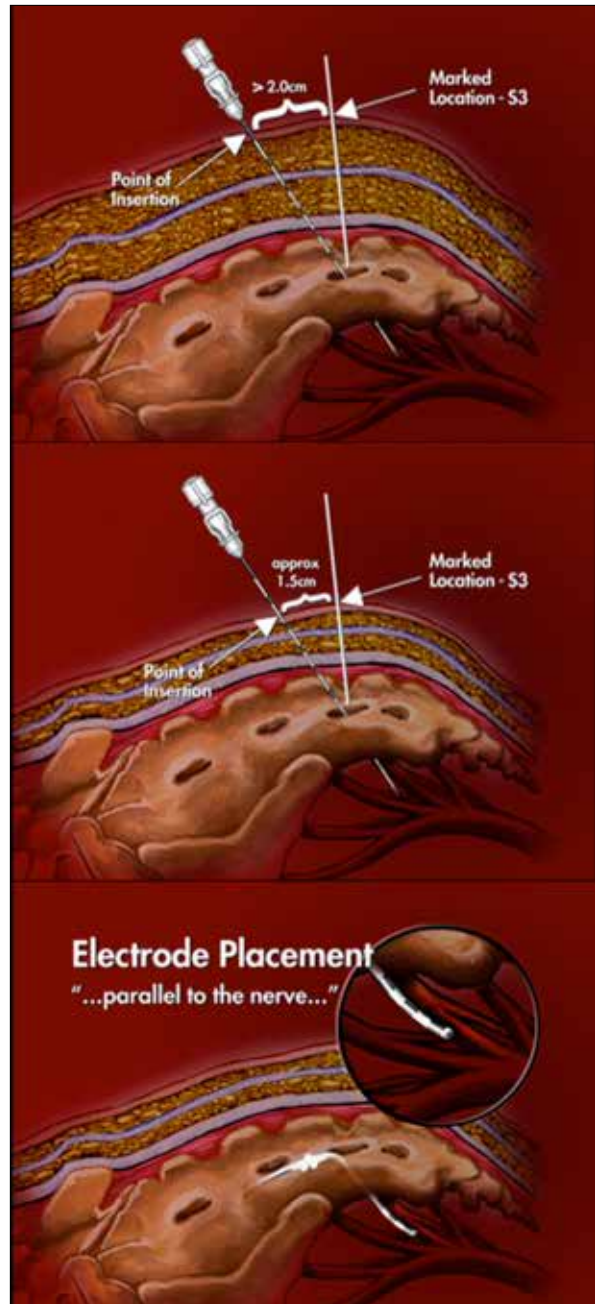


Figure 4. Sacral nerve stimulation.

Reprinted with permission from Medtronic Images, Inc. © 2006. InterStim Therapy is not approved by the Food and Drug Administration for the treatment of chronic constipation.

tiary care centers in Europe; these studies included 117 patients with persistent symptoms of constipation who had failed dietary changes, medications, and biofeedback (90% women; mean age, 45 years).⁵⁸ The authors reported that 68 patients (58%) had undergone successful peripheral nerve evaluation during a 3-week trial period and progressed to the second part of the study, in which a sacral nerve modulator was implanted. The patients with

normal colonic transit had a better response to percutaneous nerve stimulation than patients with slow transit (76% vs 52%; $P=.048$), and younger patients seemed to respond better than older patients. At 1 year after placement of a sacral nerve modulator, 61 patients of those initially evaluated (52%) continued to use the modulator. Based on their Wexner constipation scores (0-30), these patients appeared to experience an overall decrease in the global symptoms of constipation (Wexner score of approximately 9; $n=29$) compared with baseline (Wexner score of approximately 18; $n=80$). However, because Wexner scores were not obtained in those who failed peripheral nerve evaluation and also were not obtained in those whose stimulator was removed ($n=6$), it is difficult to assess efficacy.

Ortiz and colleagues reviewed prospective outcome data gathered by 2 European centers following the implantation of a SNS device for chronic constipation ($n=48$; 39% women; median age, 39 years).⁵³ Of the 45 patients who completed peripheral nerve evaluation, 23 (47.9%; 5 with slow-transit constipation, 10 with outlet obstruction, and 8 with combined causes of constipation) proceeded to permanent device implantation. Of the patients who underwent chronic stimulation, 14 met the criteria for a successful outcome; the Wexner constipation scores decreased from 20.21 (standard deviation [SD] 3.57) at baseline to 5.79 (SD 4.14) at the latest follow-up examination ($P<.001$), and stool frequency increased from 1.4 (SD 0.77) at baseline to 6.07 (SD 2.22) evacuations per week at the latest follow-up examination ($P<.001$). Uniquely, the authors reported that the results did not differ between constipation subtypes.

Knowles and colleagues conducted a prospective, randomized, double-blind and placebo-controlled crossover trial ($n=13$; 100% women) to evaluate the efficacy of SNS therapy for patients with chronic constipation secondary to evacuatory dysfunction and rectal hyposensitivity.⁵⁴ Following baseline evaluation (PRE) and temporary placement of a SNS device, patients were randomized to 2-week intervals of ON/OFF, then switched to the opposite mode of operation for a total of 4 weeks. The authors reported a significant decrease in defecatory desire volume (PRE, 277 mL [234-320]; ON, 163 mL [133-193]; OFF, 220 mL [183-237]; $P=.006$) and in maximal tolerance volume (PRE, 350 mL [323-377]; ON, 262 mL [219-305]; OFF, 298 mL [256-340]; $P=.012$). They also reported a significant increase in the proportion of successful bowel movements (PRE, median 43% [0-100] vs ON, 89% [11-100] vs OFF, 83% [11-100]; $P=.007$) and a significant decrease in Wexner constipation scores (PRE, median 19 [9-26] vs ON, 10 [6-27] vs OFF, 13 [5-29]; $P=.01$).

In 2010, Maeda and colleagues performed a retrospective review of adverse outcomes associated with

SNS for constipation at a single institution ($n=38$; 84% women; mean age, 45.6 years).⁵⁹ The authors reported that 22 patients (58%) experienced a total of 58 adverse outcomes attributed to SNS therapy, including 26 (45%) events associated with loss of efficacy and 16 (28%) events associated with prolonged pain. Of the 58 adverse events, 28 (48%) were resolved with device reprogramming, and 3 adverse events (5.2%) led to device explantation and discontinuation of SNS therapy.

Colonic Resection

Sir Arbuthnot Lane first documented the results of operative treatment for constipation in 1908. In a review of 48 case series involving 11 different surgical treatment options for adult patients with chronic constipation (Rome III criteria) attributed to colonic inertia, Arebi and colleagues reported that mean stool frequency increased from 1.1 to 19.7 evacuations per week ($n=30$ studies; 943/1443 patients [65%]), and postoperative laxative use decreased to zero for 67% of patients ($n=34$ studies; 971/1443 patients).⁶⁰ Total abdominal colectomy with ileorectal anastomosis was the most common surgical procedure ($n=39$ studies; 1046/1443 patients [72%]). Regardless of the surgical procedure, late complications included an overall 2% risk of mortality ($n=45$ studies; 3/1324 patients), a 4.5% to 71% risk of postoperative obstruction (severity undefined; $n=40$ studies), an overall 18% risk of fecal incontinence ($n=23$ studies; 150/828 patients), and an overall 12.5% risk of recurrent constipation ($n=36$ studies; 122/973 patients). All studies emphasized the importance of appropriate patient selection during a consideration of surgical treatment options, most commonly endorsing colonic transit (95%), anorectal manometry (88%), and defecography (78%) as critical preoperative investigations.

Knowles and colleagues cautioned that although colectomy often improves stool frequency, a large proportion of patients experience persistent symptoms of abdominal pain and bloating following surgery.⁶¹ Like most other investigators, Knowles and colleagues promote careful patient selection for the surgical treatment of colonic inertia, describing the ideal patient as one with evidence of diffuse slow colonic transit in the presence of normal gastric and small-bowel transit, normal rectal sensation, and absence of an evacuatory disorder. Highly selective preoperative eligibility requirements minimize the number of patients who experience the persistent postoperative abdominal pain and bloating that are associated with panenteric motility disorders.

More recently, Vergara-Fernandez and colleagues, in a comparison with published data from open procedures, reported similar rates of symptom resolution and an apparently lower rate of postoperative complications in

a prospective case series of patients (n=8; 100% women; mean age, 38 years) with isolated colonic inertia (Rome II criteria) who underwent laparoscopic colectomy with ileorectal anastomosis.⁶² At 1-year follow-up examination, stool frequency increased from 0.84 (SD 0.24) to 6.75 (SD 3.45) evacuations per week ($P=.001$). Preoperative abdominal distension resolved in 4 patients following the surgical procedure (7/8 patients [87.6%] vs 3/8 patients [37.5%]; $P=.034$). Scores for pre- and postoperative pain, evaluated with a 10-point visual analogue scale, decreased from a preoperative mean of 6.6 (SD 0.3) to a postoperative mean of 3.6 (SD 2.3). No patients reported incontinence of liquid or solid material in either the preoperative or the postoperative period. Finally, the authors reported a significant increase in all 8 domains of the SF-36.

Multiple authors recommend a trial of minimally invasive SNS for the treatment of patients with isolated colonic inertia refractory to medical and behavioral management before colectomy,⁶¹ although no studies to date have directly compared the efficacy of SNS and definitive surgical options for the treatment of isolated slow-transit constipation. Finally, preoperative psychological testing and appropriate treatment before all operative procedures for chronic constipation are encouraged because symptoms of chronic constipation with a significant psychological etiology demonstrate only a modest response to surgical therapy.^{57,60,61}

Conclusions

Chronic constipation is a prevalent disorder, and its effective treatment remains problematic for both patients and clinicians. Our review of the published evidence for the treatment of chronic constipation with prescription medications reveals that the armamentarium is reasonably large and useful. For patients with persistent symptoms thought to be secondary to slow-transit constipation, surgery remains an option, although appropriate patient selection is critical. New and emerging treatments for chronic constipation are likely to fill an important void for many patients, particularly those who experience symptoms on a chronic basis and those who also experience significant bloating or intermittent abdominal pain.

The authors have no relevant conflicts of interest to disclose.

References

- Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. *Am J Gastroenterol*. 2011;106(9):1582-1591.
- O'Keefe EA, Talley NJ, Zinsmeister AR, Jacobsen SJ. Bowel disorders impair functional status and quality of life in the elderly: a population-based study. *J Gerontol A Biol Sci Med Sci*. 1995;50(4):M184-M189.
- Chang L. Review article: epidemiology and quality of life in functional gastrointestinal disorders. *Aliment Pharmacol Ther*. 2004;20(suppl 7):31-39.
- Johanson JF, Kralstein J. Chronic constipation: a survey of the patient perspective. *Aliment Pharmacol Ther*. 2007;25(5):599-608.
- Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology*. 2006;130(5):1480-1491.
- Bharucha AE, Dorn SD, Lembo A, Pressman A; American Gastroenterological Association. American Gastroenterological Association medical position statement on constipation. *Gastroenterology*. 2013;144(1):211-217.
- Corazzari E, Badiali D, Bazzocchi G, et al. Long term efficacy, safety, and tolerability of low daily doses of isosmotic polyethylene glycol electrolyte balanced solution (PMF-100) in the treatment of functional chronic constipation. *Gut*. 2000;46(4):522-526.
- Corazzari E, Badiali D, Habib FI, et al. Small volume isosmotic polyethylene glycol electrolyte balanced solution (PMF-100) in treatment of chronic nonorganic constipation. *Dig Dis Sci*. 1996;41(8):1636-1642.
- Dipalma JA, Cleveland MV, McGowan J, Herrera JL. A randomized, multicenter, placebo-controlled trial of polyethylene glycol laxative for chronic treatment of chronic constipation. *Am J Gastroenterol*. 2007;102(7):1436-1441.
- Attar A, Lémann M, Ferguson A, et al. Comparison of a low dose polyethylene glycol electrolyte solution with lactulose for treatment of chronic constipation. *Gut*. 1999;44(2):226-230.
- Cleveland MV, Flavin DP, Ruben RA, Epstein RM, Clark GE. New polyethylene glycol laxative for treatment of constipation in adults: a randomized, double-blind, placebo-controlled study. *South Med J*. 2001;94(5):478-481.
- Di Palma JA, Cleveland MV, McGowan J, Herrera JL. A randomized, multicenter comparison of polyethylene glycol laxative and tegaserod in treatment of patients with chronic constipation. *Am J Gastroenterol*. 2007;102(9):1964-1971.
- FDA announces discontinued marketing of GI drug, Zelnorm, for safety reasons [news release]. Silver Spring, MD: U.S. Food and Drug Administration; March 30, 2007.
- Loughlin J, Quinn S, Rivero E, et al. Tegaserod and the risk of cardiovascular ischemic events: an observational cohort study. *J Cardiovasc Pharmacol Ther*. 2010;15(2):151-157.
- Prather CM, Camilleri M, Zinsmeister AR, McKinzie S, Thomforde G. Tegaserod accelerates orocecal transit in patients with constipation-predominant irritable bowel syndrome. *Gastroenterology*. 2000;118(3):463-468.
- 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(9):796-805.
- Kamm MA, Müller-Lissner S, Talley NJ, et al. Tegaserod for the treatment of chronic constipation: a randomized, double-blind, placebo-controlled multinational study [published correction appears in *Am J Gastroenterol*. 2005;100(3):735]. *Am J Gastroenterol*. 2005;100(2):362-372.
- Prucalopride Investigator's Brochure*. 7th ed. Janssen Research Foundation; 1999:90.
- Van de Velde V, Ausma J, Vandeplassche L. Food does not affect the oral bioavailability of prucalopride [DDW abstract T1270]. *Gastroenterology*. 2009;136(5 suppl 1):A-536.
- Camilleri M, Kerstens R, Rykx A, Vandeplassche L. A placebo-controlled trial of prucalopride for severe chronic constipation. *N Engl J Med*. 2008;358(22):2344-2354.
- Tack J, van Outryve M, Beyens G, Kerstens R, Vandeplassche L. Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives. *Gut*. 2009;58(3):357-365.
- Quigley EMM, Vandeplassche L, Kerstens R, Ausma J. 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(3):315-328.
- Smith JAM, Beattie DT, Marquess D, Shaw JP, Vickery RG, Humphrey PP. The in vitro pharmacological profile of TD-5108, a selective 5-HT₄ receptor agonist with high intrinsic activity. *Naunyn Schmiedeberg's Arch Pharmacol*. 2008;378(1):125-137.
- Manini ML, Camilleri M, Goldberg M, et al. Effects of Velusetrag (TD-5108) on gastrointestinal transit and bowel function in health and pharmacokinetics in health and constipation. *Neurogastroenterol Motil*. 2010;22(1):42-49, e7-e8.
- Goldberg M, Li YP, Johanson JF, et al. Clinical trial: the efficacy and tolerability of velusetrag, a selective 5-HT₄ agonist with high intrinsic activity, in chronic idiopathic constipation—a 4-week, randomized, double-blind, placebo-controlled, dose-response study. *Aliment Pharmacol Ther*. 2010;32(9):1102-1112.
- Amitiza [package insert]. Bethesda, MD: Sucampo Pharmaceuticals; 2006.
- Camilleri M, Bharucha AE, Ueno R, et al. Effect of a chloride channel activa-

- tor, lubiprostone, on gastrointestinal transit, gastric sensory and motor function in healthy humans. *Am J Physiol Gastrointest Liver Physiol*. 2006;290(5):G942-G947.
28. Cuppoletti J, Malinowska DH, Tewari KP, et al. SPI-0211 activates T84 cell chloride transport and recombinant human ClC-2 chloride currents. *Am J Physiol Cell Physiol*. 2004;287(5):C1173-C1183.
29. Bao HF, Liu L, Self J, Duke BJ, Ueno R, Eaton DC. A synthetic prostone activates apical chloride channels in A6 epithelial cells. *Am J Physiol Gastrointest Liver Physiol*. 2008;295(2):G234-G251.
30. Bassil AK, Borman RA, Jarvie EM, et al. Activation of prostaglandin EP receptors by lubiprostone in rat and human stomach and colon. *Br J Pharmacol*. 2008;154(1):126-135.
31. Chan WW, Mashimo H. Lubiprostone increases small intestinal smooth muscle contractions through a prostaglandin E receptor 1 (EP1)-mediated pathway. *J Neurogastroenterol Motil*. 2013;19(3):312-318.
32. Bijvelds MJC, Bot AG, Escher JC, De Jonge HR. Activation of intestinal Cl-secretion by lubiprostone requires the cystic fibrosis transmembrane conductance regulator. *Gastroenterology*. 2009;137(3):976-985.
33. Norimatsu Y, Moran AR, MacDonald KD. Lubiprostone activates CFTR, but not ClC-2, via the prostaglandin receptor (EP4). *Biochem Biophys Res Commun*. 2012;426(3):374-379.
34. Johanson JF, Ueno R. Lubiprostone, a locally acting chloride channel activator, in adult patients with chronic constipation: a double-blind, placebo-controlled, dose-ranging study to evaluate efficacy and safety. *Aliment Pharmacol Ther*. 2007;25(11):1351-1361.
35. Johanson JF, Morton D, Geenen J, Ueno R. 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(1):170-177.
36. Barish CF, Drossman D, Johanson JF, Ueno R. Efficacy and safety of lubiprostone in patients with chronic constipation. *Dig Dis Sci*. 2010;55(4):1090-1097.
37. Lembo AJ, Johanson JF, Parkman HP, Rao SS, Miner PB Jr, Ueno R. Long-term safety and effectiveness of lubiprostone, a chloride channel (ClC-2) activator, in patients with chronic idiopathic constipation. *Dig Dis Sci*. 2011;56(9):2639-2645.
38. Busby RW, Bryant AP, Cordero EA, et al. The molecular target of MD-1100 is guanylate cyclase (GC-C), an apical receptor on intestinal epithelial cells. *Gastroenterology*. 2005;128(suppl 2):A-464.
39. Currie MG, Fok KF, Kato J, et al. Guanylin: an endogenous activator of intestinal guanylate cyclase. *Proc Natl Acad Sci USA*. 1992;89(3):947-951.
40. Hamra FK, Forte LR, Eber SL, et al. Uroguanylin: structure and activity of a second endogenous peptide that stimulates intestinal guanylate cyclase. *Proc Natl Acad Sci USA*. 1993;90(22):10464-10468.
41. Bryant AP, Busby RW, Bartolini WP, et al. Linaclotide is a potent and selective guanylate cyclase C agonist that elicits pharmacological effects locally in the gastrointestinal tract. *Life Sci*. 2010;86(19-20):760-765.
42. Busby RW, Bryant AP, Bartolini WP, et al. Linaclotide, through activation of guanylate cyclase C, acts locally in the gastrointestinal tract to elicit enhanced intestinal secretion and transit. *Eur J Pharmacol*. 2010;649(1-3):328-335.
43. Castro J, Harrington AM, Hughes PA, et al. Linaclotide inhibits colonic nociceptors and relieves abdominal pain via guanylate cyclase-C and extracellular cyclic guanosine 3',5'-monophosphate. *Gastroenterology*. 2013;145(6):1334-1346.e1-e11.
44. Lembo AJ, Schneider HA, Shiff SJ, et al. Two randomized trials of linaclotide for chronic constipation. *N Engl J Med*. 2011;365(6):527-536.
45. Solinga R, Kessler M, Busby R, et al. A comparison of the physical and pharmacological properties of plecanatide (sp-304) and the human hormone uroguanylin. *ACJ*. 2011;11(S2):332.
46. Miner PB, Surowitz R, Fogel R, et al. Plecanatide, a novel guanylate cyclase-C (GC-C) receptor agonist, is efficacious and safe in patients with chronic idiopathic constipation (CIC): results from a 951 patient, 12 week, multi-center trial. Oral presentation at: Digestive Disease Week 2013; May 18-21, 2013; Orlando, FL.
47. Camilleri M, Murphy R, Chadwick VS. Dose-related effects of chenodeoxycholic acid in the rabbit colon. *Dig Dis Sci*. 1980;25(6):433-438.
48. Bampton PA, Dinning PG, Kennedy ML, Lubowski DZ, Cook IJ. The proximal colonic motor response to rectal mechanical and chemical stimulation. *Am J Physiol Gastrointest Liver Physiol*. 2002;282(3):G443-G449.
49. Simrén M, Bajor A, Gillberg P-G, Rudling M, Abrahamsson H. Randomised clinical trial: the ileal bile acid transporter inhibitor A3309 vs. placebo in patients with chronic idiopathic constipation—a double-blind study. *Aliment Pharmacol Ther*. 2011;34(1):41-50.
50. Wong BS, Camilleri M, McKinzie S, Burton D, Graffner H, Zinsmeister AR. Effects of A3309, an ileal bile acid transporter inhibitor, on colonic transit and symptoms in females with functional constipation. *Am J Gastroenterol*. 2011;106(12):2154-2164.
51. Chey WD, Camilleri M, Chang L, Rikner L, Graffner H. A randomized placebo-controlled phase IIIb trial of a3309, a bile acid transporter inhibitor, for chronic idiopathic constipation. *Am J Gastroenterol*. 2011;106(10):1803-1812.
52. Hughes SF, Scott SM, Pilot MA, Williams NS. Electrically stimulated colonic reservoir for total anorectal reconstruction. *Br J Surg*. 1995;82(10):1321-1326.
53. Ortiz H, de Miguel M, Rinaldi M, Oteiza F, Altomare DF. Functional outcome of sacral nerve stimulation in patients with severe constipation. *Dis Colon Rectum*. 2012;55(8):876-880.
54. Knowles CH, Thin N, Gill K, et al. Prospective randomized double-blind study of temporary sacral nerve stimulation in patients with rectal evacuatory dysfunction and rectal hyposensitivity. *Ann Surg*. 2012;255(4):643-649.
55. Dinning PG, Fuentealba SE, Kennedy ML, Lubowski DZ, Cook IJ. Sacral nerve stimulation induces pan-colonic propagating pressure waves and increases defecation frequency in patients with slow-transit constipation. *Colorectal Dis*. 2007;9(2):123-132.
56. Kamm MA, Dudding TC, Melenhorst J, et al. Sacral nerve stimulation for intractable constipation. *Gut*. 2010;59(3):333-340.
57. Thomas GP, Dudding TC, Rahbour G, Nicholls RJ, Vaizey CJ. Sacral nerve stimulation for constipation. *Br J Surg*. 2013;100(2):174-181.
58. Govaert B, Maeda Y, Alberga J, Buntzen S, Laurberg S, Baeten CG. Medium-term outcome of sacral nerve modulation for constipation. *Dis Colon Rectum*. 2012;55(1):26-31.
59. Maeda Y, Lundby L, Buntzen S, Laurberg S. Sacral nerve stimulation for constipation: suboptimal outcome and adverse events. *Dis Colon Rectum*. 2010;53(7):995-999.
60. Arebi N, Kalli T, Howson W, Clark S, Norton C. Systematic review of abdominal surgery for chronic idiopathic constipation. *Colorectal Dis*. 2011;13(12):1335-1343.
61. Knowles CH, Scott M, Lunniss PJ. Outcome of colectomy for slow transit constipation. *Ann Surg*. 1999;230(5):627-638.
62. Vergara-Fernandez O, Mejía-Ovalle R, Salgado-Nesme N, et al. Functional outcomes and quality of life in patients treated with laparoscopic total colectomy for colonic inertia. *Surg Today*. 2014;44(1):34-38.