NEW AND NOVEL PHARMACOLOGIC THERAPIES FOR CHRONIC CONSTIPATION*

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ABSTRACT

Laxatives are the mainstays of pharmacologic therapy of chronic constipation. However, their lack of uniform efficacy in all patients, and even in the same patient, underscores the need for new and novel agents with different mechanisms of action to relieve constipation and its associated symptoms. This article reviews experimental and clinical studies of prescription laxatives, including polyethylene glycol and lactulose, in addition to new and novel agents for the treatment of constipation, such as tegaserod, a serotonin (5-HT₄) receptor partial agonist that has been available since 2002, and lubiprostone, a chloride channel activator that was approved by the US Food and Drug Administration in February 2006 for the treatment of chronic idiopathic constipation. It also reviews studies evaluating other agents with therapeutic potential in constipation, including renzapride, a 5-HT₄ receptor full agonist and 5-HT₃ antagonist; µ-opioid antagonists, such as naloxone, methylnaltrexone, and alvimopan; NT-3, a recombinant human neurotrophic factor; and MD-1100, a guanylate cyclase-C agonist. The article also briefly addresses the off-label use of colchicine and misoprostol, which are indicated for other conditions, but they are sometimes used to treat constipation in some patients.

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**Polyethylene Glycol and Lactulose**

Polyethylene glycol and lactulose are prescription laxatives that belong to the category of osmotic laxatives, which are poorly absorbed or nonabsorbed substances that increase the secretion of water into the intestine. Other osmotic laxatives, which are available OTC, thus they are not discussed in detail in this article, include salts (eg, magnesium and phosphate) and sugar alcohols (eg, sorbitol or mannitol).

Results from 6 randomized, double-blind, placebo-controlled trials, 2 randomized comparative trials, and other studies evaluating lactulose and PEG prompted an American College of Gastroenterology Task Force to give both agents a Grade A recommendation (ie, a recommendation supported by 2 or more Level 1 trials without conflicting evidence from other Level 1 trials). Two of the studies comparing lactulose with placebo and 3 of the studies comparing PEG with placebo found that active treatment improved stool consistency and increased the number of bowel movements per day, whereas 2 open-label studies comparing PEG to lactulose found that PEG resulted in greater stool frequency, less straining, and better overall effectiveness. A secondary analysis of 1 of these studies suggested that PEG was also more cost effective than lactulose. In the other study, which compared both agents in elderly patients for 6 months, weekly stool frequency was significantly higher and the incidence of hard stools significantly lower in those patients receiving PEG. In both of these trials, patients taking PEG reported fewer side effects, particularly bloating, and were more satisfied with therapy than patients taking lactulose.

**New and Novel Agents**

New and novel agents with mechanisms of action that differ from those of osmotic and other laxatives include tegaserod, lubiprostone, renzapride (Alizyme, Cambridge, UK), µ-opioid antagonists, human recombinant neurotrophic factor, and guanylate cyclase agonists.

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**Tegaserod**

Tegaserod is a serotonin (5-HT4) receptor partial agonist, a novel class of compounds that is structurally similar to naturally occurring 5-HT. Through its actions on 5-HT4 receptors, it increases motility and intestinal secretion of fluid and inhibits visceral sensitivity.

Two large phase III pivotal trials involving more than 2000 patients meeting the Rome II criteria for chronic constipation have shown that tegaserod is significantly more effective than placebo in relieving constipation (Table). The primary endpoint in both trials, one of which was conducted in Europe and the other in North and South America, was having 1 or more complete spontaneous bowel movement per week during the first 4 weeks in response to tegaserod. In the European trial, 40% of patients receiving tegaserod 6 mg twice daily reached the primary endpoint versus 27% of patients receiving placebo. In the North/South American trial, 43% of patients receiving tegaserod 6 mg twice daily reached the primary endpoint versus 25% of patients receiving placebo. In both trials, the difference between the treatment and placebo groups was statistically significant (P <.0001).

The secondary endpoints were the effects of tegaserod on stool form, straining, spontaneous bowel movements per week, and bothersome abdominal pain or discomfort. In the North/South American trial,

### Table. Effects of Tegaserod Versus Placebo on Chronic Constipation

<table>
<thead>
<tr>
<th>Variable Mean</th>
<th>Tegaserod 6 mg twice daily</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Weeks 1–12</td>
</tr>
<tr>
<td>Europe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSBM/week, n</td>
<td>0.5</td>
<td>1.9*</td>
</tr>
<tr>
<td>SBM/week, n</td>
<td>3.1</td>
<td>5.1*</td>
</tr>
<tr>
<td>North/South America</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSBM/week, n</td>
<td>0.6</td>
<td>1.9*</td>
</tr>
<tr>
<td>SBM/week, n</td>
<td>3.5</td>
<td>5.4*</td>
</tr>
</tbody>
</table>

CSBM = complete spontaneous bowel movement; SBM = spontaneous bowel movement. *P <.0001 vs placebo.

Data from Kamm et al; Johanson et al.

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which examined these effects in 450 patients receiving tegaserod 2 mg twice daily, 451 patients receiving tegaserod 6 mg twice daily, and 447 patients receiving placebo, those receiving either tegaserod dose had significantly better stool form, less straining, and less bothersome abdominal symptoms than those patients receiving placebo (P < .05 vs placebo for all comparisons). These clinical benefits were limited to men and women with chronic constipation who were younger than the age of 65 years.

Tegaserod appears to be safe. Headache was the most common adverse effect observed in the pivotal trials. It was reported by 9.8% and 12.3% of patients receiving tegaserod in the European and North/South American trials, respectively. However, higher proportions of patients receiving placebo reported headaches—12.8% and 13.7% in the European and North/South American trials, respectively. The most frequent side effect to occur more commonly in patients treated with tegaserod was diarrhea, which usually occurs in the first few days after starting therapy and resolves shortly thereafter. Severe diarrhea can sometimes occur. Ischemic colitis has been reported during postmarketing surveillance, but a causal link to the drug has not been established.

Based on the efficacy and safety data described above, the American College of Gastroenterology Task Force gave tegaserod a Grade A recommendation.

Lubiprostone

Lubiprostone, a chloride channel activator, represents a potential new class of agents for the treatment of constipation. It selectively activates the CIC-2 chloride channels in the gastrointestinal (GI) tract, enhances intestinal fluid secretion, and may restore mucosal barrier function. Similar to the prostaglandin analogues, lubiprostone is part of the arachidonic acid cascade. However, unlike these analogues, it does not have significant effects on smooth muscle contraction, but does have a more pronounced effect on secretion of water in the gut.

CIC-2 channels, which are found throughout the GI tract, are located on the apical surface of epithelial cells and are a driving force for intestinal fluid secretion and overall intestinal transport. As negatively charged chloride ions actively enter the lumen via chloride channels, positively charged sodium ions passively diffuse through the intracellular spaces to balance the chloride. As a result, water passively follows into the lumen. The increased amount of fluid now in the small intestine increases the net amount of fluid delivered to the colon.

Animal studies have shown that oral lubiprostone increases the chloride concentration of intestinal fluid and the amount of intestinal fluid in a dose-dependent manner. In a different animal model, lubiprostone also appeared to restore mucosal barrier function in the ileum after 45 minutes of experimentally induced ischemia.

According to the investigators reporting these findings, the salutary effect of lubiprostone on mucous membrane barrier function recovery appeared to be mediated through a reduction in paracellular permeability by the conformational change in the tight junction after activation of the CIC-2 channel. Because lubiprostone is a selective agonist of this channel, the investigators speculated that the drug may provide a pharmacologic approach to hastening recovery of mucosal barrier function that has been compromised by ischemic injury.

Preliminary results from clinical trials evaluating the effects of lubiprostone on chronic constipation have shown that it is significantly better than placebo. In a 4-week, multicenter, parallel-group, double-blind, placebo-controlled phase III trial involving 242 patients who had fewer than 3 bowel movements a week and also met the Rome II criteria for chronic constipation, lubiprostone 24 µg twice daily significantly increased the number of bowel movements per week, the study’s
primary endpoint, at all time points in the study, compared to placebo (Figure). Onset of action appears to be rapid. The first bowel movement occurred within 24 hours of starting the study medication in 63% of patients receiving lubiprostone versus 31% of patients receiving placebo. Nausea was the most common adverse event, occurring in 21% of patients receiving lubiprostone versus 4% of patients receiving placebo. Nine patients randomized to lubiprostone withdrew from the study because of adverse events, usually nausea.

The study also evaluated the effect of lubiprostone on straining and overall effectiveness, and found that it significantly reduced straining scores and increased effectiveness scores at each of the 4 time points at which these assessments were obtained ($P < .0001$ vs placebo). In a randomized withdrawal study, in which 128 patients received lubiprostone 24 µg twice daily or placebo for 4 weeks and were then randomly withdrawn, patients who received lubiprostone had more spontaneous bowel movements per week than those who received placebo (5.59 vs 3.04; $P = .046$).

Lubiprostone was approved by the US FDA in February 2006 for the treatment of chronic idiopathic constipation.

**RENZAPRIDE**

Renzapride, which has been used to improve gastric emptying in diabetic agents, is a 5-HT4 full agonist and a 5-HT3 antagonist that is currently being studied in patients with IBS-C. Thus far, a small study involving 48 women with IBS-C has found a linear dose response with renzapride 1 mg, 2 mg, and 4 mg every day versus placebo for 11 to 14 days for colonic transit and ascending colon emptying, but not for gastric emptying. Stool form and ease of passage, but not frequency, were significantly associated with accelerated colonic transit. These findings suggest that the 5-HT4 agonist properties are predominant.

Preliminary results from a study in patients with IBS-C showed that renzapride increased the frequency of bowel movements and improved stool consistency, but did not significantly relieve abdominal pain or discomfort.

Renzapride appears to have an excellent safety profile and does not have any significant cardiac toxicities.

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**CASE STUDY**

**A 42-YEAR-OLD WOMAN WITH COMPLAINTS OF CONSTIPATION**

**PRESENTATION AND HISTORY**

- 42-year-old woman with complaints of constipation that began in her early-to-mid teens, but has worsened recently
- She reports 1 bowel movement per week, on average
- She also complains of bloating, distention, and some lower abdominal discomfort that is relieved by a bowel movement
- She has tried fiber and over-the-counter (OTC) laxatives (magnesium hydroxide, senna, and bisacodyl), which sometimes provide temporary relief or sometimes produce cramps and diarrhea
- Her symptoms are affecting her social and professional life significantly
- Medical history: hypercholesterolemia, appendectomy at age 7 years, and 2 normal spontaneous vaginal deliveries
- Social history: married with 2 children, works as a paralegal, exercises 3 to 5 days a week, does not smoke, drinks 2 to 3 glasses of wine a week, and follows a healthy high-fiber diet
- Family history: father has type 2 diabetes and coronary heart disease; mother has constipation, which she self-treats with OTC laxatives

**PHYSICAL EXAMINATION AND LABORATORY FINDINGS**

- Weight: 125 lb
- Physical examination is unremarkable
- Rectal examination
  - No rectal scars, external hemorrhoids, or fissures
  - Normal resting tone with appropriate pelvic floor relaxation on simulated bear down
- Minimal guaiac-negative stool in the rectal vault
- A small rectocele is present
- Laboratory values: normal for thyroid-stimulating hormone, blood counts, glucose, calcium, magnesium, and phosphorus

**NEXT STEPS**

- Trial with polyethylene glycol (PEG) or tegaserod
- No head-to-head trials have been published
- Consider using tegaserod first when irritable bowel syndrome symptoms are present
- If symptoms persist, consider combining tegaserod and PEG, or other combinations of laxatives
**μ-Opioid Antagonists**

Three agents in this class—naloxone, methylnaltrexone, and alvimopan—have been studied in opioid-induced and/or chronic constipation, and the results are promising.

Naloxone (Narcan; Endo Pharmaceuticals Inc., Chadds Ford, Pa) has been available for some time and is effective in reversing opioid-induced constipation, but its ability to cross the blood-brain barrier with ease reduces its analgesic effects. However, it may have a role in chronic constipation, for which opioid analgesia is not required.

Methylnaltrexone, a quaternary N-methyl derivative of naltrexone, reduces oral-cecal transit and increases the frequency of bowel movements in methadone clinic patients without causing opioid withdrawal symptoms. Because it does not readily cross the blood-brain barrier, it does not blunt the analgesic effects of opioids. It too may have a role in chronic constipation.

Alvimopan (Enterig; Adolor Corporation, Exton, Pa; GlaxoSmithKline, Research Triangle Park, NC), which has 5 times the affinity for the μ-opioid receptor as naloxone, decreases postoperative ileus and, as demonstrated in a randomized, double-blind, placebo-controlled, phase III study, reduces the time to hospital discharge by 23 hours. Data on the drug’s role in postoperative ileus have recently been reviewed by the US FDA.

Studies examining the effects of alvimopan on chronic opioid-induced bowel dysfunction show that it reduces the time to onset of bowel movements, increases stool weight, and reduces straining and the incidence of hard stools in a dose-dependent manner. Another study in patients with chronic opioid-induced bowel dysfunction compared alvimopan 0.5 mg every day and 1 mg every day to placebo for 21 days and found that both doses of the drug significantly reduced the time to onset of bowel movements compared to placebo. The study also found that weekly bowel movements and overall satisfaction increased with the 1-mg dose versus placebo.

A randomized, double-blind, placebo-controlled trial involving 73 healthy volunteers found that alvimopan reversed the inhibitory effects of codeine on small bowel and colonic transit. When given alone, alvimopan increased colonic transit, suggesting a potential role in patients with chronic constipation.

Thus far, only limited data have been published on chronic idiopathic constipation. In 1 study, 23 patients were randomized to alvimopan 3 mg twice daily or placebo for 7 days. Patients receiving the drug had a decrease in colonic transit time, increased bowel frequency and complete spontaneous bowel movements, reduced straining, stool hardness, and abdominal discomfort, and increased overall satisfaction compared to placebo. Results of larger clinical trials of this agent in patients with chronic constipation are pending.

**Recombinant Human Neurotrophic Factor**

The neurotrophins in general promote growth of sensory neurons, modulate synaptic transmission, and have favorable effects on constipation. One agent in this class, recombinant human neurotrophic factor (NT-3), has been studied in a phase II trial involving 107 patients with chronic constipation who received subcutaneous injections of the drug (3 mg or 9 mg) or placebo 3 times a week for 10 weeks. NT-3 increased bowel frequency, softened stool, and eased stool passage, with the greatest increase in the number of bowel movements per week seen with the 9-mg dose at week 5 to 6, week 7 to 8, and week 9 to 10. Side effects included local irritation at the injection site and upper respiratory infections. Further clinical studies are pending.

**Guanylate Cyclase Agonists**

One agent in this class, MD-1100, stimulates the production of cGMP in intestinal cells. In a rat model, MD-1100 has been shown to stimulate chloride and bicarbonate ion secretion into the intestinal lumen, increase GI transit, and decrease perception of visceral pain.

**Other Agents**

Although colchicine and misoprostol are indicated for conditions other than constipation, they are sometimes recommended for the treatment of chronic constipation. Neither drug is recommended for this purpose in patients who are pregnant.

A few studies have examined both agents in patients with chronic constipation, but anecdotal reports suggest mixed results and numerous side effects. For example, a crossover study found a significant increase in the number of bowel movements per week in patients receiving colchicine 0.6 mg three times daily compared to those receiving placebo (9.9
However, patients receiving colchicine reported a small increase in abdominal pain while taking the drug.

**Conclusions**

Laxatives are the mainstays of therapy for chronic constipation. However, their limitations underscore the need for new and novel therapies.

Among these newer therapies, tegaserod, a 5-HT4 receptor partial agonist, is approved for the treatment of IBS-C in women. Clinical trials have shown that it is safe and effective in IBS-C and chronic constipation.

Preliminary data from studies suggest lubiprostone, a chloride channel activator, will be safe and effective, and it was approved by the US FDA in February 2006 for the treatment of chronic idiopathic constipation. Data are pending for other novel therapies, such as renzapride, μ-opioid antagonists, NT-3, and MD-1100.

In general, the new and novel therapies described here offer varying degrees of promise in providing significant relief of constipation and its associated symptoms.

**Discussion**

**Dr. Lee:** What do we know about the long-term efficacy of tegaserod and its side effects?

**Dr. Lembo:** Studies do not show a marked decrease in efficacy or an increase in tachyphylaxis. Although several patients report a decrease in efficacy over time, they also report that with other laxatives.

**Dr. Hasler:** A study presented at this year’s Digestive Disease Week found that approximately 60% of subjects who had a response to tegaserod at 3 months had a persistence of their response at 1 year.

**Dr. Chang:** That trial showed that 60% of those patients responding at 3 months would continue to have a response with continued therapy.

**Dr. Hasler:** We’ve done some physiologic testing in healthy volunteers, looking at barostat and other manometric parameters in the colon. We found that if you give tegaserod acutely, you get a marked increase in phasic colonic activity and an enhanced peristaltic reflex. After just a single week of therapy, we saw a loss of a lot of those initial phasic contractions, in addition to some decrease, although not abolition, of these stimulatory effects on peristaltic reflex. We think that’s a possible mechanism for the very early but self-limited diarrhea you see with tegaserod. It suggests that there is some desensitization to some of the motor effects of the drug. It is unknown if these effects become more prominent 1, 2, or 3 months down the road.

**Dr. Leung:** Would cutting the dose reduce the diarrhea?

**Dr. Chang:** You have to look at the initial dose response studies that evaluated the 2-mg and 6-mg doses to be able to determine if that would work. I don’t know if it’s significantly different.

**Dr. Rao:** I think the incidence of diarrhea was higher with the 6-mg dose compared to the 2-mg dose in the IBS studies.

**Dr. Leung:** Thus, there is a possibility that reducing the starting dose even further will reduce diarrhea.

**Dr. Chang:** I actually recommend that in some patients. If a patient, particularly with IBS, is having fairly regular bowel movements but is also having constipation symptoms, I’ll usually start with one-half or one 6-mg pill a day, thus I can see how they respond initially. Many patients get diarrhea when they take that first dose. When it resolves, I titrate the dose up.

**Dr. Lembo:** It’s important to emphasize that diarrhea occurs in the first couple of days for most people.

**Dr. Chang:** I’ve also noticed that a decreased response to tegaserod after a good initial response usually occurs within the first 2 weeks. Therefore, if they develop desensitization, it’s pretty early. What I do, and this works in some patients but not in others, is stop the medication if there’s a good positive response, and then I restart it. For example, some of my patients will take it only once a week, and they’ll get a good response, possibly because any desensitization of 5-HT4 receptors has had time to reverse. This is, of course, speculative and anecdotal.

**Dr. Hasler:** I’ve had similar results. I use tegaserod on an as-needed basis in some patients. The patients who are still responding to tegaserod 1 or 2 months later are not the ones who are going to lose their responsiveness. I’ve seen patients who say that it has stopped working after 2 or 3 weeks, and I truly do think that has a physiologic effect, although there are no data to support it. In my experience, intermediate-term responders at 2 or 3 months tend to also be long-term responders.
REFERENCES