ABSTRACT

Chronic constipation is a common condition that affects more American adults than hypertension, migraine, diabetes, asthma, and coronary heart disease. It is associated with bothersome symptoms such as straining, gas, bloating, infrequent bowel movements, incomplete evacuation, and abdominal distention and/or discomfort. Chronic constipation also imposes a significant economic burden and has a negative impact on health-related quality of life. This article reviews the definition, diagnostic criteria, etiology, and epidemiology of chronic constipation, in addition to its impact on healthcare costs, resource utilization, and quality of life. It also addresses several treatment options, including lifestyle modifications, fiber supplementation, and the prescription medications that are approved for the treatment of chronic constipation.

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CHRONIC CONSTIPATION: AN OVERVIEW

DEFINITIONS AND DIAGNOSTIC CRITERIA

Chronic constipation is clinically defined as unsatisfactory defecation characterized by infrequent stools, difficult passage of stools, or both. Difficult passage may involve straining, incomplete evacuation, hard or lumpy stools, prolonged time to passing stools, and maneuvers to pass stools such as pressing on the lower belly or inserting a finger into the rectum to remove stool. Chronic constipation is also defined by the Rome criteria, which are frequently among the entry criteria in many clinical trials. The recently published Rome III criteria define chronic constipation as the presence of at least 2 of 5 characteristics of difficult passage (ie, straining, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction or blockage, and manual maneuvers to facilitate defecation) in at least 25% of defecations for at least 12 weeks over the preceding year; no loose

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stools in the absence of laxative use; and failure to meet the diagnostic criteria for irritable bowel syndrome (IBS).\(^4\)

**CAUSES OF CHRONIC CONSTIPATION**

Chronic constipation is most frequently caused by a neuromuscular dysfunction of the colon or pelvic floor muscles. This type of constipation is sometimes referred to as chronic idiopathic or functional constipation. Subtypes of chronic idiopathic constipation include normal-transit constipation, IBS with constipation (IBS-C), slow colonic transit, and pelvic floor dyssynergia, which is characterized by an inability to relax the pelvic floor muscles to the extent needed for “normal” defecation, and responds better to anorectal biofeedback than it does to laxatives.\(^5\)

Chronic constipation is less commonly caused by secondary causes, several of which are noted in Figure 1.\(^6\) The most common of these causes are medications, particularly opioids and drugs prescribed for Parkinson’s disease, pregnancy (with calcium and iron supplementation as a contributing factor), diabetes, and multiple sclerosis. In fact, the risk for chronic constipation among patients with multiple sclerosis is 11 times higher than that for patients with other neurological disorders, many of which are also associated with an increased risk for constipation.\(^7\) Similarly, constipation, not diarrhea, is more common among patients with diabetes.\(^8\) Other less common secondary causes of constipation include mechanical obstruction, endocrine disorders such as hypothyroidism and hypercalcemia, colorectal and ovarian cancer, central nervous system disorders, and collagen vascular and muscle disorders.

**PREVALENCE**

Chronic constipation is more prevalent in the adult population than hypertension (45 million), migraine (32 million), diabetes (14 million), asthma (13 million), and coronary heart disease (12 million).\(^9\) It is more common in women, non-Caucasians, the elderly, those with depression or psychological distress, and those with low socioeconomic status.\(^10\)

**ECONOMIC IMPACT AND RESOURCE UTILIZATION**

Chronic constipation imposes significant drug costs and utilization of healthcare resources. Americans spend more than $800 million a year on OTC laxatives alone.\(^11\) Data from the National Center for Health Statistics indicate that more prescriptions are written each year for laxatives than for birth control pills or antihypertensive agents.\(^12\)

In 2001, chronic constipation accounted for 2.7 million ambulatory visits to physicians and other healthcare providers, at a direct cost of $235 million.\(^13\) More recent data addressing indirect costs indicate that chronic constipation accounts for 13.7 million days of restricted activity and 3.4 million days of bed disability each year.\(^14\) In addition, fecal impaction resulting from chronic constipation accounts for a fair number of hospitalizations each year, particularly in elderly patients.\(^15\)

**QUALITY OF LIFE**

Patients with chronic constipation often report symptoms such as gas, bloating, abdominal distention, and abdominal pain and/or discomfort that are bothersome enough to restrict physical and social activity, necessitate taking time off from work, and otherwise reduce their quality of life. In a study comparing quality of life in 309 patients with self-reported chronic constipation and 455 healthy individuals with no functional gastrointestinal disorder, those with chronic constipation had significantly lower mean scores (more than 5 points lower) in the 6 components of the Short Form-36 of the Health-Related Quality of Life

![Figure 1. Secondary Causes of Chronic Constipation](Reprinted with permission from Borum ML. Prim Care. 2001;28:577-590.)
assessment tool. The 6 components were physical functioning, vitality, social functioning, mental health index, perception of health, and pain index.

Another area that affects patient well-being and impinges on quality of life is patient satisfaction with disease management and treatment options. In an Internet-based survey conducted in 2004, only 53% of people with chronic constipation reported being completely satisfied with the treatments for constipation. Reasons for dissatisfaction included failure to produce regular, predictable bowel movements and failure to resolve (or worsening of) bloating and gas.

A similar survey of physicians found that only 9% were completely satisfied with the treatment options available before the introduction of tegaserod. The remainder were incompletely satisfied and wanted better treatment options. In addition, 60% thought that the currently available pharmacologic agents were inadequate. One explanation for the high rate of dissatisfaction among physicians is that they tend to see more refractory patients.

TREATMENT OPTIONS

An overall approach to managing chronic constipation is illustrated in Figure 2. Patients presenting with constipation should be evaluated for “red flags” (e.g., rectal bleeding, significant unexplained weight loss, family history of colon cancer, and new onset of symptoms in an older individual) to exclude secondary causes of constipation. Patients with red flags should be referred for appropriate diagnostic tests. For patients with no red flags, however, treatment options include lifestyle modifications (e.g., exercise, and increasing fiber and fluid intake) and those involving pharmacologic agents such as OTC laxatives and prescription drugs. Other options, such as herbal products, enemas, biofeedback, and surgery, are not discussed in this article. The first-line therapy is generally lifestyle modifications. If these fail, then starting pharmacologic agents is appropriate. The choice of agent will vary, depending on the patient’s clinical picture and costs.

LIFESTYLE MEASURES AND FIBER SUPPLEMENTATION

Treatment of chronic constipation begins with lifestyle modification. Patients should be encouraged to increase their intake of dietary fiber and fluid, engage in regular exercise, and set aside adequate time for bowel movements.

The recommended amount of fiber in the diet is 25 to 30 g per day. The average fiber intake in the United States is only 8 to 12 g per day. Commercial fiber supplements may also be used if patients cannot supplement their diets with extra dietary fiber. Commercially available fiber supplements include psyllium, methylcellulose, calcium polycarbophil, and guar gum. The typical starting dose is 4 to 6 g per day. The amount should be gradually increased as tolerated until the recommended intake of 20 to 25 g per day is reached. Psyllium and guar gum are natural products and appear to be effective, but they are associated with increased gas and bloating. In contrast, methylcellulose, which is semisynthetic, and polycarbophil, which is completely synthetic, produce less gas and bloating, but they are also less effective.

Setting aside sufficient time for bowel movements is often overlooked in the treatment of constipation. To take advantage of the gastrocolonic response, which is greatest in the morning, patients should attempt to set aside time in the morning after breakfast to defecate. Unfortunately, many people with constipation miss this opportunity because they are in a hurry to get to work, take the children to school, or run errands.

Another lifestyle measure that may be helpful is elevating the feet approximately 6 to 12 inches while
sitting on the toilet. This position helps to straighten the anorectal angle, thereby facilitating defecation. If these measures fail, OTC laxatives and prescription agents can be used. OTC agents include osmotic laxatives such as magnesium and phosphate salts; stimulant laxatives such as bisacodyl, castor oil, senna, and frangula; and poorly absorbed sugars such as sorbitol. Osmotics containing magnesium and phosphate salts, however, should be avoided in patients with electrolyte abnormalities or renal insufficiency.

In addition to these OTC agents, there are 2 osmotic prescription agents approved by the US Food and Drug Administration (FDA) for occasional constipation, and 2 nonosmotic prescription agents approved by the US FDA for chronic constipation. These agents are discussed in detail below.

**LACTULOSE AND POLYETHYLENE GLYCOL**

Lactulose and polyethylene glycol (PEG) 3350 are prescription osmotic laxatives that are approved by the US FDA for occasional or short-term constipation. Like osmotic agents that are available OTC, they increase the secretion of water into the intestine.

Lactulose is available in powdered form in 10- or 20-g packets of 30 and in liquid form (10 g/15 mL). It has been evaluated in 3 randomized, placebo-controlled trials, 2 of which were of high-quality design. All 3 trials favored lactulose versus placebo, with a significant improvement in stool consistency and a significantly higher mean number of bowel movements per day.

Initial dosing with lactulose may produce transient flatulence and intestinal cramps, and excessive dosage may lead to diarrhea and metabolic complications such as hypovolemia, hypokalemia, and hypernatremia. It is classified as Pregnancy Category B; meaning, no adequate, well-controlled studies in pregnant women show evidence of increased risk of fetal abnormalities.

PEG is indicated for the short-term treatment (ie, 2 weeks or less) of occasional constipation. It is supplied in powdered form for oral administration, and is available in a 14-oz or 16-oz container. PEG has been studied in 5 randomized, placebo-controlled trials and in 2 trials in which it was compared to lactulose. In the former group of studies, PEG increased stool frequency and improved stool consistency when compared with placebo. In the comparative trials, PEG produced looser stools, less frequent straining, and better overall effectiveness than lactulose.

As demonstrated in a recent study, PEG 17 g per day for 2 weeks was effective and well tolerated. However, there was no long-term holdover effect, with nearly 62% of patients participating in the study reporting that they needed laxatives 30 days after completing active treatment. High doses of PEG may produce diarrhea, excessive stool frequency, nausea, abdominal bloating, cramping, and flatulence.

PEG is classified as Pregnancy Category C; meaning, risk to the fetus cannot be ruled out because adequate, well-controlled human studies are lacking and/or because animal studies have shown risk to the fetus.

**TEGASEROD AND LUBIPROSTONE**

Tegaserod and lubiprostone are novel, nonosmotic prescription agents approved for the treatment of chronic constipation. Tegaserod, approved in 2004, is indicated in men and women younger than 65 years of age with chronic idiopathic constipation and in women with IBS-C. It is available as 2-mg and 6-mg tablets for oral administration. Lubiprostone, approved in February 2006, is indicated for chronic idiopathic constipation in adult men and women with no age restrictions. It is available as a gelatin capsule containing 24 µg of drug for oral administration.

Tegaserod is a 5-hydroxytryptamine4 (serotonin) receptor partial agonist that binds to receptors in the enteric nervous system. It accelerates gut transit by stimulating the peristaltic reflex, increases colonic motility, decreases visceral hypersensitivity, and facilitates secretion of fluid into the colonic lumen. As a partial agonist, it is not as potent as native serotonin, which is an important molecule in the gut. However, the drug augments peristalsis and is not associated with tachyphylaxis.

Lubiprostone is a chloride channel (CIC-2) activator and gastrointestinal-targeted bicyclic functional fatty acid that increases intestinal fluid secretion by selectively activating CIC-2 chloride channels. In addition, animal studies have shown that lubiprostone may restore mucosal barrier function.

Activation of the chloride channels leads to increased levels of negatively charged chloride ions in the lumen of the intestine. Positively charged sodium ions and increased amounts of water passively follow
into the lumen, thereby maintaining electrical and osmotic neutrality. Two large, 12-week studies comparing tegaserod 2 mg and 6 mg twice a day versus placebo have demonstrated that a higher percentage of patients with chronic constipation (Rome II) responded to both doses of tegaserod than to placebo (Table 1). Tegaserod, which is classified as Pregnancy Category B, was well tolerated, with the most common adverse events being diarrhea, abdominal pain, and nausea.

Studies evaluating lubiprostone in patients with chronic constipation (Rome II plus less than 3 bowel movements/week) have shown that it is effective and well tolerated. In a 4-week, placebo-controlled study involving 242 patients, lubiprostone 24 µg twice a day was significantly better at all time points than placebo with respect to bowel frequency, straining, and stool consistency (Table 2). In addition, twice as many patients receiving lubiprostone had a spontaneous bowel movement with the first 24 hours of treatment than those receiving placebo. The most common adverse event during the study was nausea, which led approximately 7% of patients to withdraw from the study.

Lubiprostone was also evaluated in a 24-week, open-label study in which patients were asked to assess severity of constipation, abdominal bloating, and abdominal discomfort at baseline and weeks 4, 8, 12, 18, and 24. By week 24, mean ratings improved from 3.1 (severe) at baseline to 1.5 (mild to moderate) for constipation severity; from 2.0 (moderate) at baseline to 1.0 (mild) for abdominal discomfort; and from 2.2 (moderate) at baseline to 1.4 (mild to moderate) for abdominal bloating.

Patients were also asked to assess treatment effectiveness at weeks 8, 12, 18, and 24. Here, too, mean ratings improved, from 2.2 at week 8 to 2.6 at week 24, with 2.0 being equivalent to “moderate” and 3.0 being equivalent to “quite a bit.”

Although lubiprostone is well tolerated, it is classified as Pregnancy Category C. Therefore, women of childbearing potential should have a negative pregnancy test prior to beginning therapy with lubiprostone and be compliant with appropriate contraceptive methods while on therapy.

### Table 1. Percentage of Patients Responding to Therapy with Tegaserod vs Placebo

<table>
<thead>
<tr>
<th>Response Rate</th>
<th>Study 1</th>
<th>Study 2</th>
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<tbody>
<tr>
<td>Tegaserod 2 mg BID</td>
<td>41%</td>
<td>36%</td>
</tr>
<tr>
<td>Tegaserod 6 mg BID</td>
<td>43%</td>
<td>40%</td>
</tr>
<tr>
<td>Placebo</td>
<td>25%</td>
<td>27%</td>
</tr>
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</table>

*Responders were defined by an increase of at least 1 spontaneous bowel movement per week and completion of at least 7 days of treatment.

BID = twice a day.

Data from Johanson et al; and Kamm et al.

### Table 2. Efficacy of Lubiprostone vs Placebo

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lubiprostone 24 µg BID</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous bowel movements/week (mean number)</td>
<td>1.5 at baseline 5.5 at 4 weeks</td>
<td>1.6 at baseline 3.0 at 4 weeks</td>
<td>P = .0002</td>
</tr>
<tr>
<td>Straining score</td>
<td>2.5 at baseline 1.6 at 4 weeks</td>
<td>2.5 at baseline 2.2 at 4 weeks</td>
<td>P &lt; .0001</td>
</tr>
<tr>
<td>Stool consistency score†</td>
<td>2.9 at baseline 1.9 at 4 weeks</td>
<td>2.6 at baseline 2.6 at 4 weeks</td>
<td>P &lt; .0001</td>
</tr>
<tr>
<td>Spontaneous bowel movement in first 24 hours</td>
<td>61.3%</td>
<td>31.4%</td>
<td>—</td>
</tr>
</tbody>
</table>

*Straining score: 0 = absent; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe.
†Consistency score: 0 = very loose; 1 = loose; 2 = normal; 3 = hard; 4 = very hard (little balls).

BID = twice a day.

Data from Johanson et al.

### Conclusions

Patients with chronic constipation should be evaluated according to the approach outlined in Figure 2. If red flags and/or secondary causes have been identified, the patient should be referred for the appropriate diagnostic tests and treated empirically with fiber, osmotic laxatives, stimulant laxatives, tegaserod, or...
lubiprostone as necessary. Empiric treatment with these options also applies to patients with no red flags or apparent secondary causes. Most experts recommend increasing dietary fiber and fluid intake as the first treatment step.

It is important to keep in mind that chronic constipation is a common condition that imposes significant burdens on the patient and the healthcare system. It also has adverse effects on quality of life. New agents such as tegaserod and lubiprostone, in addition to investigational therapies with novel mechanisms of action, represent new options for the pharmacologic management of chronic constipation and additional opportunities for pharmacists to provide even better patient care.

QUESTION & ANSWER HIGHLIGHTS
OSMOTIC AND STIMULANT LAXATIVES

Q: How long does it take for an osmotic laxative to work?

Dr Lembo: Osmotic laxatives usually take approximately 3 days. Because they are not absorbed, they stay in the gut and mix with the stool. If there is a lot of stool, it will take an osmotic agent a few days to work its way around.

Q: How do stimulant laxatives work and what are the long-term side effects?

Dr Lembo: Stimulant laxatives cause the bowel to contract through direct effects on neurons. They cause spasms in the bowel. They generally work quickly, oftentimes within hours. However, they frequently cause abdominal cramping and diarrhea. There is no evidence that stimulant laxatives cause damage to the colon even when used for a prolonged period of time.

Q: What if the patient wants to use these agents long-term?

Dr Lembo: There is no evidence, in animals or humans, that they cause long-term problems. Dependence, of course, is another issue, and you have to ascertain why the patient is taking a stimulant laxative in the first place. Patients with anorexia sometimes take large amounts of bisacodyl because of the perception that it reduces food absorption and promotes weight loss. That kind of abuse gives stimulant laxatives a bad reputation and obscures the value of these agents in patients who are constipated because of lost colon function.

Another scenario is the patient who takes laxatives when they are not really necessary and then cannot stop using them. Although there is considerable debate as to whether this is dangerous, human and animal data suggest that it is not. Although I generally do not switch patients who are unable to come off a stimulant laxative to another agent, I do recommend that they try to stop the medication periodically to see what happens.

Q: What if they are using high dietary fiber? Would you recommend that they stop?

Dr Lembo: No, not the dietary fiber. There is some evidence that supplemental fiber does more than increase colon transit. It may improve glucose control and potentially protect against diverticulosis.

SIDE EFFECTS AND OTHER ISSUES

Q: What can be done for the patient who needs a higher dose of lactulose but cannot tolerate the side effects?

Dr Lembo: The gas is bad with lactulose, especially at higher doses. The wrinkle here is that many patients will not tell you how bad it is unless you ask. I recently saw a patient who has been on high doses of lactulose for a long time. Only when I asked, “You must be gassy,” did she say that the gas was terrible and that she did not take her lactulose at all if she was going out. When I asked if anyone had suggested a switch to PEG, she said that no healthcare provider had ever offered it to her.

Q: Is PEG associated with less gas?

Dr Lembo: Yes, PEG does not cause as much gas and bloating because it is not digested or broken down by bacteria. Gas is created when bacteria break down sugars.

Q: Is it possible to predict who will respond to tegaserod?

Dr Lembo: It is unclear what the response rate will be. First, there is a strong placebo effect. Also, not everybody is going to respond, although it is unclear why.

Q: Have any of the therapies you have discussed been studied or used in the pediatric population?

Dr Lembo: There are few studies in children. This may change in the near future because the US FDA has mandated that more studies be performed in the pediatric population.
Q: Could you comment on methylaltrexone and other investigational agents?

Dr Lembo: Results from 2 studies evaluating alvimopan in chronic constipation were equivocal. One study was positive, one was negative, and neither was convincing.

Q: Does hydration make a difference in treating constipation?

Dr Lembo: Increasing dietary fiber and fluid intake is the first lifestyle modification that patients should implement to relieve constipation. Although dehydration can worsen constipation, this is rare in people with free access to water and are not taking diuretics or residing in a nursing home.

Q: What is your preferred approach to treating chronic constipation in people with diabetes?

Dr Lembo: Increased fiber intake; psyllium has been shown to increase the frequency of bowel movements and also help improve glucose control.

REFERENCES