NEW TREATMENTS FOR AN OLD PROBLEM:
CHRONIC CONSTIPATION*

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ABSTRACT

Commonly used first-line treatments for chronic constipation are simple: dietary fiber, fluids, exercise, and allocating time for defecation. Often, the patient will most likely have tried the first 3 treatments on their own. It is important to document what has been tried and the results. This article describes the recommended treatments for chronic constipation once the patient presents to a healthcare provider for this problem. Frequently recommended treatments include medicinal fiber supplements, bulking agents, stool softeners, and laxatives. Two prescription treatments, tegaserod and lubiprostone, are available. Study results have proven that these treatments have shown good efficacy and tolerability. A brief review of those study results is included in this article, in addition to a discussion of when to refer a patient to the gastroenterologist and the management of pelvic dyssynergia. (Adv Stud Med. 2006;6(10B):S962-S967)

Patients suffering from chronic constipation are often willing to try almost anything to relieve their pain and discomfort. However, first-line treatments for constipation are, in fact, simple: increased dietary fiber, fluids, exercise, and allocating time to have a bowel movement. The patient will most likely have tried the first 3 treatments on their own. As Julia Pallentino, MSN, JD, ARNP-BC, notes in this monograph, it is important to document what has been tried and the results. On the other hand, allocating sufficient time for a bowel movement is often not considered, but is a common remedy for chronic constipation. The best time for a bowel movement is in the morning, after breakfast, when digestive stimuli prompt the urge to evacuate the bowels. If that urge is ignored, it tends to diminish over time. Scientific evidence showing that these simple treatments (other than increased dietary fiber) are effective is lacking, but this has not diminished their popularity or usefulness.

Fiber consists of the long-chain polysaccharides and several other plant components, such as cellulose, lignin, and waxes, which are not digested in the human stomach or small intestine. If the patient is not consuming sufficient fiber (>20 g daily), he should begin with lower doses (4–6 g daily) of dietary fiber (eg, bran), or medicinal fiber (eg, psyllium), and increase it gradually to avoid bloating and flatulence. The digestive tract needs time to adjust to the increase in fiber intake. There are many types of medicinal fiber supplements available: psyllium, methylcellulose, calcium polycarbophil, and guar gum. The total recommended daily intake of fiber (diet + supplementation) is 20 to 25 grams, but could be increased to 30 grams, if necessary.† Several Web sites provide the fiber content for different foods (Table 1); this information is also available on the nutrition labeling of products.

Bulking agents are poorly absorbed agents that act
by absorbing liquids in the intestines. The ingested bolus then swells to form a soft, bulky stool, which prompts a bowel movement. Psyllium and most other fiber supplements are bulking agents; they improve bowel frequency and consistency. Several studies have shown the efficacy of bulking agents for relieving chronic constipation. Unfortunately, the studies were not ideally designed, so the American College of Gastroenterology (ACG) Task Force gave psyllium only a Grade B recommendation.²

Stool softeners are often the second treatment patients try after bulking agents. Stool softeners are minor laxative agents that modestly reduce fluid absorption and thereby prevent dry, hard stools from forming. These products decrease the need for straining and facilitate the ability to evacuate the bowel. However, they may not be as effective as psyllium for increasing stool frequency. Although scientific studies show only minimal effects on stool frequency, many patients have had great success with stool softeners.²

There are several types of laxatives. Osmotic laxatives promote retention of water within the bowel lumen, softening the stool and increasing bowel actions. Saline laxatives, nonabsorbable sugars or sugar alcohols, and certain polymers constitute the 3 types of osmotic laxatives. Examples of saline laxatives include magnesium hydroxide (milks of magnesia), magnesium citrate, and sodium phosphate. Of note, although there is insufficient scientific evidence to support a recommendation for using magnesium hydroxide for chronic constipation, many patients try it because it is promoted as a more gentle treatment that works overnight. The taste of milk of magnesia is an issue for many patients and some claim that it stops working after a while, although it is not clear why this occurs. Other patients prefer poorly absorbable sugar and sugar alcohol laxatives (eg, lactulose, sorbitol, mannitol, and lactitol). Even though these agents increase stool frequency and consistency, excessive flatus produced by bacterial metabolism of these fermentable substrates in the colon limits their acceptance. The most widely prescribed osmotic laxative is the polymer laxative, polyethylene glycol, which is effective for the relief of constipation (Grade A recommendation).² Any osmotic laxative can create fluid or electrolyte abnormalities if used inappropriately and may cause hypovolemia or diarrhea.²

Stimulant (irritant) laxatives act on the intestinal wall, stimulating secretion of water and salt by the mucosa, in addition to increasing muscle contractions to move the stool. As a result, these products may induce cramping and discomfort associated with bowel movement and occasionally cause electrolyte imbalances. Allergic reactions complicate the use of some of the plant-based products. Therefore, they should be used for short-term relief, rather than as a long-term solution to a chronic problem.²,³

The only lubricant laxative is mineral oil, which coats the bowel and is incorporated into the stool mass, keeping it soft and easing passage through the digestive tract. It is sometimes used as an acute treatment for children, less so with adults. Aspiration of mineral oil may lead to a lipid pneumonia that may be difficult to treat.

In general, regular intake of currently available laxatives is considered unlikely to be harmful to the colon and data do not support a potential for addiction.² However, although laxative preparations are effective for short-term relief, they tend to cause unpleasant side effects that preclude their long-term use.²,³ The ACG Task Force specifically recommended psyllium, stool softeners, polyethylene glycol, and lactulose for use as laxatives, citing insufficient data to make recommendations for any other laxative treatments.²

### Table 1. Web Sites Listing the Fiber Content of Common Foods

<table>
<thead>
<tr>
<th>Web Site Description</th>
<th>URL</th>
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<tbody>
<tr>
<td>American Dietetic Association, Fiber Facts</td>
<td><a href="http://www.eatright.org/cps/rde/xchg/ada/hs.xsl/nutrition_5440_E">http://www.eatright.org/cps/rde/xchg/ada/hs.xsl/nutrition_5440_E</a> THROUGH HTML.htm</td>
</tr>
<tr>
<td>Continuum Health Partners, Dietary Fiber Chart</td>
<td><a href="http://www.wehealnewyork.org/healthinfo/dietaryfiber/fibercontentchart.html">http://www.wehealnewyork.org/healthinfo/dietaryfiber/fibercontentchart.html</a></td>
</tr>
<tr>
<td>Harvard University Health Services, Nutrition Know How</td>
<td><a href="http://hhs.harvard.edu/PDF/FiberContentNutritionFall2004a.pdf">http://hhs.harvard.edu/PDF/FiberContentNutritionFall2004a.pdf</a></td>
</tr>
<tr>
<td>The Mayo Clinic</td>
<td><a href="http://www.mayoclinic.com/health/fiber/NR00033">http://www.mayoclinic.com/health/fiber/NR00033</a></td>
</tr>
<tr>
<td>University of Arizona, College of Agriculture and Life Sciences</td>
<td><a href="http://cals.arizona.edu/pubs/health/azl127.html">http://cals.arizona.edu/pubs/health/azl127.html</a></td>
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Newer Treatments for Constipation

**Tegaserod**

Tegaserod was approved by the US Food and Drug Administration (FDA) in 2002, initially for irritable bowel syndrome (IBS) with constipation in women and then for chronic constipation in both men and women under age 65. Tegaserod acts by enhancing the peristaltic reflex (and thus moving the fecal bolus through the gastrointestinal tract) by mimicking serotonin. Tegaserod also may decrease visceral sensitivity, thus decreasing the amount of pain associated with IBS with constipation.

There are published large clinical trials showing the efficacy of tegaserod in chronic constipation. Tegaserod was significantly more effective than placebo in the percentage of subjects who met a difficult primary endpoint: increasing the number of complete spontaneous bowel movements per week by at least 1 over the first 4 weeks of treatment (Figure 1).

In both studies, patients were treated for 12 weeks and tegaserod produced a statistically significant improvement over placebo for the full 12 weeks of treatment (secondary endpoint) as well. On the basis of these studies, tegaserod was approved by the US FDA for treatment of chronic constipation in men and women younger than 65 years of age. Because the data were strong, the ACG Task Force gave tegaserod a Grade A recommendation for the treatment of chronic constipation.

Nonetheless, patients with chronic constipation typically have symptoms for more than 12 weeks; therefore, it is important to note how tegaserod works over a longer period of time. Shetzline et al recently presented the results of a long-term study of tegaserod in 111 patients who responded to tegaserod during the first 4 weeks of a 12-week study. During 13 additional months of treatment, symptom improvement was maintained in those who continued the medication.

It has been shown that tegaserod is well tolerated. During the 12-week studies, there was no rebound effect when tegaserod was discontinued over a 4-week withdrawal period. The most frequent side effect is diarrhea that typically lasts from 1 to 2 days when first starting the medication. In clinical trials, diarrhea occurred more frequently in the tegaserod-treated patients than the placebo-treated patients (6%–7% vs 2%–4%, respectively). It is helpful to warn patients about the possibility of an initial episode of diarrhea (which the patient may not mind after suffering from constipation). There are no clinically relevant drug-drug interactions with tegaserod, and no prolongation of QT intervals on electrocardiography. There is a precaution noted in the labeling for tegaserod regarding recently reported cases of ischemic colitis with tegaserod use: “[tegaserod] should be discontinued immediately in patients who develop symptoms of ischemic colitis, such as rectal bleeding, bloody diarrhea, or new or worsening abdominal pain.” However, a causal association has not been established, and the occurrence of ischemic colitis may be no higher with the drug than with the underlying condition alone.

*Figure 1. Responder Rates During the First 4 Weeks of 12-Week Studies of Tegaserod vs Placebo*

<table>
<thead>
<tr>
<th>Responders, %</th>
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<tbody>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Tegaserod 2 mg BID</td>
</tr>
<tr>
<td>Tegaserod 9 mg BID</td>
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*Adapted with permission from Johanson et al; Kamn et al.*
LUBIPROSTONE

Lubiprostone is indicated for the treatment of chronic idiopathic constipation in adults.11 It is a bicyclic functional fatty acid that selectively activates a specific subset of chloride channels on the cells lining the gastrointestinal tract (CIC-2 channels).12,13 It works locally from the intestinal lumen and does not have detectable systemic absorption. Importantly, it is not a prostaglandin and does not activate prostaglandin receptors. The activation of chloride channels by lubiprostone enhances fluid secretion into the intestine, which promotes spontaneous bowel movements, softens the stool, and reduces abdominal discomfort/pain and bloating.14,15

Lubiprostone has been studied in 2 large clinical trials. Patients taking 24 mg of lubiprostone twice a day with meals had significantly more spontaneous bowel movements per week than those receiving placebo, starting at week 1 and continuing through week 4 (Figures 2A and 2B).16,17 Lubiprostone is equally effective in men and women and, importantly, is effective in elderly patients, based on pooled study results from the 2 studies.18,19 Elderly patients receiving lubiprostone 24 mg twice a day showed significant improvement in the number of spontaneous bowel movements during each of 4 weeks of treatment compared with those receiving placebo and they tolerated the drug well.18

The most common side effects with lubiprostone noted during clinical studies were nausea, diarrhea, and headache.15,20-24 Approximately 30% of patients experienced nausea with lubiprostone compared with approximately 5% of placebo patients. Nausea can be minimized by taking lubiprostone with food or by reducing the dose. Most study subjects tolerated the nausea in order to relieve their constipation; however, approximately 10% of patients discontinued lubiprostone because of nausea. Headache occurred twice as often in the lubiprostone patients compared with the placebo patients (13% vs 6.6%), and dizziness was more common as well (4% vs 1.3%).11 Lubiprostone does not cause any electrolyte imbalances or renal dysfunction, and systemic drug-drug interactions have not been a problem.25 Finally, the prescribing information suggests that lubiprostone be used only in women who are not pregnant (verified by a negative pregnancy test) because of the potential for fetal loss observed in guinea pigs that received lubiprostone.11

WHEN TO REFER TO A GASTROENTEROLOGIST

An accurate history, careful physical examination, and appropriate specialized investigations are essential for the diagnosis and selection of appropriate treatment for chronic constipation. If patients do not respond to treatment for chronic constipation, they must be referred to a gastroenterologist. Patients should also be referred if they present with new-onset constipation with any alarm symptoms, which are described in this monograph by Ms Pallentino in “New Thoughts About an Old Problem: The Impact and Diagnosis of

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**Figures 2A and 2B. Efficacy of Lubiprostone vs Placebo in 4-Week Studies**

- **A**
  - LUB: LUB = lubiprostone; FL: FL = placebo.
  - *P < .05 vs placebo; †P < .007 vs placebo; ‡P < .0004 vs placebo.
  - In these studies, 237 patients (A) or 242 patients (B) received oral lubiprostone 24 μg or placebo twice a day for 4 weeks, preceded by a 2-week drug-free washout period. Reprinted with permission from McKeage et al. Drugs. 2006;66:873-879.11
Chronic Constipation.” Additionally, if patients require high doses of medication to adequately treat the constipation, or if constipation is not alleviated with any of the recommended treatments, they should be referred to a gastroenterologist. Lastly, patients should be referred if they are thought to have pelvic floor dyssynergia, also known as functional outlet obstruction or anismus. In this condition, the pelvic floor contracts during attempted defecation, preventing opening of the rectal outlet.

When patients are referred, the gastroenterologist may perform a colonoscopy to exclude causes of secondary constipation, such as obstructing lesions, or any of several tests to discern the pathophysiology of constipation. In clinical practice, the most useful physiologic tests are anorectal manometry, balloon expulsion, defecography, and the colonic marker transit study.3,16

Anorectal manometry assesses several aspects of intrinsic and extrinsic anal sphincter function, in addition to providing clues to the movements of the pelvic floor and the function of associated nerves. Anorectal manometry provides important information regarding the pressures generated by the anal sphincters at rest and during maximum voluntary contraction, the presence or absence of internal sphincter relaxation during balloon distention, rectal sensation, and the ability to relax the anal sphincter during straining.3 In patients with constipation, this test is especially useful to look for pelvic floor dyssynergia.

The balloon expulsion test involves placing and inflating a balloon inside the patient’s rectum, usually to a volume of 50 mL. The patient is then asked to expel the balloon as if defecating. Most normal individuals can expel the balloon voluntarily within 60 seconds. This is a simple, office-based screening test to detect a problem with defecation.3

Defecography detects structural abnormalities of the rectum and provides clues to the presence of pelvic floor dyssynergia. It involves placing barium into the rectum, having the patient sit on a radiolucent commode, and using a fluoroscope to make a videotape from the lateral position as the patient is asked to hold stool, bear down while holding, and then release stool from the rectum. Observations include the patient’s ability to completely evacuate their bowels, measuring the anorectal angle, and detecting any structural abnormalities (eg, a rectocele). This test is useful when the radiologist is experienced in its performance and interpretation, but is subject to performance anxiety by the patient and misinterpretation by less experienced observers.3

Colonic marker transit studies are used to evaluate colonic transit time and are essential for the diagnosis of slow-transit constipation. For this study, patients ingest radio-opaque markers in a gelatin capsule; laxatives or enemas are prohibited and abdominal radiography is performed 120 hours later. If any of the markers remain in the intestine, slow-transit constipation is likely. This test should always be performed before considering surgery for chronic constipation.1

Patients with pelvic floor dyssynergia often benefit from biofeedback training. This approach emphasizes appropriate coordination of the muscles during defecation. A balloon is inserted into the rectum and inflated to simulate enough stool that would prompt the urge to evacuate the bowels. Patients are then asked to note how this feels and to relax the sphincter muscles and pelvic floor while contracting the diaphragm and abdominal wall muscles to increase intra-abdominal pressure. Relaxation and contraction are monitored by electromyography and the display is shown to the patient so that they can see what they are doing. Correct relaxation and contraction are reinforced by the therapist; thus, rapport with the therapist is critical to success of this treatment.1 Studies show that approximately 70% of patients with dyssynergic defecation have complete resolution of constipation with this treatment (P = .001) and the effects appear to be long lasting (up to 1 year).28,27 Of note, biofeedback only is effective in patients with pelvic floor dyssynergia, not in patients with slow-transit disorders.28 Unfortunately, there are only approximately 12 major motility centers in the United States that can perform this treatment effectively, so availability is limited.

CONCLUSIONS

Although chronic constipation can be an uncomfortable and embarrassing problem for the patient, there are many treatment alternatives. The healthcare provider can work with patients to counsel them about their treatment options and allay fears of more serious concerns (eg, cancer) once the appropriate diagnostic tests have been performed. Although patients often have tried many of their own treatment strategies by the time they enter the doctor’s office, it is important to document exactly what treatments have been tried
and the results. Initial recommendations involve increased dietary fiber, adequate fluid intake, exercise, and a dedicated time for bowel movements. Even when the patient maintains that they have tried numerous strategies, these treatments should be reviewed first. In addition to laxatives, there are 2 prescription treatments that offer significant improvement in constipation symptoms for numerous patients. Therefore, patients need not feel a sense of hopelessness or anxiety over this symptom.

REFERENCES