ABSTRACT

Patients with chronic constipation and irritable bowel syndrome (IBS) have a variety of potential treatment options. Treatment typically begins with lifestyle changes and fiber supplementation. The predominant lifestyle changes are alteration of fluid intake, dietary modification, and physical activity. Laxatives constitute the second line of therapy. Patients can avail themselves of various emollient, osmotic, and stimulant laxatives. Among all the laxative agents, the strongest supporting evidence is for lactulose and polyethylene glycol. These conventional therapies have highly variable rates of therapeutic success. Most patients cope with their symptoms and are less than completely satisfied with therapy. Newer therapies have provided additional options that may help improve symptom relief and patient satisfaction. The 5-HT4 serotonin agonist tegaserod has demonstrated efficacy for chronic constipation and constipation-predominant IBS and is approved for treatment of men and women with chronic constipation and for women with IBS. The chloride channel activator lubiprostone recently was approved for treatment of constipation in men and women. The 5-HT3 antagonist alosetron has approval for treatment of diarrhea-predominant IBS in women. A host of investigational agents are in various stages of evaluation and clinical development, many of which represent new approaches to treatment of chronic constipation and IBS.

CURRENT THERAPY FOR CHRONIC CONSTIPATION

TRADITIONAL APPROACHES

In most cases, the discussion of therapeutic options for chronic constipation begin with lifestyle factors and fiber supplements. Much has been made of the role that lifestyle changes can play in the management of chronic constipation, but the reality is that these interventions, such as increased fluid intake, dietary modification, and exercise, have limited support. The
data indicate that fluid intake is helpful only in patients who are clinically dehydrated. Most patients think dietary modification plays a major role in management of constipation, but the evidence shows that diet works in a select group of patients—namely those individuals whose diets are woefully deficient in fiber. Much like diet, exercise often is viewed by patients as quite helpful to bowel function, but available data suggest that exercise has limited beneficial effects on gastrointestinal function, with 2 possible exceptions. First, increasing physical activity in sedentary elderly patients can improve bowel function, and second, marathon runners often have diarrhea.

After lifestyle factors, the next step in therapeutic decision making usually involves the use of fiber. When the ACG reviewed available therapies, sufficient evidence existed to give psyllium a Grade B recommendation. Psyllium has been shown to increase stool bulk and decrease transit time. The same may be true for products, such as calcium carobophil, methylcellulose, and bran, but the data supporting their use range from limited to nonexistent.

The second major category of treatments is comprised of laxatives, which can be divided into 3 categories: emollient, osmotic, and stimulant. Emollient laxatives include docusate sodium and docusate calcium. The ACG found enough evidence to give emollient laxatives a Grade B recommendation. An emollient may help soften stool, but evidence is lacking to support its use as sole therapy for chronic constipation. If fiber and stool softeners fail to improve constipation, the next therapeutic tier is often osmotic laxatives, which include milk of magnesia, citrate of magnesia, nonabsorbed sugars (ie, sorbitol and lactulose), and polyethylene glycol (PEG), which is a nonabsorbed polymer. Osmotic agents increase stool bulk and intestinal fluid volume. Overall, the evidence supporting the use of most of these agents was only of Grade B quality. Exceptions were lactulose and PEG, which received a Grade A recommendation for treating constipation. Lactulose works primarily by creating an osmotic load. Many patients experience a great deal of abdominal discomfort and gas as side effects of this agent. PEG also creates an osmotic load, but is approved by the US Food and Drug Administration (FDA) only for the short-term treatment of constipation (ie, <2 weeks). When patients do not improve with emollient or osmotic laxatives, stimulant laxatives are often the next course of action. Stimulant laxatives decrease water absorption and may influence the production or activity of kinases, adenosine triphosphatases, and prostaglandins to stimulate the intestine and promote bowel motility. These agents include senna, ricinoleic acid (castor oil), bisacodyl, and cascara. The ACG found evidence to support only a Grade B recommendation for stimulant laxatives.

The ACG did not evaluate other therapies for constipation, such as enemas (ie, tap water, phosphate, or mineral oil) or suppositories (ie, glycerin), which also are used with some frequency in the management of chronic constipation.

To summarize, laxative therapy in the treatment of chronic constipation is of variable efficacy and often has not been thoroughly evaluated, as reflected in the ACG’s preponderance of Grade B recommendations for most of these medications. Laxatives are generally recommended for short-term use, and they can cause side effects that limit their effectiveness, including bloating, cramping, diarrhea, and metabolic disturbances (ie, hypercalcemia, hyperphosphatemia, hyponatremia, and hypokalemia).

Overall, the conventional or traditional approaches to treatment of chronic constipation result in variable treatment responses. Treating constipation is not just about the frequency of bowel movements and most therapies have not been evaluated for their ability to treat the constellation of constipation symptoms, such as straining or bloating.

Table. Systematic Review of Chronic Constipation in North America

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<tr>
<th>Levels of Evidence/Grading of Recommendations</th>
<th>Description</th>
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<tr>
<td>Level I</td>
<td>Data based on high-quality, randomized, placebo-controlled studies.</td>
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<td>• Grade A recommendation</td>
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<tr>
<td>Level II</td>
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<td>Level III</td>
<td>Data based on nonrandomized studies</td>
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<td>Level IV</td>
<td>Data based on case controls or anecdotal experience</td>
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Adapted with permission from Brandt et al. Am J Gastroenterol. 2005;100:S5-S22.
Current treatment options for constipation have several limitations. In some instances, they can actually worsen constipation symptoms, such as bloating, gas, cramping, and abdominal pain or colic. Some of the treatments are associated with potential complications that include diarrhea, hypovolemia, and metabolic disturbances. Other potential adverse effects include interference with concomitant drug absorption, structural changes in the gut mucosa, and abuse potential. Conventional therapies for chronic constipation also tend to have a diminished therapeutic effect over time.6-12

Not surprisingly, many patients are not satisfied with available treatments for constipation. When asked to rate their satisfaction with treatment, between 33% and 50% of patients with constipation say they are not satisfied with their current treatments. The reasons for dissatisfaction tend to have more to do with lack of efficacy than with side effects.13,14

OTHER TREATMENT OPTIONS

Fortunately, newer treatment options for chronic constipation have become available or are being developed. One in particular, tegaserod, received a Grade A recommendation from the ACG. A serotonergic agent, tegaserod is a 5-HT 4 agonist that has US FDA approval for treatment of chronic constipation and constipation-predominant IBS (IBS-C). Tegaserod is a new class of compounds, called an aminoguanidine indole—a partial 5-HT4 agonist—which works through the 5-HT4 receptor to stimulate the peristaltic reflex and accelerate oral-cecal transit.15

Tegaserod is indicated for treatment of men and women with chronic constipation. The recommended dosage is 6 mg orally, twice daily, 30 minutes before meals. Tegaserod is recommended for men and women aged 65 or younger for chronic constipation. No dose adjustment is required for older age, mild hepatic impairment, or mild-to-moderate renal impairment.16

In 2 pivotal clinical studies involving patients with chronic constipation, tegaserod was compared to placebo with respect to complete spontaneous bowel movements (CSBM) over 12 weeks. Patients treated with tegaserod had significantly more CSBMs. Notably, in 1 of these trials, patients were followed after the drug was withdrawn, and it is important to note that once the drug was withdrawn, the number of CSBMs also decreased. Patients also had decreased straining and greater global relief of symptoms.17,18

Tegaserod has proven to be a safe drug to use for treatment of chronic constipation. It causes more diarrhea compared to placebo, but the diarrhea tends to occur during the first week of treatment and often resolves with continued therapy. The incidence of headache, including migraine, is similar between tegaserod and placebo.

Previously, the use of the agent cisapride, a combined 5-HT4 and 5-HT3 agonist, caused some concern related to the potential for induction of cardiac arrhythmias. That has not been the case with tegaserod. Tegaserod also can be safely used in conjunction with selective serotonin reuptake inhibitors (SSRI).19 This drug requires no dosage adjustment when used with other medications, and no clinically relevant drug interactions have been identified.

Other medications for chronic constipation consist largely of therapies developed for other indications (eg, colchicine and misoprostol). These are generally reserved for severely constipated patients and carry with them several potentially serious side effects.

For selected patients with severe colonic inertia, surgery is an option. To be a surgical candidate for chronic constipation, a patient must meet stringent criteria, including clear failure of other forms of medical therapy.

Agents that are being investigated as potential therapies for constipation include the chloride channel activator, lubiprostone. Granted US FDA approval in early 2006 for the treatment of chronic idiopathic constipation, lubiprostone works on the chloride channel on the apical side of the mucosal epithelial cell to increase fluid in the stool, allowing for more spontaneous bowel movements, which reduces abdominal pain, discomfort, and bloating and softens the stool. Other investigational agents for constipation are the combination 5HT4 agonists and 5HT3 antagonists, renzapride and mosapride, and the opioid antagonists, methylaltrexone and alvimopan. Lastly, neurotropic factors, which stimulate nerve activity or growth, have been evaluated as therapy for chronic constipation. Neurtrophin-3 was originally evaluated as a treatment for Alzheimer’s disease and Parkinson’s disease. Patients treated with the agent often developed diarrhea, which led to investigation of the agent as a treatment for constipation. Neurtrophin-3 appears to increase transit time, although the explanation for the effect remains unclear.

For patients with constipation as a result of pelvic floor dyssynergia, 2 types of training have been evaluat-
ed: anorectal biofeedback and simulated defecation. The former approach has been evaluated more thoroughly and has achieved success rates ranging from 48% to 62%.

TREATMENT OF IRRITABLE BOWEL SYNDROME

Management of IBS often has focused on specific symptoms, such as abdominal pain, bloating, and diarrhea or constipation. In general, patients have not achieved global relief of their complaints with such a symptom-driven approach. One recent survey of more than 5000 patients with IBS showed that 80% of the patients were receiving traditional medications, but only 14% were completely satisfied with their treatment. Satisfaction with relief of specific symptoms varied between 10% and 19%.

The ACG conducted a systematic review of IBS diagnosis and treatment in North America and provided graded recommendations, similar to those assigned in the review of therapies for constipation. Essentially, the review identified evidence that could support no more than a Grade B recommendation for most of the therapies used to treat IBS, indicative of intermediate-quality, randomized controlled trials with plus/minus statistical significance. The review encompassed the most widely used IBS therapies, including bulking agents, antispasmodics, behavioral therapy, and tricyclic antidepressants (TCA; Figure).

Again tegaserod has been given a Grade A recommendation for the treatment of IBS-C. For patients with IBS, the treatment has US FDA approval only for women at a dosage of 6 mg twice daily, taken 30 minutes before breakfast and dinner for a 4-to-6 week period. For patients who respond to this as an IBS therapy, an additional 4 to 6 weeks of treatment can be considered. Efficacy data for tegaserod in IBS treatment have come primarily from 2 clinical trials. Results of those trials showed that tegaserod effectively relieved global and individual IBS symptoms, including abdominal pain/discomfort, bloating, and constipation. Efficacy was maintained over 3 months. The time to relief was rapid, beginning as early as day 1 for the symptom of constipation and within the first week for abdominal pain/discomfort. Symptom relapse with discontinuation of the drug was seen in the trials. Another trial demonstrated that when the drug is used for 12 weeks and then stopped for 4 weeks, symptoms are relieved when the drug is reinstituted.

The 5-HT₃ antagonist alosetron slows gut function to increase water absorption. It also decreases chloride secretion and also seems to affect mechanoelastic properties of the colon by increasing compliance. The drug is indicated only for women with severe diarrhea-predominant IBS who have chronic symptoms for at least 6 months and who have failed conventional therapy. The safety and efficacy of the drug in men was not shown in the initial pivotal phase III clinical trials. However a recent analysis of the data have shown a beneficial effect in men but not to the same extent as in women. Alosetron still has US FDA approval only for women, and the starting dosage is 0.5 mg daily to be slowly titrated as necessary up to 1 mg once or twice daily. In general, treatment should stop if the condition does not respond to 1 mg twice daily. Alosetron is currently under a restricted use program, requiring physician attestation to a proficiency in treating IBS. Additionally patients must be educated with regard to potentially serious side effects of the drug, because of adverse events reported after the drug’s initial US FDA approval. These events included chronic constipation and serious complications of constipation (eg, ileus, bowel obstruction, fecal impaction, colonic perforation, or toxic megacolon) in 1 in 1000 patients and ischemic colitis (≤1 in 1000).
Tricyclic antidepressants and SSRIs have been used in the treatment of IBS. Antidepressants likely exert their beneficial effects by several different mechanisms. They can have a central modulating effect on pain perception; they may modulate gut action, locally at the gut level or centrally; and lastly, they may exert their effects by treating underlying psychological disturbances, such as anxiety, depression, or somatization. Adherence and persistence with therapy have a strong influence on the success of treatment and data are stronger for TCAs than SSRIs.29,30

Drugs under investigation for IBS include the 5-HT3 antagonist and 5-HT4 agonist renzapride, the chloride channel activator lubiprostone, the 5-HT3 antagonist cilanestron, the benzodiazepine dextofisopam, and the neurokinin-3 antagonist talnetant.

Other agents under investigation as therapy for IBS include probiotics, particularly bifidobacteria,31 antibiotics, particularly rifaxamin,32 alternative therapies (ie, peppermint oil and herbal therapies), and nonpharmacologic therapies that include hypnosis, acupuncture, and cognitive behavioral therapies.

CONCLUSIONS

Most therapies for chronic constipation have Grade B recommendations, which reflect less-than-optimal supporting evidence. A select few, such as PEG, lactulose, and tegaserod, have Grade A recommendations. Most therapies have side effects that limit their use. A similar situation exists with respect to therapies for IBS. Tegaserod and alosetron are among the very few that have strong supporting evidence that warrant Grade A recommendations. Although several newer therapies work at serotonergic receptor sites, drug development is expanding to look at a variety of potential receptors sites. The therapeutic field for chronic constipation and IBS remains wide open for the addition of better tolerated, more effective therapies.

DISCUSSION

Dr Kalloo: Why should you ever use a Grade B drug? Why not just go straight to a Grade A drug?

Dr Harris: I don’t think that giving a drug Grade A or B recommendation is a reason to give therapy. The real reason for the grading is to determine the level of evidence available that supports the use of a particular therapy and to point out that perhaps we do need to have better studies and more data about the efficacy of a particular therapy. I think that many of the drugs are useful. Patients have found them useful for individual symptom relief. Unfortunately, we don’t have enough drugs that deal with global symptoms of relief of the abdominal pain, discomfort, change in bowel function, and bloating of patients with IBS. I think that’s also the other important point to understand—that the drugs that are given a Grade A recommendation usually offer more global relief of IBS or chronic constipation symptoms but the Grade A or B recommendation is not the reason for deciding whether to use it.

Dr Lembo: I feel exactly the same way. I think the lack of data doesn’t mean the data are negative.

Dr Kalloo: Isn’t it interesting that the lack of data seems to involve medications that have been around for a long time?

Dr Lembo: Right, because the studies haven’t been well conducted in large numbers. That’s why they’ve received a lower grade.

Dr Talley: That applies to all of our older medications. Think about digoxin. We didn’t really understand its role in heart failure until quite recently, in terms of the lack of decent clinical trials early on. But it does work and, in fact, we all knew that. It just took a long time to show it with the evidence.

Dr Kalloo: Amy, do you ever go with a Grade A drug first?

Dr Foxx-Orenstein: I go with lifestyle modification first, such as encouraging breakfast each morning to stimulate the gastrocolic reflex and morning bowel activity. I also may recommend a drug, depending on the severity of the condition and what they’ve been through before. I’ll almost always try to incorporate lifestyle changes to facilitate bowel activity.

Dr Kalloo: There are some extreme therapies, such as colchicine and surgery, used for chronic constipation. When do you decide on these nontraditional but more extreme drugs or surgery?

Dr Lembo: The patients fail other therapies. These are very refractory, usually very slow-transit patients who have failed all other medical therapies, usually in combination.

Dr Chang: I only send a patient for surgery for colonic inertia, not for IBS-C.

Dr Foxx-Orenstein: Surgery is absolutely the last resort.
REFERENCES


