International Foundation for Functional Gastrointestinal Disorders
IFFGD
700 W. Virginia St., #201
Milwaukee, WI 53204
Phone: 414-964-1799
Toll-Free (In the U.S.): 888-964-2001
Fax: 414-964-7176
Internet: www.iffgd.org

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Current Pharmacologic Treatments of Irritable Bowel Syndrome

By: Tony Lembo, M.D. and Rebecca Rink, M.S., Division of Gastroenterology, Beth Israel Deaconess Medical Center, Boston, MA

[This article reviews indications, methods of action, and side effects associated with commonly available agents used to treat IBS. Any product taken for a therapeutic effect should be considered as a drug. Use medications, whether prescription or over-the-counter, herbs, or supplements carefully and in consultation with your doctor or healthcare provider.]

Pharmacologic treatments for IBS are aimed at improving the predominant symptoms such as diarrhea, constipation, and abdominal pain. The most common classes of drugs currently used are laxatives, antidiarrheals, antispasmodics, and antidepressants.

Laxatives

A laxative is a medication that increases bowel function. There are four main classes of laxatives: fiber, osmotic laxatives, stimulant laxatives, and emollients. Because most current pharmacological treatments are aimed at improving only one IBS symptom, it is often necessary to use a combination of therapies for adequate treatment. (See Table 1)

Fiber – Dietary fiber should be the first treatment method tried for constipation-predominant IBS. A recent analysis of combined results from published independent studies (meta-analysis) found that fiber improves bowel function in IBS patients by easing stool passage and increasing satisfaction with bowel movements, but has no effect on pain. Side effects such as flatulence, distension, and bloating lead to low patient compliance with fiber supplementation, especially during the first several weeks of therapy. Controlled studies show that the minimum supplementation needed to significantly alter bowel function or transit time is 12 grams per day. To improve satisfaction and usage, individuals should gradually increase their dietary fiber intake to approximately 20 to 25 grams per day over several weeks. Initially, foods rich in dietary fiber should be increased. If results from this therapy are disappointing, then commercially packaged fiber supplements should be used. If fiber has been deemed ineffective by your doctor, osmotic or stimulant laxative therapy should be considered. Osmotic laxatives should be tried first since stimulant laxatives have the potential for abuse. There are no controlled trials with laxatives in patients with IBS.

Osmotic Laxatives – Osmotic laxatives are poorly absorbed compounds that cause an influx of water into the small intestine and colon, thereby increasing stool bulk. When the recommended dosage is used, it takes approximately 1 to 2 days for osmotic laxatives to take effect. The most common poorly absorbed ions used in laxatives are magnesium and phosphate.

When these laxatives enter the intestine, only a small percentage of magnesium or phosphate is actively absorbed. The remaining magnesium or phosphate in the intestine creates an osmotic gradient along which water enters the intestine. Phosphate is better absorbed in the intestine than magnesium, so it takes a substantial dose of phosphate laxative to induce the osmotic effect.

Nonabsorbable carbohydrate laxatives (sorbitol and lactulose) are partially broken down by bacteria into compounds that cause water to accumulate in the colon, which usually produces softer stools. These laxatives can cause bloating, abdominal cramping, and flatulence. Sorbitol, 70% solution, appears to be as effective as lactulose and is significantly less expensive. Polyethylene glycol produces less intestinal gas and causes less abdominal bloating and flatulence than other osmotic laxatives.

Osmotic laxatives may cause severe diarrhea and dehydration, which occur especially when used in excess. Rarely, electrolyte disorders or retention of too much fluid (volume overload) in the colon can occur. Therefore, physicians should carefully monitor osmotic laxative use in patients with kidney disease (renal insufficiency) or heart disease (cardiac dysfunction). The polyethylene glycol solution MiraLax® does not contain electrolytes and, therefore, is the preferred osmotic laxative for these patients.

Electrolytes are chemicals that break down into ions (atoms) in the body's fluids and are essential to regulating many body functions.

Stimulant Laxatives – Stimulant laxatives should be used sparingly and only when osmotic laxatives have been ineffective. They have a direct stimulating effect on the network of nerves in the large intestine and reduce absorption of water and electrolytes from gastrointestinal contents. Stimulant laxatives take effect within hours of ingestion.

Table 1

Examples of Commonly Used Laxatives
(For directions and proper dosage, talk to your physician)

AGENT	EXAMPLES OF BRAND NAMES
Commercial Fiber Products*	
Methylcellulose	Citrucel
Psyllium	Metamucil, Konsyl
Calcium polycarbophil	Fiberall, FiberCon, Equalactin
Osmotic Laxatives	
Poorly Absorbed Ions	
Magnesium hydroxide	Uro-Mag, Milk Of Magnesia
Magnesium citrate	Citroma
Sodium phosphate	Fleet Phospho-Soda, K Phos Neutral Tablets
Poorly Absorbed Sugars	
Lactulose	Enulose, Cephulac, Kristalose, Duphalac
Polyethylene glycol	MiraLax
Sorbitol solution (70%)	Cystosol, Minilax, Resulax, Sorbilax
Stimulant Laxatives	
Anthraquinones	
Senna	Perdiem, Senokot
Ricinoleic acid	
Castor oil	
Diphenylmethane derivatives	
Bisacodyl	Dulcolax, Correctol
Emollients (Stool Softeners)	
Docusates	Colace
Mineral oil	Fleet Mineral Oil

*Take with plenty of liquids.

Classes of stimulant laxatives include diphenylmethane derivatives and conjugated anthraquinone derivatives. A third type, castor oil, acts in the small intestine and can cause significant cramps and diarrhea.

Stimulant laxatives should be used with caution since they can cause dehydration and electrolyte disturbances. Anthraquinone derivatives are generally better tolerated than the other stimulant laxatives. To reduce their potency, anthraquinone derivatives can be combined with fiber (e.g., Perdiem = senna + fiber). This allows for a smaller quantity to be taken less frequently and is equally effective.

Emollients – There are two types of emollients: docusates and mineral oil. Docusates act by allowing a greater amount of water to enter the stool, thus softening it. They are generally well-tolerated but less effective than other laxatives. Mineral oil is a stool softener that coats the bowel and stool with a waterproof film. Moisture is then retained in the stool, making it softer and easier to pass. However, it should be used cautiously as an oral laxative in patients who have difficulty swallowing because if inhaled into the lungs (aspirated) it may cause inflammation (a lipoid pneumonia).

Antidiarrheals

The common classes of antidiarrheals used in IBS are those that bind to certain cells (μ opioid receptors) in the intestines (diphenoxylate, e.g., Lomotil, Lomocot; and loperamide, e.g., Imodium, Pepto Diarrhea) and those that bind internal bile acids (cholestyramine, e.g., Questran, Cholybar).

Loperamide appears to enhance the resting internal anal sphincter tone, which helps to improve stool leakage in IBS, especially at night. It does not, however, have any effect on abdominal pain or distention. Unlike diphenoxylate, loperamide (at standard doses) does not cross the blood-brain barrier and therefore has less potential for abuse (e.g., addiction). It is also longer acting than diphenoxylate. Diphenoxylate does cross the blood-brain barrier and has potential for abuse. Lomotil®, the most common form of diphenoxylate commercially available, contains atropine which acts to reduce its potential for abuse. The preventative use of the μ opioid receptor drugs – such as before social, work, or other important events – can reduce socially undesirable urges to defecate. However, they can also cause constipation. They should be used cautiously and discontinued if the constipation becomes significant.

Occasionally bile acid malabsorption caused by rapid small intestinal transit may contribute to diarrhea in patients with IBS. Cholestyramine is not absorbed in the body. By binding [attaching to] bile acid, cholestyramine reduces the bile acid present and decreases colonic secretion. Anecdotal evidence suggests that cholestyramine may be helpful for treatment of diarrhea in people after gallbladder removal, however no controlled studies have yet been reported.

Antispasmodics

Antispasmodics inhibit smooth muscle contraction in the gastrointestinal tract. There are three major classes of antispasmodics: anticholinergics, peppermint oil, and direct smooth muscle relaxants. (See Table 2)

Anticholinergics – Anticholinergics reduce spasms or contractions in the intestine and, therefore, have the potential to reduce abdominal pain. However, their efficacy in improving IBS symptoms has not yet been proven definitively.

The most commonly prescribed antispasmodics in the United States are dicyclomine, hyoscyamine, and clidinium (in combination with chlordiazepoxide hydrochloride (Librium) = Librax). Dicyclomine or hyoscyamine can be taken regularly (e.g., 30 to 45 minutes before a meal) or as needed to reduce pain. Hyoscyamine comes in easily dissolved tablets, which can be absorbed beneath the tongue and are effective within minutes. Levbid® is a long-acting

form of hyoscyamine, which can be taken only twice daily. Donnatal® is a combination of anticholinergics and phenobarbital. Due to its sedative potential, Donnatal should be used cautiously.

The most common side effects of anticholinergics are: headache, dizziness, blurred vision, difficulty urinating, decreased sweating, nasal congestion, stuffiness, rash or itching, or a dry mouth.

Peppermint Oil – Peppermint oil relaxes the intestine by preventing calcium entry into intestinal smooth muscle cells. Because calcium triggers the cascade of events leading to muscle contraction, the inhibition of calcium in the cells causes intestinal smooth muscle relaxation. A recent meta-analysis showed that in three out of five studies, peppermint oil was an effective IBS treatment. However, because of methodological flaws in many of these studies, further research must be done to fully understand the role of peppermint oil in IBS treatment.

Rarely, peppermint oil use can cause skin rash, headache, muscle tremor, loss of muscle coordination, slow heartbeat, and heartburn. It is best to use enteric-coated peppermint oil tablets because they decrease the side effects of nausea and heartburn. [Enteric-coated tablets are covered with a material to prevent or minimize dissolution in the stomach so that the tablet dissolves in the small intestine.]

Direct Smooth Muscle Relaxants – Smooth muscle relaxants are not currently available for use in the United States. However, a recent meta-analysis concluded that smooth muscle relaxants significantly improve patients' overall well-being (global assessment), pain, and abdominal distention. The direct smooth muscle relaxants found to be effective are: cimetropium bromide, mebeverine, otilonium bromide (octilonium), pinaverium bromide, and trimebutine.

Side effects with smooth muscle relaxants appear to be rare: the meta-analysis showed that there was no significant difference in adverse effects between the subjects taking muscle relaxants and those taking placebo.

Antidepressants

Tricyclic antidepressants (TCAs) are effective in relieving pain in a number of chronic pain syndromes, including IBS. Desipramine (Norpramin) and amitriptyline (Elavil) have been the most thoroughly studied of the TCAs.

Selective serotonin reuptake inhibitors, as well as antidepressants which have unique properties (both serotonin and monoaminergic receptor activity) also appear to be effective in treating chronic pain syndromes, although they have not yet been studied in randomized placebo controlled trials in functional gastrointestinal disorders.

The benefit of antidepressants in chronic pain conditions appears to be independent of improvement of mood or decrease in anxiety.

Table 2
Examples of Antispasmodics. (For directions and proper dosage, talk to your physician.)

AGENTS	EXAMPLES OF BRAND NAME
Anticholinergics	
Dicylomine	Bentyl, Bemote
Hyoscyamine	Levsin, NuLev, Levbid
Propantheline bromide	Pro-Banthine
Mebeverine	Colofac (Australia)
Cimetropium bromide	Alginor (Italy)
Cimetropium bromide + chlordiazepoxide hydrochloride (Librium)	Librax, Clindex
Hyoscyamine +scopolamine, atropine, phenobarbital	Donnatal
Peppermint Oil	Elanco (Enteric coated), Peppermint Spirits
Direct Smooth Muscle Relaxants	
Pinaverium *	Dicetel (Canada)
Octilonium bromide *	Citanest Octapressin (Italy, Mexico, Sweden, Norway, others)
Mebeverine *	Colofac (Australia)
Trimebutine *	Modulon (Canada)
Cimetropium bromide *	Alginor (Italy)

* Not available in the United States.

Antidepressants are sometimes used in the treatment of chronic pain associated with IBS because of an effect they have on neurotransmitters that play a role in modulating pain (analgesic effect). The analgesic effect of these drugs may occur in lower dosages than when used for treatment of depression. *Neurotransmitters* are chemicals in the nervous system that help transmit messages by stimulating cells. Each cell contains a structure called a *receptor* that selectively receives and binds a specific substance, such as a neurotransmitter. After transmitting their message, the chemical neurotransmitters are taken up again by nerve endings (a process called reuptake), broken down, and inactivated. Inhibiting *reuptake* prolongs the action of the neurotransmitter.

TCAs are thought to work by blocking presynaptic reuptake of the neurotransmitters serotonin and norepinephrine ("adrenaline"), and to a lesser extent dopamine, in the body's internal (endogenous) pain inhibitory system. In treating IBS, the starting dose of a tricyclic antidepressant should be low. A recent meta-analysis of 11 randomized double-blind placebo controlled trials concluded that antidepressants are effective in reducing the symptoms associated with IBS and with functional gastrointestinal disorders in about one third of patients.

Another study, which was a 5-year retrospective review of antidepressant use in 138 patients with IBS in a specialized (tertiary) gastroenterology clinic, found overall improvement in 89% of patients and remission of symptoms in 61% of patients. In descending order of frequency the antidepressants used in this study were amitryptiline (Elavil), doxepin (Sinequan), amoxapine (Asendin), trazodone (Desyrel), and imipramine (Tofranil). Eighty-one percent of patients with pain-predominant IBS showed improvement, compared to a 60% response rate in patients with diarrhea-predominant IBS and a 50% response rate in patients with constipation-predominant IBS.

The side effects of TCAs differ significantly. Care should be taken to choose the appropriate TCA for specific individual characteristics. The drugs can sedate, stimulate the appetite, cause urinary retention, blurred vision, and constipation. Elderly patients may develop confusion, delirium, or loss of balance, especially at higher doses. TCAs also have effects on the cardiac system; therefore, they are not recommended in patients with heart disease. Likewise, TCAs should not be used in individuals diagnosed with symptomatic enlarged prostates (prostatic hypertrophy), bladder control problems (neurogenic bladder), narrow-angle glaucoma, or dementia.

Selective serotonin reuptake inhibitors, or SSRIs, have fewer side effects than TCAs. The most common side effects associated with SSRIs are nausea, headaches, insomnia, and sexual dysfunction.

Medications that Treat Multiple Symptoms

Alosetron (Lotronex) is a medication, which blocks serotonin signals (5-HT3 antagonist) that transmit sensory information from the gut to the brain. Alosetron has been found to improve overall symptoms and quality of life measurements in women with diarrhea-predominant IBS. The drug has been FDA approved for the use in women with severe diarrhea-predominant IBS. It is only prescribed under restricted use due to rare but potentially serious side effects.

Lubiprostone (Amitiza) helps to promote secretion through chloride channels in the bowel which in turn promote peristalsis, the coordinated muscle contractions that propel content through the gastrointestinal tract. The drug is used to relieve abdominal pain, bloating, and straining and produce softer and more frequent bowel movements in men and women who have chronic functional constipation, and to treat irritable bowel syndrome with constipation in women who are at least 18 years of age. Amitiza works by increasing the amount of fluid that flows into the bowel and allowing the stool to pass more easily.

Future Treatments

Linaclotide is (a guanylate cyclase type-C, or GC-C, agonist) is drug being studied to relieve symptoms of abdominal pain, discomfort, bloating, and bowel symptoms in people who have irritable bowel syndrome with constipation, or chronic constipation. It has proved safe and effective in trials, but is not yet FDA or EMA approved. In studies, patients taking Linaclotide experienced improvement in multiple symptoms including pain or discomfort, bloating, and bowel function.

Recent clinical trials have shown that antibiotics, which reduce or alter the bacteria in the gut, may relieve certain symptoms of IBS. Rifaximin is an antibiotic currently under investigation for the treatment of non-constipation irritable bowel syndrome and IBS-related bloating. Rifaximin works by reducing or altering bacteria in the gut. In studies it has been found to improve IBS symptoms of bloating, belly pain, and diarrhea (watery or loose stools) after a 10–14 day course of treatment. It is only slightly absorbed in the gut and is generally tolerated well. Rifaximin is not yet approved by the FDA for the treatment of IBS.

Summary

There are currently many possible treatment choices for patients with IBS to try, and research is continually being done to find new effective medications. Nonetheless, many of the commonly used drugs to treat IBS have not been definitively proven to be superior to placebo. More recent improvements in the design of trials has yielded evidence to support the use of smooth muscle relaxants and antidepressants in pain-predominant IBS, use of the antidiarrheal loperamide for diarrhea, and the use of fiber for constipation. The emergence of combination medications, as well as new classes of drugs, will most likely enhance the efficacy of future IBS treatments.