



Current Pharmacologic Treatments for Adults with Irritable Bowel Syndrome

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International Foundation for Gastrointestinal Disorders (www.iffgd.org)

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

Irritable bowel syndrome (IBS) is a disorder characterized by two key elements:

- 1) an abdominal component generally described as pain/discomfort and
- 2) alterations in bowel, habits including changes in stool texture and/or frequency.

Changes in stool texture includes experiencing constipation, diarrhea, or both. Constipation is commonly defined as having 3 or fewer bowel movements (BMs) a week, and/or difficulty passing BMs. Diarrhea is defined as loose, watery, or frequent BMs. From the start, pharmacologic treatments for IBS have aimed at improving one of these two symptom profiles. Pharmacologic refers to the use of drugs and how they work. Still, our better knowledge of the causes of IBS has allowed us to develop treatments that improve both the pain and bowel issues. This Fact Sheet will review available treatments for specific and global (overall) symptoms. We will discuss the pros and cons of each of these treatments.

Indications are signs or symptoms that tell a doctor what tests or medications to consider.

A **therapeutic effect** is the healing or improvement of symptoms that results from therapy, medication, or other treatment.

Over-The-Counter (OTC) Laxatives for IBS with constipation (IBS-C)

A laxative is a drug that increases bowel function. There are many laxatives available without a prescription.

Those most commonly used types include:

- Osmotic - polyethylene glycol (PEG) 3350 (such as Miralax®)
- Stimulant - senna cascara, bisacodyl (such as Dulcolax®, Correctol®)
- Magnesium-based - milk of magnesia

Of these, only PEG 3350 has been evaluated in clinical trials in people with IBS-C. PEG 3350 has been shown to improve stool texture and frequency. Stool frequency is a term describing how often someone moves their bowels. This drug does not improve the abdominal pain/discomfort symptoms of IBS. In fact, many people

report an increase in their abdominal symptoms when taking this medication. The lack of overall IBS symptom improvement makes this less recommended as a treatment for IBS-C.

Common side effects include diarrhea, abdominal cramping, bloating, and nausea. In rarer cases, dehydration and electrolyte disturbances have occurred.

Over-The-Counter Antidiarrheals for IBS with diarrhea (IBS-D)

Antidiarrheals are drugs which slow gut transit. Transit refers to the amount of time it takes for materials to move through the gut. These also decrease intestinal secretion (movement of fluid into the intestines) and increase the amount of fluid that is reabsorbed by the gastrointestinal (GI) tract. Loperamide (Imodium®) is the most commonly used OTC antidiarrheal. This drug works by binding to μ -opioid receptors in the GI tract resulting in the changes mentioned above. Loperamide also appears to increase resting internal anal sphincter tone. The internal anal sphincter is a muscle around the

anus that controls when stool can pass through. The anus is the final portion and opening of the GI tract. Increased muscle tone here helps to reduce stool leakage in people with IBS-D. Similar to the OTC laxatives used to treat IBS-C, a few small studies have shown that loperamide solidifies loose stools and reduces the frequency of diarrhea. This drug has not been shown to have a beneficial effect on abdominal pain or discomfort. The inability of this drug to improve overall IBS symptoms makes it a less attractive treatment for IBS-D. The most common side effects associated with loperamide include abdominal pain and constipation which at times can be severe. If constipation develops, discontinue use of loperamide and contact your healthcare provider.

Therapies for Predominate Pain/Discomfort Symptoms:

Antispasmodics

Antispasmodics are drugs which inhibit smooth muscle contractions in the GI tract. There are three major classes of antispasmodics: anticholinergics, direct smooth muscle relaxants, and peppermint oil (to be discussed separately).

Anticholinergics – These drugs reduce spasms or contractions in the intestine. This provides the potential to reduce abdominal pain and discomfort. The most prescribed anticholinergics include hyoscyamine (Levsin®, NuLev®, Levbid®) and dicyclomine (Bentyl®). These can be taken daily or as needed. Each dose should be taken 30-60 minutes prior to a meal. Both drugs can be taken by mouth. Hyoscyamine is also available in a sublingual formulation. The sublingual form is placed under the tongue and allowed to dissolve there. Limited clinical studies suggest that these may improve pain (more specifically cramping) in people with IBS. Their efficacy for improving overall IBS symptoms has not yet been proven. As such, this makes them less attractive treatments for IBS. The most common side effects include headaches, dry eyes and mouth, blurred vision, rash as well as mild sedation or drowsiness. Overall, these side effects are minimal, making them quite safe to use.

Direct Smooth Muscle Relaxants – Smooth muscle relaxants are not currently available for use in the United States. These drugs appear more effective for treating overall IBS symptoms than the anticholinergics. The direct smooth muscle relaxants found to be effective include cimetropium, mebeverine, otilonium (available in Mexico), pinaverium bromide, and trimebutine. Side effects with smooth muscle relaxants appear to be rare.

Peppermint Oil – Peppermint oil is generally considered an antispasmodic as it shares similar properties with other medications. However, other traits make this particular agent unique. It causes smooth muscle relaxation by blocking calcium entry into intestinal smooth muscle cells. Calcium triggers muscle contraction, so the lack of calcium results in relaxing intestinal muscles. It also has anti-inflammatory, anti-gas, and anti-serotonergic properties. Serotonin is a chemical found in the gut that accelerates movement. Limiting the amount of serotonin in the gut may be more effective for people with IBS-D. Recent studies have shown that it can be used to treat both overall symptoms and pain. This treatment may also be used either daily or as needed. Peppermint oil can be found in the form of teas, drops, gels, and capsules. There have not been any specific trials comparing one form to another. Side effects are uncommon but can include heartburn and nausea. These may be reduced by using a coated form. Coated pills minimize the activity of the peppermint oil in the stomach (IBgard®, Pepogest®). Peppermint oil use can rarely cause skin rashes, headaches, or tremors. In clinical trials, these side effects do not occur more frequently in people taking peppermint oil than in those taking placebo. A placebo is a pill or treatment with no active ingredients.

Antidepressants/Neuromodulators

Antidepressants are neuromodulators which have the ability to impact nerve signaling. Communication between the GI tract and the brain and spinal cord is specifically affected. This nerve signaling is regulated by chemicals called neurotransmitters. These chemicals are released from nerves and bind to other nerves, muscles, and glands. The result impacts pain signaling and can potentially increase or decrease GI function.

These drugs often affect GI symptoms at lower dosages than used to treat depression or anxiety.

Multiple classes of neuromodulators exist. The ones most commonly used to treat IBS symptoms include the tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). There is some agreement across international guidelines that TCAs are effective for treating IBS; however, recommendations for using SSRIs remain conflicted.

There are multiple TCAs available. Those most commonly used include amitriptyline (Elavil[®]), nortriptyline (Pamelor[®]), imipramine (Tofranil[®]) and desipramine (Norpramin[®]). The choice in many instances is based on healthcare provider preference and possible side effects. The most commonly seen side effects include drowsiness and dry mouth. Dry eyes, blurred vision, urinary retention and constipation may also occur. Urinary retention refers to an inability to empty bladder well. People diagnosed with certain conditions should likely consider other treatment options. These include symptomatic enlarged prostates (prostatic hypertrophy), bladder control problems (neurogenic bladder), narrow-angle glaucoma, and dementia. Elderly patients may develop confusion or loss of balance, especially at higher doses. It is common to start with a low daily dose of the drug (e.g., 10 or 25 mg) and to take it before bedtime. This will help to avoid or reduce many of the more common adverse events. The dose can then be increased based upon its effectiveness and tolerance. Most healthcare providers will not prescribe dosages higher than 50-100 mg per day.

The most well studied SSRI drugs include citalopram (Celexa[®]), fluoxetine (Prozac[®]) and Paroxetine (Paxil[®]). Some healthcare providers also like to use sertraline (Zoloft[®]) given its anti-anxiety properties. Unlike the TCAs, these drugs are often used in doses similar to

those used to treat anxiety and depression (10-40 mg/day). The risk of side effects with these drugs are often milder than the TCAs. Common side effects of SSRIs include drowsiness, dry mouth, diarrhea,

headaches, blurred vision, and/or reduced sexual desire.

Direct Serotonin Agonists/Antagonists

Serotonin (5-HT) is involved in gut secretion, motility, and sensation. Motility is a term that describes the movement of food through the GI tract. Sensation refers to physical feelings. Serotonin receptors in the GI tract appear to be a good target for treating IBS symptoms. Currently two therapies are FDA approved for the treatment of IBS-C and IBS-D. These drugs, tegaserod and alosetron, are discussed below.

Tegaserod (Zelnorm[®]) works on the nerves and smooth muscles of the GI tract. It increases gut movement and intestinal secretions. In multiple studies it has been shown to improve pain and bloating. An increase in the number of bowel movements has also been shown. Tegaserod is only approved for women with IBS-C under the age of 65. The women must also have no history of ischemic cardiovascular events or more than one cardiovascular risk factor. The most common side effects associated with tegaserod include headaches (migraines), dizziness, back or joint pains. Abdominal symptoms may also occur and include pain, nausea/vomiting, and diarrhea. Tegaserod was first approved by the FDA for the treatment of overall IBS-C symptoms. The drug was voluntarily removed from the market in 2007. This was due to finding a small but increased risk of cardiovascular events such heart attack, stroke, and transient ischemic attacks. In April 2019, the FDA approved the re-introduction of tegaserod for women < 65 with IBS-C as previously described after subsequent studies failed to identify a major link between the drug and increased risks for cardiovascular events in this population. Alosetron (Lotronex[®]) delays gut movement and reduces pain. It was first approved by the FDA for the treatment of overall symptoms of IBS-D in women. This

The Food and Drug Administration (FDA) is one of the U.S. government's regulatory agencies. This agency oversees a broad range of topics that pertain to food, drugs and other products used on a daily basis.

The FDA works to protect public health by assuring that foods and drugs for humans and animals are safe and properly labeled. The FDA also ensures that vaccines, other biological products, and medical devices intended for human use are safe and effective.

Products approved by the FDA have been deemed safe, with benefits that are worth the possible risks. This is done after reviewing studies and tests that have been done on a product.

drug was withdrawn from the market by the FDA in 2001. Alosetron was found to cause increased rates of severe constipation and ischemic colitis (decreased blood flow to the colon). The FDA re-introduced this drug in 2002 under a Risk Evaluation and Mitigation Strategy (REMS) program. Now, only women with severe IBS-D symptoms can be approved for this drug. Symptoms must limit their quality of life. To qualify, other conventional treatments must have been tried and failed. More recent studies have shown that rare cases of serious complications of constipation and ischemic colitis may still occur. Despite this it appears safe when prescribed within a small therapeutic window (0.5-1.0 mg twice-per-day). It should not be used as a first-line drug to treat IBS-D.

Prosecretory Agents/Secretagogues for IBS-C

Secretagogues/Prosecretory agents are a class of drugs which increase fluid secretion and movement in the GI tract. These drugs also can improve pain, discomfort, and bloating. Currently there are 4 FDA approved treatments in this class: lubiprostone, linaclotide, plecanatide, and tenapenor.

Lubiprostone (Amitiza[®]) works through the activation of chloride channels in the bowel. This leads to increased bowel movement frequency. While the direct mechanism of pain relief is not known, lubiprostone has been proven to relieve overall IBS symptoms in multiple trials.

It is currently FDA approved specifically for use in women. This is due to the limited numbers of men that were enrolled in the initial trials. This drug has proven to be effective in men as well. Common adverse events include nausea and diarrhea. Lubiprostone is also FDA approved for the treatment of chronic idiopathic constipation (CIC) and opioid induced constipation (OIC) for people with chronic non-cancer pain related illnesses.

Linaclotide (Linzess[®]) and Plecanatide (Trulance[®]) work by increasing fluid secretion and gut movement. Both have also been shown to reduce abdominal pain by decreasing activity of pain sensing nerves. Both drugs treat overall IBS-C symptoms and are FDA approved for

the treatment of IBS-C and CIC. Both improve abdominal and stool symptoms within the first week; however, their maximum effect on pain can take longer to appear. The most common side effect experienced by people taking linaclotide or plecanatide is diarrhea. These drugs have minimal systemic absorption, providing minimal risk of drug-drug interactions. Systemic absorption refers to a drug that takes effect on the whole body, rather than a specific area.

Tenapenor (Ibsrela[®]) promotes gut motility and secretion. Early trials with this drug suggest that it also reduces pain. It was approved by the FDA for the treatment of IBS-C in 2019. The most common side effects noted in clinical trials include diarrhea, abdominal distention, and flatulence. It is not currently commercially available in the United States.

Non-absorbable Antibiotics for IBS-D

Rifaximin (Xifaxan[®]) is the only antibiotic approved by the FDA for treatment of IBS-D. Its exact mechanism of action is unknown. Studies have suggested that it works by modifying bacterial structure or function in the gut potentially targeting the small intestine. It also appears to have anti-inflammatory properties. Rifaximin improves overall IBS-D symptoms. This drug differs from other IBS-D treatments as it is only taken for 2-weeks. If Rifaximin is beneficial, symptom relief should occur following the 2-week treatment. Symptoms may return after the initial treatment, and 2 successive treatments are allowed. It is minimally absorbed and generally well tolerated. The most commonly experienced adverse event is nausea.

Mixed Opioid Receptor Agonist/Antagonists for IBS-D

Eluxadoline (Viberzi[®]) is a drug which slows gut motility and reduces pain. It is FDA approved in adults for the treatment of overall IBS-D symptoms. It has also shown in clinical trials to be an effective treatment for people who have previously used and failed to obtain relief from loperamide (Imodium[®]). The most common side effects include constipation, nausea, and abdominal pain. It should not be used in people who do not have a gallbladder (e.g., previous cholecystectomy) or have a history of alcohol abuse (e.g. who drink more than 3

alcoholic beverages per day). These factors increase the risk of developing liver and pancreas complications.

Investigational Agents

Multiple other agents have been tested in small trials for the treatment of IBS.

- Bile-acid binding agents – These include cholestyramine, colestipol, and colesevelam. This group of drugs has been investigated for IBS-D. Symptoms are often similar between bile acid malabsorption (BAM) and IBS-D. Cholesterol is changed into bile acids by the liver. These acids are then absorbed back into the body in the colon. Sometimes, bile acids are not reabsorbed properly, leading to BAM. Too much bile acid in the colon can result in watery stool, urgency and fecal incontinence. This is why BAM is sometimes called bile acid diarrhea.
- Ondansetron (Zofran®) – This is a highly selective 5-HT₃ receptor blocker. It has also been evaluated for the treatment of IBS-D. While less studied, it appears to work like alosetron without the increased risk of severe constipation or ischemic colitis.
- Pregabalin (Lyrica®) - This is a calcium channel α_{2δ} ligand. Pregabalin has been shown to improve pain, bloating and diarrhea symptoms in a small study of IBS patients.
- Fecal microbial transplants (FMT) - FMT is not specifically a drug, but a treatment. These are also being studied for the relief of IBS symptoms. A recent analysis of 3 studies offered conflicting results. This suggests that the bacteria used, route

of administration of the bacteria, and specific IBS subtype may all play a role in symptom response. Fecal transplants are not currently recommended for treating IBS symptoms.

- Cannabinoids: There is currently no data to support the use of cannabinoids for treating IBS.

Common Therapies with Proven Efficacy for Global IBS Symptoms (Based on Use in Most Common IBS Subtype)

IBS-C	IBS-D
Plecanatide*	Eluxadoline*
Linaclotide*	Rifaximin *
Lubiprostone*	TCAs
Tegaserod*+	Alosetron*^
Tenapenor*	Peppermint Oil
SSRIs	

*denotes FDA approval; + approved for women with IBS-C under the age of 65 without history of cardiovascular disease; *^ approved for women with severe IBS-D when other agents have failed

Summary

Advancements in our knowledge of the causes of IBS continues to lead to many more effective treatment options. This is accomplished through research and rigorous clinical trials. Treatments can now improve both the pain/discomfort and bowel symptoms experienced by people with IBS. Nonetheless, there is no cure for IBS. It can be difficult to determine which therapy will provide the best efficacy in a patient with IBS. Choosing an appropriate treatment should be a decision made between healthcare provider and patient. It is important to have an open discussion weighing the pros and cons of each therapy.

Societal Recommendations for Treatment of Adults with IBS

Therapeutic	American College of Gastroenterology (ACG)	American Gastroenterological Association (AGA)*	Canadian Association of Gastroenterology (CAG)
Linaclotide	Strong recommendation for use IBS-C	Strong recommendation for use IBS-C	Strong recommendation for use IBS-C
Plecanatide	Strong Recommendation for use IBS-C	Strong recommendation for use IBS-C	NR (Not available in Canada)
Lubiprostone	Strong recommendation for use IBS-C	Conditional recommendation for use IBS-C	Conditional recommendation for use IBS-C
PEG laxatives	Conditional recommendations against use IBS-C	Conditional recommendation for use IBS-C	Conditional recommendation against use IBS-C
Tegaserod	Conditional recommendation for IBS-C in women ≤ 65 with ≤ 1 cardiovascular risk factor after failing secretagogues	NR	NR
Rifaximin	Strong recommendation for use IBS-D	Conditional recommendation initial treatment; Strong recommendation for re-treatment of IBS-D	No recommendation for single treatment use
Eluxadoline	Conditional recommendation for use IBS-D	Strong recommendation for use IBS-D	Conditional recommendation for use IBS-D
Alosetron	Conditional recommendation in women with IBS-D with severe symptoms refractory to other therapies	Conditional recommendation for use IBS-D	NR
Loperamide	NR	Conditional recommendation for use IBS-D	Conditional recommendation against use IBS-D
TCAs	Strong recommendation for use global symptoms	Conditional recommendation for use	Strong recommendation for use
SSRIs	NR	Conditional recommendation against use	Conditional recommendation for use
Peppermint Oil	Conditional recommendation for use global symptoms	NR	Conditional recommendation for use
Antispasmodics	Conditional recommendation against use of those available in the United States	Conditional recommendation for use	Conditional recommendation for certain antispasmodics

*Based on recommendations obtained from previewed guideline prior to peer review 2019 NR-not reported

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This Fact Sheet is being provided in part, by Allergan and Ironwood Pharmaceuticals, and donors of IFFGD.

