



# Current Pharmacologic Treatments for Adults with Irritable Bowel Syndrome



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***This article reviews the***

- **Indications** (signs or symptoms that tell a doctor what tests or medications to consider),
- **methods of action** (the process through which a drug produces its effect),
- **and side effects** (undesired physical or mental effect caused by a medication)

***associated with commonly available medications used to treat Irritable Bowel Syndrome (IBS).***

***Any product taken for the healing or improvement of symptoms that results from therapy, medication, or other treatment is considered a medication. 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 and/or discomfort and
- 2) a change in bowel habits which could include changes in stool texture (how the BM looks) and/or frequency (how often you have BM).

Changes in stool texture includes experiencing constipation, diarrhea, or both. Constipation is commonly defined as having three (3) or fewer bowel movements (BMs) a week, and/or difficulty passing BMs. Diarrhea is defined as loose, watery, or frequent BMs. At first *pharmacologic* treatments for IBS aimed at improving one of these two symptoms. However, our better knowledge of the causes of IBS has allowed us to develop treatments that improve both the abdominal component along with the 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.

**Pharmacologic** refers to the use of drugs and how they work.

### **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 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 and/or 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  $\mu$ -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 in IBS:**

### **Antispasmodics**

Antispasmodics are drugs which suppresses smooth muscle contractions in the GI tract. There are three major classes of antispasmodics: anticholinergics, direct smooth muscle relaxants, and peppermint oil.

*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 form where it 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 ability to produce an effect that improves 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 from entering into intestinal smooth muscle cells. Calcium triggers muscle contraction, so the lack of calcium results in relaxing intestinal muscles. It also has also been shown to have other properties, such as

- anti-inflammatory (reduces inflammation or swelling),
- anti-gas (relieves the bloating, pressure and discomfort of gas), and
- anti-serotonergic (limiting the amount of serotonin, which is a chemical found in the gut that accelerates movement).

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.

*Tricyclic antidepressants (TCAs)* - 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 undesirable side effects. The dose can then be increased based upon how well it works (effectiveness) and how hard the side effects are to handle (tolerance). Most healthcare providers will not prescribe dosages higher than 50-100 mg per day.

*Selective serotonin reuptake inhibitors (SSRIs)* - 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 (enzymes, fluids and mucus which helps with digestion and movement of food through the body),
- motility (movement of food through the GI tract), and
- sensation (A physical feeling or perception in the body).

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<sup>®</sup>) 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 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 the first treatment choice in a newly diagnosed patient 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 four (4) FDA approved treatments in this class: lubiprostone, linaclotide, plecanatide.

Lubiprostone (Amitiza<sup>®</sup>) works through the activation of chloride channels in the bowel. This leads to an increase in bowel movements. 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<sup>®</sup>) and Plecanatide (Trulance<sup>®</sup>) 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 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.

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 work mainly in the GI tract and have a minimal effect on the whole body. This means that there is minimal risk of interactions between it and other drugs.

#### **Retainagogues:**

Retainagogues block the absorption of sodium from food and/or drink in the GI tract. This allows for more water to be retained in the intestines, helping speed up intestinal transit time and results in softer BMs. Like the secretagogues, it has also been shown to reduce pain and other abdominal symptoms like bloating.

Tenapanor (Ibsrela<sup>®</sup>) is the first medication in the class of retainagogues. It is an NHE3 inhibitor that works in the GI tract by blocking the absorption of sodium from food and/or drink. This allows for more water to be retained in the intestines, helping speed up intestinal transit time and results in softer BMs. It has also been shown to reduce pain and other abdominal symptoms like bloating.

Tenapanor was approved by the FDA for the treatment of IBS-C in adults in 2019. The most common side effects noted in clinical trials include diarrhea, abdominal distention, and flatulence. Tenapanor works in the GI tract and is minimally absorbed. In April 2022,

it became commercially available in the United States for the treatment of IBS-C in men and women.

**Non-absorbable Antibiotics for IBS-D**

Rifaximin (Xifaxan<sup>®</sup>) 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**

Eluxadolone (Viberzi<sup>®</sup>) 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<sup>®</sup>). 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<sup>®</sup>) – This is a highly selective 5-HT<sub>3</sub> 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<sup>®</sup>) - This is a calcium channel α<sub>2δ</sub> 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*	Eluxadolone*
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)
<b>Linaclotide</b>	Strong recommendation for use IBS-C	Strong recommendation for use IBS-C	Strong recommendation for use IBS-C
<b>Plecanatide</b>	Strong Recommendation for use IBS-C	Conditional recommendation for use IBS-C	NR
<b>Lubiprostone</b>	Strong recommendation for use IBS-C	Conditional recommendation for use IBS-C	Conditional recommendation for use IBS-C
<b>Tenapanor</b>	NR	Conditional recommendation of IBS-C	NR
<b>PEG laxatives</b>	Conditional suggestion <b>against</b> use IBS-C	Conditional recommendation for use IBS-C	Conditional recommendation <b>against</b> use IBS-C
<b>Tegaserod</b>	Strong/Conditional suggestion for IBS-C in women $\leq 65$ with $\leq 1$ cardiovascular risk factor after failing secretagogues	Conditional recommendation for IBS-C in women $\leq 65$ with $\leq 1$ cardiovascular risk factor after failing secretagogues	NR
<b>Rifaximin</b>	Strong recommendation for use IBS-D	Conditional recommendation initial treatment; Conditional recommendation for 1 <sup>st</sup> re-treatment of IBS-D	No recommendation for single treatment use
<b>Eluxadoline</b>	Conditional suggestion for use IBS-D	Conditional recommendation for use IBS-D	Conditional recommendation for use IBS-D
<b>Alosetron</b>	Conditional recommendation in women with IBS-D with severe symptoms refractory to other therapies	Conditional recommendation for use IBS-D	NR
<b>Loperamide</b>	NR	Conditional recommendation for use IBS-D over no treatment	Conditional recommendation <b>against</b> use IBS-D
<b>TCAs</b>	Strong recommendation for use global symptoms	Conditional recommendation for use IBS-D	Strong recommendation for use
<b>SSRIs</b>	NR	Conditional recommendation <b>against</b> use	Conditional recommendation for use
<b>Peppermint Oil</b>	Conditional recommendation for use global symptoms	NR	Conditional recommendation for use
<b>Antispasmodics</b>	Conditional recommendation <b>against</b> use of those available in the United States	Conditional recommendation for use IBS-D over no treatment	Conditional recommendation for certain antispasmodics

NR-not reported

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