Medications for IBS

Any product taken for a therapeutic effect should be considered a drug. Use of medications for IBS, 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:

- an abdominal component generally described as pain and/or discomfort and
- a change in bowel habits which could include changes in stool texture (how the BM looks) and/or frequency (how often you have BM).

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.

- Laxatives
- Antidiarrheals
- Secretagogues/Prosecretory agents
- Retainagogues
- Antispasmodics
  - Anticholinergics
  - Direct smooth muscle relaxants
  - Peppermint oil
- Antidepressants

- Antibiotics
- Agonists/Antagonists
- Investigational Agents

Laxatives

A ***laxative*** is a drug that increases bowel function in patients experiencing constipation. There are many laxatives available without a prescription. The 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 (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 (https://aboutibs.org/signs-and-symptoms/ibs-with-diarrhea/), abdominal cramping, bloating (https://aboutibs.org/signs-and-symptoms/bloating-in-ibs/), and nausea (https://aboutibs.org/signs-and-symptoms/nausea-and-ibs/). In rarer cases, dehydration and electrolyte disturbances have occurred.

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Antidiarrheals

These are drugs which slow gut transit. They also decrease intestinal secretion (movement of fluid into the intestines) and increase the amount of fluid that is reabsorbed by the gastrointestinal (GI) tract.

In irritable bowel syndrome (IBS) patients with diarrhea, an antidiarrheal agent such as loperamide is a drug which slows gut transit.

Loperamide (https://iffgd.org/gi-disorders/long-term-use-of-loperamide/) (e.g., Imodium®) is available over-the-counter (OTC) and is the most commonly used antidiarrheal. This drug works by bonding to μ-opioid receptors in the GI tract resulting in the changes mentioned above. Similar to OTC laxatives, a few studies have shown that it solidifies loose stools and reduces the frequency of diarrhea. However, it has not been shown to have a beneficial effect on abdominal pain or discomfort.

Side effects associated with Loperamide include

- abdominal pain and
- constipation which can become severe.

Discontinue use if constipation develops and be sure to contact your healthcare provider.

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Secretagogues/Prosecretory agents

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 3 FDA approved treatments in this class: lubiprostone, linaclotide, plecanatide,

- *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 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.

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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®) 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.

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

Anticholinergics reduce spasms or contractions in the intestine. This provides the potential to reduce abdominal pain and discomfort. The most common 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.

Side effects of anticholinergics

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

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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 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.

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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 anti-inflammatory, antigas, 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 (https://aboutgerd.org/signs-and-symptoms/functional-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®).

Side Effects of Peppermint oil

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 a placebo. A placebo is a pill or treatment with no active ingredients.

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Types of Antidepressants/Neuromodulators

Antidepressants are neuromodulators that 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.

Antidepressants are considered a global treatment, meaning that it can help multiple IBS symptoms. Be aware that the effectiveness of various agents differs between individuals and a medication regimen must be carefully chosen by the patient and their healthcare provider.

- *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.

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Non-absorbable Antibiotics

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.

Rifaximin is a global treatment, meaning that it can help multiple IBS 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.

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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.

- *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 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.

Talk with your healthcare provider to see if these medications are right for you.

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Investigational Agents

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

• Bile-acid binding agents such as cholestyramine, colestipol, and colesevelam have 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®) 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®) is a calcium channel α2δ ligand. Pregaballin 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.

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

IBS-C	IBS-D
Plecanatide *	Eluxadoline*
Linaclotide*	Rifaximon*