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Drug Class Update: Laxatives, Antidiarrheals, Rifamycins

Date of Review: February 2025

Date of Last Review:
Laxatives: June 2020 (Constipation/Irritable Bowel)
Rifamycins: Nov 2019 (Traveler's Diarrhea)
Antidiarrheals: January 2017 (Diarrhea)
Rifaximin: May 2015 (Hepatic Encephalopathy)
Dates of Literature Search:
Irritable Bowel Syndrome 12/01/2019-11/06/2024
Hepatic Encephalopathy 02/01/2015-11/06/2024
Traveler's Diarrhea 12/01/2018-11/06/2024

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update: Evaluate evidence for drugs that are Food and Drug Administration (FDA)-approved to treat diarrhea or constipation. Common FDA-approved indications for therapies include irritable bowel syndrome (IBS) with constipation (IBS-C) or diarrhea (IBS-D), chronic idiopathic constipation (CIC), opioid-induced constipation (OIC), traveler's diarrhea (TD), and hepatic encephalopathy (HE).

Plain Language Summary:

- When should the Oregon Health Plan (OHP) pay for medicine to treat constipation or diarrhea? Medicines used to treat IBS and OIC are not currently funded by the Oregon Health Plan.
- Constipation and diarrhea can be caused by a variety of conditions. These conditions include:
    - Chronic idiopathic constipation (CIC) is constipation without any known cause for more than 6 months.
    - Irritable bowel syndrome (IBS) can cause stomach pain, bloating, gas, cramping and changes bowel habits. Either constipation or diarrhea can be the most common symptom of IBS.
    - Constipation caused by opioid use.
    - Traveler's diarrhea caused by drinking or eating contaminated water or food while traveling to another country.
- The American Gastroenterological Association and American College of Gastroenterology recommend the following over-the-counter medicines (also known as laxatives) to manage CIC: fiber supplements (psyllium), polyethylene glycol, or senna. If these laxatives do not work, a health care provider may prescribe prescription laxatives that are FDA-approved for CIC.
- Regular exercise and adopting healthy eating patterns will help many patients with IBS. If these lifestyle changes do not work, then prescription medicines can help relieve the stomach pain, constipation, or diarrhea.

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- Guidelines support use of prescription medicines for IBS-C, IBS-D, and OIC when medicines are FDA approved for those conditions.
- Traveler's diarrhea is caused by drinking or eating contaminated water or food while traveling to another country. Symptoms include loose, watery stools, stomach cramps, nausea, and vomiting. The symptoms usually go away without treatment in a few days. Over-the-counter medicines to help with diarrhea symptoms include bismuth subsalicylate and loperamide. For severe symptoms, evidence shows that rifaximin can reduce symptoms of traveler's diarrhea.
- People with severe liver disease, also known as cirrhosis, can develop a condition called hepatic encephalopathy which affects their brain function. When the liver is damaged, it cannot effectively remove toxins from the blood. These toxins can build up and reach the brain, causing symptoms such as difficulty concentrating, confusion, slurred speech, or changes in behavior and mood.
- In people with cirrhosis, lactulose is used to prevent and treat HE. Rifaximin is not used to treat HE, but it is used as an add-on to lactulose to help prevent HE. Studies have found that combining rifaximin with lactulose improved HE and reduced the risk of dying.
- Oregon Medicaid pays for loperamide when needed to manage diarrhea. Oregon Medicaid also pays for the following laxatives: polyethylene glycol, senna, lactulose, and psyllium when needed to manage constipation. Providers must explain why someone needs other antidiarrheal medicines including rifaximin or rifamycin or prescription laxatives (linaclotide, methylnaltrexone, naloxegol, naldemedine, lubiprostone, and plecanatide) before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

1. What is the evidence for comparative efficacy and safety of laxatives for different types of constipation including IBS-C, CIC, and OIC?
2. What is the comparative efficacy and safety of antidiarrheal drugs (e.g., bismuth subsalicylate, loperamide, diphenoxylate/atropine, paregoric, eluxadoline, and opium tincture) and antibiotics for diarrhea (e.g., rifamycin or rifaximin) in the management of IBS-D and TD?
3. What is the comparative efficacy and safety of rifaximin compared to placebo or alternative treatments (e.g., lactulose) for HE?
4. Are there subgroups of patients based on demographics (based on age, ethnicity, comorbidities, disease duration or severity), for which one treatment for constipation or diarrhea is more effective or associated with fewer adverse events?

Conclusions:

- Since the last review of laxatives, antidiarrheals, and the rifamycins, one systematic review[1] and 6 clinical guidelines[2-7] have been published or updated for the pharmacologic management of CIC, IBS, OIC, and HE.

Hepatic Encephalopathy

- A 2023 Cochrane systematic review evaluated the safety and efficacy of rifaximin versus placebo, no intervention, or lactulose for prevention and treatment of overt HE in people with cirrhosis.[1] A fixed-effect meta-analysis showed that rifaximin likely results in little to no difference in mortality, serious adverse events, or symptoms of HE when compared to placebo/no intervention or lactulose.[1] However, moderate-quality evidence showed that when rifaximin was combined with lactulose there was a reduction in overall mortality compared with lactulose alone (relative risk [RR] 0.69, 95% confidence interval [CI] 0.55 to 0.86, p=0.001; number needed to benefit [NNTB] = 22).[1] When used in combination with lactulose, rifaximin likely reduces the risk of serious adverse events compared with lactulose alone (RR 0.66, 95% CI 0.45 to 0.98; NNTB = 10; p=0.04; very low-quality evidence).[1] Combination treatment may also improve symptoms of HE compared to use of lactulose alone (RR 0.58, 95% CI 0.48 to 0.71; NNTB = 5; p<0.001; low-quality evidence).[1]
- In 2022, the European Association for the Study of the Liver (EASL) issued guidance for the management of HE.[7] Recommendations and strength of evidence are as follows:
    - Patients with overt HE (minor or no signs/symptoms but abnormalities on neuropsychological and/or neurophysiological tests) should be treated with lactulose (strong recommendation; low-quality evidence).[7]

- Lactulose is recommended as secondary prophylaxis following a first episode of overt HE, and should be titrated to obtain 2-3 bowel movements per day (strong recommendation; high-quality evidence).[7]
- Rifaximin as an adjunct to lactulose is recommended as secondary prophylaxis following ≥ 1 additional episodes of overt HE within 6 months of the first one (strong recommendation, moderate-quality evidence).[7]

Chronic Idiopathic Constipation

- The American Gastroenterological Association (AGA) and American College of Gastroenterology (ACG) provided guidance for pharmacologic management of CIC in 2023.[2] Based on available evidence, the panel made strong recommendations for the use of polyethylene glycol (PEG), linaclotide, plecanatide, and prucalopride for adults with CIC (moderate-quality evidence).[2] Fiber, lactulose, senna, magnesium oxide, and lubiprostone were conditionally recommended (low and very low-quality evidence) in adults with CIC.[2]

Irritable Bowel Syndromes

- In 2021, the ACG issued guidance for the pharmacologic management of IBS.[3] Antispasmodics (e.g., dicyclomine, hyoscyamine, hyoscine) and probiotics are not recommended to treat IBS symptoms (conditional recommendation; low-quality evidence).[3] In addition, PEG products are not recommended to relieve IBS-C symptoms (conditional recommendation; low-quality evidence) and bile acid sequestrants are not recommended to treat IBS-D symptoms (conditional recommendation; very low-quality evidence).[3] Recommendations for medications to manage IBS-C and IBS-D include:
    - For IBS-C, the ACG recommends the use of the secretagogues lubiprostone, linaclotide, and plecanatide (strong recommendation; high quality-evidence).[3]
    - In women younger than 65 years of age with one or fewer cardiovascular risk factors who have not adequately responded to secretagogues, tegaserod can be used to treat IBS-C symptoms (conditional recommendation; low-quality evidence).[3]
    - For IBS-D, the ACG recommends rifaximin (strong recommendation; high quality-evidence) or eluxadoline (conditional recommendation; moderate-quality evidence).[3]
    - In women with severe symptoms who have failed other therapies, alosetron is recommended to relieve IBS-D symptoms (conditional recommendation; low-quality evidence).[3]
- In 2022, the AGA updated guidance for the treatment of IBS-C.[4] The panel made a strong recommendation for linaclotide (high-quality evidence) and conditional recommendations for tenapanor, plecanatide, tegaserod, and lubiprostone (moderate-quality evidence), PEG laxatives, and antispasmodics (low-quality evidence) for treatment of adults with IBS-C.[4]
- In 2022, the AGA updated guidance for the pharmacologic management of IBS-D.[5] The panel made conditional recommendations for eluxadoline, rifaximin, alosetron, (moderate-quality evidence), loperamide (very low-quality evidence), and antispasmodics (low-quality evidence) for treatment of adults with IBS-D. [5]

Opioid-Induced Constipation

- In 2020, the National Institute For Health And Care Excellence (NICE) issued recommendations for the use of naldemedine.[6] After reviewing the evidence, the NICE committee recommended naldemedine for management of OIC in adults who have had at least one other laxative treatment.[6]

New Formulations

- *May 2015:* Rifaximin (XIFAXAN) received expanded FDA-approval for treatment of IBS-D in adults.[8] The recommended dosage of rifaximin for IBS-D is 550 mg taken orally three times a day for 14 days.[8] Patients who experience a recurrence of symptoms can be retreated up to two additional times with the same rifaximin dosage regimen.[8] The efficacy and safety of rifaximin for the treatment of IBS-D was evaluated in 2 placebo-controlled, randomized controlled trials (RCTs) of identical design.[8] Adequate relief of IBS-D symptoms was experienced by more patients receiving rifaximin than those receiving placebo during the month following 2 weeks of treatment.[8] The most frequently reported adverse effect in these trials was nausea (3% rifaximin vs. 2% placebo).[8]

- June 2023: Linaclotide (LINZESS) capsules received an expanded indication for the treatment of functional constipation in pediatric patients aged 6 to 17 years.[9] The recommended dose for this indication is 72 mcg once daily.[9] A 12-week double-blind, placebo-controlled RCT evaluated the least squares 12-week mean change from baseline in spontaneous bowel movement (SBM) frequency rate.[9] Patients who received linaclotide had statistically significant greater improvements in SBMs per week compared with placebo (2.6 vs. 1.3; treatment difference: 1.3; 95% CI 0.7 to 1.8).[9] The minimal clinically important difference for this outcome was not defined. Diarrhea was the most common adverse reaction and was reported in 4% of linaclotide-treated patients compared to 2% of placebo-treated patients.[9]
- There are no head-to-head trials to provide comparative evidence for the safety and efficacy of laxatives and antidiarrheals in the treatment of CIC, OIC, IBS-C, TD, or IBS-D. There was no evidence to show that there are subgroups of patients based on demographics (based on age, ethnicity, comorbidities, disease duration or severity), for which one treatment for constipation or diarrhea is more effective or associated with fewer adverse events.

Recommendations:
- Make rifaximin nonpreferred on the PDL and update rifamycins PA criteria with the expanded indication for rifaximin in management of IBS-D.
- Create an automatic prior authorization (PA) when rifamycin is prescribed with lactulose for HE.
- Based upon a review of evidence, no other changes to the PDL are warranted.
- Propose prior authorization (PA) criteria to provide a pathway to coverage for adults with IBS-C or IBS-D that need pharmacologic treatment (**Appendix 3**).
- Review medication costs in executive session.

Summary of Prior Reviews and Current Policy:

Rifaximin – 5/2015
- There is insufficient evidence that rifaximin is superior to lactulose for preventing episodes of overt HE. There is insufficient evidence for the use of rifaximin without lactulose to prevent or treat HE. The Pharmacy and Therapeutics (P&T) committee approved the recommendation to establish PA criteria so use of rifaximin is restricted to Oregon Health Plan (OHP)-funded conditions such as prevention or treatment of HE. PA criteria are presented in **Appendix 3**.

Antidiarrheals – 1/2017
- There is insufficient comparative evidence of efficacy and effectiveness between bismuth subsalicylate, loperamide, diphenoxylate/atropine, paregoric, crofelemer, and opium tincture. Opium tincture has not been evaluated by the United States Food and Drug Administration (FDA) for safety and effectiveness because it was marketed before 1962. The FDA published a warning about possible cardiac toxicity related to loperamide abuse or misuse at doses greater than 16 mg per day or when used with specific medications that delay loperamide metabolism. The P&T committee approved the recommendation designate loperamide as the preferred agent in the antidiarrheal class. Quantity limits were added to loperamide, diphenoxylate/atropine, and crofelemer to insure safe and appropriate use. (Loperamide = maximum 16 mg per 24 hours; diphenoxylate/atropine = maximum 20 mg/0.2 mg per 24 hours; crofelemer = maximum 500 mg per 24 hours). All other antidiarrheals were designated as non-preferred to restrict use to funded conditions on the HERC prioritized list.

Rifamycin – 11/2019
- There is insufficient evidence to determine the comparative safety of rifamycin or rifaximin in TD. The P&T committee approved the recommendation to designate rifamycin as non-preferred on the preferred drug list (PDL) and add rifamycin to PA criteria for rifaximin to ensure appropriate utilization of both medications for FDA-approved indications (see **Appendix 3**).

- There is insufficient comparative evidence of efficacy and effectiveness between prucalopride, tegaserod, and tenapanor in treating chronic constipation. The P&T committee approved the recommendation to designate prucalopride, tegaserod, and tenapanor as non-preferred on the PDL to ensure use in OHP-funded conditions. PA criteria laxatives for constipation were revised to include prucalopride, tegaserod, and tenapanor (see **Appendix 3**).

Current Policy and Utilization Trends

- Preferred laxatives on the PDL include PEG, docusate, senna, magnesium hydroxide, calcium polycarbophil, bisacodyl, lactulose, psyllium, magnesium citrate, and methylcellulose. Nonpreferred laxatives include linaclotide, methylnaltrexone, naloxegol, naldemedine, lubiprostone, and plecanatide. The preferred antidiarrheal medication is loperamide. Nonpreferred agents for diarrhea include bismuth subsalicylate, diphenoxylate/atropine, eluxadoline, and opium tincture. Rifamycin is non-preferred with PA criteria. Rifaximin does not have PDL status but does require PA as presented in **Appendix 3.** The PDL status for all the medications discussed in this class update is provided in **Appendix 1**.
- In the third quarter of 2024 (June 1 to August 30) most of the utilization for antidiarrheal medications was for the preferred agent, loperamide. Two percent of claims arose from requests for opium tincture, which is non-preferred. Most paid claims for laxatives in the third quarter 2024 (~2700) were for preferred agents including docusate, senna, magnesium citrate, psyllium, lactulose, and PEG. There were 4 claims each for nonpreferred prucalopride and linaclotide. Six patients had claims for rifaximin and there were no paid claims for rifamycin.

Background:

Definition of Medically Appropriate Services

Oregon Administrative Rule (OAR) defines medically necessary services in OAR 410-120-0000 (193).[10] The services must address 1) prevention, diagnosis or treatment of the member's disease, condition or disorder that may result in health impairments or a disability; 2) ability to achieve appropriate growth and development; or 3) ability to attain, maintain or regain independence in self-care, perform activities of daily living or improve health status.[10] All covered services must be medically necessary but not all medically necessary services are covered services. Covered services must also be medically appropriate. Constipation, IBS-C, and OIC are not currently funded under the HERC Prioritized List of Health Services. Funding for drugs that treat constipation is dependent on whether constipation adversely effects, or is secondary to, an underlying medical condition covered by the prioritized list (i.e., "comorbidity rule").[11]

1. Bowel Disorders: Chronic Idiopathic Constipation, Opioid Induced Constipation, and Irritable Bowel Syndromes

Functional bowel disorders are chronic gastrointestinal (GI) disorders characterized by signs or symptoms of abdominal pain, bloating, distention, or bowel habit abnormalities (e.g., constipation, diarrhea, or mixed constipation and diarrhea).[12] Bowel disorders can be distinguished from other GI disorders based on chronicity (having symptoms for 6 months or greater at the time of presentation), current activity (symptoms present within the last 3 months), frequency (symptoms present, on average, at least 1 day per week), and the absence of obvious anatomic or physiologic abnormalities identified by routine diagnostic examinations.[13] Rome I through IV criteria are the current standard for diagnosing bowel disorders (see **Table 1**).[12] The Rome criteria have been revised 4 times since they were first introduced in 1999. In 2016, the Rome IV diagnostic criteria for IBS were published, which differ from the Rome III criteria in that abdominal discomfort was deleted from the definition and abdominal pain is required to be present at least 1 day per week on average during the preceding 3 months.[12] A sixth category, OIC, is distinct from the other bowel disorders because it has a specific etiology that can produce symptoms similar to constipation.[13]

Table 1. Rome Criteria for Diagnosing Bowel Disorders

Bowel Disorder	Rome Criteria
Rome II: Functional Abdominal Bloating[14]	Feeling of abdominal fullness, bloating, or visible distension or insufficient criteria for a diagnosis of functional dyspepsia, irritable bowel syndrome, or other functional disorder.

Rome III: Functional Constipation[15]	Functional constipation is defined as ≥ 2 of the following: • straining during ≥ 25% of defecations, • lumpy or hard stools in ≥ 25% of defecations, • sensation of incomplete evacuation for ≥ 25% of defecations, • sensation of anorectal obstruction for ≥ 25% of defecations, • manual maneuvers to facilitate ≥ 25% of defecations (e.g., digital, evacuation, support of the pelvic floor), • < 3 defecations per week, • loose stools are rarely present without the use of laxatives, or • insufficient criteria for IBS.
Rome III: Functional Diarrhea[15]	Functional diarrhea is defined as loose (mushy) or watery stools without pain in ≥ 75% of stools for the last 3 months with symptom onset ≥ 6 months before diagnosis.
Rome IV: Irritable Bowel Syndrome[12]	Recurrent abdominal pain on average at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria: 1. Related to defecation 2. Associated with a change in the frequency of stool 3. Associated with a change in the form of the stool
Rome IV: Irritable Bowel Syndrome-Constipation[12]	Greater than 25% of bowel movements associated with Bristol Stool Form Scale 1 or 2 (hard lumps like nuts or sausage shaped but lumpy) with Bristol Stool Form Scale 6 or 7 (mushy stool or watery stool) occurring less than 25%.
Rome IV : Irritable Bowel Syndrome-Diarrhea[12]	Greater than 25% of bowel movements associated with Bristol Stool Form Scale 6 or 7 (mushy or watery stool) with less than 25% of bowel movements with Bristol Stool Form Scale 1 or 2 (hard lumps like nuts or sausage shaped but lumpy).
Rome IV: Opioid-Induced Constipation[12]	Change from baseline bowel habits and defecation patterns after initiating opioid therapy, characterized by any of the following: • reduced bowel frequency (less than 3 spontaneous bowel movements per week) • development or worsening of straining to pass a bowel movement • a sense of incomplete evacuation • or a patient's perception of distress related to bowel habits.

Chronic idiopathic constipation (CIC) is a subtype of functional constipation in which symptoms of difficult, infrequent, or incomplete defecation frequently occur.[13] Patients with CIC do not meet IBS criteria, although abdominal pain or bloating may be present but are not predominant symptoms.[13] Constipation can arise secondary to neurological conditions (Parkinson's disease, multiple sclerosis), endocrine disorders (hypothyroidism, hypercalcemia) and prescribed medications (tricyclic antidepressants, calcium-containing antacids, iron supplements, anticholinergics).[16] Chronic idiopathic constipation affects approximately 8% to 12% of the United States (U.S.) population.[2] Non-modifiable risk factors for CIC include female gender, nursing home residence, and age over 65 years.[13] Modifiable risk factors include insufficient physical activity, depression, and inadequate caloric intake.[13]

Objective measures that assess the severity of constipation and its impact on quality of life may help providers decide on course of treatment or whether to pursue more diagnostic studies.[17] Although the Rome criteria are used to identify functional constipation, they do not assess severity of the condition.[17] Several

measures have been developed to assess constipation specifically, with variable psychometric properties.[17] The current FDA responder criteria for CIC trials are based on a complete spontaneous bowel movement (CSBM) weekly response (i.e., ≥ 3 CSBMs/week plus an increase of ≥ 1 CSBM/week from baseline).[2]

Treatment of CIC should begin by educating the patient about constipation, eliminating medications (prescription, over-the-counter, complementary) that can cause or worsen constipation and asking the patient to maintain a diet that contains an adequate amount of fiber.[13] Fiber has been recognized as important for normal laxation, primarily because it increases stool weight, and this has the secondary effect of reducing transit time.[2] Constipated patients with severely delayed colon transit or obstructed defection are less likely to improve with fiber.[13] If a patient fails fiber therapy, over-the-counter (OTC) laxative therapy can be initiated.[18] Laxatives either increase stool water content or accelerate bowel transit to alleviate constipation.[16] They are subdivided into 5 different categories depending on their mechanism of action:

- bulk-forming: psyllium
- stool softener: docusate
- stimulant: senna
- osmotic: lactulose and PEG
- saline: magnesium hydroxide

If OTC laxatives are ineffective in resolving CIC symptoms, prescription options include linaclotide, plecanatide, lubiprostone and prucalopride. The secretagogues (linaclotide, plecanatide, and lubiprostone) activate ion channels on the intraluminal surface of enterocytes, resulting in an efflux of ions and water into the intestinal lumen.[19] Linaclotide and plecanatide are peptides that act as a guanylate cyclase-C agonists, which increase cyclic guanosine monophosphate concentrations in the GI tract.[2] This increases luminal chloride and bicarbonate secretion, thereby increasing intestinal fluid and GI transit.[3] Lubiprostone is a locally acting prostaglandin analog that activates chloride channels on epithelial cells.[3] Consequently, the intestinal lumen experiences an influx of chloride and water, which accelerates movement of materials through the GI tract.[3] Prucalopride is a selective, high-affinity serotonin agonist that promotes neurotransmission by the enteric neurons resulting in stimulation of the peristaltic reflex, intestinal secretions, and GI motility.[2] The prucalopride label cautions clinicians to be alert to unusual changes in mood and behavior and suicidal ideation.[2] In a safety database of 4,476 subjects treated with prucalopride, 4 individuals attempted suicides and 2 completed suicides, both of whom had discontinued prucalopride more than 1 month before the event.[2] It is unclear what the mechanism of action is or whether there is a causal association between the use of prucalopride and risk of suicide.[2] Mechanisms of action and warnings/contraindications for medications FDA-approved to treat constipation are summarized in **Table 2**.

Opioid-induced constipation has been defined by Rome IV criteria as a change from baseline bowel habits and defecation patterns after initiating opioid therapy.[12] Some patients may also develop fecal impaction with overflow incontinence, while others may report symptoms compatible with overlapping opioid-induced bowel disorders (e.g., reflux, nausea, bloating).[12] In a systematic review of 8 placebo-controlled trials, the prevalence of OIC was 41% in patients with chronic non-cancer pain taking opioids.[20] In a study of cancer patients taking opioids for pain, the incidence of constipation was approximately 94%.[21] Three different classes of opioid receptors mediate the GI effects of opioid medications: kappa, delta and mu.[22] Opioids exert their GI effects via kappa-receptors in the stomach and small intestine and mu-receptors located in the small intestine and proximal colon.[22]

The initial treatment of OIC is similar to the treatment of CIC. Stimulant laxatives as monotherapy or in combination with a stool softener are initially recommended for both the prophylaxis and management of OIC in patients with cancer.[23] Bulk-forming laxatives for not recommended for OIC due to the increased risk of bowel obstruction. Peripheral-acting mu-opioid-receptor antagonists (i.e., methylnaltrexone, naloxegol, and naldemedine) are FDA-approved for the treatment of OIC in adults with non-cancer pain. These drugs block opioid receptors in the GI tract, antagonizing the constipating effects of opioids in the

periphery without affecting analgesia. Lubiprostone is also FDA-approved to manage OIC in people with chronic, non-cancer pain. Since no head-to-head comparative trials between prescription medications for OIC have been conducted and outcome measures of published trials vary considerably, direct comparisons among these therapies is difficult.[23] Another agent, alvimopan, is only indicated for short-term use to prevent or decrease the course of postoperative ileus after bowel resection and is therefore available for hospital use only.[20] **Table 2** provides a summary of FDA-approved medications to treat OIC in an outpatient setting.

The world-wide prevalence of IBS is estimated as 14% in women and 8.9% in men.[24] Prevalence rates are higher for people less than 50 years of age.[13] Although not a life-threatening condition, IBS is associated with significant disease burden, including decreased quality of life, elevated rates of psychological comorbidities, and high economic costs.[4] The impact of IBS on daily functioning can be demonstrated by high rates of absenteeism (average of 13.4 days of work or school per year compared with 4.9 days for those without IBS) and presenteeism. Of people with IBS, 87% report reduced productivity at work in the past week resulting in nearly 14 hours per week of lost productivity due to IBS.[4] Socially, IBS can negatively impact activities like eating outside the home, going out with friends, traveling, and going to new or unfamiliar places.[4]

Responder definitions varied in multicenter IBS RCTs until the establishment of FDA composite primary end points for IBS-C in 2012, which allowed greater standardization of the efficacy of IBS treatments.[25] The section on trial endpoints was modified to note that a drug can be specifically developed to treat only one of two major signs or symptoms of IBS (abnormal defecation or abdominal pain).[26] Demonstration of significant and clinically meaningful changes in the targeted single endpoint could serve as a basis for approval, as long as the other important symptom or sign has not worsened on treatment.[26] The FDA recommended endpoint for patients with IBS-C is the proportion of patients experiencing at least a 30% improvement in abdominal pain accompanied by an increase of 1 or more CSBM per week from baseline for at least 50% over 12 weeks.[27] The FDA responder endpoint for IBS-D is defined as both at least a 30% reduction in average daily worst abdominal pain scores and at least a 50% reduction in number of days per week with at least 1 stool that has a consistency of type 6 or 7 (mushy or watery stool) according to the Bristol Stool Form Scale compared with baseline.[5]

IBS-C is a subtype of IBS that accounts for more than one-third of IBS cases.[4] Therapeutic options to treat IBS-C include linaclotide, plecanatide, lubiprostone, tenapanor, and tegaserod. There have not been any head-to-head trials to evaluate comparative efficacy of these agents. Lubiprostone and tegaserod are FDA-approved for the treatment of adult women with IBS-C. Linaclotide, plecanatide, and tenapanor are approved for treatment of adult men and women with IBS-C. Tegaserod was approved by the FDA in 2002 for short-term treatment of IBS-C in women and in 2004 for CIC in men and women under the age of 65 years.[4] In 2007, the FDA requested tegaserod withdrawal from the U.S. market due to a retrospective analysis of clinical trials that showed a small but higher rate of cardiovascular ischemic events with tegaserod compared with placebo (0.11% vs. 0.01%, respectively).[4] However, subsequent observational studies failed to find an association between tegaserod and adverse cardiovascular outcomes.[4] In 2019, the FDA re-examined the data and recommended a limited reapproval of tegaserod 6 mg twice a day for women with IBS-C, under 65 years of age, without a history of myocardial infarction, stroke, transient ischemic attack, or angina.[4] A summary of prescription medications FDA-approved to treat different types of constipation is presented in **Table 2.**

Table 2. Drugs FDA-Approved for Treatment of Constipation[28,29]

Generic (Brand Name)	Indications	Warnings and Precautions
Guanylate Cyclase-C Agonists		
Linaclotide (LINZESS)	Adults with CIC or IBS-C	**Black Boxed Warning** – Risk of Serious Dehydration in Pediatric Patients: Linaclotide is contraindicated in pediatric patients < 2 yo.

	FC in pediatric patients aged 6 to 17 yo	The safety and effectiveness of linaclotide in patients with functional constipation less than 6 years of age or in patients with IBS-C less than 18 years of age have not been established.
Plecanatide (TRULANCE)	Adults with CIC or IBS-C	**Black Boxed Warning** – Risk of Serious Dehydration in Pediatric Patients: Plecanatide is contraindicated in pediatric patients < 6 yo. Avoid use in pediatric patients less than 6 to 17 yo. The safety and effectiveness of plecanatide have not been established in patients < 18 yo.
Chloride Channel Activator		
Lubiprostone (AMITIZA)	Adults with CIC Adult women with IBS-C OIC in adults with chronic, non-cancer pain	Contraindicated in patients with mechanical bowel gastrointestinal obstruction. Effectiveness of lubiprostone in patients taking methadone has not been established.
Sodium/Hydrogen Exchanger		
Tenapanor (IBSRELA)	Adults with IBS-C	**Black Boxed Warning** – Risk of Serious Dehydration in Pediatric Patients: Tenapanor is contraindicated in pediatric patients <6 yo. Avoid use in pediatric patients 6 to 12 yo. The safety and effectiveness of tenapanor have not been established in pediatric patients < 18 yo.
Serotonin Type 4 Agonists		
Prucalopride (MOTEGRITY)	Adults with CIC	Contraindicated in patients with intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the intestinal tract such as Crohn's disease, ulcerative colitis, and toxic megacolon/megarectum. Clinicians should be alert to unusual changes in mood and behavior and suicidal ideation.
Tegaserod (ZELNORM)	Adult women < 65 yo with IBS-C	Contraindicated in patients with a history of myocardial infarction, stroke, transient ischemic attack, or angina; history of ischemic colitis; severe renal impairment (eGFR < 15 mL/min); moderate or severe hepatic impairment (Child-Pugh B or C); history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions. Discontinue tegaserod in patients who have not had adequate control of symptoms after 4 to 6 weeks of treatment
Peripherally Acting Mu-Opioid Antagonists		
Naldemedine (SYMPROIC)	OIC: chronic, non-cancer pain	Contraindicated in patients with known or suspected GI obstruction or at increased risk of recurrent obstruction
Naloxegol (MOVANTIK)	OIC: chronic, non-cancer pain	Contraindicated in patients with known or suspected GI obstruction or at increased risk of recurrent obstruction
Methylnaltrexone (RELISTOR)	OIC with advanced illness (injection only) OIC with chronic non-cancer pain (tablets and injection)	Contraindicated in patients with known or suspected GI obstruction or at increased risk of recurrent obstruction

Abbreviations: CIC = chronic idiopathic constipation; eGFR = estimated glomerular filtration rate; FC = functional constipation; GI = gastrointestinal; IBS-C = irritable bowel syndrome with constipation; mL = milliliters; min = minutes; OIC = opioid-induced constipation; yo = years old

The primary distinction between functional diarrhea and IBS-D is the absence of predominant abdominal pain in functional diarrhea and the presence of significant abdominal pain in IBS-D.[30] An estimated 30%–40% of IBS cases are classified as IBS-D.[5] Diarrhea associated with IBS can be managed with eluxadoline, alosetron, or rifaximin. There have been no head-to-head trials comparing the safety and efficacy of these medications in IBS-D. FDA-approval was based on data from placebo-controlled RCTs.

Alosetron is a 5-hydroxytryptamine-3 (5-HT_3) receptor antagonist and slows GI transit.[31] Alosetron received FDA-approval to treat IBS-D in February 2000.[3] It was temporarily withdrawn on November 28, 2000 due to postmarketing reports of increased rates of ischemic colitis, complicated constipation (obstruction or perforation), and death.[3] In June 2002, alosetron was reintroduced to the U.S. market under a risk evaluation and mitigation strategy, limiting use to women experiencing chronic (> 6 months), severe IBS-D symptoms who previously lacked response to traditional therapies.[3] Initial safety concerns have been addressed in follow-up data revealing low, stable adjudicated incidence rates of ischemic colitis and reduced rates of complicated constipation (1.03 cases and 0.25 cases/1,000 patient-years of exposure, respectively) compared to placebo, likely attributable to restricted prescribing dosages of 0.5–1.0 mg twice daily established by the REMS.[3] Subsequent safety analyses yielded pooled RRs of any adverse effect of 1.16 (95% CI 1.08 to 1.25); constipation was the adverse effect most likely to occur with an RR of 4.55 (95% CI 3.30 to 6.28).[3] A follow-up meta-analysis of 8 trials (n=4,987) yielded an overall number needed to harm (NNH) of 10.[3]

The efficacy of rifaximin has been evaluated in IBS-D on the basis that disturbances in the gastrointestinal microbiota may be responsible for symptoms.[19] In a meta-analysis of 2 RCTs (n = 1260), rifaximin 550 mg three times a day for 14 days was more efficacious than placebo for the FDA composite endpoint of adequate relief of abdominal pain and improvement in stool consistency measures (RR 0.92; 95% CI 0.86 to 0.98).[19] Headache was the most common adverse event, but side effects were not more common with rifaximin than with placebo.[19] A summary of medications to treat IBS-D is outlined in **Table 3**.

Table 3. Drugs FDA-Approved for Treatment of Irritable Bowel Syndrome with Diarrhea[28,29]

Generic (Brand Name)	Indications	Notes
Mixed Opioid Receptor Agonist/Antagonist		
Eluxadoline (VIBERZI)	Adults with IBS-D	Eluxadoline is contraindicated in patients with prior sphincter of Oddi problems, cholecystectomy, alcohol dependence, pancreatitis or severe liver impairment
5-HT3 Receptor Antagonist		
Alosetron (LOTRONEX)	Women with Severe IBS-D who have chronic IBS symptoms (lasting 6 months or longer) who have responded adequately to conventional therapy and have had anatomic or biochemical abnormalities of the GI tract excluded.	**Black Boxed Warning**: Serious GI adverse reactions including ischemic colitis and serious complications of constipation have resulted in hospitalization and rarely blood transfusion, surgery and death.
Nonabsorbable Antibiotic		
Rifaximin (XIFAXAN)	Adults with IBS-D	Recommended dose: A single 14-day course of treatment. If IBS-D symptoms recur, can repeat 2 additional courses of treatment.
Abbreviations: 5HT = 5-hydroxytryptamine; IBS-D = irritable bowel syndrome with diarrhea; GI = gastrointestinal		

2. Traveler's Diarrhea

Travelers' diarrhea is defined as passage of 3 or more unformed stools plus at least 1 accompanying symptom in a 24 hour period that develops during or within 14 days of returning from travel to a resource-limited location.[32] Travelers' diarrhea is the most common illness afflicting travelers, and several observational studies report an incidence of 10-40% after a 2-week travel period depending on destination and traveler characteristics.[33] As a large number of individuals experiencing symptoms self-treat, the actual magnitude of the disease burden is uncertain.[34] Travel destination has a major impact on the risk for TD. The Centers for Disease Control and Prevention (CDC) categorizes locations based on level of TD risk.[32]

- Low-risk countries include the U.S., Canada, Australia, New Zealand, Japan, and countries in Northern and Western Europe.[32]
- Intermediate-risk countries include those in Eastern Europe, South Africa, and some Caribbean islands.[32]
- High-risk areas include most of Asia, the Middle East, Africa, Mexico, and Central and South America.[32]

Travelers' diarrhea is usually infectious and is caused by microbial pathogens endemic at the travel destination.[35] Most TD cases are contracted from contaminated food and less commonly from water. Bacteria account for up to 90% of identified infectious etiologies for acute TD, predominately enterotoxigenic and enteroaggregative *E. coli* , although there is regional variability.[36] Other bacterial pathogens that can cause TD include *Campylobacter jejuni*, *Shigella* species, and *Salmonella* species.[37] There is increasing recognition of *Aeromonas* species, *Plesiomonas* species, and newly identified pathogens (*Acrobacter, Larobacter*, enterotoxigenic *Bacteroides fragilis*) as potential causes of TD.[32] Regardless of cause, most cases of TD have a similar clinical appearance, presenting as watery diarrhea with abdominal pain or cramps of variable severity.[37] Travelers are recognized as an important vector for transmission of emerging and multi-drug resistant enteropathogens globally.[32]

Bismuth subsalicylate has antibacterial properties and prevents 65% of expected TD cases when taken at recommended doses (2.1 gm per day divided into 4 doses).[37] Probiotics are not recommended due insufficient evidence demonstrating their efficacy.[32] Antimotility agents (such as loperamide or diphenoxylate) can reduce frequency of bowel movements, but are not recommended alone for patients with bloody diarrhea or those who have diarrhea and fever.[32] in June 2016, the FDA issued a warning that doses of loperamide over 16 mg/day, including through abuse or misuse of the product, can cause serious cardiac events that can lead to death.[38] The risk of cardiac events, including abnormal heart rhythms, was increased when high doses of loperamide were taken with other medications that interact with loperamide.[38] The majority of reported cardiac events occurred in individuals intentionally misusing and abusing high doses of loperamide in attempts to self-treat opioid withdrawal symptoms or to achieve a feeling of euphoria.[38]

Antimicrobial therapy is not routinely recommended for mild TD, but should be considered for people with suspected *Shigella* or *Campylobacter* species and certain *E. coli* infections and moderate to severe TD symptoms.[37] Common antibiotics recommended for TD include azithromycin, fluoroquinolones, and rifaximin. Fluoroquinolones had long been the first choice for treatment of travelers' diarrhea, but the emergence of resistance to this drug class and increased awareness of adverse events make the risk-benefit assessment less clear. Due to widespread resistance, sulfamethoxazole/trimethoprim is no longer recommended to treat TD.[32] A 2000 Cochrane review concluded that antibiotics shorten the overall duration of moderate to severe traveler's diarrhea by about a day and a half.[39] The mean duration of travelers' diarrhea, even if untreated, is 4 to 5 days.[40] The Centers for Disease Control and Prevention (CDC) antibiotic treatment recommendation for acute TD are summarized in **Table 4**.

Table 4. CDC Acute Traveler's Diarrhea Antibiotic Treatment Recommendations[41]

Antibiotic	Dose	Duration	Notes
Azithromycin	1000 mg	Single or Divided dose	• Use empirically as first-line treatment for travelers' diarrhea in Southeast Asia or other areas if fluoroquinolone- resistant bacteria are suspected.
Azithromycin	500 mg QDay	3 days	

			• Preferred treatment for dysentery or febrile diarrhea.
Ciprofloxacin	750 mg	Single Dose	• If symptoms are not resolved after 24 hours, continue daily dosing for up to 3 days.
Ciprofloxacin	500 mg QDay	3 days	
Levofloxacin	500 mg QDay	1-3 days	• If symptoms are not resolved after 24 hours, continue daily dosing for up to 3 days.
Ofloxacin	400 mg BID	1-3 days	• If symptoms are not resolved after 24 hours, continue daily dosing for up to 3 days.
Rifamycin	388 mg BID	3 days	• Do not use if clinical suspicion for *Campylobacter*, *Salmonella*, *Shigella*, or other causes of invasive diarrhea. Use may be reserved for patients unable to receive azithromycin or fluoroquinolones.
Rifaximin	200 mg TID	3 days	
Abbreviations: BID = twice daily; CDC = Centers for Disease Control and Prevention; QDay = once daily; TID = three times daily			

3. Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome associated with hepatic dysfunction.[42] The incidence and prevalence of HE are related to the severity of the underlying liver insufficiency.[42] Hepatic encephalopathy occurs in about 5-25% of patients with cirrhosis within 5 years of diagnosis, depending on other risk factors present.[23] The West Haven criteria are the gold standard for the diagnosis of overt HE.[43] However, the criteria are subjective with limited inter-observer reliability, especially for Stage 1 because signs are often overlooked in clinical examination.[23] In contrast, the detection of disorientation and asterixis has good inter-rater reliability and thus are chosen as marker symptoms of overt HE.[23] Asterixis or "flapping tremor" is often present in the early to middle stages of HE that precede stupor or coma. It is not a tremor, but a negative myoclonus consisting of loss of postural tone.[23] It is easily elicited by actions that require postural tone, such as hyperextension of the wrists with separated fingers. West Haven criteria for diagnosis of HE are as follows:[43]

- Stage 0 = no abnormalities detected
- Stage 1 = unawareness (mild), euphoria or anxiety, shortened attention span, impairment of calculation ability
- Stage 2 = lethargy or apathy, disorientation to time, inappropriate behavior, obvious personality change, asterixis
- Stage 3 = somnolence or stupor, responsive to stimuli, confusion, gross disorientation, bizarre behavior
- Stage 4 = coma

Hepatic encephalopathy is broadly classified as overt, when there clinical abnormalities and impairment of neurophysiological function and neuropsychometric performance; or minimal, when there is no clinical evidence of neuropsychiatric impairment but documented neurophysiological and neuropsychometric abnormalities.[44] Overt HE is estimated to impact 30-40% of those with cirrhosis at some time during their clinical course, and reoccurs in most cases.[23]

Treatment for HE aimed at managing the precipitating factors (i.e., electrolyte abnormality, constipation, infection, etc.) and reducing ammonia levels to improve symptoms.[45] At this time, only overt HE is routinely treated during the acute episode and as secondary prophylaxis. The non-absorbable disaccharide lactulose and rifaximin are the mainstay of pharmacological management. The 2014 guideline by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommends lactulose as initial treatment for episodic, overt HE.[46] Lactulose reduces ammonia levels by increasing acidity of the colon, causing conversion of ammonia to ammonium and shifting the colonic flora to non-urease-producing bacteria. Rifaximin is a minimally absorbed oral antibiotic that is concentrated in the gastrointestinal tract and has broad-spectrum *in vitro* antimicrobial activity.[42] Rifaximin has been primarily studied for secondary prevention of episodic, overt HE in patients in remission at time of enrollment.[42] Rifaximin is well-tolerated, but no solid data support the use of rifaximin alone.[47] As such, AASLD/EASL recommends rifaximin as an effective add-on therapy to lactulose for secondary prevention of overt HE.[47] Many other drugs (i.e., oral branched-chain amino acids, intravenous L-ornithine L-aspartate, neomycin, metronidazole, etc.) have been used for treatment of overt HE, but data to support their use are limited or lacking altogether.

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
Cochrane: Rifaximin for Prevention and Treatment of Hepatic Encephalopathy
A 2023 Cochrane evaluated the safety and efficacy of rifaximin versus placebo, no intervention, or lactulose for prevention and treatment of overt HE in people with cirrhosis.[1] Literature was searched through January 2023, and 41 RCTs (n = 4,545) met inclusion criteria.[1] Outcomes included mortality, serious adverse events, health-related quality of life (QoL), and HE. Hepatic encephalopathy was classified as acute (13 trials), chronic (7 trials), or minimal (8 trials), and 13 trials evaluated prevention in participants at risk for HE .[1] The control groups received placebo (12 trials), no/standard treatment (1 trial), or lactulose (14 trials).[1] Eighteen trials assessed rifaximin plus lactulose versus a lactulose alone.[1] Risk of bias was classified as high for mortality (11 trials), and non-mortality outcomes (28 trials), mainly due to lack of blinding, incomplete outcome data, and selective reporting.[1]

Rifaximin likely has no overall effect on mortality when compared to placebo/no intervention (RR 0.84, 95% CI 0.51 to 1.38; P = 0.69, I^2 = 0%; 13 trials, n= 1007; moderate-quality evidence), or compared to lactulose (RR 0.99, 95% CI 0.49 to 1.97; P = 0.97, I^2 = 0%; 10 trials, n = 786; low-quality evidence).[1] When comparing rifaximin plus lactulose to lactulose alone, combination therapy reduced the overall risk of mortality (RR 0.69, 95% CI 0.55 to 0.86; NNTB = 22; P = 0.001, I^2 = 0%; 14 trials, n = 1946; moderate-quality evidence).[1]

There is likely no effect on the overall risk of serious adverse events when comparing rifaximin to placebo/no intervention (RR 1.05, 95% CI 0.83 to 1.32; P = 68, I^2 = 0%; 9 trials, n = 801; moderate-quality evidence) or lactulose (RR 0.97, 95% CI 0.66 to 1.40; P = 0.85, I^2 = 0%; 8 trials, n = 681; low-quality evidence).[1] There was very low-quality evidence that use of rifaximin plus lactulose may be associated with a lower risk of serious adverse events than use of lactulose alone (RR 0.66, 95% CI 0.45 to 0.98; P = 0.04, I^2 = 60%; 7 trials, n = 1076).[1]

Very few trials investigated health-related quality of life (QoL); therefore, data for this outcome are limited.[1] Rifaximin likely improves health-related QoL when compared to placebo/no intervention in people with overt HE (mean difference (MD) -1.43, 95% CI -2.87 to 0.02; P = 0.05, I^2 = 81%; 4 trials, n = 214; moderate-quality evidence) and may benefit health-related QoL in people with minimal HE (MD -2.07, 95% CI -2.79 to -1.35; P < 0.001, I^2 = 0%; 3 trials, 176 participants; quality of evidence not graded).[1] The overall effect on health-related QoL when comparing rifaximin to lactulose is very uncertain (MD -0.33, 95% CI -1.65 to 0.98; P = 0.62, I^2 = 0%; 2 trials, n = 249; very low-certainty evidence).[1] None of the combined rifaximin and lactulose trials reported on health-related QoL.[1]

There is likely an overall improvement in HE symptoms when comparing rifaximin to placebo/no intervention (RR 0.56, 95% CI 0.42 to 0.77; NNTB = 5; P < 0.001, I^2 = 68%; 13 trials, n = 1009; moderate-certainty evidence).[1] This effect may be more marked in people with minimal HE (RR 0.40, 95% CI 0.31 to 0.52; NNTB = 3; P < 0.001, I^2 = 10%; 6 trials, 364 participants) and in prevention trials (RR 0.71, 95% CI 0.56 to 0.91; NNTB = 10; P = 0.007, I^2 = 36%; 4 trials, 474 participants).[1] There may be little overall effect on HE when comparing rifaximin to lactulose (RR 0.85, 95% CI 0.69 to 1.05; P = 0.13, I^2 = 0%; 13 trials, n= 921; low-certainty evidence).[1] There may be an overall beneficial effect on HE when comparing rifaximin plus lactulose to lactulose alone (RR 0.58, 95% CI 0.48 to 0.71; NNTB = 5; P < 0.001, I^2 = 62%; 17 trials, n = 2332; low-certainty evidence).[1]

In summary, compared to placebo/no intervention, rifaximin likely improves health-related quality of life and may improve symptoms of HE, but has no effect on mortality.[1] Compared to lactulose, rifaximin likely has no overall effect on mortality, serious adverse events, health-related quality of life, or HE symptoms.[1] However, when used in combination with lactulose, rifaximin likely reduces overall mortality risk, the risk of serious adverse events, and improves symptoms of HE mor then lactulose alone.[1] The certainty of evidence for these outcomes is very low to moderate.[1]

After review, 34 systematic reviews were excluded due to poor quality (e.g., indirect network meta-analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
High Quality Guidelines:

1. Chronic Idiopathic Constipation

American Gastroenterological Association/American College of Gastroenterology: Management of Chronic Idiopathic Constipation

In 2023 the AGA/ACG published guidance for pharmacologic management of adults with CIC.[2] Literature was searched through November 2022 for RCTs with a duration of at least 4 weeks that evaluated treatments for CIC.[2] The comparison group included placebo, no intervention, or standard of care.[2] The following outcomes were considered by the guideline development panel: CSBMs per week; spontaneous bowel movements (SBMs) per week; responder rate (defined as CSBM per week $\geq$ 3 and increased by at least 1 from baseline); diarrhea leading to discontinuation of treatment; serious adverse events; global relief outcome; QoL scores (using the Patient Assessment of Constipation-Quality of Life, or PAC-QoL); and stool form.[2] The outcomes of CSBMs per week, SBMs per week, and adverse events leading to discontinuation of medication were deemed critical outcomes.[2]

An important limitation of this body of evidence was that clinical trials did not uniformly evaluate interventions on efficacy, adverse effects, and tolerability.[2] There is a paucity of data for the most commonly used treatments of CIC such as fiber, lactulose, senna, and docusate.[2] In addition, there is variability in the definition of inclusion criteria, efficacy, and tolerability outcomes, as well as variance in acceptable clinical trial length by regulators over time.[2] Most of the included studies followed the patients for the short term, and the safety and tolerance of these medications in the long term is not well studied.[2]

Recommendations and supporting evidence are as follows:

- *In adults with CIC, the panel suggests the use of fiber supplementation over management without fiber supplements (conditional recommendation, low-quality evidence).*[2]

The overall certainty of evidence for the use of fiber in the management of CIC was low.[2] The panel rated down certainty of evidence because of high risk of bias (concerns about methods of randomization and allocation concealment in 2 studies and high attrition in another study), indirectness, and imprecision.[2] Among the evaluated fiber supplements, only psyllium appears to be effective, with very limited and uncertain data on bran and inulin.[2] Based on the meta-analysis of

data from 3 RCTs conducted between 1986 and 1995, the use of psyllium may lead to an increase in SBMs per week (MD 2.32, 95% CI 0.86 to 3.79).[2] Combined data from 2 studies showed that the use of psyllium may increase global relief symptoms (RR 1.86, 95% CI 1.49 to 2.30), but there was little to no difference in stool consistency (MD −1.08, 95% CI −1.33 to 0.83).[2] One study examined withdrawal from the study because of diarrhea, but events were infrequent (n=3) and the summary estimate was too imprecise to make any conclusive statement (RR 0.47, CI 0.04 to 5.06); and no serious adverse events were reported in either arm.[2] There were no data on CSBMs per week, responder rate, diarrhea, quality of life, or stool form.[2]

- *In adults with CIC, the panel recommends the use of PEG over management without PEG (strong recommendation, moderate-quality evidence).[2]*

The certainty of evidence for the outcomes of CSBMs, SBMs, responder rate, and global relief was moderate (downgraded based on imprecision).[2] The certainty of evidence for serious adverse events was low because there was no statistical difference between groups.[2] Polyethylene glycol likely results in an increase in CSBMs per week compared with placebo (MD 2.90, 95% CI 2.12 to 3.68) based on one study, and SBMs per week (MD 2.30, 95% CI 1.55 to 3.06) based on a meta-analysis of 3 studies.[2] A higher proportion of participants had global relief of symptoms with PEG compared with placebo.[2] There were no data for changes in stool form and quality of life.[2] Two studies examined serious adverse events, but the number of events was very small, and no conclusive statements could be made about risk of serious adverse events with the use of PEG compared with placebo (RR 0.47, 95% CI 0.16 to 1.33).[2]

- *In adults with CIC, the panel suggests the use of magnesium oxide over management without magnesium oxide (conditional recommendation, very low-quality evidence).[2]*

Two randomized, placebo-controlled trials evaluated the use of magnesium oxide for the management of CIC over 4 weeks.[2] Both trials were completed in Japan.[2] Compared with placebo, treatment with magnesium oxide may increase the number of CSBMs per week (MD 4.29, 95% CI 2.93 to 5.65) and SBMs per week (MD 3.59, 95% CI 2.64 to 4.54).[2] Participants treated with magnesium oxide achieved a higher treatment response compared with placebo (RR 3.93, 95% CI 2.04 to 7.56).[2] The certainty of evidence was very low for the outcomes of CSBMs per week and SBMs per week because of concerns related to inconsistency, indirectness, and imprecision.[2]

- *In adults with CIC who fail or are intolerant to OTC therapies, the panel suggests the use of lactulose over management without lactulose (conditional recommendation, very low-quality evidence).[2]*

The overall certainty of evidence for lactulose was very low.[2] There were significant limitations in the 2 RCTs of lactulose; both trials were conducted over 40 years ago, included relatively small numbers of elderly participants, and did not report the diagnostic criteria for constipation.[2] Based on data from one study, lactulose may have little to no effect on SBMs per week (MD 0.35, 95% CI −0.91 to 1.61). A second study, however, showed that lactulose may be associated with a large increase in global relief (RR 2.42, 95% CI 1.29 to 4.54).[2] In both studies, there was a higher rate of individuals taking lactulose who met the responder definition (defined as improvement in at least 1 SBM from baseline in 1 study and lack of need of other laxatives in other study) compared with placebo.[2] The studies did not report on CSBMs per week, diarrhea, serious adverse events, quality of life, or stool form.[2] The certainty of evidence for SBMs was very low because of risk of bias (unclear methods of randomization and blinding) and imprecision.[2] The certainty of evidence for global relief and responder rate was low because of concerns for risk of bias and imprecision.[2]

- *In adults with CIC, the panel suggests the use of senna over management without senna (conditional recommendation, low-quality evidence).*

The overall certainty of evidence for senna was low.[2] One placebo-controlled RCT examined the safety and efficacy of senna in the management of CIC.[2] Participants were randomly assigned to 1 g of senna (n = 30) or placebo (n = 30) and treated for 28 days.[2] Participants treated with senna may have higher CSBMs per week (MD 7.60, 95% CI 5.90 to 9.30) and SBMs per week (MD 7.6, 95% CI 6.42 to 8.78) compared with the placebo group.[2] No participants in the senna and placebo arms experienced a severe treatment-related adverse event.[2] Evidence limitations to consider include the following: only a single, small RCT

from Japan supports its efficacy; the dose of senna used in the trial is higher than that typically used in clinical practice; there are no long-term effectiveness data; and very limited short-term and no long-term data on harms.[2]

- *In adults with CIC who do not respond to OTC agents, the panel suggests the use of lubiprostone over management without lubiprostone (conditional recommendation, low-quality evidence).[2]*

Three 4-week double-blinded, placebo-controlled RCTs conducted in the U.S. and Japan evaluated the use of lubiprostone for the management of CIC.[2] The pooled data showed that lubiprostone increased number of SBMs per week compared with placebo (MD 1.98, 95% CI 1.17 to 2.79).[2] Data on CSBMs per week were not reported.[2] Lubiprostone may also increase risk of diarrhea leading to discontinuation of treatment compared with placebo (RR 5.30, 95% CI 1.53 to 18.44).[2] There was little to no difference in serious adverse events; however, the CI around the summary estimate was wide, and increased risk of serious adverse events could not be ruled out (RR 1.22, 95% CI 0.62 to 2.42).[2] The certainty of evidence was moderate for the outcome of SBMs per week (because of imprecision) and low for the remainder of the outcomes (because of very serious imprecision).

- *In adults with CIC who do not respond to OTC agents, the panel recommends the use of linaclotide over management without linaclotide (strong recommendation, moderate-quality evidence).[2]*

Three 12-week double-blinded, placebo-controlled RCTs conducted in the US and Canada evaluated the use of linaclotide for the management of CIC.[2] Compared to placebo, linaclotide increases in the number of CSBMs per week (MD 1.37, 95% CI 1.07–1.95) and SBMs per week (MD 1.97, 95% CI 1.59 to 2.36), improves stool consistency (MD 1.25, 95% CI 1.1 to 1.39 higher), and increases the rates of global relief (RR 1.96, 95% CI 1.63 to 2.35).[2] However, participants treated with linaclotide might be 3 times more likely to have diarrhea leading to treatment discontinuation compared with placebo (RR 3.35, 95% CI 2.09 to 5.36).[2] The certainty of evidence was high for outcomes of CSBMs per week, SBMs per week, stool form, and global relief and moderate for rates of diarrhea (downgraded for imprecision).[2] The certainty of evidence for the outcome of serious adverse events was graded as low because of very serious imprecision.[2]

- *In adults with CIC who do not respond to OTC agents, the panel recommends the use of plecanatide over management without plecanatide (strong recommendation, moderate-quality evidence).[2]*

Three 12-week double-blinded, placebo-controlled RCTs conducted in the US and Canada evaluated the use of plecanatide for the management of CIC.[2] The pooled data showed that the use of plecanatide in adults with CIC increases the number of CSBMs per week (MD 1.1, 95% CI 85 to 1.35) and SBMs per week (MD 1.66, 95% CI 1.37 to 1.94) and improves the QoL scores.[2] The intervention group had increased responder rates compared with placebo (RR 1.78, 95% CI 1.46 to 2.18).[2] Responders were defined as people with at least 3 CSBMs per week and 1 or more CBSM over baseline for at least 9 of 12 weeks including 3 of the last 4 weeks, [2] Participants treated with plecanatide had higher rates of reported diarrhea leading to treatment discontinuation (RR 5.39, 95% CI 2.40 to 12.11).[2] The certainty of evidence was high for outcomes of CSBM, SBM, and QoL and moderate for diarrhea leading to treatment discontinuation and serious adverse events.[2] The panel rated down certainty of these outcomes because of imprecision.[2]

- *In adults with CIC who do not respond to OTC agents, the panel recommends the use of prucalopride over management without prucalopride (strong recommendation, moderate-quality evidence)*

Five 12-week double-blinded, placebo-controlled RCTs evaluated the use of prucalopride for the management of CIC.[2] The studies were conducted in the United States, Europe, and the Asia-Pacific region.[2] Compared with placebo, prucalopride increased number of CSBMs per week (MD 0.96, 95% CI 0.64 to 1.29).[2] SBMs per week were not studied in any of the included studies.[2] Responder rates, defined as ≥ 3 CSBMs per week, were higher in the prucalopride group (RR 2.37, 95% CI 1.97 to 2.85) compared with placebo.[2] Diarrhea leading to treatment discontinuation was higher in the prucalopride group compared with placebo (RR 3.00, 95% CI 1.89–4.78).[2] The occurrence of serious adverse events was low; however, the CI around the summary estimate was imprecise and included a possible

increased risk.[2] The certainty of evidence was high for outcomes of CSBM frequency, responder rate, and moderate for diarrhea leading to treatment discontinuation and serious adverse events (because of small event rates and wide CIs around the summary).[2]

2. Irritable Bowel Syndrome

American College of Gastroenterology: Management of Irritable Bowel Syndrome

In 2021, the ACG issued guidance for the management of IBS.[3] Literature was searched through February 1, 2020 to identify placebo-controlled RCTs conducted in at least 10 subjects with a study duration greater than 4 weeks to provide evidence for each recommendation.[3] This guideline focuses primarily on the evaluation and management of patients in North America. Recommendations were developed with an emphasis on evaluating global response to IBS symptoms for each therapeutic agent, based on FDA guidance.[3] A limitation to this approach is that not all therapies were evaluated in double-blind, placebo-controlled RCTs with the primary endpoint of an improvement in global IBS symptoms.[3] Most therapeutic agents used to treat IBS symptoms were developed with an emphasis on one specific IBS subtype (IBS-C or IBS-D).[3] Currently, there are no approved medications for the treatment of mixed IBS or those with a significant pattern of abnormal stool (IBS-U).[3]

Irritable Bowel Syndrome: Evidence for Fiber, Antispasmodics, and Probiotics

- *Dietary fiber (25 to 35 grams/day) should be used to treat global IBS symptoms (strong recommendation; moderate-quality evidence).[3]*

Evidence evaluating efficacy of dietary fiber for IBS is limited. However, recommendations are based on improved stool viscosity and frequency which logically supports the use of fiber in patients with IBS-C despite limited evidence.[3]

- *Antispasmodics (e.g., dicyclomine, hyoscyamine, hyoscine) are **not** recommended to treat global IBS symptoms (conditional recommendation; low-quality evidence).[3]*

Three antispasmodics, dicyclomine, hyoscyamine, and hyoscine, are commercially accessible in the U.S., with a paucity of data to support their efficacy.[3] Published studies are methodologically limited because of small sample size, lack of standardized enrollment criteria, different trial designs, and different endpoints.[3]

- *Probiotics are **not** recommended for the treatment of global IBS symptoms (conditional recommendation; very low-quality evidence).[3]*

Studies examining probiotics in IBS do not consistently evaluate the same organisms, are generally small, single center, and do not consistently evaluate clinical outcomes recommended by the FDA for pharmacologic therapies.[3]

Irritable Bowel Syndrome with Constipation: Evidence for PEG, Lubiprostone, Linaclotide, Plecanatide, and Tegaserod

- *PEG products are **not** recommended to relieve global IBS-C symptoms (conditional recommendation; low-quality evidence).[3]*

Polyethylene glycol is FDA-approved for occasional constipation based on several RCT studies.[3] However, RCTs in IBS-C have failed to show that PEG improves either overall symptoms or pain in patients with IBS-C.[3] The ACG recommends against use of PEG alone for the treatment of global IBS-C symptoms, although clinicians may use PEG as first-line treatment of constipation in IBS, given its low cost and availability.[3]

- *For IBS-C, the ACG recommends the use of the secretagogues lubiprostone, linaclotide, and plecanatide (strong recommendation; high quality-evidence).[3]*

Lubiprostone has been evaluated in 3 RCTs and one high-quality systematic review.[3] Over 12 weeks lubiprostone improved overall IBS-C symptoms compared to placebo with a relative risk of symptom persistence of 0.91 (95% CI 0.87 to 0.95) and a number needed to treat (NNT) of 13.[3] Diarrhea (6%–14%) and nausea (8%–19%) were the most frequently reported events in RCTs.[3] The overall incidence rate of treatment-emergent nausea in RCTs was significantly greater in

patients receiving lubiprostone than placebo (10.9% vs 6.4%, respectively; P<0.01).[3] Nausea is dose-dependent, but may be reduced by consuming lubiprostone with meals.[3]

There are currently 2 FDA-approved guanylate cyclase-C agonists for the treatment of IBS-C, linaclotide and plecanatide. Linaclotide has been studied in 3 RCTs and evaluated in several systematic reviews/meta-analyses.[3] The safety and efficacy of plecanatide has been evaluated in 3 RCTs and one subsequent systematic review/meta-analysis.[3] Indirect comparative analyses suggest that both are comparably effective, safe, and well-tolerated.[3] Diarrhea is the most common reported adverse event, but discontinuation rates due to diarrhea are low and both medications are well-tolerated.[3]

- *In women younger than 65 years of age with 1 or fewer cardiovascular risk factors who have not adequately responded to secretagogues, tegaserod can be used to treat IBS-C symptoms (conditional recommendation; low-quality evidence).[3]*

Eleven placebo-controlled RCTs have evaluated the efficacy of tegaserod for IBS-C.[3] A systematic review and meta-analysis of these 11 trials was performed and overall, patients treated with tegaserod were less likely to have persistent IBS-C symptoms compared with those treated with placebo (RR 0.85; 95% CI 0.80 to 0.90).[3] In clinical trials, the most common adverse effect was diarrhea, occurring in 6% of patients treated with tegaserod compared with 2% for those treated with placebo.[3]

Irritable Bowel Syndrome with Diarrhea: Evidence for Bile Acid Sequestrants, Rifaxamin, Alosetron and Eluxadoline

- *Bile acid sequestrants are **not** recommended to treat global IBS-D symptoms (conditional recommendation; very low-quality evidence).[3]*

There is a need for methodologically rigorous, adequately powered trials of bile acid sequestrants (e.g., cholestyramine) in patients with IBS-D.[3] Bile acid malabsorption is a condition characterized by an inability to reabsorb sufficient bile acids in the terminal ileum. Excessive bile acids in the colon are exposed to colonic flora leading to production of secondary bile acids which can increase colonic secretion of fluid, thereby resulting in diarrhea. Widely accessible, reliable testing for bile acid malabsorption is not available, and there is a lack of controlled trials to evaluate efficacy and safety of bile acid sequestrants in patients with IBS-D.[3]

- *Rifaximin is recommended to treat global IBS-D symptoms (strong recommendation; high quality-evidence).[3]*

The safety and efficacy of rifaximin for IBS-D is supported by multiple clinical trials and one meta-analysis.[3] The FDA has approved rifaximin for a single 14-day course of treatment in IBS-D. If patients relapse, 2 additional treatment courses are approved for recurrence of IBS-D.

- *In women with severe symptoms who have failed conventional therapy, alosetron is recommended to relieve global IBS-D symptoms (conditional recommendation; low-quality evidence).[3]*

Two meta-analyses have evaluated the efficacy of alosetron for IBS-D compared to placebo.[3] Alosetron improved IBS-D symptoms compared to placebo (RR 0.79. 95% CI 0.69 to 0.90; NNT = 8) based on a meta-analysis of 8 RCTs and overall symptom improvement in 3 RCTs (RR 1.58, 95% CI 1.42 to 1.75).[3] Alosetron was voluntarily withdrawn from the market in 2000 after postmarketing reports of increased rates of ischemic colitis, complicated constipation (obstruction or perforation), and death.[3] It is now marketed with a REMS program to monitor adverse events. The current evidence supports using alosetron to relieve global symptoms in women with severe IBS-D when other interventions have failed.[3]

- *Eluxadoline is recommended to treat global IBS-D symptoms (conditional recommendation; moderate-quality evidence).[3]*

One randomized, prospective study and a retrospective analysis have shown that eluxadoline improves symptoms in patients with IBS-D who have failed previous trials of loperamide.[3] Loperamide is not recommended as first-line therapy for treating IBS-D symptoms because it may improve diarrhea but not global

IBS symptoms.[3] Two large, phase 3, randomized, double-blind, placebo-controlled studies have evaluated the efficacy and safety of eluxadoline for adults meeting Rome III criteria for IBS-D.[3] The primary endpoint of these studies, defined a priori to meet FDA guidelines, was a decrease from baseline of ≥30% in the daily average score for worst abdominal pain on ≥ 50% days evaluated, and on the same days, a daily stool consistency score of <5 using the Bristol Stool Form Scale.[3] Efficacy results were pooled from a 26-week study and the first 26 weeks of a separate 52-week study.[3] In these 2 studies, the primary efficacy endpoint was more likely to be met by patients treated with eluxadoline 75 mg (n = 806) or 100 mg (n = 809) twice daily compared with those treated with placebo (n = 808) during both the first 12 weeks (26.2% and 27.0%, vs 16.7%, respectively) (P < 0.001, vs placebo) and the first 26 weeks of the 2 trials (26.7% and 31.0%, vs 19.5%; P < 0.001, vs placebo).[3] The most common reported adverse effect with eluxadoline use was constipation (8% vs. 2.5% for placebo). Nausea was reported by 7.7% of patients (vs. 5% for placebo) and cardiac events were few and not different between groups.[3]

American Gastroenterological Association: Management of Irritable Bowel Syndrome with Constipation

In 2022, the AGA updated guidance for the treatment of IBS-C.[4] Literature was searched through April 2020.[4] The AGA panel focused on adults (aged 18 years and older) with IBS using symptom-based diagnostic criteria.[4] Important outcomes included abdominal pain response, CSBM response, and improvement in IBS-QoL score.[4] The FDA responder criteria for IBS-C was defined as a 30% or more reduction in average daily worst abdominal pain scores and an increase of at least 1 complete spontaneous bowel movements (CSBMs) per week compared with baseline for at least 6 of 12 weeks.[4] For the IBS-QoL score, the range is 0 to 100 and a minimal important difference was defined as 14.[4] The minimal clinically meaningful improvement for each patient was defined by the authors as an improvement over placebo in an outcome of ≥ 10%.[4] This threshold was used to make contextualized judgments about imprecision.[4] For all recommendations, the comparator was no drug treatment.[4]

Recommendations and rationale for the specific recommendations are as follows:

- *In patients with IBS-C, the AGA suggests using tenapanor (conditional recommendation; moderate-quality evidence).[4]*

Evidence shows that tenapanor improved abdominal pain and CSBM response compared with placebo in individuals with IBS-C, with low rates of diarrhea leading to treatment discontinuation.[4] The panel rated the FDA responder end points (reduced abdominal pain and increased in CSBMs per week) down for imprecision because the confidence interval crossed the AGA threshold of a clinically meaningful difference.[4] The trials were considered to have a low risk of bias.[4] Tenapanor was associated with improvement in other clinically important end points, including SBM frequency; stool consistency; and global measures of IBS severity, constipation severity, and treatment satisfaction compared with placebo.[4] Diarrhea was the most common adverse event, leading to discontinuation of medication in 6.6% of patients in the tenapanor group compared with 1.0% in the placebo group.[4]

- *In patients with IBS-C, the AGA suggests using plecanatide (conditional recommendation; moderate-quality evidence).[4]*

The panel rated the FDA responder end points down for imprecision because the confidence interval crossed the AGA threshold of a clinically meaningful difference.[4] The trials were considered to have a low risk of bias.[4] In individuals with IBS-C, plecanatide treatment results in greater improvement in abdominal pain and CSBM response compared with placebo.[4] However, the improvement in these end points may be small in some patients.[4] Plecanatide was also associated with improvement in stool frequency, bloating, straining, and global measures of treatment satisfaction compared with placebo.[4] Diarrhea was the most common adverse event (4.3% plecanatide vs. 1.0% placebo), and 1.2% of patients withdrew from the trials due to diarrhea from plecanatide.[4]

- I*n patients with IBS-C, the AGA recommends using linaclotide (strong recommendation; high-quality evidence).[4]*

The individual linaclotide trials were considered to have a low risk of bias.[4] The panel rated down the quality of evidence for inconsistency (IBS-QoL) and imprecision (adverse events leading to treatment discontinuation).[4] Across 4 RCTs, linaclotide improved global assessment of IBS-C symptoms, abdominal pain, and CSBM response compared with placebo.[4] A 2018 network meta-analysis ranked linaclotide first in efficacy among secretagogues for IBS-C, although head-to-

head trials are lacking.[4] The rate of diarrhea is higher with linaclotide than placebo (16.2% vs. 2.3%) and resulted in more discontinuations (3.4% vs. 0.23%); however, no serious adverse effects due to diarrhea were reported in any of the trials.[4] The odds of diarrhea and diarrhea-related withdrawals were similar between plecanatide and linaclotide, based on indirect comparisons in a meta-regression analysis, which controlled for differences in diarrhea rates in the placebo arm.[4]

- *In women under 65 years of age with IBS-C, without a history of cardiovascular ischemic events, the AGA suggests using tegaserod (conditional recommendation; moderate-quality evidence).[4]*

The panel made a conditional recommendation for the use of tegaserod in individuals with IBS-C, noting that the FDA approval is for women under the age of 65 years without a history of cardiovascular events.[4] In patients with IBS-C, treatment with tegaserod probably results in greater improvement in the modified FDA end point for IBS-C, global relief, abdominal pain/discomfort, and BM frequency compared with placebo; however, there was no improvement in overall quality of life.[4] With the exception of BM frequency, the AGA panel rated down the quality of evidence for imprecision because the confidence intervals for the other outcomes crossed the threshold for clinically meaningful differences.[4]

- *In patients with IBS-C, the AGA suggests using lubiprostone (conditional recommendation; moderate-quality evidence).[4]*

No new RCTs of lubiprostone for the management of IBS-C were identified since the 2014 guidance was published.[4] Although lubiprostone improved global outcomes and abdominal pain response compared with placebo, these differences did not meet the threshold for clinically meaningful changes.[4] Furthermore, lubiprostone was not superior to placebo for adequate SBM response and CSBM was not measured.[4]

- *In patients with IBS-C the AGA suggests using PEG laxatives (conditional recommendation; low-quality evidence).[4]*

Although PEG has been shown to improve symptoms of constipation, larger high-quality studies are needed to adequately evaluate the efficacy of PEG in patients with IBS-C in whom abdominal pain is a more predominant symptom.[4]

- *In patients with IBS-C the AGA suggests using antispasmodics (conditional recommendation; low-quality evidence).[4]*

Antispasmodics include a wide array of pharmacological therapies that been used clinically for many years but have not been subjected to rigorous large multicenter trials.[4] Trials have considerable variation and the quality of the studies was generally low.[4] However, antispasmodics improved global symptoms and abdominal pain compared to placebo, although the latter did not meet the ACG criteria for being clinically meaningful.[4] It is not clear whether antispasmodics are more efficacious in specific IBS subtypes, but their regular use in constipation may be limited by anticholinergic effects.[4] Although these medications are often recommended for treatment of postprandial symptoms in IBS, this has not been studied specifically in RCTs.[4]

American Gastroenterological Association: Pharmacologic Management of Irritable Bowel Syndrome with Diarrhea

In 2022 the AGA updated 2014 guidance for the management of IBS-D.[5] Literature was searched through April 2020. The FDA responder end point for IBS-D was a critical outcome. Responders had both a 30% or more reduction in average daily worst abdominal pain scores and at least a 50% reduction in number of days per week with at least 1 stool that has a consistency of type 6 or 7 (mushy or watery stool) according to the Bristol Stool Form Scale compared with baseline.[5] Other important outcomes included abdominal pain response, complete spontaneous bowel movement response, improvement in IBS-QoL, improvement in stool consistency, urgency, and bloating.[5] Undesirable outcomes included adverse effects leading to treatment discontinuation. For IBS-QoL score, the range is 0 to 100 and a minimal important difference is 14.[5] No minimal clinical important threshold has been established for improvement in stool consistency, urgency, or bloating.[5] The minimal clinically meaningful improvement was defined by the authors as an improvement in an outcome of $\geq$ 10% compared to placebo.[5] This threshold was used to make contextualized judgments about imprecision.[5]

Recommendations and rationale for the specific recommendations are as follows:

- *In patients with IBS-D, the AGA suggests using eluxadoline. Eluxadoline is contraindicated in patients without a gallbladder or those who drink more than 3 alcoholic beverages per day (conditional recommendation; moderate-quality evidence).*[5]

Evidence supporting the efficacy of eluxadoline in IBS-D based on 2 phase 3 RCTs.[5] Eluxadoline improved the proportion of patients with a response to treatment and improved adequate global relief of IBS symptoms compared with placebo, but the improvement may be small in some patients.[5] The panel downgraded evidence for imprecision across many of the outcomes because the lower boundary of the confidence interval crossed the threshold of a clinically meaningful difference, and the range of possible effects included benefits that may not be meaningful to patients.[5] Although eluxadoline was associated with clinically meaningful improvements in stool consistency and urgency, it had less effect on abdominal pain.[5] Thus, eluxadoline may be more ideal in patients with IBS-D with predominant and bothersome diarrhea than in those with predominant or more severe abdominal pain.[5] Eluxadoline is contraindicated in patients without a gallbladder and excessive alcohol abuse, as well as a history of Sphincter of Oddi disease, pancreatitis, bile duct obstruction, and severe liver impairment.[5]

- *In patients with IBS-D, the AGA suggests using rifaximin (conditional recommendation; moderate-quality evidence).* [5]
- *In patients with IBS-D with initial response to rifaximin who develop recurrent symptoms, the AGA suggests retreatment with rifaximin (conditional recommendation; moderate-quality evidence).*[5]

Although the evidence shows that initial treatment and retreatment with rifaximin is efficacious, the improvements across many outcomes may be small and may not be clinically meaningful.[5] The panel rated down for imprecision across many of the outcomes because the lower boundary of the CI crossed the threshold of significance and for a clinically meaningful improvement.[5] In the retreatment trial, rifaximin was associated with a greater durable response and prevention of symptom recurrence compared with placebo.[5] In addition, rifaximin retreatment improved abdominal pain, urgency, and IBS-QoL more than placebo, but had not impact on stool consistency and bloating.[5]

- *In patients with IBS-D, the AGA suggests using alosetron (conditional recommendation; moderate-quality evidence).*[5]

There is moderate- to high-quality evidence that alosetron improves symptoms of IBS compared with placebo, but careful selection of patients and education about the risks and benefits of alosetron is recommended.[5] Of note, the 9-year follow-up data on the postmarketing safety of alosetron under the risk management program have shown a decline over time in the incidence of complications of constipation, but incidence of ischemic colitis has remained stable.[5]

- *In patients with IBS-D, the AGA suggests using loperamide (conditional recommendation; very low-quality evidence).*[5]

In clinical studies, loperamide did not improve global symptoms of IBS and urgency, but did improve abdominal pain and stool consistency.[5] Improvements in these symptoms occurred within 3 to 5 weeks of starting treatment, but details of how this was determined were poorly described.[5] However, this review was based on only 2 very small studies. Both studies were published in 1987 and were conducted at a time when there was less guidance on the conduct of high-quality clinical trials.[5] Loperamide is effective in reducing diarrhea and is commonly used in IBS-D, but there is a lack of data evaluating its efficacy in relieving abdominal symptoms.[5]

- *In patients with IBS, the AGA suggests using antispasmodics (conditional recommendation; low-quality evidence).*[5]

Antispasmodics include a wide array of pharmacological therapies that have been used clinically for many years but have not been subjected to rigorous large multicenter trials.[5] There was considerable variation among the trials and the quality of the studies was generally low.[5] However, antispasmodics were significantly associated with a greater relief of global symptoms and abdominal pain, although the latter did not meet the AGA criteria for being clinically meaningful.[5]

3. Opioid Induced Constipation

National Institute for Health and Care Excellence: Naldemedine for Treating Opioid-Induced Constipation

In 2020, NICE issued recommendations for the use of naldemedine in people with OIC.[6] Treatment may include a peripherally acting mu-opioid receptor antagonist (PAMORA) alone.[6] But, commonly a PAMORA (oral naloxegol or subcutaneous methylnaltrexone) and a conventional laxative are used together.[6] Naldemedine is an oral PAMORA for adults who have had laxative treatment.[6] The clinical evidence shows that naldemedine increases the frequency of bowel movements compared with no treatment.[6]

- Naldemedine is recommended by NICE for OIC in adults who have had laxative treatment.[6]

4. Hepatic Encephalopathy

European Association for the Study of the Liver: Clinical Practice Guideline on Management of Hepatic Encephalopathy

In 2022, EASL issued guidance for the management of HE.[7] In terms of its severity, HE is qualified as covert (minor or no signs/symptoms but abnormalities on neuropsychological and/or neurophysiological tests) or overt (grades II or over according to the West Haven criteria).[7] An open-label RCT showed that patients who had recovered from an episode of overt HE and were receiving lactulose had a 14-month HE recurrence risk of 20% compared to risk of 47% among those who did not receive lactulose.[7] A 2020 systematic review and network meta-analysis including 1,828 participants demonstrated that lactulose was effective at preventing overt episodes of HE with only mild gastrointestinal adverse effects.[7] A 2016 Cochrane review evaluated 38 trials that demonstrated a beneficial effect of lactulose on preventing overt episodes of HE (RR 0.58, 95% CI 0.50 to 0.69; 1,415 participants; 22 RCTs) but only 2 of these RCTs specifically addressed the effectiveness of lactulose in the secondary prophylaxis of overt HE.[7] Rifaximin compared to placebo decreased the risk of recurrence of overt HE in patients with cirrhosis and 2 or more episodes of overt HE within the previous 6 months, with HE episodes occurring in 22.1% of patients in the rifaximin group versus 45.9% in the placebo group (NNT =4) (hazard ratio [HR] 0.42; 95% CI 0.28 to 0.64; p <0.001).[7] Rifaximin also decreased the risk of hospitalization (13.6%) compared to placebo (22.6%), with a NNT of 9. Of these patients, 91% were on concurrent lactulose therapy, supporting the use of rifaximin in addition to lactulose for the prevention of HE after a second overt HE episode.[7] A systematic review and meta-analysis including 2 RCTs estimated rifaximin had a beneficial effect on the secondary prevention of overt HE (RR 1.32; 95% CI 1.06 to 1.65).[7] Recommendations and strength of evidence are as follows:

- Patients with overt HE should be treated with lactulose (strong recommendation; low-quality evidence).[7]
- Lactulose is recommended as secondary prophylaxis following a first episode of overt HE, and should be titrated to obtain 2 to 3 bowel movements per day (strong recommendation; high-quality evidence).[7]
- Rifaximin as an adjunct to lactulose is recommended as secondary prophylaxis following ≥ 1 additional episodes of overt HE within 6 months of the first episode (strong recommendation, moderate-quality evidence).[7]

New Indications:

- May 2015: Rifaximin (XIFAXAN) received expanded FDA-approval for treatment of IBS-D in adults.[8] The recommended dosage of rifaximin for IBS-D is 550 mg taken orally three times a day for 14 days.[8] Patients who experience a recurrence of symptoms can be retreated up to two times with the same dosage regimen.[8] Rifaximin is also approved to reduce the risk of overt recurrence of HE in adults at a dose of 550 mg twice daily and to treat TD caused by noninvasive strains of *E. Coli* in adults and pediatric patients 12 years of age and older.[8] Dosing for TD is rifaximin 200 mg taken orally three times a day for 3 days.[8]

  The efficacy and safety of rifaximin for the treatment of IBS-D was evaluated in 2 double-blind, placebo-controlled RCTs of identical design.[8] In these trials, a total of 1,258 patients meeting Rome II criteria for IBS-D and alternating IBS (bowel habits alternating between diarrhea and constipation) were randomized to receive rifaximin 550 mg three times a day (n=624) or placebo (n=634) for 14 days and then followed for a 10-week treatment-free period.[8] The primary

endpoint for both trials was the proportion of patients who achieved adequate relief of IBS signs and symptoms for at least 2 of 4 weeks during the month following 14 days of treatment.[8] Adequate relief was defined as a response of "yes" to the following weekly Subject Global Assessment (SGA) question: "In regards to your IBS symptoms, compared to the way you felt before you started study medication, have you, in the past 7 days, had adequate relief of your IBS symptoms? [Yes/No]."[8] Adequate relief of IBS symptoms was experienced by more patients receiving rifaximin than those receiving placebo during the month following 2 weeks of treatment (SGA-IBS Weekly Results: Trial 1: 41% vs. 31%, treatment difference: 10%; 95% CI 2.1 to 17.1 and Trial 2: 41% vs. 32%, treatment difference: 8%; 95% CI 1.0 to 15.9).[8] The most frequently reported adverse effect in these trials was nausea (3% rifaximin vs. 2% placebo).[8]

A third RCT evaluated the safety and efficacy of rifaximin in patients who received 1 open-label treatment and 2 double-blind repeat treatments of 14 days each over a period of up to 46 weeks.[8] Responders to treatment were defined as achieving both of the following: 1) ≥30% improvement from baseline in the weekly average abdominal pain score based on the daily question: "In regards to your specific IBS symptoms of abdominal pain, on a scale of 0-10, what was your worst IBS-related abdominal pain over the last 24 hours? 'Zero' means you have no pain at all; 'Ten' means the worst possible pain you can imagine" and 2) at least a 50% reduction in the number of days in a week with a daily stool consistency of Bristol Stool Scale type 6 or 7 compared with baseline where 6=fluffy pieces with ragged edges, a mushy stool; 7=watery stool, no solid pieces; entirely liquid.[8] The response rate for each IBS symptom during the open-label phase of Trial 3 is similar to the rates seen in Trials 1 and 2.[8]

A total of 636 patients who responded to initial treatment subsequently had sign and symptom recurrence and were randomized to the repeat treatment phase.[8] The median time to recurrence for patients who experienced initial response during the open-label phase with rifaximin was 10 weeks (range 6 to 24 weeks).[8] The primary endpoint in the double-blind, placebo-controlled portion of the trial was the proportion of patients who were responders to repeat treatment in both IBS-related abdominal pain and stool consistency as defined above during the 4 weeks following the first repeat treatment with rifaximin.[8] Compared with placebo, more patients receiving rifaximin were monthly responders for abdominal pain and stool consistency in the primary analysis (31% vs. 38%; treatment difference: 7%: 95% CI 0.9 to 16.9).[8] The adverse reaction that occurred more frequently in rifaximin-treated patients (n=328) than placebo (n=308) during the double-blind treatment phase was increased alanine aminotransferase (rifaximin 2%, placebo 1%).[8] The manufacturer states that rifaximin should be used with caution in patients with severe (Child Pugh Class C) hepatic impairment.[8]

- June 2023: Linaclotide (LINZESS) capsules received an expanded indication for the treatment of functional constipation (FC) in pediatric patients aged 6 to 17 years.[9] The recommended dose for this indication is 72 mcg once daily.[9] For adults with IBS-C, the recommended dose is 290 mcg orally once daily.[9] For adults with CIC, the recommended dose is 72 mcg to 145 mcg once daily based on presentation on tolerability.[9]

  The efficacy of linaclotide for the treatment of FC in pediatric patients 6 to 17 years of age was established in a 12-week double-blind, placebo-controlled RCT.[9] Patients in the trial had a mean age of 11 years (range 6 to 17 years); 55% were female; 45% identified as Hispanic or Latino; 70% identified as White, 26% as Black or African American, 2% as Asian, and 2% identified as another racial group.[9] A total of 328 patients received treatment with linaclotide 72 mcg or placebo once daily.[9] Enrolled patients had less than 3 SBMs per week and 1 or more of the following criteria at least once per week for at least 2 months before the screening visit:
  - history of stool withholding or excessive voluntary stool retention;
  - history of painful or hard bowel movements;
  - history of large diameter stools that may obstruct the toilet;
  - presence of a large fecal mass in the rectum or
  - at least 1 episode of fecal incontinence per week.[9]

Patients were excluded if they met criteria for pediatric IBS-C or had fecal impaction. Patients were permitted to continue previously stable doses of bulk laxatives, fiber, stool softeners, or probiotics. During the trial, patients could use bisacodyl or senna as needed, but were not allowed to take other laxatives, bismuth, prokinetic agents, or other drugs to treat FC.[9]

The primary efficacy endpoint was the least squares 12-week mean change from baseline in SBM frequency per week. The results demonstrated that patients who received linaclotide had statistically significant improvements compared with placebo in number of SBMs per week (2.6 vs. 1.3; treatment difference: 1.3; 95% CI 0.7 to 1.8).[9] The minimal clinically important difference for this outcome was not defined. Diarrhea was the most common adverse reaction and was reported in 4% of linaclotide-treated patients compared to 2% of placebo-treated patients.[9] One patient in the linaclotide-treated group reported severe diarrhea and discontinued treatment.[9] No patient in the placebo-treated group discontinued treatment due to severe diarrhea.[9] Most reported cases of diarrhea started within the first 2 weeks of linaclotide treatment.[9] Other adverse reactions reported at a higher incidence in the linaclotide group compared to placebo included nausea (2 patients),abdominal discomfort, and dehydration (1 patient each).[9]

New FDA Safety Alerts:

Table 6. Description of new FDA Safety Alerts[48]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Naloxegol Oxalate	MOVANTIK	4/2020	Warnings and Precautions	Cases of gastrointestinal (GI) perforation have been reported with use of peripherally acting opioid antagonists, including MOVANTIK. Postmarketing cases of GI perforation, including fatal cases, were reported when MOVANTIK was used in patients at risk of GI perforation (e.g., infiltrative gastrointestinal tract malignancy, recent gastrointestinal tract surgery, diverticular disease including diverticulitis, ischemic colitis, or concomitantly treated with bevacizumab). MOVANTIK is contraindicated in patients with known or suspected gastrointestinal obstruction or in patients at risk of recurrent obstruction. Consider the overall risk-benefit profile when using MOVANTIK in patients with these conditions or other conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g., Crohn's disease). Monitor for the development of severe, persistent or worsening abdominal pain; discontinue MOVANTIK in patients who develop this symptom.[49]
Linaclotide	LINZESS	8/2021	Black Boxed Warning	The previous black boxed warning stated that children less than 6 years of age were at risk of serious dehydration. The updated warning now states linaclotide is contraindicated in patients less than 2 years of age due to the risk of serious dehydration.[9] Linaclotide is contraindicated in patients less than 2 years of age.[9]
Linaclotide	LINZESS	6/2023	Warnings and Precautions	Diarrhea has been reported in pediatric patients 6 to 17 years of age with FC treated with LINZESS. In a double-blind placebo-controlled trial, diarrhea was the most common adverse reaction and was reported in 4% of pediatric patients 6 to 17 years of age treated with LINZESS 72 mcg once daily. Severe diarrhea was reported in one LINZESS-treated patient.[9]

			Pediatric Use	The safety and effectiveness of LINZESS in patients with functional constipation [50] less than 6 years of age or in patients with IBS-C less than 18 years of age have not been established.[9]
Telotristat	XERMELO	9/2022	Contraindications Warnings and Precautions	Telotristat is contraindicated in patients with a history of a hypersensitivity reaction to telotristat. Reactions have included angioedema, rash and puritis. Telotristat reduces bowel movement frequency and may lead to constipation. Serious complications of constipation have been reported during clinical trials and postmarketing.
Alvimopan	ENTEREG	11/2020	Warnings and Precautions	The Single Shared System REMS (Alvimopan REMS) replaces the ENTEREG Access Support and Education (E.A.S.E.) REMS *www.alvimopanREMS.com replaces www.ENTEREGREMS.com*

Randomized Controlled Trials:
A total of 201 citations were manually reviewed from the initial literature search. After further review, 201 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

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Appendix 1: Current Preferred Drug List

Rifamycins

Generic	Brand	Route	Form	PDL
rifamycin sodium	AEMCOLO	ORAL	TABLET DR	N
rifaximin	XIFAXAN	ORAL	TABLET	
rifaximin	XIFAXAN	ORAL	TABLET	

Laxatives, Chronic Constipation

Generic	Brand	Route	Form	PDL
bisacodyl	LAXATIVE	ORAL	TABLET	Y
bisacodyl	BISACODYL	ORAL	TABLET DR	Y
bisacodyl	GENTLE LAXATIVE	ORAL	TABLET DR	Y
bisacodyl	LAXATIVE	ORAL	TABLET DR	Y
bisacodyl	MODANE	ORAL	TABLET DR	Y
bisacodyl	WOMEN'S GENTLE LAXATIVE	ORAL	TABLET DR	Y
calcium polycarbophil	FIBER	ORAL	TABLET	Y
calcium polycarbophil	FIBER LAXATIVE	ORAL	TABLET	Y
calcium polycarbophil	FIBER-LAX	ORAL	TABLET	Y
cellulose	UNIFIBER	ORAL	POWDER	Y
docusate calcium	DOCUSATE CALCIUM	ORAL	CAPSULE	Y
docusate calcium	KAOPECTATE	ORAL	CAPSULE	Y
docusate calcium	STOOL SOFTENER	ORAL	CAPSULE	Y
docusate sodium	COLACE	ORAL	CAPSULE	Y
docusate sodium	COLACE CLEAR	ORAL	CAPSULE	Y
docusate sodium	DOCUSATE SODIUM	ORAL	CAPSULE	Y
docusate sodium	STOOL SOFTENER	ORAL	CAPSULE	Y
docusate sodium	DOCUSATE SODIUM	ORAL	LIQUID	Y
docusate sodium	SILACE	ORAL	LIQUID	Y
docusate sodium	COLACE	ORAL	SYRUP	Y
docusate sodium	DOCUSATE SODIUM	ORAL	SYRUP	Y
docusate sodium	PEDIA-LAX STOOL SOFTENER	ORAL	SYRUP	Y
docusate sodium	SILACE	ORAL	SYRUP	Y
docusate sodium	DOCUSATE SODIUM	ORAL	TABLET	Y
docusate sodium	DOK	ORAL	TABLET	Y
docusate sodium	STOOL SOFTENER	ORAL	TABLET	Y
fructooligosaccharides/polydex	FIBEREX F15	ORAL	LIQUID	Y
lactulose	CONSTULOSE	ORAL	SOLUTION	Y
lactulose	ENULOSE	ORAL	SOLUTION	Y

lactulose	GENERLAC	ORAL	SOLUTION	Y
lactulose	LACTULOSE	ORAL	SOLUTION	Y
magnesium citrate	MAGNESIUM CITRATE	ORAL	SOLUTION	Y
magnesium hydroxide	MILK OF MAGNESIA	ORAL	ORAL SUSP	Y
magnesium hydroxide	PEDIA-LAX	ORAL	TAB CHEW	Y
magnesium sulfate	EPSOM SALT	ORAL	GRANULES	Y
methylcellulose	FIBER	ORAL	TABLET	Y
methylcellulose	FIBER LAXATIVE	ORAL	TABLET	Y
methylcellulose	FIBER THERAPY	ORAL	TABLET	Y
methylcellulose (with sugar)	FIBER THERAPY	ORAL	POWDER	Y
polyethylene glycol 3350	CLEARLAX	ORAL	POWDER	Y
polyethylene glycol 3350	GAVILAX	ORAL	POWDER	Y
polyethylene glycol 3350	LAXATIVE PEG 3350	ORAL	POWDER	Y
polyethylene glycol 3350	POLYETHYLENE GLYCOL 3350	ORAL	POWDER	Y
psyllium husk	KONSYL	ORAL	POWDER	Y
psyllium seed	KONSYL	ORAL	POWDER	Y
psyllium seed	NATURAL VEGETABLE LAXATIVE	ORAL	POWDER	Y
psyllium seed	NATURAL VEGETABLE POWDER	ORAL	POWDER	Y
psyllium seed	NVP	ORAL	POWDER	Y
psyllium seed (with dextrose)	KONSYL-D	ORAL	PACKET	Y
psyllium seed (with dextrose)	KONSYL-D	ORAL	POWDER	Y
psyllium seed (with dextrose)	MODANE BULK	ORAL	POWDER	Y
psyllium seed (with sugar)	NATURAL PSYLLIUM LAXATIVE	ORAL	POWDER	Y
psyllium seed (with sugar)	NATURAL VEGETABLE LAXATIVE	ORAL	POWDER	Y
psyllium seed (with sugar)	NVP	ORAL	POWDER	Y
psyllium seed/aspartame	KONSYL	ORAL	POWDER	Y
psyllium seed/sod bicarb	KONSYL EFFERVESCENT	ORAL	PACKET	Y
senna leaf extract	SENNA	ORAL	SYRUP	Y
sennosides	SENNA	ORAL	CAPSULE	Y
sennosides	SENNA	ORAL	SYRUP	Y
sennosides	CHOCOLATED LAXATIVE	ORAL	TAB CHEW	Y
sennosides	LAXATIVE	ORAL	TABLET	Y
sennosides	SENNA	ORAL	TABLET	Y
sennosides	SENNA LAX	ORAL	TABLET	Y
sennosides	SENNA LAXATIVE	ORAL	TABLET	Y
sennosides	SENOKOT	ORAL	TABLET	Y
sennosides/docusate sodium	COLACE 2-IN-1	ORAL	TABLET	Y
sennosides/docusate sodium	SENEXON-S	ORAL	TABLET	Y
sennosides/docusate sodium	SENNA PLUS	ORAL	TABLET	Y
sennosides/docusate sodium	SENNA-S	ORAL	TABLET	Y

sennosides/docusate sodium	SENNA-TIME S	ORAL	TABLET	Y
sennosides/docusate sodium	SENNOSIDES-DOCUSATE SODIUM	ORAL	TABLET	Y
sennosides/docusate sodium	SENOKOT-S	ORAL	TABLET	Y
sennosides/docusate sodium	STIMULANT LAXATIVE PLUS	ORAL	TABLET	Y
sennosides/docusate sodium	STOOL SOFTENER-LAXATIVE	ORAL	TABLET	Y
sennosides/docusate sodium	STOOL SOFTENER-STIMULANT LAX	ORAL	TABLET	Y
alvimopan	ALVIMOPAN	ORAL	CAPSULE	N
alvimopan	ENTEREG	ORAL	CAPSULE	N
bran	BRAN	ORAL	TABLET	N
bran	OAT BRAN FIBER	ORAL	TABLET	N
casanthranol/docusate sodium	DOCUSATE SODIUM W/CASANTHRANOL	ORAL	CAPSULE	N
casanthranol/docusate sodium	DOCUSATE SODIUM-CASANTHRANOL	ORAL	CAPSULE	N
casanthranol/docusate sodium	PERI-COLACE	ORAL	CAPSULE	N
casanthranol/docusate sodium	STOOL SOFTENER W/LAXATIVE	ORAL	CAPSULE	N
cascara sagrada/mag hydrox	MILK OF MAGNESIA W/CASCARA	ORAL	ORAL SUSP	N
castor oil	CASTOR OIL	ORAL	OIL	N
lactulose	KRISTALOSE	ORAL	PACKET	N
linaclotide	LINZESS	ORAL	CAPSULE	N
lubiprostone	AMITIZA	ORAL	CAPSULE	N
lubiprostone	LUBIPROSTONE	ORAL	CAPSULE	N
methylcellulose	CITRUCEL	ORAL	POWDER	N
methylcellulose	FIBER THERAPY	ORAL	POWDER	N
methylcellulose (with sugar)	FIBER THERAPY	ORAL	POWDER	N
methylnaltrexone bromide	RELISTOR	ORAL	TABLET	N
methylnaltrexone bromide	RELISTOR	SUBCUT	SYRINGE	N
methylnaltrexone bromide	RELISTOR	SUBCUT	VIAL	N
mineral oil	MINERAL OIL	ORAL	OIL	N
naldemedine tosylate	SYMPROIC	ORAL	TABLET	N
naloxegol oxalate	MOVANTIK	ORAL	TABLET	N
plecanatide	TRULANCE	ORAL	TABLET	N
polyethylene glycol 3350	CLEARLAX	ORAL	POWD PACK	N
polyethylene glycol 3350	HEALTHYLAX	ORAL	POWD PACK	N
polyethylene glycol 3350	POLYETHYLENE GLYCOL 3350	ORAL	POWD PACK	N
polyethylene glycol 3350	SMOOTHLAX	ORAL	POWD PACK	N
prucalopride succinate	MOTEGRITY	ORAL	TABLET	N
psyllium husk/sweetleaf	KONSYL DAILY FIBER	ORAL	POWD PACK	N
senna leaf extract	SENOKOT	ORAL	TAB CHEW	N

senna leaf extract	SENOKOT KIDS	ORAL	TAB CHEW	N
sennosides/docusate sodium	SENNA PLUS	ORAL	CAPSULE	N
sennosides/docusate sodium	STOOL SOFTENER-STIMULANT LAX	ORAL	CAPSULE	N
tenapanor HCl	IBSRELA	ORAL	TABLET	N
mineral oil	MINERAL OIL	ORAL	EMULSION	
senna leaf/herbal no.324	SENOKOT-CHAMOMILE	ORAL	TEA (EA)	

Medicines for Diarrhea

Generic	Brand	Route	Form	PDL
loperamide HCl	ANTI-DIARRHEAL	ORAL	CAPSULE	Y
loperamide HCl	LOPERAMIDE	ORAL	CAPSULE	Y
loperamide HCl	ANTI-DIARRHEAL	ORAL	LIQUID	Y
loperamide HCl	LOPERAMIDE	ORAL	LIQUID	Y
loperamide HCl	LOPERAMIDE HCL	ORAL	LIQUID	Y
loperamide HCl	ANTI-DIARRHEAL	ORAL	TABLET	Y
diphenoxylate HCl/atropine	DIPHENOXYLATE-ATROPINE	ORAL	LIQUID	N
alosetron	LOTRONEX	ORAL	TABLET	N
bismuth subsalicylate	KAOPECTATE	ORAL	ORAL SUSP	N
bismuth subsalicylate	PINK BISMUTH	ORAL	ORAL SUSP	N
bismuth subsalicylate	STOMACH RELIEF	ORAL	ORAL SUSP	N
bismuth subsalicylate	BISMUTH SUBSALICYLATE	ORAL	TAB CHEW	N
bismuth subsalicylate	PINK BISMUTH	ORAL	TAB CHEW	N
bismuth subsalicylate	STOMACH RELIEF	ORAL	TAB CHEW	N
loperamide HCl/simethicone	ANTI-DIARRHEAL-ANTI-GAS	ORAL	TABLET	N
diphenoxylate HCl/atropine	DIPHENOXYLATE-ATROPINE	ORAL	TABLET	N
diphenoxylate HCl/atropine	LOMOTIL	ORAL	TABLET	N
loperamide HCl/simethicone	LOPERAMIDE-SIMETHICONE	ORAL	TABLET	N
bismuth subsalicylate	PINK BISMUTH	ORAL	TABLET	N
bismuth subsalicylate	STOMACH RELIEF	ORAL	TABLET	N
eluxadoline	VIBERZI	ORAL	TABLET	N
crofelemer	MYTESI	ORAL	TABLET DR	N
opium tincture	OPIUM TINCTURE	ORAL	TINCTURE	N
attapulgite	KAO-TIN	ORAL	ORAL SUSP	
difenoxin HCl/atropine sulfate	MOTOFEN	ORAL	TABLET	
telotristat etiprate	XERMELO	ORAL	TABLET	

Appendix 2: Medline Search Strategy

IBS and Constipation
Ovid MEDLINE(R) ALL <1946 to November 06, 2024>

1	Bisacodyl/	467
2	calcium polycarbophil.mp.	181
3	Cellulose/	36340
4	docusate.mp. or Dioctyl Sulfosuccinic Acid/	950
5	Lactulose/	2446
6	magnesium citrate.mp.	536
7	Magnesium Hydroxide/ or Aluminum Hydroxide/ or Calcium Carbonate/	13254
8	Methylcellulose/	4892
9	polyetheylene glycol.mp.	3
10	psyllium.mp. or Psyllium/	1189
11	senna.mp. or Senna Extract/	1556
12	wheat dextrin.mp.	25
13	alvimopan.mp.	274
14	Castor Oil/	1180
15	Dextrins/	1139
16	Lactulose/	2446
17	linaclotide.mp.	412
18	Lubiprostone/	221
19	Methylcellulose/	4892
20	methylnaltrexone.mp.	509
21	Mineral Oil/	2146
22	naldemedine.mp.	147
23	naloxegol.mp.	165
24	plecanatide.mp.	103
25	polyetheylene glycol.mp.	3
26	Psyllium/	762
27	casanthranol.mp. or Cascara/	4
28	prucalopride.mp.	477
29	sodium phosphate.mp.	6877
30	tegaserod.mp.	534
31	Gastrointestinal Motility/ or Irritable Bowel Syndrome/	31936
32	Constipation/	16834

33	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	74124
34	31 or 32	46599
35	33 and 34	2403
36	limit 35 to (english language and humans and yr="2020 -Current" and (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or comparative study or meta-analysis or multicenter study or randomized controlled trial or "systematic review"))	122

IBS and Diarrhea

Ovid MEDLINE(R) ALL <1946 to November 06, 2024>

1	exp Loperamide/	1357
2	exp Diphenoxylate/	240
3	exp Antidiarrheals/	8659
4	Bismuth/	7388
5	eluxadoline.mp.	147
6	crofelemer.mp.	56
7	opium tincture.mp.	46
8	attapulgite.mp.	734
9	difenoxin.mp.	19
10	telotristat.mp.	105
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	16565
12	exp irritable bowel syndrome/	10116
13	Diarrhea/	54233
14	12 or 13	62843
15	11 and 14	1692
16	limit 15 to (english language and humans and yr="2018 -Current" and (clinical trial, phase iii or comparative study or equivalence trial or meta-analysis or practice guideline or "systematic review"))	23

Traveler's Diarrhea

Ovid MEDLINE(R) ALL <1946 to November 06, 2024>

1	rifaxamin.mp.	5
2	exp Rifamycins/	24755
3	exp Levofloxacin/	4306
4	exp Ciprofloxacin/	15986
5	Ofloxacin/	6353
6	exp Azithromycin/	7176
7	Loperamide/	1357

8	Diphenoxylate/	240
9	Bismuth/	7388
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	62074
11	Diarrhea/ or Enterotoxigenic Escherichia coli/ or Travel/ or Escherichia coli Infections/ or traveler's diarrhea.mp.	114200
12	10 and 11	1890
13	limit 12 to (english language and humans and yr="2019 -Current")	237
14	limit 13 to (clinical trial, phase iii or comparative study or meta analysis or practice guideline or "systematic review")	18

Hepatic Encephalopathy

Ovid MEDLINE(R) ALL <1946 to November 06, 2024>

1	rifaxamin.mp.	5
2	Rifamycins/	2387
3	Lactulose/	2446
4	Hepatic Encephalopathy/	11525
5	1 or 2 or 3	4733
6	4 and 5	588
7	limit 6 to (english language and humans and yr="2016 -Current")	172
8	limit 7 to (clinical trial, phase iii or comparative study or guideline or meta-analysis or multicenter study or practice guideline or "systematic review")	38

Rifaximin (Xifaxan®) and Rifamycin (Aemcolo®)

Goal(s):

- Promote use that is consistent with medical evidence and product labeling.

Length of Authorization:

- 3 days for traveler's diarrhea caused by non-invasive strains of *E. Coli* for rifaximin or rifamycin.
- Up to 12 months for hepatic encephalopathy for rifaximin.
- 14 days for irritable bowel syndrome with diarrhea – may repeat a 14-day course of treatment up to 2 additional times for rifaximin.

Requires PA:

- Rifaximin and Rifamycin

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication at the FDA-approved dose?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis traveler's diarrhea caused by non-invasive strains of *E. Coli*?	**Yes:** Go to #5	**No:** Go to #7

Approval Criteria		
4. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee. • Preferred products for traveler's diarrhea are dependent on traveler's destination and resistance patterns in that area. Refer to **Table 1** for adult treatment recommendations.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #6
5. Does the patient have a contraindication or allergy to azithromycin or ciprofloxacin?	**Yes:** Approve at a dose of 200 mg 3 days	**No:** Pass to RPh Deny; medical appropriateness
6. Is the request for rifaximin to prevent or treat hepatic encephalopathy?	**Yes**: Go to #7	**No**: Go to #9
7. Is the patient currently managed with a regularly scheduled daily regimen of lactulose?	**Yes**: Approve for 12 months	**No**: Go to #8
8. Does the patient have a contraindication to lactulose? Note: studies demonstrate effectiveness of rifaximin as add-on therapy to lactulose.	**Yes**: Approve for 12 months	**No**: Pass to RPh Deny; medical appropriateness
~~9. Is the patient currently prescribed a benzodiazepine drug?~~	~~**Yes**: Go to #11~~	~~**No**: Approve for up to 12 months~~

Approval Criteria		
~~13. Is the patient tapering off the benzodiazepine?~~ ~~Note: tapering process may be several months~~	~~**Yes:** Approve for up to 12 months~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~ ~~Note: studies explicitly excluded use of benzodiazepines and benzodiazepine-like drugs because of their risk for precipitating an episode of hepatic encephalopathy.~~
~~21.~~9. Is the request for rifaximin to treat irritable bowel syndrome with diarrhea in an adult?	**Yes:** Not eligible for EPSDT review: Pass to RPh. Deny; medical appropriateness Eligible for EPSDT review: Approve for 14-day course of therapy. for a total 3 courses in one year.	**No**: Pass to RPh: Deny; medical appropriateness

Table 1. CDC Acute Traveler's Diarrhea Antibiotic Treatment Recommendations[1]

Antibiotic	Dose	Duration	Notes
Azithromycin	1000 mg	Single or Divided dose	• Use empirically as first-line treatment for travelers' diarrhea in Southeast Asia or other areas if fluoroquinolone- resistant bacteria are suspected. • Preferred treatment for dysentery or febrile diarrhea.
Azithromycin	500 mg QDay	3 days	
Ciprofloxacin	750 mg	Single Dose	• If symptoms are not resolved after 24 hours, continue daily dosing for up to 3 days.

Ciprofloxacin	500 mg QDay	3 days	
Levofloxacin	500 mg QDay	1-3 days	• If symptoms are not resolved after 24 hours, continue daily dosing for up to 3 days.
Ofloxacin	400 mg BID	1-3 days	• If symptoms are not resolved after 24 hours, continue daily dosing for up to 3 days.
Rifamycin	388 mg BID	3 days	• Do not use if clinical suspicion for *Campylobacter*, *Salmonella*, *Shigella*, or other causes of invasive diarrhea. Use may be reserved for patients unable to receive azithromycin or fluoroquinolones.
Rifaximin	200 mg TID	3 days	
Abbreviations: BID = twice daily; CDC = Centers for Disease Control and Prevention; QDay = once daily; TID = three times daily			

1. Center for Disease Control. The Yellow Book, Chapter 2: Traveler's Diarrhea. https://wwwnc.cdc.gov/travel/yellowbook/2018/the-pre-travel-consultation/travelers-diarrhea. Accessed 11/4/24.

P&T/DUR Review: 2/25 (DM); 11/19 (DM), 7/15; 5/15 (AG)
Implementation: TBD; 1/1/20; 10/15; 8/15

Drugs for Constipation

Goal(s): Promote use that is consistent with medical evidence and product labeling.

Length of Authorization:

- Up to 12~~6~~ months

~~Not Covered by OHP:~~

- ~~Disorders of function of stomach and other functional digestive disorders which includes constipation and Irritable Bowel Syndrome (ICD-10: K3183-3184, K310, R1110, K30, K3189, K319, K314-315, K312, K589, K591, K594, K5900-5902, K5909, K910-911, K9189, K598-599, R159, R150, R152)~~

Requires PA:

- Non-preferred drugs (pharmacy and provider administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Gastrointestinal Drugs FDA-Approved for Treatment of Constipation in an Outpatient Setting

Generic (Brand Name)	Indications
Linaclotide (LINZESS)	• CIC in adults • IBS-C in adults • FC in pediatric patients aged 6 to 17 yo
Lubiprostone (AMITIZA)	• CIC in adults • IBS-C in females > 18 yo • OIC in adults: chronic, non-cancer pain including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation
Methylnaltrexone (RELISTOR)	• OIC in adults with advanced illness (injection only) • OIC in adults with chronic, non-cancer pain (tablets and injection)
Naldemedine (SYMPROIC)	OIC in adults with chronic, non-cancer pain
Naloxegol (MOVANTIK)	OIC in adults with chronic, non-cancer pain
Plecanatide (TRULANCE)	• CIC in adults • IBS-C in adults
Prucalopride (MOTEGRITY)	CIC in adults
Tegaserod (ZELNORM)	IBS-C in females < 65 yo
Tenapanor (IBSRELA)	IBS-C in adults
Abbreviations: CIC = chronic idiopathic constipation; FC = functional constipation; IBS-C = irritable bowel syndrome with constipation; IBS-D = irritable bowel syndrome with diarrhea; OIC = opioid-induced constipation; yo = years old	

Table 2. Initial Management Strategies for Constipation

Dietary Modification	Increased dietary fiber (25 grams/day) and increased fluid consumption
Bulk-forming Laxatives	Psyllium (not recommended for opioid-induced constipation)
Osmotic Laxatives	Polyethylene glycol, lactulose, magnesium hydroxide, milk of magnesia
Stool Softener	Docusate
Stimulant Laxatives	Senna, bisacodyl

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Is the diagnosis funded by the OHP?	**Yes:** Go to #3	**No:** Not eligible for EPSDT review: Pass to RPh. Deny; medical appropriateness. Eligible for EPSDT review: Go to #3
~~2.~~3. Is the request for an FDA-approved age and indication (**Table 1**)?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
~~3.~~4. Is there documentation of failure to have benefit with, or contraindication to, at least 2 of the recommended conventional first-line treatments including dietary modifications for at least 4 weeks (**Table 2**)?	**Yes:** Current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP. Current age < 21 years: Go to #5	**No:** Pass to RPh. Deny for funding Constipation is not funded under the OHP. Therefore, funding for drugs that treat constipation are dependent whether the constipation adversely affects, or is secondary to, the underlying medical condition covered by the Prioritized List. Chronic constipation caused by a funded condition or adversely affecting a funded condition is approvable if medically appropriate and justification is provided for not meeting criterion #4.

Approval Criteria		
5. Is the drug prescribed by one of the following: -gastroenterologist OR -other provider after patient consultation with a dietician OR -if patient has PA approval for long-term opioid therapy OR -pain management specialist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny for medical appropriateness
~~4.~~6. Is the request to treat irritable bowel syndrome with constipation in an adult female assigned at birth with lubiprostone or an adult female less than 65 years old with tegaserod?	**Yes**: Go to #7	**No:** Go to #8
7. Is the request for tegaserod in a woman with any of these contraindications to therapy: o History of a myocardial infarction, stroke, or transient ischemic attack OR o Severe renal impairment (eGFR < 15 mL/min) OR o Moderate or severe hepatic impairment (Child-Pugh B or C) OR o Symptomatic gall bladder disease OR o Suspected sphincter of Oddi dysfunction OR o Abdominal adhesions?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No:** Approve for 12 months
~~5.~~8. Is the request to treat opioid-induced constipation in an adult with lubiprostone?	**Yes**: Go to #9	**No:** Approve for 12 months
~~6.~~9. Is request for lubiprostone in a patient that has been the prescribed methadone?	**Yes:** Pass to RPh. Deny; medical appropriateness. The efficacy of lubiprostone in patients taking methadone has not been established.	**No:** Approve for 12 months

Approval Criteria

~~1. RPh only:~~

~~Constipation is not covered under the OHP. Therefore, funding for drugs that treat constipation are dependent whether the constipation adversely affects, or is secondary to, the underlying medical condition covered by the Prioritized List.~~

- ~~Alvimopan (ENTEREG): FDA labeling, including a black boxed warning for risk of myocardial infarction, limit use to *in hospital use only* for a maximum of 15 doses. Evidence is primarily for the immediate post-operative period only.~~
- ~~Linaclotide (LINZESS): Constipation secondary to irritable bowel is not approvable. Chronic constipation caused by a funded condition or adversely affecting a funded condition is approvable if medically appropriate and justification is provided for not meeting criterion #4.~~
- ~~Lubiprostone (AMITIZA): Constipation secondary to irritable bowel syndrome or opioid-induced constipation is not approvable. Chronic constipation caused by a funded condition or adversely affecting a funded condition is approvable if medically appropriate and justification is provided for not meeting criterion #4.~~
- ~~Methylnaltrexone (RELISTOR): Opioid-induced constipation in patients with non-cancer pain is not approvable. Chronic constipation secondary to continuous opioid use as part of a palliative care regimen is approvable if justification is provided for not meeting criterion #4.~~

~~Naldemedine (SYMPROIC): Opioid-induced constipation in with non-cancer pain is not approvable. Justification must be provided for not meeting criterion #4.~~

- ~~Naloxegol (MOVANTIK): Opioid-induced constipation in with non-cancer pain is not approvable. Justification must be provided for not meeting criterion #4.~~
- ~~Plecanatide (TRULANCE): Chronic idiopathic constipation is not approvable. Chronic constipation caused by a funded condition or adversely affecting a funded condition is approvable if medically appropriate and justification is provided for not meeting criterion #4.~~
- ~~Prucalopride (MOTEGRITY): Chronic idiopathic constipation is not approvable. Chronic constipation caused by a funded condition or adversely affecting a funded condition is approvable if medically appropriate and justification is provided for not meeting criterion #4.~~
- ~~Tegaserod (ZELNORM): Constipation secondary to irritable bowel syndrome is not approvable. Justification must be provided for not meeting criterion #4.~~

~~Tenapanor (ISBRELA): Constipation secondary to irritable bowel syndrome is not approvable. Justification must be provided for not meeting criterion #4.~~

P&T Review: *TBD, 2/25 (DM): 6/20 (DM), 7/17 (DM); 3/15; 3/09*
Implementation: *TBD: 7/1/20; 9/1/17; 5/1/16; 10/15, 4/18/15*

Drugs for Diarrhea

Goal(s):

- Promote use that is consistent with medical evidence and product labeling.

Length of Authorization:

- Up to 12 months

Requires PA:

- Eluxadoline (Viberzi) and Alosetron (Lotronex)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by the OHP?	**Yes:** Go to #3	**No:** Not eligible for EPSDT review: Pass to RPh. Deny; diagnosis not covered by OHP. Eligible for EPSDT review: Go to #3
3. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4

Approval Criteria		
4. Is the diagnosis irritable bowel syndrome (IBS) with diarrhea with the following symptoms for the past 3 months: • Frequent and severe abdominal pain and discomfort AND • Frequent bowel urgency or fecal incontinence AND • Disability or restriction of daily activities due to IBS	**Yes:** Go to #5	**No:** Pass to RPh. Deny for medical appropriateness
5. Is the request for eluxadoline in an adult?	**Yes:** Go to #6	**No:** Go to #9
6. Have baseline liver function tests been obtained?	**Yes:** Go to #7	**No:** Pass to RPh. Deny for medical appropriateness
7. Is there documentation of sphincter of Oddi problems, cholecystectomy, alcohol dependence, pancreatitis or severe liver impairment?	**Yes:** Pass to RPh. Deny for medical appropriateness	**No:** Go to #8
8. Does the patient have normal hepatic function or if they have mild or moderate hepatic function has the eluxadoline dose been adjusted to 75 mg twice daily?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny for medical appropriateness
9. Is the request for alosetron in an adult woman who has chronic IBS-D symptoms (e.g., last longer than 6 months)?	**Yes:** Go to #10	**No:** Pass to RPh. Deny for medical appropriateness
10. Have anatomic or biochemical abnormalities of the gastrointestinal tract been excluded?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny for medical appropriateness

Renewal Criteria		
1. Is the request for irritable bowel syndrome with diarrhea?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
2. Does the provider attest that the patient's symptoms have improved with therapy as evidenced by less frequent bowel movements compared to baseline?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *2/25 (DM):*
Implementation: *TBD*