Treatment of irritable bowel syndrome in adults

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Literature review current through: **Sep 2023.**
This topic last updated: **Aug 31, 2022.**

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional disorder of the gastrointestinal tract characterized by chronic abdominal pain and altered bowel habits in the absence of an organic disease. Approximately 10 to 15 percent of adults and adolescents have symptoms consistent with IBS, and although not all individuals with IBS seek medical care, patients with IBS make up a significant percentage of all outpatient visits to gastroenterologists and other healthcare providers [1].

This topic will review the management of IBS. Our recommendations are largely consistent with the American College of Gastroenterology and American Gastroenterological Association guidelines [2-5]. The clinical manifestations and diagnosis of IBS are discussed separately. (See "Clinical manifestations and diagnosis of irritable bowel syndrome in adults".)

DEFINITIONS

- **Irritable bowel syndrome (IBS)** – Irritable bowel syndrome is defined as recurrent abdominal pain on average, at least one day per week in the last three months with two or more of the following: related to defecation, associated with a change in frequency of stool, or associated with a change in form (appearance) of stool [6].

Subtypes of IBS have been defined as follows [7]:

- IBS with predominant constipation (IBS-C) – Patient reports that abnormal bowel movements are usually constipation (type 1 and 2 in the BSFS)
- IBS with predominant diarrhea (IBS-D) – Patient reports that abnormal bowel movements are usually diarrhea (type 6 and 7 in the BSFS)
- IBS with mixed bowel habits (IBS-M) – Patient reports that abnormal bowel movements are usually both constipation and diarrhea (more than one-fourth of all the abnormal bowel movements were constipation and more than one-fourth were diarrhea)
- IBS unclassified – Patients who meet diagnostic criteria for IBS but cannot be accurately categorized into one of the other three subtypes.

INDICATIONS FOR REFERRAL

Even in patients with an established diagnosis of IBS, it is important to assess for alarm features for which endoscopic evaluation should be considered. Alarm features include the following:

- More than minimal rectal bleeding (see "Approach to minimal bright red blood per rectum in adults", section on 'Clinical assessment')
- Weight loss
- Unexplained iron deficiency anemia
- Nocturnal symptoms
- Family history of selected organic diseases including colorectal cancer, inflammatory bowel disease, or celiac sprue

INITIAL THERAPY

Establishment of a clinician-patient relationship and continuity of care are critical to the management of all patients with irritable bowel syndrome (IBS). In patients with mild and intermittent symptoms that do not impair quality of life, we initially recommend lifestyle and dietary modification alone rather than specific pharmacologic agents.

In patients with mild to moderate symptoms who fail to respond to initial management and in patients with moderate to severe symptoms that affect quality of life, we suggest pharmacologic therapy as adjunctive treatment. (See 'Adjunctive pharmacologic therapy' below.)

Education and reassurance — It is important to establish a therapeutic clinician-patient relationship to validate the patient's symptoms. Patients should also be counseled that

although IBS does not increase their risk of malignancy, it is a chronic disorder. The clinician should establish realistic expectations with consistent limits and involve the patient in treatment decisions [8-10]. (See "Pathophysiology of irritable bowel syndrome" and "Patient education: Irritable bowel syndrome (Beyond the Basics)".)

Dietary modification — A careful dietary history may reveal patterns of symptoms related to specific foods. Patients with IBS may benefit from exclusion of gas-producing foods; a diet low in fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs); and in select cases, lactose avoidance (table 1). There is insufficient evidence to support routine food allergy testing in patients with IBS.

Both a low FODMAP diet and a strict traditional IBS diet improve IBS symptoms. In a randomized trial, 75 patients with IBS were assigned to a low FODMAP diet or a more traditional IBS diet (regular meal pattern; avoidance of large meals; reduced intake of fat, insoluble fibers, caffeine, and gas-producing foods such as beans, cabbage, and onions) [11]. Note the traditional diet did include some food restriction of high FODMAP foods. At the end of the four-week trial, there was a significant reduction in IBS symptom severity in both dietary groups as compared with baseline. However, there was no significant difference in the reduction of symptom severity or the proportion of responders between the two groups.

Exclusion of gas-producing foods — Patients with IBS should be advised to exclude foods that increase flatulence (eg, beans, onions, celery, carrots, raisins, bananas, apricots, prunes, Brussels sprouts, wheat germ, pretzels, and bagels), alcohol, and caffeine [12]. Underlying visceral hypersensitivity may explain the exaggerated discomfort experienced by patients with IBS with the consumption of gas-producing foods [13]. (See "Overview of intestinal gas and bloating" and "Patient education: Gas and bloating (Beyond the Basics)" and "Pathophysiology of irritable bowel syndrome".)

Lactose avoidance — Patients with known lactose intolerance should be placed on a lactose-restricted diet. We also suggest an empiric trial of a lactose-free diet in patients who complain of persistent abdominal bloating despite exclusion of gas-producing foods. As improvement of symptoms does not necessarily imply lactose maldigestion, the diagnosis of lactose intolerance can be confirmed with breath testing in patients who do not want to be on a lactose-restricted diet in the long term without clear evidence of maldigestion [14]. Individuals who have no evidence of lactose intolerance on breath test but who have symptoms with ingestion of milk may have intolerance to other milk components (eg, cow milk protein) and may tolerate milk from other mammals or ingestion of soy. (See "Lactose intolerance and malabsorption: Clinical manifestations, diagnosis, and management", section on 'Diagnostic evaluation' and "Food allergens: Clinical aspects of cross-reactivity", section on 'Cow's milk'.)

Although the incidence of lactose malabsorption is not higher in patients with IBS, patients with IBS and lactose intolerance have an exaggerated symptom response to lactose ingestion [13]. Patients with undiagnosed lactose intolerance can have lasting clinical improvement when placed on a lactose-restricted diet [15,16]. The clinical manifestations and diagnosis of lactose intolerance are discussed in detail, separately. (See "Lactose intolerance and malabsorption: Clinical manifestations, diagnosis, and management".)

Low FODMAP diet — We suggest a diet low in fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs) in patients with IBS with abdominal bloating or pain despite exclusion of gas-producing foods (table 1) [3]. These short-chain carbohydrates are poorly absorbed and are osmotically active in the intestinal lumen where they are rapidly fermented, resulting in symptoms of abdominal bloating and pain. A low FODMAP diet involves elimination of a larger number of high FODMAP foods that would not be excluded in a diet that only required avoidance of gas-producing foods (eg, foods that contain fructose, including honey, high-fructose corn syrup, apples, pears, mangoes, cherries, or oligosaccharides, including wheat). Low FODMAP dietary education should be provided by a trained dietician to avoid unnecessary dietary over-restriction and a nutritionally replete diet [17]. Low FODMAP education consists of initially eliminating FODMAPs from the diet for six to eight weeks and then, following symptom resolution, gradual reintroduction of foods high in fermentable carbohydrates to determine individual tolerance to specific fermentable carbohydrates [18].

Studies have demonstrated an improvement in IBS symptoms with FODMAP restriction [19-23]. In a randomized, single-blind, crossover trial, 30 patients with IBS and 8 healthy controls were assigned to 21 days of a diet low in FODMAPs or a moderate FODMAP Australian diet followed by a 21-day washout period before crossing over to an alternate diet [24]. Subjects with IBS, but not controls, had significantly lower overall gastrointestinal symptoms scores with an improvement in scores for abdominal pain, bloating, flatulence, and dissatisfaction with stool consistency while on a low FODMAP diet as compared with the moderate FODMAP diet and their diet at baseline. In another randomized trial 92 patients with IBS-D were assigned to a four week trial of a low FODMAP diet or modified National Institute for Health and Care Excellence dietary recommendations (small frequent meals, avoid trigger foods, and avoid excess alcohol and caffeine). There was no significant difference in the proportion of patients reporting adequate relief of IBS-D [23]. However, the low FODMAP group exhibited significantly higher rates of improvement in pain (51 versus 23 percent) and greater reductions in average daily scores for abdominal pain, bloating, stool consistency, frequency, and urgency.

Gluten avoidance — Gluten has been demonstrated to alter bowel barrier functions in patients with IBS-D [25]. Nonceliac gluten sensitivity (NCGS) has been hypothesized as an

underlying mechanism for symptom generation in patients with IBS but evidence to support gluten avoidance in patients with IBS has been conflicting [26-28].

It is feasible that symptomatic improvement associated with a gluten-free diet may not be caused by removal of the gluten protein, but rather the reduction of fructans. In a randomized double blind crossover trial, 59 patients with self-reported NCGS were assigned to diets containing gluten (without fructan), fructan (without gluten), or placebo for seven days followed by a minimum one week washout period [29]. Thirteen patients met Rome III criteria for IBS. Overall gastrointestinal symptom rating scores and bloating, were significantly higher with fructan exposure as compared with gluten. There was no significant difference in symptom scores between gluten and placebo groups. Limited data suggest that antigliadin IgG may be a useful biomarker to identify patients with IBS who might benefit from a gluten-free diet [30]. However, further studies are needed. (See "Pathophysiology of irritable bowel syndrome", section on 'Gluten sensitivity'.)

Fiber — Soluble fiber should be offered to patients with IBS [31]. The use of insoluble fiber should be avoided (eg, bran) as it is not significantly better than placebo in improving symptoms of IBS and can cause bloating [32]. Studies suggests that soluble (eg, ispaghula husk/psyllium) but not insoluble (eg, wheat bran) fiber has a significant effect for the treatment of IBS symptoms [3,22,31,33,34]. In a meta-analysis of 15 trials that included 946 patients, fiber was associated with an improvement in IBS symptoms (RR 0.87; 95% CI, 0.80–0.94). However, the benefit was only in RCTs on soluble fiber with no improvement in symptoms with bran [31].

Psyllium has been shown to improve both constipation and diarrhea. Fiber may increase bulk of stool and may also include alterations in the production of gaseous fermentation products and changes to the gut microbiome. As some patients may experience increased bloating and gas, we suggest a low starting dose of psyllium that provides approximately 3 to 4 grams of soluble fiber per day. The soluble fiber content of psyllium products (ie, per packet, teaspoon, or pill) vary widely; refer to product-specific label to determine dose. The dose should then be slowly titrated up based on response to treatment.

Food allergy testing — The role of food allergy in IBS is unclear. Although it is possible that food allergy has a role in the development of symptoms, there are also no reliable means to identify such individuals. Testing for serum immunoglobulins directed at specific dietary antigens and elimination of responsible foods has been proposed, but the relationship between results of such testing and improvement of symptoms requires additional study before such an approach can be recommended [35]. Other methods used in evaluating food allergies (eg, skin prick testing, RAST testing, and atopy patch testing) have not been well studied in IBS. (See "Diagnostic evaluation of IgE-mediated food allergy".)

Physical activity — Physical activity should be advised in patients with IBS given a potential benefit with regard to IBS symptoms and the general health benefits of exercise. In a randomized trial, 102 patients with IBS were assigned to increased physical activity or maintenance of current activity levels [36]. Increased physical activity composed 20 to 60 minutes of moderate to vigorous activity three to five days per week. The amount of physical activity prescribed was determined in part by the patient's baseline level of activity. Seventy-five patients completed the study (38 in the physical activity arm and 37 in the control arm). After 12 weeks, there was a trend toward more patients in the physical activity arm showing clinical improvement in the severity of IBS symptoms as compared with the control group (43 versus 26 percent). In addition, patients in the physical activity arm were significantly less likely to have worsening of their IBS symptoms as compared with controls (8 versus 23 percent).

ADJUNCTIVE PHARMACOLOGIC THERAPY

We treat patients with moderate to severe symptoms of irritable bowel syndrome (IBS) that impair quality of life with pharmacologic agents. Since IBS generally presents as a complex of symptoms, treatment should be based on the predominant symptom and subtype. We make incremental changes in therapy. (See 'Definitions' above.)

Randomized trials evaluating specific pharmacologic agents have demonstrated their superiority as compared with placebo. However, there have been few controlled trials evaluating specific strategies for how these drugs should be used in conjunction with other types of treatment (eg, fiber therapy), how long they should be used, or whether they should be given continuously or as needed. We often use pharmacologic intervention to control symptom flares (eg, antidiarrheals) but also use continuous pharmacologic therapy (eg, tricyclic antidepressant drugs) for periods of months or years.

Constipation — In patients with IBS with constipation (IBS-C) who have failed a trial of soluble fiber (eg, psyllium/ispaghula), we suggest polyethylene glycol (PEG). We treat patients with persistent constipation despite treatment with PEG with lubiprostone, linaclotide, or plecanatide [4]. We use tenapanor in patients who fail other therapies for constipation. (See 'Definitions' above and 'Fiber' above.)

Osmotic laxatives — PEG is inexpensive, widely available, and has fewer side effects as compared with other osmotic laxatives (eg, lactulose, milk of magnesia). We initially start with 17 g of powder dissolved in 8 ounces of water once daily and titrate up or down (to a maximum of 34 g daily) to effect. However, side effects of bloating and abdominal discomfort limit the use of PEG. (See "Management of chronic constipation in adults", section on 'Osmotic agents'.)

Treatment with PEG improves constipation but not abdominal pain [37,38]. Randomized trials in children have demonstrated that PEG has greater or similar efficacy to lactulose and magnesium hydroxide in treating constipation, but in adults, PEG has not been directly compared with other osmotic laxatives [39-48]. In a randomized trial, 139 adults with IBS-C were assigned to PEG or placebo for 28 days [38]. As compared with placebo, patients treated with PEG had significantly more spontaneous bowel movements, improvement in stool consistency, and reduction in the severity of straining. However, there was no significant difference in the severity of bloating or abdominal pain in patients treated with PEG as compared with placebo. (See "Chronic functional constipation and fecal incontinence in infants, children, and adolescents: Treatment", section on 'Polyethylene glycol'.)

Lubiprostone — Lubiprostone is a locally acting chloride channel activator that enhances chloride-rich intestinal fluid secretion. We use lubiprostone in patients with IBS with persistent constipation despite PEG. The approved dose for IBS-C (8 micrograms twice daily in women) is lower than the approved dose for treatment of chronic idiopathic constipation. We discontinue lubiprostone in patients who fail to respond to a 12-week trial [49]. (See 'Osmotic laxatives' above.)

Lubiprostone has not been directly compared with other treatment options for IBS-C, and its long-term safety remains to be established. While the efficacy of lubiprostone has been demonstrated in two randomized trials in which the majority of patients were women, the placebo response in the studies was far lower than expected [49]. In these two multicenter, placebo-controlled trials, 1154 adults (92 percent women) with IBS and constipation were randomly assigned to lubiprostone (8 micrograms twice daily) or placebo for 12 weeks. Patients randomized to lubiprostone were significantly more likely to achieve an overall response (18 versus 10 percent). Serious adverse events were similar to placebo. The most common adverse event was nausea (8 versus 4 percent). A follow-up open-label study that included 522 patients demonstrated that benefits of lubiprostone persisted or increased at 52 weeks.

Guanylate cyclase agonists — Linaclotide and plecanatide are guanylate cyclase agonists that stimulates intestinal fluid secretion and transit. As the long-term risks are unknown, their role in the treatment of IBS-C is limited to patients with persistent constipation despite treatment with PEG. (See 'Osmotic laxatives' above.)

Linaclotide is used for treatment of IBS-C at a dose of 290 micrograms daily [50]. In patients with side effects to linaclotide, the dose may be reduced if the patient develops diarrhea (typically occurs within two weeks). However, smaller doses may not mitigate this side effect. We discontinue linaclotide in patients who fail to respond in 8 to 12 weeks [51].

The efficacy of linaclotide in the treatment of IBS-C has been demonstrated in two randomized controlled phase III trials [52,53].

- In one randomized controlled trial, 800 patients with IBS-C were assigned to linaclotide (266 micrograms daily) or placebo for 12 weeks followed by a four-week withdrawal period [52]. During the withdrawal period, patients previously randomized to placebo received linaclotide, and patients who originally received linaclotide were randomized to either linaclotide or placebo. After 12 weeks, the percentage of patients meeting the composite endpoint (≥30 percent reduction in abdominal pain, ≥3 complete and spontaneous bowel movements [CSBM], increase in ≥1 CSBM from baseline; in the same week) was significantly greater with linaclotide as compared with placebo (34 versus 21 percent). Patients who received linaclotide also demonstrated a significant improvement in secondary endpoints of abdominal pain/discomfort, bloating, straining, stool consistency, number of CSBMs and spontaneous bowel movements per week, compared with placebo. After the initial 12 weeks, patients originally given linaclotide and who remained on linaclotide showed sustained improvement in abdominal pain, but patients who were switched to placebo experienced recurrence of abdominal pain. Patients initially randomized to placebo had significant improvement in abdominal pain within one week after being switched to linaclotide. Diarrhea was the most common side effect, causing discontinuation of treatment in 5.7 percent of patients treated with linaclotide as compared with 0.3 percent in patients receiving placebo.

- A second randomized trial assessed the efficacy of long-term use of linaclotide [53]. In this trial, 804 patients with IBS-C were randomly assigned to receive linaclotide (266 micrograms daily) or placebo for 26 weeks. Patients randomized to linaclotide demonstrated a significant improvement in the same composite primary endpoint as compared with placebo (38 versus 14 percent).

The efficacy of plecanatide is comparable to linaclotide [54]. We discontinue plecanatide in patients who fail to respond in four weeks.

Sodium/hydrogen exchanger 3 (NHE3) inhibitor — Tenapanor, a sodium/hydrogen exchanger 3, reduces the absorption of sodium and phosphate and enhances intestinal fluid volume and transit. We use tenapanor in patients who fail other therapies for constipation. Improvement may be seen within seven days; we discontinue tenapanor in patients who fail to respond to a four-week trial [55]. Approval for the use of tenapanor in IBS-C has been based on data from randomized trials in adult patients. In these trials, treatment with tenapanor (50 mg twice daily) resulted in improvement in both average weekly complete spontaneous bowel movements and abdominal pain as compared with placebo [56]. Diarrhea, abdominal

distension, flatulence, and dizziness were the most frequent side effects, with severe diarrhea in 2.5 percent of patients as compared to 0.2 percent of patients receiving placebo.

5-hydroxytryptamine (serotonin) 4 receptor agonists — Agonists of the 5-hydroxytryptamine-4 (5-HT4) receptor stimulate the release of neurotransmitters and increase colonic motility [57]. Tegaserod has been withdrawn from the market but has been demonstrated to reduce abdominal pain in IBS and improve constipation [58]. The safety of tegaserod has not been established in men with IBS-C or women above age 65. A history of ischemic colitis, intestinal ischemia, bowel obstruction or adhesions, symptomatic gallbladder disease, and suspected sphincter of Oddi dysfunction are some of the contraindications to the use of tegaserod. Prucalopride has not been evaluated in patients with IBS.

Diarrhea — In diarrhea-prone patients with IBS, the stools are characteristically loose and frequent but of normal total daily volume. In patients with diarrhea-predominant symptoms, we use antidiarrheals (eg, loperamide) as initial treatment and use bile acid sequestrants as second-line therapy [5].

Antidiarrheal agents — In patients with IBS-diarrhea (IBS-D), we suggest loperamide 2 mg 45 minutes before a meal on regularly scheduled doses. Antidiarrheal agents inhibit peristalsis, prolong transit time, and reduce fecal volume. However, loperamide should not be used in patients with IBS-C and should be used in limited doses, on an as-needed basis, in patients with alternating diarrhea and constipation (maximum daily dose 16 mg/day).

A systematic review included three controlled trials evaluating loperamide in the treatment of IBS [15,59-61]. All three trials were of short duration, enrolled a small number of patients, and had methodologic limitations. Overall, the trials suggested that loperamide was more effective than placebo for treatment of diarrhea by decreasing stool frequency and consistency, but not for the symptoms of bloating, abdominal discomfort, or global IBS symptoms.

Bile acid sequestrants — In patients with persistent diarrhea despite antidiarrheals, we use bile acid sequestrants (eg, cholestyramine, colestipol, colesevelam). However, their use is controversial and is limited by associated gastrointestinal side effects including bloating, flatulence, abdominal discomfort, and constipation [2].

The rationale for the use of bile acid sequestrants in patients with IBS-D is that up to 50 percent of patients with functional diarrhea and IBS-D have bile acid malabsorption [62,63]. Bile acids cause diarrhea by stimulating colonic secretion and motility. In a randomized trial in which 24 patients with IBS-D were assigned to treatment with colesevelam (1.875 g twice daily) or placebo, treatment with colesevelam increased colonic transit time with an average delay of four hours as compared with placebo [64].

5-hydroxytryptamine (serotonin) 3 receptor antagonists — Alosetron, a 5-hydroxytryptamine-3 receptor (5HT-3) antagonist, is approved for the treatment of severe diarrhea-predominant IBS in female patients whose symptoms have lasted for six months and who have failed to respond to all other conventional treatment. Alosetron modulates visceral afferent activity from the gastrointestinal tract, thereby decreasing colonic motility and secretion, and may improve abdominal pain [65-67]. In a meta-analysis that included 14 randomized trials, treatment with 5HT-3 antagonists, alosetron or cilansetron resulted in a global improvement in IBS symptoms and relief of abdominal pain and discomfort [68]. Side effects of ischemic colitis and complications of severe constipation led to the withdrawal of alosetron from the market in the United States. However, following evaluation of postmarketing data, alosetron is now available in the United States but can be prescribed under restricted conditions, at a lower starting dose than previously approved, and by physicians enrolled in the alosetron prescribing program. (See "Alosetron hydrochloride (Lotronex) for irritable bowel syndrome".)

Ondansetron is an alternative to alosetron but may have no benefit over placebo in terms of abdominal pain. In a randomized crossover trial in which 120 patients with IBS-D were assigned to treatment with ondansetron (starting dose 4 mg) or placebo for five weeks, ondansetron significantly improved stool consistency, frequency, and urgency but was not associated with a significant improvement in abdominal pain [69].

Eluxadoline — Eluxadoline is an agent that combines a mu-opioid receptor agonist and a delta-opioid receptor antagonist and only has modest efficacy in reducing diarrhea in patients with IBS [70]. Eluxadoline should only be used in **selected** patients with **severe** IBS-D that is refractory to **all other agents as it is associated with a high incidence of severe acute pancreatitis** [5,71]. **Eluxadoline should be discontinued in patients who do not respond to a 12-week trial**. A history of biliary disorders, pancreatitis, severe liver impairment (Child-Pugh Class C), and heavy alcohol use are contraindications to its use. Eluxadoline is contraindicated in patients who do not have a gallbladder due to a high incidence of severe acute pancreatitis noted in postmarketing surveillance [72]. Efficacy of eluxadoline was demonstrated in two phase 3 studies; 2427 adults with IBS-D were randomly assigned to eluxadoline at a dose of 75 mg, 100 mg, or placebo twice daily for 26 and 52 weeks, respectively [73]. The primary endpoint was the proportion of patients who had a composite response of decrease in abdominal pain and improvement in stool consistency on the same day, for at least 50 percent of the days from weeks 1 through 12 and from weeks 1 through 26. For weeks 1 through 26, a significantly higher proportion of patients receiving eluxadoline (100 mg twice daily) achieved the primary endpoint as compared with placebo in both trials (29 versus 19 percent; 33 versus 20 percent). The most common adverse events associated with eluxadoline were nausea, constipation, and

abdominal pain. Pancreatitis developed in 0.3 percent of patients treated with eluxadoline. All cases of pancreatitis occurred in patients with either biliary disorders (spasm of the sphincter of Oddi and biliary sludge) or alcohol use.

Abdominal pain and bloating — In patients with abdominal pain due to IBS, we use antispasmodics on an as-needed basis. In patients with IBS with constipation, we initiate antispasmodics only if the abdominal pain persists despite treatment of constipation. In patients with persistent abdominal pain despite antispasmodics, we recommend a trial of antidepressants. In patients with moderate to severe IBS without constipation, particularly those with bloating, who have failed to respond to other therapies, we suggest a two-week trial of rifaximin. (See 'Dietary modification' above.)

Antispasmodic agents — Antispasmodics should be administered on an as-needed basis and/or in anticipation of stressors with known exacerbating effects. Antispasmodics provide short-term relief in symptoms of abdominal pain in patients with IBS, but their long-term efficacy has not been established [15,74].

Antispasmodic include those that directly affect intestinal smooth muscle relaxation (eg, mebeverine and pinaverine), and those that act via their anticholinergic or antimuscarinic properties (eg, dicyclomine and hyoscyamine) [15]. The selective inhibition of gastrointestinal smooth muscle by antispasmodics and peppermint oil reduce stimulated colonic motor activity and may be beneficial in patients with postprandial abdominal pain, gas, bloating, and fecal urgency [75-80]. In a 2011 meta-analysis, antispasmodics were associated with a significant improvement in abdominal pain, global assessment and symptom score as compared with placebo. Subgroup analyses demonstrated statistically significant benefits for cimetropium/dicyclomine, peppermint oil, pinaverium, and trimebutine [81].

Typical doses include:

- Dicyclomine 20 mg orally four times daily as needed
- Hyoscyamine 0.125 to 0.25 mg orally or sublingually three to four times daily as needed
- Sustained release hyoscyamine 0.375 mg orally every 8 to 12 hours or 0.75 mg orally every 12 hours

Antidepressants — Antidepressants have analgesic properties independent of their mood improving effects [15,81-84]. Tricyclic antidepressants (TCAs), via their anticholinergic properties, also slow intestinal transit time, which may provide benefit in diarrhea-predominant IBS [5]. Given their effect on intestinal transit, TCAs should be used cautiously in patients with constipation [82,85].

For the treatment of abdominal pain in IBS, antidepressants should be started at low doses. The initial dose should be adjusted based upon tolerance and response. Due to the delayed onset of action of antidepressants, three to four weeks of therapy should be attempted before increasing the dose. Amitriptyline, nortriptyline, desipramine, and imipramine can be started at a dose of 10 to 25 mg at bedtime. If the patient is intolerant of one TCA, another may be tried.

As compared with TCAs, there is less published experience with other antidepressants such as selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), and results of the few published trials (mainly with SSRIs) have been inconsistent [81,84,86-93]. A 2015 meta-analysis that included 12 randomized trials of antidepressants in adults with IBS concluded that antidepressants were significantly more effective as compared with placebo in improving global IBS symptoms (RR 1.38, 95% CI 1.08-1.77) [93]. However, in subgroup analysis, treatment with TCAs, but not SSRIs, showed an improvement in global symptoms as compared with the control groups. Given the lack of consistent high-quality evidence demonstrating an improvement in symptoms, we do not use SSRIs/SNRIs for the treatment of IBS [4,94]. For patients with IBS in whom depression is a cofactor, SSRIs/SNRIs can also be used [86].

In contrast to adults, there is limited evidence to support antidepressant use in children [95]. This was illustrated in a multicenter trial of 83 children with functional gastrointestinal disorders who were randomly assigned to an antidepressant or placebo for four weeks [96]. The primary endpoint was the child's assessment of pain relief and sense of improvement. At four weeks, there was no significant difference between amitriptyline and placebo in the frequency of attaining the primary endpoint (63 versus 58 percent). The authors noted that a longer period of treatment and a higher dose of antidepressant may have produced different results and that there may be a large placebo effect in children due to multiple factors. In another trial of 33 adolescents assigned to an antidepressant or placebo, an antidepressant was effective in reducing diarrhea and pain after a longer period of treatment with an improvement in both self-reported diarrhea and right lower quadrant pain at 10 weeks [97]. However, the results of this study should be interpreted with caution due to methodologic limitations and small sample size.

Antibiotics — While antibiotics should not be routinely recommended in all patients with IBS, in patients with moderate to severe IBS without constipation, particularly those with bloating, who have failed to respond to other therapies (eg, a diet low in fermentable oligo-, di-, and monosaccharides and polyols [FODMAPs], antispasmodics, and TCAs), we suggest a two-week trial of rifaximin. Patients with a response to rifaximin, who develop recurrent symptoms, can be retreated with rifaximin [5]. (See 'Dietary modification' above.)

In a meta-analysis of five randomized trials, rifaximin was more efficacious than placebo for global IBS symptom improvement (OR 1.57) and was significantly more likely to be associated with decreased bloating as compared with placebo (OR 1.55) [98]. However, the randomized trials included in the meta-analysis had a relatively short-term follow-up and the improvement in abdominal bloating in patients with IBS without constipation was modest [99-103].

In the two largest randomized trials (TARGET 1 and TARGET 2) that were included in the meta-analysis, rifaximin-treated patients also experienced an improvement in diarrhea as compared with those treated with placebo. In these trials, 1260 patients with IBS without constipation were assigned to receive either rifaximin 550 mg three times daily or placebo for a total of 14 days and were then followed for 10 weeks [103]. During the first four weeks of follow-up, patients who received rifaximin were more likely to report adequate relief of global IBS symptoms than patients who received placebo (41 versus 32 percent). They also were more likely to report adequate relief of bloating (40 versus 30 percent) and an improvement in daily stool consistency (76 versus 66 percent). Patients who received rifaximin also continued to report better symptom relief during the remainder of the follow-up period.

Probiotics — Probiotics are not routinely recommended in patients with IBS. Although they have been associated with an improvement in symptoms, the magnitude of benefit and the most effective species and strain are uncertain [104]. (See "Probiotics for gastrointestinal diseases", section on 'Irritable bowel syndrome'.)

REFRACTORY SYMPTOMS

A small subset of patients with irritable bowel syndrome (IBS) has refractory symptoms. Patients with continued symptoms despite adjunctive pharmacologic therapy should be carefully reassessed, paying specific attention to the type of ongoing symptoms, the degree to which symptoms have changed, compliance with medications, and the presence of alarm features that should prompt further evaluation. (See 'Indications for referral' above.)

Behavior modification — Patients with unrelenting symptoms that are associated with psychiatric impairment may benefit from behavioral modification in conjunction with antidepressants [105]. (See 'Antidepressants' above.)

Anxiolytics — The use of anxiolytic agents in patients with IBS should be **limited** to short-term (less than two weeks) reduction of acute situational anxiety that may be contributing to symptoms [9]. Side effects of anxiolytics include the risk of habituation, rebound withdrawal,

and drug interactions. Furthermore, benzodiazepines may lower pain thresholds by stimulating gamma aminobutyric acid (GABA) receptors, thereby decreasing brain serotonin.

Other therapies — Other therapies have been evaluated in patients with IBS (eg, herbs, acupuncture, enzyme supplementation, fecal microbiota transplantation, and mast cell stabilizers) but their role in the treatment of IBS remains uncertain [106-110].

- Ketotifen – Ketotifen, a mast cell stabilizer, has been studied for the treatment of IBS based upon the theory that mast cell activation contributes to visceral hypersensitivity. In a randomized trial of 60 patients, the use of ketotifen for eight weeks increased the threshold for discomfort with rectal distension in patients who were hypersensitive to rectal balloon distension at baseline, but not in those with normal sensitivity at baseline [110]. While there was a suggestion of symptom improvement in patients who received ketotifen as compared with those who received placebo, the results did not reach statistical significance.

- **Fecal microbiota transplantation** – In a randomized trial, 90 patients with IBS-diarrhea and mixed IBS were assigned to active (fresh or frozen) donor fecal microbiota transplantation (FMT) or placebo FMT administered via colonoscopy [111]. At three months, significantly more patients treated with active FMT had a reduction in IBS symptom severity scores as compared with placebo (65 versus 43 percent). However, this difference was not sustained at 12 months. This study did not include an evaluation of fecal microbial diversity at baseline or following FMT and excluded patients with IBS-constipation. Other RCTs have failed to demonstrate the efficacy of FMT [112,113]. Additional studies are needed to determine if there are subgroups of patients who may benefit from FMT and the optimal FMT dose [114].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Irritable bowel syndrome".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given

condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Irritable bowel syndrome (The Basics)")
- Beyond the Basics topics (see "Patient education: Irritable bowel syndrome (Beyond the Basics)" and "Patient education: High-fiber diet (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Definitions** – Irritable bowel syndrome (IBS) is defined as recurrent abdominal pain on average, at least one day per week in the last three months with two or more of the following: related to defecation, associated with a change in frequency of stool, associated with a change in form (appearance) of stool. (See 'Definitions' above.)
- **Indications** – In patients with IBS, it is important to assess for alarm features that may require additional endoscopic evaluation. Alarm features include more than minimal rectal bleeding, weight loss, unexplained iron deficiency anemia, nocturnal symptoms, and a family history of organic diseases including colorectal cancer, inflammatory bowel disease, or celiac sprue. (See 'Indications for referral' above.)
- **Initial management** – Establishment of the clinician-patient relationship and continuity of care are critical to the management of all patients with IBS. In patients with mild and intermittent symptoms, we suggest not using pharmacologic therapy for initial management (**Grade 2C**). We begin with lifestyle and dietary modification (eg, exclusion of gas-producing foods; a diet low in fermentable oligo-, di-, and monosaccharides and polyols [FODMAPs]; and in select cases, lactose and gluten avoidance) and a trial of psyllium in patients with IBS with predominant constipation (IBS-C). (See 'Initial therapy' above.)

  In patients with mild to moderate symptoms who fail to respond to lifestyle and dietary modification and in patients with moderate to severe symptoms of IBS that affect quality

of life, we use pharmacologic therapy as adjunctive treatment. Since IBS presents as a complex of symptoms, pharmacologic treatment should be based on the predominant symptom with incremental changes in therapy at two- to four-week intervals. (See 'Adjunctive pharmacologic therapy' above.)

- **Patients with constipation** – In patients with IBS-C who fail a trial of psyllium, we recommend polyethylene glycol (**Grade 1B**). We suggest a trial of lubiprostone or linaclotide in patients with symptoms of constipation that are refractory to osmotic laxatives (**Grade 2B**).

- **Patients with abdominal pain** – In patients with abdominal pain due to IBS, we use antispasmodics on an as-needed basis and/or in anticipation of stressors with known exacerbating effects. We reserve the use of antidepressants to patients with persistent abdominal pain despite antispasmodics and those with coexisting depression. (See 'Abdominal pain and bloating' above.)

- **Patients with diarrhea** – In patients with diarrhea-predominant symptoms, we use antidiarrheals as initial treatment and use bile acid sequestrants as second-line therapy. Given the modest benefit and relatively short-term follow-up demonstrated in the trials of rifaximin, we suggest **not** using antibiotics routinely in patients with IBS (**Grade 2B**). We reserve a two-week trial of rifaximin for patients with moderate to severe IBS without constipation, particularly those with bloating, who have failed to respond to other therapies, including a low FODMAP diet, bile acid sequestrants, antispasmodics, and tricyclic antidepressants. (See 'Antibiotics' above and 'Low FODMAP diet' above.)

- **Refractory symptoms** – Patients with refractory symptoms should be carefully reassessed, paying specific attention to the type of ongoing symptoms, the degree to which symptoms have changed, compliance with medications, and the presence of any alarm features. (See 'Refractory symptoms' above and 'Indications for referral' above.)

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GRAPHICS

Characteristics and sources of common FODMAPs

	Word that corresponds to letter in acronym	Compounds in this category	Foods that contain these compounds
F	**F**ermentable		
O	**O**ligosaccharides	Fructans, galacto-oligosaccharides	Wheat, barley, rye, onion, leek, white part of spring onion, garlic, shallots, artichokes, beetroot, fennel, peas, chicory, pistachio, cashews, legumes, lentils, and chickpeas
D	**D**isaccharides	Lactose	Milk, custard, ice cream, and yogurt
M	**M**onosaccharides	"Free fructose" (fructose in excess of glucose)	Apples, pears, mangoes, cherries, watermelon, asparagus, sugar snap peas, honey, high-fructose corn syrup
A	**A**nd		
P	**P**olyols	Sorbitol, mannitol, maltitol, and xylitol	Apples, pears, apricots, cherries, nectarines, peaches, plums, watermelon, mushrooms, cauliflower, artificially sweetened chewing gum and confectionery

FODMAPs: fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.

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Graphic 90186 Version 2.0

Contributor Disclosures

Arnold Wald, MD No relevant financial relationship(s) with ineligible companies to disclose. **Nicholas J Talley, MD, PhD** Patent Holder: Australian Provisional Patent [Diagnostic marker for functional gastrointestinal disorders]; Biomarkers of irritable bowel syndrome [Irritable bowel syndrome]; Mayo Clinic [Dysphagia questionnaire]; Mayo Clinic [Bowel Disease questionnaire]; Nepean Dyspepsia Index [Dyspepsia]; Nestec [Irritable bowel syndrome]; Singapore Provisional Patent [BDNF Tissue Repair Pathway]. Grant/Research/Clinical Trial Support: Alimetry [Gastric mapping device research collaboration]; Allakos [Gastric eosinophilic disease]; AstraZeneca [Eosinophilic gastritis, eosinophilic gastroenteritis]; Intrinsic Medicine [Bowel syndrome with constipation]; NHMRC Centre for Research Excellence in Digestive Health [NHMRC Investigator grant]. Consultant/Advisory Boards: Adelphi Values [Functional dyspepsia]; Allakos [Gastric eosinophilic disease, AK002]; AstraZeneca [Eosinophilic gastritis, eosinophilic gastroenteritis]; AusEE [Eosinophilic gut diseases]; Bayer [Inflammatory bowel syndrome]; BluMaiden [Microbiome Ad Board]; Comvita Mānuka Honey [Digestive health]; Dr Falk Pharma [Eosinophilia]; GlaxoSmithKline Australia [Educational speaker eosinophilic gut disease]; Glutagen [Celiac disease]; International Foundation for Functional Gastrointestinal Disorders [Advisory board, functional GI disorders]; Intrinsic Medicine [Human milk oligosaccharide]; IsoThrive [Esophageal microbiome]; Planet Innovation [Gas capsule, inflammatory bowel syndrome]; Progenity Inc [Intestinal capsule]; Rose Pharma [IBS]; Viscera Labs [Inflammatory bowel syndrome, diarrhea]. Other Financial Interest: Elsevier textbook royalties [Medical education]. All of the relevant financial relationships listed have been mitigated. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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