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Womens Health (Lond Engl). Author manuscript; available in PMC 2009 September 1.

Published in final edited form as:
Womens Health (Lond Engl). 2008 November ; 4(6): 605–623. doi:10.2217/17455057.4.6.605.

New treatments for irritable bowel syndrome in women

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Abstract

The estimated prevalence of irritable bowel syndrome (IBS) in Western countries is 7–15%, with a female:male ratio of 2–2.5:1 in IBS patients who seek healthcare services; however, the female predominance is lower in the general population. IBS has a significant impact on health-related quality of life and is associated with a significant healthcare and economic burden. Management of IBS is comprised of general measures and pharmacologic and nonpharmacologic treatment. However, there are ongoing efforts to find more effective therapeutic approaches. As advancements in the understanding of the pathophysiology of IBS continue to grow, new and effective treatments with novel mechanisms of action that have the potential to improve relief of IBS symptoms over current treatments are likely to be developed. This article provides an overview of current and emerging therapies for IBS and also highlights sex and gender differences in clinical trials and treatment response.

Keywords

constipation; diarrhea; gender; irritable bowel syndrome; treatment; women

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Editor
Elisa Menotti, Editorial Director, Future Science Group. Disclosure: Elisa Manzotti has disclosed no relevant financial relationships.

Financial & competing interests disclosure
CME Author
Charles P Vega, MD, Associate Professor; Residency Director, Department of Family Medicine, University of California, Irvine, USA. Disclosure: Charles P Vega, MD, has disclosed that he has served as an advisor or consultant to Novartis, Inc.

Authors and Credentials
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Disclosure: Mopelola A Adeyemo, MPH, has disclosed no relevant financial relationships.
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Disclosure: Lin Chang, MD, has disclosed that he has received grants for clinical research from GlaxoSmithKline and Prometheus, and has served as an advisor or consultant to GlaxoSmithKline, Prometheus, Takeda, Tioga, Synergy, Forest, Allergan, Albireo, Ironwood and Salix.

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Irritable bowel syndrome (IBS) is a functional bowel disorder in which recurrent abdominal pain and/or discomfort is associated with a change in bowel habit [1]. The diagnosis of IBS is currently based on the Rome III symptom-based criteria for IBS (Box 1). IBS is subtyped, based on predominant bowel habit: IBS with constipation (IBS-C), diarrhea (IBS-D) and mixed pattern (IBS-M). The subtype classifications are based on the prevalence of altered stool form (i.e., loose/watery stool and/or hard/lumpy stool) (Box 2) [1]. Individuals who are classified as not fitting IBS-D or IBS-C subtypes are classified as either IBS-M or IBS-A. IBS-M is preferred for individuals for whom both diarrhea and constipation-type stool form 25% or more of their bowel movements. The IBS-A subtype is now used in cases where an individual's bowel habits transitions between IBS-C and IBS-D over time. In this review, IBS-M and IBS-A will be referred to as IBS-M/A. Supportive symptoms of IBS include change in frequency of stool, abnormal stool form, straining with defecation, urgency, feeling of incomplete defecation, passage of mucus and bloating.

The estimated prevalence of IBS in Western countries is 7–15% [2–6]. There is a 2–2.5:1 ratio of women to men who seek healthcare services for IBS, although the female predominance is less in the general population. Symptoms of IBS greatly impact the health-related quality of life (HRQOL) of affected individuals and is associated with a significant healthcare and economic burden. Several studies have found that individuals with IBS have a significantly diminished HRQOL when compared with the general population, and it is lower or comparable to patients with other chronic illnesses [7–10]. The economic impact of IBS on society is significant, with annual direct costs estimated at US$1.35 billion and indirect costs of at least $200 million [1]. Treatment of IBS is comprised of a multicomponent approach, although it is commonly targeted towards the predominant subtype and/or other symptoms, such as abdominal pain/discomfort and bloating.

Several studies have reported that women have a higher prevalence of pain [11,12], bloating and distension [12–15] and hard or lumpy stools [16] than men. Women are more likely than men to be classified into the IBS-C subtype [17]. In addition, it appears that female sex is a risk factor for the development of postinfectious IBS, which occurs in a subset of individuals who develop IBS-like symptoms after an enteric infection [18]. Women with IBS report greater IBS severity [14,19,20], greater impact of symptoms on daily life and lower HRQOL [19,21, 22] than men with IBS. There is also some evidence suggesting that women with IBS respond differently to pharmacologic and psychological treatment compared with their male counterparts [23–27]. The reasons for sex- and gender-related differences in the prevalence, symptom presentation, pathophysiology and treatment response are not well understood. Explanations include differences in pain sensation, cognitive response to pain, reporting bias, gender role and fluctuation in ovarian hormones [28].

This article will review current and emerging therapies for IBS and will also highlight sex and gender differences in clinical trials and treatment response if present.

General guidelines

Patient–physician relationship

A good patient–physician relationship is essential to the treatment of IBS. Effective patient–physician relationships have been associated with improved health status and increased efficiency of care [29]. In order to establish an effective and interactive relationship with patients, healthcare providers should obtain a medical history through a patient-centered interview, conduct a cost-efficient investigation including a physical examination, provide a clear explanation of IBS and the patient's symptoms that takes into consideration the patient's beliefs, address the patient's expectations, involve the patient in the treatment and establish a long-term relationship with the patient [30]. It is also important to determine if a link exists

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between the patient's stressors and symptoms, since stress can exacerbate IBS symptoms and reduce chances of disease remission [30,31]. Recognizing stressors or other inciting factors can be beneficial in the management of a patient's symptoms. Psychosocial trauma and early adverse events, such as sexual abuse, have been found to have a significant negative impact on gastrointestinal symptoms and health outcome [32,33]. Therefore, it is important to conduct a psychosocial interview that investigates the interaction between social and psychological factors of the patient [34]. Response to treatment and health status may be improved by treating IBS symptoms and addressing relevant psychosocial issues, if they exist, which may impact symptoms and disease management.

Box 1. Rome III criteria for the diagnosis of irritable bowel syndrome

Recurrent abdominal pain or discomfort* for at least 3 days per month in the last 3 months that is associated with two or more of the following:

- Improvement with defecation
- Onset associated with a change in stool frequency
- Onset associated with change in stool form (appearance)

*Discomfort means an uncomfortable sensation not described as pain. Symptom onset at least 6 months prior to diagnosis.

Diet

Up to 65% of patients report that their IBS symptoms are triggered by food; however, studies to support the relationship between diet, specifically, food allergies or food intolerances, and IBS symptoms are limited [35,36]. Food intolerances are common among IBS patients and may result in diarrhea and/or abdominal pain [35]. The most common foods associated with food intolerance include milk, wheat, eggs, nuts, shellfish and soybeans. Although lactose intolerance is not a cause of IBS, lactose consumption may exacerbate symptoms in some IBS patients or can be a coexistent condition. Since lactose intolerance can mimic the symptoms of IBS, it is important to determine whether lactose intolerance is a factor through laboratory tests or experimenting with lactose-free diets, particularly in patients with IBS symptoms associated with the intake of dairy products. The exclusion of lactose from the diet may lead to improvement in abdominal pain and diarrhea symptoms. However, the efficacy of lactose-free diets as treatment for IBS symptoms has not been well studied [37]. Food-derived antigens can trigger inflammation if there is a break in the gut barrier. It has been suggested that IgE-mediated food hypersensitivity exists in typically atopic IBS patients (those with a history of allergic reactions) [35,36]. In addition, studies have demonstrated an elevated expression of IgG in IBS patients, which may indicate food intolerance, as having an influence on symptoms in some IBS patients [38,39]. Although exclusion diets as treatment for IBS have demonstrated some benefit, ranging from 15 to 71%, additional studies are necessary to determine if food avoidance is an effective treatment for IBS [36,39]. An interesting and recently published, controlled study found that dietary restriction of fructose and/or fructans is associated with symptom improvement in IBS patients with fructose intolerance, which was determined by a positive fructose hydrogen breath test [40]. This study suggested that foods which are highly fermentable and poorly absorbed exert an osmotic effect, causing distension and exacerbating IBS symptoms. These foods are collectively termed fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) [41]. The results need to be confirmed in larger IBS patient populations. In addition, it would be interesting to see if this diet also helps those without a positive breath test for fructose malabsorption.

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Box 2. Subtypes of irritable bowel syndrome based on predominant stool pattern

IBS with constipation (IBS-C)

- Hard or lumpy stools ≥25% and loose (mushy) or watery stools <25% of bowel movements

IBS with diarrhea (IBS-D)

- Loose (mushy) or watery stools ≥25% and hard or lumpy stools <25% of bowel movements

Mixed IBS (IBS-M)

- Hard or lumpy stools ≥25% and loose (mushy) or watery stools ≥25% of bowel movements

Unsubtyped IBS

- Insufficient abnormality of stool consistency to meet criteria for IBS-C, IBS-D or IBS-M

IBS: Irritable bowel syndrome.

Pharmacologic treatment based on predominant symptom

Information regarding the various available pharmacologic agents used to treat IBS symptoms are listed in TABLE 1.

IBS-C subtype

Traditional treatments—Bulking agents, such as calcium polycarbophil, fiber, ispaghula husk, methylcellulose and wheatbran, are commonly used as initial treatment for IBS. Bulking agents increase stool frequency by adding water and bulk to stool. Quartero *et al.* conducted a systematic review on IBS treatments in which the efficacy of bulking agents to improve abdominal pain, global assessment and symptom score was assessed [42]. They concluded that there was insufficient evidence to determine the benefit of bulking agents as therapy for IBS. One exception is ispaghula husk, which has been demonstrated to be efficacious in the treatment of constipation symptoms, such as straining and formed stools [43,44]. Common side effects of bulking agents include bloating, intestinal gas and additional abdominal pain. Therefore, low doses are sometimes recommended at treatment initiation, particularly in patients who have little fiber in their diet, followed by a gradual increase in dose.

Tegaserod is a 5-hydroxytryptamine 4 (5-HT_4) agonist, which acts on the 5-HT_4 receptors in the GI tract where it stimulates motility and peristalsis [45]. Several studies have found that tegaserod is effective in treatment of IBS in women with IBS-C [46–49]. In addition to the relief of IBS-C symptoms (abdominal pain/discomfort, bloating and constipation), tegaserod has recently been shown to improve HRQOL and work productivity in IBS women [47]. In 2002, tegaserod was initially approved for treatment of IBS-C in women. In August 2004, tegaserod was approved for the treatment of chronic constipation in men and women under the age of 65 years. However, in March 2007, tegaserod was removed from the market owing to an imbalance in the risk of serious cardiovascular events. In an analysis consisting of 11,614 study participants who took tegaserod and 7031 study subjects who took placebo for 3 months, there was an event occurrence of 0.1% in the tegaserod group versus 0.01% in the placebo group [201]. Based on these results, the US FDA determined that the potential risk of treatment with tegaserod outweighed the benefit. Currently, tegaserod is only available for emergency use and must be requested from the FDA.

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Osmotic laxatives function by drawing water into the lumen of the intestine by means of an osmolar gradient, thereby increasing water in the stool, which leads to softened stool form, shortened stool transit time and an improvement in ease of stool evacuation [50–52]. Common osmotic laxatives are lactulose, magnesium-based products, sorbitol and polyethylene glycol (PEG). Although these agents are frequently used in clinical practice to treat constipation symptoms in patients with IBS-C, there are no studies assessing their efficacy in this patient population. PEG, a mixture of nonabsorbable and nonmetabolized polymer, was initially approved by the FDA for the short-term treatment of constipation in 1999 and was released as an over-the-counter medication for constipation in 2007. Recently, studies have been conducted to assess the efficacy of long-term use of PEG for treatment of chronic constipation [53]. In a randomized, multicenter, placebo-controlled 6-month study consisting of 304 patients (85% women) diagnosed with chronic constipation by modified Rome criteria, the efficacy of PEG at a dose of 17 g daily was assessed. Compared with placebo, a significantly higher percentage of individuals taking PEG experienced an improvement in constipation symptoms, such as straining, hard stools, incomplete evacuation, stool frequency and complete spontaneous bowel movements. There were significantly more gastrointestinal complaints in the PEG group versus the placebo group (39.7 vs 25%, respectively), which included diarrhea, flatulence and nausea. However, individually these symptoms were not significantly different between treatment groups. This study suggests that PEG treatment is effective for long-term use up to 6 months, which is how it is commonly used in clinical practice.

Stimulant laxatives, such as bisacodyl, cascara and senna, are thought to exert their effect by increasing intestinal motility and inhibiting water absorption by affecting epithelial transport of water and electrolytes [54]. Similar to osmotic laxatives, the efficacy of stimulant laxatives has not been studied in IBS. However, they are often used off-label for the treatment of IBS-C. Osmotic laxatives are usually tried before stimulant laxatives because frequent use of the latter may cause abdominal cramping, urgency and straining [55,56].

Available treatments—Lubiprostone is a selective chloride-channel activator of the ClC-2 channels in the GI tract, which results in increased chloride and intestinal fluid secretion, and acceleration of small intestinal and colon transit [57]. Lubiprostone was initially shown to be effective in relieving symptoms in patients with chronic constipation in randomized, placebo-controlled clinical trials [58]. In January 2006, lubiprostone was approved by the FDA at a dose of 24 μg twice daily for the treatment of chronic idiopathic constipation in men and women [202]. More recently, in April 2008, lubiprostone was approved for the treatment of IBS-C in adult women at a lower dose of 8 μg twice daily [203]. A 3-month, Phase II, randomized, placebo-controlled, dose-ranging trial was conducted evaluating the efficacy of lubiprostone (16, 32 and 48 μg daily) in 195 IBS-C patients (89.7% women) [58]. The primary end point of this study was a change in abdominal pain/discomfort from baseline to 1 month. This study demonstrated that lubiprostone was significantly associated with improvement in abdominal pain/discomfort symptoms at both 1 and 2 months of treatment. A significantly greater improvement in abdominal pain/discomfort at 1 month was demonstrated with the 48 μg dose. After 2 months, all treatment groups had significantly greater improvement in abdominal pain/discomfort when compared with the placebo group, but there was a nonsignificant trend after 3 months of treatment. In addition, abdominal bloating, straining and severity of constipation significantly improved from baseline at all time points, excluding the 3-month time point for abdominal bloating. Two subsequent, Phase III, randomized, placebo-controlled clinical trials consisting of 1167 IBS-C adults, comprised of 91.6% women, were conducted to evaluate the efficacy of a 12-week course of lubiprostone 8 μg twice daily in IBS-C [59]. The studies found that a significantly greater number of patients treated with lubiprostone reported an overall improvement in IBS symptoms than individuals receiving placebo (lubiprostone 17.9% vs placebo 10.1%). The lower than expected response rates for both active drug and placebo were probably caused by the relatively restrictive primary end point. Furthermore, there was

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significant improvement in abdominal discomfort/pain, stool consistency, straining, constipation severity and HRQOL in individuals receiving lubiprostone versus those receiving placebo. The most common side effects reported with lubiprostone as compared with the placebo group were nausea (8 vs 4%, respectively) and diarrhea (6 vs 4%, respectively). It is recommended to take lubiprostone with meals in order to minimize nausea. Owing to the low inclusion of men in the IBS-C clinical trials, the efficacy of lubiprostone in men with IBS-C has not been adequately assessed.

Agents under investigation—Linaclotide is a guanylate cyclase C (GC-C) agonist. The GC-C receptor is found in the lining of the intestine, resulting in increased chloride and bicarbonate secretion into the lumen of the intestine. This increased secretion leads to accelerated intestinal transit and secretion, which may lead to improvement in IBS symptoms. In a 5-day, Phase IIB, randomized clinical trial of linaclotide, 36IBS-C women were randomized to either a placebo group or a 100 μg or 1000 μg treatment group in order to assess the effects of linaclotide on gastrointestinal transit, which was the primary end point, and IBS symptoms [60]. The study demonstrated a significant treatment effect on ascending colon emptying and overall colonic transit at 48 h, but not on gastric emptying and colonic filling. Significant acceleration in colonic transit was observed with the 1000 μg dose but not with the 100 μg dose. In addition, the study found that there was a significant treatment effect on stool consistency, ease of passage and time to first bowel movement; yet, there was no significant effect on stool frequency and sense of complete evacuation was observed. The most common gastrointestinal-related side effect of linaclotide was borborygmi and the most common nongastrointestinal-related side effect was headache. This study suggests that linaclotide is effective in improving colonic transit and IBS symptoms in women with IBS-C. Currently, Phase IIb trials for treatment of both IBS-C and chronic constipation are ongoing. Phase III trials are expected to be initiated in the latter part of 2008.

Opioid antagonists are being studied for the treatment of postoperative ileus, opioid bowel dysfunction and functional bowel disorders. The analgesic agents, opioids, including endorphins and dynorphins, bind to their receptors located in the CNS and GI tract [61]. Through their mechanism of action, opioids produce the negative effects of increased intestinal fluid absorption and inhibition of both peristalsis and secretion, which often results in opioid-induced constipation [62]. The unwanted side effects of opioids have led to the investigation of opioid antagonists, such as methylnaltrexone, naloxone and naltreoxone, as potential pharmacological agents for IBS-C. In 2001, Hawkes *et al.* conducted a randomized, double-blinded, placebo-controlled trial in which 25 IBS patients with either constipation or alternating bowel habits were randomized to placebo group or naloxone at a dose of 10 mg twice daily for 8 weeks [63]. Naloxone was not associated with significantly greater adequate relief of abdominal pain and discomfort compared with the placebo. Another opioid antagonist, naltreoxone, was evaluated in a 4-week, single-arm pilot study using low-dose naltreoxone in 42 IBS patients (64.2% women) [64]. There was a statistically significant mean increase in the number of pain-free days with naltreoxone in IBS subjects overall and in IBS-C patients. Additional larger, randomized investigations are needed to assess the efficacy of treatment in IBS. Two other μ-opioid antagonists, which have been recently approved for indications other than IBS-C or chronic idiopathic constipation, are also being considered as treatment for IBS-C. Alvimopan was approved for short-term use for the treatment of postoperative ileus in patients who have undergone intestinal resection [65]. Another μ-opioid antagonist, methylnaltrexone, was approved by the FDA in 2008 for the treatment of opioid-induced constipation in patients with late-stage, advanced illness, such as terminal cancer [204]. Several studies have demonstrated that treatment with methyl naltrexone rapidly induces laxation in patients receiving opioids [66–68].

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Prucalopride is a highly selective 5-HT_4-receptor agonist, which increases intestinal motility and may improve constipation symptoms. A Phase III, randomized, placebo-controlled trial was conducted to determine the efficacy of prucalopride at 2 and 4 mg doses for 12 weeks in 620 adults (87.9% women) with severe chronic constipation [69]. The primary end point of this study was the percentage of patients having an average of three or more complete spontaneous bowel movements (CSBMs) per week. Averaged over the entire 12-week period as well as monthly, a significantly higher percentage of patients receiving 2 and 4 mg of prucalopride had an average of three or more CSBMs per week than those taking placebo (30.9, 28.4 and 12.0%, respectively). In addition, there were significant improvements in straining, percent of bowel movements with normal consistency, treatment that was self-rated as quite effective or extremely effective, satisfaction with bowel function, constipation severity and HRQOL within both prucalopride groups. The most commonly reported side effects in the 2 and 4 mg treatment groups were headache, nausea and abdominal pain. Currently, prucalopride is not FDA approved.

IBS-D subtype

Traditional treatments—Loperamide is an opioid-receptor agonist, which acts on the μ-opioid receptors in the intestine. It functions by decreasing intestinal motility and secretion, which allows for greater absorption of fluids in the GI tract. Loperamide appears to improve diarrhea symptoms, including stool consistency and frequency and urgency [70]. Loperamide is FDA approved as an over-the-counter medication for control and symptomatic relief of acute nonspecific diarrhea and chronic diarrhea associated with inflammatory bowel disease. The recommended initial dose is 4 mg of loperamide followed by 2 mg after each unformed stool. The efficacy of loperamide has not yet been investigated in the treatment of IBS-D, although a study is being planned. In the management of IBS-D, loperamide is commonly used and is often recommended to be used on a more prophylactic basis to prevent diarrhea. Loperamide is also used for diarrheal episodes in IBS-M/A, although constipation may be a potential side effect. Clinically, these drugs appear to be effective in relieving patients' anxiety about recurrent diarrhea and other IBS symptoms [71].

Alosetron is a 5-HT_3-receptor antagonist that is currently FDA approved for the treatment of severe IBS-D in women. The 5-HT_3 receptors are extensively distributed on enteric neurons in the human GI tract as well as other peripheral and central locations, and they are known to be present on myenteric intrinsic primary afferent neurons. Activation of these receptors affects intestinal motility, secretion and pain. Blockade of 5-HT_3 receptors by alosetron slows intestinal transit, decreases chloride and water secretion, increases rectal compliance and reduces visceral sensitivity [72,73].

In a recent meta-analysis and systematic review of alosetron, 14 randomized, controlled trials of alosetron or cilansetron (5-HT_3 antagonist with similar effects to alosetron) versus mebeverine or placebo evaluated the efficacy of the 5-HT_3 antagonists in nonconstipated IBS or IBS-D [74]. The study found that both 5-HT_3 antagonists, when compared independently and jointly, were more effective than comparators in achieving global improvement in IBS symptoms and relief of abdominal pain and discomfort. In addition, the 5-HT_3 antagonists were more likely to cause constipation. Results from this analysis support that both 5-HT_3 antagonists improve symptoms of IBS-D in women and men (although alosetron had a less robust effect in men [25]). In February 2000, alosetron was approved by the FDA for the treatment of IBS-D in women. Later that year in November 2000, alosetron was removed from the market owing to concerns about ischemic colitis and serious complications of constipation. Ischemic colitis was found to occur in 1.1 per 1000 patient-years of alosetron and serious complications of constipation in 0.66 per 1000 patient-years of alosetron use [75]. In 2006, a systematic review of reported cases of adverse events was performed and it was concluded that

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while alosetron was associated with ischemic colitis compared with placebo (0.15 vs 0%, respectively), it was not associated with serious complications of constipation [75]. All of the ischemic colitis cases associated with alosetron were reversible without long-term sequelae.

Since alosetron's withdrawal in 2000 and reintroduction in 2002, several clinical trials have demonstrated the efficacy of alosetron in severe IBS-D and also for long-term use. In two studies conducted by Lembo *et al.*, the efficacy of alosetron for treatment of IBS at a 1 mg dose twice daily was investigated in women with severe IBS-D in 12-week randomized, placebo-controlled studies [76,77]. Both studies found that women with severe IBS-D who were treated with alosetron had a greater percentage of days with satisfactory urgency and a higher proportion of global improvement responders than those taking placebo. In a recent dose-ranging study, the efficacy of alosetron was compared at 0.5 mg daily, 1 mg daily and 1 mg twice daily in a randomized, placebo-controlled study in 705 women with severe IBS-D [78]. The study reported that, at all doses, there was a significant improvement in global IBS symptoms, which was the primary end point, compared with the placebo group at 12 weeks. Furthermore, bowel symptoms, which include urgency and stool frequency and consistency, were improved in all groups. This study suggests that alosetron is also effective in the treatment of severe IBS-D women at lower doses, such as 0.5 and 1 mg daily. A recent, multicenter, randomized, placebo-controlled 48-week clinical trial demonstrated the long-term efficacy of alosetron at a dose of 1 mg twice daily in women with IBS-D [79].

Under a risk-management program, alosetron is available for the treatment of severe IBS-D in women who have failed conventional therapy. The recommended initial dose of alosetron is 0.5 mg twice daily but it can be increased to 1 mg twice daily if needed. Alosetron is not currently approved for use by men owing to a lack of inclusion of men in initial clinical trials prior to FDA approval.

Agents under investigation—Asimadoline is a selective κ-opioid receptor agonist. κ–opioids, which are found in the GI tract, are believed to play a role in visceral pain [80]. Recently, a randomized, double-blind, placebo-controlled study was conducted in order to investigate the efficacy of asimadoline 0.15, 0.5 and 1.0 mg doses for treatment of IBS in 596 patients (78% women) [81]. The primary end point of the study was the number of months that a patient was a responder for adequate relief of pain. An adequate responder was defined as having a positive response to the adequate relief question for three out of 4 weeks of assessment. Although the study did not find a significant difference in adequate relief of IBS pain or discomfort between the active drug and placebo groups, individuals receiving 1 mg of asimadoline who had at least moderate pain at baseline experienced significantly more months of adequate relief of pain or discomfort than the placebo group. Furthermore, the IBS-D subgroup with at least moderate pain at baseline, and who received active treatment, had a higher mean percentage of months with adequate relief of IBS pain or discomfort with both the 0.5 mg (46 vs 20%, respectively) and 1 mg (36.7 vs 20%, respectively) doses compared with placebo. In addition, significant improvement of urgency and stool frequency, but not stool consistency, was demonstrated in IBS-D patients. There was also a higher responder rate in IBS-M/A with 1 mg of asimadoline versus placebo (50 vs 27.6%, respectively) but no significant improvement in other IBS symptoms. The most common side effects in this study were constipation and diarrhea. These results suggest that asimadoline may be an effective agent for the IBS-D subgroup and, to a lesser degree, in the IBS-M/A subgroup.

Studies have established that the corticotropin-releasing factor (CRF) signaling pathways play a role in mediating the endocrine, autonomic, behavioral and visceral response to stress [82]. Extensive animal research has demonstrated the relationship between activation of central and peripheral CRF receptors and increases in gastrointestinal motility and visceral sensitivity [83–88]; more specifically, CRF-1 antagonists have been demonstrated to inhibit stimulation

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of colonic motor function in animal models of stress [89]. For these reasons, the CRF-1 antagonist has been identified as a potential target for treatment in IBS. The effect of a nonselective CRF-receptor antagonist on gastrointestinal motility, visceral perception and negative mood in response to rectal electrical stimulation was measured in ten IBS patients and ten controls [90]. Compared with baseline measurements, the CRF antagonist decreased gastrointestinal motility and abdominal pain and anxiety ratings to gut stimulation in IBS patients. Currently, Phase I and II clinical trials are being conducted to evaluate the safety and efficacy of a CRF-1 antagonist for the treatment of IBS.

Crofelemer is a novel proanthocyandin that has an antisecretory mechanism of action, which reduces excess chloride ion secretion via the cystic fibrosis transmembrane conductance-regulator channel [91]. Increased chloride ion secretion results in excess fluid in the intestines, which may lead to diarrhea. By reducing excess chloride ion secretion, crofelemer may reduce diarrhea symptoms in IBS-D patients. In order to evaluate the safety and efficacy of crofelemer in the treatment of IBS-D, a randomized, double-blind, placebo-controlled 12-week Phase IIa study was conducted in 246 IBS-D patients randomized to placebo or crofelemer at doses of 125, 250 or 500 mg twice daily [92]. End points assessed included pain score, stool frequency and consistency, urgency and adequate relief of symptoms. The study found that only the 125 mg dose of crofelemer was significantly beneficial in reducing pain in IBS-D patients. Future large clinical trials are needed to further investigate this.

Dextofisopam, which is an autonomic modulator, is the R-enantiomer of the drug tofisopam. Tofisopam is a benzodiazepine derivative that has anxiolytic properties, but does not produce muscle relaxant or sedative effects [93]. Dextofisopam binds the 2,3-benzodiazepine receptors, which are thought to play a role in gastrointestinal motility and sensation. Dextofisopam's possible effect on motility has made it an agent of interest for the treatment of IBS. In a recent, 12-week, double-blind, randomized, placebo-controlled, Phase IIb study, which consisted of 140 adults (73% women) with IBS-D or IBS-M/A, subjects were randomized to treatment with either dextofisopam at a dose of 200 mg twice daily or a placebo [94]. The primary end point was the number of months that patients were classified as adequate relief responders. A responder was defined as any individual who experienced adequate relief in two or more out of four weekly assessments in 1 month. The study found that individuals who received dextofisopam were responders at significantly more months than those taking placebo (1.7 vs 1.3 months, respectively). However, while the dextofisopam was significantly associated with a greater number of responders during the first month of treatment, there was only a similar trend during the second month and similar response rate to placebo during the third month. A similar treatment effect was observed with respect to stool frequency. Thus, the initial benefit of dextofisopam on adequate relief and stool frequency diminished over time. Dextofisopam was associated with a small improvement in stool consistency, but this was not statistically significant compared with placebo. The most common side effects of dextofisopam were abdominal pain, influenza and nausea, but the rates of occurrence did not differ significantly from placebo. The study suggests that dextofisopam is effective in treatment of IBS symptoms in IBS-D and IBS-M/A patients, but it may be an ideal drug in the setting of intermittent flares and on an as-needed basis.

Pain &/or discomfort

Traditional treatments—Antispasmodics, such as mebeverine and hyoscine, function by inhibiting intestinal smooth muscle contractions via a direct effect or an antimuscarinic or anticholinergic effect [52]. Although there is a lack of high-quality studies evaluating the efficacy of antispasmodics in IBS, a meta-analysis of 23 randomized, controlled trials found that smooth muscle relaxants improved the global rating of symptoms and reduced pain in patients with IBS [95]. A second meta-analysis of 24 randomized, placebo-controlled trials

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found that 12 of the studies were negative [96]. Although beneficial effects have been reported with cimetropium bromide, octylonium bromide, mebeverine, hyoscine and peppermint oil, only octylonium bromide was found to be effective in relieving the global symptoms of IBS when low-quality studies were excluded. The beneficial effects of octylonium were based upon results from only two studies. Owing to poor study quality, heterogeneity of treatment trials, small sample sizes and high number of dropouts during the follow-up periods, the efficacy of antispasmodic agents in IBS could not be confidently determined. Despite these limitations, antispasmodics can sometimes be helpful in partially relieving abdominal pain, in particular postprandial symptoms, in clinical practice.

Tricyclic antidepressants (TCAs) are a class of antidepressants that function by inhibiting the reuptake of the neurotransmitters norepinephrine and serotonin, but also have varying degrees of anticholinergic and antihistamine receptor activity. Although the exact mechanism is unknown, TCAs are believed to have a beneficial effect in IBS, even at low doses, via their peripheral and central actions. TCAs have been demonstrated to reduce the frequency of nerve impulses evoked by noxious distension in primary afferent fibers leaving the colon [97]. In addition, imipramine, a TCA with noradrenergic, serotonergic and anticholinergic action, was associated with a prolongation of the orocecal transit time [98]. The central actions of TCAs, which may help reduce pain in IBS, were assessed in a brain imaging study by Morgan and colleagues [99]. In women with IBS, amitriptyline, a commonly used TCA in IBS and other chronic pain disorders, was associated with reduced pain-related cerebral activations in the perigenual anterior cingulate cortex and the left posterior parietal cortex.

Although the efficacy of TCAs has been studied in IBS, they are not FDA approved for the treatment of IBS. A systematic review of seven randomized clinical trials conducted in 2002, which were assessed to be of low quality, found evidence that TCAs may decrease abdominal pain although their effects may be limited [52]. In 2003, Drossman *et al.* published the results from a randomized, placebo-controlled trial consisting of 431 women with functional bowel disorders (87.2% had IBS), which evaluated the efficacy and safety of desipramine [100]. The study found that desipramine was not significantly more efficacious than placebo in the intention-to-treat analysis, but was significant in the per-protocol analysis (i.e., only in those who completed the study). Treatment was more beneficial for those with moderate symptoms, abuse history, no depression and IBS-D symptoms. Common side effects of TCA treatment are dizziness and drowsiness [101]. These side effects suggest that desipramine is efficacious in those who are able to remain on the medication. For this reason, TCAs are frequently initiated at low doses (e.g., 10–25 mg at bedtime) and gradually increased as tolerated.

New agents—Selective serotonin-reuptake inhibitors (SSRIs), such as fluoxetine and paroxetine, function by increasing the level of the neurotransmitter serotonin. Once present in the GI tract, serotonin initiates motility and secretion in the intestine, which can reduce transit time [98]. In addition to their potential benefits in the gut, SSRIs also have well known central effects, which collectively may improve IBS symptoms. SSRIs are increasingly prescribed as treatment for IBS patients; however, they are not FDA approved for use in IBS and there are a limited number of controlled trials on which to draw conclusions about the efficacy of SSRIs [102]. Several studies have evaluated the efficacy of SSRIs in patients with IBS, but they have enrolled relatively small numbers of patients. The largest study was conducted by Creed and colleagues [103], which compared the efficacy of paroxetine (n = 86), psychotherapy (n = 85) and usual treatment (n = 86) in patients with severe IBS (79.8% women). Paroxetine was found to improve the physical component of HRQOL and reduce healthcare costs compared with usual care. While there was a reduction in the number of days of abdominal pain but not pain severity, at 3 months with paroxetine over usual care, this effect was not maintained at the 1-year follow-up.

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Five other smaller SSRI trials demonstrate conflicting results in IBS. Three trials reported an effect on overall well-being, symptom frequency and abdominal pain [104–106], while two failed to demonstrate a beneficial effect on relieving abdominal pain and/or global symptoms [107,108]. Larger, high-quality studies are needed to evaluate the efficacy of SSRIs in IBS and to determine if SSRIs can relieve IBS symptoms irrespective of their effects on mood. Similarly to SSRIs, serotonin–norepinephrine-reuptake inhibitors (SNRIs) block the reuptake of serotonin, but they also block the reuptake of norepinephrine. The recently approved SNRI duloxetine, which is FDA approved for the treatment of generalized anxiety disorder and diabetic neuropathic pain, and other SNRIs are being studied in IBS and the chronic somatic pain disorder, fibromyalgia. This suggests that these classes of agents are effective analgesic agents, but more studies are needed to assess their efficacy in IBS. Common side effects of SSRIs include vomiting, dizziness, drowsiness and nausea [101].

Bloating & gas

Traditional treatments—The estimated average prevalence of bloating is 64% in IBS [109]. Currently, there are no approved, traditional treatments that specifically address treatment of bloating and/or gas in IBS patients. Instead, many drugs that target other predominant symptoms of IBS offer relief of bloating as a secondary effect. Over-the-counter antigas agents are often used to treat bloating and gas, but have not been studied in IBS.

Available treatments—Probiotics, such as *Lactobacillus*, *Bifidobacterium* and VSL#3 (combination of *Bifidobacterium*, *Lactobacillus* and *Streptococcus salivarius*) are nonpathogenic organisms that exert a positive effect on the host's health. Probiotics may have beneficial effects against bacterial pathogens and several other functions, including gastrointestinal motility and mucosal barrier protection. In a randomized, placebo-controlled, 8-week study consisting of 77 IBS patients (64% women), the response of symptoms and serum cytokine profiles in IBS patients to a malted milk drink containing either *Lactobacillus salivarius* UCC4331, *Bifidobacterium infantis* 35624 or placebo were studied [110,111]. Patients treated with *B. infantis*, but not *L. salivarius*, experienced a significantly greater improvement of abdominal pain/discomfort, bloating/distension and bowel movement difficulty compared with those on placebo. However, no significant effects were observed on bowel movement frequency and consistency. In a larger, 4-week, randomized, placebo-controlled study consisting of 362 women with IBS, subjects were randomized to placebo or *B. infantis* 35624 at either a 1×10^6, 1×10^8 or 1×10^{10} cfu/ml dosage in order to assess the efficacy of an encapsulated form of the probiotic in IBS [112]. The study found that the 1×10^8 cfu/ml dosage of the probiotic was significantly better than placebo and all other treatment groups in improving abdominal pain, bloating, bowel dysfunction, incomplete evacuation, straining and the passage of gas. No significant adverse events were reported. Several other studies that have evaluated the efficacy of probiotics in IBS have found that treatment results in some improvement in symptoms [110,111,113–120], such as abdominal pain [110,117], bloating [119,120], distension/bloating [110] and difficult defecation. However, the majority of studies employ different organisms, strains and dosages, which makes comparisons between studies difficult. Results from the above-mentioned studies support the belief that probiotics play a role in improving IBS symptoms, such as bloating and flatulence [110,112].

Rifaximin is a nonabsorbed, broad-spectrum antibiotic approved by the FDA in 2004 as treatment for diarrhea caused by *Escherichia coli*. The efficacy of this medication and other antibiotics has been investigated in IBS after initial studies suggested that small intestinal bacterial overgrowth may play a role in IBS symptoms [121,122]; however, the significance of its role in IBS and the method of diagnosis (e.g., resulting from the inaccuracy of breath tests and the insensitivity of culture of jejunal aspirates) have long been in question. Rifaximin has been demonstrated to have a significant benefit on symptoms of flatulence and bloating in

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IBS. Pimentel *et al.* investigated whether nonabsorbed antibiotic rifaximin is more efficacious in reducing symptoms in adults with IBS compared with placebo [123]. In the study, 87 participants (67.7% women) were randomly assigned to 10 days of 400 mg three-times daily of rifaximin or placebo. Follow-up assessment was conducted for 10 weeks post-treatment. The study found that the rifaximin group reported a significantly higher percentage mean improvement in global symptoms when compared with the placebo group (36.4 vs 21.0%, respectively). However, bloating was the only individual IBS symptom that significantly improved with treatment of rifaximin compared with placebo. The most common side effects with rifaximin were abdominal pain and a bad taste in the mouth; however, these side effects were not significantly different from the placebo. Sharara *et al.* compared the efficacy of rifaximin at a dose of 400 mg twice daily and placebo in 124 patients (54.8% women) who reported predominant abdominal bloating (56.5% with IBS) [124]. The study found a significant difference in global symptom relief with rifaximin versus placebo at the end of a 10-day treatment period (41.3 vs 22.9%, respectively) and 10-day post-treatment period (28.6 vs 11.5%, respectively). In addition, there was a significant decrease in bloating-specific scores and hydrogen breath-test excretion in the rifaximin group. No adverse events were reported during this study. Similar results were found in a larger, multicenter, Phase II double-blind trial by Lembo and colleagues [125], which compared the efficacy of rifaximin at a dose of 550 mg twice daily versus placebo for 14 days in IBS-D patients, followed by 14 days of placebo in both groups and a 12-week follow-up phase. Rifaximin significantly improved global symptoms and bloating in IBS-D subjects for up to 12-weeks of follow-up. Results from these studies suggest that rifaximin may be an effective treatment of abdominal bloating and flatulence. Further investigation is necessary to evaluate the efficacy of rifaximin for treatment of IBS and its long-term management of this chronic or recurrent condition.

Nonpharmacologic & other treatments

Behavioral & psychological treatment

Behavioral and psychological treatments can be helpful to IBS patients in several ways, but are usually not directed towards a specific IBS symptom. They can assist in the self-management of IBS symptoms, address current stressors or previous adverse or traumatic events (e.g., family death, sexual and physical abuse), which may be associated with symptom flares or have a negative impact on illness severity, and treat comorbid psychological conditions if present. Behavioral and psychological therapies can be used alone or in combination with pharmacological treatment in IBS patients.

Cognitive behavioral therapy (CBT) is a form of psychotherapy based on cognitions, assumptions, beliefs and behaviors. The objective of CBT is to identify maladaptive thoughts and beliefs and how they are dysfunctional and inaccurate. This is done in an effort to reject the unrealistic thoughts and to replace them with more realistic and self-helping alternatives [126]. In IBS, negative thoughts and stressors may exacerbate symptoms; thus, CBT offers patients a technique to modify maladaptive behaviors and thoughts, which may alleviate IBS symptoms. CBT has been shown to improve global symptoms of IBS [100,127]. A randomized, controlled trial investigating 431 women with IBS evaluated the efficacy of CBT versus education in treating moderate-to-severe functional bowel disorders, including IBS, over a 12-week study period [100]. Individuals in the CBT group received therapy, which focused on modifying the influence of attention, personal appraisal, sex-related cognitive schemas and illness attribution as related to the gastrointestinal symptoms as a means to develop more effective coping strategies. CBT had a significantly greater benefit over education in global well-being and satisfaction with treatment. Recently, a 12-week, randomized, controlled trial, consisting of 75 IBS patients (86% women) was conducted to assess the efficacy of self-administered CBT for moderate-to-severe IBS patients [126]. Participants were randomized into a waiting list control or one of two versions of CBT (ten-session, therapist-administered

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CBT or four-session, patient-administered CBT). Both treatment groups had a significantly higher percentage of participants who reported adequate relief from pain and bowel symptoms and global improvement of symptoms. Furthermore, compared with waiting-list control patients, both CBT groups reported significantly improved HRQOL and IBS symptom severity, but not psychological distress. Results from this study suggest that both patient- and therapist-administered CBT are effective in relieving IBS symptoms.

Gut-directed hypnotherapy (GDH) is aimed at returning gastrointestinal function back to normal by assuring the patient that they have a clear understanding of the pathophysiological concepts of their illness and providing suggestions to the patient for improvement of symptoms on a repetitive basis [128]. GDH has been extensively investigated as a treatment for IBS. Although end points of investigation of GDH vary, several studies have reported the efficacy of GDH in IBS treatment. In a systematic review that evaluated the effectiveness of hypnotherapy in the management of IBS in 18 trials (four randomized, controlled trials, two nonrandomized controlled trials and 12 uncontrolled trials), the majority of studies (ten of 18) reported that there was a significant benefit of GDH in IBS [129]. Yet, the majority of these trials were not compared with a control arm (12 of 18). In a hypnotherapy study conducted in the UK, investigating 250 treatment-refractory IBS patients, women with IBS demonstrated an overall greater improvement in response to treatment (52 vs 33%, respectively) and better long-term outcome with hypnotherapy as compared with men [23].

Complementary & alternative medicine

Patients with IBS often combine several forms of therapy for adequate treatment of their IBS symptoms, particularly in those with more severe symptoms. Many patients have tried complementary and alternative medicine (CAM) as treatment for IBS. The efficacy of CAM is open to dispute because of the lack of high-quality studies and the high placebo response rate in randomized, clinical trials of CAM [130].

Acupuncture is a form of alternative treatment that has been used to treat IBS. Acupuncture is believed to have an effect on both gastro intestinal motility [131] and gastric secretion [132]. In addition, acupuncture is believed to have an effect on pain. Recent data suggest that acupuncture triggers the release of endogenous opioid-like substances, which may act to alleviate pain [133,134]. Reports on the efficacy of acupuncture treatment in IBS are conflicting. A review of six randomized, controlled trials assessed the efficacy of acupuncture in the treatment of IBS symptoms versus sham (placebo) acupuncture, or other treatment intervention [135]. There was no significant improvement in global symptom score or overall general well-being with acupuncture treatment in comparison with sham acupuncture or a combination of one or more of the following drugs: diazepam, perphenazine and domperidone. A significant improvement of symptoms has been reported with acupuncture versus herbal medication and a combination of acupuncture and psycho therapy versus psychotherapy alone. Caution in evaluating the significance of these results must be taken because most of the trials in the review were determined to be of poor quality. In a recent randomized, controlled trial comparing patients who received acupuncture for ten sessions over 3 months plus general practitioner care versus general practitioner care alone, 30 IBS patients (60% women) were assessed to evaluate the effectiveness of acupuncture as a treatment for IBS [136]. The study found that treatment with acupuncture and general practitioner care resulted in a significantly greater improvement in symptom severity than treatment with practitioner care alone. Future studies are needed to determine the efficacy of acupuncture as treatment.

Herbal medicine is another type of CAM and is frequently used by IBS patients. A *Cochrane* systematic review of herbal medicine treatment was recently conducted to evaluate its effectiveness in treatment of IBS [137]. The study consisted of 75 randomized clinical trials,

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including 7957 participants with IBS. The study concluded that herbal medicines might be effective in improving the symptoms of IBS; however, future high-quality studies are needed.

Conclusion

Irritable bowel syndrome is a prevalent chronic or recurrent gastrointestinal condition that can be impacted by multiple factors, making it potentially challenging to treat and manage. Traditional treatments are often ineffective in providing adequate relief of global IBS symptoms; however, they can be effective for individual symptoms. There have been new agents that also offer benefit as well as a number of drugs in development. As our understanding of the pathophysiology of IBS continues to grow, new and effective treatments with novel mechanisms of action will hopefully be developed. As a result, emerging treatments in IBS have the potential to provide improved relief of IBS symptoms over current treatments.

Future perspective

There are a number of challenges the field of functional gastrointestinal disorders faces currently and over the next 5–10 years. Our ultimate goals will be to:

- More completely understand the evolving path physiology of these conditions, including IBS with continued basic and translational research;
- Determine biomarkers that will help diagnose patients rather than solely relying on symptom criteria;
- Determine valid and clinically meaningful physiologically-derived and patient-reported outcomes to assess illness severity and treatment response;
- Further develop valid and clinically relevant animal models of IBS;
- Conduct rigorous assessment of candidate drugs and other therapeutic modalities using validated end points;
- Develop more effective treatments for patients with functional gastrointestinal disorders.

In addition to these goals, there will also be expected changes in the field in the near future. From a patient perspective, there will be a growing awareness of IBS and similar conditions with more affected individuals seeking healthcare. With limited available treatments, increased use of complementary alternative medicine for symptom relief will occur even in the absence of a thorough evaluation of the efficacy and safety of these modalities. From a clinician perspective, the recognition and understanding of these conditions will continue to grow. The use of diagnostic biomarkers will increase while the use of diagnostic tests for exclusion of other diseases will decrease. A multicomponent management approach for the treatment of these disorders will be recognized as more successful than a focused treatment approach for a specific symptom. From a scientific viewpoint, there will certainly be challenges in the development of valid patient-reported outcomes for clinical trials and in the development of drugs with an optimal benefit–risk ratio. There will be changes on all fronts and while there will be ups and downs and some changes may be initially perceived as steps backward, the more knowledge we gain and the more we work together in a collaborative spirit, the more likely that, overall, the field will move forward and progress will be made.

Executive summary

Introduction

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- Irritable bowel syndrome (IBS) is a common gastrointestinal disorder associated with a significant healthcare and economic burden.
- IBS is subtyped by predominant bowel habit, and pharmacologic treatments are currently instituted based on these subtypes.
- IBS is a female-predominant condition and women with IBS are more likely than men to report constipation, bloating, distension, extraintestinal symptoms, greater illness severity and a greater impact of symptoms on daily life.

General guidelines

- A successful patient–physician relationship is essential to the treatment of IBS and has been associated with improved health status and increased efficiency of care.
- A significant number of IBS patients report meal-related symptoms, but the interaction of food with physiologic disturbances in the gut in IBS patients is not well understood.
- Avoidance of food intolerances in IBS patients can sometimes provide symptom relief.

IBS with constipation subtype

- With the exception of ispaghula husk, bulking agents have not been shown to be efficacious in the global relief of IBS but may improve constipation symptoms, such as straining and hard stools.
- Tegaserod, a 5-hydroxytryptamine-4 (5-HT4) agonist, has been shown to be efficacious in the treatment of IBS with constipation, but owing to concerns of an association with cardiovascular events, it is currently only available for emergency use by the US FDA.
- While laxatives have been studied for the treatment of occasional or chronic constipation, their efficacy in IBS has not been evaluated. However, they are often used in clinical practice to treat patients with IBS with predominantly constipation.
- Lubiprostone, a chloride-channel activator, is a newer agent that is FDA approved for the treatment of IBS-C in women and for chronic idiopathic constipation in men and women.
- Agents under investigation include linaclotide, opioid antagonists and prucalopride.

IBS with diarrhea subtype

- Antidiarrheal agents, such as loperamide, can be effective in the treatment of diarrhea, but have not been shown to relieve the global symptoms of IBS.
- Alosetron is a 5-HT_3 antagonist that has been shown to be quite efficacious for the treatment of IBS with diarrhea, but is currently only available for the treatment of women with severe IBS-D under a risk-management program owing to its association with ischemic colitis and serious complications of constipation.
- Agents under investigation include asimadoline, corticotropin-releasing factor type 1 antagonist, crofelemer and dextofisopam.

Pain and/or discomfort

- With the exception of octylonium bromide, antispasmodics have limited proven efficacy in the treatment of IBS.

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- Tricyclic antidepressants have been shown to have efficacy for the treatment of IBS at lower than usual doses, particularly in patients with moderate symptoms and in IBS-D, but their use is limited because of frequent side effects.
- Selective serotonin-reuptake inhibitors (SSRIs) and serotonin–norepinephrine-reuptake inhibitors have not been studied in multicenter, large, randomized, placebo-controlled trials in IBS, but initial studies with SSRIs demonstrate some improvement in overall well-being.

Bloating & gas

- High-quality IBS studies are lacking with probiotics, but so far, trials have demonstrated improvement in gas-related symptoms.
- Antibiotics, such as rifaximin, are being used for the treatment of IBS, particularly for gas and bloating, but further studies on their efficacy and mechanism of action in IBS are needed.

Nonpharmacologic & other treatments

- Behavioral and psychological treatments, such as cognitive behavioral therapy and hypnotherapy, have been shown to be efficacious in the management of IBS.
- Complementary alternative medicine, including acupuncture and herbal therapy, is being increasingly used by IBS patients, but further studies evaluating their efficacy and safety are needed.

Learning objectives

Upon completion of this activity, participants should be able to:

- Describe sex differences in the prevalence and severity of irritable bowel syndrome (IBS)
- Identify medications with evidence of efficacy for IBS with constipation
- Specify first-line treatment for patients with IBS with diarrhea
- Describe treatments for IBS that do not require a prescription

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Table 1

Available medications for the treatment of irritable bowel syndrome symptoms.

Drug class	Generic name	Dose	Evidence for IBS
Bulking agent	Psyllium	1–3 tbsp q.d.	—
	Methylcellulose	1–3 tbsp q.d.	—
	Polycarbophil	2–4 tablets q.d.	—
5-HT_4 agonist	Tegaserod*#	6 mg b.i.d.	≠
Osmotic laxative	Lactulose	1–2 tbsp q.d.–b.i.d.	—
	Milk of magnesia	1–2 tspn q.d.–b.i.d.	—
	Polyethylene glycol	17 g in 8 oz fluid	—
Stimulant laxative	Cascara sagrada	325 mg or 1 tspn qhs	—
	Senna	187 mg tablets; 1–2 tablets qhs	—
Prostone (type-2 chloride-channel activator)	Lubiprostone*	8 μg b.i.d.	≠
Antidiarrheal	Loperamide	1–2 tablets q.d.–q.i.d.¶	—
5-HT_3 antagonist	Alosetron*	0.5 mg to 1 mg q.d.–b.i.d.	≠
Antibiotic	Rifaximin	400 mg t.i.d.	≠
Antispasmodic	Hyoscyamine + scopolamine + atropine + Phenobarbital	1–2 tablets t.i.d.–q.i.d.	§
	Hyoscyamine sulfate	0.125 mg q.i.d. prn, 0.375 mg b.i.d.	—
Tricyclic antidepressant	Amitriptyline	10–150 mg qhs	≠
	Desipramine	10–150 mg qhs	≠
	Nortriptyline	10–150 mg qhs	—
SSRI	Fluoxetine	10–40 mg q.d.	≠
	Paroxetine	20–50 mg q.d.	≠
	Citalopram	20–40 mg q.d.	≠
SNRI	Duloxetine	30 mg b.i.d.	—
Probiotic	*Bifidobacterium infantis*	1 tablet q.d.	≠
	VSL#3®	1 packet b.i.d.	≠

*Medication is US FDA approved for IBS.

≠At least one controlled trial with evidence of efficacy in IBS.

[§] Only scopolamine has been studied in a controlled trial.

[¶] Dosage of loperamide should be titrated to symptoms.

[#] Tegaserod is only available under an investigational new drug application.

5-HT: 5-hydroxytryptamine; a.c.: Before meals; b.i.d.: Twice daily; IBS: Irritable bowel syndrome; prn: Whenever necessary; q.d.: Daily; qhs: At night; q.i.d.: Four-times daily; SNRI: Serotonin–norepinephrine-reuptake inhibitor; SSRI: Selective serotonin-reuptake inhibitor; tbsp: Tablespoon; t.i.d.: Three-times daily; tspn: Teaspoon.

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