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LARGE INTESTINE (B CASH AND S KHAN, SECTION EDITORS)

Update on Pharmacotherapy for Irritable Bowel Syndrome

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Abstract

Purpose of Review Irritable bowel syndrome (IBS) is a functional GI disorder that affects a large percentage of the population and presents a significant socio-economic burden on the society. In this article, we reviewed the evidence supporting various pharmacological treatment options for IBS.

Recent Findings Rifaximin, eluxadoline, and alosetron have demonstrated that they reduce symptom severity improving quality of life in patients with IBS–diarrhea. Ramosetron is a promising agent in development. Peppermint oil has also demonstrated a positive impact on some symptoms of IBS. For IBS with constipation, traditional laxatives have failed to demonstrate significant benefit. However, lubiprostone, linaclotide, and plecanatide have demonstrated improvement of IBS with constipation in large, placebo-controlled trials. Tenapanor, a sodium/hydrogen exchanger 3 inhibitor, appears to be a promising treatment option in the pipeline.

Summary There are multiple pharmacologic agents with a variety of mechanisms that have demonstrated efficacy in IBS with diarrhea and constipation. There are no established pharmacologic agents for IBS with a mixed bowel pattern. There is a promising pipeline for additional novel therapies for IBS.

Keywords Irritable bowel syndrome · Pharmacologic therapies · Diarrhea · Constipation

Introduction

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal (GI) disorder affecting a sizable percentage of the adult population, with a prevalence as high as 15% in Europe and North America [1]. IBS has an especially high prevalence in working-age adults and represents a significant socio-economic burden on patients and society. There is a significant reduction in the quality of life of patients afflicted with IBS and higher utilization of healthcare resources. Patients with severe IBS symptoms miss more days of work leading to decreased productivity. Many patients undergo extensive medical evaluation including endoscopic, laboratory, and radiologic tests that are often unrevealing as IBS has no reliable biomarkers [2]. Multiple proposed theories and mechanisms regarding the pathophysiology of IBS include altered GI motility, visceral hypersensitivity, alteration in the brain-gut axis, alteration of the gut microbiome, including food intolerances, post-infectious immune reactivity, and chronic intestinal inflammation. However, the exact etiology is still unclear and it is likely that there are multiple and inter-related factors leading to IBS symptom generation [3]. Based on the Rome IV criteria [4, 5], IBS is characterized by pain or discomfort associated with altered bowel habits, including both constipation and diarrhea, and can include postprandial urgency, abdominal bloating, or distention. Conventional therapies for many years have consisted of anti-diarrheal and laxative medications for bothersome bowel habits and anti-spasmodic or pain medications for the sensory symptoms of IBS. This article will focus on recent pharmacological advances in IBS pharmacotherapy.

IBS is broadly classified based on abnormal bowel habits into four broad categories: IBS-D (predominantly diarrhea),

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IBS-C (predominantly constipation), IBS-M (mixed pattern including both diarrhea and constipation), and IBS-U (unclassifiable within the three previously mentioned subtypes) [5]. In addition, IBS is not static and patient symptoms can change over time between different subtypes. An overview of pharmacologic therapies that are frequently used to treat the spectrum of IBS as well as emerging pharmacologic therapies is listed in Table 1.

Irritable Bowel Syndrome–Diarrhea

Alosetron

Alosetron is a 5-HT3 receptor antagonist approved by the US Food and Drug Administration (FDA) for treating IBS-D in women refractory to "conventional" therapies. 5-HT3 receptor stimulation is associated with increased gastrointestinal motility and secretion, and alosetron, being an antagonist, slows down fecal transit through the colon and provides more time for water absorption, resulting in a decrease in total moisture and volume of fecal waste products. Alosetron has been associated with adverse events such as colon ischemia (incidence of 0.3% in pooled meta-analysis studies) [6] and complications arising from constipation. The medication was withdrawn from the market in 2000 due to safety concerns; however, due to its clinical utility in appropriately selected patients, it was made available again in 2002 under the auspices of strict prescribing restrictions and a risk management program. In January 2016, the FDA removed the restrictive requirements of the risk evaluation and mitigation strategy (REMS) due to accumulated favorable safety data.

Table 1 Existing and emerging (*) IBS therapies

- IBS–Diarrhea
  - Anti-diarrheals
    - Loperamide
    - Diphenoxylate/atropine
  - Anti-spasmodics
    - Dicyclomine
    - Hyoscyamine
    - Peppermint oil
  - Antibiotics
    - Rifaximin
  - 5-HT3 antagonists
    - Alosetron
    - Ramosetron*
  - Mixed opioid receptor agonist/antagonist
    - Eluxadoline
- IBS–Constipation
  - Laxatives
    - Osmotics
    - Stimulants
  - Chloride channel activators
    - Lubiprostone
  - Guanylate cyclase receptor activators
    - Linaclotide
    - Plecanatide
  - Sodium/hydrogen exchanger 3 inhibitor
    - Tenapanor*

The body of evidence demonstrating beneficial effects of alosetron is large. A randomized controlled trial by Cremonini et al. studied 705 women with IBS-D over a period of 12 weeks [7]. Subjects were randomized into various treatment groups with different doses of alosetron vs placebo. This study showed a statistically significant improvement in quality of life in IBS-D patients who received one or more doses of alosetron when compared with placebo, with the most common adverse effect being constipation. Treatment with alosetron 0.5 mg daily and 1 mg BID decreased lost workplace productivity hours -11.0 ± 3.3 and -21.1 ± 4.1 h, $p < 0.05$, and lost social/leisure hours -6.7 ± 0.8 and -7.0 ± 0.9 days, $p < 0.01$, respectively. Another study by Camilleri et al. on 647 females with IBS-D or alternating bowel patterns (IBS-A) yielded similar results. Patients were randomized into placebo vs 1 mg alosetron daily. It was found that a greater proportion of participants in the alosetron group reported adequate relief compared with the placebo (133 (41%) vs 94 (29%), respectively), for the 3 months of treatment, with a statistically significant difference of 12% (4.7–19.2) between the groups. They also reported that patients in the treatment group had decreased urgency and stool frequency and firmer stool texture [8].

Currently, the use of alosetron is restricted to women with severe IBS-D without adequate response to conventional therapy and with chronic IBS symptoms (greater than 6 months) without any anatomical or biochemical abnormalities of the GI tract. Contraindications to the drug include history of chronic or severe constipation, strictures of the GI tract, history of perforation or adhesions, ischemic colitis, inflammatory bowel disease, diverticulitis, and severe hepatic impairment.

Rifaximin

Rifaximin is a gut-specific oral broad-spectrum antibiotic with very low systemic absorption and bioavailability. It primarily acts by interfering with bacterial DNA transcription. Its exact effects on the generation and perception of IBS symptoms are unknown, but leading theories suggest alterations in the gut microbiome metabolism and/or host–microbiome interaction.

Two large randomized clinical trials (TARGET 1 and TARGET 2) of 1260 IBS patients without constipation evaluated the efficacy of rifaximin for improving IBS symptoms. Patients were randomized to receive 550 mg of rifaximin three

times daily vs placebo for 2 weeks and then followed up for a period of 10 more weeks. It was observed that a significantly higher proportion of patients in the rifaximin group had adequate relief of global IBS symptoms during the first 4 weeks after treatment (41% vs 31% in TARGET 1 and 41% vs 32% in TARGET 2) with a similar incidence of adverse effects [9]. Rifaximin has also been studied in a randomized trial in patients with IBS-C (Rome II criteria), and this study found that rifaximin plus neomycin was superior to neomycin alone in improving IBS-C symptoms [10]. A third large randomized clinical trial (TARGET 3) was performed due to FDA concerns regarding the use of antibiotics to treat IBS and to evaluate the effect of multiple courses of rifaximin in patients with recurrent symptoms after a successful first course [11]. This study found that, among the approximately two thirds of responders to an initial course of rifaximin 550 mg three times a day who experienced recurrent IBS-D symptoms within 6 months, a significantly greater percentage responded to up to 2 additional treatments with rifaximin vs placebo. Additionally, rifaximin was extremely well tolerated and no clinically significant antimicrobial resistance was shown to develop over the course of the study.

Based on the TARGET 1, 2, and 3 trials, the FDA approved the use of rifaximin in IBS-D patients at a dose of 550 mg three times daily for 2 weeks. Patients with an initial response to rifaximin who develop recurrent symptoms can be retreated up to two additional times with the same regimen according to current labeling. The optimal timing of retreatment, if necessary, must be individualized.

Eluxadoline

Eluxadoline is another pharmacotherapy that was recently approved by the FDA for the treatment of IBS-D. Eluxadoline is a μ and κ-opioid receptor agonist and δ-opioid receptor antagonist that acts locally at the level of the gut mucosa and the enteric nervous system. Local μ receptor agonism reduces colonic secretions and slows GI transit while δ-opioid receptor antagonism counteracts excessive μ receptor inhibition and prevents excessive constipation from unopposed μ receptor stimulation [12]. In addition, concomitant μ agonism and δ antagonism have been shown to have synergistic analgesic effects, [13] which may be helpful in relieving the abdominal discomfort in patients with IBS. Kappa-opioid receptor agonism has also been shown to reduce visceral hypersensitivity. In preclinical murine trials, it was observed that eluxadoline reduced gut transit in a dose-dependent fashion whereas loperamide at higher doses completely abolished gut transit. This suggested that eluxadoline can normalize gut motility with a decreased risk of constipation when compared with loperamide [12].

A phase 2 study to evaluate the efficacy of eluxadoline at various doses vs placebo demonstrated significant clinical improvement in groups randomized to 100 mg and 200 mg BID dosing when compared with placebo. The 200 mg BID regimen was associated with more adverse effects, and therefore, only 75 mg and 100 mg BID regimens were chosen for phase 3 trials [14].

The study population for the two phase 3 trials included patients who met Rome III criteria for IBS-D. Patients were randomized to receive either eluxadoline at a dose of 75 mg BID or 100 mg BID or placebo for 26 weeks. In IBS-3001, the participants received eluxadoline for an additional 26 weeks for collection of safety data. In IBS-3002, the initial 26-week treatment period was followed by a 4-week single-blinded, placebo withdrawal period to assess for rebound worsening of symptoms. The primary endpoint for both studies was a composite response of (1) daily improvement in abdominal pain (reduction of ≥ 30% worst abdominal pain (WAP) score from baseline) and (2) stool consistency (Bristol Stool Form Scale (BSFS) < 5 or absence of bowel movement) on at least 50% of days over the first 12 weeks (FDA endpoint) or the first 26 weeks (European Medicines Agency (EMA) endpoint). The study populations included 1280 patients in IBS-3001 and 1145 patients in IBS-3002. The FDA endpoint was met by a significantly higher proportion of patients receiving 75 mg or 100 mg of eluxadoline in both trials compared with placebo (23.9% and 25.1% vs 17.1%, $p = 0.01$ and $p = 0.004$, respectively in IBS 3001 and 28.9% and 29.6% vs 16.2%, $p < 0.001$ in IBS-3002). The proportion of patients meeting the EMA endpoint was also higher in the 100 mg BID eluxadoline group compared with placebo in both trials (29.3% vs 19%, $p < 0.001$ in IBS-3001 and 32.7% vs 20.2%, $p < 0.001$ in IBS-3002) [13–15, 16••].

Eluxadoline is used for both adult men and women with IBS-D and has been shown to be effective in controlling IBS symptoms at a dose of 100 mg BID. It is recommended to decrease the dose to 75 mg BID in patients who are unable to tolerate the 100 mg BID dose, patients with mild-moderate hepatic impairment, or patients on OATP1B1 inhibitors (ex: rifampicin, clarithromycin, erythromycin, cyclosporine, gemfibrozil). Importantly, safety reports from the clinical trials and post-marketing surveillance of sphincter of Oddi spasm and pancreatitis have led to the contraindication of eluxadoline in patients without gallbladders or who ingest 3 or more alcoholic beverages per day. The most common adverse effects seen in the clinical trials of eluxadoline included constipation, abdominal pain, and nausea.

Ramosetron

Ramosetron, a potent and selective 5-HT3 receptor antagonist, has a mechanism of action similar to alosetron and acts by decreasing colonic motility and providing more time for water absorption.

A randomized, placebo-controlled phase IV study of ramosetron was performed in 98 patients diagnosed with IBS-D using Rome III criteria. Patients were given either 5 mcg of ramosetron or placebo once daily for 12 weeks. This study found that 53.2% of patients receiving ramosetron had better relief of IBS-D symptoms vs 42.0% in the placebo group with the greatest relief being observed in the improvement of stool consistency [17]. Since ramosetron was previously only studied and approved for men, a randomized study was conducted involving 576 women with IBS-D according to Rome III criteria. A significantly higher proportion of patients treated with ramosetron 2.5 mcg daily reported global improvement compared with placebo (50.7% vs 32.0%, $p < 0.001$) [18]. A recent meta-analysis encompassing 4 randomized trials of ramosetron including 1623 patients demonstrated relief of overall IBS symptoms in both males and females compared with placebo (RR; 95% CI 1.94; 1.58–2.38 and 1.49; 1.25–1.79) with no serious adverse events reported [19].

Currently, ramosetron is approved for use in Japan and certain Southeast Asian countries and is not FDA approved for use in the USA. The 5 mcg daily dose is for IBS-D and other dosages are used for nausea and vomiting.

Serum-Derived Bovine Immunoglobulin/Protein Isolate (SBI)

Serum-derived bovine immunoglobulin/protein isolate (SBI) or EnteraGam is a nutritional supplement that is marketed as a therapy for diarrheal diseases. The mechanism of action of SBI is unclear. It is believed to act by binding to toxic substances released by gut bacteria, preventing them from translocating across the epithelium, and thereby decreasing their pathogenic effects [20].

A randomized double-blind placebo-controlled study to evaluate the impact of SBI on quality of life in IBS-D patients included a total of 66 patients who were randomized to receive either 10 g/day or 5 g/day of SBI vs placebo for 6 weeks [21]. This study found that SBI was well tolerated in both groups without any major adverse effects. Subjects receiving SBI at 10 g/day had a statistically significant within-group reduction in abdominal pain ($p < 0.01$), loose stools ($p < 0.01$), bloating ($p < 0.05$), flatulence ($p < 0.01$), urgency ($p < 0.01$), and any symptoms ($p < 0.01$) at end of treatment vs baseline. Similar results were obtained in the group receiving 5 g/day of SBI. This pilot study concluded that SBI was safe and well tolerated, but was underpowered to show differences relative to placebo. Currently, there are no large, high-quality randomized controlled studies evaluating the effects of SBI in IBS.

Peppermint Oil

Peppermint oil (PO) is a widely used therapy for IBS symptoms. The primary effect of PO is likely as an anti-spasmodic, although there is evidence that PO has a range of other effects including anti-nociception, anti-inflammatory, and carminative effects [22]. Most of the data for PO comes from Europe and has studied commercial products that are not available in the USA. The most commonly reported adverse event with PO is heartburn. To minimize this adverse event, a novel formulation of PO (PO-SST) designed to release beyond the pylorus has been developed and studied in the USA. A recent 4-week randomized, double-blind, placebo-controlled trial of PO-SST vs placebo done in patients fulfilling Rome III criteria for IBS-M or IBS-D showed that the sustained release formulation provided safe and effective IBS treatment and rapid relief of symptoms [23••]. The primary endpoint of this study was a change from baseline in the total IBS symptom score (TISS) after 4 weeks of treatment. The TISS decreased by 40% in the treatment group vs 24.3% in the placebo group after 4 weeks of treatment ($p = 0.0246$). Even more recently, a systematic review and meta-analysis of PO for IBS evaluated 9 studies involving 726 patients and concluded that PO was superior to placebo in improving global IBS symptoms (5 studies, 392 patients, RR 2.23; 95% CI 1.78–2.81) and improvement in abdominal pain (5 studies, 357 patients, RR 2.14; 95% CI 1.64–2.79) [24]. A novel ileocolic release PO capsule is currently being studied in a phase 1 trial [25].

Irritable Bowel Syndrome–Constipation

Lubiprostone

Lubiprostone is a locally acting type-2 chloride channel activator located on the apical membrane of intestinal epithelial cells and acts by increasing fluid secretion and colonic transit [26]. Lubiprostone is approved for use in adult women with IBS-C at an 8 mcg twice daily dose.

Two randomized double-blind, placebo-controlled phase 3 trials including 1171 patients diagnosed with IBS-C using Rome II criteria demonstrated that patients treated with lubiprostone 8 mcg twice daily had better relief of IBS symptoms compared with placebo (17.9% vs 10.1%, $p = 0.001$), with a similar incidence of adverse effects in both groups. A balanced 7-point Likert scale was used to assess for response, and a rigorous definition for responders was used in an attempt to keep the placebo response low [27]. In 2012, the FDA issued new guidance for IBS-C clinical trials and a post hoc analysis on the two phase 3 trials using the new FDA composite endpoint (simultaneous improvement in both abdominal pain and stool frequency) demonstrated higher response rates compared with placebo (26.3% vs 15.3%, $p = 0.008$) [28]. An open-label extension study of lubiprostone enrolled 522 patients with IBS-C who had completed one of the 2 randomized phase 3 studies and looked at long-term safety and tolerability

over 9–13 treatment months. Results similar to previous trials were observed in this study with the most common GI adverse effects being diarrhea (11.0%), and nausea (11.0%). No serious adverse events were observed in this study, and only 17 patients discontinued the drug because of adverse effects [29].

Linaclotide

Linaclotide is one of the newer agents approved for use in IBS-C. It is a 14-amino acid peptide that binds to guanylate cyclase-C receptors located on the luminal surface of the GI tract, causing a cyclic-GMP-mediated increase in chloride and bicarbonate secretion while inhibiting absorption of sodium ions, therefore increasing the net secretion of fluid into the GI tract [30].

Linaclotide was investigated in two randomized, double-blind, multicenter phase 3 trials for patients with IBS-C. A once-daily regimen of 290 mcg for 12 weeks (trial 31) or 26 weeks (trial 302) was used. EMA recommended co-primary endpoints were used which were (1) 12-week abdominal pain/discomfort responders (> 30% reduction in mean abdominal pain and/or discomfort score (11-point scale) with neither worsening from baseline, for ≥ 6 weeks) and (2) 12-week IBS degree-of-relief responders (symptoms "considerably" or "completely" relieved for ≥ 6 weeks). One thousand six hundred eight patients were enrolled and randomized in these two trials, $n = 803$ in trial 31 and $n = 805$ patients in trial 302. A significantly greater proportion of linaclotide-treated patients met the first primary endpoint when compared with placebo (trial 31, 54.8% vs 41.8%; trial 302, 54.1% vs 38.5%; $p < 0.001$). Similarly, a greater proportion of treated patients met the second primary endpoint (IBS degree of relief) (trial 31, 37.0% vs 18.5%; trial 302, 39.4% vs 16.6%; $p < 0.001$). Linaclotide-treated patients also showed sustained response when compared with placebo (response for ≥ 2 of the last 4 weeks of treatment) ($p < 0.001$). Both trials concluded that patients on linaclotide had a significant improvement in abdominal pain/discomfort and degree-of-relief of IBS-C symptoms when compared with placebo over 12 and 26 weeks [30, 31].

The most common side effect of linaclotide is diarrhea (16–20% in clinical trials) [30, 31]. Absolute contraindications include patients with known or suspected mechanical gastrointestinal obstruction and pediatric patients younger than 18 years of age due to safety signals in a pediatric animal model in clinical development trials. This latter contraindication applies to the entire class of guanylate-cyclase-C agonists.

Plecanatide

Plecanatide is a uroguanylin analog which also works on guanylate cyclase-C receptors similar to linaclotide to increase fluid secretion in the GI tract. Plecanatide also has low oral bioavailability and no measurable systemic absorption and appears safe and well tolerated with minimal systemic adverse effects [32]. A phase 2 trial to evaluate dose-range of plecanatide in IBS-C patients found that 3 and 9 mg both had favorable efficacy and safety profile, with the lower dose showing best overall efficacy [33].

The safety and efficacy of plecanatide were evaluated in 2 identical randomized, double-blind, placebo-controlled phase 3 trials in patients with IBS-C. A total of 2189 adults meeting Rome III criteria for IBS-C were randomized (1:1:1) to placebo or plecanatide (3 mg or 6 mg daily) for 12 weeks. The primary endpoint of the study was to evaluate for overall response (patients reporting ≥ 30% reduction from baseline in WAP, plus an increase of ≥ 1 complete spontaneous bowel movement (CSBM) per week from baseline in the same week for ≥ 6 of the 12 treatment weeks). A total of 1879 participants completed the study. The first study found that 30.2% and 29.5% of patients in the 3- and 6-mg groups, respectively, met the primary endpoint vs 17.8% in the placebo group ($p < 0.001$ for each dose vs placebo). The second study had similar results with 21.5% ($p = 0.009$) and 24% ($p < 0.001$) in plecanatide 3- and 6-mg groups being responders vs 14.2% in the placebo group. Both studies also found that the percentage of sustained efficacy responders (overall plus weekly responders for ≥ 2 of the last 4 weeks of the study period) was significantly greater in the plecanatide groups compared with placebo [34••].

The use of plecanatide, 3-mg daily tablet, is indicated in adult with IBS-C, and the contraindications are similar to those of linaclotide. In clinical trials, the most common adverse effect of plecanatide was diarrhea and it should not be used in patients < 18 years of age.

Tenapanor

Tenapanor, is a novel, first-in-class, potent small-molecule inhibitor of the sodium/hydrogen exchanger isoform 3 (NHE3) localized in the apical membrane of intestinal epithelial cells, which is minimally absorbed and acts locally in the GI tract to inhibit sodium absorption. It also modulates tight junctions in the small intestine, and increases transepithelial electrical resistance (TEER) and reduces phosphate ion permeability reducing paracellular phosphate absorption in the presence of NHE3 [35, 36]. The increased sodium in the gut leads to increased fluid secretion. In two phase 1 trials, tenapanor produced dose-dependent increases in stool sodium excretion and decreases in urinary sodium excretion vs placebo. Tenapanor softened stool consistency and increased stool frequency and weight from baseline compared with placebo. During these trials, the drug had minimal systemic absorption; adverse effects were mostly mild and typically gastrointestinal, without any clinically significant changes in serum electrolytes [37].

Tenapanor for IBS-C was investigated in two phase 3 trials, T3MPO-1 and T3MPO-2, and a third trial, T3MPO-3, was a safety extension study looking at the tolerability profile over 1 year. T3MPO-1 and T3MPO-2 were 12-week and 26-week,

double-blind, placebo-controlled, multicenter randomized trials conducted on 610 and 593 patients meeting Rome III criteria for IBS-C, respectively. In addition, T3MPO-1 included a 4-week randomized withdrawal period. Both trials had a 2-week screening period for randomization of patients with active disease based on bowel movement frequency and abdominal pain score. Patients in both studies were randomized to receive tenapanor 50 mg BID vs placebo. The primary endpoint was to assess for combined response (decrease in abdominal pain ≥ 30% from baseline and CSBM increase of at least 1 from baseline) for 6 of 12 weeks. In T3MPO-1, a greater proportion of tenapanor-treated patients achieved the primary endpoint when compared with placebo (27.0% vs 18.7%, $p = 0.02$). A significantly higher proportion of patients on tenapanor had a sustained and durable combined response for 9 of the 12 treatment weeks (13.0% vs 3.3%, $p < 0.001$). The second study, T3MPO-2, showed similar results, and a significantly greater proportion of tenapanor-treated patients showed combined response (36.5% vs 23.7%, $p < 0.001$). Similarly, a durable and sustained response was seen in a higher proportion of patients when compared with placebo for 9 out of 12 weeks and ≥ 3 of the last 4 treatment weeks. Both studies found that the adverse effects were also greater in the treatment group and included diarrhea, flatulence, and abdominal distention. The T3MPO-3 study looking at the long-term safety profile of the drug in 240 patients found that it was well tolerated by patients with a compliance rate of approximately 98%. About 9.2% of the patients reported diarrhea with only 1.7% of the patients discontinuing the treatment because of that adverse effect. The overall discontinuation rate in the study was 2.1%. Currently, tenapanor is in the pipeline for approval and a new drug application was recently filed in September 2018 for use in IBS-C based on its favorable efficacy and safety profile.

Conclusions

Irritable bowel syndrome is among the most frequently encountered GI conditions in primary and specialty care. While IBS is not associated with appreciable mortality, it does contribute to significant morbidity, diminished quality of life, and excess health care resource utilization. Treatment of IBS symptoms is based on predominant stool form and alleviation of primary symptoms, such as abdominal pain and bloating. Typically, initial therapy consists of lifestyle modifications such as diet and exercise and these interventions are effective in a minority of patients seeking care. Escalation to pharmacotherapy often begins with over-the-counter laxatives and anti-spasmodics. If ineffective, prescription therapies should be explored. For IBS-D, there are currently three FDA-approved prescription therapies with divergent mechanisms of action: alosetron, rifaximin, and eluxadoline. All of these therapies have been subjected to rigorous randomized, placebo-controlled trials and have been found to be effective at reducing IBS-D symptoms. Similarly, there are currently three FDA-approved prescription therapies for IBS-C. These three medications, lubiprostone, linaclotide, and plecanatide, work similarly to effect fluid influx into the GI tract, but they have slightly different mechanisms of action in terms of receptor targets and site of action within the GI tract. All of the currently FDA-approved IBS therapies have favorable safety profiles, and several have been shown to decrease cost and health-related quality of life burden associated with IBS.

Emerging therapies for IBS include ramosetron for IBS-D and tenapanor for IBS-C. Other therapies currently approved for chronic diarrhea and chronic constipation (e.g., prucalopride) may also be considered potential IBS therapies, but have not been subjected to large randomized controlled studies in appropriate patients. As our understanding of the varied pathophysiology of IBS and the mechanisms underpinning GI function and sensation evolves, it is likely that we will see additional therapies targeting specific symptom complexes, such as pain and bloating, emerging as potential IBS therapies.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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