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# Medication Management of Irritable Bowel Syndrome

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**Key Words**
Irritable bowel syndrome · Medications · Therapeutics · Functional gastrointestinal disorders · Constipation · Diarrhea

**Abstract**
***Background:*** Irritable bowel syndrome (IBS) is a complex syndrome that is difficult to manage. Here we present the evidence supporting medication treatments for specific IBS symptoms, discuss evidence-based management of IBS with medications including dose regimens and adverse effects and review progress on research for new IBS treatments. ***Summary:*** Currently, there is evidence to support improvements in specific IBS symptoms following treatment with loperamide, psyllium, bran, lubiprostone, linaclotide, amitriptyline, trimipramine, desipramine, citalopram, fluoxetine, paroxetine, dicyclomine, peppermint oil, rifaximin, ketotifen, pregabalin, gabapentin and octreotide and there are many new medications being investigated for the treatment of IBS. ***Key Message:*** Of the medications with demonstrated improvements for IBS symptoms, rifaximin, lubiprostone, linaclotide, fiber supplementation and peppermint oil have the most reliable evidence supporting their use for the treatment of IBS. Onset of efficacy for the various medications has been noted to be as early as 6 days after initiation; however, the efficacy of most medications was not assessed prospectively at predefined periods. Additional studies of currently available and new medications are ongoing and are needed to better define their place in therapy and expand therapeutic options for the treatment of IBS. The most promising new medications for IBS include a variety of novel pharmacologic approaches, most notably the dual μ-opioid receptor agonist and δ-opioid antagonist, JNJ-27018966.



## Background

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder that affects nearly 15% of the US population [1]. It presents as a constellation of symptoms with marked inter-individual variability. IBS is categorized into three main types, which are constipation-predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D) and mixed-IBS (IBS-M). While patients with IBS-C or

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IBS-D experience constipation or diarrhea, respectively, most days, persons with IBS-M may experience both constipation and diarrhea. Regardless of IBS type, each is often associated with additional symptoms, which may include flatulence, feeling of incomplete evacuation, or abdominal pain. As a consequence of the burden of IBS, patients with IBS may have a decreased quality of life and productivity [1].

Treatment of IBS can improve quality of life and prevent lost productivity. Since there is no cure for IBS, treatment is targeted to alleviate the specific symptom(s). Treatment options for IBS include dietary and lifestyle modifications, as well as psychological and medication therapies. While there are many treatment options for IBS, there is no clear first-line treatment for all persons with IBS, because of the variable presentation of IBS and the limited evidence supporting efficacy of many of the treatment options. The challenge of choosing one treatment modality over another is often the first of many when managing IBS. If medications are the treatment modality chosen, the choice of medication is the next challenge, followed by optimally using the medication in patients.

When choosing a medication for a given patient with IBS, the medication chosen should have demonstrated efficacy for that patient's specific symptom(s), including IBS type (IBS-C, IBS-D, IBS-M). Deciding on a given medication requires an understanding of the evidence to date, which as mentioned earlier, is limited. Beyond the challenge of choosing the best medication for a given patient's symptom(s), clinicians are faced with the final challenge of managing the medication to optimize treatment response and safety in patients. While many of the medications to treat IBS are used for indications other than IBS, the dosing regimens and onset of efficacy for the medications are often different when treating IBS compared to other conditions. Optimizing medication therapies should improve the probability patients will benefit from treatment.

The purpose of this review is to present the evidence supporting medication treatments for specific IBS symptoms and discuss evidence-based management of medications for the treatment of IBS, including dose regimens, efficacy, and adverse effects in patients. While many of the medications reviewed here are extensively used in patient care, a detailed review of optimal medication therapy including mechanism of action, dosage requirement, efficacy and adverse effects has not been published. Further, this review summarizes potential emerging therapies for the treatment of IBS.

## Methods

To review the evidence supporting the use of currently available medications for the treatment of IBS, a Medline search was conducting from 1973 until September 2013 using the following search terms: 'irritable bowel syndrome', 'therapeutics', 'antidiarrheal', 'laxatives', 'loperamide', 'dietary fiber', 'psyllium', 'calcium polycarbophil', 'methylcellulose', 'bulking agents', 'lubiprostone', 'linaclotide', 'tricyclic antidepressive agents' and its representative agents, 'serotonin reuptake inhibitors' and its representative agents, 'dicyclomine', 'hyoscyamine', 'hyoscine', 'peppermint oil', 'parasympatholytics', 'rifaximin', 'pregabalin', 'gabapentin', 'clonidine', 'octreotide', and 'ketotifen'.

All placebo-controlled trials assessing the efficacy of a medication for the treatment of the specific IBS symptoms of abdominal pain, bloating, stool form or consistency, frequency of bowel movements, presence of mucus upon defecation, bowel urgency, feelings of incomplete evacuation, flatulence, or borborygmi were included. In addition, studies assessing global improvement of IBS were included. IBS symptoms assessed as combined endpoints were not included. Studies were excluded if they were not available in the English language. Further exclusions included drugs not available in the USA, drugs available only through restricted access programs, and probiotics. Probiotics were excluded because of the wide variety of bacteria present in these products and the inconsistencies among various products.

All studies were critically evaluated for the strength of evidence supporting the efficacy of each medication for explicit IBS symptoms, similar to the criteria used by the American College of Gastroenterology and as described in table 1 [2, 3]. Further, the studies were critically evaluated to determine the optimal management of each medication for the treatment of IBS, including careful assessment for safe and efficacious dosing regimens, onset of efficacy, duration of effect, and adverse effects. When applicable, additional resources, including FDA product labeling, were referenced to identify additional medication management issues that were not addressed in the trial(s).

To identify emerging therapies for and progress on the treatment of IBS, clinicaltrials.gov was queried, using the search terms 'irritable bowel syndrome' and 'IBS'. All trials registered that were ongoing or completed that included a medication as an intervention for IBS treatment were reviewed. Trials registered with medications that were no longer being investigated for the treatment of IBS were not reviewed, nor were trials of dietary supplements.

## Results and Discussions

### *Medications Currently Available for the Treatment of Irritable Bowel Syndrome*

The literature search resulted in 43 studies meeting the inclusion criteria that assessed the efficacy of medications for the treatment of IBS. Table 2 describes the studies that met inclusion criteria and their respective outcomes, whereas table 3 describes the overall efficacy of each medication by IBS type and symptom. With few exceptions,

**Table 1.** Criteria used to evaluate the quality and strength of evidence in studies of medications for IBS. Adapted from the American College of Gastroenterology [3]

| Level of evidence | Benefit vs. risk | Methodological quality of evidence |
|---|---|---|
| 1A High-quality | Benefits clearly outweigh risk | RCT without important limitations |
| 1B Moderate-quality | Benefits clearly outweigh risk | RCT with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) |

many of the studies were limited by short treatment duration and follow-up, imprecise or variable methods of identifying IBS and subtype, and small sample sizes. Medications with the most robust evidence supporting their use for the treatment of IBS were lubiprostone, linaclotide, rifaximin, fiber supplementation and peppermint oil. Table 4 describes the proposed mechanism of action of the medications for treating IBS.

Medication management issues that were often not addressed in the clinical trials included onset of efficacy and adverse effects. Many of the clinical trials inconsistently reported medication-related adverse effects and IBS symptom relief was only assessed at specific time points, making it hard to assess medication safety and determine the true onset of efficacy for medications. As a result, and as indicated below, other drug information references, most commonly FDA product labeling, were used to make recommendations on the desired medication-specific management of IBS.

*Lubiprostone*

Lubiprostone is a novel agent, FDA-approved for the treatment of IBS-C. The FDA-approved dose of lubiprostone for IBS-C is 8 μg twice daily [4]. However, lubiprostone doses of 8, 16, 24 and 48 μg twice daily have been found to be effective and safe for most symptoms of IBS, with only 24 μg twice daily consistently demonstrating efficacy for all symptoms studied [5]. If symptom improvement is not satisfactory with 8 μg twice daily, a trial of higher doses may be reasonable. Onset of efficacy was apparent beginning at 1 month of treatment, but some symptoms were not improved until month 2 of treatment [5]. These data suggest patients should continue lubiprostone therapy for at least 1 month before discontinuing due to lack of efficacy. Adverse effects associated with lubiprostone included nausea, vomiting, diarrhea, flatulence, abdominal pain and distension, which were dose-related [5]. Administration with food and water or decreasing the dose may improve tolerability of lubiprostone.

Given the clear evidence supporting the use, lubiprostone appears as a viable and preferred option for the treatment of IBS-C. Limiting lubiprostone's use are its high cost and lack of long-term studies.

*Linaclotide*

Another novel treatment and the newest FDA-approved drug for IBS-C is linaclotide. The FDA-approved dose of linaclotide is 290 μg once daily. While 75 and 150 μg once daily were proven efficacious for some IBS symptoms and 600 μg once daily was found effective in a dose-finding study, 300 μg once daily was efficacious for all symptoms studied and was better tolerated than 600 μg daily [6]. Linaclotide at 290 μg once daily consistently improved IBS symptoms and was well tolerated [7–9]. Linaclotide is recommended to be taken on an empty stomach 30 min before breakfast to improve efficacy. Onset of symptom relief has occurred as early as week 1 [6, 7], which is a significant advantage when compared to most other IBS treatments. Diarrhea [6–9], flatulence [6, 8, 9] and abdominal pain [6, 8, 9] were the most common adverse effects associated with linaclotide. Diarrhea appeared to be dose-related [6] and most commonly occurred within the first 4 weeks of treatment [9].

Given the robust evidence supporting the use of linaclotide, linaclotide is a viable option for the treatment of IBS-C. Limitations of linaclotide's use are its high cost and lack of long-term studies.

*Rifaximin*

Rifaximin has been approved by the FDA for travelers' diarrhea and hepatic encephalopathy, but not for IBS. It has been approved, however, for IBS in many other countries. Some high-quality studies demonstrated its efficacy for IBS. The doses of rifaximin studied included 400 mg three times daily, 550 mg twice daily, and 550 mg three times daily. Advantages of rifaximin were that the starting doses did not require titration and the treatment duration was limited to 10–14 days. After the short treatment period, the efficacy of rifaximin was observed to persist up

**Table 2.** Placebo-controlled trials assessing the efficacy of medications for the treatment of IBS symptoms

| Medication | Patients and IBS subtype | Dose and treatment duration | Study design | Level of evidence | Clinical efficacy results by symptom(s) |
|---|---|---|---|---|---|
| Lubiprostone [5] | n = 193<br>IBS-C | 1) 8 μg BID,<br>2) 16 μg BID, or<br>3) 24 μg BID for 12 weeks | RCT double-blind; 2 weeks' follow-up | 1A | Global improvement: significant improvement with 24 μg BID<br>Abdominal pain: significant improvement<br>Bloating: significant improvement<br>Consistency: significant improvement with 24 μg BID<br>Frequency: significant improvement |
| Lubiprostone [48] | n = 62<br>IBS-C | 48 μg QDay for 2 weeks | RCT double-blind crossover; 2 weeks' washout | 1A | Abdominal pain, frequency: no significant improvement<br>Consistency: significant improvement |
| Linaclotide [7] | n = 1,604<br>IBS-C | 290 μg QDay for 12 weeks | RCT double-blind | 1A | Global improvement, abdominal pain, bloating: significant improvement |
| Linaclotide [8] | n = 800<br>IBS-C | 290 μg QDay for 12 weeks | RCT double-blind; 4 weeks' follow-up in which the linaclotide group was randomized to linaclotide or placebo | 1A | Abdominal pain, frequency, consistency, flatulence: significant improvement |
| Linaclotide [9] | n = 804<br>IBS-C | 290 μg QDay for 12 weeks | RCT double-blind | 1A | Global improvement, abdominal pain, frequency: significant improvement |
| Linaclotide [6] | n = 420<br>IBS-C | 1) 75 μg QDay,<br>2) 150 μg QDay,<br>3) 300 μg QDay, or<br>600 μg QDay for 12 weeks | RCT double-blind; 2 weeks' follow-up | 1A | Global improvement: significant improvement with 150, 300, and 600 μg QDay<br>Abdominal pain, consistency, frequency: significant improvement<br>Bloating: significant improvement with 75, 300 and 600 μg QDay |
| Rifaximin [49] | n = 87<br>IBS-All | 400 mg TID × 10 days for 10 days | RCT double-blind placebo; 10 weeks' follow-up | 1A | Bloating: significant improvement |
| Rifaximin [10] | n = 388<br>IBS-D | 550 mg BID × 14 days for 14 days | RCT double-blind; 12 weeks' follow-up | 1A | Bloating: significant improvement |
| Rifaximin [50] | n = 125<br>IBS-D and mixed | 550 mg TID for 2 weeks | RCT double-blind; 10 weeks' follow-up | 1A | Global improvement, abdominal pain, bloating, consistency: significant improvement |
| Psyllium [15] | n = 80<br>IBS-All | 3.6 g sachet TID for 12 weeks | RCT double-blind | 1B | Global improvement: significant improvement<br>Frequency: significant improvement |
| Psyllium [13] | n = 20<br>IBS-All | 30 g QDay for 4 weeks | RCT double-blind crossover; 7–10 days' washout | 1B | Global improvement: significant improvement<br>Frequency: no significant improvement |
| Psyllium [16] | n = 80<br>IBS-All | 3 g sachet BID for 4 weeks | RCT double-blind | 1B | Global improvement: no significant improvement |
| Psyllium [17] | n = 12<br>IBS-All | 3.5 g BID for 16 weeks | RCT double-blind | 1B | Global improvement: significant improvement |
| Psyllium [18] | n = 77<br>IBS-All | 6.4 g TID for 8 weeks | RCT double-blind | 1B | Global improvement, abdominal pain, consistency: no significant improvement |
| Psyllium or Bran [14] | n = 275<br>IBS-All | 1) 5 g psyllium, BID, or<br>2) 5 g bran BID for 12 weeks | RCT double-blind | 1A | Global improvement: psyllium – significant; bran – no improvement<br>Abdominal pain: psyllium – significant improvement; bran – significant improvement |
| Peppermint oil [21] | n = 50<br>IBS-All | 550 mg QDay for 4 weeks | RCT double-blind; 4 weeks' follow-up | 1A | Global improvement, abdominal pain, bloating, urgency, incomplete evacuation: significant improvement |
| Peppermint oil [19] | n = 110<br>IBS-All | 187 mg TID or QID for 4 weeks | RCT double-blind | 1B | Abdominal pain, frequency, flatulence, borborygmi: significant improvement |
| Peppermint oil [20] | n = 74<br>IBS-All | 187 mg (2 ml) TID 30 min before meals for 6 weeks | RCT double-blind | 1B | Abdominal pain: significant improvement<br>Bloating, consistency, frequency, urgency, incomplete evacuation, flatulence: no significant improvement |
| Peppermint oil [51] | n = 90<br>IBS-All | 187 mg (2 ml) TID 30 min before meals for 8 weeks | RCT double-blind | 1A | Abdominal pain: significant improvement<br>Consistency, frequency, flatulence: no significant improvement |
| Hyoscine [17] | n = 12<br>IBS-All | 10 mg QID for 16 weeks | RCT double-blind | 1B | Global improvement: no significant improvement |

**Table 2** (continued)

| Medication | Patients and IBS subtype | Dose and treatment duration | Study design | Level of evidence | Clinical efficacy results by symptom(s) |
|---|---|---|---|---|---|
| Dicyclomine [22] | n = 97 IBS-C | 40 mg QID for 2 weeks | RCT double-blind | 1B | Global improvement, abdominal pain: significant improvement |
| Loperamide [52] | n = 60 IBS-All | 4 mg QHS for 3 weeks | RCT double-blind | 1B | Global improvement, abdominal pain, consistency, frequency: significant improvement |
| Loperamide [23] | n = 28 IBS-All | 2 mg BID, then titrate to max. 12 mg as tolerated for 5 weeks (mean dose 4.8 mg/day) | RCT double-blind crossover | 1B | Consistency, frequency, urgency, borborygmi: significant improvement |
| Loperamide [24] | n = 90 IBS-All | 2 mg QHS, then titrate to max. 6 mg for 5 weeks as needed and tolerated (mean dose 3 mg/day) | RCT double-blind | 1A | Consistency, frequency: significant improvement |
| Loperamide [25] | n = 25 IBS-D | 2 mg QHS, titrated Qweek to max. 8 mg QHS for 13 weeks as needed and tolerated (mean dose 4 mg/day) | RCT double-blind | 1B | Global improvement, abdominal pain, consistency, urgency: significant improvement<br>Frequency, flatulence, borborygmi: no significant improvement |
| Amitriptyline [31] | n = 40 IBS-All | 25 mg QHS × 1 week titrated to 50 mg QHS × 1 week, then 75 mg QHS for 10 weeks | RCT double-blind | 1B | Global improvement, abdominal pain: significant improvement<br>Frequency, flatulence: no significant improvement |
| Amitriptyline [32] | n = 33 IBS-All adolescents without psychiatric disorders | 1) if 30–50 kg: 10 mg QHS,<br>2) if 50–80 kg: 20 mg QHS, or<br>3) if >80 kg: 30 mg QHS for 8 weeks | RCT double-blind; 3 weeks' follow-up | 1B | Global improvement, abdominal pain: significant improvement |
| Amitriptyline [30] | n = 54 IBS-D | 10 mg QHS for 8 weeks | RCT double-blind | 1A | Global improvement, consistency, incomplete evacuation: significant improvement<br>Abdominal pain, mucus, flatulence: no significant improvement |
| Trimipramine [33] | n = 61 IBS-All | 50 mg QDay for 4 weeks | RCT double-blind | 1B | Mucus: significant improvement |
| Trimipramine [34] | n = 428 IBS-All | 1) 50 mg QHS,<br>2) 10 mg QAM + 40 mg QPM,<br>3) 35 mg QPM, or<br>4) 10 mg TID for ≥6 weeks | RCT double-blind | 1B | Abdominal pain: significant improvement with 50 mg QHS, and 10 mg QAM + 40 mg QPM<br>Frequency: no significant improvement |
| Imipramine [53] | n = 51 IBS-All without psychiatric disorders | 25 mg QHS × 2 weeks, then 50 mg QHS for 10 weeks | RCT double-blind | 1A | Global improvement, abdominal pain, frequency: no significant improvement |
| Desipramine [35] | n = 28 IBS-All | 50 mg QHS × 1 week,<br>100 mg QHS × 1 week, then 150 mg QHS for 4 weeks | RCT double-blind crossover;<br>2 weeks' washout | 1B | Global improvement: improvement, significance not reported<br>Abdominal pain: significant improvement in IBS-D subgroup<br>Frequency: significant improvement |
| Desipramine [54] | n = 31 IBS-All with depression | 150 mg QHS for 6 weeks | RCT double-blind | 1B | Abdominal pain: no significant improvement |
| Doxepin [36] | n = 44 IBS-All | 75 mg QHS for 6 weeks | RCT double-blind; 4 weeks' follow-up | 1B | Global improvement, abdominal pain, incomplete evacuation: significant improvement |
| Citalopram [53] | n = 51 IBS-All without psychiatric illness | 20 mg QAM × 2 weeks, then 40 mg QAM for 10 weeks | RCT double-blind | 1A | Global improvement, abdominal pain, frequency: no significant improvement |
| Citalopram [19] | n = 23 IBS-All without depression | 20 mg QDay × 3 weeks, then 40 mg QDay × 3 weeks | RCT crossover;<br>3 weeks' washout | 1B | Global improvement, abdominal pain, bloating, urgency, incomplete evacuation: significant improvement |
| Citalopram [55] | n = 54 IBS-All | 20 mg QDay for 8 weeks | RCT double-blind | 1A | Global improvement: no significant improvement |

**Table 2** (continued)

| Medication | Patients and IBS subtype | Dose and treatment duration | Study design | Level of evidence | Clinical efficacy results by symptom(s) |
|---|---|---|---|---|---|
| Fluoxetine [56] | n = 40 IBS-All without depression | 20 mg QHS for 6 weeks | RCT double-blind | 1B | Global improvement, abdominal pain, bloating, urgency, incomplete evacuation, flatulence: No significant improvement |
| Fluoxetine [28] | n = 44 IBS-C | 20 mg QDay for 12 weeks | RCT double-blind; 4 weeks' follow-up | 1A | Bloating, consistency, frequency: significant improvement |
| Paroxetine CR [29] | n = 72 IBS-All without psychiatric disorders | 12.5 mg titrated to 50 mg QDay as tolerated for 2 weeks (mean dose 30 mg/day) | RCT double-blind | 1A | Global improvement: significant improvement<br>Abdominal pain: no improvement |
| Ketotifen [37] | n = 60 IBS-All | 2 mg BID × 2 weeks, 4 mg BID × 2 weeks, then 6 mg BID × 4 weeks | RCT double-blind; 2 weeks' follow-up | 1B | Global improvement: no significant improvement<br>Abdominal pain, bloating, consistency, frequency, incomplete evacuation, flatulence: significant improvement |
| Pregabalin [39] | n = 26 IBS-All without psychiatric disorders | 50 mg TID × 3 days titrated to 100 mg TID × 4 days, 150 mg TID × 4 days, then 200 mg TID for 13 days | RCT double-blind | 1B | Abdominal pain, urgency: significant improvement |
| Gabapentin [38] | n = 40 IBS-D | 100 mg TID × 3 days titrated to 200 mg TID × 2 days | RCT double-blind | 1B | Abdominal pain, bloating: significant improvement |
| Clonidine [42] | n = 44 IBS-D | 0.1 mg BID for 4 weeks | RCT double-blind; pilot study | 1B | Global improvement: significant improvement<br>Consistency, frequency: no significant improvement |
| Octreotide [40] | n = 46 IBS-D and A | 20 mg IM Q4weeks for 8 weeks | RCT double-blind | 1B | Global improvement, abdominal pain, bloating, frequency, flatulence, incomplete evacuation: no significant improvement<br>Consistency: significant improvement |

to 12 weeks [10]. Given the high cost of rifaximin, the short treatment duration makes treatment more feasible for many patients. Although the onset of efficacy is unclear, it may occur as early as 3 weeks. Adverse effects with rifaximin were no different than placebo in clinical trials, yet patients should be counseled on the potential for peripheral edema, dizziness, fatigue, and nausea [11]; however, the incidence of these adverse effects during short courses of treatment so far appears to be extremely low.

The favorable adverse effect profile of rifaximin in IBS trials in combination with the robust evidence supporting its efficacy suggest rifaximin may become a preferred option for the treatment of IBS. However, the manufacturer's supplemental new drug application for treating nonconstipation IBS has been rejected by the FDA. Additional data were needed by the FDA [12]. Limiting rifaximin are also its high cost and lack of long-term studies. The lasting duration of rifaximin's effect on IBS after treatment cessation is not yet well defined.

*Fiber Supplements*

Although fiber supplements are not regulated by the FDA, it has been found to be efficacious for a number of IBS symptoms. Both psyllium and bran have been studied and found effective for treating some symptoms associated with IBS. Efficacious doses of psyllium ranged from 3 g twice daily to 6.4 g three times daily to 30 g once daily. Onset of efficacy with psyllium has occurred within 4 weeks of use [13, 14]. At 10 g twice daily, bran was found to improve IBS symptoms, but the onset of efficacy was delayed until month 3 of treatment [14]. In clinical trials, psyllium and bran were well tolerated when initiated at the aforementioned maintenance doses, suggesting titration may not be necessary [13–18]; however, clinical experience with poor patient tolerance when no titration was performed suggests titration is important with fiber supplementation. Similarly, although adverse effects were found to be similar to placebo in clinical trials, patients were still at risk for adverse effects observed in persons without IBS, including abdominal pain, constipation, nausea, flatulence, and diarrhea.

There are several advantages to fiber supplementation for treating IBS, including its low cost, long-term experience with use, ease of access, and generally mild adverse effect profile. Further, the level of evidence supporting fiber supplementation has been greater than many other

**Table 3.** Efficacy of medications for the treatment of specific IBS symptoms: clinical outcomes of placebo-controlled trials

| Medication | Global improvement | Abdominal pain | Bloating | Consistency | Frequency | Mucus | Urgency | Incomplete evacuation | Flatulence | Borborygmi |
|---|---|---|---|---|---|---|---|---|---|---|
| Lubiprostone | C: + | C: +– | C: + | C: + + | C: + – | | | | | |
| Linaclotide | C: + + + | C: + + + + | C: + + | C: + + | C: + + + | | | | C: + | |
| Rifaximin | D: + | D: + | A: +<br>D: +<br>D and M: + | D: + | | | | | | |
| Psyllium | A: + + + – – | A: – | | A: – | A: + – | | | | | |
| Bran | A: – | A: + | | | | | | | | |
| Dicyclomine | C: – | | | | | | | | | |
| Hyoscine | A: – | | | | | | | | | |
| Peppermint oil | A: + | A: + + + + | A: + – | A: – – | A: + – – | | A: + – | A: + – | A: + – – | A: + |
| Loperamide | A: + + | A: + + | | A: + + + + | A: + + + – | | A: + + | | A: – | A: + – |
| Amitriptyline | A: + +<br>D: + | A: + +<br>D: – | | D: + | A: – | D: – | | D: + | A: –<br>D: – | |
| Trimipramine | A: + | A: + – | | A: + | A: – | A: – + | | A: + | A: – | |
| Imipramine | A: – | A: – | | | A: – | | | | | |
| Desipramine | A: + | A: –<br>D: + | | | A: + | | | | | |
| Doxepin | A: + | A: + | | | | | | A: + | | |
| Citalopram | A: + – – | A: + – | A: + | | A: – | | A: + | A: + | | |
| Fluoxetine | A: – | A: – | A: –<br>C: + | C: + | C: + | | A: – | A: – | A: – | |
| Paroxetine | A: + | A: – | | | | | | | | |
| Ketotifen | A: – | A: + | A: + | A: + | A: + | | | A: + | A: + | |
| Pregabalin | A: + | | | | | | A: + | | | |
| Gabapentin | | D: + | D: + | | | | | | | |
| Clonidine | D: + | | | | | | | | | |
| Octreotide | A and D: – | A and D: – | A and D: – | A and D: + | A and D: – | | | A and D: – | A and D: – | |

A = Subject with all types of IBS were included; C = subjects included were IBS-C; D = subjects included were IBS-D; M = subjects included were IBS-M. Each + indicates one study with positive results; each – indicates one study with negative results.

medications and fiber appears to be beneficial for all types of IBS.

*Antispasmodics: Peppermint Oil, Dicyclomine, Hyoscyamine*

Antispasmodics used for the treatment of IBS include peppermint oil, dicyclomine, and hyoscyamine. Hyoscyamine should not be confused with hyoscine, commercially available in the USA as scopolamine; scopolamine is not commonly used for IBS and there is no oral form of scopolamine available in the USA, while hyoscyamine is used commonly for the treatment of IBS despite a lack of a placebo-controlled study assessing its efficacy. The antispasmodics are commonly used for the treatment of IBS, largely because of their generally favorable outcomes in clinical studies.

When recommending peppermint oil for IBS, important considerations are product availability and batch-to-batch consistency, as these products are available over-the-counter and are not FDA-regulated. Despite the lack of regulation, peppermint oil has been well studied and found to be generally effective and well tolerated by patients for the treatment of IBS. Peppermint oil can be initiated at 550 mg once daily or 187 mg three times daily. Although peppermint oil may not require dose adjustment, the dosing frequency of three times daily can make adherence challenging for some patients. Furthermore, in clinical trials, the three times daily doses were administered 30 min prior to meals, which may complicate the dosing further for patients. Once initiated, the onset of efficacy may occur as early as week 2 [19], but may be delayed until week 6 [20]. Adverse effects with peppermint oil in the trials were similar to placebo, with 2 cases of heartburn, one of which resulted from a patient chewing the medication [20, 21]. In addition to heartburn, adverse effects associated with peppermint oil in the general population included nausea and vomiting. Enteric-coated peppermint oil products may lessen or prevent heart-

**Table 4.** Mechanism of action of medications for the treatment of IBS [27, 34, 37, 39, 40, 42, 49, 57 – 61]

| Medication | Mechanism of action |
|---|---|
| Lubiprostone | Chloride channel-2 activator that increases chloride and intestinal fluid secretion, which increases motility and decreases transit time [53]; mucosal membrane stabilization may also reduce inflammation and sensitization |
| Linaclotide | Guanylate cyclase-C agonist that increases intra- and extracellular cyclic guanosine monophosphate (cGMP) concentrations, resulting in increased chloride, bicarbonate, and fluid secretion in the intestinal lumen; the increased intestinal fluid decreases transit time and the increased extracellular cGMP decreases visceral pain |
| Rifaximin | Non-absorbable, broad-spectrum and gut-selective antibiotic that stabilizes gut flora and prevents overgrowth |
| Psyllium, bran | Fiber absorbs water into the intestine, creating a viscous fluid that increases motility and decreases transit time |
| Peppermint oil | Menthol impairs calcium transmembrane transit and thereby relaxes intestinal smooth muscle |
| Dicyclomine | Non-specific antimuscarinic and direct antispasmotic that results in relaxation of intestinal smooth muscle |
| Hyoscyamine | Non-specific antimuscarinic that results in relaxation of intestinal smooth muscles; decreases gastric acid secretions |
| Loperamide | Opioid receptor agonist that decreases gut motility, fluid secretion, and increases anal sphincter tone, resulting in increased transit time and decreased fecal volume |
| Citalopram, paroxetine, fluoxetine | Selective serotonin reuptake inhibitors that increase central serotonin synaptic concentrations, which decreases motility in patients with IBS-D and increases motility in IBS-C; serotonin reuptake inhibition decreases visceral pain |
| Amitriptyline, desipramine, trimipramine, imipramine, doxepin | Serotonin reuptake inhibitors that increase central serotonin and norepinephrine synaptic concentrations which results in decreased motility and visceral pain |
| Ketotifen | Selective, non-competitive mast cell stabilizer that results in decreased inflammatory response |
| Gabapentin | GABA-mimetic that interferes with GABAergic transmission which results in decreased visceral pain; mechanism not fully understood |
| Pregabalin | GABA analogue that binds directly to $\alpha_2\delta$ centrally which results in decreased visceral pain; mechanism not fully understood |
| Octreotide | Somatostatin analogue that decreases visceral sensitivity, gastric acid and fluid secretion; mechanism not fully understood |
| Clonidine | Central α-agonist that reduces sympathetic outflow and results in decreased motility |

burn. To ensure patients purchase and take the prescribed product and dose, written instructions should be provided by the clinician to the pharmacist, as well as for patients. Detailed instructions for peppermint oil may assist the patient in finding the correct product from among the abundance of over-the-counter products with complicated labels at the pharmacy or health food store.

In contrast to peppermint oil, the antispasmodics of hyoscyamine and dicyclomine are regulated by the FDA and available by prescription, but there is less evidence to support their use when compared to peppermint oil. One clinical trial studied dicyclomine and found favorable outcomes with doses of 40 mg four times daily after 2 weeks of treatment [22]. Although there is no evidence outside of clinical experience to support the use of hyoscyamine, it is commonly used in clinical practice. Frequently used doses of hyoscyamine for the treatment of IBS have ranged from 0.125 to 0.25 mg four times daily and were often used on an as-needed basis. Adverse effects of dicyclomine and hyoscyamine were anticholinergic in nature. Anticholinergic effects reported more frequently with dicyclomine than placebo in the clinical trial included dry mouth, dizziness and blurred vision, which appeared to be dose-related [22]. Other anticholinergic effects to be monitored include constipation, confusion, and falls.

Of the antispasmodics, peppermint oil has the most evidence supporting its use for the treatment of IBS, with limited evidence supporting dicyclomine and no evidence supporting the use of hyoscyamine outside of clinical experience. Although the lack of FDA regulation is limiting, peppermint oil may be a preferred agent for IBS, given the evidence supporting its use and its favorable adverse effect profile. If an alternate antispasmodic is preferred, dicyclomine may be chosen over hyoscyamine given the favorable evidence supporting dicyclomine and its lower cost.

*Loperamide*

Although most commonly used in practice for symptoms of diarrhea, loperamide has been found to be efficacious for multiple symptoms of IBS in persons with all types of IBS. Starting doses of loperamide for IBS have varied from 2 mg at bedtime, 2 mg twice daily and 4 mg at bedtime, with each dosing regimen being well tolerated. Based on the doses found to be efficacious in clinical trials, doses of 3–5 mg daily may be needed to produce symptom relief [23–25], but doses up to 12 mg daily have been safely tolerated [23]. Although the efficacy of loperamide given on an as-needed basis for the treatment of IBS has not been assessed, this is a common practice for managing IBS symptoms of diarrhea with loperamide. Onset of efficacy was apparent in clinical trials beginning at week 3 for some symptoms, but the full benefit of loperamide may not be apparent until week 5 of treatment [24]. Therefore, before treatment failure with loperamide is declared, loperamide should be continued for at least 5 weeks at the doses found to be most commonly effective in clinical trials, 3–5 mg daily. Studies assessing loperamide for the treatment of IBS found adverse effects to be similar when compared to placebo; however, common adverse effects of loperamide observed in the general population included nausea, cramping, and constipation [26].

Advantages of loperamide include its low cost, ease of access for patients as an over-the-counter medication, and long history of use. Additional studies with larger sample sizes, using as-needed dosing regimens, and in specific types of IBS patients are needed to better determine the specific role of loperamide for IBS.

*Selective Serotonin Reuptake Inhibitors: Citalopram, Fluoxetine, Paroxetine*

The efficacy data for the selective serotonin reuptake inhibitors (SSRIs), specifically citalopram, fluoxetine and paroxetine, have been conflicting, but generally favorable.

Citalopram has been found to be efficacious for treating IBS when started at 20 mg daily, titrated up to the maintenance dose of 40 mg once daily after 3 weeks [27]. Onset of efficacy was observed beginning at week 3 for some symptoms, but the full effect was not apparent until week 6 of treatment [27]. Fluoxetine improved IBS symptoms at doses of 20 mg once daily and required no titration [28]. Full efficacy was evident as early as week 4 and efficacy persisted even 4 weeks after treatment ended [28]. Similar to fluoxetine, paroxetine also demonstrated positive outcomes. Starting doses for paroxetine were 12.5 mg once daily, titrated as tolerated to a maximum dose of 50 mg daily [29]. The average dose reached in the trial was 30 mg daily [29], suggesting the most efficacious and tolerable dose was 30 mg daily. Onset of efficacy has not been assessed prior to week 12 [29]. If an SSRI is chosen, treatment should not be discontinued due to lack of efficacy until 4 or 6 weeks for fluoxetine and citalopram, respectively, and perhaps 12 weeks of treatment with paroxetine.

The use of an SSRI for IBS may be especially advantageous for a patient with comorbid depression or anxiety, given SSRIs are highly effective for treating depression and anxiety. Although the adverse effects associated with any of the SSRIs studied for IBS were found to be no different than placebo in the clinical trials, each agent carries the risk of sexual dysfunction, sleep disturbance, serotonin syndrome and weight gain, as seen in the general population. Given the somewhat conflicting evidence supporting the use of the SSRIs, they are generally initiated after other treatment options have failed.

*Tricyclic Antidepressants: Amitriptyline, Desipramine, Trimipramine, Imipramine, Doxepin*

The tricyclic antidepressants, including amitriptyline, desipramine, trimipramine, imipramine, and doxepin have been studied extensively in the setting of IBS. Imipramine was found to have no benefit, thus management of this agent is not discussed here.

In adults, amitriptyline has demonstrated efficacy at maintenance doses of both 10 mg once [30] and 75 mg at bedtime [31]. Maintenance doses of 75 mg were reached by initiating amitriptyline at 25 mg and titrating up by 25 mg weekly [31]. Some symptom improvement may be apparent within 4 weeks, but it may take 8 weeks to achieve the maximum benefit of amitriptyline in adults [31]. For adolescents aged 12–18 years, the doses studied and found to be effective were weight-based: 30–50 kg received 10 mg at bedtime, 50–80 kg received 20 mg at bedtime, and at least 80 kg received 30 mg at bedtime [32]. The onset of efficacy for adolescents was not assessed until week 6 [32]; thus it is unclear if the effect occurs earlier than week 6.

Trimipramine was found to be effective at total daily doses of 50 mg, given either once at bedtime [33], or as 10 mg in the morning and 40 mg at bedtime [34]. Efficacy was not assessed until week 4 of treatment [33], thus it is unknown if the onset of efficacy occurs before week 4. The only adverse effect reported more frequently than placebo was increased tiredness at night during the first 2 weeks of treatment [34].

Desipramine, initiated at 50 mg at bedtime and titrated up by 50 mg weekly to a maintenance dose of 150 mg at bedtime, was found to be efficacious for IBS [35], another study found an initial dose of 150 mg at bedtime to be well tolerated by patients. Statistical significance of adverse effects were not reported, but more patients taking desipramine experienced adverse effects of anxiety, palpitations, sweating and constipation than those taking placebo, which were mostly dose-related [22].

The efficacy of doxepin was also demonstrated in a small study. The doses found to be effective were 75 mg at bedtime and efficacy was determined after 6 weeks of treatment [36].

Advantages of the tricyclics may include their low cost, once-daily dosing, some evidence of efficacy, and many years of experience with their use. Further, patients with concurrent neuropathies, fibromyalgia, recurrent migraines, or psychiatric illness may benefit from treatment with a tricyclic, given the efficacy of tricyclics for these comorbidities. However, adverse effects may limit their use, although these were mostly not apparent in the IBS clinical trials. With the exception of some adverse effects occurring more frequently with trimipramine and desipramine, the occurrence of adverse effects with the tricyclics were no different when compared to placebo in the IBS trials. However, the tricyclics need to be used cautiously, given the common occurrence of adverse effects observed with their use in the general population, which includes anticholinergic effects and QT interval prolongation. Because of their adverse effect profile, the tricyclics are generally reserved for selective patients who have not responded to other treatments.

*Ketotifen*

Ketotifen is a new option for treating IBS symptoms. Whereas the oral product studied in clinical trials is not available in the USA, the ophthalmic preparation is commercially available and the oral product may be compounded for a specific patient. Ketotifen's efficacy was observed at maintenance doses of 6 mg twice daily after 8 weeks [37]. It should be initiated at 2 mg twice daily and titrated up by 2 mg twice daily at 2-week intervals [37]. The onset of efficacy was not assessed prior to week 8 of treatment [37]; therefore, efficacy should not be ruled out before week 8 of treatment. The only adverse effect reported to occur more frequently in patients treated with ketotifen than placebo was 2–5 kg of weight gain [37]. Other adverse effects in the general population have included rash, weight gain, and respiratory infections.

Further studies are needed to define the role of ketotifen for the treatment of IBS, but it may be an option for patients who do not respond to other well-studied medications, especially given its low adverse effect potential.

*Anticonvulsants*

Small studies have shown that both pregabalin and gabapentin improve IBS symptoms in persons with all types of IBS and IBS-C, respectively. After a total of 6 days of treatment, gabapentin was found to be efficacious at 200 mg three times daily after an initial dose of 100 mg three times daily for 3 days [38]. No other IBS treatment has demonstrated onset of efficacy before week 1 of treatment.

The effective maintenance dose of pregabalin was 200 mg three times daily [39]. Pregabalin was initiated at 50 mg three times daily for 3 days then titrated up thereafter by 50 mg three times daily every 4 days [39]. Because efficacy was not assessed until week 3 [39], it is unclear whether onset occurs before week 3 of treatment. Therefore, pregabalin should be used for at least 3 weeks.

Adverse effects associated with gabapentin and pregabalin that occurred more frequently than with placebo were dizziness and somnolence [38, 39], which have also been common among the general population taking gabapentin and pregabalin. Given the limited evidence supporting gabapentin and pregabalin for IBS, these agents should be reserved until patients have failed better studied treatments, or perhaps reserved for patients with concomitant neuropathies who may benefit from gabapentin or pregabalin beyond their effects on IBS.

*Octreotide*

In contrast to the other IBS treatments, octreotide has required infrequent dosing of every 4 weeks, which is an advantage for some patients. Also unique to octreotide is the intramuscular administration, which may be a deterrent for other patients. One study assessed the impact of octreotide 20 mg intramuscularly every 4 weeks on IBS-M and IBS-C and found some improvement after 8 weeks; however, efficacy was not reported prior to week 8 [40]. Thus, octreotide should be utilized for at least 8 weeks prior to discontinuation. Adverse effects were not reported [40], but patients should be counseled on the risks of use found in the general population. These have included bradycardia, chest pain, fatigue, headache, dizziness, hyperglycemia, abdominal pain, nausea, respiratory infection, and myalgia [41]. Until additional studies of longer duration and larger sample sizes are available, octreotide should be reserved as a last-line option for IBS for patients with severe, refractory symptoms.

*Clonidine*

The antihypertensive clonidine has been found to be effective for some IBS symptoms at 0.1 mg twice daily [42]. The onset of efficacy was not reported, but was apparent after 4 weeks of treatment [42]. Adverse effects reported more frequently with clonidine compared to placebo were drowsiness, dizziness, and dry mouth [42]. Change in blood pressure measurements were not reported [42], but all patients taking clonidine should be monitored closely for orthostatic hypotension and drops in blood pressure. Given the effect of clonidine on blood pressure, persons with concomitant high blood pressure, or attention deficit disorder and IBS-D may benefit from clonidine, given its positive effects on these disease states. The low cost of clonidine is an advantage; however, the risk of rebound hypertension with non-adherence may be a concern (table 5).

**Table 5.** Current monthly cost of medications used for the treatment of IBS [62]

| Medication | Monthly cost (USD) |
|---|---|
| Lubiprostone | 329.80 |
| Linaclotide | 255.60 |
| Rifaximin | 570.38–634.31* |
| Psyllium and bran | Available over-the-counter; cost highly variable |
| Peppermint oil | Available over-the-counter; cost highly variable |
| Dicyclomine | 31.66 |
| Hyoscyamine | 46.44–92.88 |
| Loperamide | Available over-the-counter; cost highly variable |
| Citalopram | 76.68–79.65 |
| Paroxetine CR | 332.28 |
| Fluoxetine | 156.08 |
| Amitriptyline | 5.41–26.44 |
| Desipramine | 184.76 |
| Trimipramine | 174.07 |
| Imipramine | 36.55 |
| Doxepin | 37.29 |
| Ketotifen | Not commercially available; cost variable due to compounding |
| Gabapentin | 95.83 |
| Pregabalin | 395.59 |
| Octreotide | 3,207.67 |
| Clonidine | 15.54 |

Monthly cost based on doses used in studies and least expensive dosage form available per Medi-Span [62].

* Based on 10-day treatment with rifaximin 400 mg TID and 14 day treatment with rifaximin 550 mg BID.

*Progress in Research for Investigational Drugs for Irritable Bowel Syndrome*

A number of medications for the treatment of IBS are currently in the research pipeline. Some of these medications are currently available for other indications and others are investigational drugs. Further, there are medications available in certain countries that are effective and used for the treatment of IBS, including ramosetron.

A review of clinicaltrials.gov, using the search terms 'irritable bowel syndrome' and 'IBS', identified 22 investigational drugs for the treatment of IBS with ongoing investigation into their utility as a potential treatment [43]. The investigational drug names, proposed mechanism of action and phase in drug development are listed in table 6. Further, there are 18 drugs that are currently available in the USA that are being studied in clinical trials listed on clinicaltrials.gov for the indication of IBS [63]. Of these medications, 10 have no prior studies assessing their efficacy for the treatment of IBS, which include mesalamine for IBS-D and IBS-A, duloxetine for IBS-A with comorbid depression, crofelemer for IBS-D, milnacipran for IBS-A, escitalopram for IBS-A, dronabinol for IBS-A, colesevelam for IBS-D, nortriptyline for IBS-A, polyethylene glycol for IBS-C, and mexiletine for IBS-A. The remaining 8 currently available drugs being studied in clinical trials to better define their role in therapy for IBS and include pregabalin, rifaximin, citalopram, doxepin, paroxetine CR, alosetron, tegaserod, and desipramine.

The most promising investigational drugs that have completed phase II clinical trials with published positive outcomes and without documented discontinuation of investigational efforts include JNJ-27018966 (MuDelta), ROSE-010, AST-120, ibodutant, and asimadoline [43]. The results of these most promising investigational drugs are described here.

JNJ-27018966 is a dual μ-opioid agonist and δ-opioid receptor antagonist with demonstrated benefit in patients with IBS-D. A randomized, controlled, double-blind study compared JNJ-27018966 25, 100, and 200 mg twice daily to placebo in 807 patients with IBS-D. The composite of diarrhea and pain was significantly improved in the JNJ-27018966 25 and 200 mg twice-daily groups compared to placebo (12, 13.8 and 5.7%, respectively, $p < 0.05$ for both comparisons to placebo) [44].

ROSE-010 is a glucagon-like peptide 1 analogue that was studied in a randomized crossover, placebo-controlled trial of 160 patients with IBS and associated ab-

**Table 6.** Investigational drugs for treating IBS listed on clinicaltrials.gov: mechanism and development status [43, 63]

| Investigational drug | Mechanism of action | Phase in clinical trial development |
|---|---|---|
| JNJ-27018966 (MuDelta) | Dual μ-opioid receptor agonist and δ-opioid receptor antagonist that decreases motility and visceral pain | phase 3 ongoing |
| ROSE-010 | Glucagon-like peptide 1 analogue that decreases gastric emptying and motility | phase 2 completed |
| AST-120 | Spherical carbon adsorbent that selectively adsorbs substances in the intestinal lumen, including serotonin, histamine, Toll-like receptor ligands, bacterial adjuvants and bile acids | phase 2 completed |
| Ibodutant | Neurokinin-2 receptor antagonist that decreases motility and visceral sensitivity | phase 2 completed |
| Asimadoline | Selective κ-opioid receptor agonist that decreases visceral pain | phase 2 completed |
| LX1033 | Tryptophan hydroxylase inhibitor, which results in inhibition of intestinal serotonin synthesis and thereby decreases | phase 2 completed and waiting results to be released |
| Dextofisopam | Non-sedating benzodiazepine that selectively binds to 2,3-benzodiazepine receptors, which results in decreased motility and visceral pain | phase 2 completed, but sponsor ran out of money to continue development |
| GW876008 | Corticotropin-releasing factor inhibitor, which results in decreased motility, visceral pain and intestinal secretions | phase 2 completed |
| GW427353 (solabegron) | Selective β-adrenergic receptor agonist that decreases somatostatin release, which results in decreased visceral pain | phase 2 completed |
| DNK333 | Neurokinin-1, -2, and -3 receptor antagonist that results in decrease motility and visceral pain | phase 2 completed |
| PD-217,014 | GABA mimetic that interferes with GABAergic transmission which results in decreased visceral pain; mechanism not fully understood | phase 2 complete |
| MD-1100 acetate | Guanylate cyclase-C receptor agonist that increases intra- and extracellular cyclic guanosine monophosphate (cGMP) concentrations, resulting in increased chloride, bicarbonate, and fluid secretion in the intestinal lumen; the increased intestinal fluid decreases transit time and the increased extracellular cGMP decreases visceral pain | phase 2 completed |
| Plecanatide | Guanylate cyclase-C receptor agonist that increases intra- and extracellular cyclic guanosine monophosphate (cGMP) concentrations, resulting in increased chloride, bicarbonate, and fluid secretion in the intestinal lumen; the increased intestinal fluid decreases transit time and the increased extracellular cGMP decreases visceral pain | phase 2 recruitment |
| DA-6886 | Serotonin (5-$HT_4$) receptor agonist that results in increased motility and intestinal secretions | phase 1 ongoing |
| PPC-5650 | Acid-sensing ion channel-1a inhibitor that decreases visceral pain | phase 1 ongoing |
| Daikenchuto (TU-100) | Traditional Kampo medicine that modulates cholinergice and serotonergic activity to increase motility; mechanism not fully understood | phase 2 ongoing |
| ASP7147 | Bombesin-2 receptor antagonist that results in decreased motility and intestinal secretions | phase 2 ongoing |
| ONO-2952 | Translocator protein antagonist that inhibits central neurosteroid production, which results in decreased visceral pain | phase 2 ongoing |
| AZD1722 (RDX5791, tenapanor) | Sodium hydrogen exchange member 3 inhibitor that increases intestinal sodium and fluid, which results in increased motility and decreased visceral pain | phase 2 ongoing |
| Neu-P11 (piromelatine) | Melatonin and serotonin (5-$HT_{1A}$ and 5-$HT_{1D}$) agonist resulting in increased motility and intestinal fluid secretions | phase 1 ongoing |
| DDP733 (pumosetrag) | Serotonin (5-$HT_3$) receptor agonist that increases motility | phase 2 ongoing |

dominal pain. Patients were randomized to ROSE-010 100 μg once daily, 300 μg once daily or placebo. Treatment with ROSE-010 resulted in a twofold greater response to abdominal pain compared to placebo ($p < 0.05$ for all comparisons) and significantly greater patient-reported satisfaction with ROSE-010 ($p < 0.05$). The most common treatment-related adverse effect was nausea, which occurred in 19, 37 and 0% of ROSE-010 100 μg, ROSE-010 300 μg and placebo treatments, respectively [45].

AST-120 is a spherical carbon adsorbent originally used to delay renal failure progression and now being studied for its use in the setting of non-constipation-related IBS. A randomized, double-blind, controlled study of 115 non-constipation-related IBS patients demonstrated AST-120 2 g three times daily significantly improved the proportion of patients with at least a 50% reduction in the number of days with abdominal pain compared to placebo (26.8 vs. 10.2%, respectively). Further, AST-120 resulted in significantly improved bloating and numerically improved stool consistency compared to placebo. Adverse effects with AST-120 were similar to placebo [46].

Ibodutant is a neurokinin-2 receptor antagonist that has demonstrated efficacy for the treatment of IBS-D. The results are not published yet, but are available on the clinicaltrials.gov website. In a randomized, double-blind, controlled trial, of 559 IBS-D patients, ibodutant significantly improved abdominal pain, satisfactory relief of overall symptoms, and quality of life compared to placebo. All three doses of ibodutant (1, 3, 10 mg once daily) were superior to placebo, but 10 mg once daily was most effective and females responded better than males [43].

Asimadoline is a κ-opioid receptor agonist that has demonstrated efficacy in improving IBS symptoms of abdominal pain, urgency and stool frequency. A randomized, controlled, double-blind trial compared asimadoline 0.15, 0.5 and 1 mg twice daily to placebo in 596 patients with IBS-D. Asimadoline 0.5 mg twice daily significantly improved by twofold the total number of months with adequate relief of IBS pain, pain scores, urgency and frequency [47].

## Conclusion

The choice of medication therapy for IBS is tailored to the patient's unique symptoms and the evidence supporting the efficacy of a given medication for these symptoms. The abundance of studies assessing medications for IBS are highly variable in quality and the reported efficacy for given IBS symptoms are similarly variable across most studies for a given medication. The quality of available studies and clinical outcomes with medication treatment for IBS can assist the clinician in choosing a medication for a given patient. There are a few medication therapies for IBS with strong evidence demonstrating the safety and efficacy of treatment for IBS, which include lubiprostone, linaclotide, rifaximin, fiber supplementation, and peppermint oil. These agents may be preferred for treating IBS; however, with the exception of peppermint oil, these medications are new and expensive, which may limit their use in practice. Additional well-deigned studies are needed to define optimal dosage regimens of various drugs and to recommend cost-effective treatment strategies for patients with various types of IBS. It is encouraging that there are many ongoing studies of currently available and investigational medications for the treatment of IBS. Of the investigational drugs, JNJ-27018966, a dual μ-opioid agonist and δ-opioid antagonist in phase III clinical trials appear to be most promising as new treatment modalities for IBS.

## Disclosure Statement

The authors have no conflicts of interest to disclose.

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