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LARGE INTESTINE (B CASH, SECTION EDITOR)

New and Investigational Agents for Irritable Bowel Syndrome

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Abstract Irritable bowel syndrome (IBS) affects about 15 % of the US population and results in significant morbidity and health care costs. There remains a significant unmet need for effective treatments particularly for the pain component of IBS and other functional gastrointestinal disorders (FGIDs). Progress made in our understanding of pathophysiological mechanisms such as the role of altered bile acid metabolism, neurohormonal regulation, immune dysfunction, the epithelial barrier and secretory properties of the gut has led to advancements in therapeutic armamentarium for IBS. This review discusses the new drugs for constipation and diarrhea-predominant IBS subtypes that have been tested or have been under investigation over the last 3–4 years. Overall, there is a promising pipeline of investigational drugs for the future treatment of IBS and related FGIDs.

Keywords Functional gastrointestinal disorders · Diarrhea · Constipation · Pain · Treatment · Drugs

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Introduction

Irritable bowel syndrome (IBS) is one of the most prevalent gastrointestinal disorders and results in significant direct and indirect costs and impairment in the quality of life [1]. IBS is a complex and heterogeneous disorder with different peripheral and central pathophysiological mechanisms responsible for symptoms in subsets of patients [2••]. While there are several drugs for IBS in the pipeline, there continues to be a need for effective and approved treatments for one or more of the symptoms for various IBS subtypes [3–5]. An area of significant recent advancement has been the understanding of the role of bile acids in chronic diarrhea and diarrhea-predominant IBS (IBS-D). In about a third of the patients, bile acids induce diarrhea either through decreased ileal reabsorption or increased hepatic synthesis [6, 7] providing proof of the concept that advancements in understanding the pathophysiology may lead to a more targeted and individualized approach for treatment of IBS symptoms. Other recent advancements are the approvals of eluxadoline and rifaximin for the treatment of IBS-D.

This article reviews the new and investigational therapeutic agents for IBS with published data or trials available since 2010. The review is broadly divided by agents for constipation- and diarrhea-predominant subtypes. Drugs for functional or chronic idiopathic constipation will also be discussed.

Constipation-Predominant IBS

The major advancements in drugs for chronic constipation or constipation-predominant IBS (IBS-C) belong to the following categories: guanylate cyclase C agonists, 5-HT_4 receptor agonists, bile acid modulators and chloride channel activators.

These drug categories are broadly discussed below with details on individual trials listed in Table 1.

Guanylate Cyclase C Agonists

Linaclotide

Linaclotide is a minimally absorbed peptide agonist of the guanylate cyclase C receptor, which, on activation, increases luminal chloride and fluid secretion through cyclic GMP generation [8]. This medication was approved by the FDA in 2012 for the treatment of IBS-C and chronic constipation in adults. It has been shown to accelerate colonic transit and also has anti-nociceptive action [9]. In a 12-week, double blind, phase III, placebo-controlled trial, for at least 50 % of the weeks assessed, 34 % patients receiving linaclotide compared with 21 % receiving placebo showed ≥30 % decrease in average daily abdominal pain score and ≥1 increase complete spontaneous bowel movement (CSBM) per week compared to baseline values. The most common adverse effect was diarrhea, experienced by 20 % of linaclotide-treated patients [10]. In a more recent 12-week, double blind, phase III, placebo-controlled trial assessing the effects on severe abdominal symptoms, linaclotide improved all abdominal symptoms assessed, global response and the overall quality of life [11]. In a meta-analysis, the number needed to treat (NNT) with the 290 μg daily dose of linaclotide for an increase in 1 or more CSBM/week and a reduction in the weekly average of daily worst abdominal pain scores was 7 (95 % CI, 5–11) [12•]. The maximum increase in stool frequency occurs within 1 week of starting the treatment, whereas abdominal bloating and pain may take up to 8 to 12 weeks to maximally improve [13].

Plecanatide

Plecanatide is another guanylate cyclase C receptor agonist currently being investigated for constipation predominant symptoms. Plecanatide has been shown to loosen stool consistency in healthy volunteers [14]. In a 12-week, dose-ranging, multicenter trial of 951 patients with chronic idiopathic constipation (CIC), a 3-mg daily dose was found to be most effective in improving the number of spontaneous bowel movements for 9 of the 12 weeks studied [15•]. Further studies with plecanatide for IBS-C and CIC are awaited.

Table 1 Drugs for IBS with constipation

Citation	Drug	Number	Study design	Outcome
Guanylate cyclase C agonists				
Rao S 2014 [11]	Linaclotide	1602	12-week, DB, PC RCT (phase 3)	Improvement in all abdominal symptoms, global measures and quality of life
Miner P 2013 [15•]	Plecanatide	951	12-week, DB, PC RCT (phase 2b)	Increased responders (>3 CSBMs/week; ↑ of >1 CSBM from baseline for 9/12 weeks)
5 HT_4 agonists				
Piessevaux H 2015 [18]	Prucalopride	361	24-week, DB, PC RCT (phase 4)	No improvements in spontaneous bowel movements over 12 or 24 weeks
Shin A 2015 [19]	YKP10811	57	9-day, DB, PC RCT (phase 2)	Acceleration of colonic transit and improvement in bowel function
Lembo A 2010 [21]	Renzapride	1798	12-week, DB, PC RCT (phase 3)	Limited increase in efficacy over placebo
Goldberg M 2010 [33]	Velusetrag	401	4-week, DB, PC RCT (phase 2)	Increased weekly frequency of CSBM
Palme M 2010 [34]	Naronapride	214	4-week, DB, PC RCT (phase 2)	Increased CSBM at week 1
Bile acid modulators				
Rao A 2010 [26•]	Chenodeoxycholic acid	36 (women)	4-day, DB, PC RCT (phase 2)	Acceleration of colonic transit and improvement in bowel function
Chey W 2011 [28]	Elobixibat (A3309)	190	8-week, DB, PC RCT (phase 2)	Increased stool frequency and effects maintained over 8 weeks
Chloride channel activators				
Fukudo S 2015 [29]	Lubiprostone	124	4-week, DB, PC RCT (phase 3)	Increased average weekly CSBMs; improved quality of life
Sodium hydrogen exchange member 3 inhibitors				
Ardelyx [30]	AZD 1722 (RDX 5791)	371	12-week, DB, PC RCT (phase 2)	Completed in 2014; results awaited
Melatonin and serotonin (5-HT1A and 5-HT1D) agonists				
Ludwig M [32]	Neu P11 (piromelatine)	40	4-week, DB, PC RCT (observational)	Completed in 2014; results awaited

CIC chronic idiopathic constipation, *CSBM* complete spontaneous bowel movement, *DB* double blinded, *5 HT* 5 hydroxytryptamine, *IBS* irritable bowel syndrome, *PC* placebo-controlled, *RCT* randomized control trial, *SBM* spontaneous bowel movement

5-HT_4 Receptor Agonists

Prucalopride

Prucalopride is a 5-HT_4 receptor agonist that accelerates colonic transit and improves constipation symptoms [16]. A recent meta-analysis that included 11 randomized controlled trials showed significant improvement in the number of CSBMs in response to treatment with prucalopride. Adverse events were generally minor with headache being the most common (21 % randomized to the active treatment group) [17]. In a recent trial, however, prucalopride did not show statistically significant improvement in primary or secondary outcomes compared with placebo over the 12- or 24-week treatment period [18]. The reason for this failure to relieve constipation in one recent trial is unclear. Prucalopride is approved in Europe for the treatment of chronic constipation.

YKP10811

YKP10811 is a selective agonist of the 5-HT_4 receptor. In a randomized, placebo-controlled, dose-ranging trial of 55 patients with functional constipation, there was a significant acceleration of colonic transit at 24 and 48 h, as well as looser stool consistency (higher score on Bristol stool form scale) over 8 days with YKP10811. The 10 and 20 mg doses were the most effective in accelerating colonic transit. No serious adverse events were observed [19].

Renzapride

Renzapride is a 5-HT_4 receptor agonist, a 5-HT_3 receptor antagonist, and a weak partial antagonist of the 5-HT_{2b} receptor [20]. In a 12-week, randomized, double blind, placebo-controlled trial, small but statistically significant improvement was observed for stool consistency, frequency and scores for abdominal bloating. Of the nearly 1000 patients studied in this trial, three episodes of ischemic colitis were reported during the 12-month follow-up period. A limited increase in efficacy over placebo and the risk of ischemic colitis precludes further study with renzapride in patients with IBS-C [21]. Additionally, in a recent meta-analysis including 2528 patients, renzapride was not superior to placebo in relieving IBS symptoms and caused adverse effects such as diarrhea, headache and abdominal pain [22].

Bile Acid Modulators

Studies have shown that colonic infusion of di-α-hydroxy bile acids induces fluid and electrolyte secretion [23, 24] as well as propulsive contractions in mammalian and human colon [25, 26•]. This provides the rationale for delivering higher concentrations of bile acids to the colon by blocking the enterohepatic circulation of bile acids in order to achieve a secretory or motor effect.

Chenodeoxycholic Acid

In an experimental, proof-of-concept double blind, placebo-controlled study of 36 female patients with IBS-C, ileal-release chenodeoxycholic acid accelerated overall colonic transit at 24 h compared with placebo with a dose-related effect observed (greater with 1000 mg dose than the 500 mg dose). There were significant overall treatment effects of chenodeoxycholic acid on stool consistency, frequency and ease of passage. The most common adverse effect was lower abdominal pain. Other adverse effects include diarrhea and nausea [26•].

Elobixibat (A3309)

Elobixibat is an ileal bile acid transport inhibitor which increases bile acid delivery to the colon. In a double blind, placebo-controlled trial of 36 female patients with functional constipation, elobixibat increased the overall colonic transit at 24 h when given once daily for 14 consecutive days with the 20-mg dose showing the greatest effect. Elobixibat improved stool consistency and ease of passage, but not frequency. The most common adverse effect was abdominal pain [27].

In another 8-week, double blind, placebo-controlled, multicenter trial of 190 patients with chronic constipation, the mean increase in number of weekly spontaneous bowel movements at week 1 was 1.7 for placebo vs. 2.5, 4.0 and 5.4 for 5, 10 and 15 mg of elobixibat, respectively. This increase in stool frequency was maintained over 8 weeks. Additionally, straining during evacuation and abdominal bloating decreased with elobixibat. The most common side effects were abdominal pain and diarrhea [28]. Further clinical trials are currently being conducted with elobixibat.

Chloride Channel Activators

Lubiprostone

Lubiprostone has been approved by FDA for chronic constipation in adults at a dose of 24 μg twice daily and for IBS-C in women at a dose of 8 μg twice daily. These approvals were based on trials conducted prior to 2010. In a recent double blind, randomized, placebo-controlled, phase 3 trial of 124 patients with chronic idiopathic constipation, daily administration of lubiprostone improved the average weekly spontaneous

bowel movements (SBMs) providing further proof of efficacy [29].

In addition to the drugs discussed above, there are more drugs in the pipeline for the treatment of IBS-C (Table 1). AZD 1722 (RDX 5791) is a sodium hydrogen exchange member 3 inhibitor that increases intestinal sodium and fluid secretion, thus resulting in increased motility [30, 31]. Neu P11 (piromelatine) is a melatonin and serotonin (5-HT_{1A} and 5-HT_{1D}) agonist that also results in increased intestinal fluid secretion and motility [32]. Velusetrag [33] and naronapride [34] are both 5-HT_4 receptor agonists that have been studied and shown to increase colonic transit and number of weekly CSBM.

Diarrhea-Predominant IBS

Drugs that have been investigated in recent years for the treatment of IBS-D belong to the following categories: 5-HT_3 antagonists, tryptophan hydroxylase inhibitors, tachykinin NK2 receptor antagonists, opioid receptor modulators, adsorbents, bile acid modulators, muscarinic type 3 antagonists and antispasmodics. These drugs are discussed below, and Table 2 summarizes the results from clinical trials.

5 HT_3 Receptor Antagonists

Ramosetron

Ramosetron is a tetrahydrobenzimidazole derivative with a potent and selective antagonistic action on the 5-HT_3 receptor. In an open labeled, randomized trial, 343 male patients with IBS-D were randomized to either ramosetron 5 μg once daily for 4 weeks or mebeverine 135 mg three times daily. There were no significant differences in the responder rates among the two treatment arms. No episodes of either severe constipation or ischemic colitis were reported in the ramosetron group [35]. In a more recent trial conducted in Japan, 296 male IBS-D patients were randomized to 5 μg oral ramosetron or placebo for 12 weeks. The ramosetron-treated group showed improved stool consistency and other outcome measures [36•]. Significantly more people in the ramosetron group (8.2 %) reported "hard stools" as compared with the placebo group (1.3 %); however, the overall incidence of reported constipation was not significantly higher with ramosetron. No cases of ischemic colitis were reported. No serious adverse events of severe constipation or ischemic colitis have been reported over 28–52 weeks of follow-up evaluation of 957 patients who participated in 12-week ramosetron treatment trials, making ramosetron a promising candidate in this class for management of diarrhea-predominant symptoms [37, 38].

Tryptophan Hydroxylase Inhibitors

LX-1031

LX-1031 is an oral tryptophan hydroxylase inhibitor that decreases peripheral synthesis of serotonin [39]. In a 4-week, randomized, placebo-controlled, dose-ranging trial, reductions in 5-HT were significantly correlated with pain relief and improved stool consistency. However, the improvement in pain observed at week 1 disappeared by weeks 2, 3 and 4 [40].

Tachykinin NK2 Receptor Antagonists

Ibodutant

Tachykinins induce smooth muscle contraction in the human colon in vitro via a direct excitatory action on the smooth muscle and an inhibitory effect on nitrergic neurons [41]. In an 8-week, double blind, placebo-controlled, phase 2 trial, ibodutant was shown to be effective in relieving overall IBS symptoms for 50 % of the IBS-D patients [42•]. A 52-week, phase 3 trial is currently in progress [43••].

Opioid Receptor Modulators

Eluxadoline

Eluxadoline is a μ and κ-receptor agonist and δ-receptor antagonist. The action on the μ receptor decreases abdominal pain and gastrointestinal propulsion. The action on the δ-receptor prevents over-inhibition of gastrointestinal motility by the μ agonist activity of the drug, and provides analgesia without inducing tolerance. In animal models of gastrointestinal dysmotility, eluxadoline normalizes fecal output without completely blocking gastrointestinal transit, unlike the pure μ agonist, loperamide. In a double blind, placebo-controlled trial of 807 patients with IBS-D, the composite endpoint of diarrhea and pain improvement was significantly greater with the 25 and 200 mg twice-daily doses of eluxadoline than placebo. Furthermore, the 100 or 200 mg doses were most efficacious in reaching the FDA endpoints for response for the entire 12-week duration of the study. [44••]. The most common side effects in patients treated with eluxadoline include nausea, vomiting and abdominal pain. Constipation was generally a mild side effect with the 100-mg dose and did not result in any early withdrawals from the trial. The most serious known risk associated with eluxadoline is the risk of spasm in the sphincter of Oddi, which can result in pancreatitis. The FDA recommends that patients with a

Table 2 Drugs for IBS with diarrhea

Citation	Drug	Number	Study design	Outcome
5 HT_3 antagonists				
Fukudo S 2014 [36•]	Ramosetron	296 (males)	12-week, DB, PC RCT (phase 4)	Improved stool consistency
Tryptophan hydroxylase inhibitors				
Brown P 2011 [40]	LX-1031	155	4-week, DB, PC RCT (phase 2)	Improved stool consistency. Symptom relief associated with reduced urinary 5-HIAA levels
Tachykinin NK2 receptor antagonists				
Tack J 2013 [42•]	Ibodutant	559	10-week, DB, PC RCT (phase 2)	Improved symptoms in 50 % IBS-D patients
Opioid receptor modulators				
Dove L 2013 [44••]	Eluxadoline	807	12-week, DB, PC RCT (phase 2)	Improved pain and diarrhea
Adsorbents				
Tack J 2011 [48]	AST 120	115	8-week, DB, PC RCT (phase 2)	Reduction in pain and bloating
Bile acid sequestrant or Farnesoid X receptor agonist				
Walters J 2015 [53•]	Obeticholic acid	28	6-week, open label	Reduces bile acid synthesis and improves stool frequency and form
Bajor A 2015 [54]	Colestipol	27	8-week, open label	Improved abdominal distension, pain severity, stool frequency and interference with daily life
Camilleri M 2015 [51•]	Colesevelam	12	10 days, unblinded	Improved stool consistency
L-type calcium channel blocker				
Clave P 2011 [55]	Otilonium bromide	356	25-week, DB, PC RCT (phase 4)	Improved abdominal pain frequency, abdominal bloating severity
Chmielewska-Wilkon D 2014 [56]	Otilonium bromide	93	4-week, DB, PC RCT (phase 2)	Improved individual and global symptoms
Muscarinic type 3 antagonists				
Fukushima Y 2012 [57]	Solifenacin	20	12-week, open label	Non-inferior to ramosetron
Glutamine				
Basra S 2013 [59]	Glutamine	61	8-week, DB, PC RCT	Improved symptoms and intestinal permeability
Antispasmodics				
Lee K. 2014 [63]	Tiropramide	287	10-week, DB RCT (phase 4)	Non-inferior to octylonium for abdominal pain
Alam M 2013 [66]	Peppermint oil	65	8-week, DB, PC RCT	Transient improvement in abdominal pain
Bombesin-2 receptor antagonist				
Seldar pharma [68]	ASP 7147	64	4-week, DB, PC RCT (phase 2)	Results awaited

5 HT 5 hydroxytryptamine, *5 HIAA* 5 hydroxyindoleacetic acid, *MOP* μ-opioid receptors, *KOP* κ-opioid receptors, *IBS* irritable bowel syndrome, *DB* double blinded, *PC* placebo-controlled, *RCT* randomized control trial

history of obstruction of bile duct, pancreatitis, severe liver impairment or severe constipation, and patients who consume more than three alcoholic drinks per day should not use eluxadoline [45].

Kappa Opioid Receptor Agonist

Asimadoline

In a randomized, dose-ranging, double blind, placebo-controlled trial of asimadoline involving nearly 600 patients with the three IBS phenotypes (IBS-D, IBS-C, IBS-A), the 0.5-mg twice-daily dose significantly improved pain scores, urgency and stool frequency in IBS-D patients. No significant benefits were observed in IBS-C and IBS-A patients [46]. A phase 3 trial has also been completed and the results are awaited [47].

Adsorbents

AST 120

In a randomized, double blind, controlled study of 115 non-constipation IBS patients, AST 120, a carbon adsorbent, caused significant improvement in abdominal pain in 27 % patients as compared to 10 % with placebo. Furthermore, AST 120 significantly improved bloating and stool consistency compared to placebo at week 4 without any increased frequency of adverse effects [48].

Bile Acid Modulators

Colesevelam

Bile acid diarrhea either due to increased bile acid synthesis or impaired reabsorption occurs in up to a third of patients with chronic functional diarrhea or IBS-D [6, 7, 49]. Colesevelam is a bile acid sequestrant that binds to luminal bile acids, impedes their reabsorption and reduces colonic transit [50]. In a single-center, open label trial of 1875 mg twice-daily colesevelam, there was evidence of intraluminal binding of bile acids, compensatory increase in hepatic synthesis of bile acids (demonstrated by increased fasting serum C4 levels) and improved stool consistency. The number of bowel movements per week were significantly related to the total bile acid sequestered into the stool [51•].

Obeticholic Acid

Obeticholic acid (or 6-ethyl chenodeoxycholic acid) is a farnesoid X receptor agonist that appears to increase enterocyte synthesis of the hormone fibroblast growth factor (FGF)-19 and upregulate the feedback inhibition of hepatic bile acid synthesis [52, 53•]. In a single-center, pilot study of 25 mg daily obeticholic acid, there was significant reduction in bile acid synthesis and improvement in stool form and frequency. The treatment was well tolerated [53•].

Colestipol

Colestipol is another bile acid sequestrant. In an 8-week, open label treatment of 1 g twice-daily colestipol, there was improvement in abdominal distention, pain severity, stool frequency and less interference with daily life [54].

L-Type Calcium Channel Blocker

Otilonium Bromide

Otilonium is a spasmolytic agent that blocks L-type calcium channels in colonic smooth muscle in humans. In a 15-week, double blind, placebo-controlled trial of 356 IBS-D patients, otilonium bromide (40 mg thrice daily) was well tolerated and improved abdominal pain frequency and severity of abdominal bloating [55]. In another 4-week, dose-ranging study, 80-mg dose thrice daily dosing of otilonium bromide reduced the frequency of diarrheal episodes while intensity and frequency of abdominal pain or bloating were improved with both 40- and 80-mg thrice daily doses [56].

Muscarinic Type 3 Antagonists

Solifenacin

Solifenacin is a muscarinic type 3 receptor antagonist that is used to treat overactive bladder in adults. In an open label trial of 20 patients with IBS-D, solifenacin was non-inferior to ramosetron, a 5 HT_3 receptor antagonist. Reduction in defecation frequency, overall IBS symptom severity score and improvement in quality of life were noted at 2 and 6 weeks after initiation of solifenacin [57].

Glutamine

A subset of patients with IBS-D has been shown to have decreased intestinal glutamine synthetase levels [58]. In a preliminary report of 61 IBS-D patients, glutamine (10 g thrice a day) improved abdominal pain, bloating and diarrhea and restored small intestinal permeability when compared to placebo [59]. In a recent pilot study of colonic biopsies from 12 IBS-D patients, in vitro application of glutamine (10 mmol/L) to colonic biopsies increased expression of claudin 1, a tight junction protein [60].

Antispasmodics

Tiropramide

Tiropramide exerts an antispasmodic effect on the intestine through reducing Ca^{2+} release into the intestinal smooth muscle [61, 62]. In a phase 4, double blind, randomized controlled trial of 245 patients, the mean change of visual analog scores for abdominal pain with tiropramide (100 mg thrice a day) was non-inferior to octylonium (20 mg thrice a day) [63]. Octylonium also has similar mechanism of action as tiropramide [64, 65]. These data suggest that tiropramide is as effective as octylonium in managing abdominal pain in IBS, with a similar safety profile.

Peppermint Oil

Peppermint oil has been shown to relieve abdominal pain in IBS patients. A recent trial of 65 patients with IBS-D demonstrated that during the 6 weeks of therapy, abdominal pain is markedly improved in the peppermint oil group compared to the placebo group. However, the pain scores rebounded 2 weeks after the end of treatment. This study concluded that peppermint oil is effective in transiently relieving abdominal pain in IBS-D [66]. A multicenter randomized controlled trial using an ileo-colonic release formulation of peppermint oil (Tempocol-ColoPulse®) is in progress [67].

In addition to the drugs discussed above, other drugs in the pipeline for IBS-D are summarized in Table 2. These include

ASP 7147, a bombesin-2 receptor antagonist that decreases intestinal secretions and motility [68].

Other Drugs for IBS

Antibiotics

Small intestinal bacterial overgrowth has been speculated to play a role in the pathophysiology of IBS. Studies using lactulose breath testing have shown that a significant proportion of patients with IBS have evidence of SIBO [69]. However, the role of SIBO in pathophysiology of IBS remains controversial considering the significant limitations of breath testing in the diagnosis of SIBO and significant placebo response with the treatment [70]. Recent data suggests that antibiotics may increase the risk of development of IBS [71].

Rifaximin

Rifaximin is poorly absorbed broad-spectrum antibiotic. In two randomized clinical trials of 1260 patients with IBS without constipation (TARGET 1 and TARGET 2), patients were randomized to 550 mg of rifaximin thrice daily or placebo for 2 weeks and then followed up for 10 weeks. Significantly more 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; 41 vs. 32 %, in TARGET 2; 41 vs. 32 %, in the two studies combined). Similarly, more patients treated with rifaximin than with placebo had adequate relief of bloating (39 vs. 29 %, in TARGET 1; 41 vs. 32 %, in TARGET 2). The incidence of adverse events was similar in the two groups [72••]. In another trial, the role of rifaximin has been studied in patients with IBS-C and found that combination of rifaximin and neomycin is superior to neomycin alone with greater improvement in constipation, straining and bloating, but not abdominal pain [73]. Rifaximin has been recently approved by the FDA for IBS-D patients. The FDA recommends a dose of 550 mg thrice daily for IBS-D patients, and the treatment course can be repeated in case of recurrence of symptoms, up to two times. Rifaximin should be prescribed cautiously in patients with liver disease as it might cause an increase in alanine transferase enzyme (ALT) in some patients [45].

Anti-Inflammatory

Mesalazine

A small study demonstrated that mesalazine treatment is effective and safe in reducing infiltration of mast cells and improving the general well-being of patients with IBS [74]. However, more recent trials showed no significant improvement in abdominal pain [75, 76] or stool frequency and consistency in IBS-D patients treated with mesalazine [76].

Table 3 Other drugs for IBS

Citation	Drug	Number	Study design	Outcome
Antibiotics				
Pimentel M 2011 [72••]	Rifaximin	1260	Two 12-week, DB, PC RCTs (phase 3)	Improved abdominal pain, bloating and loose stools in non-constipated IBS
Pimentel M 2014 [73]	Rifaximin	31	2-week, DB, PC RCT	Rifaximin plus neomycin is superior to neomycin alone
5 ASA				
Barbara G 2014 [75]	Mesalazine	185	24-week, DB, PC RCT (phase 3)	No improvement in abdominal pain
Lam C 2015 [76]	Mesalazine	136	12-week, DB, PC RCT (phase 4)	No improvement in stool frequency, stool consistency and abdominal pain
Mast cell stabilizers				
Klooker T 2010 [77]	Ketotifen	60	8-week, DB, PC RCT	Increased pain threshold and improved quality of life
Purinergic drugs (A_{2A}AR antagonist)				
Bayer 2015 [84]	Iberogast (STW 5)	170	4-week, DB, PC RCT (phase 3)	Recruiting
H1 receptor antagonists				
van Wanrooij S 2013 [78]	Ebastine	55	12-week, DB, PC RCT (phase 4)	Improved abdominal pain and other IBS symptoms
GLP 1 analog				
Camilleri M 2012 [83]	Rose 010	46	4-week, DB, PC RCT (phase 1, phase 2)	Reduced gastric emptying t1/2, increased 48-h colonic transit. No effects on stool consistency or frequency

5 ASA 5 aminosalicylic acid, *H1* histamine 1, *IBS* irritable bowel syndrome, *DB* double blinded, *PC* placebo-controlled, *RCT* randomized control trial

Mast Cell Stabilizers

Ketotifen

Mast cell degranulation and immune dysregulation has been hypothesized to play a role in IBS, especially post-infectious IBS and IBS-D [4]. A study involving 60 IBS patients assessed rectal sensitivity before and after 8 weeks of treatment with ketotifen and found that this agent was associated with an increased pain threshold and improvement in health-related quality of life. This effect could be due to the mast cell-stabilizing properties of ketotifen or histamine type 1 receptor antagonism [77].

H1 Receptor Antagonists

Ebastine

In a 12-week, double blind, placebo-controlled trial, ebastine did not significantly improve rectal distension-evoked pain. However, considerable relief of IBS symptoms was observed in 46 % of patients treated with ebastine. Improvement in abdominal pain was also observed [78]. A recent 12-week, phase 4, double blind, placebo-controlled trial has been completed [79] and one is currently ongoing [80].

GLP 1 Analogs

ROSE-010

Glucagon-like peptide-1 (GLP-1) hormone analog ROSE-010 was proposed as a potential treatment for the pain component of IBS by targeting abnormal motor activity in the gut. In a cross-over clinical trial of 166 IBS patients using a definition for response as >50 % maximum total pain relief 10–60 min after treatment, twice the number of patients responded after administrating 100- and 300-μg doses of ROSE-010. The proportion of patients with response in total pain intensity remained similar [81]. GLP-1 inhibits small intestinal motility in healthy subjects and IBS patients [82]. In a trial of 46 patients with IBS-C, gastric emptying $t_{1/2}$ was significantly retarded by 100 and 300 μg of ROSE-010. However, ROSE-010 did not significantly affect gastric volumes, small bowel or colonic transit at 24 h, stool consistency or stool frequency. The 30- and 100-μg doses accelerated 48-h colonic transit. The clinical significance of this finding is unclear. Common adverse effects were nausea and vomiting [83].

Apart from the drugs discussed above, some other drugs showing promise in early stages of trials are in the pipeline. Iberogast (STW 5) is a purinergic drug [84] (Table 3). A trial of diakenchutto (TU-100), a traditional kampo medicine that modulates gastrointestinal nerves, is ongoing [85]. PPC 5650 is an acid-sensing Ca^{2+} ion channel modulator. In a double blind, placebo-controlled, cross-over trial of 25 patients, there was no improvement in rectal sensitivity to multimodal stimulation after diakenchutto [86].

Conclusion

Irritable bowel syndrome is one of the most prevalent gastrointestinal disorders, and there is still significant need for effective treatment options. The complex multifactorial nature of IBS, heterogeneity in clinical presentation and overlap with psychological factors has impeded advancements in treatment. Recent progress made in our understanding of the pathophysiology of IBS has allowed us to broaden our treatment armamentarium. Future trials should be considered in subsets of IBS patients, targeting specific pathophysiological processes such as bile acid metabolism, altered intestinal permeability, immune dysregulation and alterations in serotonergic and other neurohormonal pathways.

Compliance with Ethical Standards

Conflict of Interest Akhilesh Wadhwa declares that he has no conflict of interest; Michael Camilleri reports grants from SmithKline, grants from Albireo, during the conduct of the study; Madhusudan Grover reports grants from Takeda, Dong-A and NIDDK K23 DK 103911 during the conduct of the study.

Human and Animal Rights and Informed Consent This article does not contain any studies with animal subjects performed by any of the authors. With regard to the authors' research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

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- • Of importance
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