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Existing and Emerging Therapies for Managing Constipation and Diarrhea

Adil E. Bharucha, M.B.B.S., M.D., A.G.A.F¹, Mira M. Wouters, PhD.², and Jan Tack, M.D., Ph.D.²

¹Clinical Enteric Neuroscience Translational and Epidemiological Research Program (C.E.N.T.E.R.), Division of Gastroenterology and Hepatology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, USA

²Translational Research Center for Gastrointestinal Disorders, Dept. of Clinical and Experimental Medicine, KU Leuven, Leuven, Belgium

Abstract

Functional bowel disorders (i.e., constipation and diarrhea) are characterized by abdominal pain, bloating, distention, and/or bowel habit abnormalities in the absence of obvious anatomic or physiologic abnormalities on routine diagnostic tests. These symptoms are attributable to gastrointestinal sensorimotor dysfunctions resulting from peripheral and/or central mechanisms. Available drugs target the underlying bowel disturbance (ie, constipation, diarrhea, or both), supplemented when necessary by management of pain. Osmotic and stimulant laxatives, secretagogues, and serotonin 5-HT₄ receptor agonists are approved for treating constipation. Loperamide, anticholinergic agents, rifaximin, bile-acid binding agents, eluxadoline, and clonidine are used to treat diarrhea. Several exciting new compounds, some of which have been evaluated in humans, are currently under development.

Introduction

Functional bowel disorders (FBD) comprise a spectrum of chronic gastrointestinal (GI) disorders characterized by abdominal pain, bloating, distention, and/or bowel habit abnormalities (e.g, constipation, diarrhea, or mixed constipation and diarrhea) in the absence of obvious anatomic or physiologic abnormalities on routine diagnostic tests. The pathophysiology of constipation and diarrhea are covered elsewhere.[1,2] This article reviews the current management, especially medications and emerging therapies that have been studied in the past 2 years (Table 1). Other and older investigational medications are discussed elsewhere.[3]

Reprints: Adil E. Bharucha, MBBS, MD, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (bharucha.adil@mayo.edu Phone: 507-284-2687 Fax: 507-538-5820).

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Constipation and Constipation-Predominant IBS (IBS-C)

Laxatives

Initially, treatment with increased dietary fiber intake and/or an inexpensive osmotic agent, such as milk of magnesia or polyethylene glycol, supplemented, if necessary, with stimulant laxatives (e.g., bisacodyl suppositories) is recommended.[2] Laxative non-responders should undergo anorectal tests to evaluate for a defecatory disorder, for which pelvic floor biofeedback therapy is required. Absent defecatory disorders, the next option is a secretagogue or prucalopride.

Secretagogues

Secretagogues (i.e., lubiprostone, linaclotide, and plecanatide) increase intestinal chloride secretion by activating channels on the apical enterocyte surface, causing net efflux of ions and water into the intestine. To maintain electroneutrality, sodium is also secreted into the intestine; water follows.

Lubiprostone, is a bicyclic fatty acid derivative derived from prostaglandin E1 that activates apical type 2 chloride channels (CIC-2). Lubiprostone also activates prostaglandin EP receptors and the apical cystic fibrosis transmembrane regulator (CFTR); the latter also mediates intestinal fluid secretion. Lubiprostone is approved by the Food and Drug Administration (FDA) and in Europe for treating chronic constipation and C-IBS. Women of childbearing age require a negative pregnancy test before starting and contraceptive measures during treatment.

Similar to the natriuretic peptides uroguanylin and guanylin and the heat-stable enterotoxin (ST peptide) produced by the pathogenic *Escherichia coli* (*E. coli*), linaclotide and plecanatide are peptide agonists at guanylate cyclase C (GC-C) receptors.[4] They stimulate intracellular production of cyclic guanosine monophosphate (cGMP), leading to activation of CFTR, with chloride and water secretion. Activation of GC-C receptors by uroguanylin and plecanatide is pH-dependent, regulated by mucosal acidity in the proximal intestine. By contrast, the effects of ST-peptide and linaclotide are pH-independent. The extent to which these differences in pH-dependency between linaclotide and plecanatide influence the response and side effect profile is unclear and controversial.[5] Both drugs have minimal oral bioavailability and are FDA approved for treating chronic constipation. Linaclotide is also approved for treating constipation-predominant IBS. Diarrhea is the main side effect.

Prucalopride

Prucalopride is a selective serotonin 5-HT₄ receptor agonist, of a chemical class that differs from other older non-selective 5-HT₄ receptor ligands like metoclopramide, cisapride and tegaserod.[6] Prucalopride stimulates gastric, small intestinal and colonic propulsive contractions, including colonic high amplitude propagated contractions, which precede defecation. Prucalopride improves bowel disturbances and abdominal symptoms such as bloating and pain.[7] Outside the United States, prucalopride is approved for treating laxative-unresponsive chronic constipation in men and women. The main, usually transient, side effects of prucalopride are headache, diarrhea and nausea.

Newer Agents in Clinical and Pre-Clinical studies

Elobixibat—Elobixibat is a first-in-class drug developed for treating chronic constipation and constipation-predominant irritable bowel syndrome (IBS-C).[8] By inhibiting the ileal bile acid transporter, hence its absorption, elobixibat allows bile to promote colonic secretion and contractions, thereby accelerating colonic transit. A placebo-controlled phase 2b study showed significant symptom improvement with 10 and 15 mg elobixibat daily. An international phase 3 program with elobixibat in chronic constipation (NCT01833065 and NCT01827592) was prematurely terminated because of distribution issues with the trial medication. Based on a positive phase 3 study, a new drug application was submitted in Japan in early 2017. The drug has not been evaluated in IBS.

Tenapanor—Tenapanor is a first-in class inhibitor of the enterocyte sodium/hydrogen exchanger isoform 3 (NHE3).[9] Tenapanor is minimally absorbed, acts from the lumen to inhibit sodium and phosphate absorption, which increases intestinal fluid volume and transit. In a 12-week phase 2 study in IBS-C, tenapanor (5–50 mg b.i.d.) dose-dependently improved constipation and abdominal symptoms; the 50 mg b.i.d. dose was significantly better than placebo.[10] A press release announced that the first phase 3 trial in IBS-C with tenapanor met its primary endpoint (combined pain and stool pattern responder rate 27% vs. 18.7% with placebo, $p=0.02$). Significance was met for the secondary endpoint of abdominal pain relief, but not for the complete spontaneous bowel movements endpoint.

Diarrhea and Diarrhea-Predominant IBS (IBS-D)

Dietary modifications

In IBS-D, diets with a low content of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) provide greater symptom relief than placebo but not when compared to a common sense diet.[11] Also, these diets have profound, potentially deleterious, effects on the colonic microbiome.[12] Oligosaccharides with an alpha-galactosidic linkage have been implicated in the generation of symptoms after carbohydrate rich meals. In a twelve week placebo-controlled trial of alpha-galactosidase 400 IU capsules t.i.d. in 125 IBS patients, the supplement was no better than placebo and the withdrawal rate was higher in the active group.[13]

Antispasmodics and antidiarrheal agents

Pooled analyses suggest that antispasmodics (e.g., hyoscyamine, dicyclomine, peppermint oil) and antidepressants (e.g., serotonin reuptake inhibitors [SSRIs] and tricyclic antidepressants [TCAs]) improve abdominal pain and other IBS symptoms.[11] The non-absorbed μ opioid agonist loperamide (starting dose of 2 mg given 30 minutes before meals, maximum dose 16 mg daily), is an inexpensive initial approach for patients with diarrhea and a prominent gastrocolonic response. In some patients, finding the right balance between diarrhea and constipation, which is a side effect of loperamide, is challenging. In loperamide nonresponders, eluxadoline, rifaximin, and clonidine are options in men and women, and alosetron in women.[11,14,15] Except for clonidine, these drugs have been approved by the FDA; eluxadoline and rifaximin were approved in May 2015. Because alosetron was

associated with ischemic colitis, prescriptions for this drug in the United states require additional precautions detailed elsewhere.[11]

Eluxadoline

Eluxadoline is a μ -opioid receptor agonist and δ -opioid receptor antagonist that decreases bowel contractions, inhibits colonic transit, and reduces fluid/ion secretion. Oral bioavailability is 1.0%.[16] In phase 3 studies, the improvement in abdominal pain and diarrhea over 26 weeks was significantly higher for eluxadoline 100 mg b.i.d. than placebo (i.e., 29.3% vs. 19.0%, respectively in study 1 and 32.7% vs. 20.2% in study 2). Even in loperamide non-responders, eluxadoline was more effective than placebo.[17] The 75 mg twice-daily dose was also better versus placebo in both studies but differences were only statistically significant in study 2. Constipation, nausea, and abdominal pain were the most common adverse events. Sphincter of Oddi spasm, pancreatitis or elevated hepatic enzymes are less common but more serious side effects. In clinical trials, this adverse event occurred during the first week of treatment and resolved with drug discontinuation. In the initial FDA approval, eluxadoline was contraindicated in patients who had a history of pancreatitis or who consumed >3 alcoholic drinks per day; the lower dose (75 mg twice daily) was recommended in patients who had a cholecystectomy. Thereafter, that is between May 2015 and February 2017, 120 serious cases of pancreatitis, of which 76 required hospitalization and 2 died, were reported to the FDA database.[18] These serious side effects occurred early (e.g., after one or two doses) or with prolonged use. Of 68 cases that reported gallbladder status, 56 cases of pancreatitis or death occurred in patients who do not have a gallbladder. Hence, the FDA forbids the use of eluxadoline in patients who have had a cholecystectomy.

Rifaximin

Rifaximin is a nonsystemic antibiotic. In two identical, 12-week, phase 3 trials (TARGET 1 and 2, pooled N = 1260), in IBS-D patients treated with rifaximin (550 mg t.i.d. for 2 weeks) were more likely than placebo to report adequate relief of global IBS symptoms for 2 weeks of the first 4-week post-treatment period (i.e., 40.7% vs. 31.7%) and also at 10 weeks post-treatment.[19] Adequate relief was defined by an affirmative response to the question: "In regard to all your symptoms of IBS, as compared with the way you felt before you started the study medication, have you, in the past 7 days, had adequate relief of your IBS symptoms?" Subsequently, the TARGET 3 trial evaluated a second course of rifaximin in patients who relapsed after a treatment with rifaximin. Of 1074 patients (44.1%) who responded to open-label rifaximin, 692 (64.4%) relapsed within 18 weeks thereafter; 636 were randomized to the same regimen of rifaximin (n = 328) or placebo (n = 308) as in TARGET 1 and 2. During the 4 week follow-up period, response rates, as defined by improved abdominal pain and stool consistency, was significantly greater with rifaximin than placebo (38.1% vs 31.5%). Six weeks after the first retreatment, all patients were retreated again; again, the response to rifaximin was greater than placebo.[16] Adverse events, primarily headache, upper respiratory tract infection, and abdominal pain, were uncommon and similar between groups. No cases of *Clostridium difficile* infection were reported in these or subsequent studies but patients were not routinely tested. In summary, rifaximin is safe, modestly effective, and expensive (approximate cost of \$50 daily). The FDA has only approved 3 courses of rifaximin. However, in practice, many patients are

treated indefinitely, which is of concern. Antimicrobial effects probably mediate the response to rifaximin. The impetus to trials with rifaximin originated from studies which suggested that IBS-D was associated with small intestinal bacterial overgrowth (SIBO).[20] However, the tests used in routine clinical practice to diagnose SIBO lack standardization and validity, hence the contribution of SIBO to IBS is debatable. Moreover, trials of rifaximin in IBS did not evaluate for the presence of SIBO.

Similar to rifaximin, the efficacy of 2 weeks treatment with the poorly absorbable antibiotic *rifamycin* 600 mg b.i.d. or t.i.d. is being evaluated in IBS-D.[21]

Serotonin 5HT₃ antagonists

The 5HT₃-antagonist alosetron reduces abdominal pain and diarrhea in IBS-D patients.[22] Because it can cause, albeit rarely, severe constipation and ischemic colitis, it is approved for limited use, including the United States. However, the experience in clinical practice is largely reassuring.[23] Another 5HT₃-antagonist, ramosetron, with mainly peripheral effects, is efficacious in IBS-D, has a low incidence of constipation, does not cause ischemic colitis, and is approved in several Asian countries. In a phase III study in 296 male patients with IBS-D, overall IBS symptom relief (31.3 vs. 9.5%), improvement of stool consistency and abdominal pain relief were greater for ramosetron than placebo.[24] Similar effects were observed in a phase III study of 576 female IBS-D patients.[25]

Bile acid modulators

Bile acids stimulate colonic secretion and motility causing diarrhea in up to one third of patients with IBS-D. Uncontrolled studies suggest that bile acid sequestrants (e.g., cholestyramine, colestipol, and colesevelam) reduce colonic transit and improve stool consistency in these patients.[26–28] Obeticholic acid (or 6-ethyl chenodeoxycholic acid), a farnesoid X receptor agonist, increases enterocyte synthesis of the hormone fibroblast growth factor (FGF)-19 and upregulates the feedback inhibition of hepatic bile acid synthesis.[29] In a single-center, pilot study, obeticholic acid was well tolerated, significantly reduced bile acid synthesis, and improved stool form and frequency.

Tachykinins

Tachykinins, a family of neuropeptides including substance P, neurokinin (NK) A and B, are important mediators of gastrointestinal motility and nociception.[30] *Ibodutant*, a selective neurokinin-2 receptor antagonist (1,3 and 10 mg daily), was evaluated in a placebo-controlled phase 2 study in 559 IBS-D patients. In the overall population, the 10 mg dose tended to show benefit over placebo (39.6% vs. 27.5% responder rate, $p=0.032$, but not after correction for multiple testing). In a pre-specified analysis by gender, there was a dose-response effect in females; ibodutant (10 mg) was superior than placebo (46.8% vs. 24.4% response rate, $p=0.003$, significant after correction for multiple testing).[31] A phase 3 program with ibodutant (10 mg) in women with IBS-D is being conducted in Europe and in the U.S.A.

Translocator protein antagonists

ONO-2952, which is a novel and selective high affinity antagonist for the Translocator Protein 18 kDa (TSPO), influences neuronal excitability. It decreased visceral hypersensitivity in animal models.[32] In a 4-week study in IBS-D with approximately 65 patients per arm, ONO-2952 (60 mg) tended to improve stool consistency and diarrhea, but effects were not statistically significant versus placebo.[33]

Somatostatin

Somatostatin reduces diarrhea by inhibiting gastrointestinal motility and secretion. In a study of 33 patients with chronic idiopathic diarrhea (daily stool volume greater than 200 grams) treated with the long-acting somatostatin analogue lanreotide 120 mg s.c. every 4 weeks for 3 months, lanreotide significantly improved stool frequency and consistency and quality of life; 42% of patients had a more than 50% reduction in stool frequency after 1 month.[34]

Histamine receptor antagonists and other agents acting on TRP (Transient Receptor Potential) channels

Histamine sensitizes the nociceptor transient receptor potential cation channel V1 (TRPV1) and contributes to visceral hypersensitivity in preclinical models. In IBS patients, there is sensitization of TRPV1 channels, which is mediated by histamine and/or its metabolite imidazole acetaldehyde, in the rectal submucosal plexus.[35,36] In a 12-week, double-blind, placebo-controlled study, the HRH1 receptor antagonist ebastine (20mg once daily) reduced visceral hypersensitivity, and improved symptoms, including abdominal pain, versus placebo.[35] (Table 1). A large multicenter study is in progress.

TRPM8 agonists couple to TRPV1 and A1, inhibit their downstream chemo- and mechanosensory actions, and reduce post inflammatory visceral hyperalgesia in rats.[37] In a short (4 weeks) study in 72 patients, peppermint oil, a TRPM8 agonist, was more effective than placebo in IBS-D and IBS-M; the unconventional primary endpoint was the change from baseline in the Total IBS Symptom Score (TISS) after 4 weeks of treatment.[38]

Protease activating receptor 2 (PAR2) antagonists

In animal models of visceral hypersensitivity, PAR-2 antagonists and a PAR-4 agonist reversed colonic visceral hypersensitivity induced by supernatants from colonic biopsies from IBS patients.[39,40] Perhaps proteases such as trypsin 3 released from the epithelium of IBS patients activated sensory nerve endings.[41] Human studies are awaited.

IgE blockade

Case reports suggest that omalizumab improved IBS symptoms in IBS-D.[42–44] This non-anaphylactogenic anti-IgE antibody prevents free serum IgE from binding to cellular receptors on mast cells and basophils. While FGID patients are not allergic to food allergens, some have increased jejunal mucosal humoral responses. [45]

Other agents

A serum-derived bovine immunoglobulin/protein isolate (SBI) reduced stool frequency and abdominal pain but did not affect small bowel markers of immunity or inflammation in an uncontrolled study of 15 IBS-D patients.[46] The FDA regards SBI as a safe prescription medical food product. *In vitro* studies demonstrated that immunoglobulins in SBI reduce antigen-associated inflammation through immune and steric exclusion mechanisms.[47]

Palmitoylethanolamide (PEA) is an agonist at cannabinoid-2 and peroxisome proliferator-activated receptor- α (PPAR- α)- receptors, and stabilizes mast cells. A 12-week trial in 54 IBS patients observed that a food additive containing PEA with polydatin (200 mg/20 mg), which may also stabilize mast cells, improved abdominal pain more than placebo.[48] Whether these effects are mediated via mast cells or PPAR-alpha-receptors on enteric glial cells, which have also been implicated in animal models of postoperative ileus and IBS is unclear.[49,50] Indeed, activation of PPAR-alpha receptors in enteric glia by PEA improves colon inflammation through enteric glia/toll like receptor 4-dependent PPAR-alpha activation.[51]

In a placebo-controlled trial from Iran in 90 IBS patients, vitamin D3 (50000 IU every fortnight) improved abdominal symptoms (e.g., pain and distention) and quality of life, but not dissatisfaction with bowel habits. Vitamin D levels stayed in the normal range in the treatment group.[52] At baseline, two thirds of the patients had vitamin D levels below 20 ng/ml. Future studies to confirm and determine the mechanism of action, perhaps immune modulatory or antidepressive, are warranted.

Summary

Several drugs which target an expanding repertoire of pharmacological targets have been approved or are under development for treating functional bowel disorders in humans. These agents target the underlying bowel disturbance (ie, constipation, diarrhea, or both), supplemented when necessary by management of pain. As new agents are developed, their incremental utility over existing compounds should also be evaluated.

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Highlights

- For constipation and diarrhea, stepwise therapy is recommended
- When initial therapy is unsuccessful:
 - Secretagogues and 5-HT₄ receptor agonists are used for chronic constipation
 - Bile-acid binding agents, eluxadoline, and rifaximin are used to treat diarrhea
- Several newer compounds are being developed and tested in clinical trials

Figure 1.
Receptors and cellular mechanisms of drugs approved for treating functional bowel disorders.

Table 1Unapproved and Recently Approved Drugs in Pre-clinical and Clinical Studies of IBS¹

Drug class	Examples ²	Mechanisms	Species and model ³	Effects ³
Drugs tested in humans and belonging to classes in which other drugs are approved for use in humans				
Antibiotics[16,19,21]	Rifaximin (approved), rifamycin	Poorly absorbable antibiotics with anti-inflammatory properties, potentially modulating gut microbiota	Placebo-controlled clinical phase 3 trials in IBS-D	Improved diarrhea, bloating, and abdominal pain
Serotonin 5HT ₃ antagonist [24,25,53–55]	Ramosetron (approved in Japan), cilansetron, ondansetron, and alosetron (approved)	5HT ₃ receptor is expressed by peripheral and central neurons. Selective antagonism of peripheral 5HT ₃ receptors decreases gut transit, increases fluid absorption, and reduce visceral nociception	Placebo-controlled mechanistic studies in IBS-D	Reduced visceral sensation, slowed colonic transit, and reduced contractile and tonic responses to meal ingestion
			Placebo-controlled phase 3 clinical trials in IBS-D	Improved stool consistency and abdominal pain
Opioids, cannabinoids [16,56,57]	Methyl-orvinol (μ- and κ-opioid receptor antagonist)	Opioid receptors are present in ENS, ICC and smooth muscle cells	Mouse model of mustard oil-induced visceral hypersensitivity	Improved gastrointestinal hypermotility and reduced abdominal pain
	Eluxadoline (μ- opioid receptor agonist, δ-opioid receptor antagonist; (approved)		Placebo-controlled phase 3 clinical trials in IBS-D	Inhibited colonic transit and reduced intestinal fluid/ion secretion
	Palmitoyl- ethanolamide (PEA)	PEA is a fatty acid amide acting on peroxisome-activated receptor-γ (PPARγ) and cannabinoid-like G-protein-coupled receptors (GPCRs), potentially on mast cells	Placebo-controlled trial of 54 patients with IBS and 12 healthy volunteers	Reduced severity of abdominal pain without affecting mast cell counts
Bile acid modulators [26–29]	Bile acid sequestrants (cholestyramine, colestipol, and colesvelam, all approved for other indications) Farnesoid X receptor (FXR) agonist (obeticholic acid)	Sequestrants bind to bile acids, increase fecal excretion of bile acids, and increase synthesis of new bile acids. Fecal bile acids bound to colesvelam are biologically inactive. By binding to ileal FXRs, obeticholic acid, a FXR agonist, increases the ileal production	Uncontrolled studies of colesvelam (total of 36 patients), colestipol (27 patients), and obeticholic acid (28 patients)	Colsevelam, colestipol, and obeticholic acid reduced the frequency of bowel movements. The effects on stool consistency varied among studies. The effects of colesvelam on colonic transit were not significant.

Drug class	Examples ²	Mechanisms	Species and model ³	Effects ³
		of fibroblast growth factor 19 which reduces the production of bile acids.		
Drugs tested in humans. No other drugs in these classes are approved for use in humans with functional bowel disorders				
Neurokinin-2 (NK2) receptor antagonist [31]	Ibodontant	NK2 is expressed by smooth muscle cells of the muscularis mucosae and propria and few inflammatory cells of the lamina propria. It is not involved in visceromotor function	Placebo controlled study in 559 patients with IBS-D	Improved stool consistency in women but not men
Translocator protein 18 kDa (TSPO) antagonist [32,33]	ONO-2952	TSPO is involved in steroidogenesis and transport of neurosteroids	Rat model with restraint stress	Suppressed restraint stress-induced defecation
			Placebo-controlled study in 200 patients with IBS	Tendency to improve abdominal pain, stool consistency and stool frequency
Somatostatin analogs [34]	Lanreotide (approved for other indications)	Binds somatostatin receptors (types 2 and 5), which inhibits intestinal secretion and synthesis of growth hormone	33 patients with idiopathic refractory diarrhea	Decreased stool frequency and improved quality of life
Histamine receptor antagonists [35,58]	Histamine receptor H1 (HRH1) antagonists (pyrilamine, ebastine, approved ebastine, approved for other indications in some countries) HRH1 and HRH4 antagonist (levocetirizine, JNJ7777120)	Inhibition of neuronal expressed HRH1 prevents sensitization of transient receptor potential cation channel 1 TRPV1 channels HRH4s are expressed on mast cells and immune cells. HRH4s modulate neuronal sensitivity <i>via</i> indirect mechanisms.	Human submucosal neurons and a placebo - controlled trial of 55 patients with IBS	Prevented sensitization of TRPV1 channels in human submucosal neurons. Reduced IBS symptoms and visceral pain perception in patients with IBS.
			Rat model with 2,4,6-trinitrobenzenesulfonic acid (TNBS) colitis and post inflammatory visceral hypersensitivity	Normalizes post-inflammatory visceral hypersensitivity
TRPM8 agonist [38]	Pepper mint oil	TRPM8 couples to TRPV1 and A1 to inhibit downstream chemo- and mechanosensory actions	Rat model: TNBS colitis with post-inflammatory visceral hypersensitivity	Decreased post-inflammatory visceral hypersensitivity
			Placebo-controlled trial in 72 patients with IBS	Decreased abdominal pain and increased quality of life
Protease-activated receptor (PAR)-targeting molecules and serine protease inhibitors [39,41,59]	PAR2 antagonist (ENMD-1068) PAR-4 agonist (PAR-4-AP, Cat-G, AYPGKF-NH2) Aprotinin,	(epithelium derived) proteases are upregulated in	Human submucosal neurons and mice receiving intracolonic	Decreased visceral hypersensitivity

Drug class	Examples ²	Mechanisms	Species and model ³	Effects ³
	cathepsin-G inhibitor, soybean trypsin inhibitor	IBS, they signal to enteric neurons leading to visceral hypersensitivity	instillation with IBS-supernatant	
Vitamin D ₃ [52]		Vitamin D inhibits T-cell proliferation and is capable of inhibiting the immune response	Placebo controlled trial in 90 patients with IBS	Improved abdominal pain and distention, flatulence, overall gastrointestinal symptoms (except dissatisfaction with bowel habits) and quality of life
IgE blockade [42–44]	Omalizumab (approved for other indications)	Monoclonal antibody that binds IgE receptors on mast cells and basophils	Case reports in IBS-D patients	Almost complete resolution of symptoms in patients with IBS-D
Immunotherapy [46,47]	Serum-derived bovine immunoglobulin/pr otein isolate therapy (SBI, approved)		Intestinal co-culture	Immunoglobulins in SBI reduce antigen-associated inflammation through immune and steric exclusion mechanisms
			Uncontrolled study in 15 patients with IBS-D	Improved severity of abdominal pain and stool frequency
Drugs tested in animal models only				
G protein-coupled estrogen receptor (GPER) ligands [60]	G-1, a GPER selective agonist, and estradiol, a nonselective ER agonist	Inhibition of estrogen receptors dampens the cholinergic excitatory neuronal pathway	Human colonic muscle strips Mouse model with mustard oil-induced abdominal pain	G-1 and estradiol inhibit colonic motility and improve visceral pain in mouse model of visceral hypersensitivity

Abbreviations: ENS: enteric nervous system, ICC: interstitial cells of Cajal, IBS: irritable bowel syndrome, IBS-D: diarrhea- predominant IBS

¹The emphasis is on drugs and drug classes that have been studied in the past 2 years.

²Unless stated otherwise, approved refers to approval for bowel disorders by regulatory agencies in one or more countries.

³If data from human studies are available, pre-clinical studies are not provided unless essential.