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# Emerging Pharmacologic Therapies for Irritable Bowel Syndrome

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**Abstract** New therapies are being developed for irritable bowel syndrome (IBS). These advances are based on understanding pathophysiology or the development of medications with greater selectivity in classes of agents with known efficacy. Prucalopride, the newest European Medicines Agency-approved 5-hydroxytryptamine receptor 4 (5-$HT_4$) agonist, is effective in the treatment of chronic constipation with improved cardiovascular safety relative to older 5-$HT_4$ drugs; similarly, ramosetron, the 5-hydroxytryptamine receptor 3 (5-$HT_3$) antagonist, appears efficacious in diarrhea-predominant IBS. Secretagogues with different mechanisms of action target apical domains in enterocytes that are involved in chloride secretion, such as chloride channels, the cystic fibrosis transmembrane regulator, and guanylate cyclase C. As a class, such secretagogues have high efficacy and safety for constipation. With more data obtained from phase 2 and 3 trials, we expect other classes of medications, including bile acid modulators, anti-inflammatory agents, visceral analgesics, and newer centrally acting agents to be efficacious and enter the armamentarium for the treatment of IBS in the future.

**Keywords** Constipation · Diarrhea · Treatment · 5-$HT_4$ agonist · 5-$HT_3$ antagonist · Secretagogue · Bile acid · Anti-inflammatory · Peripheral visceral analgesic · Benzodiazepine receptor modulator

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## Introduction

The irritable bowel syndrome (IBS) is a common gastrointestinal (GI) disorder associated with a significant healthcare and economic burden [1, 2]. Traditionally, the pharmacologic treatment of IBS-related bowel dysfunction consisted of bulking agents and/or laxatives, opioid agents, and antispasmodics. However, these therapies may not satisfactorily improve symptoms, may have only short-term efficacy, or may cause side-effects. The exact pathophysiologic mechanisms of IBS are not completely understood; however, alterations in GI motility, secretion, bacterial ecology, and possibly bile acid malabsorption and a low-grade inflammatory state contribute to the pathogenesis of IBS. A growing understanding of the roles of neurotransmitters and mediators involved in these processes may provide a basis for developing more effective therapies for IBS (Fig. 1) [3]. Despite the large number of medications in the development pipeline for IBS and the exciting research on possible mechanisms of IBS, the evidence for most of these medication classes remains at the hypothesis or proof-of-concept stage. Proof from phase 3 clinical trials is required before the pipeline is translated into new drugs that can be used in patients. The risk of failure in new drug development is very high; Table 1 summarizes some of the investigated therapies that have not fulfilled their promise. These will not be discussed further.

This review addresses emerging pharmacologic therapies for IBS and lower functional GI disorders. They were selected based on at least one of the following criteria: 1) phase 2a studies demonstrating impact on motility, sensory, or secretory biomarkers; 2) phase 2b or phase 3 studies showing evidence of symptom-based efficacy. Thus, we focused on new generation 5-hydroxytryptamine receptor 4 (5-$HT_4$) agonists, intestinal secretagogues (chloride channel

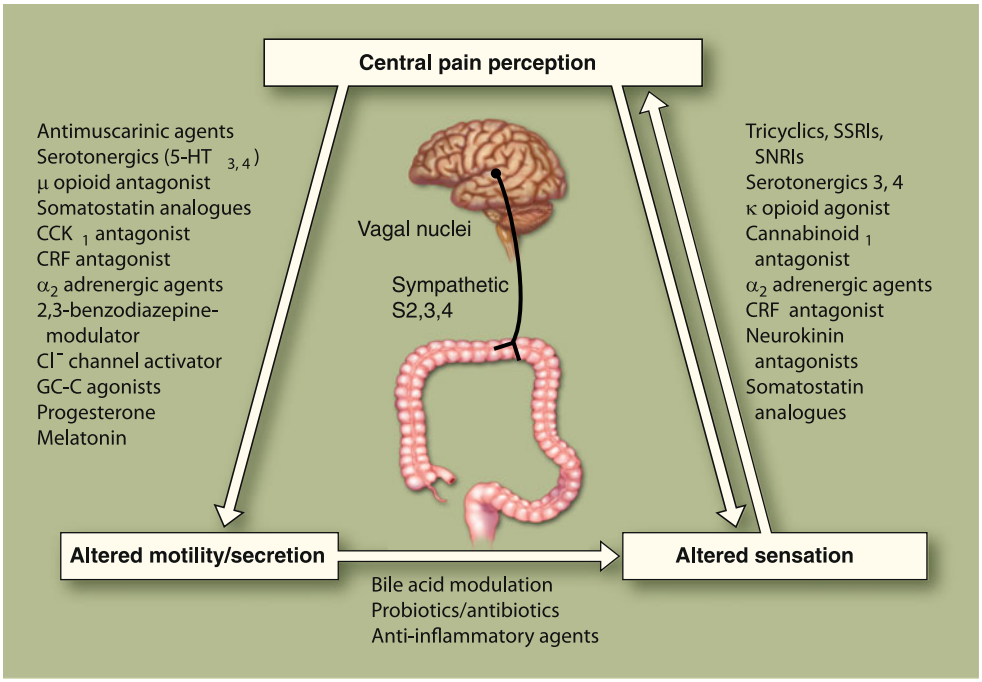


**Fig. 1** The pipeline in IBS. Candidate medications and possible mechanisms of action. CCK—cholecystokinin; CRF—corticotropin-releasing factor; GC-C—guanylate cyclase C; 5-$HT_3$—5-hydroxytryptamine receptor 3; 5-$HT_4$—5-hydroxytryptamine receptor 4; SNRI—serotonin–norepinephrine reuptake inhibitor; SSRI—selective serotonin reuptake inhibitor. (*From* Camilleri et al. [1], with permission)

activators, guanylate cyclase C [GC-C] agonists), bile acid modulators, anti-inflammatory agents, peripheral visceral analgesics, and new centrally acting agents (a benzodiazepine receptor) (Table 2) [4].

## New Generation 5-$HT_4$ Agonists

Although the older generation 5-$HT_4$ receptor agonist, tegaserod, was effective in treating chronic constipation and constipation-predominant IBS (C-IBS), it was nonselective and serious cardiovascular adverse events were attributed to it, leading to its removal from the US market in 2007. New generation 5-$HT_4$ receptor agonists have been shown to be selective, with high intrinsic activity for intestinal 5-$HT_4$ receptors and devoid of effects on the human ether-à-go-go related gene (hERG) channel. At doses that are effective in the lower GI tract, they are without clinically meaningful effects on 5-$HT_4$ receptors in the heart. These medications include prucalopride, ATI-7505, and velusetrag.

### Prucalopride

Prucalopride belongs to a class of benzofuran drugs [4-amino-5-chloro-2,3-dihydro-N-[1-(3-methoxypropyl)-4-piperidinyl]-7-benzofurancar-boxamide monohydrochloride], and was recently approved by the European Medicines Agency (EMEA) for the treatment of chronic constipation. Prucalopride is a high-selective, high-affinity agonist that binds to 5-$HT_4$ receptors on enteric neurons, facilitating both cholinergic and nonadrenergic, noncholinergic neurotransmission.

Three pivotal phase 3 trials have evaluated the efficacy of prucalopride in patients with chronic constipation. Most of the participants reported being dissatisfied with laxatives they were receiving [5••, 6, 7••]. The design, endpoints, and results of the three trials were very uniform. After a 2-week, no-treatment, run-in phase, patients were assigned to 12 weeks of treatment with placebo, 2 mg prucalopride, or 4 mg prucalopride. Compared to 11% of patients on placebo, 23.6% (2 mg) and 24.7% (4 mg) of patients achieved the primary endpoint, that is, three or more spontaneous and complete bowel movements (SCBM) per week, averaged over a 12-week treatment period. Several secondary endpoints, including an increase of one or more SCBM per week, and satisfaction with prucalopride treatment based on a validated quality-of-life instrument (patients' assessment of constipation quality of life: PAC-QOL) showed significant benefit in favor of prucalopride over placebo.

Prucalopride is well tolerated. The most common adverse events are headache, nausea, abdominal pain, and diarrhea, occurring in 10% or more of treated participants [5••, 8–11]. Most adverse events are independent of dose, transient, and mild or moderate in severity, occurring mainly on day 1 of treatment. Less than 10% needed to discontinue the drug due to treatment-related adverse events in a large cohort [5••, 8–11]. There has been a cumulative experience of more than 1,000 patient-years with prucalopride during the open trials, with no significant safety signal identified.

**Table 1** Candidate medications being developed for irritable bowel syndrome with inconclusive evidence of efficacy on bowel symptoms

| Drug class | Examples | Rationale or action | Pharmacodynamic (intestine or colon) | Clinical efficacy: phase 2B or 3 |
|---|---|---|---|---|
| NK antagonists | $NK_1$ antagonist, ezlozipant | $NK_1$-receptors' role in nociception | Reduce the emotional response of IBS patients to rectosigmoid distension | None |
| | $NK_2$ antagonist, nepadutant | $NK_2$-receptors' influence muscle contractility | Reduce contraction frequency and amplitude on MMC in small bowel in healthy males | None |
| | $NK_3$ antagonist, talnetant | $NK_3$-receptors' role in nociception | No effect on rectal compliance, sensory thresholds or intensity rating in healthy controls | Two 2B trials in 1350 IBS patients: no benefit |
| $CCK_1$ antagonist | Dexloxiglumide | Competitive antagonist of the $CCK_1$ receptor | Slower ascending colon emptying with no significant effect on overall colonic transit | Two initial 2B or 3 trials in C-IBS: not efficacious<br>A randomized withdrawal-design trial showed longer time to loss of therapeutic response with dexloxiglumide |
| $CRF_1$ antagonist | Pexacerafont | Competitive antagonist of the $CCK_1$ receptor | No significant effect on overall colonic transit; the selective antagonist, GW876008, attenuated psychological stress-induced rectal hyper sensitivity in 9 patients with IBS | Randomized, double-blind, placebo-controlled, two-period crossover trial of 19 weeks' duration with GW876008 showed no significant difference in the global improvement scale, daily self-assessment of IBS pain/discomfort, or individual lower GI symptoms |
| β3 adrenergic agonist | Solabegron | β3 adrenergic receptors involved in sensation, motor function, and control of somatostatin release | No significant effect on GI or overall colonic transit | Solabegron, 200 mg bid, significantly increased in the proportion of females ($P$=0.019; both genders [$P$=0.06]) with adequate relief of IBS pain and discomfort compared to placebo, but (consistent with transit results) did not affect bowel symptoms |

*bid* twice daily, *CCK* cholecystokinin, *C-IBS* constipation-predominant irritable bowel syndrome, *CRF* corticotropin-releasing factor, *GI* gastrointestinal, *IBS* irritable bowel syndrome, *MMC* migrating motor complex, *NK* neurokinin

(*Adapted from* Camilleri [4])

## ATI-7505

ATI-7505 is a benzamide 5-$HT_4$ receptor agonist that is structurally related to cisapride, the prototype benzamide with 5-$HT_4$ receptor agonist activity. Unlike cisapride, which is a mixture of (3R, 4S) and (3S, 4R) isomers of substituted piperidine-based scaffolds, ATI-7505 is the pure (3S, 4R) isomer. This difference in structure leads to a lack of cytochrome P450 3A4 (CYP3A4) metabolism, reducing the risk of drug interactions.

One phase 2a clinical trial evaluated the effects of 9 days' treatment with ATI-7505 on GI and colonic transit using validated scintigraphy [12••]. ATI-7505 accelerated colonic transit at 24 h and ascending colonic emptying and induced a looser stool consistency at doses of 10 and 20 mg, three times daily. This prokinetic property in the colon led to ongoing phase 2 trials. Preliminary results of thorough cardiac safety monitoring suggest that ATI-7505 has a safe cardiac profile [13].

## Velusetrag (TD-5108)

Velusetrag (TD-5108) is a potent agonist of human 5-$HT_4$ receptors. It has high intrinsic activity and displays preferential selectivity of binding to the 5-$HT_4$ receptor compared with all other 5-HT receptor subtypes (≥500-fold).

Two phase 2 clinical trials have demonstrated clinical efficacy of this drug. In a predominantly pharmacodynamic transit study [14••] of 60 healthy volunteers randomly assigned in double-blind fashion to placebo, 5, 15, 30 or 50 mg velusetrag, single-dose velusetrag significantly accelerated both overall colonic transit at 24 h and

**Table 2** Summary of action and clinical efficacy of new or promising medications in treatment of irritable bowel syndrome

| Drug class | Examples | Rationale and putative action | Pharmacodynamic (intestinal or colon) | Clinical efficacy: phase 2B or 3 primary endpoints | Safety issues/ comments |
|---|---|---|---|---|---|
| 5-$HT_4$ agonists | Prucalopride | Stimulate intrinsic cholinergic neurons to enhance motility | Increases small bowel, colon motility, and transit in healthy controls and patients with chronic constipation | 2B and 3 in chronic constipation: bowel movement frequency and satisfaction with bowel function both improved | Greater selectivity for 5-$HT_4$ than 5-$HT_{1B}$ or hERG channel |
| | ATI-7505 | Stimulate intrinsic cholinergic neurons to enhance motility | Increases colon transit in healthy controls | None | Greater selectivity for 5-$HT_4$; not metabolized by CYP 3A4 |
| | Velusetrag (TD-5108) | Stimulate intrinsic cholinergic neurons to enhance motility | Dose-related increase in small bowel and colon transit in healthy controls | 2B: dose-ranging study in 401 chronic constipation patients increased bowel movement frequency and proportion with adequate relief | Greater selectivity for 5-$HT_4$ |
| 5-$HT_3$ antagonist | Ramosetron | Inhibits secretion, motility, nociception | None | 2B: dose-ranging studies document benefit on global relief and bowel function endpoints in D-IBS | Safety concern regarding ischemic colitis with same drug class |
| ClC-2 channel activator | Lubiprostone | Increase intestinal water and electrolyte | Accelerates small bowel and colonic transit in healthy controls | Two phase 3 in several hundred chronic constipation and C-IBS patients: efficacious | Nausea, usually mild, in ~20%; FDA approved |
| Guanylate cyclase-C agonist | Linaclotide | Increase intestinal water and electrolyte | Accelerated ascending colonic transit and altered bowel function in 36 women with C-IBS | 2A and 2B studies in chronic constipation or IBS: increased bowel movement frequency | |
| κ-Opioid agonist | Asimadoline | κ-Opioid receptors in visceral perception | Reduced sensation in response to colon distensions in the non-noxious range; relax colon tone in healthy controls; increase sensory thresholds in patients with IBS | On-demand dosing not effective in reducing severity of abdominal pain in 100 IBS patients; 2B, dose-ranging study, 596 IBS patients: at least average moderate pain benefit in D-IBS and alternating type IBS | |
| 2,3-Benzodiazepine modulator | Dextofisopam | Potential to reduce stimulation-induced colonic motility and visceral sensitivity | None | 2B study in 140 IBS patients: increased number of months of adequate overall relief of IBS symptoms; efficacy lower over time | Possibly more abdominal pain or headache vs placebo |

*C-IBS* constipation-predominant irritable bowel syndrome, *ClC-2* type 2 chloride channel, *CRF* corticotropin-releasing factor, *D-IBS* diarrhea-predominant irritable bowel syndrome, *FDA* Food and Drug Administration, *GI* gastrointestinal, *hERG* human ether-à-go-go related gene, *5-$HT_{1B}$* 5-hydroxytryptamine receptor 1B, *5-$HT_3$* 5-hydroxytryptamine receptor 3, *5-$HT_4$* 5-hydroxytryptamine receptor 4, *IBS* irritable bowel syndrome (*From* Camilleri [4])

ascending colon emptying half-time. With multiple doses over 6 days, velusetrag, 30 mg, accelerated overall colonic transit at 24 h and overall gastric emptying half-time at 15 to 50 mg. In patients with chronic constipation and matched healthy controls administered 15 mg velusetrag per day in open-label fashion, velusetrag pharmacokinetics and effects on laxation and bowel function were similar.

Another phase 2 study of velusetrag in 401 patients with chronic constipation showed significant effects on average number of bowel movements compared to placebo [15].

Adverse experiences with velusetrag were mild, consistent with prokinetic activity (eg, diarrhea and nausea), and did not result in subject discontinuation [16].

## Novel 5-$HT_3$ Antagonist

Ramosetron is a potent and selective synthetic 5-$HT_3$ receptor antagonist. In experimental animal models, ramosetron exhibits properties that are consistent with the expected effects of a drug in this class: inhibition of stress-induced or exogenous corticotropin releasing hormone–induced water secretion, inhibition of stress-induced acceleration of colonic transit, and colonic nociception [17, 18]. In a double-blind, placebo-controlled, parallel-group study of 418 patients with diarrhea-predominant IBS (D-IBS), once-daily doses of ramosetron, 5 and 10 μg, increased monthly responder rates of "patient-reported global assessment of relief of IBS symptoms" compared to placebo; the benefit was similar in men and women. A single 1-μg dose was not effective [19]. In a second double-blind, placebo-controlled, parallel-group study of 539 patients with D-IBS, ramosetron, 5 μg once daily, was effective and well tolerated in the treatment of abdominal pain, discomfort, and altered bowel habits [20•]. Adverse events during treatment were abdominal distension, constipation, and hard stool, which are typical pharmacologic effects of the 5-$HT_3$ receptor antagonist agents. The incidence of constipation due to administration of ramosetron was only 5.19%, whereas the incidence observed with alosetron was 29% ($N$=8,328) [20•]. This augurs well to avoid one of the two main adverse effects that led to Food and Drug Administration warnings about alosetron. Further studies are necessary to elucidate whether safety, including the risk of ischemic colitis, differentiates this drug from alosetron (rate of ischemic colitis in clinical trials, ~1 in 1,000).

## Secretagogues

Chloride ion ($Cl^-$) secretion is the major determinant of mucosal hydration throughout the GI tract; $Cl^-$ transport is pivotal in the regulation of fluid secretion into the intestine. Through fluxes of $Cl^-$ into the cell via the basolateral $Na^+$-$K^+$-$2Cl^-$ co-transporter, $Cl^-$ accumulates in the cell above its electrochemical equilibrium. Thus, when apical chloride channels are opened, $Cl^-$ flows out of the cell, which then elicits fluid secretion. A major portion of $Cl^-$ movement across the apical membrane is via the cyclic adenosine monophosphate–dependent cystic fibrosis transmembrane regulator (CFTR) chloride channel. Intestinal and colonic epithelial cells also express the type 2 $Cl^-$ channel (ClC-2), one of the nine-member $Cl^-$ channel family, which are widely distributed in the human body. Currently, three targets of medical therapy are directed at chloride channels.

### CFTR Antagonist: Crofelemer

Crofelemer is an antagonist of the CFTR $Cl^-$ channel. In a double-blind, randomized, placebo-controlled trial of 242 patients with IBS [21], crofelemer did not show overall treatment effects on bowel function, although an increase in the number of pain- and discomfort-free days in female patients with D-IBS was observed. Further studies are necessary to elucidate its potential.

### Chloride Channel Activators: Lubiprostone

Lubiprostone is a bicyclic fatty acid compound derived from a metabolite of prostaglandin $E_1$. However, unlike prostaglandins, lubiprostone has little or no effect on prostaglandin E (EP) or F (FP) receptors and does not stimulate smooth muscle contraction. Lubiprostone has highly selective activity on ClC-2. Activation of ClC-2 located in the GI tract increases $Cl^-$ transport to the lumen and enhances intestinal fluid secretion [22]. There is some evidence that lubiprostone may alter function of tight junctions and transepithelial resistance; however, this has been demonstrated in an ischemia-injury model [23] and it is unclear whether it also applies to patients with IBS.

In a randomized, parallel-group, double-blind, placebo-controlled study of 30 healthy volunteers [24], lubiprostone accelerated small intestinal and colonic transit. An intracolonic measurement of motor function showed no activation of peristaltic contractions by lubiprostone, 24 μg [25], suggesting that the acceleration of transit probably results from intestinal secretion. A clinical trial to assess the efficacy and safety of lubiprostone, 16 μg, 24 μg, or 48 μg/day, for C-IBS showed that it significantly improved GI symptoms of C-IBS at all three doses. However higher doses of lubiprostone—especially the group receiving 48 μg/day—were associated with more GI adverse events (eg, nausea). The 16-μg/day dose demonstrated the optimal combination of efficacy and safety [26]. In summary, the secretory effects appear to be the main mechanism responsible for the efficacy of lubiprostone on constipation [25].

### GC-C Agonist: Linaclotide

GC-C functions as the principal receptor mediating intestinal secretion in response to heat-stable enterotoxins, the major cause of *Escherichia coli*–induced secretory diarrhea. GC-C is enriched in intestinal epithelium. Two endogenous ligands of mammalian GC-C are small cysteine-rich

peptides, guanylin and uroguanylin, which are released in an autocrine or paracrine fashion into the intestinal lumen and activate GC-C, resulting in elevation of the intracellular second messenger, cyclic guanosine monophosphate. This situation in turn results in increased chloride, bicarbonate, and fluid secretion into the intestinal lumen.

Linaclotide is a first-in-class, 14-amino acid peptide that binds and activates the receptor of GC-C on the luminal membrane of the enterocyte. In a dose-dependent fashion, linaclotide accelerated intestinal transit and secretion in rodents, and at low doses also influenced visceral perception. In women with C-IBS, linaclotide significantly accelerated ascending colonic transit and altered bowel function, increasing the number of bowel movements and loosening stool consistency [27••]. Beneficial effects were replicated in a phase 2a, randomized, controlled trial in chronic constipation [28] and in a phase 3, randomized, controlled trial in chronic constipation [29••].

## Bile Acid Modulation

Disruption of the enterohepatic circulation of bile acids caused by ileal disease (eg, Crohn's disease, radiation ileitis, or idiopathic bile acid malabsorption [BAM]) causes chronic secretory diarrhea. Both conjugated and nonconjugated bile acids induce secretion in the human colon. In addition, the di-α-hydroxy bile salt, sodium chenodeoxycholate (CDC) induces propulsive contractions in the human colon. Recent randomized, double-blind, placebo-controlled studies demonstrated that ileocolonic delivery of CDC at doses of 500 and 1,000 mg/day accelerated colonic transit and loosened stool consistency in healthy volunteers [30••] and in patients with C-IBS [31]. Considerable safety information is available from several years of clinical trials and use of CDC in the dissolution of gallstones; CDC, 7 to 20 $mg\,kg^{-1}\,day^{-1}$, was not hepatotoxic in humans, and among those who received CDC (>1,000 $mg\,day^{-1}$ for several months) or underwent partial ileal bypass for hyperlipidemia, there are no reports of colon cancer.

On the other hand, up to 70% of patients with chronic watery diarrhea have BAM [32•] and 20% of unselected patients with D-IBS had serologic evidence of BAM [33]. Therefore, bile acid binding is a known approach to relieve chronic diarrhea; regrettably, patient tolerability of the bile acid sequestrant cholestyramine is poor. We tested the pharmacodynamic effects of the newer and better tolerated bile acid binding agent, colesevelam hydrochloride, in a randomized, double-blind, placebo-controlled study of patients with D-IBS. Colesevelam affected overall colonic transit at 24 h and delayed emptying of the ascending colon by an average of 4 h compared with placebo; this treatment effect was associated with fasting serum 7αC4 levels, a marker of endogenous bile acid synthesis. Colesevelam was also associated with greater ease of stool passage and somewhat firmer stool consistency [30••]. Further large clinical trials are required to determine the role of colesevelam hydrochloride in chronic diarrhea and D-IBS.

## Anti-inflammatory Agents

Epidemiologic studies show that IBS can arise after bacterial gastroenteritis in up to one quarter of cases, and a subgroup of patients with IBS has subtle inflammatory changes in colonic biopsies (eg, T lymphocytes [34] and mast cells [34]) and changes in peripheral cytokine profile (eg, reduced interleukin [IL]-10/IL-12 ratio [35]). These and similar findings provide the rationale for testing anti-inflammatory agents and mast cell stabilizers in IBS.

### Disodium Cromoglycate

Disodium cromoglycate (DSCG) inhibits the release of inflammatory mediators such as histamine, leukotrienes, and slow-reacting substance of anaphylaxis by inhibiting degranulation of mast cells following contact with an allergen; it is used in the treatment of allergic respiratory diseases. A pilot human study tested its potential in IBS. Jejunal fluid and biopsies were obtained in healthy subjects and IBS patients, 6 months after random allocation to no treatment (IBS, $N=7$) or oral DSCG, 200 mg/8 h ($N=11$). Bowel movement frequency, stool consistency, abdominal pain, mast cell degranulation by luminal tryptase release, and transmission electron microscopy were monitored. DSCG resulted in clinical improvement of bowel function in D-IBS [36]. Further studies in larger samples are needed to assess its effects on other symptoms, including abdominal pain.

### Mast Cell Stabilizer: Ketotifen

Ketotifen, a mast cell stabilizer, is a drug extensively used to prevent mast cell activation. In animal experiments, ketotifen stabilized intestinal mucosal mast cells and prevented mucosal mast cell stimulation in response to the release of endogenous cholecystokinin.

In a preliminary report of 60 patients with IBS, it was claimed that ketotifen, but not placebo, increased the threshold for discomfort in visceral hypersensitive IBS patients ($N=30$); however, the post-treatment thresholds in the two treatment arms were not compared. There was also no significant effect observed on rectal sensory thresholds in normosensitive IBS patients ($N=30$). Importantly, the percentage of patients reporting severe abdominal pain was significantly decreased by ketotifen ($P=0.031$), but not by

placebo; similarly, abdominal bloating, flatulence, diarrhea, and quality-of-life subscales of sleep, diet, and sexual functioning improved with ketotifen compared to placebo. Sedation or drowsiness [37], which were observed in the study and are recognized adverse effects of the drug, may have resulted in unintentional unblinding and may have influenced patient reported outcome. Contrary to prior studies in the literature, spontaneous release of tryptase from rectal mucosal biopsies of IBS patients was lower (not higher) than in healthy volunteers, and ketotifen treatment in IBS patients did not affect the release of tryptase. These provocative data underscore the need for further studies.

### 5-Aminosalicylic Acid

5-Aminosalicylic acid (5-ASA) is an anti-inflammatory widely used to treat chronic inflammatory bowel disease. In a randomized, double-blind, placebo-controlled trial of 20 patients with IBS, 5-ASA significantly reduced total immunocytes and mast cells, as well as mucosal release of the proinflammatory cytokines IL-1β, histamine, and tryptase. This result was associated with improvement of general well-being, but primary colonic symptoms did not significantly change. The small numbers of patients enrolled in this trial suggest the need for cautious interpretation and replication [38]. This "positive" trial contrasts with the "negative" result observed in a trial comparing prednisone, 30 mg/day, with placebo in patients with postinfectious IBS [39].

## Peripheral Visceral Analgesic: Asimadoline—A Peripheral κ-Agonist

The three major opioid receptors—κ, μ, and δ—are distributed in the peripheral and central nervous systems, and are known to modulate visceral nociception. Available μ-opioid receptor agonists relieve pain, and may result in constipation or in central side effects including opioid dependence. In contrast, peripheral κ-opioid receptor agonists seem to be devoid of these side effects. The κ-opioid receptors inhibit perception of noxious stimuli in well-validated models of visceral sensation [40]. Asimadoline has high affinity and selectivity for the κ-opioid receptor and does not cross the blood-brain barrier. In a pharmacodynamic study of visceral sensation and GI motor functions in healthy volunteers, asimadoline reduced pain sensation rating during relatively low-pressure (but not noxious range) colonic distension; no significant treatment effect was observed for GI transit or colonic contractile responses [41]. In a randomized, double-blind, placebo-controlled clinical study, Mangel et al. [42] demonstrated that asimadoline produced improvement in symptoms in patients with D-IBS who had at least moderate pain at baseline. Intermittent use of asimadoline during attacks of IBS pain was not found to be an effective therapy [43•].

## New Centrally Acting Agents

### Benzodiazepine Receptor Modulator: Dextofisopam

Dextofisopam is the R-enantiomer of tofisopam, which binds to the 2,3-benzodiazepine receptor, and is distinct from the classical 1,4 or 1,5-benzodiazepine receptor. The 2,3-benzodiazepine receptors are concentrated in the subcortical ganglia, substantia nigra, and hypothalamus, and they do not appear to be present in the GI tract. In animal studies, dextofisopam influenced GI motor and visceral sensitivity [44]. In a double-blind, placebo-controlled study of D-IBS or alternating IBS, dextofisopam was superior to placebo, particularly during the first 4 weeks of treatment, with adequate relief and improved consistency and frequency of bowel movements. However, significantly more patients experienced worse abdominal pain during treatment with asimadoline compared to placebo [45]. Further studies are required.

## Conclusions

Exciting progress has occurred in the development of novel agents to treat IBS symptoms, including effective treatments for constipation (new generation 5-$HT_4$ agonists, secretagogues including a chloride channel activator and GC-C agonist), and diarrhea (a 5-$HT_3$ antagonist and bile acid sequestrant). Furthermore, treatments originally used for different indications, such as inflammatory bowel disease (anti-inflammatory agents), are now being applied to IBS, but it is unclear who should receive such treatments. Ongoing rigorous pharmacologic assessments using validated biomarkers and safety evaluations are required to continue the development of promising new therapies for IBS.

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