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Clinical Review

Esophageal, gastrointestinal, and colonic diseases resulting from disorders of the motor and sensory functions represent almost half the patients presenting to gastroenterologists. There have been significant advances in understanding the mechanisms of these disorders, through basic and translational research, and in targeting the receptors or mediators involved, through clinical trials involving biomarkers and patient responses. These advances have led to relief of patients' symptoms and improved quality of life, although there are still significant unmet needs. This article reviews the pipeline of medications in development for esophageal sensorimotor disorders, gastroparesis, chronic diarrhea, chronic constipation (including opioid-induced constipation), and visceral pain.

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Introduction

Gastrointestinal motility and functional disorders result in either abnormal propulsion of content or excessive sensation of normal or abnormal functions in different regions of the gut. These conditions constitute about 40% of referrals to gastroenterologists, and they result in significant disease burden. Advances in clinical management of these disorders are based on understanding the basic mechanisms involved in sensorimotor and secretory functions, coupled with clinical investigation and trial methodology.

The most frequent gastrointestinal motility and functional disorders are esophagitis, gastroparesis, chronic diarrhea, chronic idiopathic constipation (CIC), opioid-induced constipation (OIC), and visceral pain. This review summarizes the pathophysiology, lists commonly used current medications, and focuses on pharmacological agents in development for each disorder. At present, several approved medications relieve constipation and diarrhea; the major unmet needs are in gastroparesis, OIC, and visceral pain.

Mechanisms of gastrointestinal motility and sensation

Several neurotransmitters in the gut wall and intraluminal chemicals are involved in the control of the motor, sensory, and secretory functions of the gastrointestinal tract. Peristalsis involves sensing of intraluminal stimuli such as nutrients, distension, and motion by mucosal enteroendocrine cells activating intrinsic primary afferent neurons, and release of bioactive substances such as 5-hydroxytryptamine (5-HT; also known as serotonin) and neurokinins to activate ascending contraction and descending relaxation. The main excitatory transmitters are acetylcholine and substance P; the main relaxatory substances are nitric oxide, somatostatin, and vasoactive intestinal peptide.

Afferent signals from the gut activate a three-neuron chain to transmit sensation to the central nervous system along vagal, splanchnic (visceral), and pelvic afferents. In addition, the afferents activate prevertebral, spinal, or brain reflexes that modify visceral motor and secretory functions. The neurotransmitters involved in sensation include 5-HT, substance P, calcitonin gene–related peptide, and norepinephrine. Selective modification of receptors by agonists and antagonists provide the basis for pharmacological restoration of normal motility. Figure 1 summarizes treatments for gastrointestinal motility and functional disorders.

Esophageal disorders

The common esophageal sensorimotor disorders are gastroesophageal reflux disease (GERD), esophageal spasm, and esophageal chest pain. There are several pathophysiological mechanisms that constitute targets for therapy in esophageal disease. These include excess acid contact with esophageal mucosa resulting in symptoms of heartburn or chest pain; activation of esophageal muscle contraction or increased sensitivity of the esophagus that manifest as chest pain; excessive acid reflux associated with transient lower esophageal relaxation not triggered by swallowing (TLESR; a normal function during belching) in patients with GERD; and eosinophilic esophagitis (EoE), an inflammatory process that ultimately alters the compliance and results in rings of esophageal contractions. Thus, the mainstays of current treatment remain proton pump inhibitors (PPIs), calcium channel blockers, and low-dose tricyclic antidepressants (TCAs) for reflux disease and chest pain, and orally administered or topical corticosteroids (e.g., budesonide and fluticasone) for EoE. However, new concepts are being explored with refined or novel therapeutics.

A combination of PPIs and prokinetics is being used for GERD (1). In addition to inhibition of acid secretion, this approach attempts to enhance clearance of refluxed acid, thereby reducing contact time and erosive effects of acid on the squamous epithelium in the esophageal mucosa. Different approaches to treat GERD are based on inhibition of TLESR by $GABA_B$ receptor agonists that act both centrally and peripherally (2) or selective metabotropic glutamate receptor 5 (mGluR5) antagonists (3). The prototype $GABA_B$ agonist baclofen crosses the brain-blood barrier, causing neurologic side effects (e.g., dizziness and drowsiness). New approaches currently being tested include arbaclofen placarbil (R-isomer; prodrug of baclofen) and lesogaberan. The mGluR5 antagonist AZD2066 (13 mg/d) reduced TLESRs and reflux episodes (3).

Apart from heartburn and regurgitation, the other common esophageal symptom is noncardiac chest pain. This continues to be clinically challenging, especially when double-dose PPIs, sublingual nitrates, or TCAs do not resolve the components due to esophageal hypercontractility ("spasm") or hypersensitivity. Other

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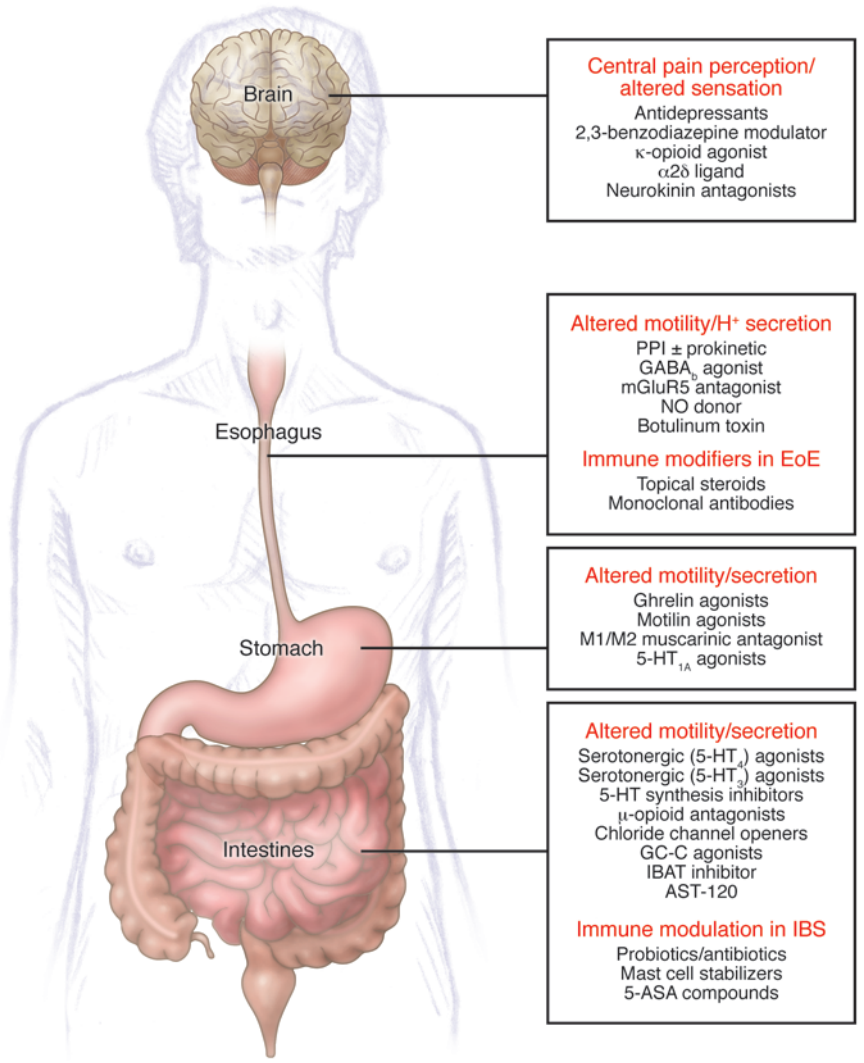

Figure 1
Classes of medications in development for treating esophageal, gastrointestinal, and colonic disorders by targeting sensation and central pain mechanisms, motility and secretion, and immune function.

approaches are being tested, including NO donors (or inhibitors of NO metabolism, e.g., with sildenafil; ref. 4); both approaches increase intracellular cGMP, resulting in smooth muscle relaxation. An alternative approach in patients with esophageal spasm and pain is injection of botulinum toxin, which blocks the presynaptic release of acetylcholine from efferent nerves. In the only placebo-controlled, crossover trial of botulinum toxin for chest pain to date (5), there was reduced dysphagia, but no benefit for chest pain or reflux symptoms, in contrast to nine open-label studies (reviewed in ref. 6).

With greater understanding of the role of pain mechanisms (including acid-sensing ion channels and vanilloid receptors; ref. 7) in the esophagus, candidate pharmacological approaches include transient receptor vanilloid 1 (TRPV1) antagonists, whose pharmacology has been extensively studied (8). However, small clinical trials have not confirmed the analgesic potential of TRPV1 antagonists in human esophageal experimental pain (9).

Increased awareness of EoE in recent years has been associated with increased annual incidence, making this condition about 10 times as prevalent in a U.S. community as the classical motility disorder achalasia (10, 11). Food and aeroallergens are thought to play a crucial role in EoE, and first-line therapies are elimination diets and orally administered or topical corticosteroids (e.g., budesonide and fluticasone; ref. 12). Antiinflammatory approaches to esophagitis include monoclonal antibodies directed at IL-5 and other cytokines in reflux esophagitis or eotaxin, or IgE in EoE (reviewed in ref. 13). Eotaxin is a peptide secreted by esophageal epithelial cells that functions as a strong eosinophil attractant. The high-affinity neutralizing human anti-eotaxin antibody CAT-213 inhibited eosinophil chemotactic activity in sputum from patients with moderate to severe bronchial asthma (14). The potential of monoclonal antibodies directed against eotaxin (CAT-213), IgE (omalizumab), and IL-5 (mepolizumab) in reducing chemotaxis and infiltration in EoE is the subject of ongoing research.

Gastroparesis

Gastroparesis is characterized by delayed gastric emptying in the absence of mechanical obstruction of the stomach, and symptoms include early satiety, postprandial fullness, bloating, nausea, vomiting, and abdominal or epigastric pain. Gastroparesis is usually associated with disorders in the extrinsic or intrinsic neural or pacemaker control of the stomach musculature. The most common associated conditions are postsurgical and idiopathic diabetes. Recent clinical guidelines and approved treatments for gastroparesis are reviewed elsewhere (15). The traditional molecular targets, dopamine-D_2 receptor antagonists and 5-HT_4 receptor

agonists, respectively suppress the vomiting center and stimulate intrinsic cholinergic neurons to activate gastric smooth muscle contractions. Short-term treatment with the motilin receptor agonist erythromycin "dumps" food and residue from the stomach, but tachyphylaxis reduces even medium-term efficacy.

The new targets in gastroparesis are receptors of ghrelin and motilin. Although there is high receptor identity, similar genomic organization, and function (stimulating gastrointestinal motility), each fails to recognize the ligand of the other. Moreover, whereas ghrelin and ghrelin receptors are widespread outside the gastrointestinal tract, motilin and its receptors are largely restricted to the gut (16).

Ghrelin receptor agonists: TZP-101, TZP-102, and RM-131. Intravenously administered ulimorelin (TZP-101), a macrocyclic peptidomimetic with potent binding affinity for the ghrelin receptor, accelerated gastric emptying of solids in 10 diabetics with moderate to severe gastroparesis symptoms (17). Small studies have shown reduced overall post-meal symptom intensity, postprandial fullness, and symptom improvement after treatment with TZP-101 (80 μg/kg) for four days in six patients with severe gastroparesis, compared with six who received placebo. This improvement was sustained in the 30-day follow-up period (18, 19). Higher doses were not as effective for symptom relief as the 80-μg/kg dose, possibly because ghrelin receptor agonists reduce gastric accommodation, which may induce upper gastrointestinal symptoms (20).

TZP-102 is an oral ghrelin receptor agonist that was tested in a 28-day placebo-controlled, dose-response trial in 92 patients with diabetic gastroparesis and moderate to severe symptoms. The 20-mg TZP-102 dose was superior to placebo for nausea, early satiety, postprandial fullness, bloating, upper abdominal pain, and patient-reported overall treatment effect (21). In patients with baseline gastric emptying $t_{1/2}$ exceeding 168 minutes (on ^{13}C-octanoate breath test), TZP-102 did not accelerate gastric emptying, but it reduced a composite symptom score of nausea, inability to finish meals, upper abdominal pain, and bloating (22). However, in a preliminary report of a randomized, placebo-controlled, 12-week trial of 10 and 20 mg oral TZP-102 in 201 patients with diabetic gastroparesis, there was no significant symptomatic benefit of either dose over placebo (23).

RM-131, a pentapeptide synthetic ghrelin receptor agonist, has a longer plasma $t_{1/2}$ and more than 100-fold the potency in reversing ileus in animals compared with native ghrelin. The effects of RM-131 (100 μg, s.c.) and placebo were tested in two randomized, crossover studies in patients with type 1 or 2 diabetes, upper gastrointestinal symptoms, and prior documented gastric emptying delay. In both studies, Shin et al. demonstrated that RM-131 accelerated gastric emptying and reduced gastrointestinal symptoms (24, 25). Results from phase IIB studies are required to appraise symptom benefit.

Motilin receptor agonist: GSK962040. GSK962040 is a nonmotilide motilin receptor agonist with low molecular mass that increases gastrointestinal motility in dogs (26). It selectively activates the motilin receptor in humans; activates predominantly antrum rather than fundus, small intestine, or colon in human tissue in vitro (27); and has been evaluated to determine safety and tolerability in humans (28). It is currently being investigated in phase 2 clinical trials (ClinicalTrials.gov trial ID NCT01262898).

Chronic diarrhea

In the absence of mucosal diseases, such as celiac and inflammatory bowel diseases, chronic diarrhea generally results from increased intestinal or colonic motility or secretion, increased colorectal sensitivity, or altered intestinal content and barrier function. The roles of intraluminal milieu, including microbial flora, organic (bile and short-chain fatty acids), and intestinal permeability are under investigation. Bile acid malabsorption (BAM) accounts for approximately 25% of patients with chronic diarrhea (29). This can be positively diagnosed by ^{75}SeHCAT retention (30), measurement in serum of 7α-hydroxy-4-cholesten-3-1 (31), or quantitative fecal bile acid measurement (32, 33); regrettably, such tests are not available in the United States, and response to a bile acid sequestrant is most commonly used to tentatively diagnose BAM.

Current treatments of chronic diarrhea are opioids, such as loperamide (the first-line drug) and diphenoxylate, which may be combined with atropine in some formulations and may induce adverse effects, such as bladder dysfunction, glaucoma, and tachycardia. Bile acid binders — classically, cholestyramine (4 g, 3 times per day) and off-label colesevelam (625 mg, 1–3 tablets 2 times per day) — are indicated for BAM.

Alosetron, a 5-HT$_3$ receptor antagonist, is approved for severe, diarrhea-predominant irritable bowel syndrome (IBS-D) that is not responding to other therapy. Alosetron was initially withdrawn because of reported association with ischemic colitis. Drugs approved for other indications are commonly used in IBS-D; these include opioids, other 5-HT$_3$ receptor antagonists (such as ondansetron), and psychoactive agents (with anticholinergic effects). Nonabsorbable antibiotics appear not to be effective for chronic diarrhea. Thus, rifaximin, a nonabsorbable antibiotic, was associated with adequate relief that was even documented for 10 weeks after cessation of treatment (34); however, stool consistency and number and urgency of bowel movements were not improved. Similarly, a meta-analysis that included five clinical trials demonstrated global IBS symptom and bloating improvement, but no significant effect on bowel function (35). Future treatments for chronic diarrhea are summarized in Table 1, and salient features are highlighted here.

5-HT synthesis inhibition. About 90% of the body's 5-HT is located in the enterochromaffin cells in the gastrointestinal tract mucosa. Mucosal 5-HT receptors are involved in secretion, motility, and nociception (36). LX-1031 is an oral tryptophan hydroxylase (TPH) inhibitor that reduces synthesis of 5-HT peripherally (37) without crossing the blood-brain barrier, thus avoiding risk of depression. In a randomized, placebo-controlled, 4-week, phase II trial, dose-dependent reductions in 5-HT correlated with adequate relief and improved stool consistency in the 1,000-mg dose group (38). No phase III trials have been reported to date.

New 5-HT$_3$ receptor antagonist: ramosetron. A selective 5-HT$_3$ receptor antagonist, ramosetron, slows colonic transit and reduces pain sensation in animal models subjected to stress (39, 40). Ramosetron (5 and 10 μg) was tested in two studies of approximately 1,000 patients with IBS-D and was superior to placebo in global relief of symptoms, with similar efficacy in men and women. Constipation and hard stool occurred in approximately 5% of patients (41, 42). Ramosetron (5 μg, once per day) is as effective as the antispasmodic mebeverine (135 mg, 3 times per day) in male patients with IBS-D (43). It is still unclear whether ramosetron causes ischemic colitis, which had been observed with alosetron.

Muscarinic type 3 receptor antagonists. Darifenacin retarded human small bowel and colonic transit (44), otilonium reduced rectal sensations (45), and hyoscine reduced enterocyte secretion (46). Therefore, this class of agents can counteract three mechanisms

Table 1
Examples of new medications for chronic diarrhea

Drug	Rationale and putative action	Pharmacodynamics in humans	Clinical efficacy	Safety issues, approval, other
TPH_1 blockers				
LX-1031	Inhibits synthesis of 5-HT by blocking TPH_1	Inhibited urine 5-HIAA excretion; no studies of PD efficacy	Phase IIB trial in non–IBS-C (1,000 mg): improved adequate relief, stool consistency	Under investigation
5-HT_3 antagonists				
Ramosetron	Inhibits secretion, motility, nociception	ND	Phase IIB studies in IBS-D (5 and 10 μg): benefit on global relief and bowel function	Under investigation; ischemic colitis with same drug class (alosetron)
Muscarinic type 3 receptor antagonists				
Otilonium	Inhibits secretion, motility, nociception	Increased rectosigmoid distention sensory thresholds	Phase IV studies: greater relief of pain vs. placebo, equivalence to mebeverine	EMA approved
Darifenacin	Inhibits secretion, motility, nociception	Retarded small bowel and colonic transit	ND	Under investigation
Solifenacin	Inhibits secretion, motility, nociception	ND	Open-label phase IIB trial (2.5–10 mg): equivalent efficacy to 5 μg ramosetron	Under investigation
Oral carbon adsorbents				
AST-120	Adsorbs luminal factors causing colon dysfunction	ND	Phase IIB study in non–IBS-C: reduced pain and bloating, improved stool consistency	Under investigation
Mast cell stabilizers				
DSCG	Reduces tryptase, immune activation, visceral sensitivity	Reduced jejunal biopsy mast cell mediators in IBS patients	Phase IV study: enhanced benefit from food restriction diet in IBS-D patients with food "allergies"	Off-label use
Ketotifen	Reduces tryptase, immune activation, visceral sensitivity	Increased rectal sensation threshold in those with baseline visceral hypersensitivity	Phase IIA study: relief of symptoms and pain in subset with baseline visceral hypersensitivity	Somnolence; off-label use
5-ASA				
Mesalamine, mesalazine	Reduces mucosal inflammation	Reduced proteases, cytokines in colonic biopsies in IBS	Phase IIA small studies: 2 of 4 showed relief of pain or diarrhea	Off-label use
2,3-benzodiazepine modulators				
Dextofisopam	Potential to reduce colonic motility and visceral sensitivity	None	Phase IIB study in IBS: increased number of months of adequate overall relief of IBS symptoms	Under investigation
κ-opioid agonists				
Asimadoline	κ-opioid receptors in visceral perception	Reduced sensation of colon distensions in healthy; increased sensory thresholds in IBS	Phase IIB dose-ranging study: at least average benefit for moderate pain in IBS-D and IBS-A	Under investigation
Amino acids				
Glutamine	Potential to correct for lower glutamine synthase in IBS	Restored intestinal permeability	Phase IIB study: improved abdominal pain, bloating, and diarrhea	Off-label use

HIAA, hydroxyindoleacetic acid; PD, pharmacodynamic. Adapted from ref. 71 and ref. 120.

that contribute to chronic diarrhea. Clinical trials show greatest effect of otilonium on abdominal sensation rather than bowel dysfunction in patients with IBS (47, 48). A small trial using crossover design showed similar efficacy of solifenacin and ramosetron (49).

Carbon adsorbent: AST-120. AST-120 consists of porous, spherical carbon particles of 0.2–0.4 mm diameter and large surface area (1,600 m^2/g); it adsorbs small–molecular weight and bacterial toxins, inflammatory mediators, digestive enzymes, and bile acid products (50). In a phase II, 8-week treatment trial, AST-120 transiently reduced pain and bloating in 115 patients with IBS-D or alternating IBS (IBS-A); however, stool consistency was not significantly improved (51).

Mast cell stabilizers. Disodium cromoglycate (DSCG) inhibits mast cell release of mediators such as histamine, leukotrienes, and a slow-reacting substance of anaphylaxis. A small study in IBS-D tested no treatment (n = 7) or oral DSCG (200 mg, 3 times per

day; n = 11). Six months later, DSCG was associated with reduced release of tryptase from jejunal biopsies, reduced expression of TLR2 and TLR4, and improved bowel function (52, 53). In an earlier study of 66 IBS-D patients with food intolerance assessed by skin prick test, DSCG (250 mg, 4 times per day) plus exclusion diet was associated with prolonged symptomatic benefit compared with exclusion diet alone (54).

Ketotifen, a mast cell stabilizer with antihistamine effects, was compared with placebo in 60 IBS patients (unselected for subgroup; ref. 55); it reduced discomfort induced by rectal balloon distension in 30 IBS patients with visceral hypersensitivity, but not in 30 normosensitive IBS patients. Compared with placebo, ketotifen had beneficial effects on pain, bloating, flatulence, diarrhea, quality of life, sleep, and sexual function. Side effects included sedation and drowsiness. In the future, nonsedating mast cell stabilizers will need to be tested.

5–aminosalicylic acid agents. The mechanism of 5–aminosalicylic acid (5-ASA) benefit in IBS may reflect reduced total colonic mucosal immunocytes and mast cells and mucosal release of IL-1β, histamine, and tryptase (56). Two of four small clinical trials suggest it may be beneficial in IBS patients, including some benefit on bowel function. In a 20-patient study, general well-being was improved, but the colonic symptoms did not change (56). In a trial involving 12 IBS-D patients, mesalazine (1.5 g, 2 times per day) was associated with symptomatic response of global relief, decreased number of days with discomfort, and increased bowel movement satisfaction in 8 patients (57). Mesalazine induced relief of pain and diarrhea in patients with these predominant symptoms in a third trial (58), but efficacy was not replicated in a recent small trial (59).

Benzodiazepine receptor modulator dextofisopam. Dextofisopam binds to the 2,3-benzodiazepine receptors in subcortical ganglia, substantia nigra, and hypothalamus and does not induce sedation. These receptors are not located in the gastrointestinal tract. Dextofisopam reduced gastrointestinal motor dysfunction and visceral sensitivity in response to stress in an animal model of IBS (60). In a 4-week, placebo-controlled trial, dextofisopam (200 mg, 2 times per day) improved consistency and frequency of bowel movements in patients with IBS-D or IBS-A (61). Further studies of action, safety, and efficacy in humans are required.

Peripheral κ-opioid receptor agonist: asimadoline. The κ-, μ-, and δ-opioid receptors are distributed widely in the central and peripheral nervous systems. Peripheral κ-opioid receptor agonists do not induce central side effects, but they reduce visceral sensation. The κ-opioid receptor agonist asimadoline, which does not cross the blood-brain barrier, reduced pain sensation (62) with no significant effects on gastrointestinal transit or colonic motility (63); however, asimadoline reduced urgency and stool frequency in IBS-D patients who had at least moderate pain at baseline (64).

Glutamine. Patients with IBS-D have increased permeability and symptomatic IBS (65) and decreased intestinal glutamine synthetase levels. In a preliminary report of a trial of glutamine (10 g, 3 times per day) in 61 IBS-D patients with high intestinal permeability and reduced claudin-1 expression in intestinal biopsies (66), the glutamine treatment arm was associated with significantly improved abdominal pain, bloating, and diarrhea as well as restored intestinal permeability compared with placebo.

CIC and OIC

CIC is associated with reduced colonic motility; however, in one tertiary referral study, almost 30% of patients with chronic constipation had evidence of rectal evacuation disorders (67). Patients with evacuation disorders are less likely to respond to colonic prokinetic agents, as demonstrated in a comparison of prucalopride and PEG3350 in patients with chronic constipation, many of whom endorsed symptoms suggestive of rectal evacuation disorders (68). Chronic constipation with hard stools reflects absorption of water, possibly from deficiency of natural colonic secretagogues (e.g. endogenous, secretory bile acids, particularly chenodeoxycholic acid; refs. 33, 69).

There are many approved treatments for CIC, including osmotic laxatives (e.g., PEG3350 and magnesium salts), surface active agents (e.g., docusate), stimulants (e.g., bisacodyl and senna alkaloids), and the recently approved secretagogues lubiprostone (rINN; trade name Amitiza) and linaclotide, which activate chloride secretion through chloride-2 channels and cystic fibrosis transmembrane regulator (CFTR).

New approaches to treat CIC

There are three general categories of medications in development for the treatment of CIC: colonic prokinetics (5-HT_4 receptor agonists), new secretagogues, and bile acid modulators. Medications are being specifically developed for OIC, including peripherally restricted μ-opioid receptor antagonists (PAMORAs). These medications are summarized in Table 2.

5-HT_4 receptor agonists. Whereas older-generation 5-HT_4 receptor agonists (e.g., cisapride) had relatively poor receptor selectivity and affected other receptors or ion channels in the heart (e.g., the delayed rectifier K^+ [IKr] channel) with risk of cardiac arrhythmias unrelated to the 5-HT_4 receptor, the new-generation 5-HT_4 receptor agonists have more than 100-fold greater selectivity for 5-HT_4 receptors than for the IKr channel, great specificity at intestinal 5-HT_4 receptors, and low intrinsic activity in cardiac muscle (70).

Agonists at 5-HT_4 receptors induce fast excitatory postsynaptic potentials in intrinsic neurons, release neurotransmitters such as acetylcholine, and induce mucosal secretion by activating submucosal neurons. Three 5-HT_4 receptor agonists in development are prucalopride, velusetrag, and naronapride (Table 2 and ref. 71). There is considerable evidence supporting prucalopride's pharmacodynamic effects, safety, and efficacy in chronic constipation (72); it is approved in most countries, but not in the United States. Velusetrag and naronapride are also in development in phase IIB studies. Both have been efficacious in pharmacodynamic studies (71), and velusetrag is efficacious in patients with chronic constipation (73).

New chloride secretagogues. Plecanatide activates guanyl cyclase C (GC-C) receptors in intestinal epithelium, stimulating chloride and bicarbonate secretion through the opening of apical CFTR chloride channels (74) and inhibition of sodium absorption through blockade of an apical Na^+/H^+ exchanger. In a 14-day treatment trial in 80 patients with CIC, plecanatide improved stool frequency and consistency, straining, and abdominal discomfort (75). A preliminary report documents the efficacy of plecanatide (0.3, 1, and 3 mg) in 951 CIC patients treated for 12 weeks (76).

Bile acid modulation. Delivery of bile acids into the colon results in secretory diarrhea, increasing permeability, activating adenylate cyclase, and increasing colonic motility. A novel approach to bile acid delivery to the colon involves selective inhibition of the ileal bile acid transporter (IBAT) with elobixibat (A3309). This drug accelerated colonic transit (77) and significantly increased stool frequency and improved constipation-related symptoms over 8 weeks of treatment in CIC patients (78). Long-term exposure to

Table 2
Examples of new drugs for CIC and OIC

Drug class	Drug name	Pharmacodynamic efficacy in humans	Clinical trial optimal efficacy and safety	Approval status
CIC				
Benzofuran 5-HT_4 agonist	Prucalopride	Accelerated colonic transit in health and chronic constipation	Phase II and III trials completed; open-label experience of ~1,000 cumulative patient-years; no clinical cardiac adverse events in clinical trials of >4,000 humans	EMA
Quinolone 5-HT_4 agonist	Velusetrag	Accelerated colonic transit in health in dose-related fashion	Phase IIB efficacy; no effect on QT in health or in 400 patients with constipation	Under investigation
Benzamide 5-HT_4 agonist	Naronapride	Accelerated colonic transit in health	Phase IB efficacy	–
IBAT inhibitor	Elobixibat	Accelerated colonic transit in female chronic constipation	Phase IIA and IIB efficacy	–
GC-C receptor activation	Plecanatide	ND	Phase IIA and IIB efficacy in chronic constipation	–
OIC				
Nonselective opioid antagonist	Oral naloxone	Reversed opiate-induced delay in orocecal and colonic transit	Naloxone PR formulation prevents OIC in patients receiving PR oxycodone	Off-label
μ-opioid antagonist	Methylnaltrexone	Reversed effects of opiate in health and of chronic methadone treatment on orocecal transit; no effect on colonic transit delayed by codeine (30 mg, 4 times per day) in opiate-naive healthy	Methylnaltrexone (0.15 mg/kg s.c., alternate days) effective in inducing laxation in patients with advanced illness	FDA, Canada
μ-opioid antagonist as core (4% naltrexone/ morphine ratio)	Naltrexone ER	ND	Open-label 12-month safety of combination ER pellets of morphine (median 59 mg/d) with a sequestered naltrexone core (1 or 2 times per day); OIC, 31.8%, nausea, 25.2%; opiate withdrawal, <5%	EMA
PAMORA	Alvimopan	8 mg accelerated colonic transit, reverse delayed colonic transit by codeine (30 mg, 4 times per day) in opiate-naive healthy	Alvimopan (0.5 mg, 2 times per day) efficacious in treating OIC; rare instances of ischemic heart disease	Off-label
PAMORA; PEGylated naloxol	NKTR-118	Normalized morphine-induced delay in orocecal transit	NKTR-118 (25 and 50 mg) increased number of SBMs during the first week and 4 overall weeks of treatment of OIC patients	Under investigation
PAMORA	TD-1211	ND	TD-1211 (5 and 10 mg/d) increased average SBM/wk over 2 weeks in OIC patients	Under investigation
μ-opioid agonist plus norepinephrine reuptake inhibitor	Tapentadol	Delayed gastric emptying; no retardation of colonic transit	Tapentadol ER (100–250 mg 2 times per day) equally effective for moderate to severe chronic osteoarthritis–related knee pain or chronic low back pain compared with oxycodone HCl CR (20–50 mg, 2 times per day) with fewer bowel dysfunction symptoms	Off-label
Bicyclic fatty acid	Lubiprostone	ND	Phase III clinical trials of lubiprostone (24 μg, 2 times per day); 2 of 3 positive	FDA
5-HT_4 agonist	Prucalopride	ND	1 phase IIB trial of prucalopride (2 or 4 mg/d) shows efficacy	Off-label

CR, controlled release; ER, extended release; ND, not done. Adapted from ref. 13 and ref. 71.

high colonic bile acids after partial ileal bypass for hyperlipidemia was not associated with increased prevalence of colorectal cancer at 25-year follow-up (79).

New approaches to treat OIC

The δ-, κ-, and μ-opioid receptors (all GPCRs) affect human gastrointestinal function, reducing neuronal excitability and neurotransmitter (acetylcholine) release (80) in nonsphincteric muscle, increasing tone in gastrointestinal sphincters such as the pylorus and ileocecal region, and inhibiting transit (81). About 40% of patients receiving long-term opioid treatment for noncancer chronic pain (most frequently musculoskeletal) experience OIC. The presence of constipation may influence patients to reduce analgesic dose, thereby not achieving effective pain relief. Moreover, less than 50% of

patients with OIC report achieving satisfaction with laxatives more than 50% of the time (82). Opiates cause constipation by inhibiting colonic transit and reducing intestinal and colonic secretion. There are three approaches to resolving this form of chronic constipation: avoidance, reversal with μ-opioid receptor antagonists, and overcoming the inhibitory effects of opiates by inducing intestinal and colonic secretion or motility. Approved medications include tapentadol (avoidance of OIC) as well as naloxone and methylnaltrexone (μ-opioid receptor antagonists). These and experimental therapies for OIC are summarized in Table 2.

Tapentadol HCl is a μ-opioid agonist and norepinephrine reuptake inhibitor that has approximately equivalent pain relief efficacy, but a more favorable gastrointestinal side-effect profile than the classic μ-opioid receptor agonist, oxycodone, for chronic pain related to arthritis, back pain, or postoperative analgesia (83–85).

Although μ-opioid receptor antagonists can reverse OIC, the widespread tissue distribution (e.g., with naloxone) can inhibit central actions of opioids, causing withdrawal symptoms or blocking the analgesia (86).

Modifications of naloxone are efficacious in OIC. A prolonged-release (PR) naloxone preparation in combination with PR oxycodone was effective for moderate to severe chronic pain (87) and improved bowel function compared with oral PR oxycodone alone (88), even up to 52 weeks in patients with noncancer chronic pain (89).

Several PAMORAs with modest central nervous system penetration are in development, including methylnaltrexone, alvimopan (Entereg), naloxegol (NKTR-118), and TD-1211. The pharmacodynamic effects of these agents are reviewed elsewhere (90). Methylnaltrexone is FDA approved in the United States for the treatment of OIC in patients receiving palliative care when response to laxative therapy has not been sufficient (91); however, it is not yet approved for adults with chronic, noncancer pain.

Alvimopan is an orally administered PAMORA that does not cross the blood-brain barrier at clinically relevant doses. In several clinical trials in patients with OIC and noncancer pain, alvimopan restored bowel movements without compromising analgesia (91–93), although superiority over placebo was not demonstrated in one phase III trial (94).

Naloxegol is an oral PEGylated conjugate of naloxone with rapid absorption, opioid receptor antagonist properties peripherally, and reduced central nervous system penetration. Three randomized, controlled trials in OIC patients showed that naloxegol (12.5 or 25 mg/d) significantly increased numbers of spontaneous bowel movements (SBMs) and OIC responders over 12 weeks (based on a rigorous, composite, FDA-sanctioned endpoint), with no evidence of opioid withdrawal or reversal of analgesia (95, 96).

TD-1211 is a PAMORA with high affinity for human μ- and δ-opioid receptors that reverses opiate-induced inhibition of colonic motility without reversing the central or analgesic effects (97). In a phase IIa study in 70 patients with OIC, TD-1211 (5 and 10 mg, once per day) significantly increased the average number of SBMs per week and shortened median time to first SBM (98). In a 5-week phase IIb study in 217 chronic noncancer pain OIC patients, TD-1211 (10 and 15 mg) significantly increased complete SBMs and SBMs per week (99).

Two meta-analyses of μ-opioid receptor antagonists involving 22 articles (100) or 20 studies (101) generally showed proof of concept, but insufficient clinical efficacy. These analyses did not include the newer medications, such as TD-1211 or naloxegol.

The third approach to treating OIC does not target opiate receptors, but increases secretion or motility to relieve the OIC. Prucalopride (2 or 4 mg for 4 weeks) was efficacious in a phase II study of 196 patients with OIC compared with placebo (102).

Lubiprostone is a prostaglandin E1–derived bicyclic fatty acid that specifically activates CIC-2 chloride channels on the apical aspect of gastrointestinal epithelial cells, increasing chloride release. Its effects in vitro and in vivo in models of OIC are reviewed elsewhere (90). Lubiprostone (24 μg, 2 times per day) was recently approved by the FDA for treatment of OIC related to noncancer pain, based on three phase IIB or III trials (103, 104). In vitro studies suggest that lubiprostone may not be effective in reversing OIC caused by methadone treatment (105).

Drugs for visceral pain associated with gastrointestinal motility disorders

The neurotransmitters involved in sensation include 5-HT, substance P, calcitonin gene–related peptide, and norepinephrine. There are no drugs approved for visceral pain in motility and functional disorders; the most frequently used off-label medications are antidepressants in both IBS and functional dyspepsia. A Cochrane meta-analysis showed a beneficial effect over placebo for improvement of abdominal pain with antispasmodics, cimetropium, dicyclomine, peppermint oil, pinaverium, and trimebutine, of which only peppermint oil is available in the USA. There was also a beneficial improvement of abdominal pain over placebo for TCAs, but not for selective 5-HT reuptake inhibitors (106). TCAs are also being used for other symptomatic disorders. A preliminary report of the TCA nortriptyline in 130 patients with idiopathic gastroparesis showed no significant symptomatic relief over placebo (107). The field of drug development for visceral pain should be enhanced by the demonstration that different endpoints recommended by two regulatory agencies, the FDA and the European Medicines Agency (EMA), were associated with similar response rates when applied in a large database of constipation-predominant IBS (IBS-C) patients participating in two phase III trials (108).

Two drugs in development for relief of visceral pain in IBS-D and IBS-A are asimadoline and dextofisopam (discussed above). Asimadoline failed to improve symptoms in a small pilot study of patients with functional dyspepsia (109).

Glucagon-like peptide–1 (GLP-1) is an incretin that suppresses gastric and small intestinal motility. The GLP-1 analog ROSE-010 (s.q. injection) was effective in twice as many patients as placebo when evaluated for on-demand treatment of IBS pain episodes in a crossover, double-blind, randomized design (110). As expected, ROSE-010 slowed gastric emptying, but it did not retard colonic transit or alter gastric accommodation (111).

A preliminary report assessed the efficacy of a histamine H1-receptor antagonist, ebastin, in the treatment of visceral pain associated with IBS in a 12-week trial with 28 patients randomized to ebastin and 27 to placebo (112). Visual analog scale (VAS) pain scores of symptoms evoked by rectal distentions (a pharmacodynamics endpoint) were not significantly influenced by treatment group; however, treatment over 12 weeks was associated with considerable relief of symptoms in 46% of the ebastin group and 12% of placebo group. There were also lower average abdominal pain scores with ebastin.

Ibodutant is a selective and potent antagonist of NK_2 receptors, which reduced intestinal hypermotility and hyperalgesia in disease models. Oral ibodutant (1, 3, and 10 mg, once per day) was compared with placebo for 8 weeks in 559 patients with IBS-D (Rome III criteria), which showed a significant effect of the 10-mg/d dose in females in a prespecified analysis (113). These data contrast with

other studies of other neurokinin receptor antagonists, such as talnetant, and suggest that NK_2 receptors may be optimal targets for visceral pain and diarrhea (113).

Two drug classes are in development for the relief of symptoms arising from functional dyspepsia, which is associated with motor dysfunctions such as impaired gastric emptying and reduced gastric accommodation (114). An approved 5-HT_{1A} receptor agonist, buspirone (10 mg, 3 times per day), enhanced gastric accommodation and provided symptom improvement in 17 patients with functional dyspepsia in a 4-week, placebo-controlled, crossover study (115). Similarly, an experimental 5-HT_{1A} receptor agonist, tandospirone (10 mg, 3 times per day), reduced abdominal symptom scores (including pain and discomfort) and anxiety in a 4-week, placebo-controlled study of 144 patients with functional dyspepsia (116).

Acotiamide enhances acetylcholine release via antagonism of M1 and M2 muscarinic receptors and functions as a cholinesterase inhibitor (117). In a multicenter, placebo-controlled, randomized trial involving 892 Japanese patients with functional dyspepsia (postprandial distress syndrome by Rome III criteria), oral acotiamide (100 mg, 3 times per day) was more efficacious than placebo for overall efficacy and for elimination of early satiation, upper abdominal bloating, and postprandial fullness (118). The mechanisms of action of acotiamide are enhanced gastric accommodation and gastric emptying (119).

Conclusion

There is a significant pipeline of novel medications for the treatment of gastrointestinal motility disorders (including gastroparesis, OIC, and visceral and esophageal pain), which represent substantial unmet clinical need (Tables 1 and 2). The main unanswered questions that require further research in order to affect clinical care are: first, identification, standardization, validation and regulatory approval of tests of motor and sensory functions to enhance clinical diagnosis and be used as biomarkers for proof-of-concept and dose-ranging studies of novel medications; second, definition and regulatory approval of patient response outcomes for motility disorders, particularly for gastroparesis; and third, further understanding the pivotal central and peripheral mechanisms involved in visceral sensation in order to more specifically target pain.

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