

Pharmacologic, Pharmacokinetic, and Pharmacogenomic Aspects of Functional Gastrointestinal Disorders



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This article reviews medications commonly used for the treatment of patients with functional gastrointestinal disorders. Specifically, we review the animal models that have been validated for the study of drug effects on sensation and motility; the preclinical pharmacology, pharmacokinetics, and toxicology usually required for introduction of new drugs; the biomarkers that are validated for studies of sensation and motility end points with experimental medications in humans; the pharmacogenomics applied to these medications and their relevance to the FGIDs; and the pharmacology of agents that are applied or have potential for the treatment of FGIDs, including psychopharmacologic drugs.

Keywords: Pain; Diarrhea; Constipation; Animal Models; Dyspepsia; Transit; Sensation.

Medications are commonly used for the treatment of patients with functional gastrointestinal disorders (FGIDs). This article summarizes the pharmacokinetics and pharmacology of medications used to treat FGIDs. Methods included literature review, consensus evaluation of the evidence for each topic assigned originally to 1 or 2 authors, and broader review at a harmonization session as part of the Rome IV process. Clinicians and basic scientists involved in the treatment or investigation of FGIDs or disease models need to have a comprehensive understanding of a vast range of medications.

Preclinical Pharmacology: Animal Models Validated for Study of Sensation and Motility

The development of new drugs for the treatment of patients with FGIDs is facilitated by preclinical animal models that must reproduce the pathophysiology of FGIDs as closely as possible. This section reviews the most commonly used animal models of visceral pain and disturbed gastrointestinal motility (Figure 1).

Visceral Pain

Mechanical Stimuli. Experiments are performed in awake or anesthetized rats, and the most frequently used stimulus of pain in animals is distention of a gut segment

with a balloon connected to a barostat to measure simultaneously compliance and the response to gastrointestinal distention. Balloons can be acutely or chronically implanted in the gut.¹ A number of factors influence reproducibility of balloon distention studies across laboratories: balloon construction and unfolding, distention protocols, and frequency of balloon distentions in the same animal (which can lead to sensitization), and species (eg, rats vs mice) or strain differences within species.

Chemical Stimuli. In rats, infusion of glycerol into the colon through an implanted catheter induces abdominal cramps that are typically demonstrated by observed behaviors (eg, back arching or writhing) or by psychoactive responses, including reflex electromyographic activity measured in the abdominal wall muscles (discussed in the section End Points Used to Evaluate Sensation).² Intracolonic injection of glycerol results in an increase in long spike burst activity, which was eliminated by previous administration of lidocaine, suggesting there is an induction of a viscerovisceral reflex.³ Two separate studies provide contradictory results regarding the role of glycerol-induced activation of serotonin/5-hydroxytryptamine (5-HT) type 3 receptors on visceral afferent pathways. The 5-HT₃ antagonist granisetron did not modify this reflex in a human study, whereas alosetron significantly attenuated the glycerol-induced visceral pain in rats.^{2,3} It is conceivable that glycerol's effects on contractile activity and tone might be inhibited by alosetron independently of any effects on visceral afferents or viscus compliance.⁴ Other stimuli are used to sensitize the colon to balloon distention in order to investigate visceral pain modulation in animal models; they produce an initial inflammatory response⁵ that resolves, but

[†]Deceased.

Abbreviations used in this paper: CFTR, cystic fibrosis transmembrane regulator; cGMP, cyclic guanosine monophosphate; CYP, cytochrome P450; FD, functional dyspepsia; FDA, Food and Drug Administration; FGID, functional gastrointestinal disorder; GC-C, guanylate cyclase-C; GI, gastrointestinal; 5-HT, 5-hydroxytryptamine; IBS, irritable bowel syndrome; IBS-C, constipation-predominant irritable bowel syndrome; IBS-D, diarrhea-predominant irritable bowel syndrome; OIC, opioid-induced constipation.

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Animal models for preclinical pharmacology

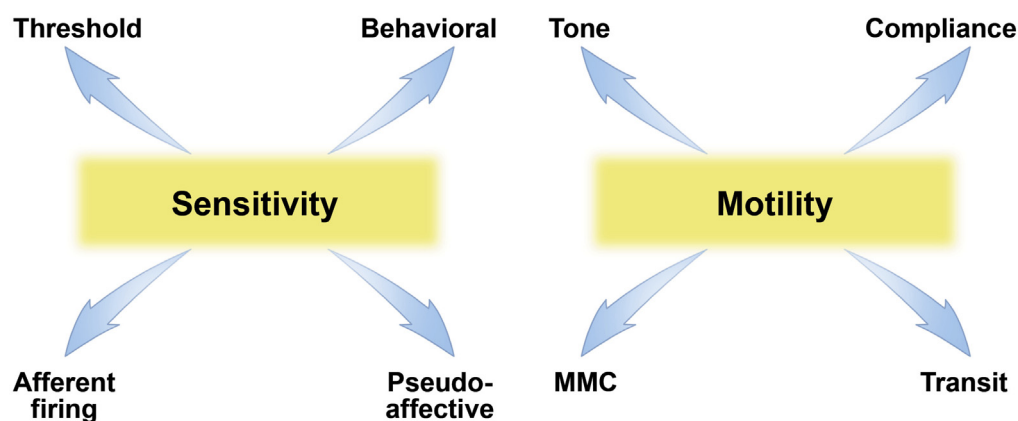


Figure 1. End points in experimental animal models of sensitivity and motility are applied in pre-clinical pharmacology of lead compounds.

later leads to sensitization of visceral afferents. Other chemical irritants include trinitrobenzene sulfonic acid, dioctyl sodium sulfosuccinate, and zymogen and parasite infestations (such as *Nippostrongylus brasiliensis* or *Trichinella spiralis*). Long-term colonic hyperalgesia may also be induced by colonic inflammation.⁶ At present, there is no consensus on the best model to study visceral pain.

Nonchemical Models Used to Study Visceral Sensitivity

Other models used to study colonic and rectal hypersensitivity are stress (eg, maternal deprivation, water avoidance models) and lipopolysaccharide injection.^{7,8} Long-term colonic hyperalgesia may be induced by neonatal maternal deprivation.⁹

End Points Used to Evaluate Sensation

Nociceptive responses to stimuli, called “pseudo-affective” responses, are brainstem or spinal reflexes that cease when the noxious stimulus is terminated. The most commonly used end point in the rat is the contraction of abdominal muscles induced by rectal or colorectal distention; the contractions are typically recorded by electromyography.^{2,5,10} The numbers of spike bursts or integrated signals correspond to abdominal contractions during the period of distention, and they correlate with the intensity of the stimulus applied.⁵

In mice, colorectal distention triggers only one sustained contraction at the onset of the distention.¹¹ It is, however, also possible that the electromyographic recording may reflect contractions associated with a distention-induced defecation reflex, rather than being a measure of pain. This inference is supported by the observation that gastric distention in rats does not induce abdominal contractions. In contrast, stretching of the body or lifting of the head and electromyography of neck muscles appear to reflect nociceptive responses to gastric distention.¹²

Visceral distension also induces viscerovisceral reflexes, such as relaxation of anal sphincters during rectal distention or rectocolonic inhibition of gastric emptying.¹³

Change in blood pressure is a pseudo-affective response widely used to assess visceral pain. Cardiovascular and muscular responses are mediated via brainstem reflexes; both are vigorous in decerebrated, but not spinalized, rats.

Electrophysiologic recordings from sensory neurons or second order neurons in the spinal cord may provide the most direct evidence that a drug alters afferent function.^{14,15}

Measurements of the effect of the medication on viscus compliance are essential to differentiate effects on volume thresholds to activate sensory fibers from drug-induced contraction or relaxation.¹⁶

Several behavioral end points have been used and involve brain centers higher than the brainstem. They do not cease when the noxious stimulus is terminated and, therefore, are not pseudo-affective responses. Referred somatic hyperalgesia is evaluated in mice by application of von Frey hairs on the abdomen; the subsequent behavioral response is a measure of sensation. Functional magnetic resonance imaging studies of rat brain activity in response to colorectal distention have also been reported.¹⁷

Allodynia and Hyperalgesia

Several models permit evaluation of allodynia (decrease in the sensitivity threshold to distention) and hyperalgesia (enhanced response to painful stimulus). Gastric hypersensitivity to distention has been induced by inflammation and intestinal hypersensitivity by helminth infection.^{12,18}

Motility

The techniques used to record motility or measure transit in animals may differ from techniques used in humans, but the end points are identical.

Delayed Gastric Emptying

Numerous stressors have been proposed to inhibit gastric emptying in rats, including restraint, acoustic stress, cold stress, combined acoustic and cold stress, and passive avoidance. Prolonged colonic distension inhibits gastric emptying, and this is considered relevant because, in humans, voluntary suppression of defecation for 4 days inhibits gastric emptying.^{19,20} Another experimental method used to inhibit gastric emptying is duodenal infusion of lipids in humans or animals (reviewed in Lee and Tack²¹).

Altered Duodenojejunal Migrating Motor Complex Pattern

Acute stress affects migrating motor complex patterns²²; however, there are no models of chronic disruption of the migrating motor complex in animals.

Altered Colonic Motility and Transit

Intestinal motility can be measured in animal models of gastrointestinal (GI) transit. A traditional model is the charcoal meal model, where animals are administered test agents before or followed by a bolus of a charcoal meal. The distance traveled by this charcoal along the GI tract is measured and quantified as a percentage of distance traveled after administering vehicle alone.²³ Colonic transit in response to fluid hypersecretion is harder to measure in rodents due to the high fluid reabsorption in the cecum; however, preclinical models to study distal colonic propulsion have been described in rodents.²⁴ Colonic motility can be inhibited by drugs such as α_2 -adrenoceptor and μ -opioid receptor agonists. Stress has been used to stimulate colonic motility, colonic transit, and fecal excretion in rats.²⁵ Induction of intestinal peristalsis by pharmacologic agents has also been modeled using isolated guinea pig colonic segments.²⁶

In summary, because the present knowledge of the pathophysiology of FGIDs is limited, selection of one or more reliable animal models is not possible. It is also difficult, based on results in a single animal model, to predict efficacy of a compound in clinical trials. Studying more than one animal model can enhance the probability of selecting effective drugs for further development. Several medications with track records of proven efficacy in animal models (for both transit and sensation) were subsequently shown to have clinical efficacy (eg, 5-HT₄ agonists, 5-HT₃ antagonists, opioid agonists, guanylate cyclase-C receptor agonists); however, other classes of medications that appeared to influence sensory functions in animal models were not efficacious in clinical trials (eg, NK₂ antagonist, β_3 -adrenergic agonist). In addition, it is worth emphasizing that pain is not the only symptom of FGIDs affecting quality of life, and animal models providing information on motility effects may be relevant to the assessment of new drugs.

Human Studies of Motility and Sensation: Utility in Drug Development for Functional Gastrointestinal Disorders

This section reviews the application of physiologic tests as potential biomarkers used to understand the mode of action and to predict efficacy of new drug treatments of FGIDs.

Measurements of Colonic Transit

The radiopaque marker test for colonic transit is a commonly performed and widely available test used to assess whole-gut transit time. Studies with fiber or loperamide suggest that overall effects of these therapies can be predicted by the marker transit test, although there was considerable overlap.^{27,28} Examples from the literature support the use of detailed scintigraphic colonic transit measurement in the development of medications for irritable bowel syndrome (IBS)—associated changes in bowel function. Alosetron, a 5-HT₃ receptor antagonist that slows colonic transit, was shown to be effective in female diarrhea-predominant IBS (IBS-D) patients,²⁹ and tegaserod and prucalopride, 5-HT₄ receptor agonists that accelerate colonic transit, are effective in constipation-predominant IBS (IBS-C) and functional constipation.^{30–34} Linaclotide, a novel agonist of guanylate cyclase-C, accelerated ascending colonic transit and altered bowel function; thus, it was shown to be effective in IBS-C.^{35–37}

Intraluminal Measurements of Rectal or Colonic Motility and Sensation

Intracolonic measurements of postprandial tone showed the potential of 5-HT₃ receptor antagonists to prevent diarrhea and other postprandial symptoms in IBS and carcinoid diarrhea.³⁸ However, measurements of rectal or colonic sensation in human subjects do not reliably predict clinical efficacy. Changes in rectal sensitivity are observed with octreotide and opiates, but rectal sensory thresholds are not altered by tegaserod when using rapid distention.^{39–44}

Gastric Biomarkers in Functional Dyspepsia

Gastric emptying rates, gastric electrical rhythm, gastric sensitivity, and gastric accommodation are targets for testing new drugs. Gastric emptying rates can explain symptoms and aid in diagnosis of gastroparesis. Scintigraphic gastric emptying has been a classic measurement for testing drug efficacy in gastroparesis; however, the prediction of clinical efficacy is not consistent.^{45,46} A recent extensive review questions the use of gastric emptying measurement to direct drug development for gastroparesis.⁴⁷ This analysis is also complicated by the occurrence of tachyphylaxis to some medications and by changes in gastric emptying rate with placebo.^{48–51}

Gastric accommodation is a new target for treatment, as it reflects meal-related satiety. The gastric barostat is the gold standard test used to measure compliance, tone, and

sensitivity. The κ -opioid agonist fedotozine and the 5-HT_{1A} receptor agonist R-137696 produced acute effects on barostat measurements of sensitivity or tone that did not translate into significant clinical benefit during placebo-controlled studies of several weeks in functional dyspepsia (FD).^{52,53} Single-photon emission computed tomography and magnetic resonance imaging can evaluate accommodation by measuring gastric volume, but their usefulness has not been proven in clinical trials.

Induction of symptoms by a standardized provocative meal of water or a liquid nutrient drink or a solid meal shows differences between healthy controls and FD, and was used in clinical trials.^{54–56} One open trial of the dopamine-2 receptor antagonist and acetylcholinesterase inhibitor itopride (discussed further in the subsection Dopamine Receptor Antagonists) demonstrated that a provocative meal can quantify dyspeptic symptoms and reflected therapeutic effects of itopride treatment in FD. However, it is still unclear whether changes in symptom severity after meal provocative tests will prove effective predictors of the clinical efficacy of medications.

Combined use of the nutrient drink test with assessment of symptoms, and measurement of gastric volume and emptying or intragastric pressure monitoring, may simultaneously measure several potential biomarkers.^{57–59} Improved methods or further validation of those mentioned will more accurately assess changes in symptoms and sensorimotor function in future trials.

Preclinical Considerations

An outline of some general pharmacodynamic, pharmacokinetic, and safety aspects that are important for the development of new drugs for FGIDs is included in the [Supplementary Material](#).

Pharmacokinetics

Ideal pharmacokinetics features of a drug with systemic action are the ability to reach clinically relevant drug concentrations at the target receptor; half-life or dosage formulation suitable for once daily administration; not a cytochrome P450 (CYP) substrate (lack of drug interactions); no metabolites with different or unwanted pharmacologic actions; and no interactions with food.

CYP2D6, CYP3A4, and CYP2C19 are important isoenzymes because of their involvement in the metabolism of many drugs and drug–drug interactions. The prevalence of altered CYP450 differs among different populations. [Figure 2](#) shows the distribution of CYP2 altered activity variants in different geographic regions.⁶⁰

Significant interactions with these enzymes should be ruled out in early drug discovery and may be achieved by computational prediction. Specifically, it is important to distinguish between pharmacokinetic modification resulting from drug metabolism by one of the enzymes vs drug interactions, which may be inhibition or induction, at one of the enzymes. In both situations, drug–drug interactions can occur; if inhibition or induction occurs at clinically relevant doses.

Principles of Pharmacogenomics in Functional Gastrointestinal Disorders

Pharmacogenetics refers to the study of individual variations in DNA sequence related to drug response. Pharmacogenomics is the study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual, or population levels.

Polymorphisms may be markers associated with predisposition to FGIDs. For example, there may be an inflammatory or genetic component (eg, serotonin transporter, polymorphism in 5-hydroxytryptamine transporter linked polymorphic region) in some cases of IBS,^{61,62} or polymorphism (C825T) in the gene controlling G-protein synthesis in functional dyspepsia and IBS.⁶³ Such genetic variations can influence response to medications. There may also be genetic polymorphisms in drug metabolism. For instance, the number of functional CYP2D6 genes determines the pharmacokinetics and plasma levels of the commonly used tricyclic agent, nortriptyline,⁶⁴ or the action of codeine (which is converted to morphine by the CYP2D6 isoenzyme to be effective). Note also that several antidepressants are metabolized by these enzymes, and this might affect their clinical efficacy and safety.

Genetic polymorphisms may also involve transporters⁶⁵ that may influence drug response. Two examples of pharmacodynamic variation in FGIDs are provided. 5-Hydroxytryptamine transporter linked polymorphic region polymorphisms in the gene *SLC6A4* (solute carrier family 6 [neurotransmitter transporter], member 4) were associated with a greater colonic transit response in those with long homozygous polymorphisms compared to those with heterozygous or short homozygous polymorphisms in IBS-D.⁶⁶ Conversely, IBS-C patients carrying the S allele of 5-hydroxytryptamine transporter linked polymorphic region have greater response to the 5-HT₄ agonist tegaserod.⁶⁷

Holtmann et al⁶³ found that *GNB3* polymorphisms were predictors of symptom outcomes in FD, based on the rationale that G proteins act as second messengers and may influence multiple receptor-mediated mechanisms.

Thus, pharmacogenetics may affect drug response and need to be considered in drug development programs and in clinical therapeutics in FGIDs. Further examples and discussion of pharmacogenetics in IBS are provided in the [Supplementary Materials](#).

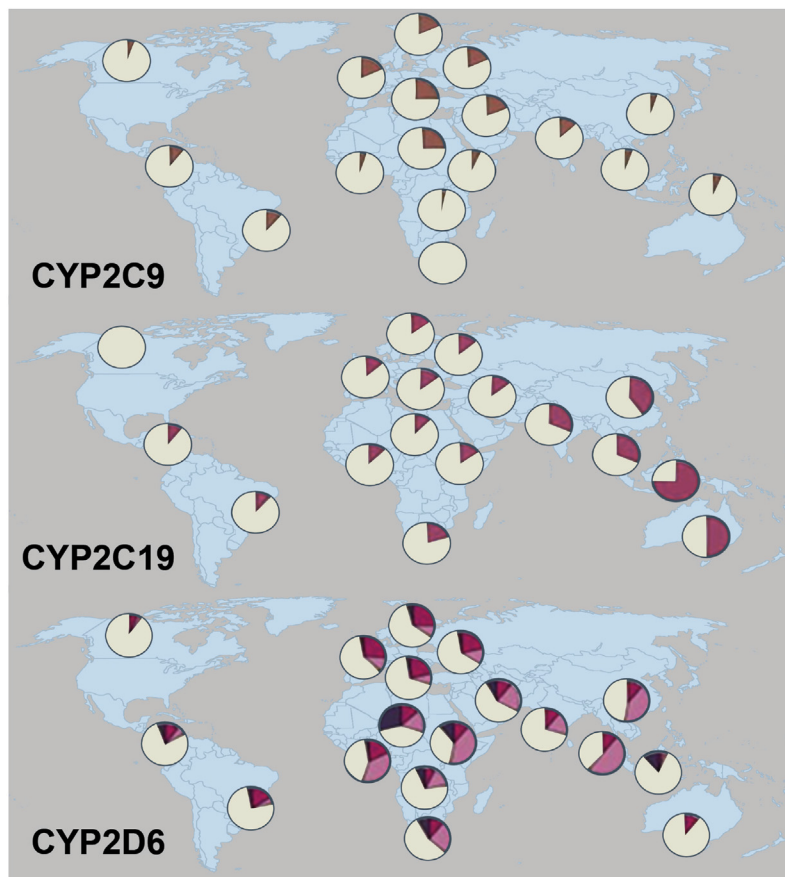
The conclusion as far as pharmacodynamics is that clinicians and basic investigators involved in the treatment or investigation of FGIDs or disease models need to have a comprehensive understanding of a vast range of medications. It is anticipated that the interactions among basic scientists, applied pharmacologists, and clinical trials will lead to better treatment for these disorders.

Human Pharmacology: Nonpsychotropic Agents

Gastrointestinal motor and sensory functions can be altered through several pharmacologic approaches; the

Figure 2. Cytochrome P450 (CYP) refers to a family of enzymes that are responsible for the metabolism of endogenous and exogenous compounds. CYP2 is associated primarily with metabolism (including oxidation, dehydrogenation, and esterification) of a large number of exogenous compounds. The CYP2 metabolizing enzymes are encoded by polymorphic genes. Molecular variations in the genes encoding CYP2D6, CYP2C19, and CYP2C9 have the greatest clinical impact. The figure shows the distribution of CYP2 altered activity variants in different geographic regions: (A) CYP2C9, (B) CYP2C19, and (C) CYP2D6. This suggests that population substructure can strongly affect the variation in pharmacogenetic loci and therefore, the metabolism of drugs. Adapted from Sistonen et al,⁶⁰ with permission.

■ Not present
■ Decreased
■ Normal
■ Increased



most important are summarized in [Supplementary Table 1](#) and are discussed in this section. However, it is also important to recognize 2 other classes of agents commonly used in FGIDs: laxatives in the treatment of constipation (alone or in IBS-C⁶⁸) and probiotics.⁶⁹ Several meta-analyses of pharmacologic treatments for IBS have been published in recent years.⁷⁰ Although not a focus of this article, the pharmacologic actions of psychotropic drugs on monoamine reuptake and receptors are summarized in [Supplementary Table 2](#). [Figure 3](#) shows potential cellular and mechanistic targets for drug action in functional and motility disorders. [Figure 4](#) provides a summary of receptors located on different cellular targets and their potential as treatments for FGIDs. [Figure 5](#) summarizes the interaction of gut mucosal barrier, microbiome, and gut–brain interactions in FGIDs, focusing on colonic disorders.

Upper Gastrointestinal Tract: Gastroparesis, Functional Dyspepsia

Current Drug Treatments for Gastroparesis or Functional Dyspepsia

Serotonergic agents. Serotonin, or 5-HT, plays a key role in the control of gastrointestinal motility, sensitivity, and secretion. Actions of 5-HT are terminated by the action of the serotonin transporter, which is inhibited by selective

serotonin reuptake inhibitor antidepressants.⁷¹ Selective serotonin reuptake inhibitor alter motility in the stomach, small bowel, and colon,⁷² but, to date, no convincing beneficial therapeutic effects have been reported in FGIDs. Several 5-HT receptor types are present on nerves and smooth muscle and mediate multiple effects on gut motility, secretion, and sensation.⁷³

5-HT₄ receptor agonists, such as prucalopride or mosapride, act on intrinsic neurons to stimulate esophageal, gastric, small bowel, and colonic transit in health, in gastroesophageal reflux disease, in FD, in constipation, and in IBS-C.^{74–80}

In the stomach, 5-HT₄ receptor agonists enhance (postprandial) proximal gastric volumes in health, but do not alter sensation.⁸¹ While prucalopride has been studied mainly in the lower GI tract and is primarily approved for the treatment of constipation (outside the United States), mosapride has also been investigated in the upper GI tract and is approved for the treatment of dyspepsia and gastroesophageal reflux disease in a variety of Asian and South American countries. [Supplementary Table 3](#) shows a comparison of novel 5-HT₄ agonists that are efficacious in stimulating gut motility or transit and are sufficiently selective to predict clinical safety from cardiovascular perspectives (discussed in section on constipation and IBS-C).

Dopamine receptor antagonists. Dopamine-2 receptor antagonists have gastropromotile effects and central

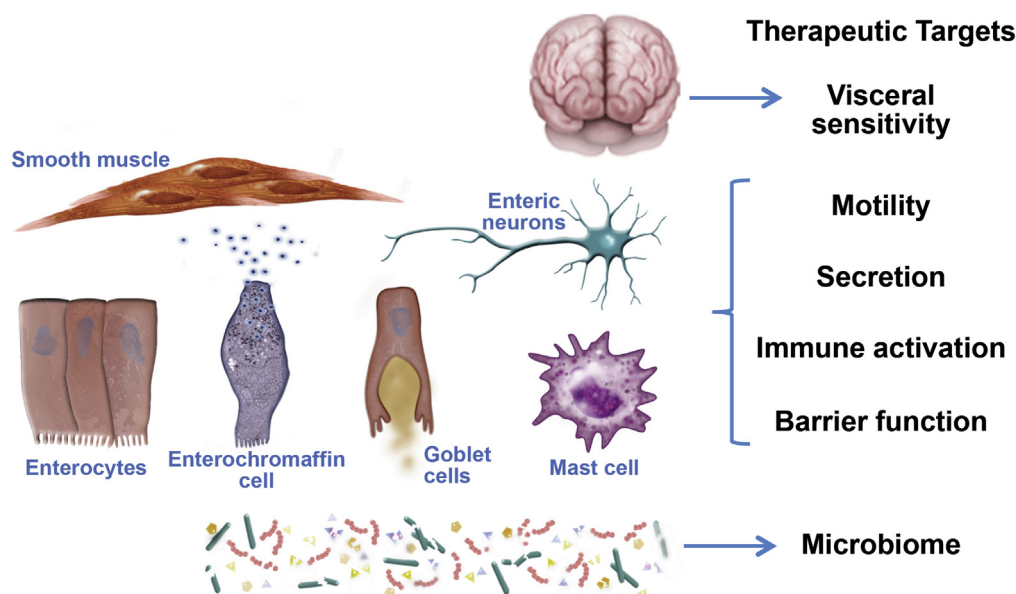


Figure 3. Potential local therapeutic targets for drug action in the gut include visceral sensitivity, microbiome, motility, secretion, immune activation, and barrier function.

antiemetic properties resulting in suppression of nausea and vomiting. Although metoclopramide and domperidone are used clinically in the treatment of FGIDs and gastroparesis, efficacy has not been established by high-quality studies.⁸²⁻⁸⁴ and treatment is recommended for short periods. A recent 4-week trial of oral dissolving metoclopramide shows efficacy in gastroparesis compared with placebo.⁸⁵ It should be kept in mind that domperidone is listed among drugs with known risk of torsades de pointes, and the European Medicines Agency Pharmacovigilance Committee recommended restrictions on its use^{86,87} (www.crediblemeds.org).

Itopride is a benzamide that acts as a dopamine-2 receptor antagonist and an acetylcholinesterase inhibitor. Itopride has been investigated in FD with conflicting results.⁸⁸⁻⁹⁰ It is approved for the treatment of FD in Asia.

Motilides. Activation of motilin receptors on smooth muscle and cholinergic nerves enhances gastric contractility.⁹¹ Motilin receptor agonists, such as erythromycin, azithromycin, and clarithromycin enhance antral contractility, fundic tone, and gastric emptying in health and in gastroparesis.^{48,92-95} However, the symptomatic impact of enhanced emptying by erythromycin in gastroparesis has

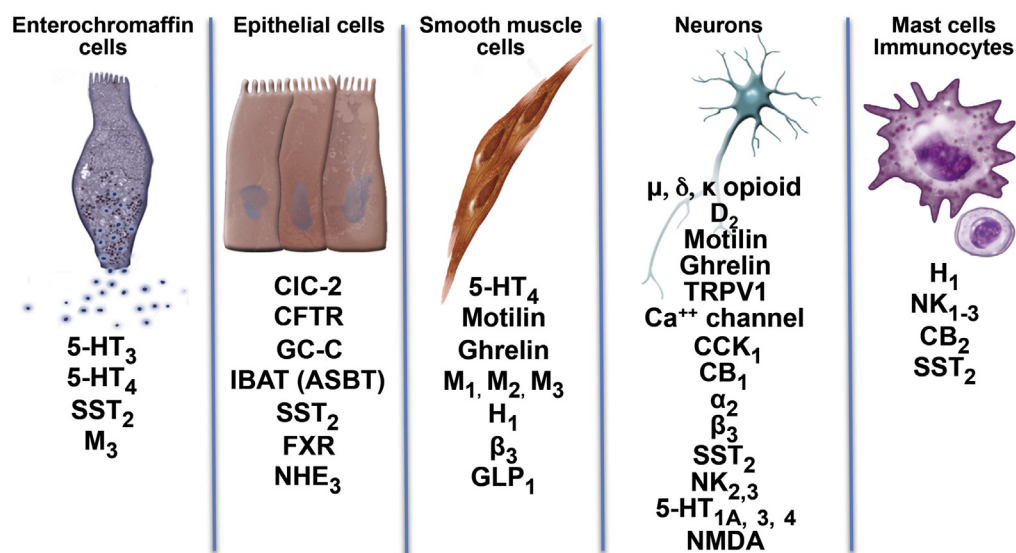


Figure 4. Localization and nature of major targeted receptors in the treatment of functional bowel disorders. α₂, alpha-2 adrenoceptor; α_{2δ}, calcium channel α_{2δ}, subunit; β₃, beta adrenoceptor 3; CB₂, cannabinoid receptor 2; CCK₁, cholecystokinin receptor 1 (or A); CB₁, cannabinoid receptor 1; CIC₂, chloride channel 2; D₂, dopamine receptor 2; FXR, farnesoid X receptor; GHSR1a, ghrelin receptor; GLP₁, glucagon-like peptide1 receptor; H₁, histamine receptor 1; 5-HT₃, 5HT₄, 5-HT_{1A}, serotonin receptors; IBAT, ileal bile acid transporter; M₁, M₃, muscarinic receptors 1 and 3; M₃, muscarinic receptor 3; Mot-R, motilin receptor; NHE₃, Na⁺/H⁺ exchanger receptor 3; NK₂, NK₃, tachykinin receptor 2 and 3; NMDA, N-methyl-D-aspartate receptor; SST₂, somatostatin receptor 2; TRPV1, transient receptor potential vanilloid 1.

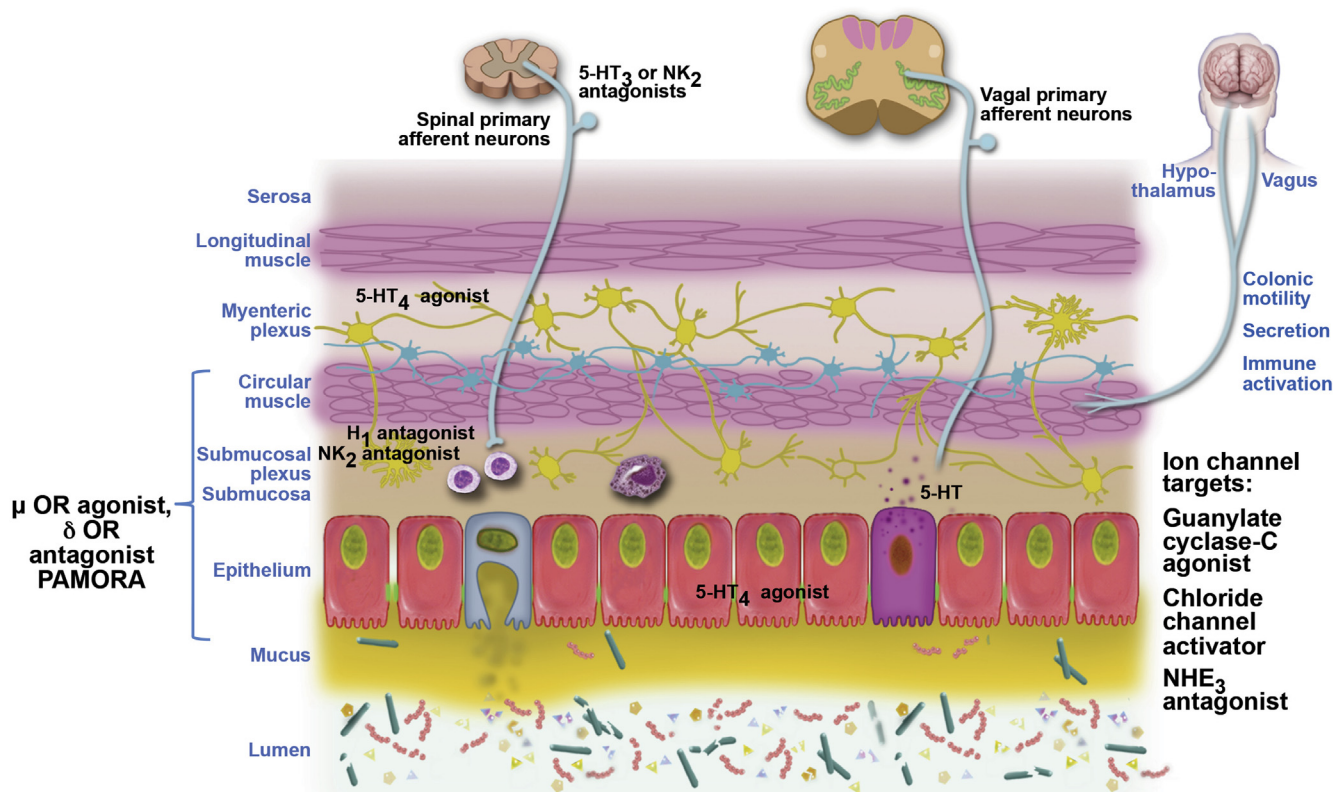


Figure 5. Site of action of different classes of medications on the brain–gut axis to alter colonic motility, secretion, immune activation, and sensation. For example, the sites of action of different drug classes are shown in the myenteric plexus, submucosal plexus and ion channels or receptors in enterocytes. H, histamine; 5-HT, serotonin; NHE, sodium-hydrogen exchanger; NK, neurokinin; OR, opioid receptor; PAMORA = peripherally active mu-opioid receptor antagonist. Adapted from Camilleri,²⁶⁸ with permission.

been questioned.⁴⁶ The occurrence of tachyphylaxis with erythromycin and some motilides (eg, ABT-229) may also be an important factor.⁹⁶ A novel motilin receptor agonist (that does not appear to be associated with tachyphylaxis) is the experimental drug, camicinal.⁹⁷ It is efficacious in vitro⁹⁸ and has been shown to induce phasic contractions and increase gastrointestinal motility in conscious dogs.⁹⁹

Acetylcholinesterase inhibitor. Acotiamide is an acetylcholinesterase inhibitor that was recently approved in Japan for the treatment of FD. In phase 2 trials conducted in Europe, United States, and Japan, acotiamide had beneficial effects in FD, particularly for meal-related FD symptoms, such as postprandial fullness, upper abdominal bloating, and/or early satiation. A 4-week, phase 3 trial conducted in Japan in patients with postprandial distress syndrome confirmed the efficacy of acotiamide, 100 mg 3 times a day, in meal-related symptoms (ie, postprandial fullness, upper abdominal bloating and early satiation) compared with placebo.^{100–102}

New Drugs for Treatment of Gastroparesis and Functional Dysplasia

Ghrelin agonists: RM-131. TZP-101 (ulimorelin, an intravenous formulation) and TZP-102 (oral) were not consistently efficacious in early trials.^{103–108}

Relamorelin, a pentapeptide synthetic ghrelin agonist, has a longer plasma half-life and >100 times greater potency than native ghrelin in reversing ileus in rats and primates. In a randomized, placebo-controlled single-dose study, relamorelin accelerated gastric emptying in type 2 diabetes mellitus patients with gastrointestinal cardinal symptoms and prior documentation of delayed gastric emptying.¹⁰⁹ In a large (n = 204) 4-week, phase 2b study in patients with diabetic gastroparesis, relamorelin, 10 μg given subcutaneously twice daily, improved gastric emptying and reduced vomiting episodes.¹¹⁰ Larger studies with longer treatment duration for the assessment of symptom improvement in gastroparesis are warranted.

Motilin receptor agonists. Camicinal (GSK962040) is a small molecule, non-motilide motilin receptor agonist that selectively activates the motilin receptor in humans and has been evaluated to determine safety and tolerability in humans.¹¹¹ It is currently being investigated in phase 2 trials (NCT01262898).¹¹²

Motilin agonists may increase gastric tone or inhibit gastric accommodation and, potentially, worsen symptoms, even when gastric emptying improves.

Cholecystokinin. Cholecystokinin has multiple effects on gastrointestinal motility and secretion.¹¹³ Clinical usefulness of cholecystokinin-1 receptor antagonists, such as lorglumide and dexlorglumide, is uncertain.^{114,115}

Capsaicin. The transient receptor potential ion channel of the vanilloid type 1 (transient receptor potential cation channel, vanilloid member 1), expressed by primary afferent neurons, is a chemo- and thermoreceptor that may be up-regulated in some FGIDs.¹¹⁶ Long-term administration of capsaicin, which is a transient receptor potential cation channel, vanilloid member 1 agonist, was more effective than placebo in decreasing symptoms in FD.¹¹⁷

Cannabinoids. Cannabinoid CB1 receptors are expressed on nociceptive primary afferents and some enteric neurons. CB1 receptor agonists slow gastrointestinal transit in animals by inhibiting acetylcholine release. δ -9-Tetrahydrocannabinol has strong antiemetic properties and delays gastric emptying in humans.^{118,119} It is unclear whether the abuse potential of CB1 agonists would preclude regulatory approval for treatment of FGIDs.

Chronic Constipation and Irritable Bowel Syndrome With Constipation

Current drug treatments. A discussion of the large number of available laxatives for chronic constipation is beyond the scope of this article. Among treatments for IBS-C, there is one large randomized controlled trial of polyethylene glycol showing improvement of constipation, but not pain.¹²⁰

Novel drug developments. There are 3 drug categories under development for treating chronic idiopathic constipation and IBS-C: 5-HT₄ receptor agonists, intestinal secretagogues, and bile acid modulators. Medications are being developed for specific treatment of opioid-induced constipation (OIC). Enhancing coordinated motor function is conceptually attractive, based on the demonstration of increased but uncoordinated motility, or retrograde or nonpropagated colonic contractility in disorders associated with constipation.^{121,122}

5-Hydroxytryptamine type 4 receptor agonists. 5-HT is an important neurotransmitter and paracrine signaling molecule involved in gastrointestinal secretion, sensation, and motility.¹²³ 5-HT₄ receptors are expressed by enteric neurons and in the heart. 5-HT₄ receptor agonists facilitate fast excitatory cholinergic synaptic transmission between enteric neurons, which stimulates gastrointestinal motility and secretion.^{34,77} Activation of colonic mucosal 5-HT₄ receptors can inhibit visceral hypersensitivity in rodents.¹²⁴

Prucalopride, a new 5-HT₄ receptor agonist, has >150-fold greater selectivity for the 5-HT₄ receptors than for the I_{Kr} channel and other 5-HT receptors.¹²⁵ Prucalopride, mosapride, and 3 other 5-HT₄ receptor agonists (velusetrag, naronapride, and YKP10811) in recent and current development, including human trials are summarized in [Supplementary Table 3](#). With high intrinsic activity and great specificity at intestinal 5-HT₄ receptors and with low intrinsic activity in cardiac muscle, these drugs have greater cardiovascular safety in comparison with older 5-HT₄ agonists.¹²⁵

There is considerable evidence supporting prucalopride's pharmacodynamic and clinical efficacy and safety

in patients with chronic constipation.^{126–132} Prucalopride did not show significant adverse effects in a study of elderly patients.¹³³ Doses of 2 mg per day in adults and 1 mg per day in the elderly were approved for chronic constipation by the European Medicines Agency and a number of other regulatory bodies outside the United States.

Velusetrag and naronapride are in development stages (see [Supplementary Table 3](#)).^{134–136}

YKP10811 is a 5-HT₄ receptor agonist that enhances colonic transit and improves stool consistency, and it reduced pain in an animal model of IBS.^{137,138}

Intestinal Cl[−] secretagogues. Cl[−] secretagogues enter enterocytes through the basolateral Na⁺-K⁺-2Cl[−] co-transporter. Na⁺ and K⁺ are then exported through the Na⁺/K⁺, ATPase, and KCNQ1/KCNE3 heteromeric K⁺ channels. Cl[−] secretion in the apical membrane of epithelial cells occurs through cystic fibrosis transmembrane regulator (CFTR) and ClC-2 Cl[−] channels¹³⁹ and is activated by intracellular Ca²⁺ and cyclic guanosine monophosphate (cGMP).

Lubiprostone and linaclotide are approved drugs, while plecanatide and tenapanor are still in drug development ([Supplementary Table 4](#)).¹⁴⁰

Lubiprostone is a bicyclic fatty acid, most closely related in structure to 15-keto-13,14-dihydro-PGE1, without the functional characteristics of PGE1.^{141,142} It stimulates intestinal Cl[−] secretion through apical membrane ClC-2 channels and CFTR¹⁴³; the action on CFTR is still controversial, with recent data suggesting CFTR is not a target of lubiprostone at relevant concentrations.¹⁴⁴ Lubiprostone has demonstrated efficacy in chronic constipation (24 μ g bid) and in IBS-C (8 μ g bid), and is approved by the US Food and Drug Administration (FDA) and several other countries.^{143,145–150} Lubiprostone is also approved for treatment of OIC (discussed in the section Other Medications for OIC).

Linaclotide and plecanatide activate guanylate cyclase-C (GC-C) receptors in intestinal epithelium, resulting in the elevation of cGMP intracellularly and extracellularly. This receptor is the target for heat-stable enterotoxin (STa) of *Escherichia coli*. Activation of GC-C results in stimulation of chloride and bicarbonate secretion through cGMP-dependent phosphorylation of CFTR, resulting in the opening of chloride channels, and it results in inhibition of Na⁺ absorption through blockade of an apical Na⁺/H⁺ exchanger.^{151,152} The principal effector of ion transport is cGMP-dependent protein kinase type II. In addition to the secretory effects, linaclotide induces extracellular release of cGMP that inhibited visceral nociceptors.¹⁵³ Linaclotide accelerates colonic transit, enhances intestinal secretion, and improves symptoms of constipation and abdominal pain in phase 2b and phase 3 trials of patients with chronic constipation and IBS-C.^{154–162} It is approved for the treatment of IBS-C (290 μ g/d) by the FDA, the European Medicines Agency, Health Canada, COFEPRIS (Mexico), and the Swiss Agency for Therapeutic Products (Swissmedic), and for the treatment of chronic constipation (145 μ g/d) by the FDA, Health Canada, and COFEPRIS (Mexico).

Plecanatide is another GC-C currently being developed for IBS-C and chronic constipation.¹⁶³ In a large (n = 946)

12-week, phase 2b study, plecanatide was effective in treating the symptoms of constipation, particularly at the highest dose (3 mg once daily).¹⁶⁴

Tenapanor is an inhibitor of **sodium-hydrogen exchanger 3** that blocks absorption of Na^+ through the **sodium-hydrogen exchanger 3** transporter. In a phase 2b clinical trial in IBS-C, tenapanor, 50 mg twice daily, increased spontaneous bowel movements responder rate and was well tolerated.¹⁶⁵

Bile Acid Modulation

Delivery of bile acids into the colon due to inadequate (less than the normal approximately 95%) ileal reabsorption results in secretory diarrhea by increasing permeability, activating adenylate cyclase, and increasing colonic motility.¹⁶⁶ It is estimated that approximately 25% of patients diagnosed with IBS-D actually have bile acid malabsorption.¹⁶⁷ Treatment of these patients with bile acid sequestrants may be helpful, although well-controlled studies are lacking (see in subsection Bile acid binders).

Given the pharmacologic effects of bile acids on GI function, a novel approach for treatment of chronic constipation involves selective inhibition of the ileal bile acid transporter (also called apical Na^+ -dependent bile acid transporter) with elobixibat, resulting in greater delivery of bile acids to the colon. This drug accelerated colonic transit, significantly improved stool consistency, constipation rating, ease of stool passage, and reduction of straining; and significantly increased stool frequency and improved constipation-related symptoms over 8 weeks of treatment.^{168,169} Long-term exposure of patients to high colonic bile acids after partial ileal bypass for hyperlipidemia is not associated with increased prevalence of colorectal cancer at 5-year or 25-year follow-up.¹⁷⁰

Peripherally Acting μ -Opioid Receptor Antagonists in Opioid-Induced Constipation

Peripherally acting μ -opioid receptor antagonists, such as N-methylnaltrexone and naloxegol are designed to reverse the peripheral effects of opioids without compromising central opioid analgesia.

Although efficacy in OIC has been demonstrated,^{171,172} alvimopan has only been approved by the FDA for the short-term treatment of postoperative ileus because of a suspected increase of cardiovascular events in one long-term trial.

Methylnaltrexone is currently available in subcutaneous injection and approved for use in palliative care patients and chronic noncancer pain. An oral form of methylnaltrexone also appears to be effective for OIC, but is not yet approved by regulators.

Naloxegol is an oral therapy that is approved by the FDA for treatment of OIC in adult patients with chronic noncancer pain. In 2 large phase 3 clinical trials, 25 mg once daily of naloxegol significantly improved OIC response rates compared with placebo. Naloxegol, 12.5 mg once-daily dose, also showed efficacy, though it met statistical significance in only 1 of the 2 trials.^{173,174} Other peripherally acting

μ -opioid receptor antagonists in clinical development are naldemedine and TD-1211. These agents are summarized in **Supplementary Table 5**.

Other Medications in Opioid-Induced Constipation

Prucalopride,¹⁷⁵ lubiprostone,^{176,177} and the experimental GC-C agonist, SP-333,¹⁷⁸ are also potentially efficacious in treatment of OIC. Of these, only lubiprostone at a dose of 24 μg twice daily is approved by the FDA for the treatment of OIC.

Chronic Diarrhea and Diarrhea-Predominant Irritable Bowel Syndrome

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 alterations of the intestinal content (bile and short-chain fatty acids or the microbiome) and barrier function.

Current Drug Treatments for Chronic Diarrhea and Diarrhea-Predominant Irritable Bowel Syndrome

μ -Opioid receptor agonists. The μ -opioid receptor agonist loperamide has limited ability to penetrate the blood–brain barrier and inhibits secretion, reduces colonic transit, and increases resting anal sphincter tone.¹⁷⁹ In contrast to loperamide, which is available over-the-counter, diphenoxylate can cross the blood–brain barrier and, therefore, is combined with atropine to reduce abuse potential and is available only by prescription. While both μ -opioid receptor agonists reduce diarrhea, particularly acute diarrhea, neither has been subjected to high-quality clinical trials in IBS-D.¹⁸⁰ In the case of loperamide, several small studies have shown improvement in diarrhea-related symptoms associated with IBS-D, but have not evaluated individual or global symptoms in IBS-D. Adverse effects are rare, but include bladder dysfunction, glaucoma, and tachycardia.

Bile acid binders. Bile acid binders (cholestyramine, 4 g 3 times daily, and off-label colesevelam, 625 mg, 1–3 tablets bid) are indicated for bile acid diarrhea and those with IBS-D and bile acid diarrhea.¹⁸¹ Cholestyramine granules are often poorly tolerated, owing to poor taste and sticking to teeth.

5-Hydroxytryptamine type 3 receptor antagonists. 5-HT₃ receptor antagonists, such as alosetron, delay orocecal and colonic transit times and reduce colonic compliance, but not sensitivity to isobaric distention.^{182–184} Several clinical studies confirmed the efficacy of alosetron in IBS-D.²⁹ Alosetron was temporarily withdrawn due to suspected association with ischemic colitis¹⁸⁵; it is now available for restricted use only in the United States. Other 5-HT₃ antagonists (such as ondansetron), approved for the treatment of chemotherapy-induced nausea and vomiting, are

often used as off-label treatment for IBS-D. Ondansetron was shown to be effective in IBS-D.¹⁸⁶

Psychoactive agents. Psychoactive agents with anticholinergic effects are commonly used off label in IBS-D. These are reviewed elsewhere (Biopsychosocial Aspects of FGIDs).

Novel Drugs in Development or Recently Approved for Chronic Diarrhea and Diarrhea-Predominant Irritable Bowel Syndrome

5-Hydroxytryptamine type 3 receptor antagonists. Ramosetron slows colonic transit and reduces pain sensation in animal models subjected to stress.^{187,188} Ramosetron (5 μ g and 10 μ g) was tested in 4 studies of approximately 1300 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.^{189–193} Ramosetron, 5 μ g once daily, is as effective as the antispasmodic, mebeverine, 135 mg 3 times daily, in male patients with IBS-D.¹⁹⁴ To date, ramosetron has not caused ischemic colitis.

Nonabsorbable antibiotics. Rifaximin is a minimally absorbed antibiotic that is FDA-approved for treating traveler's diarrhea and hepatic encephalopathy; it is also approved for IBS-D. In 2 large, phase 3 trials, rifaximin, 550 mg tid for 2 weeks, significantly improved adequate relief of IBS symptoms and abdominal bloating, as well as the FDA Responder End point for IBS-D during the 10 weeks after treatment. Patients receiving rifaximin had an approximately 10% greater likelihood of being a responder for adequate relief of IBS symptoms and bloating than patients receiving placebo.¹⁹⁵ A meta-analysis that included 3 additional clinical trials also found improvement of global IBS symptoms and bloating, but no significant effect on bowel function.¹⁹⁶ Retreatment with rifaximin is also efficacious.¹⁹⁷

Mixed μ -opioid receptor agonist and δ -opioid receptor antagonist (eluxadoline). The combination of mixed μ -opioid receptor agonist and δ -opioid receptor antagonist eluxadoline has been studied in phase 2 and two phase 3 clinical trials for 26 and 52 weeks in IBS-D patients.^{198,199} A greater percentage of patients receiving 100 mg eluxadoline met responder definitions proposed by regulatory agencies, compared with patients receiving placebo. Few cases of pancreatitis and sphincter of Oddi spasm were reported in patients at high risk (eg, history of alcohol abuse or history cholecystectomy). The drug is approved by the FDA, and risk–benefit is being carefully watched.

Serotonin synthesis inhibition. LX-1031 is an oral tryptophan hydroxylase (TPH) inhibitor that reduces synthesis of 5-HT peripherally,²⁰⁰ as it does not cross the blood–brain barrier and, thus, avoids risk of depression. In a 4-week, phase 2 trial, LX-1031 dose-dependently reduced 5-HT, and there was correlation with adequate relief and improved stool consistency with the 1000-mg dose group.²⁰¹ There appears to be wide variability in effect of the drug, possibly related to *TPH1* polymorphisms and the observation that 15 of 43 patients who showed a fall in urinary 5-hydroxyindoleacetic acid excretion responded

better than those who did not show a fall in urine 5-hydroxyindoleacetic acid. No phase 3 trials have been reported to date.

Tachykinin receptor antagonists. Three distinct receptors, neurokinin-1, neurokinin-2, and neurokinin-3, mediate the biological effects of endogenous tachykinins, substance P, and neurokinin A and B in the gastrointestinal tract. Through their locations on intrinsic nerves, extrinsic nerves, inflammatory cells, and smooth muscle, inhibition of tachykinin receptors has the potential to inhibit motility, sensitivity, secretion, and inflammation in the gastrointestinal tract.^{202,203} Tachykinin 1 receptor antagonists also have antiemetic properties.²⁰²

An NK₂ receptor antagonist, ibodutant (1, 3, and 10 mg, once daily), was compared with placebo for 8 weeks in 559 patients with IBS-D. There was significant effect of the 1 mg/d dose in females in a prespecified analysis.²⁰⁴ Ibodutant is currently being evaluated in phase 3 studies in female patients with IBS-D.

Muscarinic type 3 receptor antagonists. There are beneficial pharmacodynamic effects of this class of medications that can relieve chronic diarrhea: darifenacin retarded human small bowel and colonic transit, otilonium reduced rectal sensation, and hyoscine (nonselective) reduced enterocyte secretion.^{205–207} Clinical trials show greatest effect of otilonium on abdominal sensation rather than bowel dysfunction in IBS.^{208,209} A cross-over design trial showed similar efficacy of solifenacin and ramosetron.²¹⁰

Carbon adsorbent: AST-120. AST-120 consists of porous, spherical carbon particles that adsorb substances in the lumen that can cause secretion (eg, bacterial toxins and bile acid products).²¹¹ In a phase 2, 8-week treatment trial, AST-120 transiently reduced pain and bloating in 115 patients with IBS-D or IBS-alternating; however, stool consistency was not significantly improved.²¹²

Mast cell stabilizers. The rationale for this class of medications is supported by mast cell activation and hyperplasia in the jejunal mucosal biopsies in IBS-D patients.²¹³

Disodium cromoglycate reduced release of tryptase from jejunal biopsies, reduced expression of toll-like receptor 2 and 4, and improved bowel function in IBS-D.^{214,215} In an earlier study of 66 IBS-D patients with food intolerance assessed by skin prick test, disodium cromoglycate, 250 mg 4 times daily, plus exclusion diet, was associated with prolonged symptomatic benefit compared with exclusion diet alone.²¹⁶

Ketotifen, a mast cell stabilizer with antihistamine effects,²¹⁷ had beneficial effects on pain, bloating, flatulence, diarrhea, quality of life, sleep, and sexual functioning, but it induced sedation and drowsiness. The precise mechanism of action is unclear, because increased mast cell tryptase release from rectal biopsies was not observed in the IBS patients and histamine and tryptase release were not altered by ketotifen.²¹⁷

Mesalamine derivatives. Mesalamine reduced total colonic mucosal immunocytes and mast cells and mucosal release of interleukin 1 β , histamine, and tryptase in IBS

patients.²¹⁸ Clinical efficacy is unclear: 2 of 4 small clinical trials suggest it may be beneficial in IBS patients, including some benefit on bowel function.^{218–221} Two recent larger trials both failed to demonstrate significant efficacy in IBS-D.^{222,223}

Farnesoid X receptor agonist obeticholic acid. In an open-label trial, obeticholic acid improved stool consistency and bowel function index in patients with bile acid diarrhea.²²⁴

Glutamine. Patients with IBS-D have increased permeability, and symptomatic IBS patients have decreased intestinal glutamine synthetase levels.^{225,226} In a preliminary report of a placebo-controlled trial of 10 g glutamine tid in 61 IBS-D patients with high intestinal permeability and reduced claudin-1 expression in intestinal biopsies,²²⁷ the glutamine arm was associated with improved abdominal pain, bloating, and diarrhea, and restored intestinal permeability.

Visceral Sensation, Functional Abdominal Pain, and Irritable Bowel Syndrome—Related Pain

Some medications that are discussed here because of their efficacy in the treatment of bowel dysfunction may also be independently efficacious in the relief of pain.^{228,229}

Current Treatments

Antispasmodics. Muscarinic receptor antagonists and smooth muscle relaxants are used in most countries for the treatment of IBS. Meta-analysis suggests they are superior to placebo in IBS-related pain,^{230,231} although the quality of trials has been questioned.

Guanylate cyclase-C agonist. Linaclotide has demonstrated improvement in abdominal pain in 2 large, phase 3 studies in IBS-C, with one trial extending treatment out to 26 weeks.^{157,232}

Psychoactive agents. Antidepressants are commonly used to treat chronic functional abdominal pain syndromes, and a Cochrane meta-analysis suggests efficacy of antidepressants in IBS.^{233,234} In randomized controlled trials, low-dose tricyclic antidepressants have demonstrated some improvement in global improvement in abdominal pain.²³⁴ However, the quality of the evidence is considered low²³⁵ due to the generally weak trial designs.

There is no approval of any psychoactive drug for specific IBS therapy, but some agents, such as amitriptyline, have approval in many countries for neuropathic pain therapy.

Future Treatments for Centrally Mediated Abdominal Pain or Irritable Bowel Syndrome—Related Pain

Pregabalin. The $\alpha 2\delta$ -ligand pregabalin was shown to increase distension sensory thresholds to normal levels in IBS patients with rectal hypersensitivity.²³⁶ Studies evaluating effects on clinical symptom end points in centrally mediated abdominal pain syndrome, formerly known in

Rome III as functional abdominal pain syndrome, are awaited (ClinicalTrials.gov Identifier: NCT00977197).

Histamine1-receptor antagonists. A nonsedating, histamine H1-receptor antagonist, ebastin, was tested in a 12-week, placebo-controlled trial of 55 patients²³⁷ and was associated with considerable relief of symptoms in 46% of the ebastin group and 12% of the placebo group. There were also lower average abdominal pain scores with ebastin.

Other Agents for Motility and Functional Gastrointestinal Disorders

[Supplementary Table 6](#) and [Figure 4](#) summarize new or promising drugs targeting motility and secretion.

Role of Biomarkers in Individualizing Therapy in Irritable Bowel Syndrome

The article “Design of Treatment Trials” addresses the potential of biomarkers in individualizing therapy for IBS. There have been a number of reviews discussing the potential role of biomarkers in IBS.^{238–240} Biomarkers are objectively measurable indicators of normal or pathologic processes or pharmacologic responses to a therapeutic intervention.²⁴¹

Biomarkers should meet basic requirements, such as a reasonable diagnostic performance, noninvasiveness, reproducibility, low costs, and applicability on a large scale. Biomarkers may identify pathophysiologic mechanisms that are present only in subsets of patients. Clearly, the multifactorial nature of IBS will necessitate the development of biomarkers for subgroups, just as bowel function subtype can identify only a subgroup of patients with IBS-C, IBS-D, or IBS with mixed bowel habits.

For example, the biomarker for total fecal bile acid excretion over 48 hours (low ⁷⁵SeHCAT [selenium-75 labeled homocholic acid taurocholate] retention, or high fecal bile acid excretion) may allow selection of IBS-D patients to receive interventions that alter bile acid excretion, such as bile acid sequestrants. The proof of this principle is demonstrated by the recent observation in IBS-D patients with high fecal bile acid excretion that colesevelam, 1.875 g bid, improved stool consistency and increased hepatic bile acid synthesis, thereby avoiding worsening of steatorrhea.²⁴² Future research may target patients with specific pathophysiology (eg, increased expression of mast cells, high mucosal serotonin levels, high fecal proteases, alterations in the microbiome, or barrier function).

Supplementary Material

Note: The first 50 references associated with this article are available below in print. The remaining references accompanying this article are available online only with the electronic version of the article. Visit the online version of *Gastroenterology* at www.gastrojournal.org, and at <http://dx.doi.org/10.1053/j.gastro.2016.02.029>.

References

- Rouzade ML, Fioramonti J, Bueno L. A model for evaluation of gastric sensitivity in awake rats. *Neurogastroenterol Motil* 1998;10:157–163.
- Mori T, Kawano K, Shishikura T. 5-HT₃-receptor antagonist inhibits visceral pain differently in chemical and mechanical stimuli in rats. *J Pharmacol Sci* 2004;94:73–76.
- Louvel D, Delvaux M, Staumont G, et al. Intracolonic injection of glycerol: a model for abdominal pain in irritable bowel syndrome? *Gastroenterology* 1996;110:351–361.
- Bouin M, Delvaux M, Blanc C, et al. Intrarectal injection of glycerol induces hypersensitivity to rectal distension in healthy subjects without modifying rectal compliance. *Eur J Gastroenterol Hepatol* 2001;13:573–580.
- Morteau O, Hachet T, Caussette M, et al. Experimental colitis alters visceromotor response to colorectal distension in awake rats. *Dig Dis Sci* 1994;39:1239–1248.
- Al Chaer ED, Kawasaki M, Pasricha PJ. A new model of chronic visceral hypersensitivity in adult rats induced by colon irritation during postnatal development. *Gastroenterology* 2000;119:1276–1285.
- Gue M, Rio-Lacheze C, Eutamene H, et al. Stress-induced visceral hypersensitivity to rectal distension in rats: role of CRF and mast cells. *Neurogastroenterol Motil* 1997;9:271–279.
- Coelho AM, Fioramonti J, Bueno L. Systemic lipopolysaccharide influences rectal sensitivity in rats: role of mast cells, cytokines, and vagus nerve. *Am J Physiol* 2000;279:G781–G790.
- Barreau F, Cartier C, Ferrier L, et al. Nerve growth factor mediates alterations of colonic sensitivity and mucosal barrier induced by neonatal stress in rats. *Gastroenterology* 2004;127:524–534.
- Woodworth RS, Sherrington CS. A pseudo affective reflex and its spinal path. *J Physiol* 1904;31:234–243.
- Kamp EH, Jones RC III, Tillman SR, et al. Quantitative assessment and characterization of visceral nociception and hyperalgesia in mice. *Am J Physiol* 2003;284:G434–G444.
- Ozaki N, Bielefeldt K, Sengupta JN, et al. Models of gastric hyperalgesia in the rat. *Am J Physiol* 2002;283:G666–G676.
- Ness TJ, Gebhart GF. Colorectal distension as a noxious visceral stimulus: physiologic and pharmacologic characterization of pseudo affective reflexes in the rat. *Brain Res* 1988;450:153–169.
- Su X, Julia V, Gebhart GF. Effects of intracolonic opioid receptor agonists on polymodal pelvic nerve afferent fibers in the rat. *J Neurophysiol* 2000;83:963–970.
- Booth CE, Kirkup AJ, Hicks GA, et al. Somatostatin sst(2) receptor-mediated inhibition of mesenteric afferent nerves of the jejunum in the anesthetized rat. *Gastroenterology* 2001;121:358–369.
- Fioramonti J, Gaultier E, Toulouse M, et al. Intestinal antinociceptive behaviour of NK₃ receptor antagonism in conscious rats: evidence to support a peripheral mechanism of action. *Neurogastroenterol Motil* 2003;15:363–369.
- Johnson AC, Myers B, Lazovic J, et al. Brain activation in response to visceral stimulation in rats with amygdala implants of corticosterone: an fMRI study. *PLoS One* 2010;5:e8573.
- McLean PG, Picard C, Garcia-Villar R, et al. Effects of nematode infection on sensitivity to intestinal distension: role of tachykinin NK₂ receptors. *Eur J Pharmacol* 1997;337:279–282.
- Gue M, Junien JL, Bueno L. The kappa agonist fedotazine modulates colonic distention-induced inhibition of gastric motility and emptying in dogs. *Gastroenterology* 1994;107:1327–1334.
- Tjeerdema HC, Smout AJ, Akkermans LM. Voluntary suppression of defecation delays gastric emptying. *Dig Dis Sci* 1993;38:832–836.
- Lee KJ, Tack J. Duodenal implications in the pathophysiology of functional dyspepsia. *J Neurogastroenterol Motil* 2010;16:251–257.
- Gue M, Peeters T, Depoortere I, et al. Stress-induced changes in gastric emptying, postprandial motility, and plasma gut hormone levels in dogs. *Gastroenterology* 1989;97:1101–1107.
- Al-Qarawi AA, Ali BH, Al-Mougy SA, et al. Gastrointestinal transit in mice treated with various extracts of date (*Phoenix dactylifera* L.). *Food Chem Toxicol* 2003;41:37–39.
- Broccardo M, Improta G, Tabacco A. Central effect of SNC 80, a selective and systemically active delta-opioid receptor agonist, on gastrointestinal propulsion in the mouse. *Eur J Pharmacol* 1998;342:247–251.
- Williams CL, Peterson JM, Villar RG, et al. Corticotropin-releasing factor directly mediates colonic responses to stress. *Am J Physiol* 1987;253:G582–G586.
- Kadowaki M, Wade PR, Gershon MD. Participation of 5-HT₃, 5-HT₄, and nicotinic receptors in the peristaltic reflex of guinea pig distal colon. *Am J Physiol* 1996;271:G849–G857.
- Cann PA, Read NW, Holdsworth CO. What is the benefit of coarse wheat bran in patients with irritable bowel syndrome? *Gut* 1984;25:168–173.
- Cann PA, Read NW, Holdsworth CD, et al. Role of loperamide and placebo in management of irritable bowel syndrome. *Dig Dis Sci* 1984;29:239–247.
- Cremonini F, Delgado-Aros S, Camilleri M. Efficacy of alosetron in irritable bowel syndrome: a meta-analysis of randomized controlled trials. *Neurogastroenterol Motil* 2003;15:79–86.
- Muller-Lissner SA, Fumagalli I, Bardhan KD, et al. Tegaserod, a 5-HT₄ receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. *Aliment Pharmacol Ther* 2001;15:1655–1666.
- Novick J, Miner P, Krause R, et al. A randomized, double-blind, placebo-controlled trial of tegaserod in female patients suffering from irritable bowel syndrome with constipation. *Aliment Pharmacol Ther* 2002;16:1877–1888.

32. Kellow J, Lee OY, Chang FY, et al. An Asia-Pacific, double blind, placebo controlled, randomised study to evaluate the efficacy, safety, and tolerability of tegaserod in patients with irritable bowel syndrome. *Gut* 2003;52:671–676.
33. Emmanuel AV, Roy AJ, Nicholls TJ, et al. Prucalopride, a systemic enterokinetic, for the treatment of constipation. *Aliment Pharmacol Ther* 2002;16:1347–1356.
34. Bouras EP, Camilleri M, Burton DD, et al. Prucalopride accelerates gastrointestinal and colonic transit in patients with constipation without a rectal evacuation disorder. *Gastroenterology* 2001;120:354–360.
35. Andresen V, Camilleri M, Busciglio IA, et al. Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. *Gastroenterology* 2007;133:761–768.
36. Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol* 2012;107:1702–1712.
37. Rao S, Lembo AJ, Shiff SJ, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. *Am J Gastroenterol* 2012;107:1714–1724.
38. von der Ohe MR, Camilleri M, Kvols LK, et al. Motor dysfunction of the small bowel and colon in patients with the carcinoid syndrome and diarrhea. *N Engl J Med* 1993;329:1073–1078.
39. Plourde V, Lembo T, Shui Z, et al. Effects of the somatostatin analogue octreotide on rectal afferent nerves in human. *Am J Physiol* 1993;265:G751.
40. Hasler WL, Soudah HC, Owyang C. A somatostatin analogue inhibits afferent pathways mediating perception of rectal distention. *Gastroenterology* 1993;104:1390–1397.
41. Hasler W, Soudah HC, Owyang C. Somatostatin analog inhibits afferent response to rectal distention in diarrhea-predominant irritable bowel patients. *J Pharmacol Exp Ther* 1994;268:1206–1211.
42. Bradette M, Delvaux M, Staumont G, et al. Octreotide increases thresholds of colonic visceral perception in IBS patients without modifying muscle tone. *Dig Dis Sci* 1994;39:1171–1178.
43. Lembo T, Naliboff BD, Martin K, et al. Irritable bowel syndrome patients show altered sensitivity to exogenous opioids. *Pain* 2000;87:137–147.
44. Coffin B, Farmachidi JP, Rueegg P, et al. Tegaserod, a 5-HT₄ receptor partial agonist, decreases sensitivity to rectal distension in healthy subjects. *Aliment Pharmacol Ther* 2003;17:577–585.
45. Sturm A, Holtmann G, Goebell H, et al. Prokinetics in patients with gastroparesis: a systematic analysis. *Digestion* 1999;60:422–427.
46. Maganti K, Onyemere K, Jones MP. Oral erythromycin and symptomatic relief of gastroparesis: a systematic review. *Am J Gastroenterol* 2003;98:259–263.
47. Janssen P, Harris MS, Jones M, et al. The relation between symptom improvement and gastric emptying in the treatment of diabetic and idiopathic gastroparesis. *Am J Gastroenterol* 2013;108:1382–1391.
48. Verhagen MA, Samsom M, Maes B, et al. Effects of a new motilide, ABT-229, on gastric emptying and postprandial antroduodenal motility in healthy volunteers. *Aliment Pharmacol Ther* 1997;11:1077–1086.
49. Talley NJ, Verlinden M, Snape W, et al. Failure of a motilin receptor agonist (ABT-229) to relieve the symptoms of functional dyspepsia in patients with and without delayed gastric emptying: a randomized double-blind placebo-controlled trial. *Aliment Pharmacol Ther* 2000;14:1653–1661.
50. Talley NJ, Verlinden M, Geenen DJ, et al. Effects of a motilin receptor agonist (ABT-229) on upper gastrointestinal symptoms in type 1 diabetes mellitus: a randomized, double-blind, placebo-controlled trial. *Gut* 2001;49:395–401.

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Conflicts of interest

The authors disclose no conflicts.

Glossary

Acetylcholinesterase: an enzyme (more precisely a hydrolase) that hydrolyzes acetylcholine.

Allodynia: a form of hypersensitivity with an abnormal pain response to an innocuous or non-noxious afferent signal.

ASBT: apical sodium dependent bile acid transporter.

Bioavailability: one of the main pharmacokinetic properties of a drug; it is the fraction of an administered dose of drug that reaches the systemic circulation, eg, after oral administration, with respect to the dose that would be available if the drug were given by the intravenous route (which implies 100% bioavailability).

Biomarker: objectively measurable indicator of normal or pathological processes, or pharmacological responses to a therapeutic intervention; it may be used for diagnostic purposes or to evaluate drug activity/efficacy.

Blood–brain barrier: a highly selective barrier that separates the circulating blood from the extracellular fluid in the central nervous system.

CYP450: cytochrome P450 enzyme system, responsible for drug metabolism.

FXR: farnesoid X receptor, also known as bile acid receptor; it is highly expressed in the liver and in the intestine.

G proteins: G proteins (guanine nucleotide-binding proteins) are a family of proteins acting as molecular switches in cells; they are involved in the transmission of signals from stimuli arising outside a cell to the inside.

hERG: human ether-a-go-go related gene, encoding a potassium channel responsible for cardiac repolarization; its blockade may cause arrhythmias.

5-HT: serotonin, or 5-hydroxytryptamine.

Hyperalgesia: increased sensitivity to pain.

Hypersensitivity: enhanced sensitivity.

Intestinal permeability: a normal function of the gut wall, which exhibits “permeability,” ie, allows nutrients to pass through the gut, while also maintaining a barrier function to keep away potentially harmful substances (such as antigens).

PAMORA: peripherally active μ -opioid receptor antagonist.

Pharmacodynamics: the branch of pharmacology studying the mechanisms of drug action and the relationship between a drug concentration and its effect.

Pharmacogenetics: the study of individual variations in DNA sequence related to drug response.

Pharmacogenomics: the study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual, or population levels (a broader term when compared to pharmacogenetics).

Pharmacokinetics: the branch of pharmacology studying the fate of substances (absorption, distribution, metabolism, and elimination) administered externally to a living organism: substances may be drugs as well as toxic substances.

Polymorphism: natural variations in a gene, DNA sequence, or chromosome that have no adverse effects on the individual and occur with fairly high frequency in the

general population. However, single nucleotide polymorphisms in the human genome may correlate with disease, drug response, and other phenotype.

Pseudo-affective response: response to nociceptive stimuli mediated by brainstem or spinal reflexes that cease when the noxious stimulus is terminated, eg, a change in blood pressure after a noxious stimulus is a pseudo-affective response widely used to assess visceral pain.

Psychoactive: of an agent affecting the central nervous system.

Reverse pharmacokinetics: in contrast to classical pharmacokinetics (which is performed well in advance of clinical development of a new drug), reverse pharmacokinetics is based on the thorough pharmacokinetics assessment of natural medicines, for which purported clinical benefits are documented by historical use, while target tissues and mechanisms remain unclear; its goal is to provide clues for the target identification and mechanistic understanding of pharmacodynamics.

SERT: serotonin transporter.

SNRI: serotonin-norepinephrine reuptake inhibitor.

SSRI: selective serotonin reuptake inhibitor.

SPECT: single-photon emission computed tomography.

Toxicology: the branch of pharmacology studying the adverse effects of chemicals on living organisms.

Preclinical Pharmacology, Toxicology, and Concepts in Development of Novel Therapeutic Agents

This section outlines some general pharmacodynamic, pharmacokinetic, and safety aspects that are important for the development of new drugs for FGIDs.

The Pharmacodynamic Target

Drug selectivity. Selectivity refers to the ability of a compound to interact with only one receptor subtype, leaving other receptors unaffected at concentrations achieved at clinically used doses, thereby avoiding side effects.

Considerations of drug selectivity should appraise all biological effects of a drug, not just in the digestive tract. For example, cisapride was a partial 5-HT₄ receptor agonist,²⁴³ a 5-HT₃ receptor antagonist (both of which convey potentially beneficial GI effects), and a fairly potent hERG (human ether-a-go-go related gene) K⁺ channel blocker.²⁴⁴

Due to the multifactorial pathophysiology of FGIDs, single receptor modulating drugs might be less efficacious than balanced modulation of multiple targets, which may provide a superior therapeutic effect and side-effect profile compared with the action of a selective ligand.²⁴⁵ A key challenge in the design of a ligand with multiple actions is to achieve a balanced potency and activity at each target of interest and a suitable pharmacokinetic profile. The less selective a ligand is, the harder it is to predict toxicity or its mechanistic explanation. This may jeopardize the development and regulatory approval of less-selective ligands.

Because more than one mechanism may be responsible for the same symptom in FGIDs, the selective approach to

relieving symptoms or groups of symptoms (eg, pain and constipation or diarrhea) was efficacious in approximately 60% of patients with tegaserod or alosetron or linaclotide or lubiprostone.^{30,31,145,154,245} Diversity in underlying mechanisms rather than inadequate dosing is more likely the reason for lack of efficacy in approximately 40% of patients. Hence, there is the need to consider using multiple therapies or “designed” multiple ligands to enhance the benefit/risk ratio.

Pharmacodynamic vs Pathophysiologic Target

Theoretically, ideal new drugs should target the entire pathophysiologic mechanism(s) contributing to the functional disorder rather than only an individual part or a specific receptor. Thus, nonselective agents designed to modulate multiple targets contributing to the whole pathophysiologic process (eg, dysmotility, sensory disorder, and inflammation) would potentially be advantageous over highly selective medications addressing a single mechanism. Should appropriate patient subgroups be recruited to test the therapeutic properties of a medication, even if this might reduce the generalizability of the trial results? At the present time, there is no drug that addresses all the mechanisms underlying patients' symptoms. In the future, the selection of patients based on valid biomarkers (see section Pharmacogenetics in IBS) rather than symptoms would usher in an era of greater personalization of treatment based on the affected mechanism.

Concepts for developing functional gastrointestinal disorder drugs. There are at least 3 key aspects that deserve rethinking in FGID drug development. First, functional gut disorders have multifactorial pathophysiology, which should be addressed by designed multiple ligands.²⁴⁶ Second, by restricting the drug to the intraluminal compartment, systemic adverse effects are avoided. Peripheral restriction of the effects of the medication can be achieved by excluding penetration of the blood–brain barrier (eg, peripherally acting μ -opioid receptor antagonists or eluxadoline, a locally active μ -opioid receptor agonist and δ -opioid receptor antagonist). A third approach is to develop drugs acting exclusively in the GI tract and liver (eg, farnesoid X receptor agonists, such as obeticholic acid).

The gut microbiome is a target for therapeutic intervention^{247,248}; the microbiome may itself affect the actions of the drug, and drugs may alter the microbiome. Insight into the actions of lubiprostone¹⁴³ provides an example of possible interaction with the microbiome. In an ex vivo model, lubiprostone decreased the thickness of the inner mucus layer in both proximal and distal colon and, more importantly, caused qualitative changes of stool microbiome by increasing abundance of *Lactobacillus* and *Alistipes*, which theoretically reflect a more “protective” microbiome with anti-inflammatory properties.²⁴⁹ These findings are consistent with previous in vitro and in vivo data²⁵⁰ and suggest that active mucosal hydration functions as a primitive innate epithelial defense mechanism; and that intestinal microbiome could be a potential target in IBS.

Reverse pharmacokinetics (Figure 3) and reverse pharmacodynamics are innovative ways to develop new drugs,

especially those from natural sources.²⁵¹ Classical pharmacokinetics were designed to determine the desirable pharmacokinetic features of a new chemical entity to be developed for clinical use. However, for most natural compounds already used in traditional medicine, the molecular targets are unknown and, without exact knowledge, it is difficult to optimize the pharmacokinetic profile of drug candidates and fulfill current regulatory standards. The concept of “reverse pharmacokinetics” is based on the thorough pharmacokinetic assessment of natural medicines, for which purported clinical benefits are documented by historical use, while target tissues and mechanisms remain unclear.²⁵¹ Examples would be curcumin in inflammatory conditions or STW5 (Iberogast) in FD.²⁵² Thus, the purpose of reverse pharmacokinetics is to provide clues for target identification and mechanistic understanding of agents tested.

After oral administration, the drug's pharmacokinetics depend on intestinal and hepatic metabolism, as well as drug delivery to intestinal epithelia or specialized intestinal cells, such as M cells, goblet cells, and dendritic cells.^{253,254}

Safety Aspects

Apart from the standard safety evaluations of every new drug, 2 new concerns deserve special attention because of recent experience. Cisapride resulted in tachyarrhythmia associated with prolongation of the QT interval of the electrocardiogram due to blockade of the hERG K⁺ channels.²⁵⁵ Alosetron and cilansetron were associated with ischemic colitis in about 1 in 1000 patients.¹⁸⁵ Although these are very rare events, even a low risk may not be acceptable from a regulatory perspective for drugs that provide relief of nonfatal diseases, such as FGIDs. The drug development process should identify such undesired effects as early as possible.²⁵⁶ Finally, the potential for drug interactions is relevant, given the polypharmacy and frequent use of psychotropic agents (which often depend on CYP2D6 metabolism).

Pharmacogenetics in Irritable Bowel Syndrome

In addition to understanding the pathophysiology of IBS, insight into pharmacogenetics and, specifically, the manner in which genetic abnormalities influence drug activity, binding, and metabolism has become central to proposing control mechanisms in IBS and may impact the management of individual IBS patients.

Drug Metabolism and Pharmacogenetics

The enzymatic metabolism of drugs involves modifications of functional groups (phase I reactions, such as oxidation, dehydrogenation, and esterification) or conjugation with endogenous substituents (phase II reactions).²⁵⁷ The most common and most relevant drug modifications in IBS result from CYP2D6 metabolism, which is an example of phase I drug metabolism. There are distinct geographic variations of the CYP genes, suggesting that population

substructure can strongly affect the variation in pharmacogenetic loci⁶⁰ (Supplementary Table 7).

The number of functional alleles (≥ 3 , 2, 1, and 0) determines whether CYP2D6 metabolism is ultrarapid, extensive, intermediate, or poor. About 1% of Asians and 5%–10% of Caucasians (Figure 2) are poor metabolizers.²⁵⁸ Gene multiplication may result in 3 or more functional alleles,⁶⁴ are infrequent among northern Europeans, rarer in Chinese,²⁵⁹ but frequent (as high as 29%) in East African populations.²⁶⁰ The most common nonfunctional alleles are CYP2D6*3, CYP2D6*4, CYP2D6*5, and CYP2D6*6, which constitute approximately 98% of nonfunctional alleles in Caucasians.²⁶¹

CYP2D6 metabolism impacts the extensively used tricyclic antidepressants and selective serotonin reuptake inhibitors in FGIDs and visceral hypersensitivity.²⁶² Although not yet fully appreciated in IBS practice, a multitude of drugs are metabolized by CYP2D6, and there are many drugs that inhibit or activate CYP2D6, thus creating the possibility of significant drug interactions. In some ethnic groups, CYP2D6 testing may be warranted if antidepressants will be prescribed.²⁶³

The second category of pharmacogenetic modulation of drug effects in IBS reflects variations in receptors, transporters, or function of rate-limiting enzymes.

Serotonergic Pharmacogenetics

The most informative studies of pharmacogenetics in IBS revolve around 5-HTTLPR genetics and the efficacy of alosetron in normalizing colonic transit in IBS-D²⁴² and the efficacy of tegaserod in the treatment of bowel dysfunction in IBS-C.⁶⁶ Thus, the 5-HT₃ antagonist alosetron is more effective when the 5-HTTLPR LL genotype results in increased SERT expression and greater 5-HT clearance. Alosetron competes more effectively for the 5-HT₃ receptor when extracellular 5-HT is lower. There is also evidence, from a study of the 5-HT₃ receptor antagonist ondansetron, that the SL genotype is associated with a trend ($P = .07$) to effects on change in stool consistency and on the increase in whole-gut transit time in an analysis of 87 patients in a randomized, double-blind, placebo-controlled, crossover study of 5 weeks of ondansetron, 4 mg, vs placebo with dose titration allowed.²⁶⁴ Differences in the latter study with the results reported with alosetron may reflect the different medications, the dose titration of ondansetron, and the greater sensitivity of scintigraphy to measure colonic transit compared with radiopaque marker whole-gut transit time. Conversely, the 5-HT₄ receptor agonist tegaserod results in lower efficacy in carriers of the SS genotype,¹⁸⁶ because there is more endogenous 5-HT to complement the effects of the exogenous tegaserod in activating the 5-HT₄ receptor.

Bile Acids and Pharmacogenetics in Constipation-Predominant and Diarrhea-Predominant Irritable Bowel Syndrome

In addition to the observations that genetic variations in Klotho- β (*KLB*) and, possibly, fibroblast growth factor

receptor 4 (*FGFR4*) are associated with accelerated colonic transit in patients with IBS-D,²⁶⁵ variations in the same genes influence the colonic transit response to chenodeoxycholic acid in IBS-C²⁶⁶ and to colestevlam in IBS-D patients.²⁶⁷

References (Online Only)

51. Cremonini F, Mullan BP, Camilleri M, et al. Performance characteristics of scintigraphic transit measurements for studies of experimental therapies. *Aliment Pharmacol Ther* 2002;16:1781–1790.
52. Tack J, Van Elzen B, Tytgat G, et al. A placebo-controlled trial of the 5-HT_{1A} agonist R-137696 on symptoms, visceral hypersensitivity and on impaired accommodation in functional dyspepsia. *Gastroenterology* 2004; 126(Suppl 2):A70.
53. Read NW, Abitbol JL, Bardhan KD, et al. Efficacy and safety of the peripheral kappa agonist fedotozine versus placebo in the treatment of functional dyspepsia. *Gut* 1997;41:664–668.
54. Chial HJ, Camilleri C, Delgado-Aros S, et al. A nutrient drink test to assess maximum tolerated volume and postprandial symptoms: effects of gender, body mass index and age in health. *Neurogastroenterol Motil* 2002; 14:249–253.
55. Arts J, Caenepeel P, Verbeke K, et al. Influence of erythromycin on gastric emptying and meal related symptoms in functional dyspepsia with delayed gastric emptying. *Gut* 2005;54:455–460.
56. Braak B, Klooker TK, Wouters MM, et al. Randomised clinical trial: the effects of amitriptyline on drinking capacity and symptoms in patients with functional dyspepsia, a double-blind placebo-controlled study. *Aliment Pharmacol Ther* 2011;34:638–648.
57. Janssen P, Verschueren S, Ly HG, et al. Intragastric pressure during food intake: a physiological and minimally invasive method to assess gastric accommodation. *Neurogastroenterol Motil* 2011;23:316–322, e153.
58. Simonian HP, Maurer AH, Knight LC, et al. Simultaneous assessment of gastric accommodation and emptying: studies with liquid and solid meals. *J Nucl Med* 2004; 45:1155–1160.
59. Bouras EP, Delgado-Aros S, Camilleri M, et al. SPECT imaging of the stomach: comparison with barostat, and effects of sex, age, body mass index, and fundoplication. *Single photon emission computed tomography. Gut* 2002;51:781–786.
60. Sistonen J, Fuselli S, Palo JU, et al. Pharmacogenetic variation at CYP2C9, CYP2C19, and CYP2D6 at global and microgeographic scales. *Pharmacogenet Genomics* 2009;19:170–179.
61. Gonsalkorale WM, Perrey C, Pravica V, et al. Interleukin 10 genotypes in irritable bowel syndrome: evidence for an inflammatory component? *Gut* 2003;52:91–93.
62. Camilleri M. Is there a SERT-ain association with IBS? *Gut* 2004;53:1396–1399.
63. Holtmann G, Siffert W, Haag S, et al. G-protein beta 3 subunit 825 CC genotype is associated with unexplained

- (functional) dyspepsia. *Gastroenterology* 2004;126:971–979.
64. Dalen P, Dahl ML, Ruiz ML, et al. 10-Hydroxylation of nortriptyline in white persons with 0, 1, 2, 3, and 13 functional CYP2D6 genes. *Clin Pharmacol Ther* 1998;63:444–452.
65. Glatt CE, Reus VI. Pharmacogenetics of monoamine transporters. *Pharmacogenomics* 2003;4:583–596.
66. Camilleri M, Atanasova E, Carlson PJ, et al. Serotonin-transporter polymorphism pharmacogenetics in diarrhea-predominant irritable bowel syndrome. *Gastroenterology* 2002;123:425–432.
67. Li Y, Nie Y, Xie J, et al. The association of serotonin transporter genetic polymorphisms and irritable bowel syndrome and its influence on tegaserod treatment in Chinese patients. *Dig Dis Sci* 2007;52:2942–2949.
68. Lembo A, Camilleri M. Chronic constipation. *N Engl J Med* 2003;349:1360–1368.
69. O'Mahony L, McCarthy J, Kelly P, et al. A randomized, placebo-controlled, double-blind comparison of the probiotic bacteria *Lactobacillus* and *Bifidobacterium* in irritable bowel syndrome (IBS): symptom responses and relationship to cytokine profiles. *Gastroenterology* 2005;128:541–551.
70. Lesbros-Pantoflickova D, Michetti P, Fried M, et al. Meta-analysis: the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 2004;20:1253–1269.
71. Gershon MD, Jonakait GM. Uptake and release of 5-hydroxytryptamine by enteric 5-hydroxytryptaminergic neurones: effects of fluoxetine (Lilly 110140) and chlorimipramine. *Br J Pharmacol* 1979;66:7–9.
72. Gorard DA, Libby GW, Farthing MJ. 5-Hydroxytryptamine and human small intestinal motility: effect of inhibiting 5-hydroxytryptamine reuptake. *Gut* 1994;35:496–500.
73. De Ponti F. Pharmacology of serotonin: what a clinician should know. *Gut* 2004;53:1520–1535.
74. Bouras EP, Camilleri M, Burton DD, et al. Selective stimulation of colonic transit by the benzofuran 5HT₄ agonist, prucalopride, in healthy humans. *Gut* 1999;44:682–686.
75. Poen AC, Felt-Bersma RJ, Van Dongen PA, et al. Effect of prucalopride, a new enterokinetic agent, on gastrointestinal transit and anorectal function in healthy volunteers. *Aliment Pharmacol Ther* 1999;13:1493–1497.
76. Degen L, Matzinger D, Merz M, et al. Tegaserod, a 5-HT₄ receptor partial agonist, accelerates gastric emptying and gastrointestinal transit in healthy male subjects. *Aliment Pharmacol Ther* 2001;15:1745–1751.
77. Lim HC, Kim JH, Youn YH, et al. Effects of the addition of mosapride to gastroesophageal reflux disease patients on proton pump inhibitor: a prospective randomized, double-blind study. *J Neurogastroenterol Motil* 2013;19:495–502.
78. Fukazawa K, Furuta K, Adachi K, et al. Effects of mosapride on esophageal motor activity and esophago-gastric junction compliance in healthy volunteers. *J Gastroenterol* 2014;49:1307–1313.
79. Cho YK, Choi MG, Park EY, et al. Effect of mosapride combined with esomeprazole improves esophageal peristaltic function in patients with gastroesophageal reflux disease: a study using high resolution manometry. *Dig Dis Sci* 2013;58:1035–1041.
80. Hongo M, Harasawa S, Mine T, et al. Large-scale randomized clinical study on functional dyspepsia treatment with mosapride or teprenone: Japan Mosapride Mega-Study (JMMS). *J Gastroenterol Hepatol* 2012;27:62–68.
81. Tack J, Vos R, Janssens J, et al. Influence of tegaserod on proximal gastric tone and on the perception of gastric distension. *Aliment Pharmacol Ther* 2003;18:1031–1037.
82. Tonini M, Cipollina L, Poluzzi E, et al. Review article: clinical implications of enteric and central D₂ receptor blockade by antidopaminergic gastrointestinal prokinetics. *Aliment Pharmacol Ther* 2004;19:379–390.
83. Moayyedi P, Soo S, Deeks J, et al. Pharmacological interventions for non-ulcer dyspepsia. *Cochrane Database Syst Rev* 2004:CD001960.
84. Veldhuyzen van Zanten SJ, Jones MJ, Verlinden M, et al. Efficacy of cisapride and domperidone in functional (nonulcer) dyspepsia: a meta-analysis. *Am J Gastroenterol* 2001;96:689–696.
85. Parkman HP, Carlson MR, Gonyer D. Metoclopramide nasal spray is effective in symptoms of gastroparesis in diabetics compared to conventional oral tablet. *Neurogastroenterol Motil* 2014;26:521–528.
86. Rossi M, Giorgi G. Domperidone and long QT syndrome. *Curr Drug Saf* 2010;5:257–262.
87. European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) recommends restricting use of domperidone. (http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Domperidone_31/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500162559.pdf). Accessed February 23, 2015.
88. Huang X, Lv B, Zhang S, et al. Itopride therapy for functional dyspepsia: a meta-analysis. *World J Gastroenterol* 2012;18:7371–7377.
89. Talley NJ, Tack J, Ptak T, et al. Itopride in functional dyspepsia: results of two phase III multicentre, randomised, double-blind, placebo-controlled trials. *Gut* 2008;57:740–746.
90. Holtmann G, Talley NJ, Liebrechts T, et al. A placebo-controlled trial of itopride in functional dyspepsia. *N Engl J Med* 2006;354:832–840.
91. Itoh Z. Motilin and clinical application. *Peptides* 1997;18:593–608.
92. Cuomo R, Vandaele P, Coulie B, et al. Influence of motilin on gastric fundus tone and on meal-induced satiety in man: role of cholinergic pathways. *Am J Gastroenterol* 2006;101:804–811.
93. Bruley d, V, Parys V, Ropert A, et al. Erythromycin enhances fasting and postprandial proximal gastric tone in humans. *Gastroenterology* 1995;109:32–39.
94. Piessevaux H, Tack J, Wilmer A, et al. Perception of changes in wall tension of the proximal stomach in humans. *Gut* 2001;49:203–208.
95. Annese V, Janssens J, Vantrappen G, et al. Erythromycin accelerates gastric emptying by inducing antral contractions and improved gastroduodenal coordination. *Gastroenterology* 1992;102:823–828.

96. Bologna SD, Hasler WL, Owyang C. Down-regulation of motilin receptors on rabbit colon myocytes by chronic oral erythromycin. *J Pharmacol Exp Ther* 1993; 266:852–856.
97. Broad J, Mukherjee S, Samadi M, et al. Regional- and agonist-dependent facilitation of human neurogastrointestinal functions by motilin receptor agonists. *Br J Pharmacol* 2012;167:763–774.
98. Sanger GJ, Westaway SM, Barnes AA, et al. GSK962040: a small molecule, selective motilin receptor agonist, effective as a stimulant of human and rabbit gastrointestinal motility. *Neurogastroenterol Motil* 2009; 21:657–664, e30–e31.
99. Leming S, Broad J, Cozens SJ, et al. GSK962040: a small molecule motilin receptor agonist which increases gastrointestinal motility in conscious dogs. *Neurogastroenterol Motil* 2011;23:958–e410.
100. Matsueda K, Hongo M, Tack J, et al. A placebo-controlled trial of acotiamide for meal-related symptoms of functional dyspepsia. *Gut* 2012;61:821–828.
101. Matsueda K, Hongo M, Tack J, et al. Clinical trial: dose-dependent therapeutic efficacy of acotiamide hydrochloride (Z-338) in patients with functional dyspepsia—100 mg t.i.d. is an optimal dosage. *Neurogastroenterol Motil* 2010;22:618–e173.
102. Tack J, Masclee A, Heading R, et al. A dose-ranging, placebo-controlled, pilot trial of Acotiamide in patients with functional dyspepsia. *Neurogastroenterol Motil* 2009;21:272–280.
103. Ejlskjaer N, Vestergaard ET, Hellström PM, et al. Ghrelin receptor agonist (TZP-101) accelerates gastric emptying in adults with diabetes and symptomatic gastroparesis. *Aliment Pharmacol Ther* 2009;29:1179–1187.
104. Ejlskjaer N, Dimcevski G, Wo J, et al. Safety and efficacy of ghrelin agonist TZP-101 in relieving symptoms in patients with diabetic gastroparesis: a randomized, placebo-controlled study. *Neurogastroenterol Motil* 2010;22:1069–e281.
105. Wo JM, Ejlskjaer N, Hellström PM, et al. Randomised clinical trial: ghrelin agonist TZP-101 relieves gastroparesis associated with severe nausea and vomiting—randomized clinical study subset data. *Aliment Pharmacol Ther* 2011;33:679–688.
106. Ang D, Nicolai H, Vos R, et al. Influence of ghrelin on the gastric accommodation reflex and on meal-induced satiety in man. *Neurogastroenterol Motil* 2009;21: 528–533.
107. Ejlskjaer N, Wo JM, Esfandyari T, et al. A phase 2a, randomized, double-blind 28-day study of TZP-102, a ghrelin receptor agonist for diabetic gastroparesis. *Neurogastroenterol Motil* 2013;25:e140–e150.
108. McCallum RW, Lembo A, Esfandyari T, et al; TZP-102 Phase 2b Study Group. Phase 2b, randomized, double-blind 12-week studies of TZP-102, a ghrelin receptor agonist for diabetic gastroparesis. *Neurogastroenterol Motil* 2013;25:e705–e717.
109. Shin A, Camilleri M, Busciglio I, et al. Randomized, placebo-controlled, single-dose, crossover study of the effects of RM-131 in type 2 diabetics with documented delayed gastric emptying. *Gastroenterology* 2012;142:S839.
110. Lembo A, Camilleri M, McCallum RW, et al. A phase 2, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of RM-131 in patients with diabetic gastroparesis. *Gastroenterology* 2014; 146(Suppl):S158–S159.
111. Dukes GE, Barton M, Dewit O, et al. Safety/tolerability, pharmacokinetics (PK), and effect on gastric emptying (GE) with 14-days repeat oral dosing of the motilin receptor agonist, GSK962040, in healthy male and female volunteers. *Neurogastroenterol Motil* 2010;22:14–15.
112. Barshop K, Kuo B. The investigational drug camicinal for the treatment of gastroparesis. *Expert Opin Investig Drugs* 2014;24:1–8.
113. Walsh JH. Gastrointestinal hormones. In: *Physiology of the Gastrointestinal Tract*. New York: Raven, 1994: 1–128.
114. De Ponti F, Malagelada JR. Functional gut disorders: from motility to sensitivity disorders. A review of current and investigational drugs for their management. *Pharmacol Ther* 1998;80:49–88.
115. Scarpignato C, Pelosini I. Management of irritable bowel syndrome: novel approaches to the pharmacology of gut motility. *Can J Gastroenterol* 1999;13(Suppl A):50A–65A.
116. Chan CL, Facer P, Davis JB, et al. Sensory fibres expressing capsaicin receptor TRPV1 in patients with rectal hypersensitivity and faecal urgency. *Lancet* 2003; 361:385–391.
117. Bortolotti M, Coccia G, Grossi G, et al. The treatment of functional dyspepsia with red pepper. *Aliment Pharmacol Ther* 2002;16:1075–1082.
118. Frytak S, Moertel CG, O'Fallon JR, et al. Delta-9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy. A comparison with prochlorperazine and a placebo. *Ann Intern Med* 1979; 91:825–830.
119. McCallum RW, Soykan I, Sridhar KR, et al. Delta-9-tetrahydrocannabinol delays the gastric emptying of solid food in humans: a double-blind, randomized study. *Aliment Pharmacol Ther* 1999;13:77–80.
120. Chapman RW, Stanghellini V, Geraint M, et al. Randomized clinical trial: macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. *Am J Gastroenterol* 2013;108:1508–1515.
121. Connell AM. The motility of the pelvic colon. II. Paradoxical motility in diarrhoea and constipation. *Gut* 1962; 3:342–348.
122. Dinning PG, Wiklendt L, Maslen L, et al. Colonic motor abnormalities in slow transit constipation defined by high resolution, fiber-optic manometry. *Neurogastroenterol Motil* 2015;27:379–388.
123. Kim DY, Camilleri M. Serotonin: a mediator of the brain-gut connection. *Am J Gastroenterol* 2000;95:2698–2709.
124. Hoffman JM, Tyler K, MacEachern SJ, et al. Activation of colonic mucosal 5-HT(4) receptors accelerates propulsive motility and inhibits visceral hypersensitivity. *Gastroenterology* 2012;142:844–854.
125. Demaeveer JH, Lefebvre RA, Schuurkes JAJ. 5-HT4 receptor agonists: similar but not the same. *Neurogastroenterol Motil* 2008;20:99–112.

126. Camilleri M, Kerstens R, Rykx A, et al. A placebo-controlled trial of prucalopride for severe chronic constipation. *N Engl J Med* 2008;358:2344–2354.
127. Ke M, Zou D, Yuan Y, et al. Prucalopride in the treatment of chronic constipation in patients from the Asia-Pacific region: a randomized, double-blind, placebo-controlled study. *Neurogastroenterol Motil* 2012;24:999–e541.
128. Mendzelevski B, Ausma J, Chanter DO, et al. Assessment of the cardiac safety of prucalopride in healthy volunteers: a randomized, double-blind, placebo- and positive-controlled thorough QT study. *Br J Clin Pharmacol* 2012;73:203–209.
129. Camilleri M, Van Outryve MJ, Beyens G, et al. Clinical trial: the efficacy of open-label prucalopride treatment in patients with chronic constipation—follow-up of patients from the pivotal studies. *Aliment Pharmacol Ther* 2010;32:1113–1123.
130. Camilleri M, Beyens G, Kerstens R, et al. Safety assessment of prucalopride in elderly patients with constipation: a double-blind, placebo-controlled study. *Neurogastroenterol Motil* 2009;21:1256–e117.
131. Quigley EM, Vandeplasse L, Kerstens R, et al. Clinical trial: the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation—a 12-week, randomized, double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2009;29:315–328.
132. Coremans G, Kerstens R, De Pauw M, et al. Prucalopride is effective in patients with severe chronic constipation in whom laxatives fail to provide adequate relief. Results of a double-blind, placebo-controlled clinical trial. *Digestion* 2003;67:82–89.
133. Müller-Lissner S, Rykx A, Kerstens R, et al. A double-blind, placebo-controlled study of prucalopride in elderly patients with chronic constipation. *Neurogastroenterol Motil* 2010;22:991–998; e255.
134. Goldberg M, Li YP, Johanson JF, et al. Clinical trial: the efficacy and tolerability of velusetrag, a selective 5-HT₄ agonist with high intrinsic activity, in chronic idiopathic constipation—a 4-week, randomized, double-blind, placebo-controlled, dose-response study. *Aliment Pharmacol Ther* 2010;32:1102–1112.
135. Manini ML, Camilleri M, Goldberg M, et al. Effects of velusetrag (TD-5108) on gastrointestinal transit and bowel function in health and pharmacokinetics in health and constipation. *Neurogastroenterol Motil* 2010;22:42–49; e7–e8.
136. Camilleri M, Vazquez-Roque MI, Burton D, et al. Pharmacodynamic effects of a novel prokinetic 5-HT receptor agonist, ATI-7505, in humans. *Neurogastroenterol Motil* 2007;19:30–38.
137. Shin A, Acosta A, Camilleri M, et al. A randomized trial of 5-hydroxytryptamine 4-receptor agonist, YKP10811, on colonic transit and bowel function in functional constipation. *Clin Gastroenterol Hepatol* 2015;13:701–708; e1.
138. Gilet M, Eutamene H, Han H, et al. Influence of a new 5-HT₄ receptor partial agonist, YKP10811, on visceral hypersensitivity in rats triggered by stress and inflammation. *Neurogastroenterol Motil* 2014;26:1761–1770.
139. Barrett KE, Keely SJ. Chloride secretion by the intestinal epithelium: molecular basis and regulatory aspects. *Annu Rev Physiol* 2000;62:535–572.
140. Camilleri M. Pharmacology of the new treatments for lower gastrointestinal motility disorders and irritable bowel syndrome. *Clin Pharmacol Ther* 2012;91:44–59.
141. Anggård E. The biological activities of three metabolites of prostaglandin E 1. *Acta Physiol Scand* 1966;66:509–510.
142. Cuppoletti J, Malinowska DH, Chakrabarti J, et al. Effects of lubiprostone on human uterine smooth muscle cells. *Prostaglandins Other Lipid Mediat* 2008;86:56–60.
143. Raschi E, De Ponti F. Lubiprostone: pharmacokinetic, pharmacodynamic, safety and regulatory aspects in the treatment of constipation-predominant irritable bowel syndrome. *Expert Opin Drug Metab Toxicol* 2014;10:293–305.
144. Cuppoletti J, Chakrabarti J, Tewari KP, Malinowska DH. Differentiation between human CIC-2 and CFTR Cl⁻. *Am J Physiol Cell Physiol* 2014;307:C479–C492.
145. Drossman DA, Chey WD, Johanson JF, et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome—results of two randomized, placebo-controlled studies. *Aliment Pharmacol Ther* 2009;29:329–341.
146. Johanson JF, Ueno R. Lubiprostone, a locally acting chloride channel activator, in adult patients with chronic constipation: a double-blind, placebo-controlled, dose-ranging study to evaluate efficacy and safety. *Aliment Pharmacol Ther* 2007;25:1351–1361.
147. Johanson JF, Morton D, Geenen J, et al. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. *Am J Gastroenterol* 2008;103:170–177.
148. Johanson JF, Drossman DA, Panas R, et al. Clinical trial: phase 2 study of lubiprostone for irritable bowel syndrome with constipation. *Aliment Pharmacol Ther* 2008;27:685–696.
149. Fukudo S, Hongo M, Kaneko H, et al. Efficacy and safety of oral lubiprostone in constipated patients with or without irritable bowel syndrome: a randomized, placebo-controlled and dose-finding study. *Neurogastroenterol Motil* 2011;23: 544–e205.
150. Chey WD, Drossman DA, Johanson JF, et al. Safety and patient outcomes with lubiprostone for up to 52 weeks in patients with irritable bowel syndrome with constipation. *Aliment Pharmacol Ther* 2012;35:587–599.
151. Joo NS, London RM, Kim HD, et al. Regulation of intestinal Cl⁻ and HCO₃⁻ secretion by uroguanylin. *Am J Physiol* 1998;274:G633–G644.
152. Donowitz M, Cha B, Zachos NC, et al. NHERF family and NHE3 regulation. *J Physiol* 2005;567:3–11.
153. Castro J, Harrington AM, Hughes PA, et al. Linaclotide inhibits colonic nociceptors and relieves abdominal pain via guanylate cyclase-C and extracellular cyclic guanosine 3',5'-monophosphate. *Gastroenterology* 2013;145:1334–1346; e1–e11.

154. Lembo AJ, Schneier HA, Shiff SJ, et al. Two randomized trials of linaclotide for chronic constipation. *N Engl J Med* 2011;365:527–536.
155. Lembo AJ, Kurtz CB, Macdougall JE, et al. Efficacy of linaclotide for patients with chronic constipation. *Gastroenterology* 2010;138:886–895.
156. Quigley EM, Tack J, Chey WD, et al. Randomised clinical trials: linaclotide phase 3 studies in IBS-C—a pre-specified further analysis based on European Medicines Agency-specified endpoints. *Aliment Pharmacol Ther* 2013;37:49–61.
157. Rao S, Lembo AJ, Shiff SJ, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. *Am J Gastroenterol* 2012;107:1714–1724.
158. Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol* 2012;107:1702–1712.
159. Macdougall JE, Johnston JM, Lavins BJ, et al. An evaluation of the FDA responder endpoint for IBS-C clinical trials: analysis of data from linaclotide Phase 3 clinical trials. *Neurogastroenterol Motil* 2013;25:481–486.
160. Johnston JM, Kurtz CB, Macdougall JE, et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome with constipation. *Gastroenterology* 2010;139:1877–1886; e2.
161. Lembo AJ, Kurtz CB, Macdougall JE, et al. Efficacy of linaclotide for patients with chronic constipation. *Gastroenterology* 2010;138:886–895; e1.
162. Andresen V, Camilleri M, Busciglio IA, et al. Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. *Gastroenterology* 2007;133:761–768.
163. Miner PB, Surowitz R, Fogel R, et al. Plecanatide, a novel guanylate cyclase-C (GC-C) receptor agonist, is efficacious and safe in patients with chronic idiopathic constipation (CIC): results from a 951 patient, 12 week, multicenter trial. *Gastroenterology* 2013;144(Suppl):S163.
164. Miner P, DeLuca R, La Portilla M, et al. Plecanatide, a novel uroguanylin analog: a 12-week, randomized, double-blind, placebo-controlled, dose-ranging trial to evaluate efficacy and safety in patients with irritable bowel syndrome with constipation (IBS-C). *Am J Gastroenterol* 2014;109(Suppl 2):S541.
165. Spencer AG, Jacobs JW, Leadbetter MR, et al. RDX5791, a first-in-class minimally systemic NHE3 inhibitor in clinical development for CIC and IBS-C, increases intestinal sodium leading to enhanced intestinal fluid volume and transit. *Gastroenterology* 2011;140(Suppl):S99.
166. Appleby RN, Walters JR. The role of bile acids in functional GI disorders. *Neurogastroenterol Motil* 2014;26:1057–1069.
167. Camilleri M, Busciglio I, Acosta A, et al. Effect of increased bile acid synthesis or fecal excretion in irritable bowel syndrome-diarrhea. *Am J Gastroenterol* 2014;109:1621–1630.
168. Wong B, Camilleri M, McKinzie S, et al. Effects of A3309, an ileal bile acid transporter inhibitor, on colonic transit and symptoms in females with functional constipation. *Am J Gastroenterol* 2011;106:2154–2164.
169. Chey WD, Camilleri M, Chang L, et al. A randomized placebo-controlled phase IIb trial of A3309, a bile acid transporter inhibitor, for chronic idiopathic constipation. *Am J Gastroenterol* 2011;106:1803–1812.
170. Buchwald H, Rudser KD, Williams SE, et al. Overall mortality, incremental life expectancy, and cause of death at 25 years in the program on the surgical control of the hyperlipidemias. *Ann Surg* 2010;251:1034–1040.
171. Jansen JP, Lorch D, Langan J, et al. A randomized, placebo-controlled phase 3 trial (Study SB-767905/012) of alvimopan for opioid-induced bowel dysfunction in patients with non-cancer pain. *J Pain* 2011;12:185–193.
172. Irving G, Péntzes J, Ramjattan B, et al. A randomized, placebo-controlled phase 3 trial (Study SB-767905/013) of alvimopan for opioid-induced bowel dysfunction in patients with non-cancer pain. *J Pain* 2011;12:175–184.
173. Chey WD, Webster L, Sostek M, et al. Naloxegol for opioid-induced constipation in patients with noncancer pain. *N Engl J Med* 2014;370:2387–2396.
174. Webster L, Dhar S, Eldon M, et al. A phase 2, double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the efficacy, safety, and tolerability of naloxegol in patients with opioid-induced constipation. *Pain* 2013;154:1542–1550.
175. Sloots CE, Rykx A, Cools M, et al. Efficacy and safety of prucalopride in patients with chronic noncancer pain suffering from opioid-induced constipation. *Dig Dis Sci* 2010;55:2912–2921.
176. Cryer B1, Katz S, Vallejo R, et al. A randomized study of lubiprostone for opioid-induced constipation in patients with chronic noncancer pain. *Pain Med* 2014;15:1825–1834.
177. Jamal MM, Mareya SM, Woldegeorgis F, et al. Lubiprostone significantly improves treatment response in non-methadone opioid-induced bowel dysfunction patients with chronic, non-cancer pain: results from a phase 3, randomized, double-blind, placebo-controlled clinical trial. *Gastroenterology* 2012;142(Suppl 1):S144–S145.
178. Palejwala V, Ioshi A, Patwa V, et al. SP-333, a D-amino acid containing peptide agonist of guanylate cyclase-C is a novel drug candidate for treatment of gastrointestinal disorders and diseases. *Am J Gastroenterol* 2014;109(Suppl 2):S538.
179. Corazzini E. Role of opioid ligands in the irritable bowel syndrome. *Can J Gastroenterol* 1999;13(Suppl A):71A–75A.
180. Cann PA, Read NW, Holdsworth CD, et al. Role of loperamide and placebo in management of irritable bowel syndrome (IBS). *Dig Dis Sci* 1984;29:239–247.
181. Smith MJ, Cherian P, Raju GS, et al. Bile acid malabsorption in persistent diarrhoea. *J R Coll Physicians Lond* 2000;34:448–451.
182. Talley NJ, Phillips SF, Haddad A, et al. GR 38032F (ondansetron), a selective 5HT₃ receptor antagonist, slows colonic transit in healthy man. *Dig Dis Sci* 1990;35:477–480.

183. Gore S, Gilmore IT, Haigh CG, et al. Colonic transit in man is slowed by ondansetron (GR38032F), a selective 5-hydroxytryptamine receptor (type 3) antagonist. *Aliment Pharmacol Ther* 1990;4:139–144.
184. Scolapio JS, Camilleri M, der Ohe MR, et al. Ascending colon response to feeding: evidence for a 5-hydroxytryptamine-3 mechanism. *Scand J Gastroenterol* 1995;30:562–567.
185. Moynihan R. Alosetron: a case study in regulatory capture, or a victory for patients' rights? *BMJ* 2002;325:592–595.
186. Garsed K, Chernova J, Hastings M, et al. A randomised trial of ondansetron for the treatment of irritable bowel syndrome with diarrhoea. *Gut* 2014;63:1617–1625.
187. Hirata T, Funatsu T, Keto Y, et al. Pharmacological profile of ramosetron, a novel therapeutic agent for IBS. *Inflammopharmacology* 2007;15:5–9.
188. Hirata T, Keto Y, Nakata M, et al. Effects of serotonin 5-HT₃ receptor antagonists on stress-induced colonic hyperalgesia and diarrhoea in rats: a comparative study with opioid receptor agonists, a muscarinic receptor antagonist and a synthetic polymer. *Neurogastroenterol Motil* 2008;20:557–565.
189. Matsueda K, Harasawa S, Hongo M, et al. A phase II trial of the novel serotonin type 3 receptor antagonist ramosetron in Japanese male and female patients with diarrhea-predominant irritable bowel syndrome. *Digestion* 2008;77:225–235.
190. Matsueda K, Harasawa S, Hongo M, et al. A randomized, double-blind, placebo-controlled clinical trial of the effectiveness of the novel serotonin type 3 receptor antagonist ramosetron in both male and female Japanese patients with diarrhea-predominant irritable bowel syndrome. *Scand J Gastroenterol* 2008;43:1202–1211.
191. Fukudo S, Ida M, Akiho H, et al. Effect of ramosetron on stool consistency in male patients with irritable bowel syndrome with diarrhea: randomized and placebo-controlled trial. *Clin Gastroenterol Hepatol* 2014;12:953–959.
192. Grover M, Camilleri M. Invited editorial: ramosetron in irritable bowel syndrome with diarrhea: new hope or the same old story? *Clin Gastroenterol Hepatol* 2014;12:960–962.
193. Chiba T, Yamamoto K, Sato S, et al. Long-term efficacy and safety of ramosetron in the treatment of diarrhea-predominant irritable bowel syndrome. *Clin Exp Gastroenterol* 2013;6:123–128.
194. Lee KJ, Kim NY, Kwon JK, et al. Efficacy of ramosetron in the treatment of male patients with irritable bowel syndrome with diarrhea: a multicenter, randomized clinical trial, compared with mebeverine. *Neurogastroenterol Motil* 2011;23:1098–1104.
195. Pimentel M, Lembo A, Chey WD, Zakko S, et al; TARGET Study Group. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med* 2011;364:22–32.
196. Menees SB, Maneerattannaporn M, Kim HM, et al. The efficacy and safety of rifaximin for the irritable bowel syndrome: a systematic review and meta-analysis. *Am J Gastroenterol* 2012;107:28–35.
197. Lembo A, Pimentel M, Rao SS, et al. Efficacy and safety of repeat treatment with rifaximin for diarrhea-predominant irritable bowel syndrome (IBS-D): results of the TARGET 3 study. Presented at the American College of Gastroenterology Annual Scientific Meeting and Postgraduate Course. Philadelphia, Pennsylvania, October 17–22, 2014.
198. Dove LS, Lembo A, Randall CW, et al. Eluxadoline benefits patients with irritable bowel syndrome with diarrhea in a phase 2 study. *Gastroenterology* 2013;145:329–338.
199. Lembo A, Dove S, Andrae D, et al. Eluxadoline for the treatment of diarrhea-predominant irritable bowel syndrome: results of 2 randomized, double-blind, placebo-controlled phase 3 clinical trials of efficacy and safety. *Gastroenterology* 2014;146(Suppl 1):S159.
200. Freiman J, Jackson J, Frazier KS, et al. LX1031: inhibition of 5-HT synthesis as a new target in the management of irritable bowel syndrome (IBS). *Neurogastroenterol Motil* 2009;21:250.
201. Brown PM, Drossman DA, Wood AJ, et al. The tryptophan hydroxylase inhibitor LX1031 shows clinical benefit in patients with nonconstipating irritable bowel syndrome. *Gastroenterology* 2011;141:507–516.
202. Holzer P. Tachykinin receptor antagonists: silencing neuropeptides with a role in the disturbed gut. In: Spiller R, Grundy D, eds. *Pathophysiology of the Enteric Nervous System*. London: Blackwell, 2004:212–227.
203. Lecci A, Capriati A, Maggi CA. Tachykinin NK₂ receptor antagonists for the treatment of irritable bowel syndrome. *Br J Pharmacol* 2004;141:1249–1263.
204. Tack JF, Dochev YS, Bochenek A, et al. Efficacy of ibodutant, a selective antagonist of neurokinin 2 receptors, in irritable bowel syndrome with diarrhea (IBS-D): the results of a double-blind, randomized, placebo-controlled, parallel-group phase II study. *Gastroenterology* 2013;144(Suppl 1):S92–S93.
205. Bharucha AE, Ravi K, Zinsmeister AR. Comparison of selective M₃ and nonselective muscarinic receptor antagonists on gastrointestinal transit and bowel habits in humans. *Am J Physiol* 2010;299:G215–G219.
206. Czimmer J, Süto G, Király A, et al. Otilonium bromide enhances sensory thresholds of volume and pressure in patients with irritable bowel syndrome. *J Physiol Paris* 2001;95:153–156.
207. Krueger D, Michel K, Allam S, et al. Effect of hyoscine butylbromide (Buscopan®) on cholinergic pathways in the human intestine. *Neurogastroenterol Motil* 2013;25:e530–e539.
208. Clavé P, Acalovschi M, Triantafyllidis JK; OBIS Study Investigators. Randomised clinical trial: otilonium bromide improves frequency of abdominal pain, severity of distention and time to relapse in patients with irritable bowel syndrome. *Aliment Pharmacol Ther* 2011;34:432–442.
209. Chang FY, Lu CL, Luo JC, et al. The evaluation of otilonium bromide treatment in Asian patients with irritable bowel syndrome. *J Neurogastroenterol Motil* 2011;17:402–410.
210. Fukushima Y, Suzuki H, Matsuzaki J, et al. Efficacy of solifenacin on irritable bowel syndrome with diarrhea:

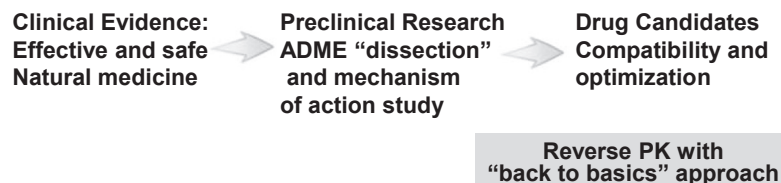
- open-label prospective pilot trial. *J Neurogastroenterol Motil* 2012;18:317–323.
211. Anderson K, Fischer L. Prevention of GI absorption of bacterial toxins: an in vitro evaluation of the potential for prophylactic use of a novel oral adsorbent (AST-120). *Gastroenterology* 2008;134(Suppl 1):A–675.
212. Tack JF, Miner PB Jr, Fischer L, et al. Randomised clinical trial: the safety and efficacy of AST-120 in non-constipating irritable bowel syndrome—a double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2011;34:868–877.
213. Guilarte M, Santos J, de Torres I, et al. Diarrhoea-predominant IBS patients show mast cell activation and hyperplasia in the jejunum. *Gut* 2007;56:203–209.
214. Lobo B, Vicario M, Martinez C, et al. Clinical benefit in IBS after disodium cromoglycate involves mast cell-mediated recovery of healthy-like innate immunity genes expression profile in the jejunal mucosa. *Gastroenterology* 2009;136(Suppl 1):S156.
215. Lobo B, Vicario M, Martinez C, et al. Clinical improvement in IBS after disodium cromoglycate involves mast cell-mediated toll-like receptor signaling downregulation. *Gastroenterology* 2011;140(Suppl 1):499–500.
216. Leri O, Tubili S, De Rosa FG, et al. Management of diarrhoeic type of irritable bowel syndrome with exclusion diet and disodium cromoglycate. *Inflammopharmacology* 1997;5:153–158.
217. Klooker TK, Braak B, Koopman KE, et al. The mast cell stabiliser ketotifen decreases visceral hypersensitivity and improves intestinal symptoms in patients with irritable bowel syndrome. *Gut* 2010;59:1213–1221.
218. Corinaldesi R, Stanghellini V, Cremon C, et al. Effect of mesalazine on mucosal immune biomarkers in irritable bowel syndrome: a randomized controlled proof-of-concept study. *Aliment Pharmacol Ther* 2009;30:245–252.
219. Andrews CN, Griffiths TA, Kaufman J, et al. Mesalazine (5 aminosalicylic acid) alters faecal bacterial profiles, but not mucosal proteolytic activity in diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther* 2011;34:374–383.
220. Dorofeyev AE, Kiriyan EA, Vasilenko IV, et al. Clinical, endoscopic and morphological efficacy of mesalazine in patients with irritable bowel syndrome. *Clin Exp Gastroenterol* 2011;4:141–153.
221. Tuteja AK, Fang JC, Al-Suqi M, et al. Double-blind placebo-controlled study of mesalamine in post-infective irritable bowel syndrome—a pilot study. *Scand J Gastroenterol* 2012;47:1159–1164.
222. Lam C, Tan W, Leighton M, et al. A multi-centre, parallel group, randomised placebo controlled trial of mesalazine for treatment of diarrhoea-predominant irritable bowel syndrome (IBS-D). *Gastroenterology* 2014;146(Suppl 1):S123–S124.
223. Barbara G, Cremon C, Bellacosa L, et al. Randomized placebo controlled multicenter trial of mesalazine in patients with irritable bowel syndrome (IBS). *Gastroenterology* 2014;146(Suppl 1):S124.
224. Walters JR, Johnston IM, Nolan JD, et al. The response of patients with bile acid diarrhoea to the farnesoid X receptor agonist obeticholic acid. *Aliment Pharmacol Ther* 2015;41:54–64.
225. Camilleri M, Lasch K, Zhou W. Irritable bowel syndrome: methods, mechanisms, and pathophysiology. The confluence of increased permeability, inflammation, and pain in irritable bowel syndrome. *Am J Physiol* 2012;303:G775–G785.
226. Zhou Q, Souba WW, Croce CM, et al. MicroRNA-29a regulates intestinal membrane permeability in patients with irritable bowel syndrome. *Gut* 2010;59:775–784.
227. Basra S, Verne GN, Zhou Q. Randomized placebo-controlled trial of glutamine for the treatment of diarrhea-predominant irritable bowel syndrome. *Gastroenterology* 2013;144(Suppl):S160.
228. Chang L, Lembo A, Sultan S. American Gastroenterological Association Institute technical review on the pharmacological management of irritable bowel syndrome. *Gastroenterology* 2014;147:1149–1172.
229. Ford AC, Moayyedi P, Lacy BE, et al; Task Force on the Management of Functional Bowel Disorders. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. *Am J Gastroenterol* 2014;109(Suppl 1):S2–S26.
230. Poynard T, Regimbeau C, Benhamou Y. Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 2001;15:355–361.
231. Ford AC, Talley NJ, Spiegel BM, et al. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. *BMJ* 2008;337:a2313.
232. Chey WD, Lembo AJ, Lavins BY, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol* 2012;107:1702–1712.
233. Ruepert L, Quatero AO, de Wit NJ, et al. Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. *Cochrane Database Syst Rev* 2011 Aug 10;(8):CD003460.
234. Ford AC, Quigley EM, Lacy BE, et al. Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: systematic review and meta-analysis. *Am J Gastroenterol* 2014;109:1350–1365.
235. Weinberg DS, Smalley W, Heidelbaugh JJ, et al. American Gastroenterological Association Institute Guideline on the pharmacological management of irritable bowel syndrome. *Gastroenterology* 2014;147:1146–1148.
236. Houghton LA, Fell C, Whorwell PJ, et al. Effect of a second-generation alpha2delta ligand (pregabalin) on visceral sensation in hypersensitive patients with irritable bowel syndrome. *Gut* 2007;56:1218–1225.
237. van Wanrooij S, Wouters MM, Van Oudenhove L, et al. Effect of the H1-receptor antagonist ebastin on visceral perception and clinical symptoms in IBS. *Gastroenterology* 2013;144(Suppl 1):S160.

238. Sood R, Law GR, Ford AC. Diagnosis of IBS: symptoms, symptom-based criteria, biomarkers or 'psychomarkers'? *Nat Rev Gastroenterol Hepatol* 2014;11:683–691.
239. Corsetti M, Van Oudenhove L, Tack J. The quest for biomarkers in IBS—where should it lead us? *Neurogastroenterol Motil* 2014;26:1669–1676.
240. Barbara G. IBS: biomarkers for IBS: ready for prime time? *Nat Rev Gastroenterol Hepatol* 2015;12:9–10.
241. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther* 2001;69:89–95.
242. Camilleri M, Acosta A, Busciglio I, et al. Effect of colessevelam on fecal bile acids and bowel functions in diarrhea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther* 2015;41:438–448.
243. Briejer MR, Veen GJ, Akkermans LM, et al. Cisapride and structural analogs selectively enhance 5-hydroxytryptamine (5-HT)-induced purinergic neurotransmission in the guinea pig proximal colon. *J Pharmacol Exp Ther* 1995;274:641–648.
244. Morphy R, Kay C, Rankovic Z. From magic bullets to designed multiple ligands. *Drug Discov Today* 2004;9:641–651.
245. Camilleri M, Northcutt AR, Kong S, Dukes GE, McSorley D, Mangel AW. Efficacy and safety of alosetron in women with irritable bowel syndrome: a randomised, placebo-controlled trial. *Lancet* 2000;355:1035–1040.
246. Camilleri M, Bueno L, De Ponti F, et al. Pharmacological and pharmacokinetic aspects of functional gastrointestinal disorders. *Gastroenterology* 2006;130:1421–1434.
247. Shanahan F, Quigley EM. Manipulation of the microbiota for treatment of IBS and IBD—challenges and controversies. *Gastroenterology* 2014;146:1554–1563.
248. Mayer EA, Savidge T, Shulman RJ. Brain-gut microbiome interactions and functional bowel disorders. *Gastroenterology* 2014;146:1500–1512.
249. Musch MW, Wang Y, Claud EC, Chang EB. Lubiprostone decreases mouse colonic inner mucus layer thickness and alters intestinal microbiota. *Dig Dis Sci* 2013;58:668–677.
250. Keely S, Kelly CJ, Weissmueller T, Burgess A, et al. Activated fluid transport regulates bacterial-epithelial interactions and significantly shifts the murine colonic microbiome. *Gut Microbes* 2012;3:250–260.
251. Hao H, Zheng X, Wang G. Insights into drug discovery from natural medicines using reverse pharmacokinetics. *Trends Pharmacol Sci* 2014;35:168–177.
252. Cremonini F. Standardized herbal treatments on functional bowel disorders: moving from putative mechanisms of action to controlled clinical trials. *Neurogastroenterol Motil* 2014;26:893–900.
253. Chow EC, Pang KS. Why we need proper PBPK models to examine intestine and liver oral drug absorption. *Curr Drug Metab* 2013;14:57–79.
254. Zhang X, Wu W. Ligand-mediated active targeting for enhanced oral absorption. *Drug Discov Today* 2014;19:898–904.
255. De Ponti F, Poluzzi E, Montanaro N. Organising evidence on QT prolongation and occurrence of Torsades de Pointes with non-antiarrhythmic drugs: a call for consensus. *Eur J Clin Pharmacol* 2001;57:185–209.
256. De Ponti F, Poluzzi E, Cavalli A, et al. Safety of non-antiarrhythmic drugs that prolong the QT interval or induce torsade de pointes: an overview. *Drug Saf* 2002;25:263–286.
257. Evans WE, Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. *Science* 1999;286:487–491.
258. Xie H-G, Kim RB, Wood AJJ, et al. Molecular basis of ethnic differences in drug disposition and response. *Annu Rev Pharmacol Toxicol* 2001;41:815–850.
259. Yue QY, Zhong ZH, Tybring G, et al. Pharmacokinetics of nortriptyline and its 10-hydroxy metabolite in Chinese subjects of different CYP2D6 genotypes. *Clin Pharmacol Ther* 1998;64:384–390.
260. Akillu E, Persson I, Bertilsson L, et al. Frequent distribution of ultrarapid metabolizers of debrisoquine in an Ethiopian population carrying duplicated and multi-duplicated functional CYP2D6 alleles. *J Pharmacol Exp Ther* 1996;278:441–446.
261. Givens RC, Watkins PB. Pharmacogenetics and clinical gastroenterology. *Gastroenterology* 2003;125:240–248.
262. Ford AC, Talley NJ, Schoenfeld PS, et al. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. *Gut* 2009;58:367–378.
263. Zhang JP, Malhotra AK. Pharmacogenetics and anti-psychotics: therapeutic efficacy and side effects prediction. *Exp Opin Drug Metab Toxicol* 2011;7:9–37.
264. Li Y, Jie Y, Xie J, et al. The association of serotonin transporter genetic polymorphisms and irritable bowel syndrome and its influence on tegaserod treatment in Chinese patients. *Dig Dis Sci* 2000;52:2942–2949.
265. Wong BS, Camilleri M, Carlson PJ, et al. A Klotho β variant mediates protein stability and associates with colon transit in irritable bowel syndrome with diarrhea. *Gastroenterology* 2011;140:1934–1942.
266. Rao AS, Wong BS, Camilleri M, et al. Chenodeoxycholate in females with IBS-constipation: a pharmacodynamic and pharmacogenetic analysis. *Gastroenterology* 2010;139:1549–1558.
267. Wong BS, Camilleri M, Carlson PJ, et al. Pharmacogenetics of the effects of colessevelam on colonic transit in IBS with diarrhea. *Dig Dis Sci* 2012;57:1222–1226.
268. Camilleri M. Physiological underpinnings of irritable bowel syndrome: neurohormonal mechanisms. *J Physiol* 2014;592:2967–2980.
269. Camilleri M. Opioid-induced constipation: challenges and therapeutic opportunities. *Am J Gastroenterol* 2011;106:835–842; quiz 843.

Development of new chemical entity



Existing natural medicines



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Supplementary Figure 1. Drug discovery from natural medicines. In contrast to the traditional or classical approach, where new chemical entities are identified by screening a compound library for target-based activity followed by validation and drug development, an alternative approach is to build on the clinical evidence that a medicine derived from natural materials is efficacious and safe, and to identify the active compound, its mechanism of action and pharmacokinetics to optimize the efficacy of the natural remedy. ADME, absorption, distribution, metabolism, and excretion; PK, pharmacokinetics. This concept and figure are adapted from Hao et al,²⁵¹ with permission.

Supplementary Table 1. Agents Directed to Amines/Receptors and Peptides to Affect Functions of the Upper and Lower Gastrointestinal Tract

Target system/ receptor	Type of ligand	Distribution of receptors	Pharmacologic action in animals	Pharmacologic action in humans
5-HT	5-HT ₃ -receptor antagonists (eg, alosetron, ondansetron, ramosetron)	Intrinsic and extrinsic neurons	Inhibits visceral sensitivity, absorption/secretion, motility	Slows transit, increases colonic compliance
	5-HT ₄ receptor agonists (eg, prucalopride, velusetrag, mosapride, naronapride, YKP10811)	Enteric neurons, smooth muscle cells	Enhances secretion and motility, reduces visceral sensitivity	Accelerates transit, increases colonic HAPC and gastric accommodation, reduces inhibition of RIII reflex during rectal distension
	5-HT _{1A} receptor agonists (eg, buspirone)	Enteric neurons, extrinsic afferent neurons	Inhibits motility and enhances compliance	Increases accommodation; central actions anxiolytic agent and tranquilizer
ACh (Muscarinic)	M ₃ receptor antagonists	Smooth muscle	Increases smooth muscle relaxation, compliance	No published data
	M ₁ and M ₂ receptor antagonists Acetylcholinesterase inhibitors (eg, acotiamide, itopride)	Enteric neurons and smooth muscle Enteric neurons and smooth muscle	Increases gastric emptying Increases gastric emptying	May enhance accommodation Increases gastric emptying and accommodation
Adrenoceptors	β_3 -Adrenoceptor agonists	Smooth muscle	Inhibits motility	No published data
	α_2 -Adrenoceptor agonists	Enteric neurons and enterocytes	Reduces secretion, enhances compliance, and reduces motility and tone	Reduces secretion, enhances compliance, and reduces motility, tone, and sensation
Dopamine	D ₂ -receptor antagonists (eg, domperidone, levosulpiride, metoclopramide, itopride)	Area postrema, smooth muscle, enteric neurons	Contracts muscle	Antiemetic, prokinetic, reduces sensation?
Motilin	Motilides	Smooth muscle, enteric neurons	Stimulates motility	Stimulates motility and transit
Ghrelin	Ghrelin agonists	Hypothalamus, ? ^a	Stimulates appetite	Accelerates gastric emptying, reduces gastric accommodation
Cannabinoid	δ -9-Tetrahydrocannabinol	Enteric neurons Nucleus tractus solitarius neurons	Slows gastrointestinal transit	Delays gastric emptying; antiemetic properties
Opioid	μ -Receptor agonists (eg, loperamide)	Enterocyte, enteric neurons, afferent neurons, and inflammation	Reduces intestinal secretion and transit	Slows colonic transit, antidiarrheal, increases resting anal tone
	μ -Receptor antagonists (eg, naloxone, methylnaltrexone, alvimopan, naloxegol)	Enteric neurons, afferent neurons, and inflammation	Reverses opioid effects on motility	Accelerates colonic transit, reverses OIC, reduces duration of PO ileus
	κ -Receptor agonists (eg, fedotozine, asimadoline)	Enteric neurons and afferent neurons	Reduces sensation, variable effect on motility	Reduces sensation
Somatostatin	SSR-2 receptor agonists (eg, octreotide, lanreotide)	Enterocytes, submucosal neurons, myenteric neurons	Retards transit, reduces afferent firing and sensation	Slows transit, reduces sensitivity, enhances absorption
Tachykinin	NK ₁ -receptor antagonists (eg, aprepitant)	Enteric neurons, interstitial cells of Cajal, smooth muscle, immune cells	Inhibits motility, fluid secretion, vagal afferent sensation, and inflammation	Antiemetic
	NK ₂ -receptor antagonists (eg, ibodutant)	Enteric neurons, smooth muscle, extrinsic afferents	Inhibits motility, H ₂ O secretion, sensation, inflammation	Inhibits NKA-induced motility
	NK ₃ -receptor antagonists (eg, talnetant)	Enteric neurons, extrinsic afferents	Inhibits motility and sensation	No published data

Supplementary Table 1. Continued

Target system/ receptor	Type of ligand	Distribution of receptors	Pharmacologic action in animals	Pharmacologic action in humans
Guanylate cyclase-C	GC-C agonists (eg, linaclotide, plecanatide)	Luminal side of the enteric mucosa	Induces secretion of HCO_3^- , Cl^- , H_2O and inhibits visceral nociceptors via cGMP	Looser stool consistency, accelerates colonic transit, decreases visceral pain
Chloride channels	ClC_2 activators (eg, lubiprostone)	Enteric mucosa	Induces secretion of bicarbonate, chloride, H_2O	Looser stool consistency, accelerates colonic transit
NHE_3 transporter	NHE_3 inhibitor (eg, tenapanor)	Enteric mucosa	Inhibits absorption of Na^+	Improves stool consistency

ACh, acetylcholine; ClC, chloride channel; HAPC, high-amplitude propagated contraction; NHE, sodium-hydrogen exchange; NK, tachykinin; OBD, opioid bowel dysfunction; PO, postoperative; SSR, somatostatin receptor.

^aThe question mark (?) refers to a hypothetical action or site of action that is not proven.

Supplementary Table 2. Pharmacologic Actions of Psychotropic Drugs on Monoamine Reuptake and Receptors^a

Drug	Neurotransmitter reuptake blockade			Receptor blockade						
	5-HT	Norepinephrine	Dopamine	α_1	α_2	H ₁	ACh	5-HT _{1A}	Other 5-HTR	D ₂
Tricyclic agents										
Amitriptyline	+++++	+++	– ^b	+++	+	++++	+++	+	+++	–
Imipramine	++++	+++++	–	++	+	++++	++	++	++	–
Desipramine	+++	+++++	–	++	+	++	++	–	–	–
Clomipramine	+++++	+++	–	++		+++	++	–	–	–
SSRIs										
Fluoxetine	+++++	++	–	–	–	–	–	–	–	0
Paroxetine	+++++	+++	+	–	–	0 ^c	++	–	–	0
Sertraline	+++++	+	+++	++	+	0	+	–	–	0
Citalopram	+++++	–	0	+	+	+	0	–	–	0
SNRIs										
Venlafaxine	++++	+	–	0	0	0	0	0	0	0
Duloxetine	+++++	++++	+	–	–	–	–	–	–	0
Atypical agents										
Bupropion	0	+	+	–	–	–	0	–	–	0
Nefazodone	++	++	++	+++	–	++	–	+	++	0
Mirtazapine	–	0	0	+	++++	++++	+	–	++ ^d	0
Quetiapine	0	0	0	+	+	+	+	+	+++	++
Azapirones										
Buspirone	0	0	0	0	0	0	0	++	0	++

α , α -adrenoceptor; ACh, muscarinic acetylcholine receptor; D, dopamine; H, histamine; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

^aSymbols + to ++++++ indicate increasing levels of potency.

^b– indicated weak.

^c0 indicates no effect.

^dMirtazapine also blocks 5-HT₃ receptors (+++), which reduces nausea, and it has acute anxiolytic effects in humans.

Supplementary Table 3. Comparison of Novel 5-HT₄ Agonists

	Prucalopride	Mosapride	Velusetrag	Narlapride	YKP10811
Chemistry	Benzofuran-carboxamide	Benzamide	Quinolinone-carboxamide	Benzamide	Benzamide
Selectivity and affinity for 5-HT ₄ receptor	Highly selective, high affinity; weak affinity for human D ₄ and σ_1 , and mouse 5-HT ₃ receptors at concentrations exceeding the K _i for 5-HT ₄ receptors by 290-fold	High selectivity and affinity for 5-HT ₄ , But major metabolite (M1) with 5-HT ₃ -antagonistic activity	High affinity and selectivity for h5-HT _{4c} over other biogenic amine receptors; >500-fold selectivity over other 5-HT receptors (including h5-HT _{2B} , h5-HT _{3A})	Specific 5-HT ₄ full agonist activity in the GI tract, but a partial agonist activity in the heart	High binding affinity to the 5-HT ₄ receptor; 120-fold and 6-fold lower affinity, respectively, for 5-HT _{2A} and 5-HT _{2B} receptors than for 5-HT ₄ ; antagonist activity at 5-HT _{2B} receptor
Hepatic metabolism	Limited, not CYP 3A4	CYP 3A4	CYP 3A4	Hydrolytic esterase, not CYP 3A4	Oxidation of aromatic rings and N-dealkylation may involve CYP 3A4
Pharmacodynamic efficacy in humans	Accelerated colonic transit in health and in chronic constipation	Accelerated esophageal motility, gastric emptying and small bowel transit in health	Accelerated colonic transit in health in dose-related fashion	Accelerated colonic transit in health	Accelerated colon filling at 6 hours, t _{1/2} of ascending colon emptying, and colonic transit in functional constipation
Clinical trial efficacy	Phase 2 and 3 portfolio in chronic constipation	Clinical trials in dyspepsia, GERD, IBS-C, capsule endoscopy	Phase 2b	Phase 1b	Phase 2a study: increased stool consistency over 8 days (ITT analysis) in functional constipation
Open label effectiveness	Open label experience of ~1000 cumulative patient-years	Several years of market experience in Asian and South American countries	—	—	—
Arrhythmogenicity	No arrhythmic activity in human atrial cells; inhibited hERG channel only at μ M concentration (IC ₅₀ ~ 4.9 10 ⁻⁶ M); no clinically relevant cardiac AEs in clinical trials of >4000 humans	Low potency to inhibit hERG channels, no arrhythmic activity in clinical trials, no clinically relevant effects on QT-intervals	At 3 μ M, no effect on hERG channel current; safety ratio vs cisapride >1000-fold; no effect on QT in health or in 400 patients with constipation	At 100 μ M, no effect on hERG channel; affinity ratio between I _{Kr} and 5-HT ₄ receptors of >1000-fold	Inhibited hERG channel only at μ M concentration
Cardiovascular safety including elderly	Healthy subjects “thorough” QTc study; safety in elderly cohort 80% on CV drugs	Healthy subjects, no effects of mosapride on heart rate, blood pressure variabilities, autonomic nervous activity parameters, QT intervals, or QT dispersions	Healthy subjects “thorough” QTc study; transient increase in heart rate not different from placebo	Healthy subjects “thorough” QTc study	QTc prolonged at doses of 100 to 600 mg (target dose likely 10–20 mg)

Supplementary Table 3. Continued

	Prucalopride	Mosapride	Velusetrag	Narlapride	YKP10811
Most common adverse events	Diarrhea, headache	Diarrhea, abdominal pain, headache	Diarrhea, nausea, headache	Diarrhea, headache	Diarrhea, headache, borborygmi
Approval status	EMA, Canada, Mexico	A variety of Asian and South American countries	NA	NA	NA
Approved dose	2 mg/d in adults; 1 mg/d in >65 years	5 mg tid in adults	NA	NA	NA

NOTE. Adapted from Camilleri,¹⁴⁰ with permission.

AE, adverse event; CV, cardiovascular; EMA, European Agency for Evaluation of Medicinal Products; GERD, gastroesophageal reflux disease; hERG, human ether-à-go-go–related gene; IC₅₀, half maximal inhibitory concentration; ITT, intention to treat; Ki, dissociation constant; NA, not available (drug not approved).

Supplementary Table 4. Comparison of Secretagogues

	Lubiprostone	Linaclotide	Plecanatide	Tenapanor
Chemistry	Bicyclic fatty acid called a prostone	14 amino acid peptide, analog of guanylin and uroguanylin	16 amino acid peptide, analog of uroguanylin	Tetrahydroisoquinoline dimer
Target receptor	Chloride channel (ClC ₂); CFTR involved	Guanylate cyclase-C activation with CFTR-mediated secretion	Guanylate cyclase-C activation with CFTR-mediated secretion	Inhibitor of the intestinal sodium transporter NHE3
Pharmacodynamics in humans	Accelerated small bowel and colonic transit in health	Accelerated colonic transit in IBS-C in dose-related fashion	ND	ND
Clinical trial efficacy	Phase II and III portfolio in chronic constipation and IBS-C	Phase 2b and 3 in chronic constipation and IBS-C	Phase 2a in chronic constipation and 2b study in IBS-C	Phase 2b in IBS-C
Open label effectiveness	Clinical practice experience	—	—	—
Arrhythmogenicity	No arrhythmic activity	Low bioavailability No arrhythmic activity	Low bioavailability No expected arrhythmic activity	Low bioavailability No expected arrhythmic activity
Cardiovascular safety	Healthy subjects “thorough” QTc study	Healthy subjects “thorough” QTc study	Phase I safety	Safe on ECG studies
Most common adverse events	Nausea, diarrhea	Diarrhea	Diarrhea	Diarrhea
Potential other actions	Mucosal protection	Anti-nociceptive effects on afferent nerves	Anti-inflammatory, anti-apoptotic	—
Approval status	FDA, some other countries	FDA, EMA, Canada, Mexico	—	—
Approved doses	24 µg bid for constipation 8 µg bid for IBS-C	145 µg qd for constipation 290 µg qd for IBS-C	—	—

NOTE. Adapted from Camilleri,¹⁴⁰ with permission.
ECG, electrocardiogram; ND, not done; NHE3, sodium-hydrogen exchanger 3.

Supplementary Table 5. Opioid Antagonists Used to Treat Opioid-Induced Constipation

Drug name	Drug class	Pharmacodynamic efficacy in humans	Clinical trial optimal efficacy and safety	Approval specific to OIC
Oral naloxone	Nonselective opioid receptor antagonist	Reverses opioid-induced delay in orocecal and colonic transit	Naloxone PR formulation prevents OIC in patients receiving PR oxycodone	—
Methyl-naltrexone	PAMORA	Reverses effects of opioid in health and of chronic methadone treatment on orocecal transit; no effect on small intestinal or colonic transit delayed by codeine 30 mg qid in opioid-naïve healthy subjects	Subcutaneous MNTX 0.15 mg/kg on alternate days effective in inducing laxation in patients with advanced illness and chronic noncancer pain (12 mg daily or alternate days); side effect: diarrhea	FDA, Canada, and EMA (for OIC in palliative care)
Naltrexone ER	μ -opioid antagonist as sequestered core: ratio naltrexone to morphine 4%	ND	Open-label 12-month safety of combination ER pellets of morphine (median 59 mg/d) with a sequestered naltrexone core (qd or bid): OIC 31.8%, nausea 25.2%; opioid withdrawal <5%	—
Alvimopan	PAMORA	8-mg oral dose accelerates colonic transit and reverses effects of codeine in opioid-naïve healthy volunteers receiving codeine 30 mg qid	0.5 mg bid dose efficacious in treating OIC; rare instances of ischemic heart disease	Approved for postoperative ileus
Naloxegol	PAMORA; PEGylated naloxone conjugate	Normalized morphine-induced delay in orocecal transit	In two phase 3, twelve-week trials in adult patients with OIC and chronic noncancer pain, naloxegol 25 mg showed significant improvement in response rate vs placebo; adverse events in >9% abdominal pain and diarrhea	FDA, EMA
TD-1211	PAMORA	ND	5 mg and 10 mg/d TD-1211 increased average SBM/wk over 2 wk in OIC patients	—

NOTE. Adapted from Camilleri,²⁶⁹ with permission.

ER, extended release; ND, not done; PAMORA, peripherally acting μ -opioid receptor antagonist; PR, prolonged release; SBM, spontaneous bowel movement.

Supplementary Table 6. Examples of Potential Medications Targeting Motility and Secretion in Other Treatment Classes

Drug class	Examples	Rationale and putative action	Pharmacodynamic (intestinal or colon)	Clinical efficacy: phase 2b or 3 primary endpoints	Safety issues/ comments
TPH ₁ blocker	LX-1031	Inhibits synthesis of 5-HT by blocking TPH ₁ in enterochromaffin cells	Inhibits urinary 5-HIAA excretion; no studies of PD efficacy	Phase 2b trial in 155 non-IBS-C patients; 1000-mg dose improved global assessment of adequate relief and stool consistency	
Oral carbon adsorbent	AST-120	Adsorbs luminal factors that may be causing colonic dysfunction	No data	Phase 2b study in nonconstipated IBS; reduced pain and bloating, improved stool consistency	
$\alpha 2\delta$ ligand	Pregabalin	Reduced visceral afferent firing by blocking Ca ²⁺ channels	Increases rectal sensation thresholds in IBS; reduces colonic sensation ratings in healthy subjects	None	
NK2 receptor	Ibodutant	Inhibits visceral hypersensitivity		Phase 2b study: significant effect of the 10 mg/d dose in females in a prespecified analysis	
GLP-1 analog	Rose-010	Inhibits intestinal contractility	Reduces intestinal contractility and MMCs	Phase 2b study: reduced abdominal pain severity and increased number of responders in IBS	Nausea, vomiting
ASBT (IBAT) inhibitor	Elobixibat	Inhibits transport of bile acids	Accelerates colonic transit	Phase 2b study: increased SBMs and CSBMs in CIC	
FXR agonist	Obeticholic acid	Inhibits hepatic BA synthesis	Increases FGF-19 production in ileum	Improved stool frequency and form in open-label study in BA diarrhea	
Mast cell stabilizers	Disodium cromoglycate	Reduces tryptase and mediators that mediate immune activation, visceral hypersensitivity	Reduces jejunal biopsy mast cell mediators in IBS patients	Enhanced benefit from food restriction diet in IBS-D patients with food "allergies"	
	Ketotifen	Reduces tryptase and mediators that mediate immune activation, visceral hypersensitivity	Increases rectal sensation threshold in patients with baseline visceral hypersensitivity; rectal mucosal biopsy histamine and tryptase release not affected	Phase 2a study suggested benefit in relief of symptoms and pain in subset with baseline visceral hypersensitivity	Somnolence
Mesalamine	Mesalamine or mesalazine	Reduces mucosal inflammation	Reduces cytokines in rectal mucosal biopsies in IBS; effects on proteases of mesalamine compounds not consistently shown (positive results in n = 10 study not confirmed in n = 44 study)	Phase 2a small study with PD measurements showed improved overall well-being, but no significant effect on specific IBS symptoms; ineffective in 2 phase 2b larger trials	

NOTE. Adapted from Camilleri,¹⁴⁰ with permission.

ASBT, apical sodium dependent bile acid transporter; BA, bile acid; CIC, chronic idiopathic constipation; CSBM, complete spontaneous bowel movement; FGF-19, fibroblast growth factor 19; FXR, farnesoid X receptor; GLP, glucagon-like peptide; 5-HIAA, 5-hydroxyindoleacetic acid; IBAT, ileal bile acid transporter; MMC, migrating motor complex; NK, neurokinin; PD, pharmacodynamic; SBM, spontaneous bowel movement; TPH, tryptophan hydroxylase.

Supplementary Table 7. Gastrointestinal Conditions, Drugs, Genes, and Polymorphisms

Condition	Drug	Protein (gene)	Alleles or polymorphisms	Clinical effects
GERD <i>Helicobacter pylori</i> infection	PPIs	Cytochrome P450 2C19 (CYP2C19)	CYP2C19*2, CYP2C19*3, CYP2C19*4, CYP2C19*5	Wild-type predicts slower healing of esophagitis and lower cure rates of <i>H. pylori</i> infection. CYP2C19*5 results in decreased metabolism of drug.
FD, IBS	Tricyclic antidepressants, SSRIs Clonidine	CYP2D6 Serotonin transporter α 2-adrenoceptor	<i>CYP2D6</i> *3 <i>CYP2D6</i> *4 <i>CYP2D6</i> *5 <i>CYP2D6</i> *6 5HTT-LPR α 2A (C-1291G) SNPs	The extensively used TCAs and SSRIs are metabolized by CYP2D6; it causes drug interaction. In Caucasians, <i>5-HTTLPR</i> may be a predictor of antidepressant response and remission, while in Asians it does not appear to play a major role. Post-clonidine responses were associated with α 2A (C- 1291G) SNPs for gastric accommodation and rectal sensations of gas and urgency.
IBS-D	Alosetron Colesevelam	Serotonin transporter (SLC6A4) FGFR4 KLB	5HTT-LPR rs351855 rs497501	Patients with diarrhea and <i>5-HTTLPR</i> *LL homozygotes may predict better response and slowing of colonic transit. Differential colesevelam effects on ascending colon half- emptying time and on overall colonic transit at 24 hours.
IBS-C	Tegaserod CDC	Serotonin transporter (SLC6A4) FGFR4 KLB	5HTT-LPR rs376618 KLB Arg728 or rs17618244 (G allele)	Patients with constipation and <i>5-HTTLPR</i> *LL homozygotes may predict worse clinical response. Genetic variation in negative feedback inhibition of bile acid synthesis may affect CDC-mediated acceleration of colonic transit; rs376618 in <i>FGFR4</i> was associated with differences in the effects of CDC on colonic transit; effect of rs17618244 genotype on dose response in patients with IBS-C.

CDC, chenodeoxycholic acid; *FGFR4*, fibroblast growth factor receptor 4; GERD, gastroesophageal reflux disease; *5-HTTLPR*, serotonin transporter linked polymorphic region.

PPI, proton pump inhibitors; SLC, solute carrier; SNP, single nucleotide polymorphisms.