

Pharmacological, Pharmacokinetic, and Pharmacogenomic Aspects of Disorders of Gut–Brain Interaction



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We conducted a literature review of preclinical, animal and human pharmacology, pharmacokinetics, and pharmacogenomics related to disorders of gut–brain interaction (DGBI). This article reviews animal models of visceral pain, abnormal motility, and epithelial transport, and human models of motility and sensation and their utility in drug development for DGBI with focus on colorectal and gastric biomarkers. We highlight preclinical studies related to pharmacology, pharmacokinetics, and toxicology required for development of novel therapeutic agents, and principles of pharmacogenomics based on drug metabolism and the few examples of pharmacogenetics related to targets in treatment of IBS. Finally, we summarize the human pharmacology of medications used for treatment of DGBI based on the individual indications - specifically psychopharmacologic and nonpsychotropic agents for DGBI associated with dyspepsia, constipation, diarrhea, and visceral pain, as well as introduction of biomarkers for individualizing therapy for IBS and recommendations for future research.

Keywords: Sensation; Motility; Irritable Bowel Syndrome; Dyspepsia.

Our overall objectives are to appraise the pharmacology (including relevant pharmacokinetics) of medications used in patients with disorders of gut–brain interaction (DGBI), specifically validated animal models to study the effects on sensation and motility, preclinical pharmacology, pharmacokinetics, and toxicology data usually required for novel therapeutic agents, biomarkers validated for studies of sensation and motility endpoints in humans, pharmacogenomics of medications' metabolism and mechanistic targets of DGBI, and pharmacology of agents with potential including psychopharmacologic agents. We conducted literature reviews using key words, including pharmacology,

pharmacokinetics, pharmacodynamics, pharmacogenomics, and toxicology, as well as the names of each subtype of DGBI, in-person discussions, and a broader review at a harmonization session as part of the Rome V process.

Animal Models of Visceral Pain and Abnormal Motility Targeting New Drug Development

Preclinical research models remain important for the discovery and validation of novel therapeutics for DGBI. However, there are still major challenges, including the complex etiology and pathophysiology of DGBI, heterogeneous clinical phenotype overlapping other neuropsychiatric conditions, and dysfunctions of gastrointestinal (GI) motility, visceral hypersensitivity, enhanced gut permeability, environmental stressors, prior enteric infections, an abnormal microbiome, and altered immune responses. [Supplementary Figure 1](#) shows endpoints in experimental animal models applied in preclinical pharmacology of lead compounds.

Challenges to Developing Animal Models of Irritable Bowel Syndrome

Animal models should have etiology close to that of humans (face validity). The experimental condition used in the animal model should replicate the cause of the human disease (construct validity), and the responses to drugs in the animal model should reliably predict responses in humans (predictive validity).¹

Although no animal model reproduces all phenotypes and the multifactorial complexity of irritable bowel syndrome (IBS), some address one or more components consistent with IBS, including diverse stress models (eg, water avoidance, restraint, early life stress), chemical

Abbreviations used in this paper: 5-HT, serotonin/5-hydroxytryptamine; ACh, acetylcholine; BAD, bile acid diarrhea; bid, twice a day; C, cannabinoid; CB, cannabinoid; CBD, cannabidiol; CI, confidence interval; CIC, chronic idiopathic constipation; Cl, chloride; CYP, cytochrome; D, dopamine; DGBI, disorders of gut–brain interaction; EMA, European Medicines Agency; FD, functional dyspepsia; FDA, Food and Drug Administration; GF, germ-free; GI, gastrointestinal; H, histamine; hpf, high-power field; IBS, irritable bowel syndrome; IBS-C, constipation-predominant irritable bowel syndrome; IBS-D, diarrhea-predominant irritable bowel syndrome; IBS-M, IBS-mixed; Na, sodium; NHE, Na/H exchanger; NK, neurokinin; NNT, number needed to treat; OIC, opioid-induced constipation; PAMORAs, peripherally-acting μ receptor

antagonists; PDS, postprandial distress syndrome; PEA, palmitoylethanolamide; PEG, polyethylene glycol; qid, 4 times a day; RCT, randomized, controlled trial; RR, relative risk; SERT, serotonin transporter; SERT-P, promoter for synthesis of SERT; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; tid, 3 times a day; TRPV1, transient receptor potential ion channel of the vanilloid type 1.



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irritants, infection, and postinflammation – all of which induce visceral hypersensitivity that can be monitored with readouts such as abdominal wall electromyography during colonic distension. Given the female predominance of IBS,^{2,3} and sexually dimorphic effects of early life stress on visceral sensitivity reported in rodent models,^{4–7} further research on sex-related differences is warranted in rodent models of IBS.

Rodents/rats are also ideally suited for longitudinal studies due to their short lifespan. To ensure experimental reproducibility, it is essential to document the strain, sex, and age of the animals, their housing conditions, and diet.^{8,9}

Examples of Rodent Models of Irritable Bowel Syndrome–Like Pathophysiology

In rodents, repetitive daily stress models inform the neural mechanisms of sensitization and nociceptive signaling. Water avoidance stress for 1 hour induces acute visceral hypersensitivity while chronic exposure (1 hour daily for 7–10 consecutive days) induces colonic hypersensitivity for up to 28 days.¹⁰ Juvenile social defeat stress also induces IBS-like symptoms in mice.¹¹

Among models of early life stress, the best-studied model involves neonates separated from their dam for 3 hours a day during the postnatal period,¹² or odor attachment learning, which aims to recapitulate an abusive caregiver that leads only female pups to develop visceral hypersensitivity in adulthood.⁴ Other models of neonatal colonic irritation (mustard oil or repeated colorectal distension) in neonatal pups leads to altered colonic permeability, as well as visceral hypersensitivity in adult animals.^{13–16}

A transient colitis can be induced in male and female mice and rats by intracolonic instillation of acetic acid, zymosan, dextran sodium sulfate, or trinitrobenzenesulfonic acid leading to postinflammatory visceral hypersensitivity.¹

Other spontaneous models of IBS include Wistar Kyoto rats (hypersensitivity¹⁵ as well as impaired intestinal permeability¹⁶), BioBreeding rat (hypersensitivity, anxiety-like behavior),¹⁷ and genetic knock-out models (eg, decreased colonic sensitivity in corticotropin-releasing factor-1 receptor knock-out mice).¹⁸

Germ-free (GF) mice and colonoids from GF and humanized mice (eg, GF mice colonized with human stool from patients with diarrhea-predominant irritable bowel syndrome [IBS-D], compared with stool from healthy controls¹⁹) permit exploration of the role of microbiota and metabolites on host functions such as GI transit, barrier function, immune activation, inflammation, and anxiety-like behavior.

Assessment of Visceral Pain in Rodent Models Using Mechanical Stimuli

Experiments are performed in awake, freely moving or lightly restrained animals. The most frequently used stimulus is distension of a gut segment with a balloon connected to a barostat to measure compliance and the response to the painful stimulus simultaneously. A significant limitation of these models of visceral hypersensitivity is that the pain behavior is evoked and not spontaneous.

However, the paradigm mimics the quantitative measurements of visceral hypersensitivity in humans.

In the awake rat, the most commonly used endpoint is the contractions of abdominal muscles induced by rectal or colorectal distension. These correlate with the intensity of the stimulus and are measured using electromyography electrodes or strain gauges implanted surgically in the external oblique muscle.²⁰

Assessment of Motility and Epithelial Transport in Animal Models

Extrinsic primary afferent neurons link visceral pain to colonic motility through a spinal reflex in a murine model.²¹

Gastric emptying can be measured via a breath test in which freely moving mice in a chamber are given a test meal, often comprising heated egg yolk and 0.2 μ L ¹³C-octanoic acid.²²

In rodents, small intestinal motility is assessed by measuring progression of a marker in the GI tract after gavage (ie, distance of an orally administered dye or a radiolabeled meal). After a standardized period, the animal is euthanized and the entire GI tract is isolated and usually separated into the stomach, 10 equally sized segments of the small intestine, the cecum, and 3 equally sized segments of the colon. The geometric center of the distribution of the radioactivity is an index of GI motility.

Other in vivo methods to quantify small intestinal motility noninvasively include ultrasonography in anesthetized mice,²³ or telemetry for continuous measurements in awake, freely moving rats using strain gauges sutured onto the GI tract.²⁴

In preclinical models, epithelial transport, secretion and barrier function can be assessed in vitro or ex vivo, and in vivo,²⁵ such as the ex vivo Ussing chamber for assessing intestinal permeability,²⁶ in colonic biopsy specimens from humans and animals.²⁷ Parallel studies measure tight junction protein expression.

Human Models of Motility and Sensation: Utility in Drug Development for Disorders of Gut–Brain Interaction

Physiological tests (Figure 1 illustrating the tests applicable for lower DGBI) are potential biomarkers to understand the mode of action and to predict efficacy of experimental medicines for treatment of DGBI. Abnormal motility in DGBI is reviewed elsewhere.²⁸ The diverse methods available are described in the [Supplementary Material](#).^{29–72}

Preclinical Pharmacology, Pharmacokinetics, and Toxicology Studies Required for Novel Therapeutic Agents for Disorders of Gut–Brain Interaction

The Pharmacodynamics and Target Selectivity

Selectivity refers to the ability of a compound to interact with only 1 receptor subtype, at clinically used doses while avoiding adverse effects.

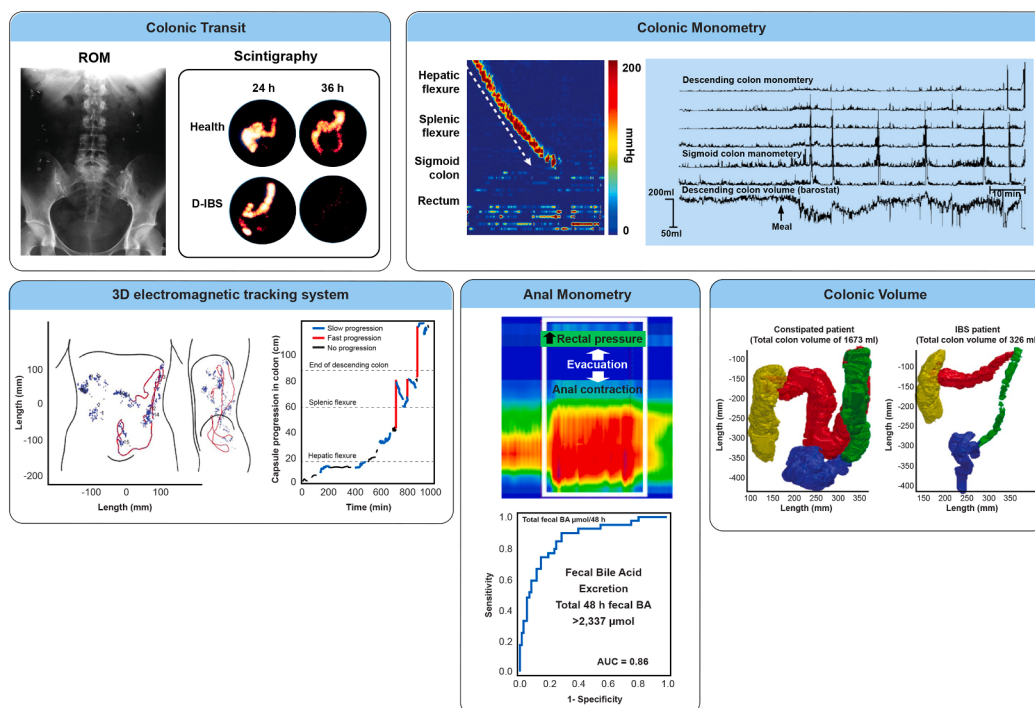


Figure 1. Examples of techniques to measure GI functions in lower DGBI. These techniques include 3D electromagnetic tracking to measure colonic transit, barostat-manometry measurement of left colon motility using barostat (for tone) and multilumen manometry, and high-resolution anorectal manometry. Adapted with permission from Gut 2023;72:590–599. AUC, area under the curve; ROM, radiopaque markers.

However, drug selectivity should also refer to all the desirable biological effects of a single agent at therapeutic doses, potentially with different biological targets within the GI tract.

Because of the multifactorial pathophysiology of DGBI and interindividual differences, single receptor-modulating drugs may be less likely to achieve a substantial therapeutic gain. However, a ligand with multiple actions may not achieve balanced potency and activity at each target, a suitable pharmacokinetic profile, and avoidance of toxicity.

It would be ideal to define the likely mechanism(s) underpinning DGBI symptoms in an individual patient using validated actionable biomarkers to individualize therapy (discussed below). However, recruitment of patient subgroups based on a specific phenotype or biomarker may reduce the generalizability of the outcomes of the trial. Currently, no drug addresses all potentially relevant mechanisms. In summary, clinicians and investigators involved in the treatment or investigation of DGBI or disease models need to have a comprehensive understanding of a vast range of medications.

Pharmacokinetics

Ideal pharmacokinetics of a drug with systemic action include high oral bioavailability, half-life suitable for once-daily administration, lack of drug-drug interactions, absence of unwanted pharmacologic actions of metabolites,

and no interactions with food or other drugs. Further details on drug metabolism and interactions are briefly discussed in the [Supplementary Material](#).⁷³

Concepts for Developing Agents for Disorders of Gut–Brain Interaction

There are at least 4 key aspects that need to be integrated into treatment of DGBI where low systemic bioavailability may be desirable.

1. Multifactorial pathophysiology should either be addressed by designed multiple ligands⁷⁴ or by restricting availability to the enteric environment (eg, rifaximin, lubiprostone, linaclotide, plecanatide, tenapanor, or probiotics), or excluding penetration of the blood–brain barrier (eg, with peripherally-acting μ receptor antagonists [PAMORAs], or eluxadoline), or by action exclusively in the GI tract and liver (eg, farnesoid X receptor agonists such as obeticholic acid).
2. Gut microbiome is a target for therapeutic intervention,^{75,76} and may affect the actions of a drug. Conversely, the drug may alter the microbiome.
3. Development of novel agents from natural sources: reverse pharmacokinetics and reverse pharmacodynamics have been proposed as innovative approaches to the development of new drugs, especially

those from natural sources,⁷⁷ to take advantage of the purported clinical benefits documented by historical use. Examples include curcumin in inflammatory conditions or Iberogast (STW5) in functional dyspepsia.⁷⁸

4. Local or systemic actions: physiologically based pharmacokinetic models to examine oral drug absorption and actions on intestine and liver⁷⁹ additionally include targeted drug delivery to intestinal epithelia or specialized intestinal cells such as M cells, goblet cells, and dendritic cells.⁸⁰ These approaches include nanoparticles, nanobiologics, or extracellular vesicles.^{81,82}

Safety Aspects

Apart from the standard safety evaluations of every new medicine, some examples relevant to DGBIs warrant specific attention, such as tachyarrhythmia, prolongation of QT interval, and blockade of the human ether-a-go-go related gene K^+ channels with 5-HT₄ agonists,⁸³ colonic ischemia with 5-HT₃ antagonists (in about 1 in 1000 patients),⁸⁴ and pancreatitis associated with eluxadoline.⁸⁵ From a regulatory perspective, drugs for DGBI must demonstrate safety, although patients with IBS are willing to accept substantial risks associated with medications.⁸⁶ Undesired effects must be identified as early as possible in drug development.⁸⁷ The potential for drug interactions is exacerbated by polypharmacy in DGBI, particularly in view of the frequent use of psychotropic agents, which often depend on CYP2D6 metabolism.

Pharmacogenomics in Disorders of Gut–Brain Interaction

Principles. 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, and drug response at cellular, tissue, individual, or population levels.

Influence of genetics on the response to medications. There may be genetic polymorphisms in drug metabolism. For example, CYP2D6 determines the pharmacokinetics and plasma levels of central neuromodulators including tricyclic agents,⁸⁸ and the action of codeine (which must be converted to morphine by the CYP2D6 isoenzyme to be effective).

Genetic polymorphisms may also involve transporters⁸⁹ that may lead to pharmacodynamic variations in DGBI. Serotonin (5-HT) undergoes reuptake by serotonin transporter (SERT). SERT polymorphisms are associated with a greater colonic transit response in those with long homozygous than heterozygous or short homozygous polymorphisms in IBS-D.⁹⁰

These principles are illustrated in the section on the pharmacogenetics effects on treatment of DGBI, especially IBS.

Pharmacologic Agents for Disorders of Gut–Brain Interaction

Agents Not Directed at Central Neuromodulation

GI motor and sensory functions can be altered through several pharmacologic approaches (Figure 2); Figure 2 upper panel shows potential cellular and mechanistic targets for drug actions in DGBI and motility disorders. Figure 2 lower panel summarizes receptors located on different cellular targets and their potential as treatments for DGBI.

The most important clinically applicable therapeutic choices as well as pharmacologic targets in DGBI are summarized in Table 1 and Figures 3 and 4 and are discussed in this section. Two other classes of agents that are commonly used in DGBI are laxatives for the treatment of constipation (alone or in association with IBS)⁹¹ and probiotics.⁹² There have been several meta-analyses on pharmacologic treatments for IBS.⁹³ The pharmacologic actions on monoamine reuptake and receptors are summarized in Supplementary Table 1.

Current Drug Treatments for Upper Disorders of Gut–Brain Interaction

Serotonergic agents. 5-HT plays a key role in the control of GI motility, sensitivity, and secretion. Actions of 5-HT are terminated by a reuptake system that is inhibited by antidepressants.⁹⁴ Selective serotonin reuptake inhibitors (SSRIs) alter motility in the stomach, small bowel, and colon.⁹⁵ However, no convincing beneficial therapeutic effects have been reported in upper DGBI. Mirtazapine (an antidepressant and antagonist of the histamine H₁ receptor, the α 2 adrenergic receptor, and the serotonin 5-HT_{2C} and 5-HT₃ receptors) was evaluated in an 8-week trial in 34 patients with functional dyspepsia (FD) who had lost more than 10% of original body weight but without depression or anxiety. This showed no benefit on overall FD symptoms, although mirtazapine improved early satiation, quality of life, GI-specific anxiety, nutrient tolerance, and weight loss.⁹⁶

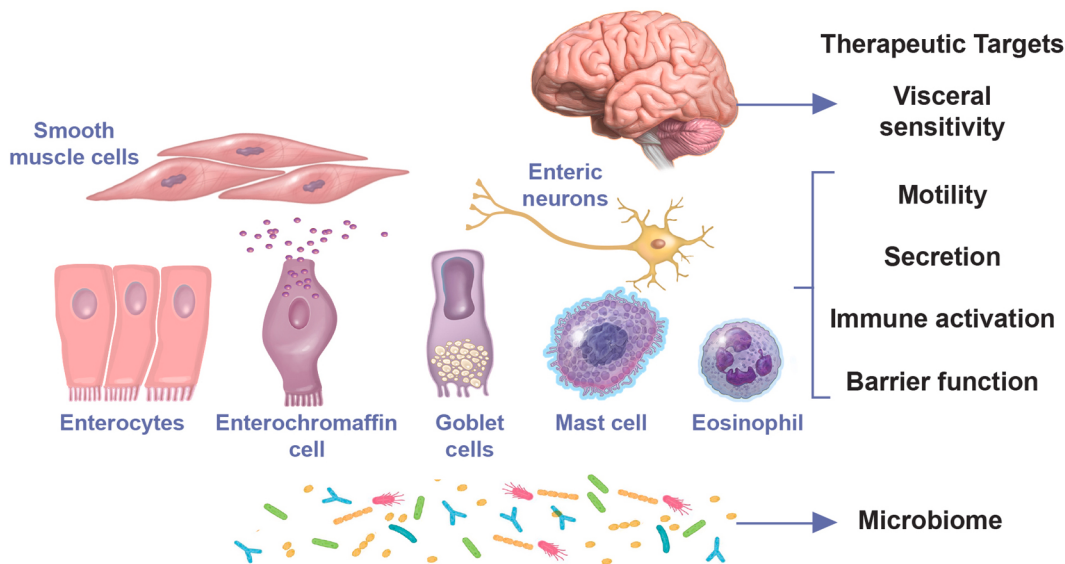
Several 5-HT receptor subtypes are present on both nerves and smooth muscle and mediate numerous different actions.⁹⁷

5-HT₄ receptor agonists, such as prucalopride and mosapride, act on intrinsic neurons to stimulate esophageal, gastric, small bowel, and colonic transit in health, gastroesophageal reflux disease, FD, constipation, and constipation-predominant irritable bowel syndrome (IBS-C).^{98–104}

In the stomach, 5-HT₄ receptor agonists enhance postprandial proximal gastric volume in health but have no effect on sensation.¹⁰⁵

Mosapride is approved for the treatment of FD and gastroesophageal reflux disease in some Asian and South American countries.

Dopamine receptor antagonists. Dopamine D₂ receptor antagonists have gastroprokinetic and central



Enterocyte	EC cell	Myocyte	Neuron	Mast cell	Eosinophil
CIC-2	5-HT _{3,4}	5-HT ₄	5-HT _{1A, 3,4}	H ₁	Siglec-8
CFTR	SST ₂	Motilin	Motilin, CCK ₁		Dupilumab
GC-C		Ghrelin	Ghrelin		
NHE ₃	M ₃	M _{1,2,3}	M ₂ , D ₃ , CB ₁	CB ₂	
SST ₂		β ₃	α ₂ , β ₃ , NMDA	SST ₂	
FXR			TRPV ₁ , NK ₂	NK _{1,2,3}	
IBAT			Opioid _{μ,δ,κ}		
			Ca ²⁺ channel		

Figure 2. (Upper Panel) Potential local therapeutic targets for drug action in the gut include visceral sensitivity, microbiome, motility, secretion, immune and eosinophilic activation, and barrier function. (Lower Panel) The therapeutic targets include central and enteric nervous systems, visceral sensitivity, microbiome, motility, secretion, immune activation, and epithelial barrier function. 5-HT₃, 5-HT₄, and 5-HT_{1a}, serotonin receptors; α₂, alpha 2 adrenal receptor; β₃, beta adrenal receptor 3; Ca²⁺, calcium channel; CB₁ and CB₂, cannabinoid receptors 1 and 2; CCK₁, cholecystokinin type 1 receptor; CFTR, cystic fibrosis transmembrane conductance regulator; CIC-2, chloride channel 2; D₃, dopamine receptor 3; FXR, farnesoid X receptor; GC-C, guanylate cyclase C; H₁, histamine receptor 1; IBAT, ileal bile acid transporter; M₁, M₂, and M₃, muscarinic receptors; NHE₃, Na⁺H⁺ exchange receptor 3; NK₁, NK₂, and NK₃, neurokinin receptors 1, 2, and 3; NMDA, N-methyl-D-aspartate receptor; opioid μ, δ, and κ, opioid receptors mu, delta, and kappa; Siglec-8, sialic acid binding Ig-like lectin 8; SST₂, somatostatin receptor; TRPV₁, transient receptor potential vanilloid 1.

antiemetic properties resulting in suppression of nausea and vomiting. Although metoclopramide and domperidone have been used in the treatment of FD and gastroparesis,¹⁰⁶ treatment is only recommended for short periods. Domperidone is listed among drugs with a known risk of torsades de pointes (www.crediblemeds.org).

Itopride is a benzamide that acts as both a D₂ receptor antagonist and acetylcholinesterase inhibitor. It has been investigated in FD^{107–109} and is approved for the treatment of FD in a number of Asian and European countries.

Peppermint oil. In a meta-analysis of 5 randomized controlled trials (RCTs; 578 participants), the combination of peppermint oil and caraway oil showed significant benefit in the global improvement of FD symptoms and in

epigastric pain; the number needed to treat (NNT) for both endpoints was estimated at 3. This combination was effective and safe for the short-term treatment of FD. However, this is based on small sample sizes and low/very low quality of evidence.¹¹⁰

Acotiamide. Acotiamide exerts prokinetic effects at least in part by inhibiting acetylcholinesterase (decreasing the degradation of acetylcholine [ACh]) and by antagonizing presynaptic muscarinic M₁ and M₂ receptors, thereby increasing the release of ACh. In patients with FD, acotiamide improved gastric accommodation and gastric emptying. It was more effective in postprandial distress syndrome (PDS) than epigastric pain syndrome.¹¹¹

Table 1. Agents Directed to Amines/Receptors and Peptides to Affect Functions of the Upper and Lower GI 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, increase colonic compliance
	5-HT ₄ receptor agonists (eg, prucalopride, velusetrag, mosapride, naronapride, felcisetrag)	Enteric neurons, smooth muscle cells	Enhances secretion and motility, reduce visceral sensitivity	Accelerate transit, increase colonic HAPC and gastric accommodation, reduce inhibition of RIII reflex during rectal distension
	5-HT _{1A} receptor agonists (eg, buspirone)	Enteric neurons, extrinsic afferent neurons	Inhibits motility and enhance compliance	Increase accommodation
Ach (Muscarinic)	M ₃ receptor antagonists (eg, darifenacin)	Smooth muscle	Increase smooth muscle relaxation, compliance	Retard small bowel and colonic transit
	M ₁ and M ₂ receptor antagonists	Enteric neurons and smooth muscle	Increase gastric emptying	May enhance accommodation
	Acetylcholinesterase inhibitors (eg, acotiamide, itopride)	Enteric neurons and smooth muscle	Increase gastric emptying	Increase gastric emptying and accommodation
Adrenoceptors	β_3 -adrenoceptor agonists	Smooth muscle	Inhibit motility	No published data
	α_2 -adrenoceptor agonists (eg, clonidine)	Enteric neurons and enterocytes	Reduce secretion, enhance compliance, and reduce motility and tone	Reduce secretion, enhance compliance, and reduce motility, tone, and sensation
Dopamine	D ₂ -receptor antagonists (eg, domperidone, metoclopramide, itopride)	Area postrema, smooth muscle, enteric neurons	Contract muscle	Antiemetic, prokinetic, reduce sensation?
Motilin	Motilides	Smooth muscle, enteric neurons	Stimulate motility	Stimulate motility and transit
Ghrelin	Ghrelin agonists (eg, relamorelin)	Hypothalamus, stimulation of vagus and pelvic nerves	Induce eating	Accelerate gastric emptying, reduce gastric accommodation
Cannabinoid	Δ -9-tetrahydro-cannabinol	CBR2 on enteric neurons, immune cells; CBR1 on enteric neurons and vomiting center	Slow GI transit	Delay gastric emptying, antiemetic properties
Opioids	μ -receptor agonists (eg, loperamide)	Enterocyte, enteric neurons, afferent neurons, and inflammation	Reduce intestinal secretion and transit	Slow colonic transit, antidiarrheal, increase resting anal tone
	μ -receptor antagonists (eg, naloxone, methyl-naltrexone, alvimopan, naloxegol, naldemedine)	Enteric neurons, afferent neurons, and inflammation	Reverse opioid effects on motility	Accelerate colonic transit, reverse OIC, reduce duration of PO ileus
	κ -receptor agonists (eg, fedotozine, asimadoline)	Enteric neurons and afferent neurons	Reduce sensation, variable effect on motility	Reduce sensation
	μ - and κ -opioid receptor agonist and δ -opioid receptor antagonist (eluxadoline)	Enteric neurons and afferent neurons	Reduce intestinal secretion and transit	Reduce sensation and diarrhea and global IBS symptoms
Somatostatin	SSR-2 receptor agonists (eg, octreotide, lanreotide)	Enterocytes, submucosal neurons, myenteric neurons	Retard transit, reduce afferent firing and sensation	Slow transit, reduce sensitivity; enhance absorption

Table 1. Continued

Target system/receptor	Type of ligand	Distribution of receptors	Pharmacologic action in animals	Pharmacologic action in humans
Tachykinin	NK ₁ -receptor antagonists (eg, aprepitant, tradipitant)	Enteric neurons, interstitial cells of Cajal, smooth muscle, immune cells	Inhibit motility, fluid secretion, vagal afferent sensation, and inflammation	Antiemetic
	NK ₂ -receptor antagonists (eg, ibodutant)	Enteric neurons, smooth muscle, extrinsic afferents	Inhibit motility, water secretion, sensation, inflammation	Inhibit NKA-induced motility
	NK ₃ -receptor antagonists (eg, talnetant)	Enteric neurons, extrinsic afferents	Inhibit motility and sensation	No published data
Guanylate-Cyclase-C	GC-C-agonists (eg, linacotide, plecanatide)	Luminal side of the enteric mucosa	Induce secretion of HCO ₃ ⁻ , Cl ⁻ , water and inhibit visceral nociceptors via cGMP	Decrease stool consistency, accelerate colonic transit, decrease visceral pain
Chloride channels	ClC2 activators (ie, lubiprostone)	Enteric mucosa	Induce secretion of HCO ₃ ⁻ , Cl ⁻ , water	Decreases stool consistency, accelerates colonic transit
NHE ₃ transporter	NHE ₃ inhibitor (ie, Tenapanor)	Enteric mucosa	Inhibits absorption of Na ⁺	Improves stool consistency

cGMP, cyclic guanosine monophosphate; ClC, chloride channel; GC-C, guanylate cyclase C; HAPC, high amplitude propagated contraction; 5-HT, serotonin; NK, tachykinin; NHE, sodium-hydrogen exchange; PO, postoperative; SSR, somatostatin receptor.

Acotiamide is approved in Japan for FD. A 4-week, phase 3 trial in Japan confirmed its efficacy as 100 mg 3 times a day in PDS, with benefit over placebo for postprandial fullness, upper abdominal bloating and early satiation.¹¹²⁻¹¹⁴ Its long-term efficacy in PDS was supported in an open label trial from Europe.¹¹⁵

Pregabalin. In patients with FD who had not responded to proton pump inhibitor treatment, pregabalin 75 mg once daily for 8 weeks was superior to placebo in self-reported adequate relief of symptoms.¹¹⁶

Drugs in development for upper disorders of gut-brain interaction. Capsaicin. The transient receptor potential ion channel of the vanilloid 1 (TRPV1), expressed by primary afferent neurons, is a trigger for chemoreception and may be up-regulated in some functional GI disorders.¹¹⁷ Capsaicin may accentuate or reproduce pain in FD.¹¹⁸⁻¹²⁰ Long-term administration of capsaicin, which is believed to desensitize TRPV1, was more effective than placebo in decreasing symptoms in FD¹²¹ by targeting receptors of TRPV1 or calcitonin gene-related peptide. Calcitonin gene-related peptide is a neurotransmitter produced by the primary afferent neurons.

Cannabinoids. Cannabinoid CB₁ receptors are expressed on nociceptive afferents and enteric nervous system neurons. Activation of CB₁ receptors slows GI transit in animals through inhibition of ACh release and, possibly, by stimulating cholecystokinin secretion via CB₁ expressed in cholecystokinin-producing cells.¹²² The nonspecific agonist Δ-9-tetrahydrocannabinol has strong antiemetic properties and delays gastric emptying in humans.^{123,124}

Despite evidence of cannabinoids delaying gastric emptying and potentially inducing nausea and hyperemesis, patients with severe nausea/vomiting and abdominal pain often use cannabis, perceiving it to be beneficial for their symptoms.^{125,126}

Cannabidiol (CBD) is a noneuphoric phytocannabinoid with weak or no ability to activate cannabinoid receptors. A randomized, placebo-controlled trial administered CBD 20 mg/kg/d off-label (a dose approved by the United States Food and Drug Administration [FDA]) for 4 weeks in patients with FD associated with normal gastric emptying of solids. There were no effects on physiological functions or patient response outcomes.¹²⁷

Similarly, a cross-over trial of a chewing gum formulation containing 50 mg of CBD showed no effect on abdominal pain.¹²⁸

Palmitoylethanolamide (PEA), an endogenous fatty acid amide chemically related to and coreleased with anandamide, has been proposed in FD, based on the observation that the acid-induced endogenous release of PEA is impaired in duodenal biopsies of patients with FD and its exogenous administration counteracts mast cell activation.¹²⁹

Targeting Microinflammation, Mast Cells, and Eosinophil Infiltration in Dyspepsia and Irritable Bowel Syndrome

There is increased recognition of the overlap of microinflammation—mast cell and eosinophil infiltration

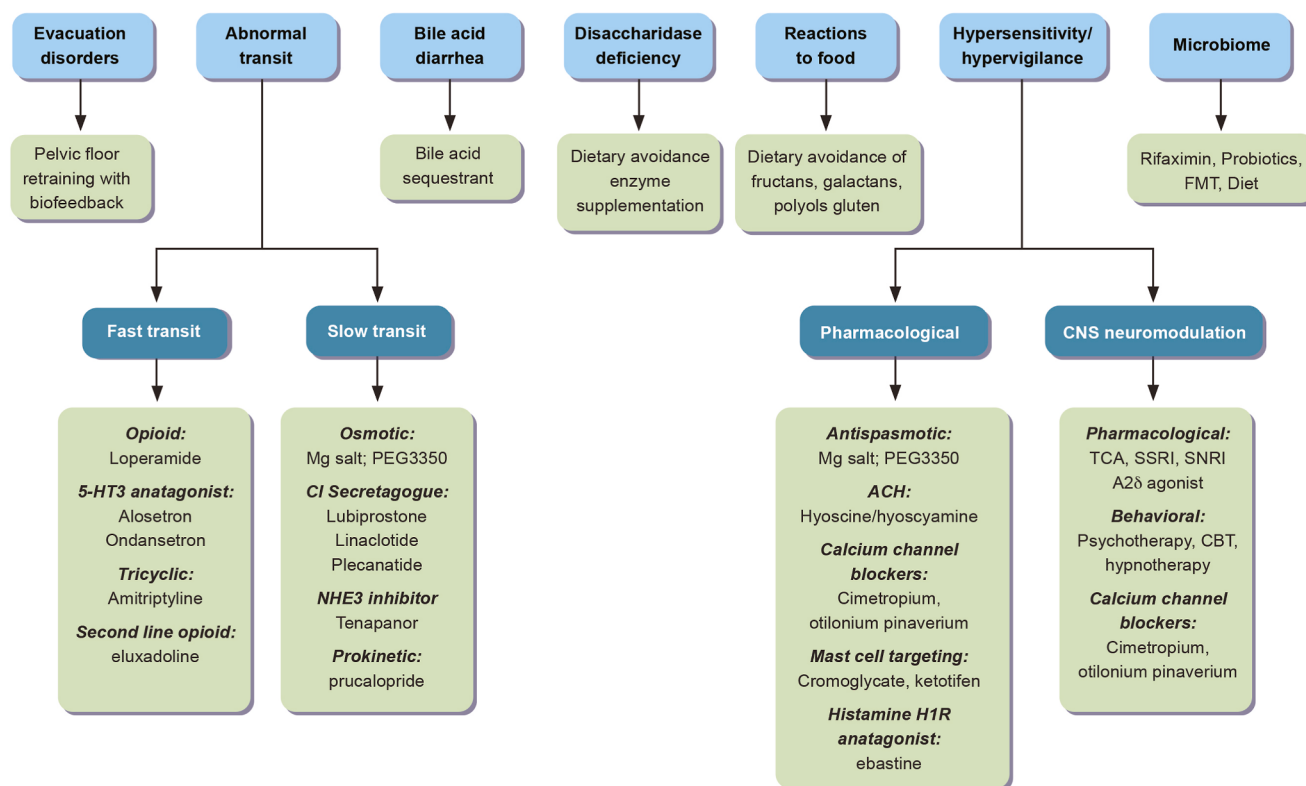


Figure 3. Therapeutic choices guided by pathophysiology and biomarkers. The therapeutic targets and biomarkers include evacuation disorders, abnormal transit, bile acid diarrhea, disaccharidase deficiency, reactions to food, and hypersensitivity or hypervigilance. Adapted with permission from Gut 2023;72:590–599. 5-HT₃, 5-hydroxytryptamine; CBT, cognitive behavioral therapy; FMT, fecal microbiota transplantation; SNRI, serotonin and norepinephrine reuptake inhibitor.

manifesting histologically as gastritis or duodenitis—and FD.^{130,131} About 4% of patients diagnosed with functional diarrhea or IBS-D have primary eosinophilic colitis.¹³² Proton pump inhibitors may improve FD, at least in part, through effects on eosinophil infiltration,¹³³ eosinophil degranulation,¹³⁴ mast cell infiltration, and duodenal permeability.¹³⁵

The optimized diagnostic criteria require the presence of ≥ 30 eosinophils/high-power field (eos/hpf) in ≥ 5 hpfs for eosinophilic gastritis, and ≥ 30 eos/hpf in ≥ 3 hpfs for eosinophilic duodenitis.^{136,137} Duodenal eosinophil degranulation may be increased in patients with FD.^{134,138,139} Treatment of eosinophilic gastritis and eosinophilic duodenitis with lirentelimab (AK-002), a nonfucosylated monoclonal antibody targeting sialic acid-binding immunoglobulin-like lectin 8, an inhibitory receptor that is selectively expressed on mature eosinophils and mast cells, improved upper GI symptoms.¹⁴⁰

Chronic Constipation and Irritable Bowel Syndrome With Predominant Constipation

Among treatments for IBS-C, 1 large RCT of PEG 3350 showed improvement of constipation, but not pain.¹⁴¹

The 3 general categories of medications in development for the treatment of chronic idiopathic constipation (CIC) and IBS-C are colonic prokinetics (5-HT₄ receptor agonists),

intestinal secretagogues, and bile acid modulators. More specific medications have been developed for opioid-induced constipation (OIC).

5-HT₄ receptor agonists. There are 7 main subtypes of 5-HT receptor.¹⁴² Those most relevant to GI motor and sensory disorders are 5-HT₃ and 5-HT₄. 5-HT₄ receptors are also present in the heart. 5-HT₄ receptor agonists induce fast excitatory postsynaptic potentials in intrinsic neurons, release neurotransmitters such as ACh, resulting in prokinetic effects,^{39,40} and induce mucosal secretion by activating submucosal neurons. In animal studies, activation of colonic mucosal 5-HT₄ receptors inhibited visceral hypersensitivity.¹⁴³

Older 5-HT₄ receptor agonists (eg, cisapride) had relatively poor receptor selectivity and affected other receptors or ion channels (eg, the delayed rectifier K⁺ channel or I_{Kr}) potentially causing cardiac arrhythmia. Newer 5-HT₄ receptor agonists (eg, prucalopride) have >150-fold greater selectivity for 5-HT₄ receptors than for I_{Kr} channel.¹⁴⁴

5-HT₄ agonists with great specificity that are in use or development (including human trials) include prucalopride, mosapride, velusetrag, naronapride, and felcisetrag (Supplementary Table 2).

There is considerable evidence to support the efficacy and safety of prucalopride in patients with CIC^{145–151} with approval by the European Medicines Agency (EMA) and the FDA. However, there are no trials conducted in IBS-C or registered with clinicaltrials.gov.

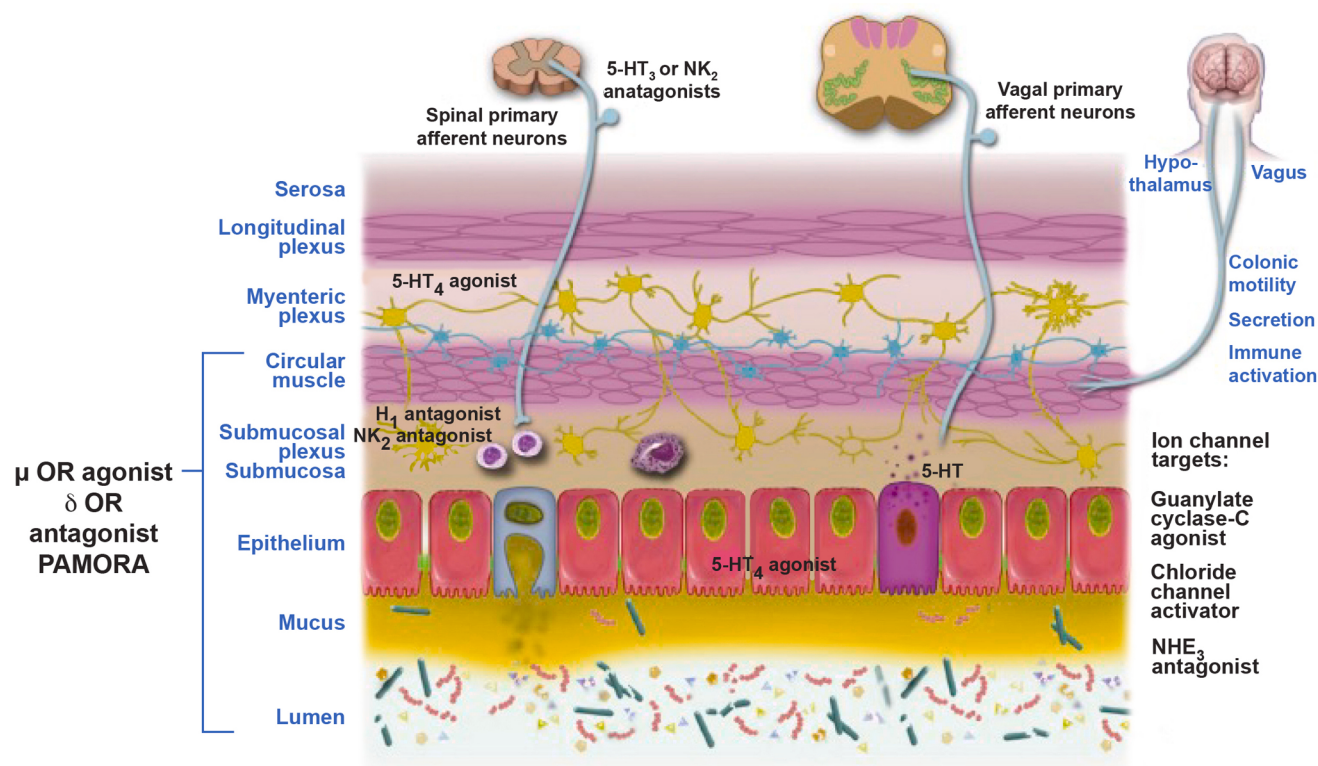


Figure 4. Localization and nature of major targeted receptors in the treatment of DGBI. The targeted receptors are located in enterochromaffin cells, epithelial cells, smooth muscle cells, neurons, and immunocytes. 5-HT₃ and 5-HT₄, serotonin receptors; H₁, histamine receptor 1; NHE₃, Na⁺/H⁺ exchanger receptor 3; NK₂, tachykinin receptor 2; μ and δ , opioid receptors mu and delta.

Velusetrag and naronapride are still in early development and have significant effects on colonic transit and constipation.^{152–154}

Intestinal chloride secretagogues. Chloride ions (Cl⁻) enter enterocytes or colonocytes through the basolateral sodium (Na⁺)-potassium (K⁺)-2Cl⁻ cotransporter. Na⁺ and K⁺ ions are then exported through the Na⁺ pump (Na⁺, K⁺, ATPase) and KCNQ1/KCNE3 heteromeric K⁺ channels. Chloride secretion in the apical membrane of epithelial cells occurs through the cystic fibrosis transmembrane regulator (activated by guanylate cyclase agonists linaclotide and plecanatide) and ClC-2 chloride channels, activated by lubiprostone.¹⁵⁵ Chloride secretion is activated by intracellular mediators including calcium ions and cyclic guanosine monophosphate.

Lubiprostone is a bicyclic fatty acid with structural similarity to prostaglandin E₁. It has demonstrated efficacy in CIC and OIC (at a dose of 24 μ g bid) and in IBS-C (at a dose of 8 μ g bid) and is approved by the FDA and several other regulatory authorities.^{156–162}

Linaclotide and plecanatide stimulate intestinal Cl⁻ secretion through apical cystic fibrosis transmembrane regulator chloride channels and inhibit sodium absorption through blockade of an apical Na/H exchanger (NHE).¹⁶³ In addition to its secretory effects, linaclotide induces extracellular release of cyclic guanosine monophosphate that

inhibits visceral nociceptors.¹⁶⁴ Linaclotide improved constipation and abdominal pain in large trials in patients with CIC or IBS-C,^{41–43,165–169} and is approved for the treatment of IBS-C (at a dose of 290 μ g/d) by the FDA, the EMA, and the Swiss Agency, and for the treatment of CIC (at doses of 72 or 145 μ g/d) by the FDA.

Plecanatide is another guanylate cyclase-C agonist effective at treating constipation and pain, at the 3 mg once daily dose¹⁷⁰ in IBS-C and CIC.¹⁷¹ It is FDA-approved for the treatment of CIC and IBS-C in adults.

Tenapanor is a sodium-hydrogen channel exchange type 3 (NHE3) inhibitor that blocks the absorption of Na⁺ through the NHE3 transporter. In IBS-C, tenapanor 50 mg bid, was efficacious and well tolerated to 26 weeks.¹⁷² It is FDA-approved for the treatment of IBS-C in adults.

Supplementary Table 3 summarizes the properties of lubiprostone, linaclotide, plecanatide, and tenapanor.¹⁷³

Bile acid modulation. Delivery of bile acids into the colon, due to <95% ileal reabsorption, increases permeability, activates colonocyte adenylate cyclase, and increases colonic motility resulting in bile acid diarrhea (BAD).¹⁷⁴

Elobixibat selectively inhibits the ileal bile acid transporter, increases intracolonic bile acids, and accelerates colonic transit.¹⁷⁵ It significantly reduces stool consistency, ease of stool passage and straining, and increases stool frequency, improving constipation-related symptoms.

Response was noted during the first week and benefit was maintained over 8 weeks.¹⁷⁶ The long-term colonic exposure to increased bile acids remains a potential concern for colonic carcinogenesis.¹⁷⁷ A study of Danish health registries showed cumulative incidence of GI cancer 6 years after BAD diagnosis of 1.6% among 5245 patients with BAD and 1.1% among 52,540 controls ($P < .01$), with significant increases in colon, rectal, anal, and pancreas cancers. In contrast, it was generally safe in the prospective, 1-year open-label extension after the short placebo-controlled phase.¹⁷⁸ Partial ileal bypass for hyperlipidemia has not been associated with increased prevalence of colorectal cancer during up to 25 years' follow-up.¹⁷⁹

Peripherally-Acting Opioid Receptor Antagonists in Opioid-Induced Constipation

PAMORAs reverse the peripheral effects of opioids without compromising central opioid analgesia.

Methylnaltrexone is available as a tablet and as a subcutaneous injection. Recommended doses are 12 mg subcutaneously once daily or 450 mg orally once daily in the morning. Methylnaltrexone, naloxegol 25 mg once daily, and naldemedine 0.2 mg once daily are all approved by the FDA and EMA for OIC in patients with chronic noncancer as well as cancer-related pain refractory to laxatives. These agents are summarized in [Supplementary Table 4](#).

Prucalopride,¹⁸⁰ lubiprostone,^{181,182} and dolcanatide (a guanylate cyclase-C agonist)¹⁸³ are also effective in OIC.

Chronic Diarrhea and Irritable Bowel Syndrome With Predominant Diarrhea

In the absence of mucosal diseases, chronic diarrhea generally results from increased intestinal or colonic motility or secretion, increased colorectal sensitivity and/or alterations of the intestinal content including microbial flora or organic (bile and short chain fatty) acids, and intestinal permeability. Current drug treatments for chronic diarrhea and IBS-D are summarized here.

Peripheral μ -opioid receptor agonists. The μ -opioid receptor agonist loperamide has limited ability to penetrate the blood-brain barrier and is available for over-the-counter purchase. It inhibits secretion, slows colonic transit, and increases resting anal sphincter tone.¹⁸⁴ Diphenoxylate can cross the blood-brain barrier and is, therefore, combined with atropine to reduce the potential for abuse. It is only available by prescription. Although each has proven efficacy in reducing diarrhea, particularly acute diarrhea, neither has been subjected to high-quality clinical trials in IBS-D³⁵ or has proven efficacy on individual or global IBS-D symptoms other than diarrhea. Adverse effects seen with diphenoxylate, due to atropine, include bladder dysfunction, glaucoma, and tachycardia.

μ -opioid receptor agonist and δ -opioid receptor antagonist (eluxadoline). Eluxadoline, a combination μ -opioid receptor agonist and δ -opioid receptor antagonist, is efficacious in IBS-D.^{185,186} The approved dose is 100 mg twice-daily taken with food; the 75 mg twice-daily dose is recommended for specific categories of patients. Safety

concerns with eluxadoline include sphincter of Oddi spasm, sometimes complicated by acute pancreatitis. Absolute contraindications are prior cholecystectomy, history of sphincter of Oddi dysfunction or acute pancreatitis or structural diseases of the pancreas, severe hepatic impairment, alcoholism, alcohol abuse, alcohol addiction, or >3 alcoholic beverages per day.

5-HT₃ receptor antagonists. 5-HT₃ receptor antagonists, such as ondansetron or alosetron, delay orocecal and colonic transit^{187–190} and increase colonic compliance,¹⁹¹ and also reduce sensitivity to isobaric distention of the colon documented by higher volume thresholds for first sensation and pain.¹⁹¹ Several clinical studies confirmed its efficacy in IBS-D.³⁷ It carries a small risk of potentially serious colonic ischemia. It is only FDA-approved for women with severe IBS-D that has not responded to other treatments; it is contraindicated in patients with any component of constipation. Ondansetron, another 5-HT₃ antagonist, is approved for the treatment of chemotherapy-induced nausea and vomiting. It is often used off-label for IBS-D as it controls diarrhea.¹⁹² In TRITON (RCT of 80 evaluable patients), symptoms of IBS-D improved compared with placebo, but failed to meet statistical significance. In a pooled analysis of 3 RCTs, ondansetron was superior to placebo for the FDA composite endpoint and for reduction in stool frequency, although not for abdominal pain.¹⁹³

Ramosetron, a selective 5-HT₃ receptor antagonist, is licensed in Japan and several other Asian countries for the treatment of IBS-D in men and women. At doses of 5 μ g and 10 μ g, it was tested in 4 studies of ~ 1300 patients with IBS-D. It was superior to placebo in global relief of symptoms, with similar efficacy in men and women. Constipation and hard stool occurred in $\sim 5\%$ patients.^{194–198} Ramosetron 5 μ g once daily was as effective as the antispasmodic mebeverine 135 mg 3 times daily in men with IBS-D.¹⁹⁹ To date, ramosetron has not been associated with colonic ischemia.

In a network meta-analysis of medications approved in at least 1 country for the treatment of IBS-D, alosetron and ramosetron were clearly superior to other agents including eluxadoline and rifaximin.²⁰⁰

Neuromodulators. Neuromodulators with anticholinergic effects are commonly used off-label in IBS-D (discussed briefly under control of pain). They may also be efficacious in the control of diarrhea (eg, in Iranian patients treated with 10 mg amitriptyline).²⁰¹

Bile acid sequestrants and modulators. Bile acid binders (classically cholestyramine, 4 g tid, colestipol 1–2 g bid, and colesevelam 625–1875 mg bid), are used for BAD. One RCT demonstrated efficacy of colesevelam in patients with BAD based on ⁷⁵SeHCAT retention or fasting serum 7 α -hydroxy-4-cholesten-3-one >46 ng/mL²⁰² and a trial documenting superiority of liraglutide over colesevelam for the same condition.²⁰³

Two FXR agonists, obeticholic acid (a bile acid-derived molecule, 6-ethyl chenodeoxycholic acid)²⁰⁴ and the non-bile acid molecule tropifexor,²⁰⁵ reduce bile acid biosynthesis and have promising effects on stool frequency, stool form, and an overall diarrhea index (obeticholic acid²⁰⁴), or slow ascending colon emptying (tropifexor).²⁰⁵

Aldafermin, a fibroblast growth factor 19 analog, administered for 4 weeks, significantly reduced serum 7α -hydroxy-4-cholesten-3-one and fecal total and secretory bile acids at days 14 and 28 of treatment, with improvement in stool consistency in the fourth week of treatment, suggesting that prolonged treatment may be necessary to achieve clinical effects.²⁰⁶

Nonabsorbable antibiotics. Rifaximin is a minimally absorbed antibiotic. In 2 large phase 3 trials, rifaximin 550 mg tid for 2 weeks significantly improved IBS-D symptoms and abdominal bloating, as well as the FDA responder endpoint for IBS-D during the 4 weeks after treatment, with ~10% greater likelihood of adequate relief compared with placebo.²⁰⁷ 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.²⁰⁸ Retreatment with rifaximin has also been shown to be effective.²⁰⁹ Rifaximin also has anti-inflammatory effects and decreases oxidative stress.²¹⁰ Rifaximin also relieves constipation symptoms in IBS-C²¹¹ and accelerates colonic transit.²¹²

Supplementary Table 5 summarizes several trials that have assessed antibiotics in patients with IBS.

Drugs in development for chronic diarrhea and diarrhea-predominant irritable bowel syndrome. *Tachykinin receptor antagonists.* Three distinct neurokinin (NK) receptors, NK₁, NK₂, and NK₃, mediate effects of endogenous tachykinins, substance P, NK-A and NK-B through actions on NK receptors located on intrinsic nerves, extrinsic nerves, inflammatory cells, and smooth muscle in the gut.^{213,214}

The NK₂ receptor antagonist ibodutant was compared with placebo in an 8-week phase 2 trial in 559 patients with IBS-D; the dose of 10 mg/d had significant benefit among women.²¹⁵

Musculotropic spasmolytic agents. Otilonium may reduce rectal sensation.²¹⁶ Hyoscine (nonselective) may reduce enterocyte secretion.²¹⁷ Clinical trials indicate the greatest effect of otilonium on abdominal sensation rather than bowel dysfunction.^{218,219}

Although mebeverine is widely available, a meta-analysis of 8 RCTs showed questionable efficacy in the treatment of IBS and pain.²²⁰

Intestinal adsorbents. AST-120 (oral charcoal adsorbent) comprises porous, spherical carbon particles that adsorb secretory substances, including bacterial toxins and bile acids, in the intestinal lumen.²²¹ In a phase 2, 8-week trial, AST-120 transiently reduced pain and bloating in 115 patients with IBS-D or IBS-M. However, stool consistency was not significantly improved.²²²

Polymethylsiloxane polyhydrate is an intestinal adsorbent that sequesters harmful molecules such as bacterial toxins and, to a lesser extent, bile acids.²²³ It is safe and effective in acute, infectious diarrhea, and was shown to be efficacious in patients with IBS-D in an 8-week placebo-controlled RCT based on a composite endpoint of abdominal pain and stool consistency score with NNT of 8.²²⁴

Mast cell stabilizers. Disodium cromoglycate decreased the release of tryptase from jejunal biopsies, reduced

expression of toll-like receptors 2 and 4, and improved bowel function in IBS-D.^{225,226} In 66 patients with IBS-D and food intolerance, disodium cromoglycate 250 mg qid, plus exclusion diet, was associated with prolonged symptomatic benefit compared with an exclusion diet alone.²²⁷

Ketotifen, a mast cell stabilizer with antihistamine effects,⁵⁰ had beneficial effects on pain, bloating, flatulence, diarrhea, quality of life, sleep, and sexual function, but induced sedation and drowsiness. Similarly, the non-sedating H₁-receptor antagonist, ebastine, reduced visceral hypersensitivity, symptoms, and abdominal pain in patients with IBS with a nonsignificant effect on diarrhea.^{228,229} Results were replicated in a large multicenter trial in nonconstipation IBS.²³⁰

Glutamine. Glutamine, 10 g tid, in 61 patients with IBS-D increased intestinal permeability and reduced claudin-1 expression in intestinal biopsies,²³¹ and improved abdominal pain, bloating, diarrhea, and intestinal permeability. These observations were confirmed in 106 patients with postinfectious IBS-D and increased intestinal permeability with glutamine 5 g tid for 8 weeks demonstrating superiority in all major IBS-related endpoints.²³²

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

Some of the medications discussed above may also be independently efficacious in the relief of pain.^{233,234}

The following is a summary of current treatments of IBS-related pain.

Antispasmodics

Muscarinic receptor antagonists and smooth muscle relaxants are superior to placebo in IBS-related pain,^{235,236} although the quality of trials has been low. In a meta-analysis, antispasmodics were associated with significant benefit over placebo in failure to achieve an improvement in global IBS symptoms at 4–12 weeks (RR, 0.76 [0.64–0.90]).²³⁶

Peppermint Oil

In 10 eligible RCTs including 1030 patients, peppermint oil was more efficacious than placebo for global IBS symptoms and abdominal pain (with NNTs of 4 and 7, respectively).²³⁷ However, a multicenter study of 190 patients showed no benefit of either the small intestinal or ileocolonic release formulations in relief of abdominal pain or overall symptoms in IBS.²³⁸

Calcium-Channel Modulating Antispasmodics

This class of medications is approved in some European countries, but not in the USA. For example, otilonium targets L-type and T-type calcium channels, and muscarinic type 2 and NK₂ receptors. Efficacy has been confirmed in several individual studies in IBS²³⁹; in a systematic review,

there was significant improvement in global symptoms and abdominal pain.²⁴⁰

Neuromodulators

Antidepressants are commonly used to treat DGBI. A Cochrane meta-analysis has suggested efficacy in IBS.^{241,242} A network meta-analysis showed superiority over placebo of tricyclic antidepressants (TCAs; RR, 0.76 [95% confidence interval (CI), 0.64–0.90]), but not SSRIs (0.81 [95% CI, 0.59–1.11]).²⁴³ ATLANTIS, a large RCT conducted at multiple primary care practices in the United Kingdom, compared amitriptyline with placebo in patients with IBS of any subtype.²⁴⁴ Amitriptyline significantly improved IBS Severity Scoring System scores by 20–30 points (on a 0–500 scale) at 3 and 12 months, with almost 50% of patients in each group still having moderately severe IBS on treatment.

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

Pregabalin. The $\alpha 2\delta$ -ligand, pregabalin, has been reported to increase distension sensory thresholds to normal levels in patients with IBS and rectal hypersensitivity.²⁴⁵ A single-center study in 85 patients with IBS²⁴⁶ showed reduced IBS Severity Scoring System and abdominal pain scores compared with placebo.

Palmitoylethanolamide. In a 12-week, placebo-controlled trial of 54 patients with IBS, PEA in combination with polydatin (a resveratrol glucoside) was effective in reducing the severity of abdominal pain, but not other GI symptoms of IBS.²⁴⁷

Network Meta-Analysis of Pharmacologic Treatments for Irritable Bowel Syndrome Pain

A network meta-analysis showed that, for improvement in abdominal pain at 4–12 weeks, TCAs were ranked first, although this was based on data from only 4 RCTs comprising 92 patients.²⁴³ A separate meta-analysis demonstrated similar treatment effects for both TCAs and SSRIs, although there was heterogeneity within the SSRI class.²⁴³

Examples of Pharmacogenetic Effects on Treatment of Irritable Bowel Syndrome

Drug Metabolism and Pharmacogenetics

Overall effects of medications result from metabolism, distribution, and effects of the agent ([Supplementary Table 6](#)).

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 are poor metabolizers.²⁴⁸ Gene multiplication may result in 3 or more functional alleles. The most common nonfunctional alleles are CYP2D6*3,

CYP2D6*4, CYP2D6*5, and CYP2D6*6, which constitute ~98% of nonfunctional alleles in Caucasians.²⁴⁹

CYP2D6 metabolism affects TCAs and SSRIs that are extensively used in DGBI.²⁵⁰ Many drugs are metabolized by or inhibit or activate CYP2D6, thus potentiating drug interactions. In some ethnic groups, it may be advisable to use CYP2D6 testing before antidepressants are prescribed.²⁵¹

The second category of pharmacogenetic modulation of drug effects in IBS reflects variations in receptors, transporters, or the function of rate-limiting enzymes. The best example in IBS pertains to serotonergic pharmacogenetics revolving around SERT-linked promoter region genetics and the effect of alosetron to slow colonic transit in IBS-D⁹³ and the efficacy of tegaserod to relieve symptoms in IBS-C.²⁵²

Role of Biomarkers in Individualizing Therapy

The article on “Design of Treatment Trials” addresses the potential for biomarkers to individualize therapy for IBS, as reviewed elsewhere.^{253–255} Biomarkers are objectively measurable indicators of normal or pathologic processes, or pharmacologic responses to a therapeutic intervention.²⁵⁶

Ideal biomarkers should have reasonable diagnostic performance, noninvasiveness, reproducibility, low cost, and applicability on a large scale. Biomarkers may identify pathophysiological mechanisms, although these may only be present in subsets of patients with IBS-C, IBS-D, or IBS-M.

The opportunity to use actionable biomarkers is summarized in detail elsewhere²⁵⁷ and focuses the attention of researchers, policy makers, and those developing guidelines for clinical practice regarding the importance of “splitting” IBS to provide specific targeted or individualized treatment. Such biomarkers include identification of bile acid diarrhea (low ⁷⁵SeHCAT retention or high fecal bile acid) for treatment with bile acid sequestrants.²⁵⁸ Future research may target patients with specific pathophysiological abnormalities, including increased expression of mast cells, high mucosal serotonin levels, high fecal proteases, alterations in the microbiome, or increased intestinal permeability.

Conclusion and Recommendations for Future Research

Validated animal models and early human trials using established biomarkers and endpoints should be incorporated into the drug development process to enhance selection of patients and doses to enhance success of phase 2B and 3 programs. Closer collaboration between pharmacologists in academia, pharmaceutical companies, and clinicians will enhance understanding of mechanism(s) of action of therapies, and design of more effective trials by incorporation of patient demographics, biomarkers, and,

possibly, pharmacogenetics, leading to precision medicine in DGBI, which may involve combination treatments.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at <https://doi.org/10.1053/j.gastro.2026.02.010>.

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Conflicts of interest

The authors disclose no conflicts.

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