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# 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, heterogenous 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,

*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 $\mu$ 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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water avoidance, restraint, early life stress), chemical 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 (hypersensitivity[15] as well as impaired intestinal permeability[16]), 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 controls[19]) 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 $\mu$L $^{13}$C-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.

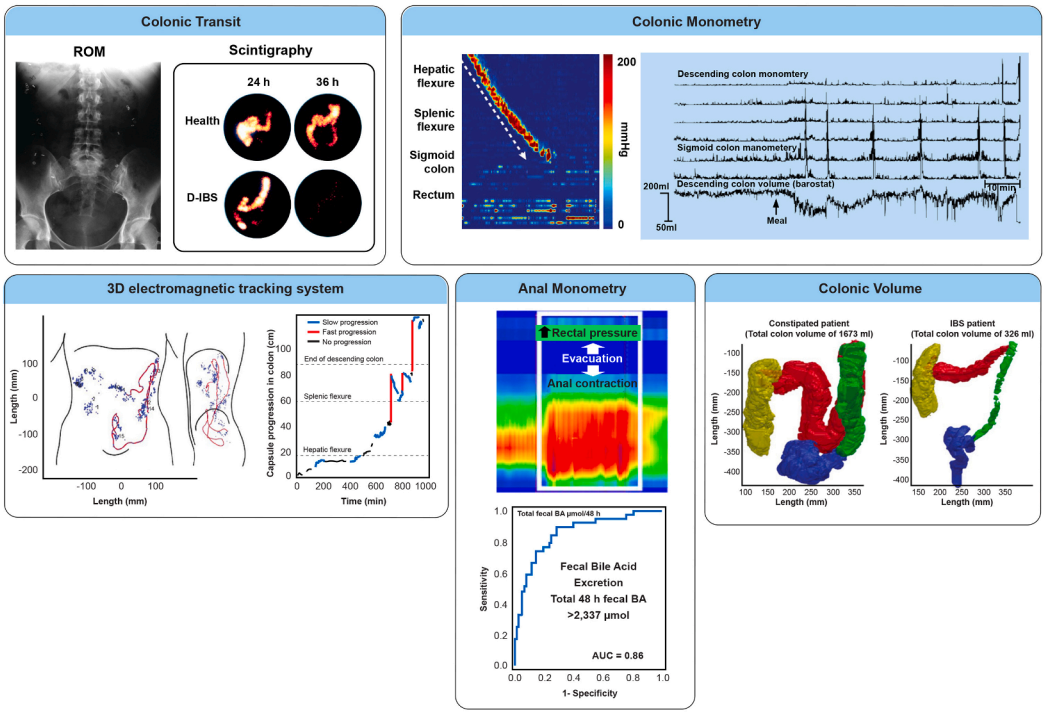



**Figure 1.** Examples of techniques to measure GI functions in lower DGBI. These techniques include 3D electromagnetic tracking to measure colonic transit, barostat-manometry measurement of left colon motility using barostat (for tone) and multilumen manometry, and high-resolution anorectal manometry. 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 ligands[74] 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 $\mu$ 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 liver[79] 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-$HT_4$ agonists,[83] colonic ischemia with 5-$HT_3$ 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 transporters[89] 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 $H_1$ receptor, the $\alpha 2$ adrenergic receptor, and the serotonin 5-$HT_{2C}$ and 5-$HT_3$ 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]

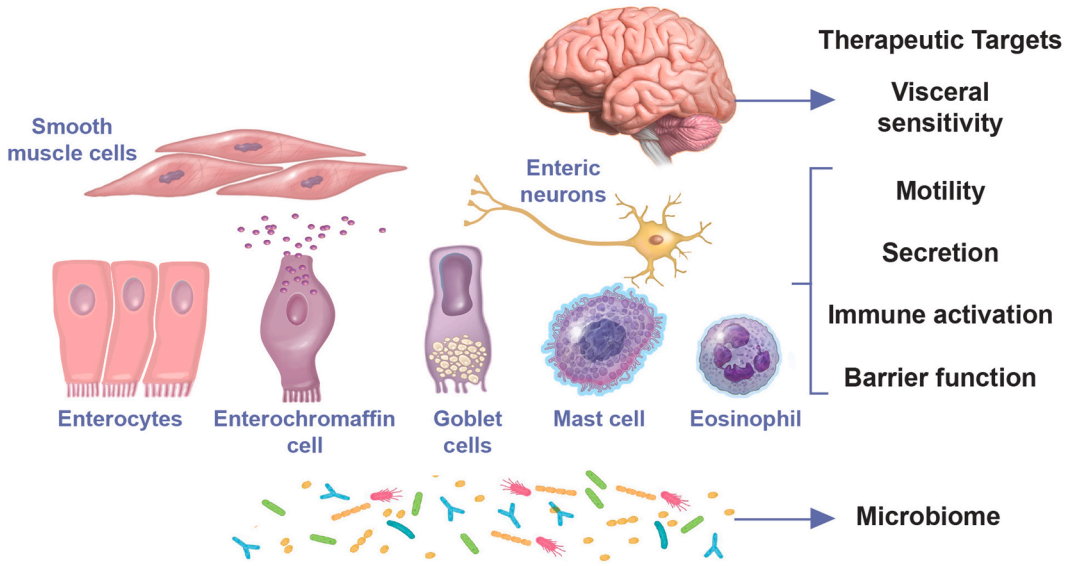
Several 5-HT receptor subtypes are present on both nerves and smooth muscle and mediate numerous different actions.[97]

5-$HT_4$ 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-$HT_4$ 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 $D_2$ 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 | | |
| $NHE_3$ | $M_3$ | $M_{1,2,3}$ | $M_2$, $D_3$, $CB_1$ | $CB_2$ | |
| $SST_2$ | | $\beta_3$ | $\alpha_2$, $\beta_3$, NMDA | $SST_2$ | |
| FXR | | | $TRPV_1$, $NK_2$ | $NK_{1,2,3}$ | |
| IBAT | | | $Opioid_{\mu,\delta,\kappa}$ | | |
| | | | $Ca^{2+}$ 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-$HT_3$, 5-$HT_4$, and 5-$HT_{1a}$, serotonin receptors; $\alpha_2$, alpha 2 adrenal receptor; $\beta_3$, beta adrenal receptor 3; $Ca^{2+}$, calcium channel; $CB_1$ and $CB_2$, cannabinoid receptors 1 and 2; $CCK_1$, cholecystokinin type 1 receptor; CFTR, cystic fibrosis transmembrane conductance regulator; ClC-2, chloride channel 2; $D_3$, dopamine receptor 3; FXR, farnesoid X receptor; GC-C, guanylate cyclase C; $H_1$, histamine receptor 1; IBAT, ileal bile acid transporter; $M_1$, $M_2$, and $M_3$, muscarinic receptors; $NHE_3$, Na+H+ exchange receptor 3; $NK_1$, $NK_2$, and $NK_3$, neurokinin receptors 1, 2, and 3; NMDA, N-methyl-D-aspartate receptor; opioid $\mu$, $\delta$, and $\kappa$, opioid receptors mu, delta, and kappa; Siglec-8, sciatic acid binding Ig-like lectin 8; $SST_2$, somatostatin receptor; $TRPV_1$, 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 $D_2$ 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 $M_1$ and $M_2$ 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 accomodation |
| Adrenoceptors | $\beta_3$-adrenoceptor agonists | Smooth muscle | Inhibit motility | No published data |
| | $\alpha_2$-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 accomodation |
| 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 | $\mu$-receptor agonists (eg, loperamide) | Enterocyte, enteric neurons, afferent neurons, and inflammation | Reduce intestinal secretion and transit | Slow colonic transit, antidiarrheal, increase resting anal tone |
| | $\mu$-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 |
| | $\kappa$-receptor agonists (eg, fedotozine, asimadoline) | Enteric neurons and afferent neurons | Reduce sensation, variable effect on motility | Reduce sensation |
| | $\mu$- and $\kappa$-opioid receptor agonist and $\delta$-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, linaclotide, 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 chemonociception 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 FD[121] 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 $CB_1$ receptors are expressed on nociceptive afferents and enteric nervous system neurons. Activation of $CB_1$ receptors slows GI transit in animals through inhibition of ACh release and, possibly, by stimulating cholecystokinin secretion via $CB_1$ 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

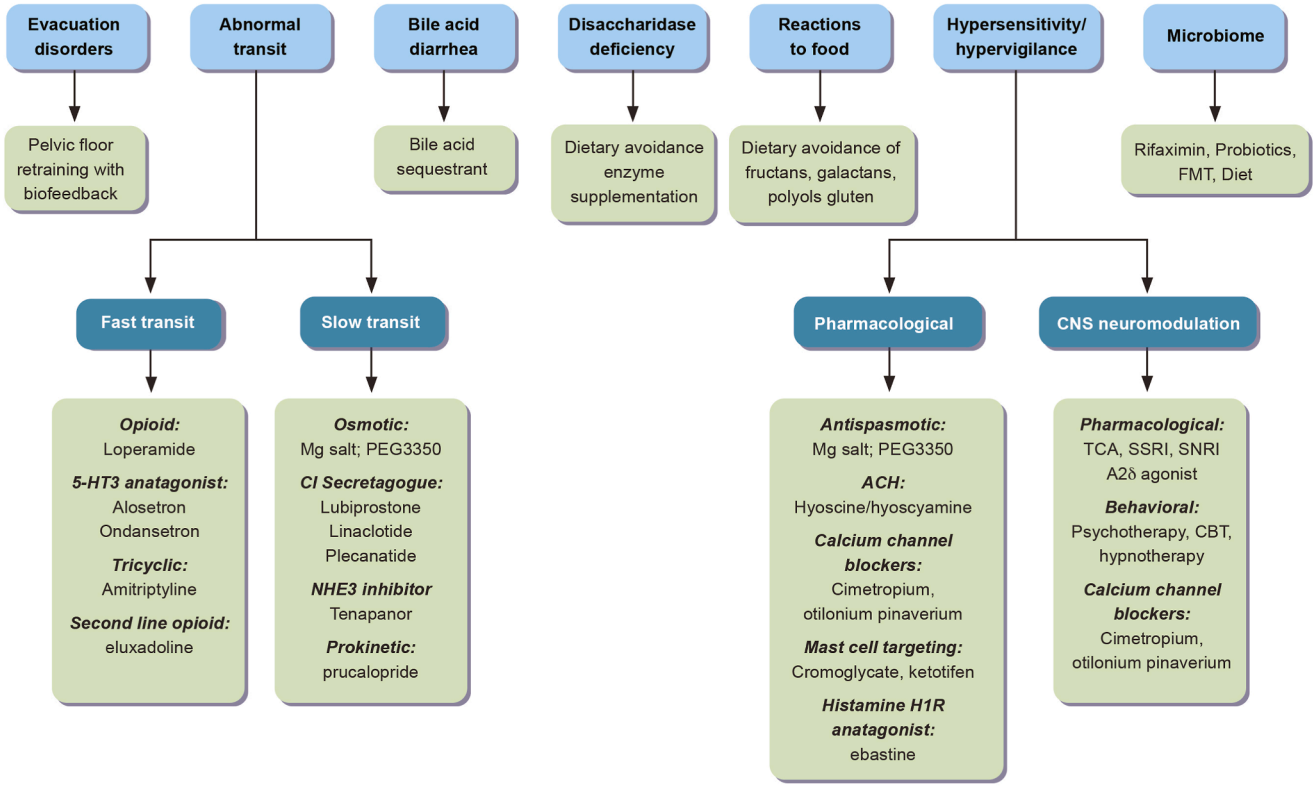



**Figure 3.** Therapeutic choices guided by pathophysiology and biomarkers. The therapeutic targets and biomarkers include evacuation disorders, abnormal transit, bile acid diarrhea, disacccharidase deficiency, reactions to food, and hypersensitivity or hypervigilance. Adapted with permission from Gut 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 lecitin 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-$HT_4$ receptor agonists), intestinal secretagogues, and bile acid modulators. More specific medications have been developed for opioid-induced constipation (OIC).

**5-$HT_4$ receptor agonists.** There are 7 main subtypes of 5-HT receptor.[142] Those most relevant to GI motor and sensory disorders are 5-$HT_3$ and 5-$HT_4$. 5-$HT_4$ receptors are also present in the heart. 5-$HT_4$ 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-$HT_4$ receptors inhibited visceral hypersensitivity.[143]

Older 5-$HT_4$ 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-$HT_4$ receptor agonists (eg, prucalopride) have >150-fold greater selectivity for 5-$HT_4$ receptors than for $I_{Kr}$ channel.[144]

5-$HT_4$ 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.

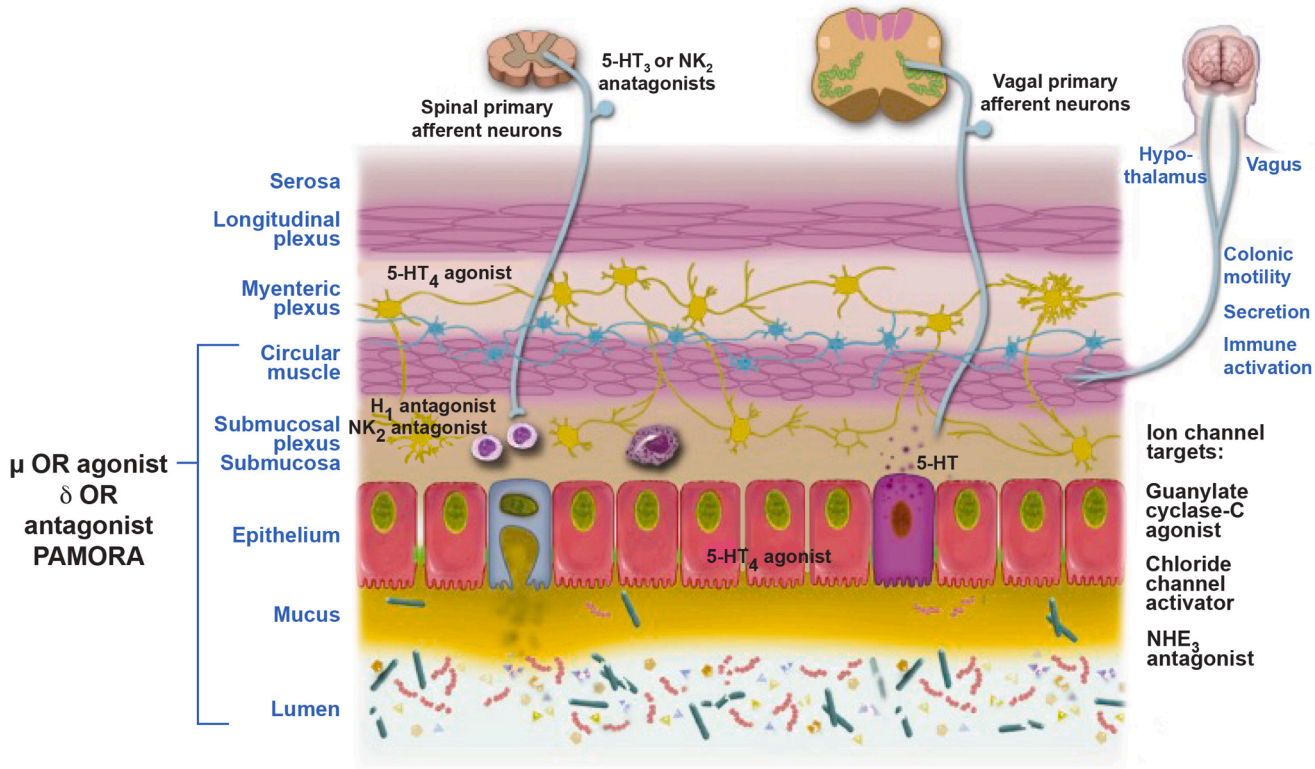



**Figure 4.** Localization and nature of major targeted receptors in the treatment of DGBI. The targeted receptors are located in enterochromaffin cells, epithelial cells, smooth muscle cells, neurons, and immunocytes. 5-HT3 and 5-HT4, serotonin receptors; H1, histamine receptor 1; NHE3, Na+/H+ exchanger receptor 3; NK2, tachykinin receptor 2; $\mu$ and $\delta$, 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 protaglandin $E_1$. It has demonstrated efficacy in CIC and OIC (at a dose of 24 $\mu$g bid) and in IBS-C (at a dose of 8 $\mu$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 $\mu$g/d) by the FDA, the EMA, and the Swiss Agency, and for the treatment of CIC (at doses of 72 or 145 $\mu$g/d) by the FDA.

Plecanatide is another guanylate cyclase-C agonist effective at treating constipation and pain, at the 3 mg once daily dose[170] 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 contipation-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 $\mu$-opioid receptor agonists.** The $\mu$-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-D[35] 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.

**$\mu$-opioid receptor agonist and $\delta$-opioid receptor antagonist (eluxadoline).** Eluxadoline, a combination $\mu$-opioid receptor agonist and $\delta$-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-HT$_3$ receptor antagonists.** 5-HT$_3$ 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-HT$_3$ 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-HT$_3$ 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 $\mu$g and 10 $\mu$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 ~5% patients.[194–198] Ramosetron 5 $\mu$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 $^{75}$SeHCAT retention or fasting serum 7$\alpha$-hydroxy-4-cholesten-3-one >46 ng/mL[202] and a trial documenting superiority of liraglutide over colesevelam for the same condition.[203]

Two FXR agonists, obetichiolic 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 acid[204]), or slow ascending colon emptying (tropifexor).[205]

Aldafermin, a fibroblast growth factor 19 analog, administered for 4 weeks, significantly reduced serum 7$\alpha$-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-C[211] 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, $NK_1$, $NK_2$, and $NK_3$, 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 $NK_2$ 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 $H_1$-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 $NK_2$ receptors. Efficacy has been confirmed in several individual studies in IBS[239]; 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 IBS[246] 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-D[93] 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 elsewhere[257] 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 $^{75}$SeHCAT 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.

## References


1. Accarie A, Vanuytsel T. Animal models for functional gastrointestinal disorders. Front Psychiatry 2020;11:509681.
2. Heitkemper M, Jarrett M, Bond EF, et al. Impact of sex and gender on irritable bowel syndrome. Biol Res Nurs 2003;5:56–65.
3. Naliboff BD, Berman S, Chang L, et al. Sex-related differences in IBS patients: central processing of visceral stimuli. Gastroenterology 2003;124:1738–1747.
4. Chaloner A, Greenwood-Van Meerveld B. Sexually dimorphic effects of unpredictable early life adversity on visceral pain behavior in a rodent model. J Pain 2013;14:270–280.
5. Prusator DK, Greenwood-Van Meerveld B. Gender specific effects of neonatal limited nesting on viscerosomatic sensitivity and anxiety-like behavior in adult rats. Neurogastroenterol Motil 2015;27:72–81.
6. Prusator DK, Greenwood-Van Meerveld B. Sex-related differences in pain behaviors following three early life stress paradigms. Biol Sex Differ 2016;7:29.
7. Bradford K, Shih W, Videlock EJ, et al. Association between early adverse life events and irritable bowel syndrome. Clin Gastroenterol Hepatol 2012;10:385–390; e1-3.
8. Greenwood-Van Meerveld B, Prusator DK, Johnson AC. Animal models of gastrointestinal and liver diseases. Animal models of visceral pain: pathophysiology, translational relevance, and challenges. Am J Physiol Gastrointest Liver Physiol 2015;308:G885–G903.
9. Johnson AC, Farmer AD, Ness TJ, et al. Critical evaluation of animal models of visceral pain for therapeutics development: a focus on irritable bowel syndrome. Neurogastroenterol Motil 2020;32:e13776.
10. Bradesi S, Schwetz I, Ennes HS, et al. Repeated exposure to water avoidance stress in rats: a new model for sustained visceral hyperalgesia. Am J Physiol Gastrointest Liver Physiol 2005;289:G42–G53.
11. Matsumoto K, Takata K, Yamada D, et al. Juvenile social defeat stress exposure favors in later onset of irritable bowel syndrome-like symptoms in male mice. Sci Rep 2021;11:16276.
12. Coutinho SV, Plotsky PM, Sablad M, et al. Neonatal maternal separation alters stress-induced responses to viscerosomatic nociceptive stimuli in rat. Am J Physiol Gastrointest Liver Physiol 2002;282:G307–G316.
13. Tyler K, Moriceau S, Sullivan RM, et al. Long-term colonic hypersensitivity in adult rats induced by neonatal unpredictable vs predictable shock. Neurogastroenterol Motil 2007;19:761–768.
14. 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.
15. Gunter WD, Shepard JD, Foreman RD, et al. Evidence for visceral hypersensitivity in high-anxiety rats. Physiol Behav 2000;69:379–382.
16. Martinez V, Ryttinger M, Kjerling M, et al. Characterisation of colonic accommodation in Wistar Kyoto rats with impaired gastric accommodation. Naunyn Schmiedebergs Arch Pharmacol 2007;376:205–216.
17. Meleine M, Accarie A, Wauters L, et al. Colonic hypersensitivity and low-grade inflammation in a spontaneous animal model for functional gastrointestinal disorders. Neurogastroenterol Motil 2019;31:e13614.
18. Trimble N, Johnson AC, Foster A, et al. Corticotropin-releasing factor receptor 1-deficient mice show decreased anxiety and colonic sensitivity. Neurogastroenterol Motil 2007;19:754–760.
19. De Palma G, Lynch MD, Lu J, et al. Transplantation of fecal microbiota from patients with irritable bowel syndrome alters gut function and behavior in recipient mice. Sci Transl Med 2017;9:eaaf6397.
20. Ness TJ, Gebhart GF. Colorectal distension as a noxious visceral stimulus: physiologic and pharmacologic characterization of pseudaffective reflexes in the rat. Brain Res 1988;450:153–169.
21. Smith-Edwards KM, Najjar SA, Edwards BS, et al. Extrinsic primary afferent neurons link visceral pain to colon motility through a spinal reflex in mice. Gastroenterology 2019;157:522–536.e2.
22. Creedon CT, Verhulst PJ, Choi KM, et al. Assessment of gastric emptying in non-obese diabetic mice using a [13C]-octanoic acid breath test. J Vis Exp 2013;73:e50301.
23. Kishi K, Kaji N, Endo M, et al. Development of a quantitative method for evaluating small intestinal motility using ultrasonography in mice. Exp Anim 2019;68:381–389.
24. Meile T, Zieker D, Konigsrainer A, et al. New telemetry device for the measurement of gastrointestinal motility in rats and comparison with standard equipment. Int Surg 2015;100:755–760.
25. Gonzalez-Gonzalez M, Diaz-Zepeda C, Eyzaguirre-Velasquez J, et al. Investigating gut permeability in animal models of disease. Front Physiol 2018;9:1962.
26. Ussing HH, Zerahn K. Active transport of sodium as the source of electric current in the short-circuited isolated frog skin. Acta Physiol Scand 1951;23:110–127.
27. Thomson A, Smart K, Somerville MS, et al. The Ussing chamber system for measuring intestinal permeability in health and disease. BMC Gastroenterol 2019;19:98.
28. Camilleri M. Abnormal gastrointestinal motility is a major factor in explaining symptoms and a potential therapeutic target in patients with disorders of gut-brain interaction. Gut 2023;72:2372–2380.
29. Bonapace ES, Maurer AH, Davidoff S, et al. Whole gut transit scintigraphy in the clinical evaluation of patients

with upper and lower gastrointestinal symptoms. Am J Gastroenterol 2000;95:2838–2847.
30. Bartholomeusz D, Chatterton BE, Bellen JC, et al. Segmental colonic transit after oral 67Ga-citrate in healthy subjects and those with chronic idiopathic constipation. J Nucl Med 1999;40:277–282.
31. Burton DD, Camilleri M, Mullan BP, et al. Colonic transit scintigraphy labeled activated charcoal compared with ion exchange pellets. J Nucl Med 1997;38:1807–1810.
32. Deiteren A, Camilleri M, Bharucha AE, et al. Performance characteristics of scintigraphic colon transit measurement in health and irritable bowel syndrome and relationship to bowel functions. Neurogastroenterol Motil 2010;22:415–423.e95.
33. Mark EB, Poulsen JL, Haase AM, et al. Ambulatory assessment of colonic motility using the electromagnetic capsule tracking system. Neurogastroenterol Motil 2019;31:e13451.
34. Nandhra GK, Mark EB, Di Tanna GL, et al. Normative values for region-specific colonic and gastrointestinal transit times in 111 healthy volunteers using the 3D-Transit electromagnet tracking system: influence of age, gender, and body mass index. Neurogastroenterol Motil 2020;32:e13734.
35. 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.
36. Camilleri M. Review article: biomarkers and personalised therapy in functional lower gastrointestinal disorders. Aliment Pharmacol Ther 2015;42:818–828.
37. 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.
38. Andresen V, Montori VM, Keller J, et al. Effects of 5-hydroxytryptamine (serotonin) type 3 antagonists on symptom relief and constipation in nonconstipated irritable bowel syndrome: a systematic review and meta-analysis of randomized controlled trials. Clin Gastroenterol Hepatol 2008;6:545–555.
39. Emmanuel AV, Roy AJ, Nicholls TJ, et al. Prucalopride, a systemic enterokinetic, for the treatment of constipation. Aliment Pharmacol Ther 2002;16:1347–1356.
40. 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.
41. 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.
42. 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.
43. 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; ; quiz p 1725.
44. Farmer AD, Ruffle JK, Hobson AR. Linaclotide increases cecal pH, accelerates colonic transit, and increases colonic motility in irritable bowel syndrome with constipation. Neurogastroenterol Motil 2019;31:e13492.
45. 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.
46. Corsetti M, Thys A, Harris A, et al. High-resolution manometry reveals different effect of polyethylene glycol, bisacodyl, and prucalopride on colonic motility in healthy subjects: an acute, open label, randomized, crossover, reader-blinded study with potential clinical implications. Neurogastroenterol Motil 2021;33:e14040.
47. Davidson JB, O'Grady G, Arkwright JW, et al. Anatomical registration and three-dimensional visualization of low and high-resolution pan-colonic manometry recordings. Neurogastroenterol Motil 2011;23:387–390.e171.
48. Paskaranandavadivel N, Lin AY, Cheng LK, et al. ManoMap: an automated system for characterization of colonic propagating contractions recorded by high-resolution manometry. Med Biol Eng Comput 2021;59:417–429.
49. Heitmann PT, Mohd Rosli R, Maslen L, et al. High-resolution impedance manometry characterizes the functional role of distal colonic motility in gas transit. Neurogastroenterol Motil 2022;34:e14178.
50. 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.
51. Lembo T, Naliboff BD, Matin K, et al. Irritable bowel syndrome patients show altered sensitivity to exogenous opioids. Pain 2000;87:137–147.
52. 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.
53. Sandberg TH, Nilsson M, Poulsen JL, et al. A novel semi-automatic segmentation method for volumetric assessment of the colon based on magnetic resonance imaging. Abdom Imaging 2015;40:2232–2241.
54. Klinge MW, Krogh K, Mark EB, et al. Colonic volume in patients with functional constipation or irritable bowel syndrome determined by magnetic resonance imaging. Neurogastroenterol Motil 2022;34:e14374.
55. Wu J, Masuy I, Biesiekierski JR, et al. Gut-brain axis dysfunction underlies FODMAP-induced symptom generation in irritable bowel syndrome. Aliment Pharmacol Ther 2022;55:670–682.
56. Sharif H, Hoad CL, Abrehart N, et al. Colon length in pediatric health and constipation measured using magnetic resonance imaging and three dimensional skeletonization. PLoS One 2024;19:e0296311.
57. Park SY, Khemani D, Nelson AD, et al. Rectal gas volume measured by computerized tomography identifies

evacuation disorders in patients with constipation. Clin Gastroenterol Hepatol 2017;15:543–552.e4.
58. Gharibans AA, Coleman TP, Mousa H, et al. Spatial patterns from high-resolution electrogastrography correlate with severity of symptoms in patients with functional dyspepsia and gastroparesis. Clin Gastroenterol Hepatol 2019;17:2668–2677.
59. Wang WJ, Foong D, Calder S, et al. Gastric Alimetry(R) expands patient phenotyping in gastroduodenal disorders compared to gastric emptying scintigraphy. Am J Gastroenterol 2024;119:331–341.
60. Camilleri M, Chedid V, Ford AC, et al. Gastroparesis. Nat Rev Dis Primers 2018;4:41.
61. Pasricha PJ, Grover M, Yates KP, et al. Progress in gastroparesis - a narrative review of the work of the Gastroparesis Clinical Research Consortium. Clin Gastroenterol Hepatol 2022;20:2684–2695.e3.
62. Tack J, Schol J, Horowitz M. Gastroparesis: a dead-end street after all? Gastroenterology 2021;160:1931–1933.
63. Sturm A, Holtmann G, Goebell H, et al. Prokinetics in patients with gastroparesis: a systematic analysis. Digestion 1999;60:422–427.
64. Maganti K, Onyemere K, Jones MP. Oral erythromycin and symptomatic relief of gastroparesis: a systematic review. Am J Gastroenterol 2003;98:259–263.
65. Buisman WJ, van Herwaarden-Lindeboom MY, Mauritz FA, et al. Validation of a novel 3-dimensional sonographic method for assessing gastric accommodation in healthy adults. J Ultrasound Med 2016; 35:1411–1418.
66. 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.
67. 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.
68. 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.
69. Scarpellini E, Van den Houte K, Schol J, et al. Nutrient drinking test as biomarker in functional dyspepsia. Am J Gastroenterol 2021;116:1387–1395.
70. 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-e154.
71. 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.
72. 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.
73. 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.
74. Camilleri M, Bueno L, de Ponti F, et al. Pharmacological and pharmacokinetic aspects of functional gastrointestinal disorders. Gastroenterology 2006; 130:1421–1434.
75. Shanahan F, Quigley EM. Manipulation of the microbiota for treatment of IBS and IBD-challenges and controversies. Gastroenterology 2014;146:1554–1563.
76. Mayer EA, Savidge T, Shulman RJ. Brain-gut microbiome interactions and functional bowel disorders. Gastroenterology 2014;146:1500–1512.
77. Hao H, Zheng X, Wang G. Insights into drug discovery from natural medicines using reverse pharmacokinetics. Trends Pharmacol Sci 2014;35:168–177.
78. 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.
79. 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.
80. Zhang X, Wu W. Ligand-mediated active targeting for enhanced oral absorption. Drug Discov Today 2014; 19:898–904.
81. Marsh SR, Pridham KJ, Jourdan J, et al. Novel protocols for scalable production of high quality purified small extracellular vesicles from bovine milk. Nanotheranostics 2021;5:488–498.
82. Gao C, Zhou Y, Chen Z, et al. Turmeric-derived nanovesicles as novel nanobiologics for targeted therapy of ulcerative colitis. Theranostics 2022;12:5596–5614.
83. 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.
84. Moynihan R. Alosetron: a case study in regulatory capture, or a victory for patients' rights? BMJ 2002; 325:592–595.
85. Gawron AJ, Bielefeldt K. Risk of pancreatitis following treatment of irritable bowel syndrome with eluxadoline. Clin Gastroenterol Hepatol 2018;16:378–384.e2.
86. Goodoory VC, Ng CE, Black CJ, et al. Willingness to accept risk with medication in return for cure of symptoms among patients with Rome IV irritable bowel syndrome. Aliment Pharmacol Ther 2022;55:1311–1319.
87. De Ponti F, Poluzzi E, Cavalli A, et al. Safety of nonantiarrhythmic drugs that prolong the QT interval or induce torsade de pointes: an overview. Drug Saf 2002; 25:263–286.
88. Dalen P, Dahl ML, Bernal 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.
89. Glatt CE, Reus VI. Pharmacogenetics of monoamine transporters. Pharmacogenomics 2003;4:583–596.
90. Camilleri M, Atanasova E, Carlson PJ, et al. Serotonin-transporter polymorphism pharmacogenetics in

diarrhea-predominant irritable bowel syndrome. Gastroenterology 2002;123:425–432.
91. Lembo A, Camilleri M. Chronic constipation. N Engl J Med 2003;349:1360–1368.
92. O'Mahony L, McCarthy J, Kelly P, et al. Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. Gastroenterology 2005;128:541–551.
93. Lesbros-Pantoflickova D, Michetti P, Fried M, et al. Meta-analysis: the treatment of irritable bowel syndrome. Aliment Pharmacol Ther 2004;20:1253–1269.
94. 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.
95. Gorard DA, Libby GW, Farthing MJ. 5-Hydroxytryptamine and human small intestinal motility: effect of inhibiting 5-hydroxytryptamine reuptake. Gut 1994;35:496–500.
96. Tack J, Ly HG, Carbone F, et al. Efficacy of mirtazapine in patients with functional dyspepsia and weight loss. Clin Gastroenterol Hepatol 2016;14:385–392.e4.
97. De Ponti F. Pharmacology of serotonin: what a clinician should know. Gut 2004;53:1520–1535.
98. 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.
99. 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.
100. 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.
101. 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.
102. Fukazawa K, Furuta K, Adachi K, et al. Effects of mosapride on esophageal motor activity and esophagogastric junction compliance in healthy volunteers. J Gastroenterol 2014;49:1307–1313.
103. 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.
104. 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.
105. 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.
106. 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.
107. Huang X, Lv B, Zhang S, et al. Itopride therapy for functional dyspepsia: a meta-analysis. World J Gastroenterol 2012;18:7371–7377.
108. 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.
109. Holtmann G, Talley NJ, Liebregts T, et al. A placebo-controlled trial of itopride in functional dyspepsia. N Engl J Med 2006;354:832–840.
110. Li J, Lv L, Zhang J, et al. A combination of peppermint oil and caraway oil for the treatment of functional dyspepsia: a systematic review and meta-analysis. Evid Based Complement Alternat Med 2019;2019:7654947.
111. Tack J, Masuy I, Van Den Houte K, et al. Drugs under development for the treatment of functional dyspepsia and related disorders. Expert Opin Investig Drugs 2019;28:871–889.
112. 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.
113. 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.
114. 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.
115. Tack J, Pokrotnieks J, Urbonas G, et al. Long-term safety and efficacy of acotiamide in functional dyspepsia (postprandial distress syndrome)-results from the European phase 3 open-label safety trial. Neurogastroenterol Motil 2018;30:e13284.
116. Kotikula I, Thinrungroj N, Pinyopornpanish K, et al. Randomised clinical trial: the effects of pregabalin vs placebo on functional dyspepsia. Aliment Pharmacol Ther 2021;54:1026–1032.
117. 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.
118. Fuhrer M, Vogelsang H, Hammer J. A placebo-controlled trial of an oral capsaicin load in patients with functional dyspepsia. Neurogastroenterol Motil 2011;23.918–e397.
119. Evangelista S. Capsaicin receptor as target of calcitonin gene-related peptide in the gut. Prog Drug Res 2014;68:259–276.
120. Wilder-Smith CH, Li X, Shen L, et al. Dysfunctional endogenous pain modulation in patients with functional dyspepsia. Neurogastroenterol Motil 2014;26:489–498.
121. Bortolotti M, Coccia G, Grossi G, et al. The treatment of functional dyspepsia with red pepper. Aliment Pharmacol Ther 2002;16:1075–1082.
122. Ochiai K, Hirooka R, Sakaino M, et al. 2-Arachidonoyl glycerol suppresses gastric emptying via the

cannabinoid receptor 1-cholecystokinin signaling pathway in mice. Lipids 2022;57:173–181.
123. 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.
124. 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.
125. Parkman HP, Sharkey EP, Nguyen LA, et al. Marijuana use in patients with symptoms of gastroparesis: prevalence, patient characteristics, and perceived benefit. Dig Dis Sci 2020;65:2311–2320.
126. Jehangir A, Parkman HP. Cannabinoid use in patients with gastroparesis and related disorders: prevalence and benefit. Am J Gastroenterol 2019;114:945–953.
127. Atieh J, Maselli D, Breen-Lyles M, et al. Cannabidiol for functional dyspepsia with normal gastric emptying: a randomized controlled trial. Am J Gastroenterol 2022; 117:1296–1304.
128. van Orten-Luiten AB, de Roos NM, Majait S, et al. Effects of cannabidiol chewing gum on perceived pain and well-being of irritable bowel syndrome patients: a placebo-controlled crossover exploratory intervention study with symptom-driven dosing. Cannabis Cannabinoid Res 2022;7:436–444.
129. Sarnelli G, Pesce M, Seguella L, et al. Impaired duodenal palmitoylethanolamide release underlies acid-induced mast cell activation in functional dyspepsia. Cell Mol Gastroenterol Hepatol 2021;11:841–855.
130. Du L, Chen B, Kim JJ, et al. Micro-inflammation in functional dyspepsia: a systematic review and meta-analysis. Neurogastroenterol Motil 2018;30:e13304.
131. Shah A, Fairlie T, Brown G, et al. Duodenal eosinophils and mast cells in functional dyspepsia: a systematic review and meta-analysis of case-control studies. Clin Gastroenterol Hepatol 2022;20:2229–2242.e29.
132. Carmona-Sánchez R, Carrera-Álvarez MA, Peña-Zepeda C. Prevalence of primary eosinophilic colitis in patients with chronic diarrhea and diarrhea-predominant irritable bowel syndrome. Rev Gastroenterol Mex (Engl Ed) 2022;87:135–141.
133. Wauters L, Tito RY, Ceulemans M, et al. Duodenal dysbiosis and relation to the efficacy of proton pump inhibitors in functional dyspepsia. Int J Mol Sci 2021; 22:13609.
134. Du L, Shen J, Kim JJ, et al. Increased duodenal eosinophil degranulation in patients with functional dyspepsia: a prospective study. Sci Rep 2016;6:34305.
135. Wauters L, Ceulemans M, Frings D, et al. Proton pump inhibitors reduce duodenal eosinophilia, mast cells, and permeability in patients with functional dyspepsia. Gastroenterology 2021;160:1521–1531.e9.
136. Dellon ES, Gonsalves N, Rothenberg ME, et al. Determination of biopsy yield that optimally detects eosinophilic gastritis and/or duodenitis in a randomized trial of lirentelimab. Clin Gastroenterol Hepatol 2022; 20:535–545.e15.
137. Reed CC, Genta RM, Youngblood BA, et al. Mast cell and eosinophil counts in gastric and duodenal biopsy specimens from patients with and without eosinophilic gastroenteritis. Clin Gastroenterol Hepatol 2021; 19:2102–2111.
138. Järbrink-Sehgal ME, Sparkman J, Damron A, et al. Functional dyspepsia and duodenal eosinophil count and degranulation: a multiethnic US Veteran cohort study. Dig Dis Sci 2021;66:3482–3489.
139. Lee MJ, Jung HK, Lee KE, et al. Degranulated eosinophils contain more fine nerve fibers in the duodenal mucosa of patients with functional dyspepsia. J Neurogastroenterol Motil 2019;25:212–221.
140. Dellon ES, Peterson KA, Murray JA, et al. Anti-Siglec-8 antibody for eosinophilic gastritis and duodenitis. N Engl J Med 2020;383:1624–1634.
141. 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.
142. Kim DY, Camilleri M. Serotonin: a mediator of the brain-gut connection. Am J Gastroenterol 2000;95:2698–2709.
143. 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.e4.
144. De Maeyer JH, Lefebvre RA, Schuurkes JA. 5-HT4 receptor agonists: similar but not the same. Neurogastroenterol Motil 2008;20:99–112.
145. 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.
146. 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.
147. 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.
148. 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.
149. 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.
150. Quigley EM, Vandeplassche 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.
151. 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.
152. 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.
153. 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; e7-8.
154. 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.
155. Barrett KE, Keely SJ. Chloride secretion by the intestinal epithelium: molecular basis and regulatory aspects. Annu Rev Physiol 2000;62:535–572.
156. Drossman DA, Chey WD, Johanson JF, et al. Clinical trial: iubiprostone in patients with constipation-associated irritable bowel syndrome–results of two randomized, placebo-controlled studies. Aliment Pharmacol Ther 2009;29:329–341.
157. 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.
158. 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.
159. 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.
160. 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.
161. 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.
162. 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.
163. Donowitz M, Cha B, Zachos NC, et al. NHERF family and NHE3 regulation. J Physiol 2005;567:3–11.
164. 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; e1-11.
165. Lembo AJ, Schneier HA, Shiff SJ, et al. Two randomized trials of linaclotide for chronic constipation. N Engl J Med 2011;365:527–536.
166. Lembo AJ, Kurtz CB, Macdougall JE, et al. Efficacy of linaclotide for patients with chronic constipation. Gastroenterology 2010;138:886–895.e1.
167. Quigley EM, Tack J, Chey WD, et al. Randomised clinical trials: linaclotide phase 3 studies in IBS-C - a prespecified further analysis based on European Medicines Agency-specified endpoints. Aliment Pharmacol Ther 2013;37:49–61.
168. 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.
169. 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; 1786.e2.
170. Miner PB. Plecanatide for the treatment of constipation-predominant irritable bowel syndrome. Expert Rev Gastroenterol Hepatol 2020;14:71–84.
171. Miner PB Jr, Koltun WD, Wiener GJ, et al. A randomized phase iii clinical trial of plecanatide, a uroguanylin analog, in patients with chronic idiopathic constipation. Am J Gastroenterol 2017;112:613–621.
172. Chey WD, Lembo AJ, Yang Y, et al. Efficacy of tenapanor in treating patients with irritable bowel syndrome with constipation: a 26-week, placebo-controlled phase 3 trial (T3MPO-2). Am J Gastroenterol 2021; 116:1294–1303.
173. Camilleri M. Pharmacology of the new treatments for lower gastrointestinal motility disorders and irritable bowel syndrome. Clin Pharmacol Ther 2012;91:44–59.
174. Appleby RN, Walters JR. The role of bile acids in functional GI disorders. Neurogastroenterol Motil 2014; 26:1057–1069.
175. Wong BS, 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.
176. 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.
177. Ellegaard AM, Kårhus ML, Winther-Jensen M, et al. Bile acid diarrhea is associated with an increased incidence of gastrointestinal cancers. Am J Gastroenterol 2024; 119:2107–2113.
178. Nakajima A, Seki M, Taniguchi S, et al. Safety and efficacy of elobixibat for chronic constipation: results from a randomised, double-blind, placebo-controlled, phase 3 trial and an open-label, single-arm, phase 3 trial. Lancet Gastroenterol Hepatol 2018;3:537–547.
179. 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.
180. 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.
181. Cryer B, 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.
182. Jamal MM, Adams AB, Jansen JP, et al. A randomized, placebo-controlled trial of lubiprostone for opioid-induced constipation in chronic noncancer pain. Am J Gastroenterol 2015;110:725–732.
183. Palejwala V, Joshi 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):S538–S539.
184. Corazziari E. Role of opioid ligands in the irritable bowel syndrome. Can J Gastroenterol 1999;13(Suppl A): 71a–75a.
185. 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.e1.
186. Lembo AJ, Lacy BE, Zuckerman MJ, et al. Eluxadoline for irritable bowel syndrome with diarrhea. N Engl J Med 2016;374:242–253.
187. 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.
188. 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.
189. Scolapio JS, Camilleri M, von der Ohe MR, et al. Ascending colon response to feeding: evidence for a 5-hydroxytryptamine-3 mechanism. Scand J Gastroenterol 1995;30:562–567.
190. Houghton LA, Foster JM, Whorwell PJ. Alosetron, a 5-HT3 receptor antagonist, delays colonic transit in patients with irritable bowel syndrome and healthy volunteers. Aliment Pharmacol Ther 2000;14:775–782.
191. Delvaux M, Louvel D, Mamet JP, et al. Effect of alosetron on responses to colonic distension in patients with irritable bowel syndrome. Aliment Pharmacol Ther 1998; 12:849–855.
192. 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.
193. Gunn D, Topan R, Barnard L, et al. Randomised, placebo-controlled trial and meta-analysis show benefit of ondansetron for irritable bowel syndrome with diarrhoea: the TRITON trial. Aliment Pharmacol Ther 2023;57:1258–1271.
194. 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.
195. 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.
196. Fukudo S, Ida M, Akiho H, et al. Effect of ramosetron on stool consistency in male patients with irritable bowel syndrome with diarrhea. Clin Gastroenterol Hepatol 2014;12:953–959.e4.
197. Grover M, Camilleri M. Ramosetron in irritable bowel syndrome with diarrhea: new hope or the same old story? Clin Gastroenterol Hepatol 2014;12:960–962.
198. 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.
199. 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.
200. Black CJ, Burr NE, Camilleri M, et al. Efficacy of pharmacological therapies in patients with IBS with diarrhoea or mixed stool pattern: systematic review and network meta-analysis. Gut 2020;69:74–82.

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