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Early Investigational Therapeutics for Gastrointestinal Motility Disorders: From Animal Studies to Phase II Trials

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Abstract

Introduction—The most common gastrointestinal disorders which include evidence of dysmotility include: gastroparesis, the lower functional gastrointestinal disorders associated with altered bowel function [such as chronic (functional) diarrhea, chronic idiopathic constipation (CIC)], and opioid induced constipation (OIC). These conditions, which are grouped as gastrointestinal motility and functional disorders, are characterized by abnormal motor, sensory, or secretory functions that alter bowel function and result in a significant disease burden, since currently available treatments do not completely alleviate symptoms. New drugs are being developed for these disorders, targeting mechanisms involved in the pathophysiology of these diseases, specifically, motor function, intestinal secretion and bile acid modulation.

Areas Covered—The article provides a brief overview of motility disorders and the drugs approved and currently available for these indications. It also provides an evaluation of the efficacy, safety and possible mechanisms of the drugs currently under investigation for the treatment of gastroparesis, chronic diarrhea, CIC and OIC, based on animal to phase II studies. Medications with complete phase III trials are excluded from this discussion.

Expert opinion—Treatment of gastrointestinal motility disorders requires the understanding of the pathophysiological mechanisms, biomarkers to identify subgroups of these disorders, and robust pharmacological studies from animal to phase II studies. These are prerequisites for the development of efficacious medications and individualizing therapy in order to enhance the treatment of these patients.

Keywords

acetylcholine; agonist; antagonist; ghrelin; motilin; muscarinic; opioids; pharmacology; prokinetics; receptor; serotonin; bile acids; secretagogues

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1. Introduction

Gastrointestinal and colonic motility disorders are defined as disorders associated with inadequate, incoordinated, or excessive gastrointestinal muscular activity. These disorders can be due to endogenous or exogenous causes, but there is usually no evidence of a structural etiology. These motility disorders result in abnormal propulsion of gastric or intestinal content and altered sensory response along the gastrointestinal tract. The abnormal transit may be the result or may be associated with abnormal intestinal fluid secretion.

The most common gastrointestinal disorders that include evidence of dysmotility include gastroparesis, the lower functional gastrointestinal disorders associated with altered bowel function [such as chronic (functional) diarrhea, chronic idiopathic constipation (CIC)], and opioid induced constipation (OIC). These constitute a large portion of the referrals to gastroenterologists and cause a significant disease burden, since currently available treatments do not completely alleviate symptoms. The disease burden associated with these disorders may lead to impaired mental and physical functioning compared to healthy controls, particularly for those patients seeking health care [1].

Pharmacological management is limited, and there are still many unmet needs for treating these disorders. Current investigations of potential drugs target motor function, intestinal secretion and bile acid modulation, which are all mechanisms involved in the pathophysiology of these disorders.

This review summarizes the pathophysiology of the common gastrointestinal motility disorders, provides a brief overview on current management, and focuses on drugs under investigation (from animal studies to phase II studies) for gastrointestinal and colonic motility disorders. Experience reported in phase III clinical trials has been excluded from this review.

2. Enteric and Central Nervous System and Hormonal Interactions Regulate Functions in the Gastrointestinal Tract

Normal peristalsis and homeostatic sensory and motor mechanisms along the gastrointestinal tract result from a series of control mechanisms involving extrinsic parasympathetic and sympathetic pathways, intrinsic nervous system and the electrical and contractile properties of the smooth muscle cells. These functions are regulated by neurotransmitters and intraluminal chemicals within the gastrointestinal tract. Responses to stimuli such as nutrients, or mechanical forces stimulate production of peptides and amines from enteroendocrine cells that activate intrinsic primary afferent neurons in the intestines and, ultimately, stimulate vagal, splanchnic and pelvic afferents to convey signals to the central nervous system. Release of substances from enteroendocrine cells can be modulated by neurotransmitters. Some of the amines and peptides released also function as hormones, being released from one region and affecting other regions of the gastrointestinal tract, having been delivered through the circulation. In the intrinsic and gut-brain pathways, there are several neurotransmitters such as 5-HT, tachykinins, acetylcholine, nitric oxide, somatostatin and vasoactive intestinal peptide. These lead to physiological responses from

ion fluxes that alter membrane potential of intrinsic nerves and gut smooth muscle; this results in the peristaltic reflex, organized contractions to propel content in the stomach and colon. In addition, the neurotransmitters also control intestinal secretion of fluid and electrolytes, and sensation that stimulates local responses to alter gastrointestinal functions or activate long afferent pathways that lead to conscious perception of gastrointestinal stimuli. Targeting receptors for these substances with selective receptor agonists or antagonists provides the pharmacological basis for treating gastrointestinal motility disorders.

3. Gastrointestinal Motility Disorders: Pathophysiology and Outline of Current Management

3.1. Gastroparesis

Gastroparesis is defined as a syndrome of objectively delayed gastric emptying in the absence of mechanical obstruction, and cardinal symptoms include early satiety, postprandial fullness, nausea, vomiting, bloating and upper abdominal pain [2]. In gastroparesis, there may be abnormal function of smooth muscle, enteric and extrinsic autonomic nerves, or the interstitial cells of Cajal (pacemakers in the stomach wall). Diabetic, postsurgical and idiopathic are the most common conditions in patients with gastroparesis [3]. Other associated conditions include Parkinsonism, paraneoplastic disease and scleroderma [4,5]. Currently approved drugs for treatment of gastroparesis target dopamine D2 receptors; metoclopramide (a D2-receptor antagonist and some 5-HT₄ receptor agonism) is the only FDA-approved medication for the treatment of gastroparesis, and the recommendation is that treatment should be for no longer than 12 weeks. Domperidone is also a dopamine D2 receptor antagonist that can be prescribed through the FDA's expanded access to investigational drugs and is approved for prescription in most other countries including European countries.

Among macrolide antibiotics, erythromycin and azithromycin have been demonstrated to act as motilin receptor agonists; however, these compounds also have multiple actions (e.g. at calcium channels, P2X channels). This class of drugs is not yet approved for specific indication of gastroparesis. Erythromycin is the most extensively studied and, like azithromycin and clarithromycin, there is support in the literature for their efficacy in gastroparesis in the short term. They improve gastric emptying, but have in the past been associated with tachyphylaxis due to down regulation of the motilin receptor, which typically starts after two weeks of the onset of therapy [6]. It is important to note that erythromycin, administered at doses generally used for treatment of bacterial infections, causes tachyphylaxis. An important study by Coulie et al. [7] demonstrated that erythromycin exerts its effects either by motilin receptors on intrinsic cholinergic neurons, or receptors on the smooth muscle itself. It is thought that tachyphylaxis is actually centered on the enteric neuronal functions of motilin receptor agonists. Thus, lower doses of erythromycin retain efficacy after multiple repeat dosing, as a result of their short-acting stimulation of motilin receptors on smooth muscle. The same can be achieved with the motilin receptor agonist, camicinal (discussed below).

3.2. Chronic Diarrhea

Chronic diarrhea is a common gastrointestinal disorder. After exclusion of mucosal diseases such as inflammatory bowel disease and celiac disease, chronic diarrhea is most often due to functional disorders such as irritable bowel syndrome with diarrhea (IBS-D) or functional diarrhea, which manifest with increased frequency, looser consistency and larger volume of stools. Chronic diarrhea, defined as the production of loose stools with or without increased stool frequency for more than 4 weeks, is a common symptom that has prevalence in the United States of approximately 3%–5% [8]. In absence of mucosal diseases, chronic diarrhea may be caused by numerous factors including increased intestinal and colonic motility, sugar or bile acid malabsorption, altered intestinal permeability and barrier function, mast cell infiltration or immune activation, increased intestinal secretion [9] and, possibly, increased colorectal sensation. The role of increased sensation is suggested by the observation that, among patients with irritable bowel syndrome, diarrhea was the bowel dysfunction that was about 4 times as frequent in patients with hypersensitivity compared to those with normal rectal sensitivity [10]. Unfortunately, no therapy that is effective in exclusively reversing colorectal hypersensitivity has been demonstrated to restore normal bowel function in IBS-diarrhea. Therefore, visceral sensitivity is not a primary target for treatment of bowel dysfunction manifesting as diarrhea.

The current first line drug for the treatment of chronic diarrhea is the oral μ -opioid receptor agonist, loperamide; diphenoxylate is also used as a first line therapy, though combination of a widely available preparation of diphenoxylate with atropine may result in adverse effects. Bile acid malabsorption accounts for 25% of the cases of chronic diarrhea [11], and bile acid binders (such as cholestyramine, 4g, three times per day, or colestipol) and off label use of colesevelam (625mg, 1–3 tablets, 2 times per day) are indicated for treatment [12–14].

3.3. Chronic Idiopathic Constipation

Constipation refers to unsatisfactory defecation and is characterized by infrequent stools, harder stool consistency, difficult stool passage, or combinations of these symptoms for at least 3 months. Constipation can be classified into three broad categories with mechanisms involved in altered (slow) colonic transit, normal colonic transit or rectal evacuation disorders (dyssynergic defecation). In the tertiary referral experience of the senior author, slow transit constipation was identified (without concomitant rectal evacuation disorder) in 61/1411 patients, whereas dyssynergic defecation was identified in 390/1411, and the remaining 950 patients had normal transit constipation [15].

Chronic idiopathic constipation (CIC), also known as functional constipation, is one of the most common types of constipation encountered by clinicians and typically corresponds to constipation in the presence of normal colonic transit. A systematic review reported a pooled prevalence of CIC of 14% and that it was more common in females and people of lower economic status [16].

There are several treatments for CIC already approved for use over the counter and these include stimulants (e.g., bisacodyl and senna alkaloids), osmotic laxatives (e.g., magnesium salts and PEG-based agents), and surface active agents (e.g., docusate). Among the

medications approved for treatment of CIC and requiring prescription are the secretagogues, lubiprostone (chloride channel activator) and linaclotide (guanylate cyclase C receptor agonist), and the 5-HT₄ receptor agonist, prucalopride. These agents are now approved in most countries, though prucalopride is still not approved by the FDA. There are no medical treatments of proven benefit in patients with dyssynergic defecation and no medications specifically developed for or proven to be beneficial in slow transit constipation.

3.4. Opioid Induced Constipation

Opioid induced bowel dysfunction is due to opioid induced alteration in gastrointestinal motility, secretory and sphincter functions. These actions are mainly mediated by the μ and opioid receptors [17]. Opioid induced constipation can occur in up to 40% of patients receiving opioid therapy [18]. Laxatives can improve bowel function to a certain extent, but are limited by the refractory nature of opioid bowel dysfunction. Naloxone in a fixed combination with oxycodone is another approved option, but its efficacy is limited by the central action of naloxone that may induce withdrawal symptoms and block analgesia. Current investigations are focused on peripherally acting μ opioid receptor antagonists (PAMORAs) that selectively target μ opioid receptors in the gastrointestinal tract (discussed below).

4. Methods to Identify Early Investigational Therapeutics

We reviewed the literature in PubMed, Web of Sciences, and Clinicaltrials.gov for articles describing current investigations on novel drugs for the treatment of gastric, intestinal and colonic motility disorders. We included articles describing animal studies to phase II studies in humans, as summarized in Table 1.

5. Early Investigational Therapeutics

5.1. New Motilin Receptor Agonist

Although erythromycin is currently used “off-label” as a gastric prokinetic, it may induce antibiotic resistance, is associated with tachyphylaxis [19], and may inhibit cytochrome P-450 CYP3A4, leading to unwanted drug interactions. In addition, because erythromycin is extensively metabolized by cytochrome P-450 CYP3A isozymes, commonly used medications that inhibit the effects of CYP3A may increase plasma erythromycin concentrations, thereby increasing the risk of ventricular arrhythmias and sudden death [20]. All of these factors point towards an urgent need for a more selective motilin receptor agonist.

Although discovery of new, efficacious motilin agonists has been a rather long and winding road [21], a novel motilin agonist has significant promise, based on the hypothesis that the motilin receptors can be induced to preferentially evoke ('biased agonism'), via particular pathways, different responses with therapeutic advantages/disadvantages, such as preferentially activating the β -arrestin pathway, enhancing the ability to more quickly recover from desensitization of the receptor [22].

GSK962040 (or **camicinal**) is a selective small molecule motilin receptor agonist [23] that has been shown to induce phasic contractions and increase gastrointestinal motility in conscious dogs [24]. A separate study has shown that GSK962040 has a greater effect in mediating cholinergic activity in the antrum when compared to the fundus and the small intestine in humans [25]. A phase II, 28-day clinical study of its effects on gastric emptying and symptoms, safety, tolerability, and pharmacokinetics in type 1 and type 2 diabetic subjects with gastroparesis has been completed (ClinicalTrials.gov NCT01262898), but no results for the study have been reported to date.

5.2. New Ghrelin Agonists

Ghrelin is a peptide hormone that possesses orexigenic properties. Administration of physiological doses of exogenous ghrelin to humans does not significantly alter gastric motility [26]; however, high doses of ghrelin agonists administered to humans increase gastric tone and emptying, and frequency of small intestinal migrating motor complexes. The potential of ghrelin agonists to be used as prokinetics is being tested in patients with gastroparesis and postoperative ileus (reviewed in ref. 27).

The ghrelin agonists currently under investigation are HM01 and RM-131. Extensive studies on ulimorelin or TZP-102 were conducted in the past decade, but there are no ongoing studies registered in Clinicaltrials.gov, suggesting that its development is no longer being pursued.

HM01 is under investigation for efficacy in gastrointestinal disorders. A recent study evaluated its *in vitro* and *in vivo* pharmacological profiles in a model of decreased frequency in 6-hydroxydopamine (6-OHDA) Parkinson's disease rat model. Acute orogastric administration of HM01 in the 6-OHDA rats significantly decreased the 4-hour fecal output and water content, with a dose of 3mg/kg having a maximum effect. Pretreatment with HM01 prevented L-dopa/carbidopa induced delayed gastric emptying, simulating the gastroparesis observed in patients with Parkinson's disease [28]. It has also been shown that HM01 has a high binding affinity to the human ghrelin receptor, good bioavailability, and it crosses the blood-brain barrier. Further studies in other gastrointestinal motility disorders, apart from models of Parkinson's disease, are eagerly awaited.

Relamorelin (RM-131) is a novel pentapeptide that acts as a potent ghrelin receptor agonist. Relamorelin reversed postsurgical gastric ileus in rats and increased the rate of gastric emptying in healthy primates that had not undergone abdominal surgery. Animal studies evaluating and comparing relamorelin with ghrelin and other synthetic ghrelin mimetics for their prokinetic efficacy in models of gastrointestinal disorders in rats showed that relamorelin was 600-to 1800-fold more potent compared to other ghrelin mimetics in increasing gastric emptying [29]. Further information in the public domain on the molecular structure and pharmacological selectivity of relamorelin and potential differences of effects in different species is eagerly awaited.

In two randomized, double-blind, placebo-controlled, crossover studies conducted in 10 patients with type 2 diabetes or type 1 diabetes and prior documentation of delayed gastric emptying, single dose administrations of relamorelin accelerated gastric half-emptying time

of solids [30,31]. In a phase II study, relamorelin, administered once or twice daily (10 or 20µg/day) for 4weeks, also accelerated gastric emptying of solids in type 1 diabetic patients and reduced upper gastrointestinal symptoms, with the most impressive effects being observed in patients with high baseline vomiting [32].

The use of relamorelin in chronic constipation has also been investigated. A phase II placebo-controlled study with daily administration evaluated the safety, efficacy and tolerability of 100µg/day for 2 weeks in patients with chronic constipation, with colonic transit as the primary measure outcome (ClinicalTrials.govID NCT01781104) [33]. The study also demonstrated acceleration of colonic transit, as well as increased number of spontaneous bowel movements (BM) and accelerated time to first BM after first dosing with relamorelin compared to placebo [33]. In a mechanistic evaluation of intra-colonically measured motor activity, 100µg relamorelin significantly increased the number of premeal propagated phasic contractions >50mmHg and numerically increased the number of postmeal propagated phasic contractions >50mmHg when compared to placebo [34]. This suggests that relamorelin may stimulate colonic motility by inducing phasic contractions in addition to the already established effect on colonic transit. Although, it is unclear whether the propagated contractions are the cause or effect of relamorelin on colonic transit, the observation in the emptied colon suggests that the primary effect is on colonic motility, with secondary effect on transit.

5.3. Mirtazapine

Mirtazapine is a noradrenergic and specific serotonergic receptor antidepressant; mirtazapine antagonizes α_2 receptor and blocks 5-HT_{2A} and 5-HT_{2C} and 5-HT₃ receptors [35], enhancing the release of norepinephrine and 5-HT. A study investigating the effect of mirtazapine on gastrointestinal motility in 12 dogs (6 under normal conditions and 6 with rectal distention) found that mirtazapine significantly accelerated gastric emptying in healthy dogs and the presence of delayed gastric emptying induced by rectal distention. Further clinical studies are necessary to assess the potential of mirtazapine in patients with functional gastrointestinal diseases [36].

5.4. New 5-HT₄ Receptor Agonists

Prokinetic drugs directed at the colon target the activity of 5-HT₄ receptors in the colonic mucosa. In the past, the inability of 5-HT₄ agonists such as cisapride and tegaserod to selectively bind to colonic 5-HT₄ receptors limited their safety in treating CIC. The multi-organ side effects were due to the affinity of tegaserod and cisapride for other receptors (e.g. 5-HT_{2B} which may contribute to vascular actions that could be deleterious) and ion channels [delayed rectifier potassium (IKr) channel] in cardiac muscle. The relative contributions of a wide variety of 5-HT₄ receptor agonists and their potential effects on other receptors are beyond the scope of this review and are extensively discussed elsewhere [37].

The new prokinetic agents currently under investigation overcome this limitation by having greater selectivity and specificity for 5-HT₄ receptors in the intestine than for the IKr channel and have less intrinsic activity on cardiac muscle [38].

In a double-blind, placebo-controlled, randomized study, subjects with CIC were treated with **velusetrag** (15, 30 or 50mg daily) for 4 weeks, and results showed that all three doses significantly increased spontaneous bowel movements (SBMs) and complete SBMs compared to placebo (with the 15mg dose having the largest effect). All doses were well tolerated [39]. A systematic review and meta-analysis of the effects of prucalopride, velusetrag and naronapride for the treatment of CIC showed that, although most studies have been done with prucalopride, all three were superior at improving stool frequency and quality of life compared to placebo and had a favorable safety profile, with headache being the most frequent reported side effect [40].

YKP10811 is a novel benzamide derivative that acts as a partial agonist of the 5-HT₄ receptor. YKP10811 did not show any significant off-target binding to any other receptors, enzymes, or serotonin-receptor subtypes at 1mmol/L, except for binding to the 5-HT_{2A} receptor (K_i = 600nmol/L) and the 5-HT_{2B} receptor (K_i = 31nmol/L). In a phase II single-center, randomized, parallel-group, multiple-dose, double-blind, placebo-controlled study, 55 patients with functional constipation were treated with YKP10811 (10, 20, 30mg) or placebo for 8 days. YKP10811 increased gastrointestinal and colonic transit and improved stool consistency, with the 10 and 20mg doses being the most effective. No significant adverse events were reported [41]. A phase II trial to assess the efficacy and safety of YKP10811 in subjects with irritable bowel syndrome with constipation is currently being conducted (ClinicalTrials.gov trial ID NCT02082457). No data have been reported to date.

A recent study evaluating the influence of YKP10811 on rat models showed that YKP10811 reduced colonic hypersensitivity induced by partial restraint stress. YKP10811 also reduced trinitrobenzene sulfonic acid induced IBS in rats after seven days of treatment, suggesting an anti-nociceptive role. Similarly, the reduction of colonic hypersensitivity in acute stress model was maintained after several administrations of the medication [42].

Overall, YKP10811 has significant activity consistent with its 5-HT₄ agonist effects; the 120-fold and 6-fold lower affinity, respectively, for 5-HT_{2A} and 5-HT_{2B} receptors than for 5-HT₄ suggest that adverse vascular effects are unlikely to occur, but further careful monitoring in larger clinical trials will be required to assess its safety.

TD-8954, another novel 5-HT₄ receptor agonist, has been tested *in vitro* and *in vivo* in the gastrointestinal tract of guinea pigs, rats, dogs and humans. It is a selective 5-HT₄ receptor agonist with good intrinsic activity [43]. Subcutaneous administration of TD-8954 (0.03–3mg/kg) increased colonic transit of carmine red dye in guinea pigs, and it evoked a dose dependent (10 and 30µg/kg) relaxation of the esophagus in rats. Oral administration of a single dose of TD-8954 (0.1–20mg) on conscious dogs increased contractility of the proximal small intestine, and in human subjects it increased bowel movement frequency and reduced time to first stool for all doses compared to placebo [44].

5.5. New Guanylate Cyclase C Agonist: Plecanatide

Linacotide, a guanylate cyclase C (GC-C) agonist, is already approved for the treatment of chronic constipation and IBS-C. An emerging secretagogue, **plecanatide**, is an analog of uroguanylin, an endogenous GC-C agonist; plecanatide also activates GC-C receptors within

the gastrointestinal tract, resulting in chloride and bicarbonate secretion through the cystic fibrosis transmembrane conductance regulator (CFTR). This secretion is associated with increased numbers of bowel movements. Plecanatide is safe and well tolerated up to doses of 48.6mg in humans [45]. Phase II studies have shown that plecanatide improves stool frequency and consistency, straining and abdominal discomfort [46,47]. Two 12-week phase III studies are currently being conducted to appraise the safety and efficacy of plecanatide in treating CIC (ClinicalTrials.gov trial ID NCT01982240, NCT02122471).

5.6. Inhibitor of a Sodium-Hydrogen Channel, RDX5791

NHE3 is an intestinal Na^+/H^+ antiporter involved in the uptake of sodium into enterocytes from the intestinal lumen. **RDX5791** is a minimally absorbed, small molecule NHE3 inhibitor that is in clinical development for the treatment of CIC and IBS-C. It is believed to decrease the absorption of sodium excretion from the kidneys and, thus, divert sodium (and water) excretion from the kidneys to the gastrointestinal lumen and, hence, to feces. Animal studies investigating *in vitro* activity in rats and *in vivo* efficacy in rats and dogs showed that NHE3 exhibits minimal systemic exposure, increases intestinal fluid secretion, accelerates intestinal transit, and increases stool score in a dose-dependent manner [48]; it also appears to have visceral antinociceptive properties in a rat model of visceral hypersensitivity [49]. As described by Bulmer and Grundy [50], translation of efficacy in visceral antinociceptive activity observed in rodents to humans with functional bowel disorders has proved difficult for several reasons including the lack of a significant pathology in the human disorders around which to build an adequate animal model, the lack of comprehensive understanding of human visceral pain processing, and the lack of an adequate measurement for similar comparison of pain processing in both rodents and humans. RDX5791 exhibited antinociceptive activity in a rat model of visceral hypersensitivity similar to the effects shown by tegaserod, which had shown some antinociceptive activity in cats [51] and humans [52] based on experiments using barostat controlled pressure distensions. Similar studies in humans may support the evidence from rat models of potential antinociceptive activity of this new drug in humans. A multicenter, phase II, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of RDX5791 for the treatment of IBS-C and two phase I studies in healthy subjects have been completed (ClinicalTrials.gov trial ID NCT01340053, NCT02176252, NCT02249936), but no data have been reported to date.

5.7. Peripherally Acting μ -Opioid Receptor Antagonists (PAMORA)

After the recent approval of naloxegol, the only PAMORA currently under investigation up to phase II studies is **TD-1211**. The oral activity of TD-1211 was investigated in *in vivo* models of the gastrointestinal tract and central nervous system in rats and dogs and was compared to other μ -opioid receptor antagonists such as naltrexone, alvimopan, and ADL-088 which generally have been reported to reverse the effects of μ -opioid receptor agonists on orocecal transit time or colonic transit in animals and humans.

TD-1211 showed a promising effect on gastrointestinal motor activity without much central nervous system activity [53]. In a double-blind, placebo-controlled study, 70 patients on chronic opioid therapy for non-cancer pain were randomized to receive 2 weeks of treatment

with either TD-1211 (0.25, 0.75, 5, 10mg, qd) or placebo. TD-1211 increased bowel movement frequency, accelerated (in a dose-dependent fashion) time to first SBM, reduced laxative rescue (at the 5 and 10mg doses), and was well tolerated [54]. In a 5-week, double-blind, parallel-group study of 217 OIC patients with chronic non-cancer pain, TD-1211 doses (10 and 15mg) increased SBMs and complete SBMs per week while reducing overall constipation symptoms [55].

5.8. Bile Acid Pathway Modulators

Bile acids (BA) are molecules that act as detergents and are mainly responsible for fat emulsification and lipid absorption in the small intestine. They are synthesized from cholesterol in the hepatocytes, secreted into the proximal portion of the small intestine, and reabsorbed in the terminal ileum where they are transported through the portal circulation and finally taken up by the hepatocytes once again. This is known as the enterohepatic circulation of BAs. BAs can increase colonic secretion of water and electrolytes and may also stimulate high amplitude, propagated contractions [reviewed in ref. 56].

Approximately 95% of the BAs are reabsorbed in the terminal ileum by the apical sodium-coupled BA transporter (ASBT or IBAT). **Elobixibat** (A3309) acts locally in the lumen of the gastrointestinal tract, selectively inhibiting the IBAT, providing a novel approach for BA delivery to the colon. In a phase I, single-center, 30-patient, prospective, randomized, double-blind, placebo-controlled, 14-day treatment study with a dose escalating design (0.1–10mg/day), elobixibat significantly increased BA synthesis and accelerated colonic transit [57]. Inhibition of bile acid absorption results in decreased stimulation of the nuclear farnesoid X receptors (FXR) in ileal enterocytes, thereby reducing the amount of fibroblast growth factor-19 (FGF-19) entering the portal circulation, and hence reducing the negative feedback on CYP7A1, the rate limiting enzyme of bile acid synthesis in the hepatocytes (for review, see ref. 58).

In a randomized, placebo-controlled, phase IIb trial of elobixibat in patients with CIC, there was significant improvement in stool frequency and constipation related symptoms over a course of 8 weeks of treatment [59]. Elobixibat significantly accelerated colonic transit and improved stool consistency in females with functional constipation when compared to placebo. The most common side effect was lower abdominal pain and cramping [60].

An excess of BAs entering the colon can induce secretory and motility changes and is a common cause of chronic diarrhea. Many of these patients have reduced levels of FGF19 which is a BA synthesis regulator produced in response to farnesoid X-receptor (FXR) activation. Thus, FXR agonists have emerged as potential novel therapeutics in the treatment of chronic diarrhea. In a phase II, proof of concept, 2-week treatment study, **obeticholic acid**, a potent FXR agonist, stimulated FGF19 synthesis, significantly reduced BA synthesis, and improved symptoms of abdominal pain and urgency in patients with primary BA diarrhea, secondary BA diarrhea, and idiopathic chronic diarrhea [61].

Two phase I studies assessing the safety and tolerability of the FXR agonist, **Px-102**, in healthy subjects have been conducted (ClinicalTrials.gov trial ID NCT0998672,

NCT0998659), but to date there are no Phase II studies in chronic diarrhea. Further studies will evaluate the effectiveness of FXR agonists in treating gastrointestinal motility disorders.

6. Conclusion

Current management of gastrointestinal motility disorders continues to prove difficult, but there are several new drugs and strategies currently under investigation. These include the PAMORA, TD-1211, for OIC, the secretagogue, plecanatide, and specific 5-HT₄ agonists for CIC, and relamorelin for gastroparesis and chronic constipation.

7. Expert Opinion

The key research findings are that medications based on understanding of pathophysiologic mechanisms of motility disorders are generally successful. Advances are predominantly in the field of disorders of lower gastrointestinal function associated with constipation where new classes of medications include general approaches involving intestinal secretion or pro-motility agents or specific agents as noted with the PAMORAs for OIC. However, research done in the field of gastroparesis, which is associated with significant morbidity and mortality, is limited by the lack of a clear regulatory path or approved patient response outcome (PRO) endpoints for approval of medications by regulatory agencies. This deficiency has hampered proof of concept and phase IIB studies and, as a result, there has not been an FDA-approved drug for this indication for almost four decades, and the only approved drug is encumbered with a black box warning clinicians not to use the drug for over three months.

Given the extensive understanding of pathophysiology and the potential mechanisms (targeting serotonergic, ghrelin, motilin and, potentially, tachykinin receptors), there is great potential to develop medications to help patients where the need is currently greatest, that is patients with gastroparesis. In addition, the American Neurogastroenterology and Motility Society has undertaken extensive psychometric and other validation studies to facilitate the development of a PRO for gastroparesis based on a daily diary gastroparesis cardinal symptom index (ANMS GCSI-DD) [62,63]. Regulatory approval is eagerly awaited in order to encourage drug development in this field. In the absence of a significant pipeline of medications, the final validation, based on responsiveness in large numbers of patients as would occur in well designed phase IIB-III studies, is unavailable and can only become available if a PRO, such as the ANMS GCSI-DD, is accepted, either as the final or an interim endpoint for use in phase III clinical trials.

The pace of progress in the coming years will likely depend on these regulatory issues, and the main pharmacological targets will remain in the same classes of drugs discussed in this article.

Conceptual and clinical advances will be facilitated by validation of biomarkers to identify subgroups of these disorders, followed by well designed pharmacological studies from animal to phase II in humans to more effectively target disorders, especially when they are multifactorial or present several potential targets to restore normal function. A valid biomarker is defined as “a characteristic that is measured and evaluated as an indicator of

normal biologic processes, pathogenic processes, or pharmacological responses to a therapeutic intervention” [64].

Development of biomarkers has the potential to usher in a new era in which efficacious medications are individualized to the underlying pathophysiology or disease mechanism in each patient. Colonic transit by scintigraphy has already been amply demonstrated as an effective biomarker for identifying the proof of concept information essential for predicting likelihood that medications will prove efficacious in phase IIB or III trials in conditions associated with abnormal colonic transit [65]. Examples of the use of biomarkers to identify subgroups of disease also have been recently published. Thus, measurements of colonic transit and fecal BA excretion can identify the patients with IBS-diarrhea [66] who should be treated with anti-motility drugs or BA sequestrants [67].

The principles for successful drug development in functional and motility disorders are similar to those recommended 15 years ago [68] and are summarized in Table 2.

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ARTICLE HIGHLIGHTS

- Enteric and central nervous system interactions and hormones regulate functions in the gastrointestinal tract and provide most of the targets for treatment of gastrointestinal motility disorders.
- Increased intestinal mucosal secretion may overcome the symptoms resulting from reduced propulsion of colonic intraluminal content.
- Novel pharmacological approaches to reverse gastrointestinal and colonic motility disorders include prokinetics (e.g. new motilin, ghrelin, and 5-HT₄ receptor agonists), secretagogues (e.g. guanylate cyclase receptor agonists and inhibitors of sodium-hydrogen exchangers).
- Peripherally active μ -opioid receptor antagonists constitute specific treatments for opioid induced constipation without adverse effects due to central inhibition such as reversal of analgesia.
- The use of biomarkers to identify subgroups of motility disorders and robust pharmacological studies from animal to phase II studies will enhance the success in developing new, efficacious and effective therapies.

Table 1

Examples of current investigational drugs for gastrointestinal motility disorders

Drug name	Mechanism of action	Clinical/Pharmacodynamic efficacy	Current status
Prokinetics			
Camicinal (GSK962040)	Selectively activates motilin receptor in humans	Induced phasic contractions and increased GI motility in dogs	Phase II studies completed; no results reported
HM01	Synthetic ghrelin agonist that binds to ghrelin receptor	High binding affinity to ghrelin receptor; good bioavailability, and prevented delayed gastric emptying in a Parkinson's disease (PD) rat model	Animal PD studies (rat models)
Relamorelin (RM-131)	Ghrelin receptor agonist	Accelerated gastric emptying and colonic transit; induced phasic contraction	Phase IIA studies completed
Mirtazapine	Antagonizes α_2 and 5-HT ₂ and 5-HT ₃ receptors, enhancing release of norepinephrine and 5-HT	Accelerated gastric emptying in healthy dogs as well as dogs with rectal distention; induced delayed gastric emptying	Approved for psychiatric disorders; GI motility investigated in animals
Velusetrag	5-HT ₄ receptor agonists	Accelerated colonic transit in healthy subjects in a dose dependent fashion	Phase IIB studies completed in CIC
YKPI0811	5-HT ₄ receptor agonist	Accelerated colonic transit in subjects with functional constipation Reduced colonic hypersensitivity in stressed rat models	Phase IIA studies completed in FC and IBS-C patients
TD-8954	5-HT ₄ receptor agonist	Increased colonic transit in guinea pigs; evoked relaxation of the esophagus in rats in a dose dependent fashion; increased small intestinal contractility in dogs; and increased bowel frequency in humans	Completed in vivo and in vitro pharmacology in guinea pigs, rats, dogs, human tissues
Secretagogues			
Plecanatide	Activates guanylate cyclase-C receptors; increases Cl ⁻ and HCO ₃ ⁻ secretion	Improved stool frequency and consistency in patients with chronic constipation	Phase IIB studies in subjects with chronic constipation and IBS-C
RDX5791	NHE-3 inhibitor decreases renal Na ⁺ excretion diverting Na ⁺ and water into GI lumen	Increased intestinal secretion and accelerated intestinal transit. It also appeared to have antinociceptive properties	Phase II study on the safety and efficacy in patients with IBS-C
Peripherally acting μ-opioid receptor antagonist			
TD-1211	Blocks effects of opioids on μ -OR outside the CNS	5 and 10 mg/d doses increased average SBMs/week over a period of 2 weeks in OIC patients	Ongoing Phase II studies in OIC patients
Bile acid modulators			
Elobixibat	Selectively blocks IBAT; increasing bile acid delivery to the colon	Accelerated colonic transit; increased bile acid synthesis; and improved stool frequency and consistency in CIC patients	Phase IIB studies completed; phase III studies ongoing
Obeticholic acid	Selective FXR-receptor agonists, activate FGF-19 synthesis, reduce hepatic BA synthesis	Obeticholic acid stimulated FGF-19 synthesis, reduced bile acid synthesis and improved pain and urgency on CID patients	Phase IIA study in BA diarrhea completed
Px-102		ND	Phase I studies completed

PD=Parkinson's disease; CIC=chronic idiopathic constipation; IBS-C=constipation-predominant irritable bowel syndrome; CNS=central nervous system; SBMs=spontaneous bowel movements; OIC=opioid induced constipation; IBAT=ileal bile acid transporter; BA=bile acid; ND=not done; information on current status generally obtained in clinicaltrials.gov

Table 2

Principles for successful drug development in functional gastrointestinal and motility disorders (adapted from [68] with permission of Elsevier).

1	Target an important mechanism, receptor or transmitter that plays an important role in the disease of interest
2	Target appropriate patient subgroups in the context of the drug's pharmacology
3	Develop strong clinical pharmacology and rationale before entering phase IIB studies
4	Use standard eligibility criteria for all trials
5	Recruit patients in reliable GI offices or academic centers
6	Use a study run-in phase to consolidate the diagnosis or subgroup of interest
7	No clinical phase III trials before it's time: Learn all you can from the animal, phase II studies and clinical pharmacology studies, preferably with validated biomarkers
8	Use validated primary endpoint based on patient determination of clinical significance (patient response outcomes)
9	Conduct placebo-controlled, parallel-group, sufficiently powered studies to evaluate efficacy of the medication, including detailed statistical analysis plan
10	Do not confuse the lack of efficacy of a new drug with inability of a trial to show the drug is efficacious