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5-HT$_4$ Receptor Agonists in the Treatment of Gastrointestinal Motility Disorders: Current Status and Perspective

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Abstract

Background: 5-HT$_4$ receptor plays important roles regulating gastrointestinal motility, enteric neuronal signaling and visceral pain in the gastrointestinal tract. Over the past decade, the 5-HT$_4$ receptor has been highlighted as an attractive drug target for the treatment of gastrointestinal motility disorders such as irritable bowel syndrome, chronic constipation, functional dyspepsia, gastroparesis and so on.

Objectives: This article aims to provide an overview of serotonin receptors related to the gastrointestinal motility disorders, and to address the characteristics of past, current and future 5-HT$_4$ receptor agonists for treatment of functional gastrointestinal disorders, focusing on the pharmacology, efficacy and safety profile.

Methods: A literature search was performed using databases including MEDLINE (1974-July 2014), SCOPUS, Google Scholar, abstracts presented at the gastroenterology meetings and unpublished data from pharmaceutical companies. Specific search terms used were "5-HT$_4$ receptor agonist", "gastrointestinal motility disorder", "irritable bowel syndrome" and "chronic constipation".

Conclusion: In contrast to nonselective 5-HT$_4$ receptor agonists such as tegaserod and cisapride, which were withdrawn due to cardiovascular adverse effects, several potent and selective 5-HT$_4$ receptor agonists have been found to display the improved safety profile and the therapeutic potential in clinical trials and preclinical studies. These include agents such as prucalopride, velusetrag, naronapride, YKP10811 and DA-6886. These compounds differ in chemistry, efficacy, adverse effects and pharmacokinetics. The various properties of 5-HT$_4$ receptor agonists will help us not only to enable adequate treatment to be tailored to the needs of each patient but also to stimulate further efforts to develop promising innovative drugs for gastrointestinal motility disorders.

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Introduction

Gastrointestinal (GI) motility disorder including irritable bowel syndrome, chronic constipation, functional dyspepsia and gastroparesis is a common and debilitating disease that has a profound effect on patient's quality of life and imposes a substantial economic burden. Irritable bowel syndrome (IBS) is characterized by abnormalities in motility and visceral hypersensitivity [1]. The underlying cause is thought to involve dysfunction in GI motility, psychological factors, hypersensitivity and inflammation of the bowel, and aberrant autonomic function. In meta-analysis, the overall IBS prevalence was 11.2% with variation by geographic region; the lowest occurring in South Asia (7.0%) and the highest in South America (21.0%) [2]. Several Asian studies showed that the prevalence of IBS in Singapore, Tokyo and South Korea was 8.6%, 9.8% and 6.6%, respectively [3,4]. According to predominant bowel habit disturbance (described in the Rome III criteria), IBS patients were classified as IBS with constipation (IBS-C), IBS with diarrhea (IBS-D) and mixed form (IBS-M). The relative proportion of IBS-C is reported to range from 5.2% to 66%[5]. Patients with IBS reported considerable impairments in health status having not only poor health-related quality of life (HRQOL) with dietary restrictions, mood disturbance and interference with daily activity but also severe symptoms as pain, bowel difficulties, bloating and eating/dietary restrictions [6,7].

In terms of GI motility, chronic constipation (CC) and IBS-C overlap symptoms. CC patients exhibit little or no abdominal pain, whereas IBS-C patients experience it. Chronic constipation is a highly common bowel disorder that affects up to approximately 27% of the North American population [8,9]. Constipation affects older age groups disproportionately, with a prevalences of 50% in community-dwelling elderly and 74% in nursing-home residents [10]. In addition, secondary constipation is caused by medication as well as pathophysiological conditions including malignancy, endocrine disorders, neurologic disorders, metabolic diseases and pregnancy. The medications causing constipation as a side effect include antacids, calcium and iron supplements, antidiarrheal agents, nonsteroidal anti-inflammatory agents, opioids, tricyclic antidepressants, diuretics, anticholinergic agents, antihistamines and so on [11,12].

Functional dyspepsia (FD) and gastroparesis (GP) are the two most common motility disorders of the upper gastrointestinal tract. The prevalence of FD was between 11.5% and 14.7%, and that of GP was approximately 1.5–3% [13,14]. Functional dyspepsia is characterized by the presence of chronic or recurrent symptoms of upper abdominal pain or discomfort in the absence of any known specific structural cause [15]. Gastroparesis is a disorder characterized by delayed gastric emptying [14,16]. It is believed to be caused by not only diseases such as diabetes mellitus, peptic ulcer and gastroesophageal reflux but also surgery with partial gastric resection.

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Currently, a variety of medication to treat these GI motility disorders are available. Traditional laxatives including bulking agents, stool softners, osmotic laxatives and stimulant are effective in defecation, but the laxatives demonstrate a limited level of efficacy in long-term use, abdominal discomfort or bloating. A number of new medications include the prokinetic selective 5-HT_4 receptor agonist (prucalopride), the intestinal chloride channel activator (lubiprostone) and the guanylate cyclase-C agonist (linaclotide). 5-HT_4 receptor has been highlighted as an attractive drug target for the treatment of GI motility disorders. 5-HT_4 receptor agonists such as tegaserod, cisapride, prucalopride and mosapride have been demonstrated to be efficacious in patients with gastrointestinal disorders [17,18,19,20]. Despite of the proven efficacy, some of these agents were not 5-HT_4 receptor-selective, and the lack of selectivity continued to make severe adverse effects. Cisapride was withdrawn due to cardiovascular adverse effects associated with QT prolongation because it is a potent blocker of the hERG (human ether-a-go-go related gene) channel [21]. Tegaserod, the first drug approved by the FDA for the treatment of chronic idiopathic constipation and IBS-C has also been withdrawn from the market due to a higher chance of ischemic adverse events. Therefore, a real need exists for more effective, well-tolerated and safe pharmacological agents to manage the common and troublesome symptoms of these GI motility disorders.

The aims of this review are to discuss how advance in our understanding of 5-HT receptors, and to overview the previous and ongoing research and development of 5-HT_4 receptor agonists in treatment for gastrointestinal motility disorders. The review focuses on seven 5-HT_4 receptor agonists that are currently of interest: Tegaserod, Cisapride, Prucalopride, Naronapride, Velusetrag, YKP10811 and DA-6886.

Serotonin Receptors in Gastrointestinal Tract

Serotonin (5-hydroxytryptamine, 5-HT) is the main enteric neurotransmitter regulating gastrointestinal motility, smooth muscle tone, mucosal secretion and neuronal signaling [22-5], and 95% of serotonin is found in the gastrointestinal tract, and released from enterochromaffin cells distributed throughout the gut mucosa [26].

The physiological role of enteric serotonin is determined by which serotonin receptors are activated. It means specific serotonin receptors provide the site of action for therapeutic agents for gastrointestinal motility disorders. Seven molecularly distinct subtypes (5-HT_1-5-HT_7) has been identified and characterized functionally. Of these, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_3, 5-HT_4 and 5-HT_7 receptors are distributed in the enteric nervous system or smooth muscle in the gut [27,28]. 5-$HT_{1A,1B}$ receptor inhibit neurotransmitter release while 5-HT_3, 5-HT_4 receptor are the excitatory subtypes. Activation of 5-HT_{1A} receptors inhibits the release of acetylcholine and the contraction of smooth muscle [29]. Buspiron, 5-HT_{1A} receptor agonist, enhanced gastric accommodation in patients with functional dyspepsia in clinical studies [30]. Also, buspiron increases lower oesophageal sphincter tone and slows gastric emptying in human [31]. Sumatriptan, a selective 5-HT_{1B} receptor agonist, induces a lag phage for gastric emptying of liquids [32], and increases the amplitude and duration of esophageal contractions in humans [33].

In smooth muscle, 5-HT_{2A} mediates contraction, while 5-HT_4 and 5-HT_7 receptor mediates relaxation [34]. 5-HT_{2B} receptors are widely distributed in peripheral tissues including heart, skeletal, intestine, CNS. In gastrointestinal tract, 5-HT_{2B} receptors contribute to 5-HT-induced colonic smooth muscle hypersensitivity [35]. It has been reported that 5-HT transport and 5-HT transporter-mediated antidepressant recognition are controlled by 5-HT_{2B} receptor in serotonergic neuronal cells [36]. In cardiovascular system, activation of 5-HT_{2B} receptors is believed to be necessary to produce 5-HT-induced valvulopathy [37,38]. The withdrawal of fenfluramine from the market in 1997 was due to valvular heart disease [39]. There have been many cases of serotonergic medications increasing the risk of developing the valvular heart disease via the activation of 5-HT_{2B} receptors [40].

5-HT_3 receptor is a ligand-gated cationic ion channel located on post-synaptic and sensory neurons in enteric nervous system, vagus and brain. This receptor exerts rapid depolarization response in myenteric neurons, leading to increased release of acetylcholine from cholinergic neurons [41]. 5-HT_3 receptor antagonists have been reported to reduce visceral pain reflex induced by duodenal distension in rats [42]. It was reported that ondansetron, a 5-HT_3 antagonist reduces the postprandial colonic hypertonic response in patients with carcinoid diarrhea [43].

5-HT_4 receptors consisting at least nine splice variants are positively linked to G_S proteins, resulting in stimulation of adenylyl cyclase and increase in cellular cyclic AMP, and located in the nerve terminals on both cholinergic interneurones and motor neurones. Activation of 5-HT_4 receptors on efferent myenteric cholinergic excitatory neurons induces neuronal release of acetylcholine, substance P and calcitonin gene-related peptide producing coordinated contraction and relaxation of gastrointestinal smooth muscle [29,44], accelerating upper gastrointestinal transit as well as increasing in colonic motor activity. Thus, it affects all components of the peristaltic reflex [45]. 5-HT_4 receptor agonists have been shown to produce tonal relaxation of smooth muscle in the rat esophagus [46] and the canine rectum and human colon [47]. There are growing evidences that the 5-HT_4 receptor may be involved in the pathophysiology of visceral pain which is a main symptom of IBS. Mosapride diminished visceral pain in a rat model [48], and tegaserod produced analgesia via activation of supraspinal 5-HT_4 receptors [49]. The mucosal administration of 5-HT_4 receptor agonists alleviated visceral pain [50]. The 5-HT_4 receptor is also expressed in brain, and functions in long-term potentiation and synaptic plasticity. It has a tonic positive influence on serotonin neurons in the dorsal root ganglia and modulates 5-HT content in the raphe nuclei, showing behavior which enhance learning and memory in animal models [51,52]. Indeed, the 5-HT_4 receptor could be a successful pharmaceutical target in functional gastrointestinal motility disorders. Some 5-HT_4 receptor agonists such as tegaserod, cisapride have been withdrawn for non 5-HT_4 receptor-associated side effects. To date, selective 5-HT_4 receptor agonists are available or in different phases of clinical studies (Table 1). In the next chapter, we will discuss in more details about the characteristics of 5-HT_4 receptor agonists in regard of chemistry, pharmacology, efficacy and safety.

5-HT_4 Receptor Agonists in the Treatment of Gastrointestinal Motility Disorders

Chemical property and pharmacology

Most of benzamides (metoclopramide, clebopride, cisapride, mosapride, renzapride; figure 1) are not highly selective 5-HT_4 receptor

Compound	Stage of development	Mechanism of action	Company	Indication
Metoclopramide (Primperan™)	Launched	D_2 antagonist, 5-HT_3 antagonist, 5-HT_4 agonist	Sanofi-Aventis	Nausea-vomiting, GERD, diabetic gastroparesis
Clebopride (Cleboril™)	Launched	5-HT_4 agonist, 5-HT_3 antagonist, D_2 antagonist	Almirall	Nausea-vomiting
Cisapride (Prepulsid™)	Restricted use	5-HT_4 agonist, 5-HT_3 antagonist, 5-HT_2 antagonist,	Johnson & Johnson	GERD, gastroparesis
Mosapride (Gasmotin™)	Launched	5-HT_4 agonist, 5-HT_3 antagonist	Dainippon-Sumitomo	Gastritis, GERD
Tegaserod (Zelnorm ™)	Restricted use	5-HT_4 agonist, 5-HT_2 antagonist, 5-HT_1 agonist, 5-HT_3 antagonist	Novartis	IBS, Chronic idiopathic constipatio
Prucalopride (Resolor™)	Launched	5-HT_4 agonist	Movetis	Chronic constipation
M0003, M0004	Phase II, discontinued	5-HT_4 agonist	Movetis	GERD, gastroparesis
Renzapride	Phase III, discontinued	5-HT_4 agonist, 5-HT_3 antagonist	Alizyme	IBS-C, IBS-M
E-3620	PhaseII, discontinued	5-HT_4 agonist, 5-HT_3 antagonist	Eisai	GI motility disorders
Naronapride	Phase II	5-HT_4 agonist	ARYx Therapeutics	Chronic idiopathic constipation, GERD, gastroparesis
Velusetrag	Phase II	5-HT_4 agonist	Theravance	Chronic constipation, gastroparesis
TD-8954	Phase I/II	5-HT_4 agonist	Theravance	Eating disorder
YKP10811	Phase II	5-HT_4 agonist	SK biopharm	Chronic constipation, IBS-C
TD-2749	Phase I	5-HT_4 agonist	Theravance	GI motility disorders
AU-228	Phase I	5-HT_4 agonist	Abbott	GI motility disorders
DA-6886	Phase I	5-HT_4 agonist	Dong-A ST	IBS-C
RQ-10	Phase I	5-HT_4 agonist	RaQualia	GI motility disorders
YH-12852	Phase I	5-HT_4 agonist	Yuhan	IBS-C

Table 1: 5-HT_4 receptor agonists in development for the treatment of GI motility disorders

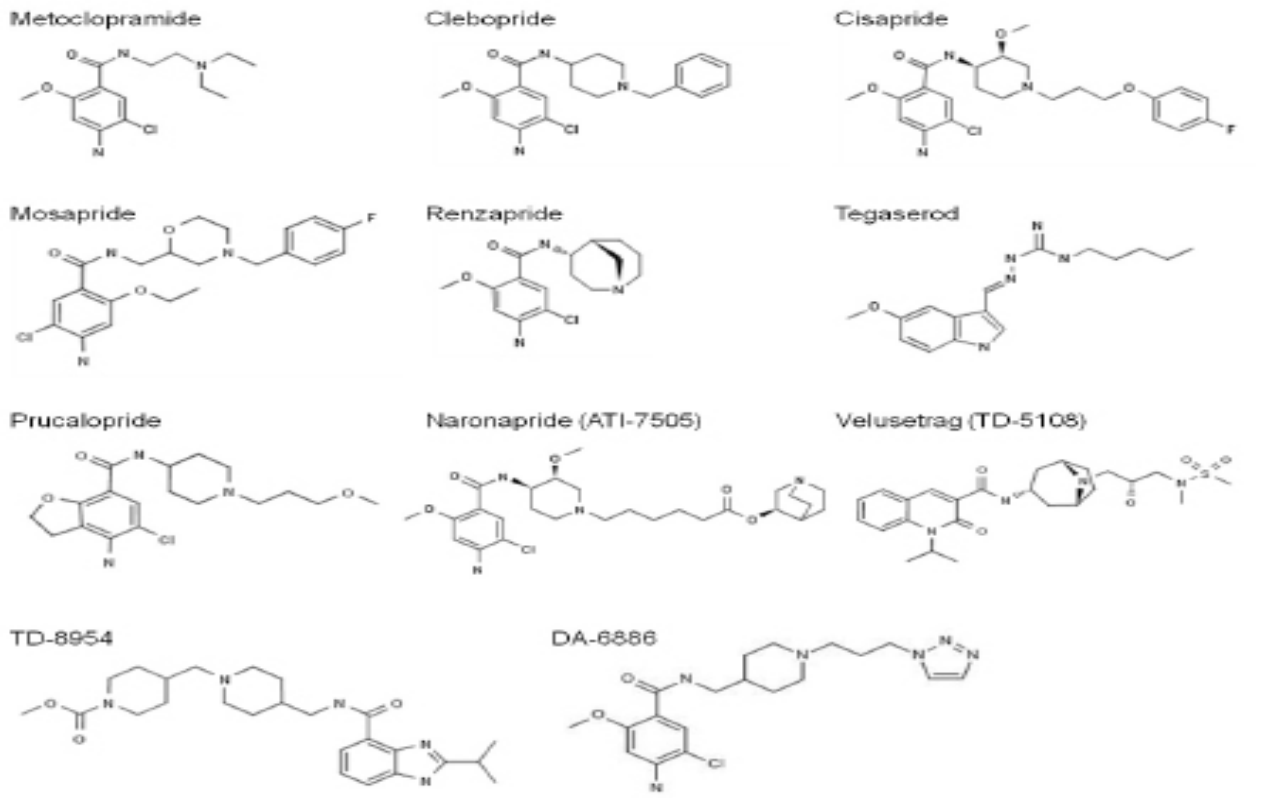

Figure 1: Chemical structures of some 5-HT_4 receptor agonists mentioned in the text. The figure shows compounds acting as prokinetic agents.

agonists. Metoclopramide (4-amino-5-chloro-N-(2-(diethylamino) ethyl)-2-methoxybenzamide), the prokinetic benzamide was originally identified in 1960s as a potential treatment for nausea and vomiting, and now it is also useful in diabetic gastroparesis and esophageal reflux, but not lower GI diseases. This compound was characterized to have dopamine (D_2) receptor antagonism, 5-HT_3 receptor antagonism and 5-HT_4 receptor agonism. Since the discovery of metoclopramide, many progenitors and congeners of the benzamide class have been synthesized by introducing other substitutions. Clebopride (4-amino-N-(1-benzylpiperidin-4-yl)-5-chloro-2-methoxybenzamide) was designed to increase the antidopaminergic activity compared to metoclopramide, and it also acts on upper GI. Unlike metoclopramide and clebopride, cisapride (4-amino-5-chloro-N-[1-[3-(4-fluorophenoxy)propyl]-3-methoxypiperidin-4-yl]-2-methoxybenzamide) showed a lack of D_2 receptor antagonism, resulting that it could be devoid of hyperprolactinaemic side effects, but inefficient in emesis. It was efficacious on gastric emptying and LES tone through 5-HT_4 agonism and 5-HT_3 antagonism. However, cisapride was a potent blocker of the hERG causing a delay in ventricular repolarization and QT prolongation [53] [54]. Like cisapride, mosapride (4-amino-5-chloro-2-ethoxy-N-((4-(4-fluorobenzyl)-2-morpholinyl)methyl)benzamide) is a gastrokinetic having 5-HT_4 receptor agonism, 5-HT_3 receptor antagonism but not D_2 antagonism. While cisapride was suspended from market, mosapride has not been limited due to the risk of arrhythmias, but it might not be safe because the metabolisms of both cisapride and mosapride are inhibited by CYP3A4 inhibitors. Renzapride (4-amino-N-[(4S,5S)-1-azabicyclo[3.3.1]nonan-4-yl]-5-chloro-2-methoxybenzamide) is a racemate of two enantiomers with the combined activities of 5-HT_3 receptor antagonist and 5-HT_4 receptor agonist. The compound is absorbed rapidly with a T_{max} of 1.4h [55], and it is unlikely to inhibit the major drug-metabolizing enzymes in the liver [56]. Naronapride ((6-[(3S,4R)-4-(4-amino-5-chloro-2-methoxy-benzoylamino)-3-methoxy-piperidin-1-yl]-hexanoic acid 1-aza-bicyclo[2,2,2]oct-(R)-3-yl ester dihydrochloride; ATI-7505) is one of the latest benzamide 5-HT_4 receptor partial agonist. Naronapride was designed to be metabolized by tissue and carboxyl esterase, not by CYP450 enzymes to induce drug-drug interactions. It is rapidly absorbed with a t_{max} of 45 min in healthy human subjects, and the plasma half-life of naronapride is 5h [57]. The compound has a low possibility to interact with hERG channels and 5-HT_3 receptors [58]. Especially, there are several evidences showing that naronapride can act locally in the intestinal mucosal epithelium. The large amounts of naronapride is present in the feces (32%) [57]. Hoffmann et al showed the mucosal administration of naronapride promotes colonic propulsive motility in guinea pig [50]. The enterokinetic 5-HT_4 agonists have been thought to facilitate the synaptic transmission in the gut myenteric plexus both systemically and locally [23,24]. DA-6886 (N-((1-(3-(1,2,3-triazol-1-yl)propyl) piperidin-4-yl)methyl)-4-amino-5-chloro-2-methoxybenzamide hydrochloride), the other developing substituted benzamide, has been recently reported to be a highly selective 5-HT_4 receptor agonist [59]. DA-6886 has no appreciable affinity for any other receptors and ion channels, including D_2, 5-HT_{1B}, 5-HT_2, 5-HT_3 receptor and hERG channel, suggesting a decreased risk for cardiovascular adverse events such as ischemic colitis or arrhythmias.

Tegaserod(3(5-methoxy-1H-indole-3-yl-methylene)-N-pentylcarbazimidamide hydrogen maleate) belongs to an indole carbazimidamide class. Tegaserod was designed from the structure of 5-HT, that is, protonated amine of 5-HT is substituted to a guanidine moiety in the indole side chain. Tegaserod is a partial agonist for 5-HT_4 receptor with a high affinity for 5-HT_4 receptors, and it has relevant affinity for 5-HT_1, 5-HT_2 receptors and monoamine transporters [60]. The bioavailability of tegaserod is approximately 10%, and plasma protein binding of this drug is 98% [61]. After oral administration, two-thirds was excreted unchanged in the faeces, and one third was excreted as main metabolite in urine [62].

Prucalopride(4-amino-5-chloro-2,3-dihydro-N-[1-(3-methoxypropyl)-4-piperidinyl]-7-benzofurancarboxamide monohydrochloride) is a new chemical class of benzofuran compounds having structural differences from other benzamide derivatives. Prucalopride is a highly selective 5-HT_4 receptor agonist having negligible binding affinity for hERG channel and 5-HT_{1B} receptor. The bioavailability of prucalopride is very high (>90%), and plasma protein binding is about 30%. Prucalopride has a plasma half-life of 21 hr, minor amounts of metabolites in human and a very low interaction potential for CYP450 inhibitors. Approximately 60% of the active prucalopride administered is excreted in urine, and 6% in feces [63].

Velusetrag(N-[(1R,3R,5S)-8-{(2R)-2-hydroxy-3-[methyl (methylsulfonyl)amino]propyl}-8-azabicyclo[3.2.1]oct-3-yl]-1-(1-methylethyl)-2-oxo-1,2-dihydroquinoline-3-carboxamide; previously known as TD-5108) is dihydroquinoline-carboxylic acid derivative. It is a highly selective 5-HT_4 receptor agonist having no effect on hERG channel [64]. Velusetrag has one major metabolite being a 5-HT_4 receptor agonist as potent as the parent drug, and the AUC ratio of the metabolite to velusetrag is approximately 0.5 in human administered with 15 mg of velusetrag. The compound has the elimination half-life of about 16 and 35 hours after single and multiple dosing, respectively [65].

Efficacy

Tegaserod was primarily indicated for the treatment of women with IBS-C, and the indication was extended to chronic idiopathic constipation. Many preclinical studies has demonstrated that tegaserod stimulates motility of both the upper and lower GI tract [61,66]. In rats, intraperitoneal administration of tegaserod attenuates both acute colorectal hypersensitivity induced by acetic acid and chronic hypersensitivity in TNBS-induced colitis model [67]. The therapeutic efficacy of tegaserod in the treatment of patients with IBS-C was shown in various clinical trials [18,68-70]. The results of these large, randomized, double-blind, placebo-controlled trials suggested tegaserod (2 and 6 mg twice daily for 12 weeks) showed that it is effective and well tolerated in the treatment of IBS-C in women. Global relief response rates, which were assessed using 5-point scale with descriptors of well-being, abdominal discomfort/pain and bowel habit, were 38.8% ($p<0.05$) with tegaserod 2 mg twice daily, 38.4%-46.8% ($p<0.05$-0.0001) with tegaserod 6 mg twice daily, superior compared to placebo (28.3-38.8%). Tegaserod was also active against chronic idiopathic constipation. In the two large randomized, double-blind, controlled trials [71,72], patients with chronic constipation treated with tegaserod (2 and 6 mg twice daily for 12 weeks) demonstrated statistically significant improvements in both complete spontaneous bowel movement (CSBM) per week and secondary endpoints (number of bowel movements, stool form, abdominal bloating, straining, and abdominal discomfort) compared to placebo.

Upper gastrointestinal motility disorders could be treated with

prokinetics such as metoclopramide, clebopride, mosapride. The 5-HT receptor agonists possessing antidopaminergic effect (metoclopramide and clebopride) were found to be effective in stimulating the motility of the upper gastrointestinal tract [73,74]. Metoclopramide has been used in the treatment of diabetic gastroparesis, gastro-oesophageal reflux, nausea, vomiting, postoperative ileum, and as a prokinetic for radiological examinations. Clebopride is available in Italy and Spain as a gastroprokinetic drug. Mosapride (which also exerts a partial 5-HT3 receptor antagonist activity) has been demonstrated to accelerate transit through increased contraction of the colon in the guinea-pig in vitro[75-79]. Mosapride, which is available in Asian countries, improves overall symptoms in patients with gastrointestinal disorders, including chronic gastritis, gastro-oesophageal reflux disease (GERD) and functional dyspepsia. But the therapeutic effect of mosapride on functional dyspepsia was not validated clearly in several clinical trials due to inconsistent diagnostic criteria and small size of controls [80,81].

A. Shin et al. [82] systematically analyzed 13 randomized controlled trials of chronic constipation patients treated with highly selective 5-HT_4 receptor agonists: 11 prucalopride, 1 velusetrag, 1 naronapride. They demonstrated that these highly selective 5-HT_4 receptor agonists were superior compared to placebo for outcomes including mean ≥3 spontaneous complete bowel movements (SCBM)/week, mean ≥1 SCBM over baseline, ≥1 point improvement in Patient-Assessment of Constipation Quality of Life (PAC-QOL) and PAC of symptoms (PAC-SYM). Prucalopride is available in Europe and Canada since 2009 and 2011. It has approval only for the treatment of chronic constipation in women who have not responded to the use of laxatives. Several preclinical studies showed that prucalopride, a highly selective 5-HT_4 receptor agonist, stimulates colonic motility as well as the contraction of intestinal muscle and high-amplitude propagated colon [83,84]. In phase III clinical trials for 12 weeks in patients with chronic idiopathic constipation (> 1977 patients) [85-87] , the patients treated with prucalopride reported a statistically significant ($p<0.001$) increase in the number of bowel movements compared with the placebo (prucalopride 2 and 4 mg, 23.6% and 24.7%, respectively vs. placebo 11.3%). Prucalopride once-daily at 2 mg dose improved the frequency of CSBM and SBM per week at 12 week (prucalopride 2 mg 48.1% vs. placebo 23.4%). A recent study found that prucalopride is effective in men with chronic constipation [88], showing the effectiveness of prucalopride 2 mg versus placebo (37.9% vs. 17.7% for ≥3 spontaneous complete bowel movements (SCBM)/week).

Velusetrag, the other highly selective 5-HT_4 receptor agonist, showed a higher intrinsic activity than that of prucalopride in guinea pig, rat and dog [89]. In a randomized, double-blind, placebo-controlled study, velusetrag (5, 15, 30, 50 mg) accelerated GI transit including colonic transit, ascending colon emptying and gastric emptying in healthy subjects [65]. In a phase II randomized, double-blind, placebo-controlled trial, velusetrag (15, 30, 50 mg) increased in the weekly frequency of SBM and CSBM compared to placebo in patients with chronic idiopathic constipation [90].

Naronapride was reported to have potential benefit in treating chronic constipation. In a phase II randomized, double-blind, placebo-controlled trial involving 210 patients with CC, naronapride 80 mg was efficacious and well tolerated for 4 weeks [91]. YKP-1081, a selective 5-HT_4 receptor agonist, has reached the Phase II clinical trial stage. It is aimed at the treatment of IBS-C and Chronic Idiopathic Constipation [92,93]. This compound enhanced gastrointestinal transit, and improved bowel functions in patients with functional constipation during the 8-day treatment [94].

DA-6886, a novel 5-HT_4 receptor agonist being under development for the potential treatment of IBS-C and CC, has passed Phase I clinical trial. DA-6886 was well tolerated and safe when administered in single (1, 2.5, 5, 10, 20, 40 mg) and repeated doses (5, 10, 20 mg) in healthy subjects [95]. Functional in vivo studies in mice showed that DA-6886 was more potent in stimulating the colonic transit more than tegaserod [59]. In conscious guinea pigs, the compound accelerated colonic motility through the 5-HT_4 receptor activation [96]. TD-8954, the other introduced selective 5-HT_4 receptor agonist, has shown gastrointestinal prokinetic activities in guinea pigs, rats, dogs and humans [97]. The safety and pharmacokinetic profile of intravenous TD-8954 is being assessed currently [98].

Safety

Several 5-HT_4 receptor agonists have been tried in the treatment of gastrointestinal motility disorders for decades, but the results are often disappointing partly due to off-target activities associated with cardiovascular, neurological side effects. Metoclopramide was found to note extrapyramidal side effects due to its dopaminergic antagonism in the central nervous system. Adverse reactions (mainly stress, somnolence, fatigue, increased mammary glands, galactorrhea and menstrual disorders) were noted in 20% of metoclopramide-treated patients. Approximately 1-2% of patients treated with metoclopramide had extrapyramidal symptoms. The U.S. FDA required boxed warning against high doses or chronic use of metochloprimde linked to tardive dyskinesia in 2009 [99]. In addition, metoclopramide caused cardiovascular adverse effects such as cardiac arrhythmias, specifically multifocal preventricular contractions [100]. The cardiovascular side effect has been a major concern since cisapride, a nonselective 5-HT_4 receptor agonist with hERG blockade activity, was withdrawn due to a high risk of QT prologation causing cardiac arrhythmias [53].

In 2007, Tegaserod was withdrawn after an an analysis found that 13 of 11,614 patients (0.11%) treated with tegaserod had ischemic cardiovascular events, compared with 1 of 7,031 placebo-treated patients (0.01%) [101]. Although the exact mechanism of ischemic cardiovascular adverse effect has not yet been elucidated, 5-HT_{1B} receptor has been proposed to mediate contraction of human coronary arteries in patients with coronary artery disease [102]. It was reported that the most common AEs of tegaserod were diarrhea, headache and abdominal pain [103-105].

Compared to these nonselective 5-HT_4 receptor agonists, selective 5-HT_4 receptor agonists exert improved safety profile for the treatment of gastrointestinal disorders without cardiovascular adverse events [58]. Highly selective 5-HT_4 receptor agonists (prucalopride, velusetrag, naronapride) have not been found to interact with the hERG channel, therefore are unlikely to prolong cardiac action potentials [106,107]. In the Phase III clinical trials, there were no differences in ECG parameters between patients randomized to placebo or prucalopride (2, 4 mg) [85-87].

A recent meta-analysis revealed that the frequent adverse event of highly selective 5-HT_4 receptor agonist including prucalopride, velusetrag, naronapride was headache (5-HT_4 receptor agonists 21.1% vs. control 13.0%) [82]. The highest relative risk (RR) was observed for diarrhea (RR=3.08; 95% CI, 2.31-4.09). The other adverse events were

nausea and abdominal pain. The majority of AEs was generally minor and transient. The pivotal Phase III trials found that common adverse events of 2 or 4 mg of prucalopride were headache (prucalopride 25-30% vs. placebo 12-17%), nausea (12-24% vs. 8-14%), abdominal pain (16-23% vs. 11-19%) and diarrhea (12-19% vs. 3-5%) [85,86,87]. Common adverse events associated with velusetrag in dose of 50 mg were reported to be diarrhea, headache, nausea and vomiting, occurring on day 1 or 2 of treatment [90]. In the 4-week Phase II trial, naronapride (20, 40, 80, 120 mg) was well tolerated, and its frequent adverse events at maximum dose were headache and abdominal pain [91].

Conclusion

There is little doubt that 5-HT_4 receptor agonists are effective in the treatment of gastrointestinal motility disorders. However, previously available agents, such as cisapride and tegaserod, were withdrawn by cardiovascular adverse effects associated with off-target activities. More selective and potent 5-HT_4 receptor agonists has shown the improved safety profile and the therapeutic potential in clinical trials and preclinical studies. Prucalopride,which is currently available for chronic constipation, velusetrag and naronapride, which has passed phase II clinical trials, provide robust GI prokinetic activity, acceptable safety and tolerability profile. The newly introduced agents such as YKP10811 and DA-6886 are progressed to anticipate advanced-phase clinical trials.

Competing Interests

The authors declare that they have no competing interests.

Author's contribution

All authors contributed substantially to conception and design, acquisition and analysis of data and interpretation of results.

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