Novel strategies and future landmarks in the treatment of irritable bowel syndrome

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterized by continuous or remittent abdominal pain, bloating and altered defecation. The population-based prevalence of IBS has been reported to be approximately 3–20%, depending on the diagnostic criteria. Despite intense research in recent decades, the pathogenesis of IBS remains only partially understood, and thus no specific and universally effective patient management has been developed so far. Current therapy for IBS focuses on the major symptoms, while a novel approach in the treatment is based on targeting specific receptors in the gastrointestinal tract that are known to be involved in the pathogenesis of the disease. In view of the severe side effects of early serotonin receptor modulators, a good safety profile is of primary importance in the treatment of functional gastrointestinal disorders. This article provides a pathogenesis-based overview of recently developed pharmaceutics and future perspectives on the therapy of IBS.

KEYWORDS: chloride channel ▪ guanilate cyclase-C ▪ irritable bowel syndrome ▪ neuropeptide ▪ opioid ▪ probiotics ▪ serotonin

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Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterized by continuous or remittent abdominal pain, bloating and altered defecation. Depending on the diagnostic criteria, the population-based prevalence of IBS has been reported to be approximately 3–20% of the general population, and IBS symptoms are major reasons for primary care visits and consultations with gastroenterologists. The first presentation of patients to a physician is typically between the ages of 30 and 50 years, and the prevalence of the disease is greater in women [1–3]. The diagnosis of IBS relies on a symptom-based classification system known as Rome criteria, Rome III being the most recent. It defines IBS as recurrent abdominal pain or discomfort lasting for at least 3 days per month over 3 months, and which is associated with two or more of the following characteristics: improvement with defecation, onset associated with change in stool frequency or onset associated with change in stool form. The Rome III criteria classifies IBS patients based on their bowel habits into three subgroups, namely diarrhea predominant (IBS-D), constipation predominant (IBS-C) and subjects with mixed pattern (IBS-M) [4]. Despite intense research in recent decades, the pathogenesis of IBS remains only partially understood, and thus no specific and universally effective patient management has been developed so far. Altered colonic motor function, visceral hypersensitivity, minimal inflammation of intestinal mucosa, changes in neural transmission within the gut and alterations of the sensory afferent system at the spinal cord or CNS may play a role in the development of IBS symptoms. Psychological and psychiatric comorbidity is common among patients with IBS, and psychosocial factors may exacerbate symptoms and affect clinical outcome of IBS patients [3,5]. The effect of gonadal hormones on visceral pain perception, gastrointestinal motility and central pain processing, and gender-related differences in psychosocial factors, may induce differences in response to psychological and pharmacologic therapy between female and male patients [6,7].

Current therapy of IBS focuses on the major symptoms experienced by patients. The therapies include: antispasmodic (anticholinergic) medication; smooth-muscle relaxants (cimetropium bromide, pinaverimun bromide and octylonium bromide and mebeverine); prokinetic agents (trimebutine), which are recommended for pain and bloating; and low-dose tricyclic antidepressants, which may be useful in the treatment of constant and disabling pain. On one hand, increased dietary fiber intake and osmotic laxatives may reduce constipation, and on the other hand loperamide and diphenoxylate can decrease the number of loose stools, urgency and fecal soiling in diarrheic patients. The treatment strategy is based on the nature and severity of the symptoms. Milder symptoms are commonly treated symptomatically with pharmacological agents directed at the gut, whereas more severe symptoms are associated

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with higher levels of psychosocial difficulties and illness behaviors, and often require psychological and antidepressant medications [3].

A novel approach in the treatment of IBS is based either on targeting specific receptors in the gastrointestinal tract that are known to be involved in the pathogenesis of the disease, or modification of disturbed gastrointestinal bacterial flora. These potential therapeutical modalities will be discussed in detail in this article.

Serotonin receptor modulation

Serotonin in the pathogenesis of IBS

Approximately 95% of the serotonin (5-hydroxytryptamine [5-HT]) in the human body is found in the gastrointestinal tract: 90% is in the secretory granules of enterochromaffin cells throughout the gut, and the remaining 5% is located in enteric neurons. Serotonin is one of the most investigated neurotransmitters in the pathogenesis of IBS, since it plays a key role in the initiation of peristaltic and secretory reflexes, and in the modulation of visceral sensations.

The 5-HT release from enterochromaffin cells is triggered by luminal mechanic and chemical stimuli, which activate intrinsic primary afferent neurons, and thus the information is transmitted to interneurons, motor and secretomotor neurons. The action of 5-HT is rapidly terminated by the activation of the serotonin reuptake transporter (SERT) to avoid receptor desensitization [8]. Several serotonin receptor subtypes have been characterized, of which 5-HT3, 5-HT4 and 5-HT1b are the most important for gastrointestinal function. The 5-HT1b receptors are responsible for initialization of peristalsis, 5-HT4 receptors play a role in augmenting the release of neurotransmitters and 5-HT3 receptors are responsible for transmitting sensory stimuli to the CNS [9]. Several studies demonstrated the possible role of increased release of 5-HT, abnormalities of SERT and SERT polymorphisms in the pathogenesis of IBS [10].

5-HT3 receptor antagonists

The 5-HT3 receptor antagonists (alosetron and cilansetron) prevent the activation of 5-HT3 receptors on extrinsic afferent neurons and decrease visceral pain in IBS. They also decrease small intestinal and colonic motility (this latter effect being more prominent in females), and therefore are effective in the treatment of the subgroup of IBS-D patients. Alosetron and cilansetron proved to be effective in symptom relief of female diarrheic IBS patients [11,12]. However, based on severe side effects (serious constipation, ischemic colitis and bowel perforation), alosetron had been withdrawn from the market and was later re-introduced under a restricted program only, while cilansetron did not receive US FDA approval due to similar side effects [13]. A novel, potent 5-HT3 antagonist (ramosetron) seems to be effective and well tolerated, demonstrating no gender difference in the treatment of abdominal pain, discomfort and altered bowel habits in patients with diarrhea-predominant IBS according to a Phase II trial in Japan [14,15].

5-HT4 agonists

5-HT4 receptor agonists potentiate peristalsis initiated by 5-HT1 receptor stimulation in the gut. Therefore tegaserod (a partial agonist of the 5-HT4 receptor) accelerates gastrointestinal transit and also intestinal secretion, thus being beneficial in the treatment of IBS patients with constipation [16,17]. However, tegaserod is now only available via a restricted access program owing to concerns of a possible risk of cardiovascular and cerebrovascular mortality [17]. Prucalopride is a more selective 5-HT4 agonist and a potential pharmaceutical in the treatment of IBS-C. It proved to be effective in the treatment of severe chronic constipation with only mild side effects, such as headache and abdominal pain [18,19], although carcinogenicity proven by animal studies may limit its clinical use [20].

Mixed 5-HT4 agonist/5-HT3 antagonist

Renzapride is a mixed 5-HT4 receptor agonist and 5-HT3 receptor antagonist with a stimulatory effect on gastrointestinal motility and transit [21]. It has been demonstrated to have a beneficial effect on abdominal pain and discomfort in IBS-C and IBS-M patients, and on colonic transit in IBS-C patients [22,23].

Tryptophan hydroxylase inhibitors

Serotonin is synthesized from tryptophan by the sequential actions of tryptophan hydroxylase (TPH) and the aromatic amino acid decarboxylase. Two isoforms of TPH have been discovered. TPH1 is primarily expressed in the enterochromaffin cells of the gastrointestinal tract, while TPH2 is expressed exclusively in neuronal cells. In an animal model, TPH inhibitors (LP-533401 and LP-615819) selectively inhibited gastrointestinal 5-HT biosynthesis, leaving the brain 5-HT levels unaffected. These compounds reduce emesis in an experimental

model system [24]. Use of specific TPH inhibitors offers new therapeutical modality in IBS; however, published clinical trials with TPH inhibitors are currently not available.

Chloride channel activators

Lubiprostone, a highly selective activator of type 2 Cl^- channels, is a member of a new class of bicyclic fatty acid compounds called prostones, which are derived from a metabolite of prostaglandin E1 [25]. Activation of type 2 Cl^- channel in the gastrointestinal tract increases Cl^- transport into the lumen, thus enhancing intestinal fluid secretion [26]. Lubiprostone accelerates human small intestinal and colonic transit, and in female subjects, in addition to inducing chloride and water secretion, it decreases compliance and relative change in postprandial tone in the colon [27,28]. Lubiprostone is a safe and effective drug for the treatment of chronic constipation, and has been approved by the US FDA in 2006 for this clinical purpose [29,30]. Moreover, lubiprostone significantly improves abdominal discomfort and pain in constipated IBS patients without significant side effects, due to its low systemic bioavailability; therefore, it is a promising pharmaceutical in the treatment of IBS-C [31,32].

Guanilate cyclase-C agonists

Linaclotide is a first-in-class 14 amino-acid peptide that binds to guanilate cyclase-C receptors on the intestinal enterocytes. Activation of the guanilate cyclase-C receptors increases anion efflux into the intestinal lumen and concomitant fluid secretion [33]. Linaclotide treatment improves bowel habits and symptoms of patients with chronic constipation, and significantly accelerates ascending colon transit in women with IBS-C [34,35]. Further randomized, controlled trials of clinical efficacy and safety of linaclotide in constipated IBS patients are warranted.

Monoamine uptake inhibitors

Serotonergic psychoactive agents have been widely used in the treatment of irritable syndrome when psychiatric comorbidities are present [36]. Besides reduction of central pain perception, anxiety and depression, the antidepressants have a direct effect on gastrointestinal functions [37]. The selective serotonin reuptake inhibitors (SSRIs) fluoxetine and citalopram significantly improve IBS symptoms. The therapeutic effect of citalopram is independent of effects on anxiety, depression and colonic sensomotory function [38,39]. Novel monoamine reuptake inhibitors, the 5-HT and norepinephrine reuptake inhibitors (SNRIs) duloxetine and venlafaxine, have beneficial effects on the treatment of chronic pain, such as painful diabetic neuropathy and fibromyalgia [40–43]. Clinical trials with SNRIs in IBS are currently not available.

Neuropeptide receptor modulators

Neurokinin antagonists

The tachykinins (substance P and neurokinin A) and their receptors (neurokinin receptors: NK1, NK2 and NK3) participate in the regulation of gastrointestinal motility, secretion, vascular permeability and pain perception [44]. Although neurokinin receptors seemed to be promising targets for IBS therapy, clinical data on NK antagonists are controversial and disappointing. The NK3 antagonist, talnetant, has no effect on rectal compliance or distension-induced rectal sensation in healthy participants [45]. In healthy male subjects, nepadutant, an NK2 antagonist, effectively antagonized the motility-stimulating effects of neurokinin A without affecting basal motility [46]. However, in the absence of clinical trials supporting the efficacy of NK antagonists in IBS, clinical use of these pharmaceuticals is dubious in the near future.

CRF1 receptor antagonists

Corticotropin-releasing hormone (CRF) is a major mediator of stress response in the brain–gut axis, and plays a major role in the stress-related pathophysiology of IBS [47]. Activation of CRF1 receptor pathways reproduces the key features of symptoms presenting in IBS-D patients, such as stimulation of colonic motility, watery diarrhea and visceral hypersensitivity in experimental models [48]. Peripheral administration of the CRH antagonist, α-helical CRH, improves gastrointestinal motility, visceral perception and negative mood in response to gut stimulation, without affecting the hypothalamic–pituitary–adrenal axis in IBS patients [49]. Peripheral administration of α-helical CRH almost normalizes pathological electroencephalography activities in response to colonic distension in IBS patients [50]. Based on the first evaluable human results, CRF1 antagonists are under development for clinical use in IBS.

α2 adrenoreceptor agonists

Clonidine, an α2 adrenoreceptor agonist, is traditionally used as an antihypertensive agent that has an additional effect on the gastrointestinal tract: it relaxes fasting colonic tone and reduces pain sensation to distension in healthy

subjects [51]. In a double-blind, randomized, parallel group, placebo-controlled trial, clonidine relieved bowel dysfunction and appeared promising in relieving IBS-D symptoms without significant alterations in gastrointestinal transit. Drowsiness, dizziness and dry mouth were the most common adverse events during the 4 weeks of clonidine treatment [52]. These side effects and the potent hypotensive action limit the clinical benefit of this compound; therefore, more studies are necessary to explore the routine use of clonidine in the treatment of IBS symptoms.

Benzodiazepines

Dextofisopam is a 2,3-benzodiazepine that has traditionally been used for the treatment of anxiety. In a preliminary study, dextofisopam has effectively improved pain relief and stool consistency in IBS patients with diarrhea or alternating bowel habits regardless of gender, and reduced stool frequency only in women [53]. Further studies are awaited to evaluate the efficacy and side-effect profile.

Opioid agents

The κ-opioid receptors have an important role in the inhibition of perception of noxious stimuli from the gastrointestinal tract [54]. In the 1980s, fedotozine, a κ-opioid agonist, appeared to be effective and safe for the treatment of abdominal pain and bloating associated with IBS [55,56]. Twelve-week dosing of asimadoline (a novel selective, peripherally active κ-opioid agonist) produced significant improvement on the total number of months with adequate relief of pain or discomfort, adequate relief of symptoms, pain scores, pain-free days, urgency and stool frequency in IBS-D patients with at least baseline moderate pain. In patients with alternating bowel habits, significant improvement was also seen on adequate relief end points [57]. In contrast to the chronic dosing, an on-demand dosing schedule of asimadoline was not effective in reducing severity of abdominal pain in IBS [58]. Enteric μ-receptors seem to be the principal mediators of opioid effects in the gastrointestinal tract. The peripherally acting μ-receptor antagonists methylnaltrexone and alvimopan are a new class of drugs designed to reverse opioid-induced side-effects on the gastrointestinal tract and are effective for the treatment of opioid-related bowel dysfunction and postoperative ileus [59]. Further studies with opioid agents in visceral pain and IBS appear to be warranted.

Somatostatin analogue

Somatostatin is a peptide hormone with a wide range of inhibitory effects on intestinal motility, gastric exocrine and endocrine function, and intestinal absorption of nutrients and ions. It also inhibits serotonin release from the gut, and this effect may contribute to modification of IBS symptoms [60]. In addition to these actions, octreotide, a synthetic somatostatin analog, has a direct effect on visceral pain perception. Acute administration of octreotide reduces rectal hyperalgesia and rectal pressure in IBS patients [61–63]. In contrast to short administration, in a clinical study with a small number of patients, long-term treatment with octreotide failed to improve symptoms of nonconstipated IBS patients [64]. Obligate parenteral administration of octreotide and the absence of studies with orally administered drugs do not support the clinical use of somatostatin analogues in IBS in the near future.

Melatonin

Melatonin, a close derivate of serotonin, is known as the hormone that regulates circadian rhythm. Although the pineal gland is the primary source of melatonin, the hormone is also detected in high concentration in the gastrointestinal tract. Melatonin has a local regulatory effect on intestinal motility as well as systemic antidepressant and anxiolytic properties [65]. In preliminary clinical studies, melatonin treatment improved IBS symptoms in female patients and significantly decreased abdominal pain in IBS patients with sleeping disturbances [65,66]. The effect of melatonin on intestinal transit is conflicting, since it increases colonic transit time only in healthy subjects, and has no significant influence on the large bowel transit in IBS patients [67]. Further randomized, controlled trials for the clinical efficacy of melatonin in IBS patients are warranted.

Altering intestinal bacterial flora

Probiotics

The term probiotic refers to live microorganisms that survive passage through the gastrointestinal tract and have beneficial effects on the host by preventing or treating specific pathological conditions [68]. The idea of using probiotics in the treatment of IBS is based on the concept that gut microflora is altered in IBS patients [69,70]. Probiotics may influence the intestinal immune function, induce qualitative and quantitative changes in the intestinal flora, and modulate colonic bacterial gas production, intestinal intraluminal milieu and colonic transit [71,72]. Numerous studies support

the efficacy of different probiotics in the therapy of IBS. *Lactobacillus plantarum* and *Lactobacillus acidophilus* significantly reduce abdominal pain or discomfort in IBS [73,74]. *Bifidobacterium lactis* improves gastrointestinal transit and relieves abdominal discomfort and bloating in constipated IBS patients [75,76]. *Bifidobacterium infantis* alleviates symptoms associated with normalization of the ratio of anti-inflammatory and pro-inflammatory cytokines, suggesting the immune-modulating role of the organism in IBS [77,78]. Probiotic combination VSL#3 appears to be promising in the relief of abdominal bloating, particularly in IBS-D [79,80]. The good safety profile of probiotics has primary importance in the treatment of a functional disorder such as IBS. Until recently, 19 randomized, controlled trials have been carried out to evaluate the efficacy of probiotics, and in conclusion the magnitude of benefit and most effective species and strains are still uncertain, and thus the issue needs further investigation [81].

Antibiotics

There is growing evidence of the pathogenetic role of disturbed gut flora in the development of IBS symptoms. Besides significantly altered fecal microbiota in IBS [69,70], small intestinal bacterial overgrowth is relatively frequent in the IBS patient [82,83]. As an indicator of small bacterial overgrowth, abnormal lactulose breath test is frequently associated with IBS, and normalization of lactulose breath test with neomycin leads to significant symptom reduction [84]. Treatment with neomycin improves constipation in IBS-C [85]. In contrast to systemic absorbtion and side effects of neomycin, rifaximin is a gut selective, nonabsorbable antibiotic with a broad-spectrum activity. Short-term use of rifaximin is a safe and effective treatment of IBS symptoms, such as bloating and flatulence [86]. Treatment with rifaximin for 10 days improves symptoms for up to 10 weeks after the discontinuation of therapy [87]. Further trials are required to examine the efficacy of long-term or cyclic rifaximin treatment in IBS.

Possible therapeutic targets based on recent pathophysiological findings

Endocannabinoid system

The endocannabinoid system is involved in the regulation of gastrointestinal motility, pain perception and secretion under both physiological and pathological conditions. Activation of cannabinoid receptors (CB1 and CB2) reduces motility, secretion and decreases hypersensitivity in the gut [88]. Dronabinol, an agonist of both CB1 and CB2 receptors, is used as an appetite stimulant and anti-emetic drug. In humans, dronabinol relaxes the colon and reduces postprandial colonic motility and tone [89]. Rimonabant and taranabant are CB1 receptor antagonists used in the treatment of obesity. In accordance with the effect of cannabinoid receptors on gastrointestinal motor function, transient diarrhea, nausea and vomiting are frequent side effects of CB1 receptor agonist treatment [90,91]. The potential use of cannabinoid drugs in IBS remains unexplored, and clinical studies are warranted.

TRPV1

Transient receptor potential vanilloid 1 (TRPV1) is a polymodal nocisensor *par excellence*, being receptive to noxious heat, acidosis and capsaicin, and therefore playing an important role in the pain perception and protection of the gastrointestinal mucosa [92,93]. In rectal biopsies of patients with rectal hypersensitivity, the density of TRPV1 immunoreactive nerve fibres was increased and this increase correlated significantly with the decrease in rectal heat, and the distension sensory thresholds [94]. The increase in TRPV1 nerve fibres is also observed in the rectosigmoid biopsies of IBS patients [95]. Based on these observations, TRPV1 is a potential target in IBS therapy, and the use of TRPV1-specific therapy in IBS needs further experimental and clinical studies.

Mucosal microinflammation

There is growing evidence that colonic microinflammation plays a role in the pathogenesis of IBS. Symptoms have been reported to frequently occur in patients in remission from ulcerative colitis and after gastrointestinal infection [96–98]. An increased number of inflammatory cells (mast cells and T lymphocytes) and pro-inflammatory cytokines have been demonstrated in the colonic mucosa of IBS patients in numerous studies [99–102]; furthermore, there is an increased concentration of systemic pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) in IBS-D patients [103]. In experimental conditions, dexamethasone treatment prevented visceral hypersensitivity coupled with a reduction of mast cell number in rats; however, in a randomized, double-blind, placebo-controlled trial in a small patient population, prednisolone treatment for 3 weeks failed to improve symptoms in postinfectious IBS [104,105]. In the absence of sufficient clinical data, further studies are necessary for the evaluation of the clinical use of anti-inflammatory drugs (corticosteroids or 5-aminosalicylic acid) in the therapy of IBS.

Executive summary

Current therapy of irritable bowel syndrome focuses on the major symptoms experienced by patients

- Antispasmodic medication and smooth-muscle relaxants are recommended for pain and bloating; low-dose tricyclic antidepressants are recommended for constant and disabling pain; increased dietary fiber intake and osmotic laxatives are recommended for constipation; and loperamide and diphenoxylate can be used for the treatment of diarrhea.

5-HT3 receptor antagonists

- Alosetron proved to be effective in symptom relief of female diarrheic irritable bowel syndrome (IBS) patients; however, based on severe side effects, it is available only under a restricted program. Ramosetron seems to be safe and beneficial in diarrhea-predominant IBS patients (IBS-D).

5-HT4 agonists

- Tegaserod is beneficial in the treatment of constipation-predominant IBS patients (IBS-C); however, tegaserod is now only available via a restricted access program owing to concerns of a possible risk of cardiovascular and cerebrovascular mortality. Prucalopride is a more selective 5-HT4 agonist and a potential pharmaceutical in the treatment of IBS-C.

Mixed 5-HT4 agonist/5-HT3 antagonist

- Renzapride has been demonstrated to have a beneficial effect on abdominal pain and discomfort in IBS-C and IBS patients with mixed pattern (IBS-M).

Chloride channel activators

- Lubiprostone significantly improves gastrointestinal symptoms in IBS-C without significant side effects.

Guanilate cyclase-C agonists

- Linaclotide treatment improves bowel habits and symptoms of patients with chronic constipation, and significantly accelerates ascending colon transit in women with IBS-C.

Monoamine uptake inhibitors

- The selective serotonin reuptake inhibitors, fluoxetine and citalopram, significantly improve IBS symptoms independently of effect on anxiety and depression.

Altering intestinal bacterial flora

- Numerous studies support the efficacy of different probiotics and nonabsorbed antibiotics (rifaximin) in the treatment of bloating in IBS.

Future perspectives based on preclinical findings

- In the coming years, studies are expected to confirm the beneficial effect of neurokinin antagonists, serotonin and norepinephrine reuptake inhibitors, κ-opioid agonists, dextofisopam and tryptophan hydroxylase inhibitors in clinical practice.

Future trends based on recent pathophysiological observations

- Further experimental and clinical studies are needed to evaluate the potential role of cannabinoid receptors, transient receptor potential vanilloid 1, anti-inflammatory drugs and protease inhibitors in the treatment of IBS.

Intestinal permeability & luminal protease activity

Increased gut permeability has been reported both in the postinfectious and sporadic forms of IBS, characteristically in the diarrhea-predominant subgroup of IBS patients [106,107]. Furthermore, the increase in proximal small bowel permeability in IBS-D is more expressed in the sporadic form of IBS than in the postinfectious form [107]. In addition, *in vitro* paracellular permeability in colonic biopsies of IBS patients demonstrated significant elevation compared with controls [108]. Fecal supernatants from diarrheic IBS patients bearing with high protease activity are able to increase colonic paracellular permeability and provoke allodynia, mediated by the protease-activated receptor-2 (PAR2) in mice [109,110]. The possible role of proteases in the development of IBS symptoms raises the potential use of protease inhibitors in the treatment of IBS. Protease inhibitors are safely used in several gastrointestinal diseases [111–113]. In the absence of selective PAR antagonists in clinical practice, protease inhibitors could represent new agents for IBS therapy in the future.

Conclusion

Recent basic research and clinical investigation have drawn attention to new neurotransmitters, receptors and mechanisms involved in the pathogenesis of IBS, and have led to the development of new agents in the treatment of the disease. In view of the severe side effects of early serotonin receptor modulators, a good safety profile is of primary importance in the treatment of functional gastrointestinal disorders. The 5-HT3 antagonist ramosetron has proven to be effective in the treatment of IBS-D, while for constipating patients, chloride-channel activators, guanilate cyclase-C agonists, the novel 5-HT4 agonist prucalopride and the 5-HT4 agonist/5-HT3 antagonist renzapride are the treatments of choice. SSRIs are promising drugs for relieving abdominal pain, while probiotics and intermittent antibiotic treatment can safely be used in the treatment of bloating in IBS (Table 1).

Table 1. Novel drugs, that are currently in use in the therapy of irritable bowel syndrome.

Drug class	Pharmaceutical	IBS subtype
5-HT3 receptor antagonists	Alosetron	IBS-D/restricted access program: ischemic colitis
	Ramosetron	IBS-D
5-HT4 receptor agonists	Tegaserod	IBS-D/restricted access program: thromboembolism
	Prucaloprid	IBS-C
Mixed 5-HT4 agonist/5-HT3 antagonist	Renzapride	IBS-C, -M
Chloride channel activator	Lubiprostine	IBS-C
Guanilate cyclase-C agonist	Linaclotide	IBS-C
Selective serotonin reuptake inhibitors	Fluoxetine Citalopram	Pain in all subtypes of IBS
Probiotics	*Lactobacillus* strains Bifidobacteria Probiotic combination VSL#3	Pain, bloating in all subtypes of IBS
Antibiotics	Neomycin Rifaximin	Bloating, flatulence in all subtypes of IBS

5-HT: Serotonin; IBS: Irritable bowel syndrome; IBS-C: Constipation-predominant IBS patients; IBS-D: Diarrhea-predominant IBS patients; IBS-M: IBS patients with mixed pattern.

Future perspective

Preclinical evidence supports the potential benefit from CRF1 agonists, neurokinin antagonists, SNRIs, κ-opioid agonists and dextofisopam in the treatment of IBS; however, further studies are expected in the coming years to confirm their beneficial effect in clinical practice. Clinical trials with selective inhibition of TPH in the gut, which are expected to be published in the near future, appear feasible, as selective inhibition does not affect brain 5-HT metabolism (Table 2). Based on recent findings, further experimental and clinical studies are needed to evaluate the potential role of cannabinoid receptors, TRPV1, anti-inflammatory drugs and protease inhibitors in the treatment of IBS.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Table 2. Novel drugs under development for the therapy of irritable bowel syndrome.

Drug class	Pharmaceutical	Putative role in therapy
CRF1 receptor antagonists	α-helical CRH	Improves gastrointestinal motility and visceral perception in IBS patients
Tryptophan hydroxylase inhibitors	LP-533401 LP-615819	Selectively inhibits gastrointestinal 5-HT biosynthesis in animals
5-HT and norepinephrine reuptake inhibitors	Duloxetine Venlafaxine	Beneficial effect in the treatment of chronic pain (diabetic neuropathy and fibromyalgia)
Neurokinin antagonists	Talnetant Nepadutant	Modulation of intestinal motility, secretion and pain perception in animal models
α2 adrenoreceptor agonists	Clonidin	Relieves bowel dysfunction in IBS-D
Benzodiazepines	Dextofisopam	Improves pain relief and stool consistency in IBS-D, -M
κ-opioid agonists	Fedotozine Asimadoline	Improves pain relief and stool consistency in IBS-D, -M
μ-receptor antagonists	Methylnaltrexone Alvimopan	Effective for the treatment of opioid-related bowel dysfunction and postoperative ileus
Melatonin	Melatonin	Significantly decreases abdominal pain in IBS

5-HT: Serotonin; IBS: Irritable bowel syndrome; IBS-D: Diarrhea-predominant IBS patients; IBS-M: IBS patients with mixed pattern.

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