

Mini-Symposium

Current and novel therapeutic options for irritable bowel syndrome management

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ABSTRACT

Irritable bowel syndrome is a functional gastrointestinal disorder affecting up to 3–15% of the general population in western countries. It is characterised by unexplained abdominal pain, discomfort, and bloating in association with altered bowel habits. The pathophysiology of irritable bowel syndrome is multifactorial involving disturbances of the brain–gut axis. The pathophysiology provides the rationale for pharmacotherapy: abnormal gastrointestinal motor functions, visceral hypersensitivity, psychosocial factors, autonomic dysfunction, and mucosal immune activation. Understanding the mechanisms, and their mediators or modulators including neurotransmitters and receptors have led to several therapeutic approaches including agents acting on the serotonin receptor or serotonin transporter system, antidepressants, novel selective anticholinergics, α -adrenergic agonists, opioid agents, cholecystokinin-antagonists, neurokinin-antagonists, somatostatin receptor agonists, corticotropin releasing factor antagonists, chloride channel activators, guanylate cyclase-c agonists, melatonin, atypical benzodiazepines, antibiotics, immune modulators and probiotics. The mechanisms and current evidence regarding efficacy of these agents are reviewed.

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1. Introduction

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders [1,2] characterised by abdominal pain and discomfort in association with altered bowel habits; symptoms are not explained by structural abnormalities using current standard diagnostic tests [3]. The pathophysiology of IBS is still not well understood, but is most likely multifactorial. Several factors such as motor and sensory dysfunction, neuroimmune mechanisms, psychological factors, and changes in the intraluminal milieu appear to play a role (Fig. 1 [3,4]). The increased release of serotonin in the circulation especially in the IBS-D group [5–7] and increased serine proteases (derived from mast cells) in stool of patients with IBS [8] provide evidence for the potential role of neurotransmitters or chemical mediators such as proteases in the disorder.

Changes in mucosal serotonin levels may affect sensory and motor functions possibly contributing to IBS symptoms [9]. There is increasing evidence of mucosal dysfunction, immune activation or inflammation [10–12] and, possibly, alterations in colonic bacterial flora. Increased number of activated mast-cells in the proximity of colonic nerves in the lamina propria is associated with abdom-

inal pain severity [13]. Mucosal immune activation is associated with systemic evidence for a pro-inflammatory state (decreased IL10/IL12 ratios) in IBS patients [14] and changes in local defense mechanisms in the sigmoid and colonic mucosa in IBS [15]. These provide novel promising targets for future therapies. Traditional IBS therapies (Fig. 1) are mainly directed at the relief of individual symptoms, e.g. antidiarrhoeals for diarrhoea, laxatives for constipation or smooth muscle relaxants for pain. They are often of limited efficacy in addressing the overall symptom complex.

This article reviews recent and novel approaches in IBS therapy (Table 1, Fig. 2) that have preclinical efficacy, Phase IIa studies of pharmacodynamics or proof of concept, and Phase IIb or phase III studies that show evidence of efficacy.

2. Serotonergic system

Serotonin (5-hydroxytryptamine) is an important neurotransmitter of the enteric nervous system (ENS [16,17]), the peristaltic reflex (chiefly 5-HT₄-receptor), the brain–gut axis and vagal and visceral afferent cell bodies or pathways, chiefly 5-HT₃-receptors [16–18]. 5-HT plays a pivotal role in the modulation of multiple gut functions such as motility, sensation, blood flow and secretion [19]. In humans, the highest level of specific binding has been found in the amygdalae, which are integral to the emotional responses to visceral stimulation.

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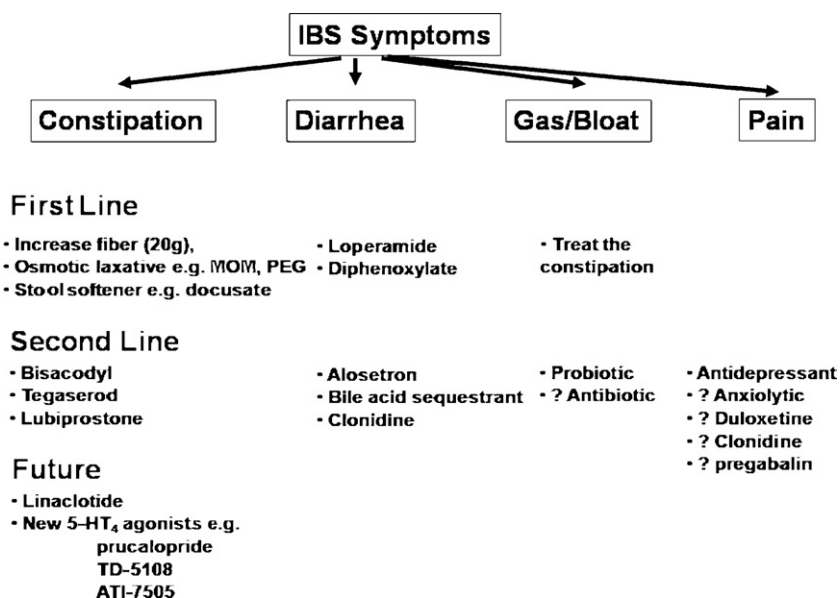


Fig. 1. Current management of IBS and potential role of therapies in pipeline for IBS.

Activity at 5-HT-receptors is regulated by the 5-HT reuptake transporter protein (SERT [20]). It is controversial whether there is reduced expression of SERT (mRNA or immunohistochemistry) in IBS [21,22].

5-HT₃ antagonists and 5-HT₄ agonists have demonstrated efficacy and effectiveness in the treatment of multiple or global symptoms of IBS. The prototype medications were alosetron and tegaserod.

2.1. 5-HT₃-receptor antagonists

5-HT₃-receptor antagonists retard colonic transit, reduce secretion, and increase colonic compliance in response to distension [23] and have central effects that contribute to their beneficial effects on sensation in IBS [24].

Alosetron and subsequently *cilansetron* were efficacious in several large, multicentre, randomised controlled clinical trials,

Table 1
Drugs in use or in clinical development for IBS.

Target system	Receptor activity	Compounds	Human physiological effects	Potential or approved indication
Serotonergic receptor system	5-HT ₄ -agonists	Prucalopride, ATI-7505 TD-5108	Prokinetic, secretagogue	IBS-C FC
	5-HT ₃ -antagonist	Alosetron, cilansetron	Decrease motility and secretion, increase compliance decrease pain	IBS-D FD
	5-HT ₃ -agonist	DDP-733	Accelerates small bowel transit	IBS-C FC
Antidepressants	SSRI SNRI	e.g. Venlafaxine	Increase compliance, decrease tone, and sensation	IBS FAP
Cholinergic system	Selective M ₃ -antagonists	Zamifenacin, darifenacin	Reduce colonic motility Decrease Pain?	IBS-D FD
α-Adrenergic system	α ₂ -agonist	Clonidine	Increases compliance, decreases tone, and sensation	IBS-D FAP
Opioid system	Peripheral μ-opioid antagonists κ-Opioid-agonist	Alvimopan, methylnaltrexone Asimadoline	Prokinetic Increase laxation Decrease sensation	IBS-C FC, OIC IBS, FAP
Corticoids	CRH antagonist CRF ₁ antagonist	αhCRH, pexacerfont	Reduce stimulation induced motility and sensitivity	IBS-D FAP
Benzodiazepine	2,3-benzodiazepine receptor	Dexofisopam	Reduces stool frequency, Increases stool consistency	IBS-D
Melatonin	Receptor?	Melatonin	Decreases Pain	IBS, FAP
CCK	CCK antagonists	Loxiglumide, dexloxiglumide	Accelerate gastric emptying, Delay prox. colonic transit	IBS
Somatostatin	Somatostatin-receptor agonist	Octreotide	Slows down transit, decreases secretion	IBS-D FD
Neurokinin (NK)	NK antagonists 1 and 2	Ezlopitant, nepadutant	Reduce visceral sensation (NK ₁) and motility (NK ₂)	IBS FAP
	NK antagonist 3	Talnetant		
Chloride channel	Activator	Lubiprostone	Accelerates transit, increases secretion	IBS-C FC
Guanylate cyclase-c	Agonist	Linaclotide	Decreases stool consistency, increases stool frequency	IBS-C FC
Antibiotics	Neomycin, rifaximin		Overall symptom relief	IBS-C FC
Probiotics	Bacterial flora	VSL#3, Lactobacilli bifidobacteriae	Decrease bloating and pain, slow colon transit	IBS bloating flatulence

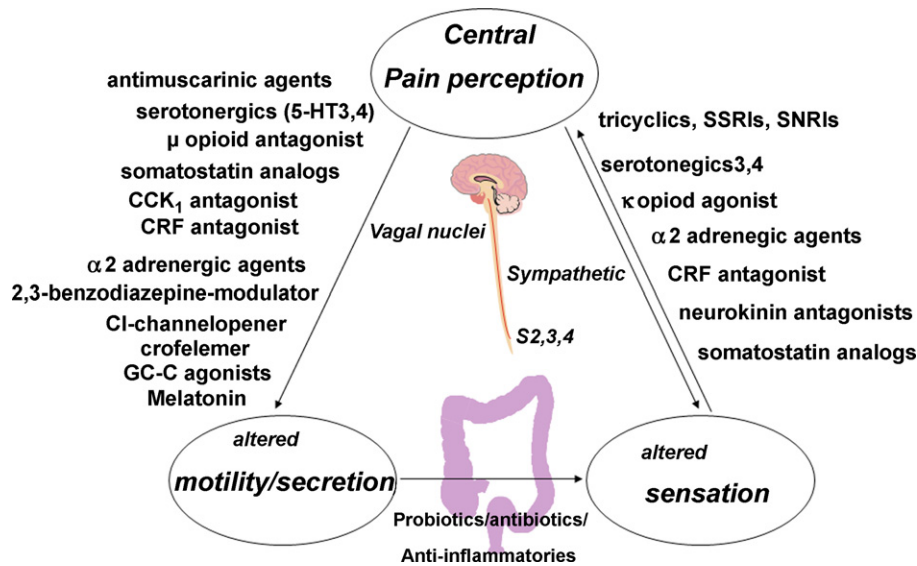


Fig. 2. Current, novel and experimental treatments for IBS.

reviewed in an updated meta-analysis [25]. 5-HT₃ antagonists more effective than the comparators in achieving global improvement in IBS symptoms (pooled relative risk, 1.60; 95% confidence interval [CI], 1.49–1.72; heterogeneity index, $I^2 = 0\%$) and relief of abdominal pain and discomfort (pooled relative risk, 1.30; 95% CI, 1.22–1.39; $I^2 = 22\%$). Benefit was apparent for both agents, in both genders. These agents were more likely to cause constipation (pooled relative risk, 4.28; 95% CI, 3.28–5.60, $I^2 = 65\%$); 0.2% using 5-HT₃ antagonists had possible ischaemic colitis versus none in control groups. Cilansetron was never approved; alosetron is associated with clear benefits on quality of life [26], but warnings about potential lack of safety has resulted in only a minority of patients being prescribed the medication.

2.2. 5HT₃-receptor agonists

The 5-HT₃ agonist, MKC-733, also named DDP733 and pumostetrag in the literature, stimulated fasting antroduodenal migrating motor complex activity and accelerated small intestinal transit [27]. A preliminary report of a phase 2a study in IBS-C showed a significant overall benefit in overall clinical response rate (54%) in patients receiving 1.4 mg t.i.d. versus to a 15% for placebo [28].

2.3. 5HT₄-receptor agonists

5HT₄-receptor agonists generally accelerate small bowel and colonic transit.

Tegaserod: Tegaserod is a selective partial agonist of the 5-HT₄-receptor. Several trials in IBS and chronic constipation were summarized in a Cochrane meta-analysis [29]. In IBS-C, tegaserod did not significantly improve the patients' individual symptoms of abdominal pain and discomfort although bowel habit showed a statistically significant improvement with tegaserod 4 mg and there was a non-significant trend in this outcome in favour of tegaserod, 12 mg. In patients with chronic constipation, the RR of being a responder in terms of complete spontaneous bowel movements per week with tegaserod 12 mg was 1.54 (95% CI, 1.35–1.75). The drug was essentially withdrawn because of possible, rare cardiovascular adverse effects.

2.4. Newer 5-HT₄-receptor agonists

ATI-7505 is a novel, potent agonist of the 5-HT₄-receptor and is chemically related to the 5-HT₄-receptor agonist, cisapride.

However, it has been chemically designed to eliminate cardiac liabilities (e.g., QT prolongation, tachycardia) and CYP450-dependent metabolism at therapeutically relevant concentrations. Pharmacodynamic data in healthy human volunteers [30] indicate prokinetic effects with acceleration of gastric emptying (20 mg t.i.d.) and colonic transit (10 mg t.i.d.; overall and ascending colon emptying), as well as inducing looser stool consistency. Thus, it appears to be promising for IBS-C. Extensive human safety data are not available. To date, there are no reports of adverse cardiac side effects.

Prucalopride is a 5-HT₄-receptor agonist that has been extensively studied, including pharmacodynamics and large clinical trials in patients with severe chronic constipation [31–34]. The medication has greater selectivity (~150-fold) for 5-HT₄-receptors than for hERG channel, and it is anticipated that this will be sufficient to prove safely from a cardiac arrhythmia perspective. Certainly, administration for approximately 1 year in more than 80 people with cardiovascular co-morbidity proved safe [35].

TD-5108 (or *velusetrag*) is a potent agonist at human 5-HT₄-receptors with high intrinsic activity that displays preferential binding to the 5-HT₄-receptor compared with other 5-HT-receptor subtypes or hERG channel [36]. In vivo studies have shown that TD-5108 increases colonic transit in guinea pigs, relaxes oesophageal body musculature in rats, and increases contractility in multiple regions of the GI tract including the gastric antrum, duodenum, jejunum and proximal colon in conscious dogs with implanted strain gauges [37]. In healthy volunteers, single dose, 30- and 50 mg, TD-5108 accelerated colonic and small bowel transit; with multiple doses, TD-5108 30 mg also accelerated colonic transit [38]. A 400-patient, randomised, controlled trial demonstrated efficacy on bowel frequency and consistency in chronic constipation [39].

3. Antidepressants

Many patients with IBS receive psychoactive agents for their co-morbid psychiatric illnesses, including anxiety, mood, and somatoform disorders, and for the potential effects on visceral sensation. Some SSRIs accelerate small bowel transit; others have effects on colorectal sensation, compliance or tone (e.g., citalopram, venlafaxine [40–42]).

There may also be racial or ethnic differences, as efficacy appears greatest in trials conducted in Iran [43,44]. In intention-to-treat analysis, complete responses were significantly more common in the amitriptyline group. Efficacy of antidepressants in treatment

of IBS has been appraised in a recent meta-analysis [45]. At first evaluation, one might conclude that this class of drugs is extremely effective. The calculated relative risk of IBS symptoms persisting or remaining unimproved after treatment with antidepressant therapy versus placebo was 0.66 (95% CI, 0.57–0.78), with the NNT with antidepressant therapy to prevent IBS symptoms persisting of 4 (95% CI, 3–6). However, it is worth noting that very few (typically small single centre) trials individually show significance, and the meta-analysis involves diverse medications and doses, study designs, endpoints, questionable generalizability, and small studies. The analysis included 13 studies comparing antidepressants (total $n=432$) to placebo ($n=357$) for IBS; 7 studies were in secondary, and 6 in tertiary care with none in primary or community cohorts. Moreover, there was marginal statistically significant heterogeneity detected between studies ($I^2=26.4\%$, $P=0.17$) and funnel plot asymmetry ($P=0.02$), suggestive of publication bias.

In the meta-analysis, only three papers are associated with clear efficacy and they involve small samples of patients: two in Iranian patients [43,44] and one in German patients [46]. Intriguingly, the most efficacious treatment attributed to a tricyclic agent was reported with a trial of amitriptyline, 10 mg, that did not significantly affect abdominal pain, bloating or diarrhoea, relative to placebo. Similarly, the trial of the SSRI, fluoxetine [43] in 44 patients in Iran shows very large differences in patients with significant abdominal discomfort and bloating, but the proportion of placebo responders over 12 weeks was uncharacteristically low (<15% average), and it is unclear whether these results are generalizable.

4. Antimuscarinics/anticholinergics/smooth muscle relaxants

Gastrointestinal effects of acetylcholine are mediated by nicotinic receptors in the myenteric plexus, and by muscarinic receptor subtypes M_{1-3} , in the myenteric plexus, as well as the neuromuscular junction [47,48]. Acetylcholine is the main excitatory neurotransmitter in the gastrointestinal (GI) tract. Nonselective anticholinergics or specific antimuscarinic agents reduce bowel motility and associated pain. Relaxant drugs act directly on the smooth muscle e.g. by blocking smooth muscle Ca^{2+} channels. Several compounds (mebeverine, otilinum, pinaverium, and cimetropium), used in Europe, have never been approved in the U.S. Several meta-analyses suggest global improvement with this class of agents [49,50], with a mean odds ratio of 2.13 [95% CI, 1.77–2.58]. The low quality (Jadad Scores) of the individual clinical trials compromises the overall interpretation of efficacy of this drug class.

Newer anticholinergics specifically targeting the muscarinic type-3 receptor (M_3) on smooth muscle decrease non-specific anticholinergic side effects (dry mouth or increased heart rate) and have promising gastrointestinal effects in animal models [51]. Amongst M_3 -selective antagonists, darifenacin (used to treat overactive bladder) is associated with constipation [52], and zamifenacin [53] significantly reduced colonic motility without other anticholinergic effects in 36 IBS patients.

5. α -Adrenergic agents

The adrenergic nervous system provides extrinsic tonic inhibitory control of non-sphincteric gut motility. The α_2 -adrenergic agents such as clonidine affect human colonic and rectal motor and sensory functions [54–56], increasing colonic compliance, reducing fasting tone without altering the colonic response to a meal or colonic transit, and significantly reducing sensation within a dose range of 0.1–0.3 mg b.i.d. In a study of 44 patients

with IBS-D [57], 67% of the patients treated with clonidine 0.1 mg twice daily compared to 46% in the placebo group achieved satisfactory relief, the primary endpoint. Clonidine also significantly improved bowel functions without altering gastrointestinal transit. Drowsiness, dizziness and dry mouth were observed at doses >0.1 mg b.i.d. This suggests benefits of α_2 -adrenergic agents in IBS.

6. GABA-ergic agents and $\alpha_2\delta$ ligand

Gabapentin, a 3-alkylated analogue of γ -amino butyric acid (GABA), has been shown to reduce elements of central sensitization in human experimental hyperalgesia. Forty patients with IBS-D were randomised for 5-day treatment with gabapentin, 300 mg/day and then 600 mg/day, which reduced rectal sensory thresholds through attenuating rectal sensitivity to distension and enhancing rectal compliance [58].

Preclinical studies suggest that the $\alpha_2\delta$ ligand, pregabalin, reduces both visceral allodynia and hyperalgesia, but is inactive on basal sensitivity. The perception of rectal distension was tested in 26 hypersensitive IBS patients randomised to increasing doses of oral pregabalin for 3 weeks or placebo control. Pregabalin significantly increased the sensory thresholds from baseline for first sensation desire to defecate and pain compared with placebo; it also increased rectal compliance, an effect unrelated to the changes in sensitivity [59]. Studies of GABA-ergic agents and $\alpha_2\delta$ ligands on clinical outcomes in IBS are not available.

7. Opioid agents

Three major opioid receptors, μ , δ , and κ , are distributed in the peripheral and central nervous systems. μ -Agonists modulate visceral nociception and to slow down gastrointestinal transit resulting in constipation or central side effects [60–62]. κ -Opioid receptors are involved in visceral perception [63].

7.1. κ -Opioid agonist

Asimadoline: The κ -opioid agonist, asimadoline [64], was shown to reduce sensation in response to distensions in the non-noxious range applied to the colon and to relax colonic and gastric tone during fasting. There were no significant effects on gastrointestinal or colonic transit or postprandial tone response to meal ingestion. Delvaux et al. [65] showed that this drug increased sensory thresholds in patients with IBS. On demand treatment of IBS pain with asimadoline was not significantly better than placebo [66]; however, a recent trial using daily administration of asimadoline demonstrated efficacy in patients with IBS-D and IBS with mixed bowel habits (IBS-M) [67].

7.2. Peripheral μ -opioid antagonists

Alvimopan: Alvimopan, a novel, peripherally restricted μ -opioid antagonist, is effective in the treatment of opioid-induced constipation and postoperative ileus [68–70]. It reverses the peripheral effects of narcotics without influencing the pain relief desired by concomitant opioid administration. A pharmacodynamic study in healthy volunteers [71] confirmed that alvimopan normalized the colonic transit delay induced by co-administered codeine. Interestingly, alvimopan alone accelerated colonic transit, suggesting that the μ -opiate mechanisms participate in the physiological control of colonic transit [71].

Oral *naltrexone* does not accelerate colonic transit [72], but oral methyl *naltrexone* accelerated gut transit in opiate-naïve controls [73] and it reversed the prolongation of orocecal transit induced by long-term methadone [74]. Trials to test the effects of peripheral

μ -opioid antagonists such as alvimopan and methylnaltrexone in patients with constipation, IBS-C, and opiate-induced constipation are warranted.

8. CRF receptor antagonists

Corticotropin releasing factor (CRF) is a key mediator of stress response in the brain gut axis [75]. Two CRF receptor subtypes have been cloned: CRF₁ and CRF₂. In animals, stress activation of the CRF receptors alters gastrointestinal motility [76], effects that can be blocked with selective CRF₁-receptor antagonists (*antalarmin* [77]) and the nonselective CRF receptor antagonist α -helical CRF₉₋₄₁ (α hCRF [78]). The increased colonic motility response to rectal electrical stimulation in IBS patients was significantly suppressed after α hCRF infusion [79]. However, the CRF₁ antagonist, *pexacerfont*, was not effective in normalizing colonic transit or bowel function in patients with diarrhoea-predominant IBS [80]. The role of CRF modulation requires further study.

9. 2,3-Benzodiazepine receptor modulator

Dextofisopam [81] is the R-enantiomer of the nonsedating homophthalazine anxiolytic, tofisopam. It binds to 2,3-benzodiazepine receptors located in subcortical and hypothalamic regions. In animal models, dextofisopam reduced stimulation-induced colonic motility and visceral sensitivity [81]. A 12-week, placebo-controlled, phase II study in patients with diarrhoea-predominant or alternating-IBS showed more months with adequate relief in the dextofisopam compared to the placebo group [82]. The effects were most prominent within the first 4 weeks of treatment, and also included an improvement of stool consistency and a reduction of stool frequency. The drug was well tolerated, with only 3% reporting constipation; however, 12% of the patients experienced a worsening of abdominal pain (versus 4% in the placebo group).

10. Melatonin

Melatonin is a pineal gland neurohormone involved in the regulation of the sleep-wake cycle; it is also synthesized in the gastrointestinal tract, and may participate in the regulation of gastrointestinal motility and sensitivity [83], possibly by blocking nicotinic channels [84] or Ca²⁺ activated K⁺ channels [85]. Two small studies of the effects of melatonin in IBS patients [86,87] reported improvement of abdominal pain and IBS symptom score or a reduction of rectal pain sensitivity. This appears to be a peripheral effect, since there was no alteration of sleep or anxiety or depression. The role of melatonin modulation in IBS requires further study.

11. CCK₁ antagonists

Cholecystokinin (CCK [88]), a neuropeptide released by endocrine cells within the duodenal and jejunal mucosa in response to a variety of nutrients, has been proposed as a mediator of IBS symptoms. Colonic responses to CCK *in vivo* and *in vitro* were increased in IBS patients [89]. The effects of CCK are mediated by two distinct receptors, CCK₁ and CCK₂ [90,91], which are located predominantly in the periphery and the central nervous system respectively. The CCK₁ (also called CCK_A) receptors are present in gastrointestinal tract smooth muscles and vagal afferents. Blockade of CCK₁ receptors in the gastrointestinal tract was proposed as an approach to stimulate gut motility and to change colonic transit time in patients with IBS-C.

Loxiglumide and *Dexloxiglumide*: Loxiglumide is a highly specific, competitive antagonist of the CCK₁ receptor [92]. Earlier pharma-

codynamic [93] and clinical [94] studies suggested that loxiglumide might improve constipation. A 12-week, phase II trial of 200 mg/day dexloxiglumide [95] in female IBS-C patients showed improvement in abdominal pain and discomfort compared to placebo, but two large phase III trials in IBS-C showed no efficacy for dexloxiglumide [96]. The latter result was consistent with a pharmacodynamics study in IBS-C [97] which showed no significant effect on overall colonic transit or satisfactory relief of IBS. However, in a phase III randomised withdrawal study, dexloxiglumide demonstrated sustained relief of symptoms in female (not male) patients [98]. Further studies with this mediation are awaited.

12. Somatostatin analogs

The somatostatin analog, *octreotide*, activates predominantly somatostatin type 2 receptors, and reduces gastrointestinal secretion, retards gastrointestinal transit and has antinociceptive properties. Octreotide retards orocecal and small bowel transit time in patients with IBS-D [99,100] and normalizes visceral perception and discomfort thresholds in IBS patients without changing rectal compliance [101,102]. There are no clinical trials with octreotide in IBS.

13. Neurokinin-antagonists

NK₁-receptors play a role in nociception [103], whereas NK₂ receptors have a greater influence on smooth muscle contractility [103–105] and of NK₂-antagonists on gut motility [105]. In a small pharmacodynamic study of IBS patients, the NK₁-receptor antagonist, *ezlozipant* [106], reduced the emotional response to rectosigmoid distension but did not significantly decrease rectal sensitivity. In healthy controls, the NK₂-receptor antagonist, *nepadutant* [107], reduced contraction frequency and amplitude on migrating motor complexes in the small intestine and effectively antagonized the motility-stimulating effects of infused NK_A.

The NK₃ antagonist, *talnetant*, was tested in pharmacodynamics [108] and clinical trials [109], and proved ineffective.

14. Chloride channel modulators

14.1. Cl⁻ channel (ClC₂) opener

Intestinal Cl⁻ secretion is critical for intestinal fluid and electrolyte transport. In the gastrointestinal tract, chloride channels type 2, ClC₂, has been found in gastric parietal cells, small intestinal and colonic epithelia. *Lubiprostone* is a prostone that acts as a selective ClC₂ activator and increases intestinal water secretion [110]. In a pharmacodynamic study, lubiprostone was shown to accelerate small bowel and colonic transit time in healthy volunteers [111]. In several clinical trials, lubiprostone, 24 μ g b.i.d., had positive effects on stool consistency, frequency and straining, and was safe and effective for treating constipation [112–114]. Interestingly, lubiprostone accelerated colonic transit without accelerating ascending colon emptying, suggesting it affects distal colonic function. Lubiprostone also reduced abdominal pain and improved bowel dysfunction in IBS-C [115,116]. Side effects of lubiprostone include diarrhoea and nausea that is usually mild and transient. In January 2006, the FDA approved lubiprostone.

14.2. Guanylate cyclase-c agonist

Linaclotide is a novel agonist of the human guanylate cyclase-c (GC-C), a transmembrane protein located in the gut epithelium. Activation of the GC-C induces secretion of fluid, sodium and bicarbonate in the intestinal lumen [117–120]. In animal and early

human safety studies, linaclotide has been observed to increase stool frequency, decrease stool consistency and decrease visceral pain [121]. A phase IIA pilot, randomised, controlled study shows efficacy of this drug in treatment of chronic constipation [122]. Therefore, the drug seems to be promising for the treatment of IBS-C and chronic constipation.

14.3. Crofelemer

Crofelemer reduces excess chloride ion secretion via the CFTR channel. Crofelemer does not affect gut motility and is not absorbed systemically to any significant level. It has been used in the past to treat diarrhoea associated with intestinal secretion. In a dose-ranging study of crofelemer versus placebo b.i.d. for 12 weeks in 242 IBS-D patients [123], crofelemer did not produce improvement in the primary endpoint related to bowel function, urgency or adequate relief. On the other hand, female IBS-D patients exposed to the highest dose of 500 mg b.i.d. crofelemer had a higher proportion of pain and discomfort free days. These post hoc observations suggest that further studies are indicated to assess the visceral analgesic potential of crofelemer.

15. Probiotics

Probiotics may have beneficial effects on altered colonic inflammation or barrier function that may be found in some IBS patients. The precise mechanism of action of probiotics is unclear and change of intraluminal milieu and modification of fermentation processes and gas production, inactivation of bile acids with decreased effect of endogenous bile acids on colonic fluid secretion and motility, and alteration of gastrointestinal motility may also contribute to the symptom improvement [124]. A recent meta-analysis [125] identified 19 randomised, controlled trials (18 papers) in 1650 IBS patients. Trial quality was generally good. Amongst 10 randomised, controlled trials involving 918 patients providing outcomes as a dichotomous variable, probiotics were significantly better than placebo with an NNT=4 (95% CI, 3–12.5); however, there was significant heterogeneity ($I^2 = 68\%$, $p = 0.001$) and possible funnel plot asymmetry. Amongst 15 trials assessing 1351 patients that reported an improvement in IBS score as a continuous outcome, the standard mean difference was -0.34 (95% CI, -0.60 to -0.07); however, there was statistically significant heterogeneity ($I^2 = 79\%$, $p = 0.001$). These data suggest overall benefit for probiotics, but the precision of the NNT is uncertain. The safety profile of probiotics suggests they may be considered for the treatment of bloating and flatulence.

16. Antibiotics

The role of bacterial overgrowth of the small intestine (SIBO) in IBS is controversial. A placebo-controlled study [126] showed that antibiotic treatment with neomycin normalized the lactulose hydrogen breath test (LBT), and this was associated with significant reduction of IBS symptoms over the short term (~1 week). More convincing evidence of the efficacy of antibiotics is provided by the randomised, controlled trials [127] and a preliminary report from Lembo et al. [128]. Although there are many unanswered questions, regarding long-term effects, and frequency of retreatment, some patients may benefit from rifaximin treatment.

17. Immune modulators

17.1. Sodium cromoglycate

Sodium cromoglycate is a mast cell stabilizer; there is experimental evidence of increased mast cell infiltration and greater proximity

of mast cells to intramural nerve endings. Proteases that may arise from mast cells have been associated with activation of visceral algia in experimental studies. Sodium cromoglycate alone or in association with dietary exclusion of suspected allergens has been tested in trials conducted in IBS-D [129] and childhood IBS [130].

17.2. 5-ASA compounds or budesonide

Given the efficacy of *budesonide* in microscopic or collagenous colitis [131–133] and the increasing evidence of immune activation in IBS, we anticipate more formal trials of these agents, especially in post-infectious IBS. In a recent meta-analysis, Chande et al. [133] report that, amongst 3 trials with budesonide for collagenous colitis, the odds ratio for inducing a response was 12.32 (95% CI, 5.53–27.46), maintaining response was OR 8.82, and NNT of 2. Similar efficacy was observed for trials that included both collagenous and lymphocytic colitis (NNT of 3). *Mesalazine* and *bismuth* compounds were less effective for microscopic colitis. However, a small, pilot clinical trial in IBS suggests that mesalazine reduced total number of immune cells and mast cells and pain severity score, and increased global relief relative to placebo treatment [134]. These interesting and provocative data suggest that 5-ASA compounds deserve further study.

18. Conclusion

The field of IBS therapeutics is vibrant, with greater understanding of neuroenteric mechanisms, effectors and transmitters in the brain–gut axis. These should provide opportunities for the development of new therapeutic agents for IBS treatment. For almost all of the drug classes described here, rigorous phase III trials and assessment of drug safety are eagerly awaited.

Conflict of interest statement

None declared.

List of abbreviations

IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with predominant constipation; IBS-D, irritable bowel syndrome with predominant diarrhoea; FC, functional constipation; FD, functional diarrhoea; FAP, functional abdominal pain; OR, odds ratio; CI, confidence interval; SNRI, serotonin and norepinephrine reuptake inhibitor.

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References

- [1] Drossman DA, Li Z, Andruzzi E, et al. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. *Dig Dis Sci* 1993;38:1569–80.
- [2] Cremonini F, Talley NJ. Irritable bowel syndrome: epidemiology, natural history, health care seeking and emerging risk factors. *Gastroenterol Clin North Am* 2005;34:189–204.
- [3] Drossman DA, Camilleri M, Mayer EA, et al. AGA technical review on irritable bowel syndrome. *Gastroenterology* 2002;123:2108–31.
- [4] Camilleri M. Mechanisms in IBS: something old, something new, something borrowed. *Neurogastroenterol Motil* 2005;17:311–6.
- [5] Dunlop SP, Coleman NS, Blackshaw E, et al. Abnormalities of 5-hydroxytryptamine metabolism in irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2005;3:349–57.

- [6] Bearcroft CP, Perrett D, Farthing MJ. Postprandial plasma 5-hydroxytryptamine in diarrhoea predominant irritable bowel syndrome: a pilot study. *Gut* 1998;42:42–6.
- [7] Houghton LA, Atkinson V, Whitaker RP, et al. Increased platelet depleted plasma 5-hydroxytryptamine concentration following meal ingestion in symptomatic female subjects with diarrhoea predominant irritable bowel syndrome. *Gut* 2003;52:663–70.
- [8] Roka R, Rosztochy A, Leveque M, et al. A pilot study of fecal serine-protease activity: a pathophysiological factor in diarrhea-predominant irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2007;5:550–5.
- [9] Borman R. Serotonergic modulation and irritable bowel syndrome. *Expert Opin Emerg Drugs* 2001;6:57–68.
- [10] Spiller RC. Postinfectious irritable bowel syndrome. *Gastroenterology* 2003;124:1662–71.
- [11] Spiller RC, Jenkins D, Thornley JP, et al. Increased rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following acute *Campylobacter* enteritis and in post-dysenteric irritable bowel syndrome. *Gut* 2000;47:804–11.
- [12] Spiller RC. Infection, immune function, and functional gut disorders. *Clin Gastroenterol Hepatol* 2004;2:445–55.
- [13] Barbara G, Stanghellini V, De Giorgio R, et al. Activated mast cells in proximity of colonic nerves correlate with abdominal pain in irritable bowel syndrome. *Gastroenterology* 2004;126:693–702.
- [14] O'Mahony L, McCarthy J, Kelly P, et al. Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology* 2005;128:541–51.
- [15] Aerssens J, Camilleri M, Talloen W, et al. Alterations in mucosal immunity identified in the colon of patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2008;6:194–205.
- [16] Gershon MD. Review article: roles played by 5-hydroxytryptamine in the physiology of the bowel. *Aliment Pharmacol Ther* 1999;13(Suppl. 2):15–30.
- [17] Gershon MD. Review article: serotonin receptors and transporters—roles in normal and abnormal gastrointestinal motility. *Aliment Pharmacol Ther* 2004;20(Suppl. 7):3–14.
- [18] Hicks GA, Coldwell JR, Schindler M, et al. Excitation of rat colonic afferent fibres by 5-HT(3) receptors. *J Physiol* 2002;544(Pt 3):861–9.
- [19] Camilleri M. Serotonin in the gastrointestinal tract. *Curr Opin Endocrinol Diabetes* 2009;16:53–9.
- [20] Gershon MD. Plasticity in serotonin control mechanisms in the gut. *Curr Opin Pharmacol* 2003;3:600–7.
- [21] Coates MD, Mahoney CR, Linden DR, et al. Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and irritable bowel syndrome. *Gastroenterology* 2004;126:1657–64.
- [22] Andrews C, Camilleri M, Bharucha AE, et al. Serotonin-transporter (SERT) polymorphism genotype and SERT expression in mucosal biopsies of patients with irritable bowel syndrome. *Gastroenterology* 2006;130:A24 [abstract].
- [23] Gunput MD. Review article: clinical pharmacology of alosetron. *Aliment Pharmacol Ther* 1999;13(Suppl. 2):70–6.
- [24] Mayer EA, Berman S, Derbyshire SW, et al. The effect of the 5-HT3 receptor antagonist, alosetron, on brain responses to visceral stimulation in irritable bowel syndrome patients. *Aliment Pharmacol Ther* 2002;16:1357–66.
- [25] Andresen V, Montori VM, Keller J, et al. Effects of 5-hydroxytryptamine (serotonin) type 3 antagonists on symptom relief and constipation in nonconstipated irritable bowel syndrome: a systematic review and meta-analysis of randomized controlled trials. *Clin Gastroenterol Hepatol* 2008;6:545–55.
- [26] El-Serag HB, Olden K, Bjorkman D. Health-related quality of life among persons with irritable bowel syndrome: a systematic review. *Aliment Pharmacol Ther* 2002;16:1171–85.
- [27] Coleman NS, Marciani L, Blackshaw E, et al. Effect of a novel 5-HT3 receptor agonist MKC-733 on upper gastrointestinal motility in humans. *Aliment Pharmacol Ther* 2003;18:1039–48.
- [28] Paterson WG, Ford D, Ganguli SC, et al. A novel, oral 5HT3 partial agonist, DDP733, improves overall response in patients with irritable bowel syndrome and constipation (IBS-C): a randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study. *Gastroenterology* 2008;134:A546–A547 [abstract].
- [29] Evans BW, Clark WK, Moore DJ, et al. Tegaserod for the treatment of irritable bowel syndrome and chronic constipation. *Cochrane Database Syst Rev* 2007;CD003960.
- [30] Camilleri M, Vazquez-Roque MI, Burton D, et al. Pharmacodynamic effects of a novel prokinetic 5-HT receptor agonist, ATI-7505, in humans. *Neurogastroenterol Motil* 2007;19:30–8.
- [31] Bouras EP, Camilleri M, Burton DD, et al. Prucalopride accelerates gastrointestinal and colonic transit in patients with constipation without a rectal evacuation disorder. *Gastroenterology* 2001;120:354–60.
- [32] Camilleri M, Kerstens R, Rykx A, et al. A placebo-controlled trial of prucalopride for severe chronic constipation. *N Engl J Med* 2008;358:2344–54.
- [33] Tack J, Van Outryve M, Beyens G, et al. Prucalopride (Resolor(R)) in the treatment of severe chronic constipation in patients dissatisfied with laxatives. *Gut* 2008 [November 5, Epub ahead of print].
- [34] Quigley EM, Vandeplassche L, Kerstens R, et al. Clinical trial: the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation—a 12-week, randomized, double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2009;29:315–28.
- [35] Camilleri M, Kerstens R, Beyens G, et al. A double-blind, placebo-controlled trial to evaluate the safety and tolerability of prucalopride oral solution in constipated elderly patients living in a nursing facility. *Gastroenterology* 2009;136(Suppl. 1):240.
- [36] Smith JA, Beattie DT, Marquess D, et al. The in vitro pharmacological profile of TD-5108, a selective 5-HT(4) receptor agonist with high intrinsic activity. *Naunyn Schmiedeberg Arch Pharmacol* 2008;378:125–37.
- [37] Beattie DT, Armstrong SR, Shaw JP, et al. The in vivo gastrointestinal activity of TD-5108, a selective 5-HT(4) receptor agonist with high intrinsic activity. *Naunyn Schmiedeberg Arch Pharmacol* 2008;378:139–47.
- [38] Camilleri M, Manini M, McKinzie S, et al. Dose-related effects of TD-5108, a selective 5-HT4 receptor agonist with high intrinsic activity, on gastrointestinal (GI) and colonic transit in healthy volunteers. *Neurogastroenterol Motil* 2008;20(Suppl. 2):6 [abstract].
- [39] Goldberg MR, Li Y-P, Pitzer K, et al. TD-5108, a selective 5-HT4 agonist, is consistently better than placebo regardless of response definition in patients with chronic constipation. *Gastroenterology* 2008;134:A 545.
- [40] Gorard DA, Libby GW, Farthing MJ. Influence of antidepressants on whole gut and oro-caecal transit times in health and irritable bowel syndrome. *Aliment Pharmacol Ther* 1994;8:159–66.
- [41] Tack J. A placebo controlled trial of buspirone, a fundus relaxing drug, in functional dyspepsia: effect on symptoms and gastric sensory and motor functions. *Gastroenterology* 2000;116:G1423.
- [42] Chial HJ, Camilleri M, Ferber I, et al. Effects of venlafaxine, buspirone, and placebo on colonic sensorimotor functions in healthy humans. *Clin Gastroenterol Hepatol* 2003;1:211–8.
- [43] Vahedi H, Merat S, Rashidooon A, et al. Effect of fluoxetine in patients with pain and constipation-predominant irritable bowel syndrome: a double-blind randomized-controlled study. *Aliment Pharmacol Ther* 2005;22:381–5.
- [44] Vahedi H, Merat S, Momtahan S, et al. Clinical trial: effect of amitriptyline in patients with diarrhea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther* 2008;27:678–84.
- [45] Ford AC, Talley NJ, Schoenfeld PS, et al. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. *Gut* 2008 [November 10, Epub ahead of print].
- [46] Bergmann M, Heddergott A, Schlosser T. Die therapie des colon irritable mit trimaprimin (Herphonal)—Eine kontrollierte studie. *Z Klin Med* 1991;46:1621–8.
- [47] Goyal RK. Muscarinic receptor subtypes. Physiology and clinical implications. *N Engl J Med* 1989;321:1022–9.
- [48] Eglen RM. Muscarinic receptors and gastrointestinal tract smooth muscle function. *Life Sci* 2001;68:2573–8.
- [49] Ford AC, Talley NJ, Spiegel BM, et al. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. *Br Med J* 2008 [November 13, Epub ahead of print].
- [50] Poynard T, Regimbeau C, Benhamou Y. Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 2001;15:355–61.
- [51] Kobayashi S, Ikeda K, Suzuki M, et al. Effects of YM905, a novel muscarinic M3-receptor antagonist, on experimental models of bowel dysfunction in vivo. *Jpn J Pharmacol* 2001;86:281–8.
- [52] Foote J, Glavind K, Kralidis G, et al. Treatment of overactive bladder in the older patient: pooled analysis of three phase III studies of darifenacin, an M3 selective receptor antagonist. *Eur Urol* 2005;48:471–7.
- [53] Houghton LA, Rogers J, Whorwell PJ, et al. Zamifenacin (UK-76, 654) a potent gut M3 selective muscarinic antagonist, reduces colonic motor activity in patients with irritable bowel syndrome. *Aliment Pharmacol Ther* 1997;11:561–8.
- [54] Bharucha AE, Camilleri M, Zinsmeister AR, et al. Adrenergic modulation of human colonic motor and sensory function. *Am J Physiol* 1997;273(5 Pt 1):G997–1006.
- [55] Malcolm A, Phillips SF, Camilleri M, et al. Pharmacological modulation of rectal tone alters perception of distention in humans. *Am J Gastroenterol* 1997;92:2073–9.
- [56] Malcolm A, Camilleri M, Kost L, et al. Towards identifying optimal doses for alpha-2 adrenergic modulation of colonic and rectal motor and sensory function. *Aliment Pharmacol Ther* 2000;14:783–93.
- [57] Camilleri M, Kim DY, McKinzie S, et al. A randomized, controlled exploratory study of clonidine in diarrhea-predominant irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2003;1:111–21.
- [58] Lee KJ, Kim JH, Cho SW. Gabapentin reduces rectal mechanosensitivity and increases rectal compliance in patients with diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther* 2005;22:981–8.
- [59] Houghton LA, Fell C, Whorwell PJ, et al. Effect of a second-generation alpha2delta ligand (pregabalin) on visceral sensation in hypersensitive patients with irritable bowel syndrome. *Gut* 2007;56:1218–25.
- [60] Borody TJ, Quigley EM, Phillips SF, et al. Effects of morphine and atropine on motility and transit in the human ileum. *Gastroenterology* 1985;89:562–70.
- [61] Steadman CJ, Phillips SF, Camilleri M, et al. Control of muscle tone in the human colon. *Gut* 1992;33:541–6.
- [62] Lembo T, Naliboff BD, Martin K, et al. Irritable bowel syndrome patients show altered sensitivity to exogenous opioids. *Pain* 2000;87:137–47.
- [63] Delvaux M, Louvel D, Lagier E, et al. The kappa agonist fedotozine relieves hypersensitivity to colonic distention in patients with irritable bowel syndrome. *Gastroenterology* 1999;116:38–45.
- [64] Delgado-Aros S, Chial HJ, Cremonini F, et al. Effects of asimadoline, a kappa-opioid agonist, on satiation and postprandial symptoms in health. *Aliment Pharmacol Ther* 2003;18:507–14.

- [65] Delvaux M, Beck A, Jacob J, et al. Effect of asimadoline, a kappa opioid agonist, on pain induced by colonic distension in patients with irritable bowel syndrome. *Aliment Pharmacol Ther* 2004;20:237–46.
- [66] Szarka LA, Camilleri M, Burton D, et al. Efficacy of on-demand asimadoline, a peripheral kappa-opioid agonist, in females with irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2007;5:1268–75.
- [67] Mangel AW, Bornstein JD, Hamm LR, et al. Clinical trial: asimadoline in the treatment of patients with irritable bowel syndrome. *Aliment Pharmacol Ther* 2008;28:239–49.
- [68] Wolff BG, Michelassi F, Gerkin TM, et al. Alvimopan, a novel, peripherally acting mu opioid antagonist: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial of major abdominal surgery and postoperative ileus. *Ann Surg* 2004;240:728–34 [discussion 734–5].
- [69] Taguchi A, Sharma N, Saleem RM, et al. Selective postoperative inhibition of gastrointestinal opioid receptors. *N Engl J Med* 2001;345:935–40.
- [70] Delaney CP, Weese JL, Hyman NH, et al. Phase III trial of alvimopan, a novel, peripherally acting, mu opioid antagonist, for postoperative ileus after major abdominal surgery. *Dis Colon Rectum* 2005;48:1114–25 [discussion 1125–6; author reply 1127–9].
- [71] Gonenne J, Camilleri M, Ferber I, et al. Effect of alvimopan and codeine on gastrointestinal transit: a randomized controlled study. *Clin Gastroenterol Hepatol* 2005;3:784–91.
- [72] Foxx-Orenstein AE, Camilleri M, Szarka LA, et al. Does co-administration of a non-selective opiate antagonist enhance acceleration of transit by a 5-HT4 agonist in constipation-predominant irritable bowel syndrome? A randomized controlled trial. *Neurogastroenterol Motil* 2007;19:821–30.
- [73] Yuan CS, Doshan H, Charney MR, et al. Tolerability, gut effects, and pharmacokinetics of methylnaltrexone following repeated intravenous administration in humans. *J Clin Pharmacol* 2005;45:538–46.
- [74] Yuan CS, Foss JF, O'Connor M, et al. Methylnaltrexone for reversal of constipation due to chronic methadone use: a randomized controlled trial. *J Am Med Assoc* 2000;283:367–72.
- [75] Owens MJ, Nemeroff CB. Physiology and pharmacology of corticotropin-releasing factor. *Pharmacol Rev* 1991;43:425–73.
- [76] Tache Y, Monnikes H, Bonaz B, et al. Role of CRF in stress-related alterations of gastric and colonic motor function. *Ann N Y Acad Sci* 1993;697:233–43.
- [77] Greenwood-Van Meerveld B, Johnson AC, Cochrane S, et al. Corticotropin-releasing factor 1 receptor-mediated mechanisms inhibit colonic hypersensitivity in rats. *Neurogastroenterol Motil* 2005;17:415–22.
- [78] Monnikes H, Schmidt BG, Tache Y. Psychological stress-induced accelerated colonic transit in rats involves hypothalamic corticotropin-releasing factor. *Gastroenterology* 1993;104:716–23.
- [79] Sagami Y, Shimada Y, Tayama J, et al. Effect of a corticotropin releasing hormone receptor antagonist on colonic sensory and motor function in patients with irritable bowel syndrome. *Gut* 2004;53:958–64.
- [80] Sweetser SR, Linker Nord SJ, Burton DD, et al. Effects of a novel corticotropin releasing factor receptor-1 antagonist, BMS-562086, on gastrointestinal and colonic transit and bowel habits in patients with diarrhea-predominant irritable bowel syndrome (D-IBS). *Gastroenterology* 2008;134:A 548.
- [81] Leventer SM, Kucharik RF, Keogh JC, et al. The potential of dextropropofol for treatment of irritable bowel syndrome and inflammatory bowel disease. *Am J Gastroenterol* 2004;99:5279.
- [82] Leventer SM, Raudibaugh K, Frissora CL, et al. Clinical trial: dextropropofol in the treatment of patients with diarrhoea-predominant or alternating irritable bowel syndrome. *Aliment Pharmacol Ther* 2008;27:197–206.
- [83] Storr M, Koppitz P, Sibae A, et al. Melatonin reduces non-adrenergic, non-cholinergic relaxant neurotransmission by inhibition of nitric oxide synthase activity in the gastrointestinal tract of rodents in vitro. *J Pineal Res* 2002;33:101–8.
- [84] Barajas-Lopez C, Peres AL, Espinosa-Luna R, et al. Melatonin modulates cholinergic transmission by blocking nicotinic channels in the guinea-pig submucous plexus. *Eur J Pharmacol* 1996;312:319–25.
- [85] Storr M, Schudziarra V, Allescher HD. Inhibition of small conductance K⁺-channels attenuated melatonin-induced relaxation of serotonin-contracted rat gastric fundus. *Can J Physiol Pharmacol* 2000;78:799–806.
- [86] Lu WZ, Gwee KA, Mochhalla S, et al. Melatonin improves bowel symptoms in female patients with irritable bowel syndrome: a double-blind placebo-controlled study. *Aliment Pharmacol Ther* 2005;22:927–34.
- [87] Song GH, Leng PH, Gwee KA, et al. Melatonin improves abdominal pain in irritable bowel syndrome patients who have sleep disturbances: a randomised, double blind, placebo controlled study. *Gut* 2005;54:1402–7.
- [88] Walsh JH. Gastrointestinal hormones. In: Physiology of the gastrointestinal tract. 3rd ed. New York: Raven; 1994. p. 49–67.
- [89] Chey WY, Jin HO, Lee MH, et al. Colonic motility abnormality in patients with irritable bowel syndrome exhibiting abdominal pain and diarrhea. *Am J Gastroenterol* 2001;96:1499–506.
- [90] Wank SA. Cholecystokinin receptors. *Am J Physiol* 1995;269(5 Pt 1):G628–46.
- [91] Fourmy D, Escrieut C, Archer E, et al. Structure of cholecystokinin receptor binding sites and mechanism of activation/inactivation by agonists/antagonists. *Pharmacol Toxicol* 2002;91:313–20.
- [92] D'Amato M, Rovati LC. Cholecystokinin-A receptor antagonists: therapies for gastrointestinal disorders. *Expert Opin Investig Drugs* 1997;6:819–36.
- [93] Meyer BM, Werth BA, Beglinger C, et al. Role of cholecystokinin in regulation of gastrointestinal motor functions. *Lancet* 1989;2:12–5.
- [94] Cann PA, Rovati LC, Smart HL, et al. Loxiglumide, a CCK-A antagonist, in irritable bowel syndrome. A pilot multicenter clinical study. *Ann N Y Acad Sci* 1994;713:449–50.
- [95] D'Amato M, Whorwell PJ, Thompson DG. The efficacy and safety of the CCKA-receptor antagonist dexloiglumide in IBS. *Gut* 1999;45(Suppl. V):A258.
- [96] Pharmabiz.com. Forest to discontinue development in U.S. of dexloiglumide for irritable bowel syndrome. Pharmabiz.com 2004;October:<http://www.pharmabiz.com/article/detnews.asp?articleid=18255§ionid=14>.
- [97] Cremonini F, Camilleri M, McKinzie S, et al. Effect of CCK-1 antagonist, dexloiglumide, in female patients with irritable bowel syndrome: a pharmacodynamic and pharmacogenomic study. *Am J Gastroenterol* 2005;100:652–63.
- [98] Whorwell PJ, Pace F, D'Amato M, et al. A phase III, 6-month, double-blind, placebo-controlled, randomized withdrawal trial of the selective CCK-1 antagonist dexloiglumide in constipation-predominant IBS: the Darwin study. *Gastroenterology* 2008;134:A-157 [abstract].
- [99] O'Donnell LJ, Watson AJ, Cameron D, et al. Effect of octreotide on mouth-to-caecum transit time in healthy subjects and in the irritable bowel syndrome. *Aliment Pharmacol Ther* 1990;4:177–81.
- [100] von der Ohe MR, Camilleri M, Thomforde GM, et al. Differential regional effects of octreotide on human gastrointestinal motor function. *Gut* 1995;36:743–8.
- [101] Schwetz I, Naliboff B, Munakata J, et al. Anti-hyperalgesic effect of octreotide in patients with irritable bowel syndrome. *Aliment Pharmacol Ther* 2004;19:123–31.
- [102] Bradette M, Delvaux M, Staumont G, et al. Octreotide increases thresholds of colonic visceral perception in IBS patients without modifying muscle tone. *Dig Dis Sci* 1994;39:1171–8.
- [103] Holzer P, Holzer-Petsche U. Tachykinins in the gut. Part I. Expression, release and motor function. *Pharmacol Ther* 1997;73:173–217.
- [104] Moriarty D, Selve N, Baird AW, et al. Potent NK1 antagonism by SR-140333 reduces rat colonic secretory response to immunocyte activation. *Am J Physiol Cell Physiol* 2001;280:C852–8.
- [105] Onori L, Aggio A, Taddei G, et al. Contribution of NK(2) tachykinin receptors to propulsion in the rabbit distal colon. *Am J Physiol Gastrointest Liver Physiol* 2000;278:G137–47.
- [106] Oh-Young L, Manakata J, Naliboff B. A double-blind, parallel group pilot study of the effects of C-11974 and placebo on perceptual and emotional responses to rectosigmoid distension in IBS patients. *Gastroenterology* 2000;118:A 846.
- [107] Lordal M, Navalesi G, Theodorsson E, et al. A novel tachykinin NK2 receptor antagonist prevents motility-stimulating effects of neurokinin A in small intestine. *Br J Pharmacol* 2001;134:215–23.
- [108] Houghton LA, Cremonini F, Camilleri M, et al. Effect of the NK3 receptor antagonist, talnetant, on rectal sensory function and compliance in healthy humans. *Neurogastroenterol Motil* 2007;19:732–43.
- [109] Dukes GE, Dewit OE, Sanger GJ, et al. Lack of effect of the NK₃ receptor antagonist, talnetant SB223242 on symptoms of IBS: results of 2 randomized, double-blind, placebo-controlled, dose-ranging trials. *Gastroenterology* 2007;132:A60.
- [110] Lubiprostone: RU 0211, SPI 0211. *Drugs R D* 2005;6:245–58.
- [111] Camilleri M, Bharucha AE, Ueno R, et al. Effect of a selective chloride channel activator, lubiprostone, on gastrointestinal transit, gastric sensory and motor functions in healthy volunteers. *Am J Physiol* 2006;290:G942–7.
- [112] Johanson JF, Gargano AM, Holland PC, et al. Phase III, efficacy and safety of RU-0211 a novel chloride channel activator, for the treatment of constipation. *Gastroenterology* 2003;124:A48.
- [113] Johanson JF, Gargano MA, Holland PC, et al. Phase III, randomized withdrawal study of RU-0211, a novel chloride channel activator for the treatment of constipation. *Gastroenterology* 2004;126(4 Suppl. 2):A-100.
- [114] Johanson JF, Gargano M, Patchen M. Efficacy and safety of a novel compound, RU-0211, for the treatment of constipation. *Gastroenterology* 2002;122(4 Suppl. 1):A-315.
- [115] Johanson JF, Drossman DA, Panas R, et al. Clinical trial: phase 2 study of lubiprostone for irritable bowel syndrome with constipation. *Aliment Pharmacol Ther* 2008;27:685–96.
- [116] Drossman DA, Chey WD, Johanson JF, et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome—results of two randomized, placebo-controlled studies. *Aliment Pharmacol Ther* 2009;29:329–41.
- [117] Currie MG, Fok KF, Kato J, et al. Guanylin: an endogenous activator of intestinal guanylate cyclase. *Proc Natl Acad Sci USA* 1992;89:947–51.
- [118] Hamra FK, Forte LR, Eber SL, et al. Uroguanylin: structure and activity of a second endogenous peptide that stimulates intestinal guanylate cyclase. *Proc Natl Acad Sci USA* 1993;90:10464–8.
- [119] Giannella RA. *Escherichia coli* heat-stable enterotoxins, guanylin, and their receptors: what are they and what do they do? *J Lab Clin Med* 1995;125:173–81.
- [120] Forte LR. Guanylin regulatory peptides: structures, biological activities mediated by cyclic GMP and pathobiology. *Regul Pept* 1999;81:25–39.
- [121] Currie MG, Kurtz C, Mahajan-Miklos S, et al. Effects of single dose administration of MD-1100 on safety, tolerability, exposure, and stool consistency in healthy subjects. *Am J Gastroenterol* 2005;100:5-328 [abstract].
- [122] Johnston JM, Kurtz CB, Drossman DA, et al. Pilot study on the effect of linaclotide in patients with chronic constipation. *Am J Gastroenterol* 2009;104:125–32.

- [123] Mangel AW, Chaturvedi P. Evaluation of crofelemer in the treatment of diarrhea-predominant irritable bowel syndrome patients. *Digestion* 2008;78:180–6.
- [124] Verdu EF, Collins SM. Irritable bowel syndrome and probiotics: from rationale to clinical use. *Curr Opin Gastroenterol* 2005;21:697–701.
- [125] Moayyedi P, Ford AC, Talley NJ, et al. The efficacy of probiotics in the therapy of irritable bowel syndrome: a systematic review. *Gut* 2008 [online first, published on December 17].
- [126] Pimentel M, Chow EJ, Lin HC. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome. A double-blind, randomized, placebo-controlled study. *Am J Gastroenterol* 2003;98:412–9.
- [127] Pimentel M, Park S, Mirocha J, et al. The effect of a nonabsorbed oral antibiotic (rifaximin) on the symptoms of the irritable bowel syndrome: a randomized trial. *Ann Intern Med* 2006;145:557–63.
- [128] Lembo A, Zakko SF, Ferreira NL, et al. Rifaximin for treatment of diarrhea-associated irritable bowel syndrome: short-term treatment leading to long-term sustained response. *Gastroenterology* 2008;134:A-545 [abstract].
- [129] Leri O, Tubili S, De Rosa FG, et al. Management of diarrhoeic type of irritable bowel syndrome with exclusion diet and disodium cromoglycate. *Inflammopharmacology* 1997;5:153–8.
- [130] Grazioli I, Melzi G, Balsamo V, et al. Food intolerance and irritable bowel syndrome of childhood: clinical efficacy of oral sodium cromoglycate and elimination diet. *Minerva Pediatr* 1993;45:253–8.
- [131] Miehle S, Madisch A, Bethke B, et al. Oral budesonide for maintenance treatment of collagenous colitis: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2008;135:1510–6.
- [132] Bonderup OK, Hansen JB, Teglbjaerg PS, et al. Long-term budesonide treatment of collagenous colitis: a randomised, double-blind, placebo-controlled trial. *Gut* 2009;58:68–72.
- [133] Chande N, Macdonald JK, McDonald JW. Interventions for treating microscopic colitis: a Cochrane inflammatory bowel disease and functional bowel disorders review group systematic review of randomized trials. *Am J Gastroenterol* 2009;104:235–41.
- [134] Barbara G, Cremon C, Gargano L, et al. Mesalazine treatment for intestinal immune activation in patient with irritable bowel syndrome: a randomized controlled pilot trial. *Gastroenterology* 2008;134:A-546 [abstract].