REVIEW ARTICLE

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Review on Various Approaches to Treat Irritable Bowel Syndrome and Superiority of Combinations Over the Existing Therapy

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Abstracts: Current paper describes potential therapies available to treat Irritable bowel syndrome is a brain gut disorder characterized most commonly by cramping, abdominal pain, bloating, constipation, and diarrhea which is the most common and fatal disease. 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.

INTRODUCTION

Irritable bowel syndrome is a brain gut disorder characterized most commonly by cramping, abdominal pain, bloating, constipation, and diarrhea. IBS causes a great deal of discomfort and distress, but it does not permanently harm the intestines and does not lead to a serious disease, such as cancer. 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. The increased release of serotonin in the circulation especially in the IBS-D group and increased serine proteases (derived from mast cells) in stool of patients with IBS provide evidence for the potential role of neurotransmitters or chemical mediators such as proteases in the disorder. [1,2]

There are Three Types of IBS

- IBS with Constipation: This comes with stomach pain and discomfort, bloating, abnormally delayed or infrequent bowel movement, or lumpy/hard stool.
- IBS with Diarrhea: This comes with stomach pain and discomfort, an urgent need to move your bowels, abnormally frequent bowel movements, or loose/watery stool.
- IBS with alternating constipation and diarrhea [3,6]

Background of IBS

Irritable bowel syndrome is a functional gastrointestinal disorder affecting up to 3–15% of the general population in western countries. Most people can control their symptoms with diet, stress management, and prescribed medications. For some people, however, IBS can be disabling. They may be unable to work, attend social events, or even travel short distances. It occurs more often in women than in men, and it begins before the age of 35 in about 50 percent of people. [4,5]

Approaches to Treat IBS

This article reviews recent and novel approaches in IBS therapy (Table 1, Figure 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.

SEROTONERGIC SYSTEM

Serotonin (5-hydroxytryptamine) is an important neurotransmitter of the enteric nervous system (ENS), the peristaltic reflex (chiefly 5-HT_4-receptor), the brain–gut axis and vagal and visceral afferent cell bodies or pathways, chiefly 5-HT_3-receptors [16,17]. 5-HT plays a pivotal role in the modulation of multiple gut functions such as motility, sensation, blood flow and secretion [18,19]. In humans, the highest level of specific binding has been found in the amygdalae, which are integral to the emotional responses to visceral stimulation.

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-HT_3 antagonists and 5-HT_4 agonists have demonstrated efficacy and effectiveness in the treatment of multiple or global symptoms of IBS. The prototype medications were alosetron and tegaserod.

5-HT_3-receptor Antagonists

5-HT_3-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, reviewed in an updated meta-analysis [25]. 5-HT_3

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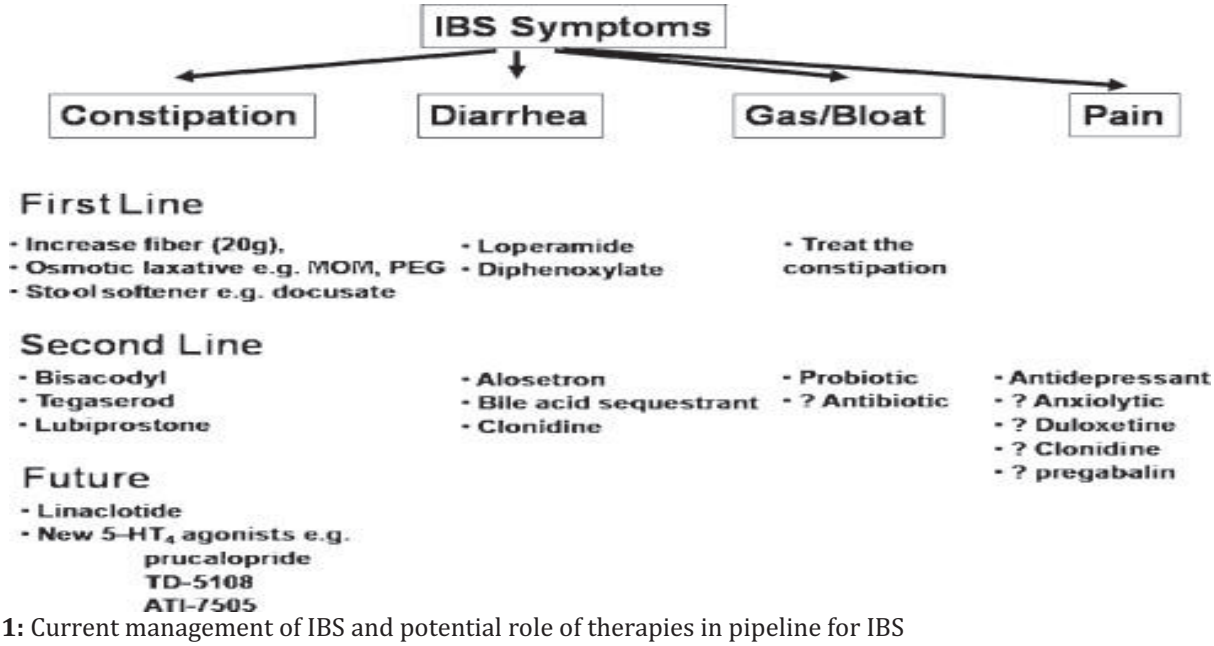

Figure 1: Current management of IBS and potential role of therapies in pipeline for IBS

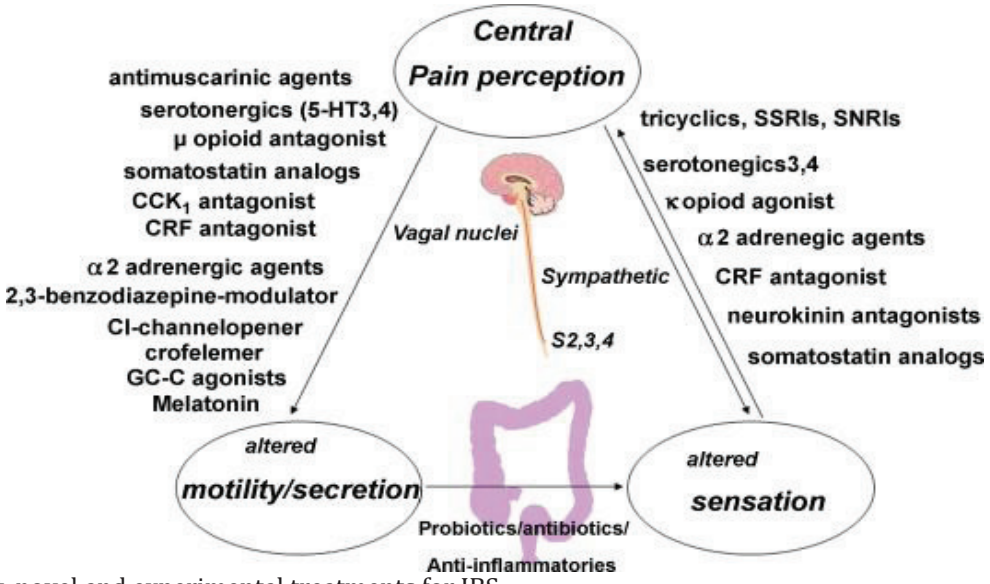

Figure 2: Current, novel and experimental treatments for IBS.

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-HT_3 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.

5HT_3-receptor Agonists

The 5-HT_3 agonist, *MKC-733, also named DDP733 and pumosetrag* in the literature, stimulated fasting antroduodenal migrating motor complex activity and accelerated small intestinal transit [27]. A preliminary report of a phase 2 a 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].

5HT_4-receptor Agonists

5HT_4-receptor agonists generally accelerate small bowel and colonic transit.

Tegaserod: Tegaserod is a selective partial agonist of the 5-HT_4-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

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-HT4-agonists	Prucalopride, ATI-7505 TD-5108	Prokinetic,secretagogue	IBS-C FC
	5-HT3-antagonist	Alosetron,cilansetron	Decrease motility and secretion, increase compliance decrease pain	IBS-D FD
	5-HT3-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 M3-antagonists	Zamifenacin, darifenacin, Clidinium bromide	Reduce colonic motility Decrease Pain?	IBS-D FD
Î±-Adrenergic system	Î±2-agonist	Clonidine	Increases compliance,decreases tone, and sensation	IBS-D FAP
Opioid system	Peripheral Î¼-opioid antagonists	Alvimopan, methylnaltrexone	Prokinetic Increase laxation	IBS-C FC, OIC
	Îº-Opioid-agonist	Asimadoline	Decrease sensation	IBS ,FAP
Corticoids	CRH antagonist CRF1 antagonist	Î±hCRH, pexacerfont	Reduce stimulation induced motility and sensitivity	IBS-D FAP
Benzodiazepine	2<comma>3-benzodiazepine receptor	Dexofisopam , Chlordiazepoxide	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 (NK1) and motility (NK2)	IBS FAP
	NK antagonist 3	Talnetant	Accelerates transit, increases secretion	
Chloride channel	Activator	Lubiprostone	Decreases stool consistency, increases stool frequency	IBS-C FC
Guanylate cyclase-c	Agonist		Overall symptom relief	IBS-C FC
Antibiotics	Neomycin, rifaximin	Linaclotide	Decrease bloating and pain, slow colon transit	IBS-C FC
Probiotics	Bacterial flora	VSL#3, Lactobacilli bifidobacteriae		IBS bloating flatulence
Proton Pump inhibitor with Antidepressant & anticholinergic	-----	Pantoprazole sodium , Chlordiazepoxide , clidinium bromide	Reduce acid secretion , Reduces stool frequency, Increases stool consistency, Reduce colonic motility Decrease Pain	IBS bloating flatulence

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.

Newer 5-HT$_4$-receptor Agonists

ATI-7505 is a novel, potent agonist of the 5-HT$_4$-receptor and is chemically related to the 5-HT$_4$-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-HT$_4$-receptor agonist that has been extensively studied, including pharmacodynamics and

Table 2: Comparative Analysis of Pantoprazole with other PPI's

Proton Pump Inhibitor	Bioavailability (%)	Cmax (µmol/L)	Duration of Effect (Hrs)	Protein Binding (%)	Drug Interaction
Pantoprazole	77	5.73 5 (40 mg)	24-72	98	None
Omeprazole	30-40	0.70 5 (20 mg)	24-72	95	Diazepam, Warfarin, Digoxin, Phenytoin, Ketoconazole
Lansoprazole	77-80	2.25 5 (30 mg)	24	97	Ketoconazol Theophylline
Rabeprazole	52	0.48 6 (20 mg)	24	96	None
Esomeprazole	64	1.86 2 (20 mg) 2.38 2 (40 mg)	24-72	97	None

Table 3: Comparison of Pantoprazole Vs Omeprazole

Pantoprazole	Omeprazole
It has least drug interaction	More drug interaction because has greater interaction with cytochrome system. It has drug interaction with Diazepam, Phenytoin , Warfarin.
Bioavailability is 77%	Bioavailability is 30-40%
Pantoprazole is a category-B drug.	Pantoprazole is a category-C drug
Can be used for maintenance therapy in duodenal ulcer.	Can not be used for maintenance therapy in duodenal ulcer

Table 4: Comparison of Pantoprazole Vs Lansoprazole

Pantoprazole	Lansoprazole
It has least drug interaction	It has drug interaction with Ketoconazole, Theophylline.
Duration of action is 24-72 hr.	Duration of action 24 hr.
It does not have drug food interaction	It has drug food interaction

Table 5: Comparison Of Pantoprazole Vs Rabeprazole

Pantoprazole	Rabeprazole
Duration of action is 24-72 hr.	Duration of action 24 hr.
Bioavailability is 77%	Bioavailability is 54%
Protein binding of Pantoprazole is 97%	Protein binding ofRabeprazole is 95%
Mechanism of action is to bind both Cysteine 813 & 833 Cysteine	It binds to Cystein 813 and not to Cysteine 822

large clinical trials in patients with severe chronic constipation [31,32,33,34]. The medication has greater selectivity (~150-fold) for 5-HT_4-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-HT_4-receptors with high intrinsic activity that displays preferential binding to the 5-HT_4-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].

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,).

There may also be racial or ethnic differences, as efficacy appears greatest in trials conducted in Iran. 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. 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 and one in German patients. Intriguingly, the most efficacious treatment attributed to a tricyclic agent was reported with a trial of amitryptiline, 10 mg, that did not significantly affect abdominal pain, bloating or diarrhoea, relative to placebo. Similarly, the trial of the SSRI, fluoxetine 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. [40,41,42]

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. 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, otilinium, 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 , 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. Amongst M_3-selective antagonists, darifenacin (used to treat overactive bladder) is associated with constipation, and zamifenacin significantly reduced colonic motility without other anticholinergic effects in 36 IBS patients. [43,44]

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, 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, 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.[45,46,47]

GABA-ERGIC AGENTS AND α2δ 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.

Preclinical studies suggest that the α2δ 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 . Studies of GABA-ergic agents and α2δ ligands on clinical outcomes in IBS are not available. [48]

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. κ-Opioid receptors are involved in visceral perception.[49]

κ-Opioid Agonist

Asimadoline: The κ-opioid agonist, asimadoline, 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. 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; however, a recent trial using daily administration of asimadoline demonstrated efficacy in patients with IBS-D and IBS with mixed bowel habits (IBS-M). [50]

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. It reverses the peripheral effects of narcotics without influencing the pain relief desired by concomitant opioid administration. A pharmacodynamic study in healthy volunteers 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.

Oral *naltrexone* does not accelerate colonic transit, but oral methylnaltrexone accelerated gut transit in opiate-naïve controls and it reversed the prolongation of orocecal transit induced by long-term methadone. 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. [51,52]

CRF RECEPTOR ANTAGONISTS

Corticotropin releasing factor (CRF) is a key mediator of stress response in the brain gut axis. Two CRF receptor subtypes have been cloned: CRF_1 and CRF_2. In animals, stress activation of the CRF receptors alters gastrointestinal motility, effects that can be blocked with selective CRF_1-receptor antagonists (*antalarmin*) and the nonselective CRF receptor antagonist *α-helical* CRF_{9-41} (*αhCRF*). The increased colonic motility response to rectal electrical stimulation in IBS patients was significantly suppressed after αhCRF infusion. However, the CRF_1 antagonist, *pexacerafont*, was not effective in normalizing colonic transit or bowel function in patients with diarrhoea-predominant IBS. The role of CRF modulation requires further study. [53,54]

3-BENZODIAZAPINE RECEPTOR MODULATOR

Dextofisopam 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. 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. 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). [55,56]

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, possibly by blocking nicotinic channels or Ca^{2+} activated K^+ channels. Two small studies of the effects of melatonin in IBS patients 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. [57,58]

CCK_1 ANTAGONISTS

Cholecystokinin (CCK), 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. The effects of CCK are mediated by two distinct receptors, CCK_1 and CCK_2 and , which are located predominantly in the periphery and the central nervous system respectively. The CCK_1 (also called CCK_A) receptors are present in gastrointestinal tract smooth muscles and vagal afferents. Blockade of CCK_1 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. [59]

Loxiglumide and *Dexloxiglumide*: Loxiglumide is a highly specific, competitive antagonist of the CCK_1 receptor. Earlier pharmacodynamic and clinical studies suggested that loxiglumide might improve constipation. A 12-week, phase II trial of 200 mg/day dexloxiglumide 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. The latter result was consistent with a pharmacodynamics study in IBS-C 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. Further studies with this mediation are awaited. [60]

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 and and normalizes visceral perception and discomfort thresholds in IBS patients without changing rectal compliance and. There are no clinical trials with octreotide in IBS. [61]

NEUROKININ-ANTAGONISTS

NK_1-receptors play a role in nociception, whereas NK_2 receptors have a greater influence on smooth muscle contractility and of NK_2-antagonists on gut motility. In a small pharmacodynamic study of IBS patients, the NK_1-receptor antagonist, *ezlozipant*, reduced the emotional response to rectosigmoid distension but did not significantly decrease rectal sensitivity. In healthy controls, the NK_2-receptor antagonist, *nepadutant*, 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 NK_3 antagonist, *talnetant*, was tested in pharmacodynamics and clinical trials, and proved ineffective. [62,63]

CHLORIDE CHANNEL MODULATORS

Cl^- Channel (ClC_2) Opener

Intestinal Cl^- secretion is critical for intestinal fluid and electrolyte transport. In the gastrointestinal tract, chloride channels type 2, ClC_2, has been found in gastric parietal cells, small intestinal and colonic epithelia. *Lubiprostone* is a prostone that acts as a selective ClC_2 activator and increases intestinal water secretion. In a pharmacodynamic study, lubiprostone was shown to accelerate small bowel and colonic transit time in healthy volunteers. In several clinical trials, lubiprostone, 24 µg b.i.d., had positive effects on stool consistency, frequency and straining, and was safe and effective for treating constipation,. 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. Side effects of lubiprostone include diarrhoea and nausea that is usually mild and transient. In January 2006, the FDA approved lubiprostone. [64]

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. In animal and early human safety studies, linaclotide has been observed to increase stool frequency, decrease stool consistency and decrease visceral pain. A phase IIA pilot, randomised, controlled study shows efficacy of this drug in treatment of chronic constipation. Therefore, the drug seems to be promising for the treatment of IBS-C and chronic constipation. [65]

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, 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. [66]

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. A recent meta-analysis 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. [67]

ANTIBIOTICS

The role of bacterial overgrowth of the small intestine (SIBO) in IBS is controversial. A placebo-controlled study 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 and a preliminary report from Lembo *et al*.. Although there are many unanswered questions, regarding long-term effects, and frequency of retreatment, some patients may benefit from rifaximin treatment. [68]

IMMUNE MODULATORS

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 algesia in experimental studies. Sodium cromoglycate alone or in association with dietary exclusion of suspected allergens has been tested in trials conducted in IBS-D and childhood IBS. [69]

ASA Compounds or Budesonide

Given the efficacy of *budesonide* in microscopic or collagenous colitis and 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*. 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. These interesting and provocative data suggest that 5-ASA compounds deserve further study. [70]

NEW COMBINATION THERAPIES AVAILABLE TO TREAT IBS

Pantoprazole Sodium, Clidinium bromide and Chlordiazepoxidem in their combined Capsule dosage form

Literature survey reveled that the newer approaches to treat IBS is the combination of Pantoprazole sodium, clidinium bromide and chlordiazepoxide. The study was done to assesse the IBS efficacy and safety of a combination of 20 mg of Pantoprazole sodium, 2.5mg of clidinium bromide and 5mg of chlordiazepoxide in comparison to Librax(®) (Clidinium bromide and chlordiazepoxide) in patients with acute uncomplicated IBS bloating flatulence. Results of completed the trial in Pantoprazole Sod. Clidinium Bromide, Chlordiazepoxide group while in Librax(®) completed the trial. Less side effects was noted in combination of Pantoprazole Sod. Chlordiazepoxide, clidinium bromide group while its Librax (®) appear side effects as upset stomach, drowsiness, weakness or tiredness, excitement, sleeplessness, dry mouth, heartburn, bloated feeling, eyes more sensitive to sunlight than usual, taste changes, changes in appetite. The available data support the evaluation of drug combination in a larger population as fixed dose combination.

ULRAX [Brand Name]

Composition

Pantoprazole -20mg
Chlordiazepoxide- 5 mg
Clidinium Bromide-2.5 mg

Pantoprazole

Benzimidazole derivative blocks the proton pump by reacting with (H+/K+)-ATPase enzyme by causing it's inhibition of action resulting long lasting inhibition of gastric acid secretion.

Proton Pump Inhibitor

Proton Pump Inhibitors binds Proton Pump (H+K+(-ATPase enzyme) that results in irreversible inhibition of acid secretion by the proton pump.

Their duration of action is much longer because of their unique mechanism of action

- PPl only effective when proton pump is actively making acid.
- Proton pump is lost after PPI interaction.
- Proton pumps are reactivated after pumps are renewed.
- Peak serum level post dose 1.5 hrs.
- PPI must be closed before a meal for maximal efficacy.

Indications

- Peptic Ulcers
- Gastric Ulcers
- Duodenal Ulcers
- NSAID Induced gastritis
- Helicobacter Pylori
- Reflux Esophagitis
- Zollinger Elison's Syndrome

Different Proton Pump Inhibitors Available in the Market

- Omeprazole
- Lansoprazole
- Pantoprozole
- Rabeprazole
- Esomeprazole

Dose

- 40 mg once daily for 6-8 week.
- 20 mg once daily for maintenance therapy for healed esophagitis low grade reflux esophagitis.
- Do not break, crush or chewtablets.

Advantages

- Less or no drug interaction.
- For H Pylori eradication.
- FDA approved (Feb 2, 2000)
- No interaction with antacids

Drug Interactions

Not significant, Advise patient to avoid alcohol, products containing NSAIDs and foods that may cause an increase in GI irritation.

Precautions

- Hepatic impairment
- Pregnancy

Chlordiazepoxide

Thus chlordiazepoxide is an anxiolytic & act as an agonist at specific benzodiazepine receptor, located on the membrane of GABA neuron which are inhibitory in nervous system, Chlordiazepoxide and GABA forms complex with chloride ion leads to stimulation of benzodiazepine receptors and potentiate the action of GABA which in turn controls the flow of chloride ions across neuron membrane, thereby relieves the patient from anxiety.

Pharmacokinetics

Peak Plasma Level -0.5 – 4 hrs.
Protein Binding -96%
Elimination -5 – 30 hrs.

Advantage over other similar drugs

- Produces a smooth long lasting effect.
- Preferred in chronic anxiety state.

Dose

15 – 100 (mg/day)

Uses

Treatment of moderate to serve depression associated with moderate to severe anxiety. Symptoms which respond in the first week of treatment are:

- Insomnia
- Feeling of guilt
- Agitation
- Psychic and somatic anxiety.
- Anorexia

Muscle pain

Alcohol withdrawal syndrome

Side effects

Drowsiness

CNS depression with concomitant alcohol intake

Contraindications

Hypersensitivity to either benzodiazepine or tricyclic antidepressants.

- During acute recovery phase following myocardial infraction.

Precautions

- Use cautions while driving or performing other tasks requiring alertness.
- Avoid alcohol and other CNS depressants

Clidinium Bromide

It is an antispasmodic agent, Antispasmodic agents relax smooth muscle in the gut and reduce propulsive contractions, decreasing postprandial abdominal pain, gas, bloating, and fecal urgency. It works through anticholinergic or antimuscarinic properties and may be used in an as-needed or in an anticipatory fashion.

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.Combination therapy more effective and safety rather than single drug therapy.

REFERENCES AND NOTES

1. D.A. Drossman, Z. Li, E. Andruzzi *et al.*: U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact Dig Dis Sci, 38 (1993), pp. 1569–1580.
2. F. Cremonini, N.J. Talley: Irritable bowel syndrome: epidemiology, natural history, health care seeking and emerging risk factors Gastroenterol Clin North Am, 34:189–204, 2005.
3. D.A. Drossman, M. Camilleri, E.A. Mayer *et al.* AGA technical review on irritable bowel syndrome Gastroenterology, 123:2108–2131, 2002.
4. M. Camilleri Mechanisms in IBS: something old, something new, something borrowed Neurogastroenterol Motil, 17:311–316, 2005.
5. S.P. Dunlop, N.S. Coleman, E. Blackshaw *et al.* Abnormalities of 5-hydroxytryptamine metabolism in irritable bowel syndrome Clin Gastroenterol Hepatol, 3:349–357, 2005.
6. C.P. Bearcroft, D. Perrett, M.J. Farthing Postprandial plasma 5-hydroxytryptamine in diarrhoea predominant irritable bowel syndrome: a pilot study Gut, 42:42–46, 1998.
7. L.A. Houghton, W. Atkinson, R.P. Whitaker *et al.:* Increased platelet depleted plasma 5-hydroxytryptamine concentration following meal ingestion in symptomatic female subjects with diarrhoea predominant irritable bowel syndrome Gut, 52:663–670, 2003.
8. R. Roka, A. Rosztoczy, M. Leveque *et al.*A pilot study of fecal serine-protease activity: a pathophysiological factor in diarrhea-predominant irritable bowel syndrome Clin Gastroenterol Hepatol, 5:550–555, 2007.
9. R. Borman Serotonergic, modulation and irritable bowel syndrome ,Expert Opin Emerg Drugs, 6:57–68, 2001.
10. R.C. Spiller,Postinfectious irritable bowel syndrome,Gastroenterology, 124:1662–1671, 2003.
11. R.C. Spiller, D. Jenkins, J.P. Thornley *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, 47:804–811, 2000.
12. R.C. Spiller,Infection, immune function, and functional gut disorders ,Clin Gastroenterol Hepatol, 2:445–455, 2004.
13. G. Barbara, V. Stanghellini, R. De Giorgio *et al.,*Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome,Gastroenterology, 126:693–702, 2004.
14. L. O'Mahony, J. McCarthy, P. Kelly *et al.,*Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles,Gastroenterology, 128:541–551, 2005.
15. J. Aerssens, M. Camilleri, W. Talloen *et al.,*Alterations in mucosal immunity identified in the colon of patients with irritable bowel syndrome,Clin Gastroenterol Hepatol, 6:194–205, 2008.
16. M.D. Gershon,Review article: roles played by 5-hydroxytryptamine in the physiology of the bowel,Aliment Pharmacol Ther, 13 (Suppl. 2) pp. 15–30, 1999.
17. M.D. Gershon,Review article: serotonin receptors and transporters—roles in normal and abnormal gastrointestinal motility,Aliment Pharmacol Ther, 20 (Suppl. 7) pp. 3–14, 2004.
18. G.A. Hicks, J.R. Coldwell, M. Schindler *et al.,*Excitation of rat colonic afferent fibres by 5-HT(3) receptors,J Physiol, 544 (Pt 3) (2002), pp. 861–869
19. M. Camilleri,Serotonin in the gastrointestinal tract,Curr Opin Endocrinol Diabetes Obes, 16 (2009), pp. 53–59
20. M.D. Gershon,Plasticity in serotonin control mechanisms in the gut,Curr Opin Pharmacol, 3 (2003), pp. 600–607
21. M.D. Coates, C.R. Mahoney, D.R. Linden *et al.,*Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and irritable bowel syndrome,Gastroenterology, 126 (2004), pp. 1657–1664
22. C. Andrews, M. Camilleri, A.E. Bharucha *et al.,*Serotonin-transporter (SERT) polymorphism genotype and SERT expression in mucosal biopsies of patients with irritable bowel syndrome,Gastroenterology, 130 (2006), p. A24 [abstract]
23. M.D. Gunput,Review article: clinical pharmacology of alosetron,Aliment Pharmacol Ther, 13 (Suppl. 2) (1999), pp. 70–76
24. E.A. Mayer, S. Berman, S.W. Derbyshire *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, 16 (2002), pp. 1357–1366

25. V. Andresen, V.M. Montori, J. Keller *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 trialsClin Gastroenterol Hepatol, 6 (2008), pp. 545–555
26. H.B. El-Serag, K. Olden, D. Bjorkman,Health-related quality of life among persons with irritable bowel syndrome: a systematic review,Aliment Pharmacol Ther, 16 (2002), pp. 1171–1185
27. N.S. Coleman, L. Marciani, E. Blackshaw *et al.,*Effect of a novel 5-HT3 receptor agonist MKC-733 on upper gastrointestinal motility in humans,Aliment Pharmacol Ther, 18 (2003), pp. 1039–1048
28. W.G. Paterson, D. Ford, S.C. Ganguli *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, 134 (2008), p. A546-A547 [abstract]
29. B.W. Evans, W.K. Clark, D.J. Moore *et al.*Tegaserod for the treatment of irritable bowel syndrome and chronic constipation Cochrane Database Syst Rev (2007), p. CD003960
30. M. Camilleri, M.I. Vazquez-Roque, D. Burton *et al.*Pharmacodynamic effects of a novel prokinetic 5-HT receptor agonist, ATI-7505, in humans Neurogastroenterol Motil, 19 (2007), pp. 30–38
31. E.P. Bouras, M. Camilleri, D.D. Burton *et al.*Prucalopride accelerates gastrointestinal and colonic transit in patients with constipation without a rectal evacuation disorder Gastroenterology, 120 (2001), pp. 354–360
32. M. Camilleri, R. Kerstens, A. Rykx *et al.*A placebo-controlled trial of prucalopride for severe chronic constipation N Engl J Med, 358 (2008), pp. 2344–2354
33. J. Tack, M. Van Outryve, G. Beyens *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. E.M. Quigley, L. Vandeplassche, R. Kerstens *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, 29 (2009), pp. 315–328
35. M. Camilleri, R. Kerstens, G. Beyens *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, 136 (Suppl. 1) (2009), p. 240
36. J.A. Smith, D.T. Beattie, D. Marquess *et al.*The in vitro pharmacological profile of TD-5108, a selective 5-HT(4) receptor agonist with high intrinsic activity,Naunyn Schmiedebergs Arch Pharmacol, 378 (2008), pp. 125–137
37. D.T. Beattie, S.R. Armstrong, J.P. Shaw *et al.*The in vivo gastrointestinal activity of TD-5108, a selective 5-HT(4) receptor agonist with high intrinsic activity,Naunyn Schmiedebergs Arch Pharmacol, 378 (2008), pp. 139–147
38. M. Camilleri, M. Manini, S. McKinzie *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, 20 (Suppl. 2) (2008), p. 6 [abstract]
39. M.R. Goldberg, Y.-P. Li, K. Pitzer *et al.*TD-5108, a selective 5-HT_4 agonist, is consistently better than placebo regardless of response definition in patients with chronic constipation ,Gastroenterology, 134 (2008), p. A 545
40. D.A. Gorard, G.W. Libby, M.J. Farthing,Influence of antidepressants on whole gut and orocaecal transit times in health and irritable bowel syndrome,Aliment Pharmacol Ther, 8 (1994), pp. 159–166
41. J. Tack ,A placebo controlled trial of buspirone, a fundus relaxing drug, in functional dyspepsia: effect on symptoms and gastric sensory and motor functions,Gastroenterology, 116 (2000), p. G1423
42. H. Vahedi, S. Merat, A. Rashidioon *et al.*Effect of fluoxetine in patients with pain and constipation-predominant irritable bowel syndrome: a double-blind randomized-controlled study,Aliment Pharmacol Ther, 22 (2005), pp. 381–385
43. R.K. Goyal,Muscarinic receptor subtypes. Physiology and clinical implications,N Engl J Med, 321 (1989), pp. 1022–1029
44. R.M. Eglen,Muscarinic receptors and gastrointestinal tract smooth muscle function,Life Sci, 68 (2001), pp. 2573–2578
45. A.E. Bharucha, M. Camilleri, A.R. Zinsmeister *et al.,*Adrenergic modulation of human colonic motor and sensory function,Am J Physiol, 273 (5 Pt 1) (1997), pp. G997–1006
46. A. Malcolm, S.F. Phillips, M. Camilleri *et al.,*Pharmacological modulation of rectal tone alters perception of distention in humans,Am J Gastroenterol, 92 (1997), pp. 2073–2079
47. A. Malcolm, M. Camilleri, L. Kost *et al.,*Towards identifying optimal doses for alpha-2 adrenergic modulation of colonic and rectal motor and sensory function,Aliment Pharmacol Ther, 14 (2000), pp. 783–793
48. L.A. Houghton, C. Fell, P.J. Whorwell *et al.*Effect of a second-generation alpha2delta ligand (pregabalin) on visceral sensation in hypersensitive patients with irritable bowel syndrome,Gut, 56 (2007), pp. 1218–1225
49. T.J. Borody, E.M. Quigley, S.F. Phillips *et al.*Effects of morphine and atropine on motility and transit in the human ileum,Gastroenterology, 89 (1985), pp. 562–570
50. S. Delgado-Aros, H.J. Chial, F. Cremonini *et al.,*Effects of asimadoline, a kappa-opioid agonist, on satiation and postprandial symptoms in health,Aliment Pharmacol Ther, 18 (2003), pp. 507–514
51. C.P. Delaney, J.L. Weese, N.H. Hyman *et al.,*Phase III trial of alvimopan, a novel, peripherally acting, mu opioid antagonist, for postoperative ileus after major abdominal surgery,Dis Colon Rectum, 48 (2005), pp. 1114–1125
52. M.J. Owens, C.B. Nemeroff,Physiology and pharmacology of corticotropin-releasing factor,Pharmacol Rev, 43 (1991), pp. 425–473
53. C.S. Yuan, J.F. Foss, M. O'Connor *et al.,*Methylnaltrexone for reversal of constipation due to chronic methadone use: a randomized controlled trial,J Am Med Assoc, 283 (2000), pp. 367–372
54. S.R. Sweetser, S.J. Linker Nord, D.D. Burton *et al.,*Effects of a novel corticotrophin 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, 134 (2008), p. A 548
55. S.M. Leventer, R.F. Kucharik, J.C. Keogh *et al.,*The potential of dextofisopam for treatment of irritable bowel syndrome and inflammatory bowel disease,Am J Gastroenterol, 99 (2004), p. S 279
56. S.M. Leventer, K. Raudibaugh, C.L. Frissora *et al.,*Clinical trial: dextofisopam in the treatment of patients with diarrhoea-predominant or alternating irritable bowel syndrome,Aliment Pharmacol Ther, 27 (2008), pp. 197–206
57. W.Z. Lu, K.A. Gwee, S. Moochhalla *et al.,*Melatonin improves bowel symptoms in female patients with irritable bowel

syndrome: a double-blind placebo-controlled study,Aliment Pharmacol Ther, 22 (2005), pp. 927–934
58. G.H. Song, P.H. Leng, K.A. Gwee *et al.*Melatonin improves abdominal pain in irritable bowel syndrome patients who have sleep disturbances: a randomised, double blind, placebo controlled study,Gut, 54 (2005), pp. 1402–1407
59. S.A. Wank,Cholecystokinin receptors,Am J Physiol, 269 (5 Pt 1) (1995), pp. G628–G646
60. B.M. Meyer, B.A. Werth, C. Beglinger *et al.,*Role of cholecystokinin in regulation of gastrointestinal motor functions,Lancet, 2 (1989), pp. 12–15
61. M.R. von der Ohe, M. Camilleri, G.M. Thomforde *et al.,*Differential regional effects of octreotide on human gastrointestinal motor function,Gut, 36 (1995), pp. 743–748
62. L.A. Houghton, F. Cremonini, M. Camilleri *et al.,*Effect of the NK3 receptor antagonist, talnetant, on rectal sensory function and compliance in healthy humans,Neurogastroenterol Motil, 19 (2007), pp. 732–743
63. G.E. Dukes, O.E. Dewit, G.J. Sanger *et al.,*Lack of effect of the NK_3 receptor antagonist, talnetant SB223242 on symptoms of IBS: results of 2 randomized, double-blind, placebo-controlled, dose-ranging trials,Gastroenterology, 132 (2007), p. A60
64. Lubiprostone: RU 0211, SPI 0211,Drugs R D, 6 (2005), pp. 245–258
65. M.G. Currie, K.F. Fok, J. Kato *et al.,*Guanylin: an endogenous activator of intestinal guanylate cyclase,Proc Natl Acad Sci USA, 89 (1992), pp. 947–951
66. A.W. Mangel, P. Chaturvedi,Evaluation of crofelemer in the treatment of diarrhea-predominant irritable bowel syndrome patients,Digestion, 78 (2008), pp. 180–186
67. E.F. Verdu, S.M. Collins,Irritable bowel syndrome and probiotics: from rationale to clinical use,Curr Opin Gastroenterol, 21 (2005), pp. 697–701
68. M. Pimentel, E.J. Chow, H.C. Lin,Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome. A double-blind, randomized, placebo-controlled study,Am J Gastroenterol, 98 (2003), pp. 412–419
69. O. Leri, S. Tubili, F.G. De Rosa *et al.,*Management of diarrhoeic type of irritable bowel syndrome with exclusion diet and disodium cromoglycate,Inflammo-pharmacology, 5 (1997), pp. 153–158
70. S. Miehlke, A. Madisch, B. Bethke *et al.,*Oral budesonide for maintenance treatment of collagenous colitis: a randomized, double-blind, placebo-controlled trial,Gastroenterology, 135 (2008), pp. 1510–1516.

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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