LEADING ARTICLE

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Irritable Bowel Syndrome
Recent and Novel Therapeutic Approaches

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Abstract

Irritable bowel syndrome (IBS) is a highly prevalent 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 IBS is considered to be multifactorial, involving disturbances of the brain-gut-axis: IBS has been associated with abnormal gastrointestinal motor functions, visceral hypersensitivity, psychosocial factors, autonomic dysfunction and mucosal inflammation. Traditional IBS therapy is mainly symptom oriented and often unsatisfactory. Hence, there is a need for new treatment strategies. Increasing knowledge of brain-gut physiology, mechanisms, and neurotransmitters and receptors involved in gastrointestinal motor and sensory function have led to the development of several new therapeutic approaches. This article provides a systematic overview of recently approved or novel medications that show promise for the treatment of IBS; classification is based on the physiological systems targeted by the medication. The article includes agents acting on the serotonin receptor or serotonin transporter system, novel selective anticholinergics, α-adrenergic agonists, opioid agents, cholecystokinin antagonists, neurokinin antagonists, somatostatin receptor agonists, neurotrophin-3, corticotropin releasing factor antagonists, chloride channel activators, guanylate cyclase-c agonists, melatonin and atypical benzodiazepines. Finally, the role of probiotics and antibacterials in the treatment of IBS is summarised.

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders, with a prevalence estimated at 3–15% in the general population in Western countries.[1,2] IBS is characterised by abdominal pain and discomfort in association with altered bowel habits; symptoms cannot be explained by any structural abnormalities using current standard diagnostic tests.[3] In addition to abdominal pain, diarrhoea or constipation, typical symptoms include bloating, flatulence, stool urgency or straining, and the feeling of incomplete evacuation.[3] Characteristic symptom patterns, as in the IBS consensus 'Rome II' criteria and in absence of alarm features or structural gut disease, allow a positive diagnosis of IBS.[4] Patients may be classified into symptom subgroups as diarrhoea-predominant IBS (D-IBS), constipation-predominant IBS (C-IBS), or IBS with alternating bowel movements. The pathophysiology of IBS is still not well understood but is most probably multifactorial. Several factors – such as motor and sensory dysfunction, neuroimmune mechanisms, psychological factors and changes in the intraluminal milieu – appear to play a role (table I).[3,5] The increased release of

Table I. Pathophysiology of irritable bowel syndrome (IBS) [reproduced from Camilleri,[10] with permission from the American Gastroenterological Association]

A biopsychosocial disorder
Altered motility and enhanced visceral perception
50% of IBS patients have psychological symptoms at time of presentation
The role of physical and sexual abuse in the development of IBS is controversial
Up to one-third (range 7–31%) of IBS presenters recall an antecedent gastroenteritis
Proposed mechanisms contributing to IBS[a]
Abnormal motility
Heightened visceral perception: peripheral or central
Psychological distress
Intraluminal factors irritating small bowel or colon:
lactose, other sugars
bile acids, short-chain fatty acids
food allergens
Post-infectious neuroimmune modulation of gut functions
Release of bioactive mediators: e.g. serotonin, tryptase

a Interaction between different mechanisms may occur in individual patients.

serotonin into the circulation[6-8] and increased serine proteases (derived from mast cells) in stools of patients with IBS[9] argue increasingly for the potential role of neurotransmitters in mediating the disorder and the potential of pharmacological agents targeting these mechanisms.

It is also considered that persisting neuroimmune interactions following infectious gastroenteritis might result in continuing sensorimotor dysfunctions. IBS affects 10–15% of patients after acute infectious enteritis.[11] Mucosal biopsies in patients with postinfectious IBS show a persistent, mild inflammatory state, defined by increased numbers of inflammatory cells in the lamina propria and serotonin-releasing enteroendocrine cells in the mucosa.[12,13] Changes in mucosal serotonin levels may affect both sensory and motor functions possibly contributing to IBS symptoms.[14] Another mucosal immune system alteration found in IBS patients is an increased number of activated mast cells in the proximity of colonic nerves in the lamina propria, where mediators secreted by mast cells such as tryptase and histamine may stimulate sensory neurons and potentially contribute to the development of abdominal pain.[15] Further evidence for a proinflammatory state in IBS patients comes from a recent study reporting decreased interleukin (IL)-10/IL-12 ratios in IBS patients.[16] The IL-10/IL-12 ratio reflects the balance between anti- and proinflammatory cytokines; a low ratio implies a tendency to evoke inflammation. This suggests that therapies with immunomodulatory effects might be beneficial in some IBS patients.

Traditional IBS therapies (table II) are directed mainly 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. Hence, there is a need for new treatment options for this highly prevalent disease. Increasing knowledge of the pathophysiology and potential mechanistic targets provide the basis for the development of new drugs for IBS.

This article provides a systematic overview of recent and novel approaches in IBS therapy (table III, figure 1) that are considered promising. They were selected for review based on at least one of the following criteria: (i) agents have passed the stage of tissue and animal models, and have already shown promising effects on lower gastrointestinal motor, sensory or secretory studies in humans; (ii) phase IIa studies show signals on important functions or

Table II. Traditional therapies for irritable bowel syndrome (reproduced from Camilleri,[10] with permission from the American Gastroenterological Association)

Diarrhoea
Antidiarrhoeal agents such as diphenoxylate or loperamide (e.g. 2mg as required up to 4 mg/day)
Diarrhoea and pain
Tricyclic antidepressants, such as desipramine (50–150mg at bedtime or amitriptyline, 10–25mg twice daily) significantly relieve diarrhoea and associated pain
Constipation
Dietary fibre supplementation (20 g/day)
Osmotic laxatives such as a magnesium salt, lactulose or polyethylene glycol are usually efficacious
Pain
Antispasmodics for pain on an as required basis; effectiveness unclear
All symptoms
Reassurance and an effective doctor-patient relationship

Table III. Drugs in clinical development for irritable bowel syndrome (IBS)

Target system	Receptor activity	Compounds	Human physiological effects	Potential or approved indication
Serotonergic receptor system	5-HT_4 agonists	Tegaserod ATI-7505	Prokinetic, secretagogue	C-IBS, FC
	5-HT_3 antagonists	Alosetron Cilansetron	Decrease motility and secretion, increase compliance, decrease pain	D-IBS, FD
	5-HT_3 agonist	MKC-733	Accelerate small bowel transit, delay gastric emptying	C-IBS, FC
	5-HT_4 agonist/5-HT_3 antagonist	Renzapride	Prokinetic	C-IBS, FC
Serotonin transporter system	SSRI SNRI	e.g. Venlafaxine	Increase compliance, decrease tone, reduce sensation	IBS, FAP
Cholinergic system	Selective M_3 antagonists	Zamifenacin Darifenacin YM-905	Reduce colonic motility, decrease pain?	D-IBS, FD
α-Adrenergic system	α_2-Agonist	Clonidine	Increase compliance, decrease tone, reduce sensation	D-IBS, FAP
Opioid system	Peripheral μ-opioid antagonist	Alvimopan	Prokinetic	C-IBS, FC, OIC
	κ-Opioid agonist	Asimadoline	Decrease sensation	IBS, FAP
Corticoids	CRF antagonist	CRH-9-41	Reduce stimulation induced motility and sensitivity	D-IBS, FAP
Benzodiazepine	2,3-Benzodiazepine receptor	Dexofisopam	Reduce stool frequency, increase stool consistency	D-IBS
Melatonin	Melatonin receptor	Melatonin	Decrease pain	IBS, FAP
Cholecystokinin	Cholecystokinin antagonists	Loxiglumide Dexloxiglumide	Accelerate gastric emptying, delay proximal colonic transit	IBS
Somatostatin	Somatostatin receptor agonist	Octreotide	Slow down transit, decrease secretion	D-IBS, FD
Neurokinin	Neurokinin antagonists 1 and 2	Ezlopitant Nepadutant	Reduce visceral sensation (NK_1) and motility (NK_2)	IBS, FAP
Chloride Channel	Chloride channel activator	Lubiprostone	Accelerate transit, increase secretion	C-IBS, FC
Guanylate cyclase C	Guanylate cyclase-C agonist	MD-1100	Decrease stool consistency, increase stool frequency	C-IBS, FC
Neurotrophin	Neurotrophin-3	Neurotrophin-3	Accelerate transit, increase stool frequency, decrease stool consistency	C-IBS, FC
Probiotics	Bacterial flora	VSL#3, Lactobacilli *Bifidobacterium*	Decrease bloating and pain, slow down transit	IBS, bloating, flatulence

C-IBS = constipation-predominant IBS; **D-IBS** = diarrhoea-predominant IBS; **FAP** = functional abdominal pain; **FC** = functional constipation; **FD** = functional diarrhoea; **NK** = neurokinin; **OIC** = opioid-induced constipation; **SNRI** = serotonin and noradrenaline (norepinephrine) reuptake inhibitor; **SSRI** = selective serotonin receptor inhibitor.

symptoms of pain or bowel function; or (iii) phase IIb or phase III studies show evidence of efficacy. It is worth noting that, for virtually all classes of agents, results of large phase III trials are still necessary unless otherwise stated. The review is based on a PubMed literature search from 1998 to November 2005. Abstracts were identified through 'Web of Science' (http://scientific.thomson.com/products/wos/) and through abstract supplements of major peer-reviewed gastrointestinal journals; some were chosen from our own recent research at the Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER) Program, provided preliminary reports have been accepted for publication. Abstracts were only included if there was ongoing research in that field.

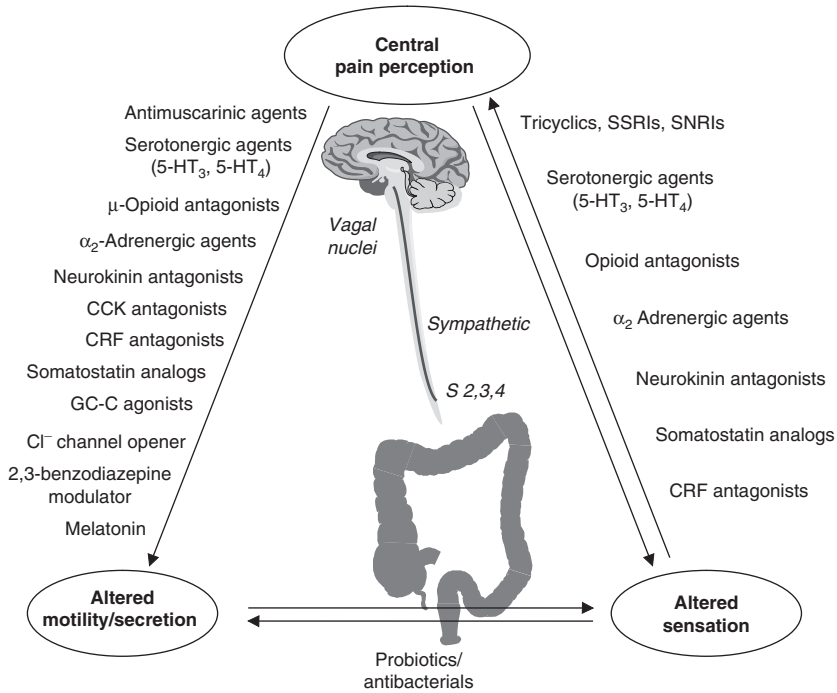

Fig. 1. Recent and novel approaches in the treatment of irritable bowel syndrome (reproduced from Camilleri,[17] with permission). **CCK** = cholecystokinin; **CRF** = corticotropin releasing factor; **GC-C** = guanylate cyclase-c; **SNRIs** = serotonin and noradrenaline (norepinephrine) reuptake inhibitors; **SSRIs** = selective serotonin receptor inhibitors.

1. Serotonergic System

Serotonin (5-hydroxytryptamine) is an important neurotransmitter of the enteric nervous system (ENS)[18,19] and the brain-gut axis, and is involved in several functions of the gastrointestinal tract, including the peristaltic reflex. Serotonin is found primarily within the gastrointestinal tract (80% of body serotonin stores), where it is stored in gut enteroendocrine cells (95%) and in enteric neurons (5%). Serotonin plays a pivotal role in the modulation of multiple gut functions such as motility, sensation, blood flow and secretion. However, serotonin also acts as a neurotransmitter in the CNS. Released from enteroendocrine cells in response to luminal mechanical or chemical stimulation, serotonin acts via a variety of serotonin receptors either directly (on muscle or enterocytes) or indirectly through intrinsic enteric neurons to modulate gastrointestinal function. Serotonergic receptors also occur on vagal and visceral afferent cell bodies.[20] The receptors involved in the gastrointestinal serotonin functions consist of serotonin 5-HT_3, 5-HT_4 and 5-HT_{1P} receptors.[18,19] The 5-HT_4 receptor appears to play a key role in the peristaltic reflex. Spinal 5-HT_3 receptors in the rat are involved in the mediation of endogenous pain inhibition in response to noxious colorectal distension. Binding of a specific 5-HT_3 ligand has been shown in the area postrema in the brain and in various limbic regions. In humans, the highest level of specific binding has been found in the amygdalae, which are integral to the emotional responses to visceral stimulation.

Serotonin activity on the receptors is regulated by the serotonin reuptake transporter protein (SERT).[21] Coates et al.[22] have found that the colonic mucosa of IBS patients had reduced expression of SERT (mRNA and immunohistochemistry), whereas the number of enteroendocrine cells and the release of serotonin under baseline conditions or in response to stimulation were normal. These data of

reduced SERT mRNA expression in D-IBS has been partly replicated by a study at the Mayo Clinic.[23]

Thus, the serotonergic network appears to play a key role in the neurohumoral brain-gut axis in health and disease, and should be an important target for new therapeutic approaches. While the role of serotonin in IBS pathophysiology is not completely understood, serotonergic agents such as 5-HT_3 antagonists and 5-HT_4 agonists are effective in the treatment of multiple symptoms of IBS.

1.1 Serotonin 5-HT_3 Receptor Antagonists

5-HT_3 receptors are located on extrinsic sensory afferent neurons. Antagonism of the 5-HT_3 receptor has been shown to delay gastrointestinal transit, reduce secretion and increase colonic compliance in response to distension.[24] Although 5-HT_3 receptor antagonists did not significantly alter visceral pain thresholds to balloon distension, an effect on abdominal pain was observed in clinical trials. There is also some experimental evidence that improvement of abdominal pain may result from central effects via 5-HT_3 receptors of the brain, where serotonin also acts as a key neurotransmitter.[25]

1.1.1 Alosetron

Alosetron was the first 5-HT_3 receptor antagonist to be developed for the treatment of D-IBS. The drug was initially approved in the US in 2000 for treating female patients with D-IBS. At least six large, multicentre, randomised, controlled clinical trials, reviewed in a meta-analysis[26] (figure 2), have demonstrated alosetron to be effective in reducing stool frequency and urgency, increasing stool consistency and improving abdominal pain and discomfort in patients (93% female) with diarrhoea predominant or non-constipated IBS. The pooled odds ratios for adequate relief of pain or global symptom improvement was 1.81 [95% CI 1.57, 2.10]. The average number of patients needed to treat (NNT) with alosetron for one patient to achieve improvement over placebo treatment was seven [95% CI 5.74, 9.43]. There is similar efficacy of alosetron in a trial of 662 men with D-IBS.[27]

The most important adverse effect of alosetron is constipation, which has been reported in 20–30% of the treated patients. Rare cases of ischaemic colitis have occurred, with an estimated incidence of 0.1–0.15%. Hospitalisation in some patients, need for surgery and deaths were attributed to treatment with alosetron, leading to voluntary withdrawal from the market in late 2000. Public pressure from patients, the proposal of a careful post-marketing surveillance and a risk-management strategy has led to the reintroduction of alosetron to the US in 2002 under severe restrictions. These restrictions aimed to ensure safer use of the drug with more favourable efficacy-safety ratio, and clarification of the risk-benefit ratio. Regrettably, the restrictive strategy has been so effective that too few patients have been treated; 3 years later, the risk component of the ratio is still unclear.

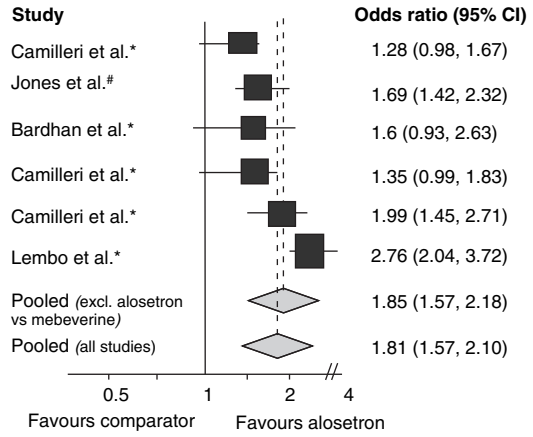

Fig. 2. Meta-analysis of the efficacy of alosetron in mostly female patients with diarrhoea-predominant irritable bowel syndrome. All studies are placebo controlled except B, in which alosetron was compared with mebeverine (reproduced from Cremonini et al.[26] with permission). * indicates placebo-controlled study; # indicates compared with mebeverine.

1.1.2 Cilansetron

Cilansetron is another 5-HT_3 receptor antagonist that is being developed for the treatment of both men and women with D-IBS. Efficacy was tested in >4000 patients in several phase II and phase III trials, and appears to be similar to that of alosetron.[28,29] However, cilansetron was found also to be associated with constipation and rare cases of ischaemic colitis. In April 2005, the US FDA denied approval of cilansetron and required further trials.[30]

The relationship between 5-HT$_3$-antagonists and ischaemic colitis is still unclear. It has been reported that IBS itself might be associated with an increased incidence of ischaemic colitis.[31] It is conceivable that in some patients, the initial diagnosis of IBS might have been incorrect because of an overlap of nonspecific symptoms. Further research is warranted to identify potential risk factors for ischaemic colitis in patients with IBS and potential interactions with 5-HT$_3$ antagonists, to provide these female and male patients with the opportunity to be treated with a class of drugs that is particularly effective for diarrhoea, urgency and pain in IBS.[26,27]

1.2 5-HT$_3$ Receptor Agonists

One study tested the effect of a 5-HT$_3$ receptor agonist pumosetrag (MKC-733)[32] on gastric and small bowel motility in healthy volunteers. At a 4mg dose, the agent delayed gastric emptying, resulted in relaxation of the proximal stomach, stimulated fasting antroduodenal migrating motor complex activity and accelerated small intestinal transit. Colonic transit was not studied, but pumosetrag induced softer stools or diarrhoea in 15% of the subjects, indicating that the agent could be useful in the treatment of constipation. However, 25% of the subjects experienced nausea, and 50% had flushing and itching, which were attributable to effects of serotonin even at a systemic level. In animal models, 5-HT$_3$ agonists induced bradycardia and hypotension. Further studies in humans are required to assess a potential role of 5-HT$_3$ agonists in IBS or other digestive diseases. At present, it appears that clinical use might be limited by gastrointestinal and systemic adverse effects.

1.3 5-HT$_4$ Receptor Agonists

1.3.1 Tegaserod

Tegaserod is a selective partial agonist of the 5-HT$_4$ receptor, which plays a key role in the peristaltic reflex. Recently, tegaserod was also shown to act as a potent 5-HT$_{2B}$ receptor antagonist, but it is currently unclear whether this contributes to the clinical efficacy profile of the drug.[33] In pharmacodynamic studies, tegaserod accelerated small bowel transit (2mg twice daily) and colonic transit (6mg twice daily) in C-IBS.[34,35] A Cochrane meta-analysis[36] reviewed eight randomised controlled trials in nearly 3000 mostly female patients with C-IBS. Overall, the studies showed significant improvement of the patients' overall assessment of relief as primary endpoint and of abdominal pain, bowel frequency and consistency as secondary endpoints.

The therapeutic gain over placebo was higher in women and higher with 12 mg/day compared with 4 mg/day. The Cochrane analysis of the four large randomised controlled trials that tested tegaserod 12 mg/day in patients with C-IBS found that the NNT was 14. The only relevant adverse effect was transient diarrhoea in about 10% of recipients. Other studies supported the efficacy of tegaserod in patients with C-IBS with regard to both repeated treatment[37,38] and long-term treatment.[39] Tegaserod also proved to be efficacious in the treatment of chronic constipation.[40,41]

Reports of cases of ischaemic colitis in association with tegaserod treatment[36] have led the US FDA to include a special alert in the drug labelling. It is unclear whether there is a causal relationship between tegaserod and ischaemic colitis.

1.3.2 ATI-7505

ATI-7505[42] 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 cytochrome P450-dependent metabolism at therapeutically relevant concentrations. Human safety data to date indicate no cardiac adverse effects. Preliminary pharmacodynamic data in healthy volunteers[43] indicate prokinetic effects, suggesting that ATI-7505 has potential for development as a prokinetic agent, with acceleration of gastric emptying (20mg three times daily) and colonic transit (10mg three times daily) [overall and ascending colon emptying] as well as inducing looser stool consistency. Thus, it appears to be promising for C-IBS.

1.4 Mixed 5-HT$_4$ Agonist/5-HT$_3$ Antagonist/ 5-HT$_{2B}$ Antagonist

1.4.1 Renzapride

Another serotonergic agent developed for the treatment of C-IBS is renzapride, a full agonist of the 5-HT$_4$ receptor and also an antagonist of 5-HT$_3$ and the 5-HT$_{2B}$ receptors. In a placebo-controlled pharmacodynamic phase II study,[44] three doses of renzapride (1, 2 and 4mg) were tested versus placebo in 48 mostly female patients with C-IBS. A statistically significant linear dose response to renzapride was detected for colonic transit and ascending colonic emptying time, but not for gastric emptying or small bowel transit time. The acceleration of colonic transit time was significantly associated with improvement of bowel function scores.[44] No significant adverse clinical, laboratory or ECG effects were observed. Phase IIb clinical trials also show efficacy in the relief of symptoms.[45,46] These studies indicate that renzapride may have beneficial effects in patients with C-IBS.

2. Serotonin Transporter System/ Antidepressants

One of the main regulators of the serotonergic system is SERT,[21] which clears serotonin from the synaptic cleft and thereby ends its action on the various serotonin receptors at the synapses. A SERT identical to that present in the CNS has been identified in the enteroendocrine cells and enteric nerves in the gut,[21,47] suggesting that local control of serotonin is important in the physiological control of gastrointestinal functions. In fact, a SERT knockout mouse developed gastrointestinal dysfunction with diarrhoea or constipation, and IBS has been associated with altered SERT expression in the gut mucosa.[22]

Many patients with IBS receive serotonergic (i.e. SERT-inhibiting) psychoactive agents for their comorbid psychiatric illnesses, including anxiety, mood and somatoform disorders. Although current data from meta-analyses are conflicting,[48,49] psychoactive agents (e.g. antidepressants and anxiolytics) with SERT-inhibiting activity are thought to directly improve IBS symptoms. These agents have been widely used, especially in the US, in the treatment of patients with IBS. It is unclear whether these medications improve symptoms through their central or peripheral effects. Some reports indicate central effects, e.g. an increased tolerance to rectal distension was associated with improved depression but not with abdominal pain.[50] Other studies suggest these medications (e.g. paroxetine, citalopram) directly affect gastrointestinal physiology.[51,52] However, different psychotropic agents may have different activity profiles depending on whether other proteins such as the noradrenaline (norepinephrine) reuptake transporter protein, are also targeted. The availability of psychoactive agents (e.g. the serotonin and noradrenaline reuptake inhibitor [SNRI] venlafaxine) that can modify colonic sensory and/or motor functions such as compliance and tone,[53] may be of potential benefit in the treatment of patients with IBS and should be further tested in clinical IBS trials.

3. Antimuscarinics/Anticholinergics/ Smooth Muscle Relaxants

The gastrointestinal effects of acetylcholine are mediated by nicotinic receptors in the myenteric plexus, and by muscarinic receptor subtypes $M_{1\text{-}3}$ in the myenteric plexus and in the neuromuscular junction.[54,55] Acetylcholine is the main excitatory neurotransmitter in the gastrointestinal tract. Nonselective anticholinergics or specific antimuscarinic anticholinergics reduce bowel motility and associated pain. They are often considered with the group of smooth muscle relaxant drugs that act directly on the smooth muscle, e.g. by blocking smooth muscle Ca^{2+} channels. Several compounds (mebeverine, otilonium bromide, pinaverium bromide and cimetropium bromide) used in European countries as standard IBS treatment have never been approved in the US. To assess the overall efficacy of these traditional smooth muscle relaxants in IBS, several meta-analyses have been performed and one by Poynard et al.[56] suggests global improvement of 56% in the active drug group versus 38% in the placebo group, with a mean odds ratio of 2.13 [95%

CI 1.77, 2.58]. This and other meta-analyses have been criticised because of low quality (Jadad Scores) of the individual clinical trials.

Newer anticholinergic agents are being developed to specifically target the muscarinic type-3 receptor (M_3) in the intestinal smooth muscle in order to decrease the nonspecific anticholinergic adverse effects (dry mouth or increased heart rate). Several agents have shown promising gastrointestinal effects in animal models.[57] The M_3-selective antagonist darifenacin is used to treat overactive bladder and is associated with increased constipation.[58] The M_3-selective antagonist zamifenacin[59] significantly reduced colonic motility without significant nonspecific anticholinergic effects in a study of 36 IBS patients.

4. α-Adrenergic Agents

Mechanistic studies suggest that the adrenergic nervous system provides extrinsic tonic inhibitory control of non-sphincteric gut motility. It has been demonstrated that, among a variety of adrenergic agents active on receptor subtypes, the α_2-adrenergic agents such as clonidine affect human colonic and rectal motor and sensory functions.[60-62] In a dose-response study in healthy volunteers,[63] clonidine increased colonic compliance, reduced fasting tone without altering the colonic response to a meal and significantly reduced sensation to distensions. Gastrointestinal or colonic transits were not significantly altered with a dose range of 0.1–0.3mg twice daily. In a small study in patients with D-IBS,[64] 67% of the patients treated with clonidine 0.1.mg twice daily compared with 46% in the placebo group achieved satisfactory relief, the primary endpoint. Moreover, clonidine significantly improved bowel functions without altering gastrointestinal transit. Drowsiness, dizziness and dry mouth were observed as adverse effects, typically at dosages >0.1mg twice daily; these usually decreased after the first week of treatment. Overall, this study suggests beneficial effects of α_2-adrenergic agents in D-IBS.

5. Opioid Agents

The three major opioid receptors, μ, δ and κ are distributed in the peripheral and central nervous systems. μ-Agonists such as codeine or morphine are known to modulate visceral nociception and to slow down gastrointestinal transit, resulting in constipation or central side effects.[65-67] κ-Opioid receptors are suggested to be involved in visceral perception.[68] New, peripherally restricted opioid receptor agonists and antagonists may offer new treatment strategies for IBS.

5.1 κ-Opioid Agonists

5.1.1 Asimadoline

The κ-opioid agonist asimadoline[69] was shown to reduce sensation in response to distensions in the non-noxious range when 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.[70] showed that this drug increased sensory thresholds in patients with IBS.

5.2 Peripheral μ-Opioid Antagonists

5.2.1 Alvimopan

Alvimopan, a novel, peripherally restricted μ-opioid antagonist, is effective in the treatment of opioid-induced constipation and postoperative ileus.[71-73] It reverses the peripheral effects of narcotics without influencing the pain relief desired by concomitant opioid administration. A pharmacodynamic study in healthy volunteers[74] confirmed that alvimopan normalised the colonic transit delay induced by coadministered codeine. Interestingly, alvimopan alone accelerated colonic transit, suggesting that the μ-opiate mechanisms participate in the physiological control of colonic transit (figure 3). Future trials to test the effects of alvimopan in patients with constipation, C-IBS and opiate-induced constipation are warranted.

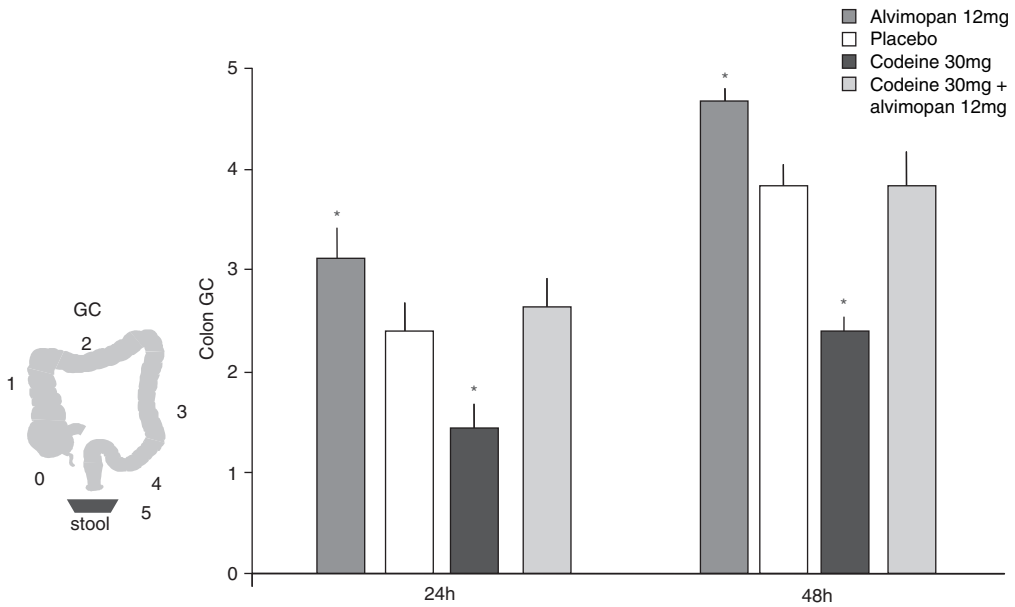

Fig. 3. The peripheral μ-opioid antagonist alvimopan inhibits the colonic retardation induced by coadministered codeine. Alvimopan alone accelerates colonic transit, suggesting that the μ-opiate mechanisms participate in the physiological control of colonic transit (reproduced from Gonenne et al.,[74] with permission from the American Gastroenterological Association). **GC** = geometric centre; * $p < 0.05$ vs placebo.

6. Corticotropin-Releasing Factor Receptor Antagonists

Corticotropin-releasing factor (CRF) is considered to be a key mediator of stress response in the brain-gut axis.[75] Two CRF receptor subtypes have been cloned: CRF_1 and CRF_2. In animal models, stress activation of the CRF receptors alters gastrointestinal functions,[76] and stress-related changes in gastrointestinal motility can be blocked by treatment with the selective CRF_1-receptor antagonist CP-154526 (antalarmin)[77] and the nonselective CRF antagonist CRH-9-41 (α-helical CRF_{9-41}).[78] There is an association of IBS with an increased gastrointestinal response to stress, and frequently concomitant anxiety or depression. Thus, these CRF antagonists appear to be promising agents for IBS treatment.

Sagami et al.[79] observed that the increased colonic motility response to rectal electrical stimulation in IBS patients was significantly suppressed after CRH-9-41 infusion. Importantly, plasma adrenocorticotropic hormone and serum cortisol levels were not suppressed. Oral formulations may be necessary for clinical use in IBS.

7. 2,3-Benzodiazapine Receptor Modulators

Dextofisopam[80] is the *R*-enantiomer of tofisopam, a nonsedating homophthalazine, which is used outside the US to treat anxiety and stress-related disorders. The receptor-binding profile of dextofisopam is distinct from that of typical benzodiazepines because it binds to 2,3-benzodiazepine receptors. These are located in subcortical and hypothalamic regions rather than the cerebral cortex.

In animal models, dextofisopam reduced stimulation-induced colonic motility and visceral sensitivity, suggesting potential in the treatment of IBS.[80] A 12-week, placebo-controlled phase II study in patients with D-IBS or alternating IBS showed more months with adequate relief in the dextofisopam group than the placebo group.[81] 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).

8. Melatonin

Melatonin, a derivative of serotonin, is a pineal gland neurohormone involved in the regulation of the sleep-wake cycle. Melatonin is also synthesised in the gastrointestinal tract, and may participate in the regulation of gastrointestinal motility and sensitivity,[82] possibly by blocking nicotinic channels[83] or Ca^{2+}-activated K^+ channels.[84] Two small studies of the effects of melatonin in IBS patients[85,86] reported improvement of abdominal pain and IBS symptom score or a reduction of rectal pain sensitivity without altering sleep, anxiety or depression.

9. Cholecystokinin-1 Antagonists

Cholecystokinin (CCK)[87] is a neuropeptide released by endocrine cells within the duodenal and jejunal mucosa in response to a variety of nutrients, notably the digestion products of fat. Its secretion is associated with contraction of the gallbladder, pancreatic enzyme secretion and inhibition of gastric emptying. CCK has been proposed as a mediator of IBS symptoms. Chey et al.[88] showed that 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,[89,90] which are located predominantly in the periphery and the CNS, 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 C-IBS.

9.1 Loxiglumide and Dexloxiglumide

Loxiglumide is a highly specific, competitive antagonist of the CCK_1 receptor[91] and is the most thoroughly studied in humans. Earlier pharmacodynamic[92] and clinical[93] studies suggested that loxiglumide might improve constipation. Dexloxiglumide is the enantiomer of loxiglumide, and is responsible for its pharmacological activity, being approximately twice as potent as loxiglumide. A 12-week, phase II trial of dexloxiglumide[94] in female patients with C-IBS showed that dexloxiglumide 200 mg/day was associated with improvement in abdominal pain and discomfort compared with placebo. Meanwhile, two large phase III clinical trials in patients with C-IBS were reported by the developing company to show no efficacy for dexloxiglumide.[95]

A pharmacodynamic approach in C-IBS[96] showed that dexloxiglumide was associated with accelerated gastric emptying half-time and slower ascending colon emptying half-time, with no significant effect on overall colonic transit or satisfactory relief of IBS. The pharmacodynamic profile suggests that dexloxiglumide should be considered for patients with delayed gastric emptying or with conditions associated with accelerated, rather than delayed, proximal colonic transit.

10. Somatostatin Analogues

The somatostatin analogue octreotide activates predominantly somatostatin type 2 receptors, and reduces gastrointestinal secretion, retards gastrointestinal transit and has antinociceptive properties. Therefore, beneficial effects of octreotide in IBS, especially in the diarrhoea subtype, would be plausible. Octreotide slows down the orocecal transit time in patients with D-IBS,[97] with effects on both gastric emptying[98] and small bowel transit.[99] Octreotide normalises visceral perception and discomfort thresholds in IBS patients without changing rectal compliance.[100,101] Despite this pharmacodynamic evidence, there are no clinical trials with octreotide in IBS.

11. Neurokinin Antagonists

Tachykinins are another class of ENS neurotransmitters. They include substance P and neurokinin A (NK_A), which exert their activity by binding on neurokinin receptors, predominantly on NK_1 and NK_2 receptors.[102,103] NK_1 receptors play a role in nociception, whereas NK_2 receptors have a greater

influence on smooth muscle contractility than NK_1 receptors.[103] Correspondingly, animal data suggest an influence of NK_1 receptor antagonists on pain perception[104] and of NK_2 antagonists on gut motility.[105] Despite considerable animal data, there are still few published data on the effects of NK antagonists in humans. In a small pharmacodynamic study of IBS patients, the NK_1 receptor antagonist ezlopitant[106] was shown to reduce the emotional response to rectosigmoid distension and showed a trend towards decreasing rectal sensitivity. In healthy volunteers, the NK_2 receptor antagonist nepadutant[107] reduced contraction frequency and amplitude on migrating motor complexes in the small intestine, and effectively antagonised the motility-stimulating effects of infused NK_A. Saredutant is another NK_2 antagonist also being developed for IBS but reports of the results of phase II trials are still awaited.

12. Chloride Channel Activators

Volume-regulated Cl^- channels such as Cl^--channel type 2 (ClC_2) and ClC_3 are found in most mammalian and non-mammalian cell types, including those in the gastrointestinal tract and liver.[108,109] These channels contribute to several cellular functions, including cell volume regulation, maintaining the membrane potential, epithelial chloride transport and fluid secretion, and cell proliferation. Intestinal chloride secretion is critical for intestinal fluid and electrolyte transport. In the gastrointestinal tract, ClC_2 has been found in gastric parietal cells, and small intestinal and colonic epithelia.

Lubiprostone is a prostone that acts as a selective ClC_2 activator and increases intestinal water secretion.[110] Though chemically derived from prostaglandins, the mechanism of action at the cellular level shows completely different properties from those of prostaglandins. Several clinical trials have demonstrated that lubiprostone has positive effects on stool consistency, frequency and straining, and that it is effective and can be safely used for treating constipation.[111-113] In a recent pharmacodynamic study, lubiprostone was shown to accelerate small bowel and colonic transit time in healthy volunteers.[114] Interestingly, lubiprostone accelerated colonic transit without accelerating ascending colon emptying, suggesting it affects distal colonic function. Adverse effects of lubiprostone include diarrhoea and nausea that is usually mild and transient and not associated with alteration of gastric function.[114] In January 2006, the FDA approved lubiprostone for the treatment of chronic 'idiopathic' constipation.[115]

13. Guanylate Cyclase-C Agonists

MD-1100 acetate is a novel, first-in-class compound acting as an 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.[116-119] In animal and early human safety studies, MD-1100 has been observed to increase stool frequency, decrease stool consistency and decrease visceral pain.[120] Therefore, the drug seems to be promising for the treatment of C-IBS and chronic constipation.

14. Recombinant Human Neurotrophin-3

Neurotrophin-3 (NT-3) is a neurotrophic factor involved in the growth, development and function of the nervous system. In studies for the treatment of several neurological disorders, this factor was found to be associated with increased stool frequency and softened stool consistency, which led to investigation of the effects of subcutaneously injected NT-3 on gastrointestinal transit and bowel functions in healthy volunteers and patients with functional constipation. In a pharmacodynamic study,[121] NT-3 accelerated overall colonic transit in health and constipation, and gastric and small bowel transit in health. This was associated with an increased stool frequency in healthy and constipated subjects, and a decreased stool consistency in constipated patients. A subsequent dose-ranging study in 107 patients with functional constipation[122] confirmed these effects by showing an increased stool frequency, a dose-related softening of stools and an improved ease of passage. Overall, the most common adverse effects were injection site reactions, mild paraesthesias, and decreases in temperature and diastolic

blood pressure. High costs related to the recombinant production of the human NT-3 may limit its further development for broad indications such as chronic constipation or C-IBS.

15. Probiotics and Antibacterials

15.1 Probiotics

Probiotics may have beneficial effects on altered colonic inflammation that may be found in some IBS patients. O'Mahony et al.[16] showed that treatment of IBS with *Bifidobacterium infantis* normalised IL-10/IL-12 ratios towards a lower inflammatory status, and this was associated with significant improvement in IBS symptoms. Some IBS symptoms, such as pain, bloating or flatulence, were also improved in other studies using the probiotic cocktail VSL#3,[123,124] and *Lactobacillus plantarum* alone,[125,126] or in combination with *Bifidobacterium breve* or *L. acidophilus*.[127] The 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.[128] Even though results from placebo-controlled clinical trials vary considerably and the evidence is still limited, the safety profile of probiotics suggests they may be considered for the treatment of bloating and flatulence.

15.2 Antibacterials

Some studies suggest that bacterial overgrowth of the small intestine (SIBO), as detected by lactulose hydrogen breath test (LBT), may be present in up to 78% of IBS patients[129] and contribute to generation of IBS symptoms. A placebo-controlled study[130] showed that treatment with neomycin normalised the LBT which was associated with significant reduction of IBS symptoms over the short-term (≈1 week). Similar results were found in an open label study[131] using rifaximin, metronidazole or fluoroquinolones. These studies suggest that in IBS patients with a positive LBT, antibacterial therapy may be an alternative treatment strategy; however, medium- to long-term effects are unclear. Moreover, the high prevalence of SIBO in IBS, as detected by LBT in these studies, is controversial. Indeed, other studies using glucose hydrogen breath test, which is even more sensitive for the detection of bacterial overgrowth than the LBT (75% vs 39%), have reported a prevalence of only 11%.[132]

16. Conclusion

A greater understanding of basic neuroenteric mechanisms and the role of effectors and transmitters within the brain-gut axis provide opportunities for development of new therapeutic agents in IBS. The risk benefit ratio is clearly a determining factor in the approval and marketing of such compounds. Rigorous pharmacological assessment using validated biomarkers and awareness of safety signals are key to successful drug development, especially in relation to IBS. For almost all of the drug classes described here, rigorous phase III trials are still awaited.

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