

# Expert Opinion

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## Emerging drugs for irritable bowel syndrome

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Irritable bowel syndrome is extremely common and its severity is widely underestimated. Unfortunately, the current pharmacological treatment of this condition is far from satisfactory which might suggest that it would be an area in which the pharmaceutical industry would take a great interest. However, drug development in this field, especially in relation to 5-hydroxytryptamine (5-HT), has been beset by difficulties with side effects and, what some authorities would claim, an unnecessarily strict regulatory climate based on the perception that irritable bowel syndrome is not a particularly serious condition. This has resulted in a rapid withdrawal from the scene by a number of companies although with the identification of some potential new therapeutic targets, the area has not been totally abandoned.

**Keywords:** 5-HT, benzodiazepine, CCK, channelopathies, chloride channel, CRH, guanylate cyclase, IBS, neurokinin, opioid, probiotics

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### 1. Background

Abdominal pain or discomfort associated with a change in consistency or frequency of stool has remained the primary diagnostic criteria for irritable bowel syndrome (IBS) since first described by Manning in 1978 [1,2]. Although there are few data available on the prevalence of IBS, based on the latest Rome III criteria [2], previous studies based on earlier criteria have consistently suggested a figure of somewhere between 10 and 20% [2,3]. It is becoming increasingly recognised that the severity of IBS has been significantly underestimated in the past and that the quality of life of sufferers can be worse than that of patients with diabetes or end stage renal failure [4]. Not surprisingly, this has major implications on healthcare costs [5,6]. The exact pathophysiology of IBS remains elusive, although neurotransmitters [7,8], hormones [9-12], infection [13,14], inflammation [15], gastrointestinal sensitivity [16,17] and motility [18-20] have all been implicated and offer targets for the development of therapies. It seems probable that no single mechanism can explain the heterogeneous nature of IBS, but it is most likely that it results from a combination of environmental, physiological and psychosocial factors.

### 2. Medical need

Most of the current treatment modalities for IBS have been directed at symptom relief rather than pathophysiology of the condition, which is still poorly understood. Furthermore, they usually only target one symptom and consequently are not especially effective as they do not address the whole symptom profile, or phenotype. This latter goal is particularly difficult to achieve in a heterogeneous condition where symptoms can change over time, even in the same patient. Despite being associated with significant suffering and an increased risk of suicidal ideation and suicide [21], IBS is generally perceived as not being life threatening. As a consequence,

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the regulatory authorities demand that new medications should be extremely safe and free from side effects, a difficult goal to achieve. The mainstays of treatment at the present time are bulking agents, antispasmodics, laxatives, anti-diarrhoeals and antidepressants. Unfortunately, most of the trials on these agents were undertaken many years ago and, therefore, do not meet the standards demanded for the modern investigation of new drugs. Consequently, systematic reviews on the efficacy of these modalities are not always very encouraging and are often rather conflicting [22-26]. Nevertheless, most of these approaches are still used and, clinically at least, seem to help a proportion of patients. However, there remains a strong need for new, hopefully more effective, medications. Drugs targeting specific 5-HT receptors have been introduced over the last 2 decades. The HT<sub>4</sub> receptor agonist cisapride was introduced in 1993 and was found to be effective in constipation predominant IBS (IBS-C) [27,28] but was withdrawn from the market in 2000 due to cardiac side effects and deaths due to arrhythmias [29]. Alosetron, a 5-HT<sub>3</sub> receptor antagonist, was subsequently developed for IBS with diarrhoea and demonstrated an improvement in abdominal pain, faecal urgency and frequency of defecation as well as global symptoms in randomised controlled trials [30,31]. In addition, the 5-HT<sub>4</sub> receptor partial agonist, tegaserod, has been shown to significantly improve global symptoms in IBS-C in large randomised controlled trials [32,33] which was confirmed in a Cochrane review [34]. Unfortunately, both alosetron and tegaserod were withdrawn from the US market because of an association with ischaemic colitis in the former and the possible increased risk of serious cardiovascular events in the latter. Although, both drugs were reintroduced, Novartis, the manufacturer of tegaserod, decided to withdraw it from the market completely [35]. Alosetron is still available under a risk management plan for women with severe diarrhoea predominant IBS (IBS-D) who are < 55 years old [36]. The development of two other drugs active on the 5-HT system, cilansetron and renzapride, has also been suspended for now.

### 3. Market review

A direct estimate of the current market size for IBS drugs is difficult to assess because of the lack of efficacy of the current medications as well as the fact that agents such as anti-diarrhoeals, antispasmodics and bulking agents are often used in other unrelated conditions, making it hard to assess the direct use of these agents in IBS alone. The sales figures of the newer drugs that have been developed, but which have subsequently been withdrawn from the market, can serve as a guide for the total market size for IBS treatment. Tegaserod achieved sales of \$295 million between the launch in July 2002 and September 2005 and was projected to have achieved sales of \$690 million by 2009 [37]. Similarly, early sales of alosetron reached \$56 million within a few months of its launch before its voluntary withdrawal and reintroduction

in the US market with restrictions. Estimates of the market potential of drug treatment for IBS is somewhere between \$2 (Pharmaprojects [38]) and \$14 billion depending on the source of information. This estimate is easily equal to the estimated market for the treatment of GORD [39].

### 4. Current research goal

The current multifactorial, pathophysiological model of IBS is not that dissimilar to how duodenal ulceration was considered before the discovery of *Helicobacter Pylori*. Consequently, unless some similar major paradigm shift takes place with respect to IBS, drug development will necessarily be targeted at the various mechanisms that have been identified as being involved in the control of gastrointestinal function both locally and in the CNS as well as events, such as infection, that disrupt this equilibrium.

### 5. Scientific rationale

Everyday experience tells us of the close integration between the gut and the brain and this is now being documented by a variety of physiological and neurophysiological investigative techniques. As the role of the various neurotransmitters and receptors involved in these processes becomes better understood, it is likely that their modulation will be considered as possible therapeutic targets for the treatment of IBS.

### 6. Competitive environment

Please see Table 1 for a brief summary of emerging drugs for IBS.

#### 6.1 5-HT receptor agonists

5-HT is an important neurotransmitter that plays a major role in the motility, secretion and sensitivity of the gastrointestinal tract [40]. There are seven classes of 5-HT receptors but three receptor subtypes have a more important role in the gastrointestinal tract, namely, 5-HT<sub>1</sub>, 5-HT<sub>3</sub> and 5-HT<sub>4</sub> [41]. Over the last 2 decades, several new drugs acting on the 5-HT receptor system have been developed and studied in IBS. In spite of significant benefits observed in initial trials, these new drugs have been beset by failures. Alosetron and tegaserod were withdrawn from the market and later reintroduced under restricted use; with the latter finally being withdrawn altogether. Similarly, the development of cilansetron has ceased and the drug company has abandoned renzapride development after unimpressive Phase III trial results [42].

##### 6.1.1 5-HT<sub>4</sub> agonists

###### 6.1.1.1 Prucalopride

Prucalopride is a highly selective 5-HT<sub>4</sub> agonist. In an *in vitro* study, it has shown > 290-fold affinity for the 5-HT<sub>4</sub> receptor compared to the affinity towards the 5-HT<sub>3</sub> or 5-HT<sub>2A/B</sub> receptors [43]. An initial dose ranging study on healthy

**Table 1. Synopsis of emerging drugs for IBS.**

Compound	Company	Description	Indication	Stage of development	Mechanism of action
Prucalopride	Movetis NV	5-HT <sub>4</sub> agonist	Chronic constipation/IBS-C	Phase III (for chronic constipation)	Increases motility and improves transit
TD-5108	Theravance, Inc.	5-HT <sub>4</sub> agonist	Chronic constipation/possible role in IBS-C	Phase II (for chronic constipation)	Improves colonic transit
ATI-7505	ARYx Therapeutics	5-HT <sub>4</sub> agonist	Possible role in IBS-C	Phase IIa (No active trials reported)	Improvement in gastric emptying and colonic transit
Pumosetrag	Dynogen Pharmaceuticals	Partial 5-HT <sub>3</sub> agonist	Chronic constipation/IBS-C	Phase III (for chronic constipation)	Increases small bowel and colonic motility
Asimadoline/ EMD61753	Tioga Pharmaceuticals	k-Opioid receptor agonist	IBS related pain	Phase II (No active trials reported)	Effect on peripheral opioid k-receptor and modulation of pain signals
Dextofisopam	Vela Pharmaceuticals	Benzodiazepine receptor modulator	IBS related pain/discomfort	Phase II (No active trails reported)	Pain perception modulation via effect on CNS benzodiazepine receptors
Dexloxiglumide	Rottapharm	Cholecystokinin 1 antagonist	IBS-C	Phase II	Probably by modulating colonic motility as well as visceral pain perception
Linaclotide/ MD110	Ironwood Pharmaceuticals	GC-C receptor agonist	IBS-C/chronic constipation	Phase III	Increased bicarbonate and chloride secretion in intestine
Guanilib/SP304	Synergy Pharmaceuticals	GC-C receptor agonist	IBS-C	Phase I	Increased bicarbonate and chloride secretion in intestine
Lubiprostone	Sucampo Pharmaceuticals	Chloride channel activator	IBS-C	Approved for use in IBS-C and functional constipation	Increased fluid and chloride secretion in intestine
GW876008	GlaxoSmithKline	Corticotrophin releasing hormone 1 receptor antagonist	IBS with predominant diarrhoea	Phase I	Improves colonic motility

GC-C: Guanylate cyclase type-C; IBS: Irritable bowel syndrome; IBS-C: Irritable bowel syndrome with predominant constipation.

volunteers demonstrated a decrease in colonic transit time with no significant effect on gastric emptying or small bowel transit time [44]. In a further study by the same research group in functional constipation, an improvement in gastric emptying, small bowel and colonic transit was found [45]. Another study in females with constipation showed a significant improvement in bowel frequency, stool consistency and overall symptoms of constipation on prucalopride 1 mg once daily compared with placebo. It also improved whole gut transit time in subjects with slow transit constipation [46]. Two recently published placebo-controlled Phase III trials on > 1300 chronic constipation patients have shown the efficacy of prucalopride in improving spontaneous complete bowel movements, which was the primary end point [47,48]. Besides improvement in patient reported quality of life, it

was also shown to improve stool consistency, reduce straining and incomplete evacuation at both 2 and 4 mg once daily with no significant advantage for the higher dose. Apart from abdominal pain, headache and diarrhoea, which are often observed in studies with IBS anyway, no significant major side effects were reported in these trials.

Other than high 5-HT<sub>4</sub> receptor affinity, prucalopride has comparatively little affinity towards the 5-HT<sub>1B/D</sub> [43] and the hERG potassium channel receptors [49], which are those that have been associated with the cardiac side effects of tegaserod and cisapride, respectively. The beneficial effects of prucalopride seen in chronic constipation [47,48,50] and opioid-induced constipation [51] have not been evaluated in IBS but the findings in the above studies suggest these benefits are likely to be applicable to patients with IBS and constipation.

### 6.1.1.2 TD-5108

TD-5108 is a 5-HT<sub>4</sub> agonist which has different structural properties compared with tegaserod. It has high intrinsic activity and > 500-fold selectivity for 5-HT<sub>4</sub> receptors with no clinically significant activity on 5-HT<sub>2A/2B</sub> receptors in contrast to tegaserod or cisapride and no activity on hERG potassium channels unlike cisapride [52]. In studies on colonic transit in the guinea-pig, TD-5108 was shown to be more potent than tegaserod and cisapride with regard to its prokinetic activity [53].

The effects of single and multiple doses of TD-5108 on gastric and colonic transit have been assessed in healthy volunteers with both showing an improvement, which was most marked at a dose of 30 mg/day [54]. A Phase II dose-ranging, placebo-controlled study in subjects with chronic idiopathic constipation showed an improvement in the primary end point of complete spontaneous bowel movement frequency. In addition, there was an improvement in the consistency of stool with reduced bloating, urgency and decreased use of laxatives [55,56]. TD-5108 was well tolerated and no major side effects have been reported so far. To date, no studies have been conducted in IBS and, although the results obtained in constipation would suggest this drug might also have utility in IBS, no trials are apparently planned at the present time.

### 6.1.1.3 ATI-7505

ATI-7505 is a 5-HT<sub>4</sub> receptor agonist, which is structurally similar to cisapride but has less affinity towards hERG potassium channel. ATI-7505 is not metabolised by the cytochrome p450 (CYP450) pathway, making it less likely to cause cardiac side effects associated with cisapride. It is being developed as a prokinetic agent and an initial study in healthy volunteers did show some improvement in gastric emptying time and colonic transit time [57]. However, further development of this drug is still pending.

## 6.1.2 5-HT<sub>3</sub> partial agonist

### 6.1.2.1 Pumosetrag

Pumosetrag (DDP-733/MKC-733) is a partial 5-HT<sub>3</sub> agonist, which is effective when taken orally and is not significantly absorbed from the gut. An initial study on healthy subjects has shown it to accelerate small bowel transit and delay gastric emptying time with a single dose [58]. A 2-week exploratory study of 0.5 mg twice a day (b.i.d.) in subjects with idiopathic constipation found that pumosetrag improved colonic transit and improved stool frequency and was well tolerated [59] without any major side effects. A further dose ranging study in IBS-C patients reported improvement in overall subjective global assessment after a month at a dose of 1.4 mg daily [60]. To date, it has not shown any vascular side effects, which have been a major problem with 5-HT agonists and antagonists.

The drug is in active development by Dynogen Pharmaceuticals and a multi-centre trial of pumosetrag in women with IBS-C [61] is in progress.

## 6.2 Opioid receptor agonists

Pain and/or discomfort are essential diagnostic features of IBS [2]. Antispasmodics and tricyclic antidepressants have been the mainstay of treatment for pain of IBS for many years, although with variable effect [23] and a significant proportion of patients remain unresponsive. The commonly used opiates, morphine and codeine, act on central receptors for analgesic effects and the constipation that accompanies their use is sometimes helpful in patients with IBS-D in order to control bowel habit. Despite these beneficial effects of opiates, there are considerable concerns about their abuse potential with long-term use for pain control [62] because of opiate bowel dysfunction [63] and the induction of narcotic bowel syndrome [64]. In order to try and avoid the side effects of opiates and other analgesics used in the management of pain in IBS, new visceral analgesics solely affecting peripheral receptors are in development [65].

### 6.2.1 Asimadoline

Asimadoline (EMD 61753) is an opioid agonist which has shown high affinity for peripheral  $\kappa$ -opioid receptors compared with  $\mu$ - and  $\delta$ -opioid receptors in animal models [66] and was primarily developed as an analgesic [67]. In animal studies, radio labelled C<sup>14</sup>-EMD 61753 has been shown to concentrate in the liver, kidneys, lungs and adrenal glands but only exhibits limited accumulation in whole brain [66] suggesting more peripheral localisation. Its antinociceptive effect is reversed by systemic naloxone in a dose-dependent manner but is also inhibited by the local injection of a  $k$ -opioid antagonist, which is additional indirect evidence of a peripheral mode of action [66]. In another study, mice treated with asimadoline demonstrated a reduced visceromotor response supporting an effect on visceral pain in experimental animal models [68]. In females with IBS, the effect of asimadoline has been assessed on colonic sensitivity using colonic distension and it did not appear to have an effect on pain perception thresholds [69].

Asimadoline has also been assessed in IBS using a novel on demand use trial over a period of 4 weeks. However, there did not appear to be any advantage for the drug over placebo with respect to reduction in pain [70]. Similarly, in another double-blind dose-ranging study using 0.15 or 0.5/1 mg asimadoline b.i.d. or placebo for 12 weeks, the number of months with adequate relief of pain remained the same in the treatment and placebo arms [71], but patients with moderate pain at baseline did report a significant improvement in pain with the 0.5 and 1 mg b.i.d. doses. Subgroup analysis of the various subtypes of IBS showed that subjects with IBS-D reported the greatest degree of pain reduction and that those with an alternating bowel habit only experienced pain relief at the highest doses. This is in contrast to the on demand study where pain in IBS-D patients actually got worse, although some improvement in those with an alternating bowel habit was noted. Asimadoline has been found to be safe and reasonably well tolerated in all the trials reported so

far although side effects were more common at doses higher than 2.5 mg a day. Common side effects reported at higher doses were headache, dizziness and polyuria.

In a recently published study, another peripheral  $\kappa$ -opioid receptor agonist JNJ-38488502 did not demonstrate any significant effect on the sensation of colonic distension in healthy male volunteers [72]. However, peripheral opioid receptor agonists remain a potentially useful approach to the treatment of pain related to IBS because of the reduced potential for abuse and the lack of CNS side effects. However, they need further evaluation in IBS related pain in longer studies on more well-defined subgroups.

### 6.3 Benzodiazepine receptor modulators

#### 6.3.1 Dextofisopam

Dextofisopam is an R-enantiomer of tofisopam, a non-sedating homophthalazine that acts on the 2, 3 benzodiazepine receptor located in the subcortical and hypothalamic regions rather than the cerebral cortex [73]. Its chemical structure and action site are dissimilar to the classical benzodiazepines, which act on the 1, 4 or 1, 5 benzodiazepine receptors located in the cerebral cortex [74]. In animal studies, dextofisopam reduced stimulated colonic transit and also reduced visceral pain in a colorectal distension model although there have been no mechanistic studies undertaken in humans [75]. In a Phase II study on 140 subjects with IBS-D or an alternating bowel habit, participants were given oral dextofisopam 200 mg b.i.d. initially and then reduced to 100 mg b.i.d. if necessary after 7 days, with a total duration of treatment of 12 weeks [76]. The primary end point was the number of months with adequate overall relief in IBS symptoms. Even though there was a statistically significant improvement initially, this diminished over time and lost its significance by the end of the study. Benefit in stool frequency and consistency was also reported in the first month but this also disappeared with longer treatment. Dextofisopam was well tolerated and abdominal pain was the more often reported adverse effect, which was more common in the treatment group (12 versus 4%,  $p = 0.115$ ) compared with placebo. Although the initial rapid response to the drug seems to be definite, there was a tendency towards tachyphylaxis but this was also previously observed with tegaserod and it did not prevent tegaserod achieving regulatory success.

#### 6.4 CCK-1 antagonists

Cholecystokinin (CCK) is a peptide gut hormone mainly secreted from endocrine cells in the duodenum and jejunum as well as from peptidergic nerve endings in the myenteric plexus and the CNS [77]. CCK acts through the CCK<sub>1</sub> (CCK-A; alimentary type) and CCK<sub>2</sub> (CCK-B; brain type) receptors which are now recognised to be not confined to the gut and brain, respectively, as originally thought, but widely distributed throughout the gut wall. However, the alimentary effects are mainly mediated through CCK<sub>1</sub> receptors [78]. The major action of CCK is postprandial gallbladder contraction but

there is some evidence that it inhibits gastric emptying and it also appears to modulate the contractility of the colon although data on this last effect is somewhat conflicting [79-82]. In the colon, CCK<sub>1</sub> receptors are found in the myenteric plexus and longitudinal smooth muscles [83] suggesting two potential sites of action for CCK and its effect on colonic motility [84]. In animal studies blocking CCK<sub>1</sub> receptors, the threshold to a noxious rectal distension stimulus in control and inflamed colon was increased [85] suggesting that CCK may have a role in visceral pain perception as well as colonic motor function. Thus, CCK<sub>1</sub> antagonists may have a role in the treatment of functional gastrointestinal disorders [84].

#### 6.4.1 Dexloiglumide

Dexloiglumide is an enantiomer of loxiglumide, which is more potent and has been developed by Rottapharm, Italy. Initial studies of the pharmacodynamic effects in females with IBS-C suggest dexloiglumide 200 mg three times a day increases proximal colonic transit time but has no overall effect on total colonic transit compared with placebo and is well tolerated [81]. Dexloiglumide has recently been assessed in IBS-C in a novel, double-blind, randomised withdrawal trial (the DARWIN study) in which the primary outcome was time to loss of therapeutic effect [86] in terms of the patients' pain relief and global improvement. In those patients randomised to continue taking dexloiglumide, the therapeutic effect was significantly sustained compared to placebo. These results suggest that dexloiglumide may have therapeutic potential in IBS-C and further trials are justified.

The development of two other CCK<sub>1</sub> antagonists, lincrintr from Sanofi-Aventis and devazepide from Merck, has been discontinued.

### 6.5 GC-C receptor agonists

Intestinal enterocytes have membrane guanylate cyclase type-C (GC-C) receptors on the luminal side, which when activated lead to a second messenger cascade that results in increased chloride and bicarbonate secretion in the intestine [87]. The endogenous peptide hormones, guanylin and uroguanylin, normally stimulate these receptors, as do the heat stable enterotoxins [87].

#### 6.5.1 Linaclotide

Linaclotide (MD-1100) from Ironwood Pharmaceuticals, (formerly Microbia, Inc., Cambridge, MA, USA) is an orally active peptide, which binds to GC-C receptors and stimulates a cGMP cascade that in turn activates bicarbonate and chloride secretion into the intestine that stimulates intestinal fluid secretion resulting in a reflex acceleration in transit, the net effect of which is a loosening of stool consistency and an increase in stool frequency. An initial Phase IIa study in IBS-C showed that linaclotide 100 and 1000  $\mu\text{g}$  once a day improved the frequency and consistency of stools [88]. A further large dose-range-finding study on 419 patients with IBS-C demonstrated that a dose as low as 75  $\mu\text{g}$  once a day

had a beneficial effect on bowel frequency and stool consistency, which increased with doses of up to 600 µg/day. In addition, linaclotide showed significant improvements in bloating, abdominal pain and global assessments of IBS symptoms [89].

Linaclotide has also been assessed in chronic constipation with a recently published randomised, double-blind, placebo-controlled study showing a significant improvement in stool frequency and consistency at doses of 100, 300 and 1000 µg/day for 14 days, achieving statistical significance at 100 µg for frequency and 1000 µg for consistency [90]. In another multi-centre, Phase II, dose-ranging study in 310 chronic constipation patients using an improvement in spontaneous bowel movements as a primary outcome, linaclotide significantly improved this parameter as well as stool consistency and straining [91]. In all these studies, linaclotide has appeared to be safe and well tolerated. In addition to an improvement in stool frequency and consistency, linaclotide has also been shown to reduce visceral hypersensitivity in animal models of experimental colitis [92,93].

The antinociceptive activity of linaclotide requires the expression of GC-C [94]. Activation of GC-C by linaclotide leads to the release of cGMP from enterocytes [94]. In animal models of visceral hypersensitivity, intraduodenal cGMP reduced colonic afferent firing [95]. This might explain its additional beneficial effect on abdominal pain and discomfort [89], which are cardinal features of IBS. Linaclotide undergoes minimal absorption and, therefore, the potential for systemic side effects is greatly reduced. So far, the most common side effect reported has been diarrhoea, which might be anticipated in a medication designed for patients affected by constipation. Linaclotide appears to be a promising new drug which continues to be developed with several large trials ongoing [96].

### 6.5.2 Guanililb (SP304)

Another oral GC-C receptor agonist called Guanililb is currently in a Phase I trial with results expected in 2009 [97].

### 6.6 Chloride channel activators

Chloride channels in cell membranes have several important functions besides the essential function of maintaining the resting membrane potential. Their additional role in preserving intracellular pH, cell volume and fluid transport across the cell has particular significance in relation to gastrointestinal function [98]. There are nine different subtypes of chloride channels but the chloride channel type-2 (ClC-2) is of specific interest in drug development for constipation. Lubiprostone stimulates ClC-2 resulting in increased chloride and fluid secretion into the intestinal lumen, which indirectly affects consistency and frequency of stool. ClC-2 activation has also been shown to play a role in tight junction repair [99]. Lubiprostone has been shown to stimulate recovery of mucosal barrier function in porcine ileum and colon through the repair of these tight junctions, which is opposite to the effect seen by osmotic laxatives [100,101].

### 6.6.1 Lubiprostone

Lubiprostone is a prostone compound obtained from a prostaglandin E1 metabolite. Lubiprostone has been found to be effective in chronic idiopathic constipation in several studies [102,103] and is currently approved by the FDA for the treatment of chronic constipation at 24 µg b.i.d. as well as for IBS-C at the dose of 8 µg b.i.d. Initial dose ranging studies with lubiprostone have shown an improvement in abdominal pain and discomfort in IBS-C patients along with an improvement in spontaneous bowel movements, stool consistency and the degree of straining [104]. There was also an increased response in the primary and secondary end points at a higher 24 µg dose although at the expense of increased side effects, especially nausea and diarrhoea. Experience from these studies in chronic constipation and IBS suggests that a dose of 8 µg b.i.d. achieves the right balance between efficacy and side effects and is also well tolerated over longer periods of time as shown in an open-label study for 48 weeks in IBS patients [105].

Analysis of two Phase III trials including 1154 subjects revealed a significant improvement in global IBS symptoms with lubiprostone, which was independent of its effect on individual IBS-C symptoms [106]. It is also interesting to note that the effect of lubiprostone appears to continue even after the withdrawal of the drug and there does not appear to be any rebound of symptoms [107]. Lubiprostone 24 µg twice daily has been submitted for approval in Europe for chronic constipation and the application is under review.

### 6.7 Neurokinin receptor antagonists

The tachykinins are neurotransmitters in the enteric nervous system primarily represented by substance P, neurokinin A (NK<sub>A</sub>) and neurokinin B (NK<sub>B</sub>) all of which act through the NK<sub>1</sub>, NK<sub>2</sub> and NK<sub>3</sub> receptors [108]. In the gastrointestinal tract, NK<sub>2</sub> is found in smooth muscle cells, NK<sub>1</sub> in both neurons and smooth muscle cells, whereas NK<sub>3</sub> is only found in neurons. These receptors have an effect on the sensitivity and the motility of the gut [109] and have generated a lot of interest for their potential role in the treatment of IBS. Besides the gastrointestinal tract, NK<sub>2</sub> receptors are also found in the hippocampus and hypothalamic areas and may modulate the gastrointestinal response to emotional stimuli [110]. An NK<sub>2</sub> receptor antagonist nepadutant, which was initially studied in animal models for IBS, is now being developed for its use in postoperative ileus [111]. Similarly, saredutant, another NK<sub>2</sub> antagonist is currently undergoing clinical trials to assess its role in depression. There is no development of either of these agents in IBS at present. Similarly, we are not aware of any ongoing human trials of the NK<sub>1</sub> receptor antagonist in IBS. In addition, an NK<sub>3</sub> receptor antagonist talnetant failed to show any effect on rectal sensitivity in humans [112], as well as failing to improve the symptoms of IBS, in a Phase II dose ranging study [113].

### 6.8 CRH receptor antagonists

Corticotrophin releasing hormone (CRH), alternatively known as corticotrophin releasing factor (CRF), is secreted from the

hypothalamus in response to stress, which in turn stimulates the pituitary to release adrenocorticotrophic hormone and  $\beta$ -endorphins. It has been suggested that CRF may have a role in the mediation of anxiety and stress responses [114,115] as well as the stress related effect on gut motility [116]. A human study suggested that the infusion of CRH analogue increases the gut motility index, more in IBS patients than in healthy volunteers [9]; furthermore, the infusion of a CRH receptor antagonist improved gut motility and visceral perception [117] in response to stress stimulation of the gut. Despite initial promise seen in preclinical studies in the development of the CRH<sub>1</sub> receptor antagonist, Pfizer has discontinued development of CP-154526. Another CRH<sub>1</sub> receptor antagonist, pexacerfont (BMS-562,028), did not demonstrate any significant effect on colonic transit in women with IBS [118]; however, it is currently being developed for use in anxiety. The CRF<sub>1</sub> receptor antagonist, GW876008, is still under active development by GlaxoSmithKline for IBS, although no results are yet available [119].

### 6.9 Probiotics

According to the WHO definition, probiotics are “live microorganisms which, when consumed in adequate amounts as part of food, confer a health benefit on the host” [120]. These organisms have a wide variety of effects that could influence many of the factors thought to be important in the pathophysiology of IBS [15,121,122]. There have been a large number of studies in IBS of a variety of probiotic preparations either containing single organisms or mixtures. Unfortunately, the design of the trials has varied considerably making comparison difficult, although the majority of these studies have been positive [123].

The most commonly utilised organisms have been the bifidobacteria and the lactobacillae and a recent study undertook a direct comparison of two examples of these. In a double-blind randomised controlled trial, *Lactobacillus salivarius* and *Bifidobacterium infantis* 35624 were compared with placebo for 8 weeks with 25 patients in each group [15]. Using a composite score combining abdominal pain, bloating and bowel dysfunction, a significant improvement was observed with *B. infantis* 35624 compared to either *L. salivarius* or placebo with the beneficial effect starting after 2 weeks and persisting for some time after treatment finished. IL-10, an anti-inflammatory cytokine and IL-12, a pro-inflammatory cytokine, were also measured before and after treatment in all groups. The ratio of IL-10:IL-12 was in a pro-inflammatory state before treatment and this was normalised in those receiving *B. infantis* 35624 suggesting one possible mechanism to explain the beneficial effect. In another study, different strengths of the *B. infantis* 35624 were compared in capsule form with the  $1 \times 10^8$  CFU per capsule once a day proving to be most effective with a wide range of symptoms being improved irrespective of bowel habit subtype [124]. It should be noted that the  $1 \times 10^{10}$  CFU per capsule dose was not effective in capsule form although, this was the optimal dose

in a previous study, which delivered the organism in malted milk. The failure of the  $1 \times 10^{10}$  CFU per capsule dose was subsequently shown to be due to poor bioavailability secondary to clumping. This highlights some of difficulties in ensuring adequate doses, which have to be high, are achieved. Another widely available probiotic mixture, VSL3, has been assessed in IBS and appears to help bloating and flatulence but does not seem to have an effect on the other symptoms of IBS [125]. *Bifidobacterium lactis* DN-173-010, marketed as Activia, has also been shown to be effective in a large study in primary care IBS patients [126] and more recently this organism has been shown to reduce objectively measured distension in IBS-C as well as improving transit times [127]. It, therefore, seems that probiotics hold out considerable promise in the treatment of IBS but the availability of quality products is currently rather patchy making it difficult for the medical profession to make specific recommendations.

### 7. Potential development issues

Hopefully, the major problems that were experienced with the 5-HT receptor agonists and antagonists will not necessarily occur when drugs modulating other potential IBS targets come on stream. However, the events surrounding alosetron and tegaserod have undoubtedly created an extremely negative regulatory climate, which seems peculiar to the field of IBS. This is presumably because this condition is considered as not particularly serious and, therefore, the treatment must be completely safe. This suggests a lack of awareness of the data demonstrating just how severe IBS can be in a large proportion of patients with this condition that affects between 10 and 15% of the population. For instance, in the secondary care settings, women with IBS liken the pain to that of childbirth [128]; the symptoms of IBS can drive patients to even contemplate suicide [21]; 20% of patients experience faecal incontinence [129] and the quality of life of sufferers has been shown to be worse than that of patients with diabetes or end stage renal failure [4].

Another difficult issue where there is still no firm agreement is the design of therapeutic trials in IBS. It has been traditional to regard abdominal pain as one of the most important symptoms of the condition but there is plenty of evidence to suggest that many patients would rank another feature of the condition, such as bloating or even lethargy, as the problem that they would most like to be ameliorated. This raises the question of what is the ideal primary outcome measure and what other features of IBS should be recorded for the purposes of a clinical trial [130]. Currently, the most commonly used primary outcome is a global rating score either in the form of a binary or graded scale and this has the advantage in that it can capture an overall improvement rather than a change in just one symptom. Some authorities suggest some form of symptom severity scale should also be adopted but this has the disadvantage that outcome can only be recorded in terms of a mean reduction in score rather than an actual

response rate. Nevertheless, symptom severity is a useful measure and there seems to be no reason why a global rating and a symptom severity score cannot be used in conjunction. With regard to secondary outcomes, these often have to be dependent on the medication under scrutiny, for instance, pain for a visceral analgesic. However, as most patients have a constellation of symptoms, recording how they change is always of interest; for example, does low back pain improve when constipation is relieved? It is also essential that instruments measuring quality of life and psychological well being are used. Unfortunately, at present, different scales for all these parameters are used in different trials and there is certainly a need for consensus on how some uniformity can be introduced.

There is a huge unmet need for new drugs for IBS but unless pharmaceutical companies can be convinced that their molecules, even when they are shown to be effective and relatively safe, stand a fair chance of reaching the market place, they are not going to risk entering the area.

### 8. Conclusion

At the present time, there are some promising new medications in the pipeline for IBS-C which are proving to be safe as well as effective. Currently, the same cannot be said for the diarrhoea predominant form of the condition. There has been a surge of interest in the use of probiotics partly because they are perceived as completely safe and are, therefore, viewed as the only alternative in the face of the many problems associated with drug development. Fortunately, probiotics do appear to be effective although it would seem reasonable to predict that their potency may not be sufficient to help the more severe cases seen in, for instance, tertiary care. Most of the approaches currently under development are directed at the gut and the possible benefit of more centrally acting moieties should not be ignored.

### 9. Expert opinion

It is still not certain whether IBS is a single entity or whether it is a conglomeration of closely related conditions. Consequently, unless there is a major paradigm shift as was witnessed with duodenal ulceration and *H. Pylori* in the 1980s, drug development is going to continue to be aimed at the various

putative mechanisms involved in the pathophysiology of this disorder.

There is a strong familial clustering of IBS suggesting a genetic component for the condition, which is supported by some but not all twin studies. This has led to the search for genetic variations, at present mainly in the adrenergic and serotonergic systems [131], although other neurotransmitters and their associated receptors will undoubtedly come under the spotlight in future. In addition, there is a growing interest in the genetic control of immunological function in relation to the pathogenesis of IBS, as well as some interesting observations on polymorphisms of mitochondrial DNA [132]. Ion channelopathies were originally associated with inherited muscle diseases and sudden death syndromes, but more recently have been implicated in epilepsy, chronic pain and migraine [133]. As there is an association between migraine and IBS [134], it seems reasonable to assume that the role of channelopathies in IBS is worthy of exploration [135].

Other receptors that are thought to deserve further investigation in relation to IBS are TRPV1 [136,137], endocannabinoid [138-140] and protease activated receptors [141,142]. However, when contemplating the modulation of single receptors in relation to the treatment of IBS, it might be salutary to bear in mind that probably the most effective treatment that is currently available for IBS is the use of a tricyclic antidepressant [143]. This class of drug is not as 'clean' as most modern medications suggesting that molecules that target more than one receptor may be more effective in IBS. Furthermore, it also suggests that the CNS must not be forgotten when contemplating new therapeutic approaches in this condition.

Lastly, it needs to be recognised that the current harsh regulatory environment that surrounds the development of new drugs for IBS is deliberately discriminating against a disorder that is silently destroying the lives of many of its sufferers.

### Declaration of interest

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