Treatment of irritable bowel syndrome: beyond fiber and antispasmodic agents

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***Abstract*:** Irritable bowel syndrome (IBS) is a chronic functional disorder of the gastrointestinal tract of unknown etiology. The diagnosis of IBS is made clinically, using symptom-based criteria such as the Manning or Rome criteria. Medical therapy for this condition has traditionally been directed towards symptom relief, using fiber or antispasmodic agents. In recent years, emerging data have confirmed the efficacy of antidepressants, psychological therapies, 5-HT_3 antagonists, 5-HT_4 agonists, and probiotics in the short-term treatment of IBS, although whether these therapies influence the long-term course of the disease is unknown. Increasing knowledge regarding the pathophysiological mechanisms underlying IBS has resulted in a number of novel molecular treatments, which show promise. These include therapies targeting gastrointestinal mucosal chloride channels and guanylate cyclase-C receptors, as well as highly selective agents influencing serotonergic transmission that, at the time of writing, do not appear to have any severe deleterious effects. In this article we provide a summary of current and emerging therapies in this field.

***Keywords*:** 5-hydroxytryptamine, antibiotics, antidepressants, chloride channel, glucagon-like peptide, irritable bowel syndrome, probiotics, psychological therapy

Definition of irritable bowel syndrome

Irritable bowel syndrome (IBS) is a chronic relapsing and remitting functional disorder of the gastrointestinal (GI) tract. The presence of IBS is defined by clinical criteria, which include the presence of abdominal pain, or discomfort, and an alteration in bowel habit, in the absence of 'red flag' alarm features such as weight loss or anemia. The first of these, the Manning criteria, were described over 30 years ago [Manning *et al.* 1978]. Subsequently, the Rome criteria were developed as a result of consensus of expert opinion [Drossman *et al.* 1990]. These have been revised on two subsequent occasions [Longstreth *et al.* 2006; Thompson *et al.* 1999]. Symptom-based criteria such as these demonstrate only modest likelihood ratios for the diagnosis of IBS [Ford *et al.* 2008b]. However, there is no accurate biomarker for this condition [Lembo *et al.* 2009]. As a result, current management guidelines from international organizations recommend their use in making a positive diagnosis of IBS, without the need for extensive GI investigations [Brandt *et al.* 2009; Spiller *et al.* 2007].

Prevalence

IBS is a common condition, affecting between 5% and 20% of the population in community surveys [Hungin *et al.* 2005; Hillila and Farkkila, 2004; Agreus *et al.* 2000]. The prevalence varies according to the diagnostic criteria used to define its presence with the Manning criteria, which do not require a minimum duration of symptoms, leading to a higher prevalence than the Rome criteria [Boyce *et al.* 2000]. In general, prevalence is increased in younger individuals, females, and those with coexisting functional GI diseases [Drossman *et al.* 1993], particularly dyspepsia [Ford *et al.* 2010]. IBS is also more common in patients with other functional disorders, such as fibromyalgia and chronic fatigue [Riedl *et al.* 2008].

Pathogenesis of irritable bowel syndrome

The cause of IBS is obscure, and it is unlikely that a single entity is responsible for the diverse presentations of this heterogeneous disorder. There is evidence that GI inflammation may precipitate IBS symptoms. Patients with inflammatory bowel disease, particularly ulcerative colitis,

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experience higher than expected levels of symptoms compatible with IBS when in remission [Isgar *et al.* 1983], and this may be due to continued subclinical low-grade inflammation [Keohane *et al.* 2010]. Ongoing postinflammatory dysmotility has also been demonstrated in inflammatory bowel disease patients [Loening-Baucke *et al.* 1989]. Furthermore, the development of IBS-type symptoms following acute bacterial or viral gastroenteritis is well-described [Thabane *et al.* 2007]. This may also reflect persistent low-grade chronic mucosal inflammation [Chadwick *et al.* 2002], or perhaps postinfectious malabsorption of bile acids [Niaz *et al.* 1997].

Another proposed etiological factor in the pathogenesis of IBS is intestinal dysbiosis. This includes both alterations in large intestinal commensal bacteria, [Kassinen *et al.* 2007] and the presence of small intestinal bacterial overgrowth (SIBO), following hydrogen breath testing, in a subset of patients with IBS [Pimentel *et al.* 2000]. There is some biological plausibility to the latter concept, as symptoms such as abdominal bloating, discomfort, and diarrhea are common to both SIBO and IBS [Riordan *et al.* 2001]. A higher prevalence of SIBO has been reported in patients with symptoms compatible with IBS, depending on both the diagnostic test and the threshold for positivity used to define its presence [Ford *et al.* 2009b]. However, the potential unreliability of hydrogen breath tests, compared with the gold-standard of jejunal aspirate and culture, brings this causal relationship into question [Corazza *et al.* 1990].

A number of other pathophysiological abnormalities have been identified within the GI tract, its associated neural pathways, and the central processing of pain perception. However, it is possible that these are secondary sequelae, rather than initiating phenomena in the development of IBS. These include immune dysregulation [Chadwick *et al.* 2002], increased intestinal permeability [Marshall *et al.* 2004], alterations in GI serotonergic transmission [Atkinson *et al.* 2006], abnormal GI motility [McKee and Quigley, 1993], and visceral hypersensitivity [Trimble *et al.* 1995].

Finally, genetic factors may play a role in IBS. The condition aggregates in families, and relatives of a patient with IBS are almost three times more likely to report symptoms compatible with IBS than relatives of the patient's spouse [Kalantar *et al.* 2003]. Whether this is due to genetic susceptibility, shared childhood environment, or learned illness behavior is unclear. Twin studies demonstrate that there is a greater concordance of IBS in monozygotic *versus* dizygotic twins [Bengtson *et al.* 2006; Levy *et al.* 2001]. However, having a parent with IBS was a stronger predictor than having a twin with IBS [Levy *et al.* 2001]. Despite these observations, the results from studies of various candidate genes are conflicting [Grudell *et al.* 2008; Pata *et al.* 2004].

Treatment of irritable bowel syndrome

Because the cause of IBS remains unknown there is no discrete lesion to target therapy towards. As a result, the management of IBS has tended to focus on the amelioration of symptoms, rather than disease modification or cure. Traditional first-line strategies include increasing fiber intake to regulate defecation, although there are concerns that insoluble fiber may exacerbate symptoms in some sufferers [Miller *et al.* 2006], and the use of antispasmodic agents, such as hyoscine and peppermint oil, to control abdominal pain and improve diarrhea. There is evidence to support both of these approaches [Ford *et al.* 2008a]. However, many of the trials that report the use of these agents do not adhere to the recommendations made by the Rome foundation for the design of treatment trials for the functional GI disorders [Irvine *et al.* 2006], although this is largely because the majority of these trials were designed and conducted before these guidelines were published.

There have been two large randomized controlled trials (RCTs) published recently that reported the efficacy of either fiber or antispasmodics in IBS, which did adhere to the Rome foundation recommendations [Wittman *et al.* 2010; Bijkerk *et al.* 2009]. Whilst both soluble and insoluble fiber [Bijkerk *et al.* 2009] and alverine [Wittman *et al.* 2010] appeared more effective than placebo in terms of improvement in symptoms, between 50% and 70% of patients failed to respond to therapy, and duration of follow up was only 4 weeks in one trial [Wittman *et al.* 2010] and 3 months in the other [Bijkerk *et al.* 2009]. These results emphasize the need for more effective therapies for the long-term treatment of IBS.

Some of the etiological mechanisms outlined above have fuelled research into a number of novel treatment modalities that will be discussed.

There is no gold standard for the treatment of IBS, meaning that when new therapies are tested, they are usually compared with placebo. However, placebo response rates in the condition are high, with between 30% and 40% of patients experiencing relief or resolution of symptoms in a recent meta-analysis that examined this issue [Ford and Moayyedi, 2010b].

Antidepressants

Tricyclic antidepressants (TCADs) are effective in the treatment of chronic pain [Saarto and Wiffen, 2007]. Thus, these drugs may have an effect in IBS via a reduction in visceral hypersensitivity, which has been demonstrated in sufferers [Trimble *et al.* 1995]. At the molecular level, TCADs inhibit the re-uptake of both serotonin and norepinephrine, increasing the bioavailability of these neurotransmitters in the synaptic cleft. They also antagonize muscarinic acetylcholine receptors [Gillman, 2007], These antimuscarinic effects of TCADs are responsible for many of their side effects, including constipation, dry mouth, and blurred vision [Gorard *et al.* 1994]. However, slowing of GI transit may be of therapeutic advantage in diarrhea-predominant IBS (IBS-D) [Drossman *et al.* 2003]. In contrast, selective serotonin re-uptake inhibitors (SSRIs) prevent the re-uptake of serotonin alone. Serotonin acts as a secretagogue, and tends to stimulate GI motility [Gorard *et al.* 1994]. Accordingly, SSRIs could particularly help those with constipation-predominant IBS (IBS-C).

Antidepressants appear to be more effective than placebo in treating patients with IBS. A recent systematic review and meta-analysis reported a number needed to treat (NNT), compared with placebo, to prevent one patient experiencing persistent global IBS symptoms or abdominal pain of four [Ford *et al.* 2009c]. There were no serious adverse events associated with antidepressant usage, although there was a nonsignificant trend towards increased side effects (most frequently drowsiness and dizziness) compared with placebo (18% *versus* 9%). Included studies evaluated both TCADs, including amitriptyline, doxepin, and desipramine, as well as SSRIs, such as fluoxetine, citalopram, and paroxetine. Three further RCTs have been published since this meta-analysis was published, but the results are conflicting, with two demonstrating a benefit of TCADs and SSRIs [Abdul-Baki *et al.* 2009; Masand *et al.* 2009] and a third demonstrating no benefit of SSRIs [Ladabaum *et al.* 2010]. However, when the results of these trials are incorporated into the prior meta-analysis the benefit of both TCADs and SSRIs remains reassuringly similar [Ford and Moayyedi, 2010a].

In summary, antidepressants are effective treatments for IBS, probably as a result of their antinociceptive effects, although additional effects on GI transit may be contributory. Whether any beneficial effect occurs via the treatment of co-existent depression remains unclear, but there was no correlation between depression scores and improvements in IBS symptoms in the studies identified in the meta-analysis that examined this issue [Ford *et al.* 2009c]. Furthermore, in the case of TCADs, the doses employed for treating IBS were generally much lower than those used for the treatment of depression. The paucity of data available on the safety and tolerability of antidepressants in IBS limits their usage to second-line therapy, according to current IBS management guidelines [Brandt *et al.* 2009; Spiller *et al.* 2007].

Agents acting on the 5-hydroxytryptamine receptor

In contrast to TCADs and SSRIs, these drugs modulate 5-hydroxytryptamine (5-HT) transmission directly, by binding to 5-HT receptors. The 5-HT_1, 5-HT_3, and 5-HT_4 receptor subtypes play major roles in motor, sensory, and secretory function of the GI tract [Gershon, 1999]. Intestinal 5-HT release is associated with smooth muscle contraction, increased luminal secretions, and reduced GI transit time [Turvill *et al.* 2000; Ruckebusch and Bardon, 1984]. The blockade of $5HT_3$ receptors, notably by antiemetics such as ondansetron, has been observed to result in constipation [Haus *et al.* 2004]. As a result, 5-HT_3 receptor antagonists, such as alosetron and cilansetron, have been developed and tested in IBS-D over the last decade. A recent systematic review and meta-analysis identified 11 RCTs comparing these two 5-HT_3 antagonists with placebo [Ford *et al.* 2009a]. These agents were effective in IBS, with a NNT for 5-HT_3 antagonists to cure or improve one patient's IBS symptoms of seven, and similar efficacy demonstrated for both alosetron and cilansetron. However, a number of rare adverse events, including ischemic colitis and severe constipation, resulted in the withdrawal of alosetron by its manufacturers [US Food and Drug Administration, 2001], and marketing of cilansetron was also suspended as a result. Alosetron is

now available on a restricted basis in the USA, for female patients with severe, intractable IBS-D who have failed to respond to first- or second-line therapies.

Ligands to the 5-HT_4 receptor have prokinetic effects, and have been evaluated in the management of IBS-C. One such agent is tegaserod, a partial agonist at the 5-HT_4 receptor. A systematic review and meta-analysis indicated that tegaserod is superior to placebo in IBS, with a NNT to cure or improve one patient's symptoms of 10 [Ford *et al.* 2009a]. The majority of trial data pertaining to tegaserod involved female participants, and as a result the drug was initially approved for the treatment of IBS-C in women only. However, marketing of tegaserod was also suspended, when a possible increase in cardiovascular and cerebrovascular events was reported [US Food and Drug Administration, 2007].

In summary, agents acting on the 5-HT receptor are modestly effective therapies for the treatment of IBS. Trials that have examined the efficacy of these agents are large, rigorously designed, and the majority adhere to the Rome committee's recommendations for the design of treatment trials for the functional GI disorders [Irvine *et al.* 2006], but associated safety concerns limit their usage at the present time. Agents with enhanced selectivity and potency, and fewer serious side effects, are being developed in this field, which appear encouraging in terms of both safety and effectiveness, and are discussed further in the following.

Probiotics

Probiotics are live microorganisms which, when administered in adequate amounts, confer a health benefit to the host [Hoffman, 2008]. The possibility of manipulating the intestinal flora in order to prolong life was first proposed by Elie Metchnikoff, a Ukranian scientist, more than 100 years ago. The ingestion of probiotics may be associated with both qualitative and quantitative alterations in GI flora [Nanda Kumar *et al.* 2008]. Probiotics have been shown to reduce the risk of antibiotic-induced GI symptoms [Colombel *et al.* 1987], traveler's diarrhea [Katelaris *et al.* 1995], and a systematic review and meta-analysis has demonstrated their efficacy in shortening the duration of illness in infectious diarrhea, compared with placebo or no treatment [Allen *et al.* 2004].

Data from both animal models and studies conducted in humans suggest that probiotics may be of benefit in IBS. Changes in the composition of GI commensals have been demonstrated in patients with IBS [Kassinen *et al.* 2007; Malinen *et al.* 2005]. Murine studies have demonstrated a reduction in visceral hypersensitivity [Verdu *et al.* 2006], and attenuation of postinfectious muscle hypercontractility [Verdu *et al.* 2004], following administration of probiotics. They may also have an influence on the host immune response to infection, as indicated by a reduction in circulating cytokine levels [O'Mahony *et al.* 2005]. Thus, it is plausible that, by altering the luminal milieu, probiotics can attenuate symptom generation by reducing both levels of inflammation and visceral hypersensitivity.

The largest RCT, to date, of probiotics in IBS compared three doses of encapsulated *Bifidobacterium infantis* 35624 with placebo [Whorwell *et al.* 2006]. The authors reported a statistically significant benefit of *B. infantis* at a dose of 10^8 colony forming units (CFU) on abdominal pain, bloating, tenesmus, and straining at study end. However, doses of 10^6 and 10^{10} CFU were not superior to placebo, although the dissolution characteristics of the capsule for the latter dose were suboptimal, leading the authors to speculate that this may have led to the nonsignificant result observed.

A recent systematic review and meta-analysis identified 19 RCTs reporting the effect of probiotics on IBS symptoms [Moayyedi *et al.* 2010]. When data from the 10 RCTs that reported the effect of probiotics as a dichotomous outcome were analyzed, probiotics were superior to placebo, with a NNT to improve or cure one patient's IBS symptoms of four. The beneficial effect of probiotics may have been overestimated, however, as there was funnel plot asymmetry suggesting publication bias, or other small study effects. In addition, there was statistically significant heterogeneity when study results were combined, perhaps due to the multiplicity of probiotic species, strains, and dosages used. Fifteen trials reported the effect of probiotics on IBS symptoms as a continuous variable. Meta-analysis of these trials demonstrated statistically significant improvements in the individual symptoms of pain and flatulence, and also a trend towards an improvement in bloating. There was no statistically significant increase in total numbers of

adverse events associated with the use of probiotics. When dichotomous data were pooled separately according to the species of probiotic used, there was no statistically significant benefit of any particular species over placebo. The continuous data, however, suggested that combinations of probiotics had the greatest efficacy, with *Bifidobacterium* species demonstrating a trend towards benefit, and *Lactobacillus* having no effect. Further RCTs are required to determine the most efficacious species, or combinations of species, of probiotics in the treatment of IBS.

Antibiotics

A number of RCTs have examined the effect of antibiotics on the symptoms of IBS. Rifaximin, in particular, has generated much interest in recent years [Lembo *et al.* 2008; Ringel *et al.* 2008; Pimentel *et al.* 2006; Sharara *et al.* 2006]. This drug is minimally absorbed providing high luminal bioavailability with few systemic side effects [Scarpignato and Pelosini, 2006]. The efficacy of rifaximin in nonconstipated patients with IBS has been evaluated in two large phase 3 RCTs, containing over 1200 patients in total [Pimentel *et al.* 2010]. Rifaximin was associated with a statistically significantly higher proportion of responders to therapy (defined as adequate relief of IBS symptoms for at least 2 of the first 4 weeks following treatment), compared with placebo (pooled data from both RCTs: 41% *versus* 32%). In addition, adequate relief from bloating was reported by 40% receiving active treatment compared with 30% allocated to placebo. These beneficial effects were sustained over a 10-week follow-up period, suggesting that treatment with rifaximin may alter the natural history of the condition in the short term.

It is assumed that the beneficial effects of rifaximin in these studies are attributable to its antimicrobial properties in treating intestinal dysbiosis. However, confirmatory evidence of the presence of SIBO and eradication rates following treatment have not been reported. Notably, one previous study has demonstrated a gradual recurrence of both IBS symptoms and SIBO (as judged by serial hydrogen breath testing at 3, 6, and 9 months) following rifaximin [Lauritano *et al.* 2008], suggesting that any beneficial effect arising as a consequence of the eradication of SIBO may not be maintained in the longer term. However, one group of investigators has demonstrated that recurrence of SIBO does appear to respond to retreatment with rifaximin [Yang *et al.* 2008].

In summary, rifaximin has been shown to be more effective in treating symptoms of IBS than placebo, particularly in terms of relief of bloating. To date, most studies have been limited by their short duration of follow up, and it remains to be seen whether improvements in IBS symptoms are sustained. Clarification of the true prevalence of SIBO, as well as the response to treatment over extended follow up, is required before the routine exclusion of SIBO and treatment of the disorder in IBS can be recommended.

Psychological therapies

An increase in psychological morbidity has been observed in patients with IBS, including anxiety, mood disorder, and neuroticism [Solmaz *et al.* 2003]. Such observations have prompted investigators to evaluate various psychological therapies in IBS. A systematic review and meta-analysis in this field has been conducted recently [Ford *et al.* 2009c]. This identified 20 RCTs, including almost 1300 patients, who were randomized to receive either psychological therapy or control therapy/usual management. The most robust evidence for any benefit of psychological therapy was observed with cognitive behavioral therapy with a NNT of three, but hypnotherapy (NNT of two), multicomponent psychological therapy (NNT of four), and dynamic psychotherapy (NNT of 3.5) also appeared to be superior to control therapy. However, the total number of studies was small for the latter three therapies. In addition, significant heterogeneity was apparent when all studies were pooled, and the majority of RCTs were of low methodological quality and involved small sample sizes. A further concern was that nine of the studies were conducted by the same group of researchers [Sanders *et al.* 2007; Keefer and Blanchard, 2001; Galovski and Blanchard, 1998; Vollmer and Blanchard, 1998; Payne and Blanchard, 1995; Greene and Blanchard, 1994; Blanchard *et al.* 1993, 1992; Neff and Blanchard, 1987], and the effect of active therapy in these studies was significantly greater than those conducted in other centers. This may mean that patients recruited to these trials were different to those in the other studies, or that there were other differences in either trial methodology or outcomes assessment in these RCTs. This, in turn, could limit the generalizability of the findings of these studies to patients

encountered in usual clinical practice in a gastroenterology outpatient clinic.

One element of the benefit apparent with psychological therapies over control therapies may relate to the regular contact with health professionals in the intervention arms of the RCTs during the study period. It is therefore particularly important to ascertain whether any improvements in IBS symptoms following treatment are sustained in the longer term. Unfortunately, such data are lacking. Further high-quality RCTs, with longer durations of follow up, are therefore required in order to make informed judgments regarding the role of psychological therapies in IBS. At present, due to the high level of one-to-one patient contact required for the administration of such therapies, their use cannot be recommended routinely, and they should be reserved for individuals who have failed more conventional therapies.

Drugs modifying pain receptors

As visceral hypersensitivity is a proposed etiological factor in IBS, one way to improve sufferers' symptoms might be to modulate pain receptors in the GI tract. Pregabalin and gabapentin, drugs believed to inhibit pain via the α2δ-subunits of voltage-gated calcium channels, have both been studied in small single-center RCTs [Houghton *et al.* 2007; Lee *et al.* 2005]. Pregabalin was more effective than placebo, in terms of increasing the sensory thresholds for perception of rectal distension, desire to defecate, and rectal pain, and also demonstrated a trend towards an improvement in average daily pain scores during 3 weeks of therapy [Houghton *et al.* 2007]. Patients treated with gabapentin demonstrated significantly increased rectal compliance, as well as higher sensory thresholds for bloating, discomfort, and pain during a 5-day treatment period [Lee *et al.* 2005].

Efficacy of agonists at the κ-opioid receptor have also been studied in IBS. After a 100-mg intravenous infusion of fedotozine thresholds to first perception of colonic distension and pain were significantly increased compared with placebo [Delvaux *et al.* 1999]. A single dose of asimadoline led to an increased pain threshold to colonic distension, and significantly reduced the area under the curve of pain intensity in a crossover RCT conducted in 20 IBS subjects [Delvaux *et al.* 2004]. However, further large RCTs of the latter drug have been disappointing. [Mangel *et al.* 2008; Szarka *et al.* 2007]. One RCT demonstrated no difference in achievement of the primary end point, average reduction in pain severity 2 hours after treatment, between asimadoline and placebo [Szarka *et al.* 2007], although in a *post hoc* analysis, there appeared to be a benefit in those with an alternating bowel habit. The second study, conducted in almost 600 IBS patients, also failed to demonstrate any superiority of the drug over placebo when the proportion of months with adequate relief of IBS pain or discomfort was the primary outcome (37% with active drug *versus* 33% with placebo) [Mangel *et al.* 2008]. In contrast to the study by Szarka and colleagues when a preplanned subgroup analysis was conducted, the drug appeared significantly more effective than placebo only in IBS-D patients (47% *versus* 20%).

Emerging therapies

Intensive research into the pathophysiological basis of IBS has led to the development of a number of novel molecular therapies in IBS, acting selectively at hormone receptors, chloride channels, 5-HT receptors, and guanylate cyclase-C receptors within the GI tract mucosa.

Cholecystokinin (CCK) and corticotropin releasing factor (CRF) are hormones implicated in the control of GI motility, whose manipulation may improve symptoms of IBS. The effect of 7 days of dexloxiglumide, a CCK-1 receptor antagonist, has been studied in female IBS-C patients [Cremonini *et al.* 2005]. However, the drug had no overall effect on colonic transit time. Despite this, the proportion of patients with satisfactory relief of their IBS symptoms was higher with dexloxiglumide than with placebo (39% *versus* 11%), although this difference was not statistically significant. Pexacerfont, a CRF-1 receptor antagonist, has been evaluated in women with IBS-D [Sweetser *et al.* 2009]. This drug had no effect on orocecal transit time, stool frequency or consistency, or subjective IBS symptoms, including pain and bloating.

Chloride channels play a pivotal role in fluid transportation within the GI tract [Murek *et al.* 2010]. Lubiprostone, a prostaglandin E_1 derivative that activates mucosal epithelial chloride channels, promotes chloride-rich fluid secretion into the lumen of the GI tract [Bao *et al.* 2008]. This leads to softening of the stool and increased intestinal motility [Camilleri *et al.* 2006]. The drug has been shown to be effective in chronic idiopathic constipation (CIC), with a rapid onset of action [Johanson *et al.* 2008b; Johanson and

Ueno, 2007]. However, side effects (specifically nausea and headache) were common, particularly at higher doses. Following phase 2 studies of lubiprostone in IBS-C patients [Fukudo *et al.* 2010; Johanson *et al.* 2008a], two 12-week placebo-controlled phase 3 trials were conducted, involving over 1000 patients with Rome II IBS-C [Drossman *et al.* 2009]. The primary outcome measure used to define response to treatment was patient-reported moderate improvement in IBS symptoms for all 4 weeks of therapy, or significant relief of symptoms for 2 out of 4 weeks. Responders for at least 2 of the 3 months of treatment were classed as overall responders. When data from the two RCTs were pooled, lubiprostone led to a statistically significant increase in the number of overall responders compared with placebo (18% *versus* 10%). Significant improvements in stool consistency, straining, and severity of constipation were also observed throughout the 3 months of treatment. Side effects included nausea and diarrhea. The unusually low placebo response rate in this study, compared with the published literature [Ford and Moayyedi, 2010b], is likely to reflect the strict criteria used to define treatment response.

In an open-label extension trial, lubiprostone appeared to be both safe and well tolerated over a 48-week treatment period [Chey *et al.* 2008a]. In addition, discontinuation of lubiprostone did not lead to rebound symptoms in a randomized trial of withdrawal of therapy [Chey *et al.* 2008b]. As the majority of participants in the above trials were female, the US Food and Drug Administration approved lubiprostone for the treatment of female patients with IBS-C in 2008. Further RCTs are therefore required both to replicate these data, and to establish whether this therapy is also effective in males with the condition.

Following the withdrawal of both alosetron and tegaserod, newer agents acting on the 5-HT receptor have been developed. Ramosetron is a potent, and selective, 5-HT_3 antagonist which has been tested in a phase 3 12-week RCT involving 539 patients meeting Rome II criteria for IBS-D [Matsueda *et al.* 2008]. In contrast to previous RCTs involving 5-HT_3 antagonists, the majority of study participants were male. Ramosetron was superior to placebo in improving global IBS symptoms (47% *versus* 27%). Significant improvements in abdominal pain (46% *versus* 33%) and abnormal bowel habit (44% *versus* 24%) were also noted. The commonest side effect was hard stools. Ramosetron is currently licensed for use in male and female patients with IBS in South-East Asia and Japan.

Prucalopride is a highly selective 5-HT_4 agonist which is more effective than placebo in the treatment of CIC, but has yet to be tested in patients with IBS. In a 12-week phase 3 RCT involving over 600 patients with severe CIC, significantly more patients receiving 2 or 4 mg of prucalopride obtained relief from constipation than with placebo (defined as an average of three or more complete spontaneous bowel movements per week) [Camilleri *et al.* 2008]. The commonest side effects associated with prucalopride were headache and abdominal pain. No cardiovascular or cerebrovascular events were observed. It is hoped that the high affinity and selectivity of this agent for 5-HT_4 receptors will provide a more favorable side effect profile than tegaserod, and RCTs in patients with IBS-C are anticipated.

Another therapy that may have therapeutic potential in IBS-C is linaclotide, a guanylate cyclase-C receptor agonist. Like lubiprostone, this agent stimulates chloride rich luminal secretion in the GI tract, but it achieves this indirectly by increasing intracellular cyclic guanosine monophosphate. This activates the cystic fibrosis transmembrane regulator chloride channel, in turn leading to increased intestinal chloride and bicarbonate [Golin-Bisello *et al.* 2005], and therefore stimulates intestinal fluid secretion [Bryant *et al.* 2010]. The drug has been shown to reduce pain in animal models of visceral hypersensitivity [Eutamene *et al.* 2010]. Scintigraphic studies in females with IBS-C indicate that linaclotide accelerates ascending colon transit times and overall colonic transit at 48 hours, compared with placebo [Andresen *et al.* 2007]. A recent phase 2 study randomized 420 predominantly female patients with IBS-C to 75, 150, 300, or 600 μg of linaclotide or placebo for 12 weeks [Johnston *et al.* 2009]. A dose of 300 μg produced the most favorable effects, in terms of improvements in constipation scores, pain scores, and global IBS symptom scores, compared with placebo. Linaclotide was well tolerated, the commonest side effect being diarrhea. A phase 3 trial of linaclotide in IBS-C patients is now underway.

The glucagon-like peptide 1 (GLP-1) analog, ROSE-010, is in development as a novel

treatment for acute pain attacks in patients with IBS. When administered subcutaneously, synthetic GLP-1 analogs bind to receptors in the GI tract, inhibiting both gastric emptying [Naslund *et al.* 1999], and reducing small intestinal motility [Tolessa *et al.* 1998]. A phase 2 RCT of ROSE-010 has been performed recently in over 160 patients with IBS [Hellstrom *et al.* 2009]. Outcome measures included pain relief and intensity of pain, assessed using visual analog scales. A higher proportion of participants randomized to receive ROSE-010 obtained at least 50% pain relief within 1 hour, compared with those receiving placebo. Rates of complete pain relief appeared to be higher in females than males. The main side effect of ROSE-010 was nausea (28% *versus* 0%), presumably arising via inhibition of gastric emptying. Although GLP-1 analogs act primarily on GI motility, the study outcome measures did not include an assessment of bowel habit. The mechanism of pain relief is yet to be elucidated. Given its subcutaneous administration it is unlikely that this treatment will be particularly convenient for patients with IBS, other than in a small minority with intractable episodes of pain.

Conclusions

IBS is a chronic relapsing condition and is associated with significant disability in some sufferers, and a considerable financial burden to the health service, due to the consumption of resources including physician time, investigations, and costs of treatment. Although there are a number of pharmaceutical agents in development for the management of IBS, it remains to be seen whether the optimal action of these treatments is as sole or adjunctive agents, and long-term safety and efficacy studies are awaited. At present, no drug has been shown to alter the clinical course of IBS, and most of the treatments available currently have only a modest effect on symptom improvement, with their efficacy in the longer term remaining unknown. There is therefore a clear need for further research into potential novel treatments for this condition. However, the number of innovative therapies in the development for the treatment of IBS discussed in this article are testament to the ongoing research that is being conducted in this field, and should provide cautious optimism for both IBS sufferers and the physicians who treat them. In the meantime management strategies for this complex condition will still need to be tailored to individuals' symptoms, and may require input from pharmacological, dietetic, behavioral, and psychological perspectives.

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