Evaluation of drug treatment in irritable bowel syndrome

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The irritable bowel syndrome (IBS) remains a therapeutic challenge in part because of the limited understanding of the pathophysiology. The placebo response rate varies in randomized controlled trials from 20 to 70%, and can persist for up to at least 1 year. It is contentious whether dietary fibre and bulking agents relieve the symptoms of IBS; constipation probably improves. Anticholinergic and antispasmodic agents are of questionable benefit in IBS despite positive meta-analyses of poor quality trials. A meta-analysis concluded that the tricyclic antidepressants were superior to placebo in IBS, although the individual trial results were variable. Selective serotonin reuptake inhibitors are of uncertain benefit. Laxatives are used for constipation but probably poorly control the IBS symptom complex. Loperamide is superior to placebo in improvement of diarrhoea but not abdominal pain in IBS. Tegaserod is a well- tolerated aminoguanidine indole derivative of serotonin that is a partial $5HT_4$–receptor agonist with prokinetic properties; a therapeutic gain over placebo of 5% to 15% has been observed in constipation-predominant IBS in females. Alosetron is a $5HT_3$-receptor antagonist that is efficacious in females with diarrhoea-predominant IBS, with a 12% to 17% therapeutic gain; the risk of ischaemic colitis is 1 in 350, with very severe constipation occurring in about 1 in 1000. Optimizing study design remains a challenge in IBS. New visceral analgesic and motility modifying agents, as well as anti-inflammatory agents are in trials, and hopefully additional efficacious therapeutic options for patients with IBS will soon emerge.

Keywords: alosetron, antidepressants, antispasmodics, irritable bowel syndrome, pharmacological methods, serotonin, tegaserod

What is IBS?

The irritable bowel syndrome (IBS) is a symptom complex of unknown aetiology characterized by abdominal pain or discomfort associated with disturbed defaecation and often bloating [1, 2]. The diagnosis is based on a positive history and the absence of alarm features (or 'red flags' such as weight loss or recurrent vomiting) [3]. In practice, young patients uncommonly need investigation, although occasionally coeliac disease or low-grade Crohn's disease can be misdiagnosed as IBS [1, 3]. Even in older patients, usually only a limited number of investigations are required to exclude, in particular, colon cancer and inflammatory bowel disease [3]. IBS is common in the general population, affecting about one in six adults and there is a female predominance for reasons that remain unclear [2, 4]. IBS is important because it can substantially impair quality of life [5] and the majority of those presenting with symptoms retain them life long [2, 6].

One of the difficulties in appropriately targeting drug therapy for IBS remains a lack of a clear disease model although there are some animal models available [7]. The majority of patients with IBS have underlying visceral hyperalgesia based on studies with balloon distension of the rectum and colon [8]. However, the level of the lesion that results in visceral hyperalgesia is uncertain. Small bowel dysmotility has been documented in IBS with, in particular, discrete clustered contractions in the jejunum and prolonged propagated contractions in the ileum in some patients, which can coincide with abdominal pain [9]. The colon in IBS is more responsive than normal to stress and hormonal factors [10, 11]. Colonic transit is disturbed in subsets of patients with IBS, and changes in transit are concordant with altered stool form (e.g. hard *vs* loose stools) [12].

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Physiological concentrations of intestinal lipids inhibit intestinal gas transit, but this appears to be up-regulated in patients with IBS; a lipid-gas challenge test could represent a useful diagnostic test in IBS although more data are needed [13].

Up to one in four patients with IBS, particularly those with diarrhoea-predominant symptoms, have a preceding gastroenteritis type illness; low grade colonic inflammation may persist in a subset if quantitative microscopy is undertaken [1, 14]. Stress may exacerbate IBS symptoms, and psychiatric comorbidity is common in patients who present for care of their IBS [2], although a causal link has not been established.

Placebo response in IBS

The placebo response rate varies in randomized controlled trials from 20 to 70% [15–17]. This placebo response can persist for up to 1 year based on recent preliminary trial evidence and does not, as anticipated, wane after 1 or 2 months [18]. As symptoms are altered by cognitive processing and IBS is a fluctuating disease, a high placebo response would be expected although the persistence of the response is unexplained.

Clinical pharmacology of drugs used in treatment

Dietary aids and bulking agents

It is contentious whether dietary fibre improves the symptoms of IBS [19–29] although some limited trial data suggest constipation will benefit. However, gas may be increased and any effect on pain is equivocal with bran or bulking agents [30]. The value of elimination diets in IBS remains unclear although some limited studies suggest that specific food intolerance can be identified in up to 50% of patients who undergo an elimination diet followed by a double-blind food challenge [31]. Cromoglycate is not of established efficacy in diarrhoea-predominant IBS as again only limited trials have evaluated this compound [32, 33].

Charcoal can result in anecdotal improvement in flatus but no controlled studies are available. Simethicone has also not been tested in IBS. Alpha D galactosidase can reduce gas production associated with black bean ingestion but whether this benefits IBS is unknown [34].

Antispasmodics

Anticholinergic drugs Many anticholinergic agents are available but their benefit in IBS remains questionable [29] although positive meta-analyses have been published [35, 36]. It is often recommended that the anticholinergic agents be taken as needed 30–45 min before a meal to reduce the exaggerated gastro-colonic response in IBS, in the hope this will improve postprandial pain as well as diarrhoea.

Sub-lingual preparations as well as oral preparations are available in addition to suppositories, but head-to-head trials with these types of agents are not available in IBS. In clinical practice, the individual response to these drugs is variable and often unimpressive. Large doses may have to be used for efficacy based on very limited evidence [37]. Side-effects are significant and include dry mouth, blurred vision, urinary retention and constipation, as well as insomnia and restlessness.

Other antispasmodics A number of nonanticholinergic antispasmodic agents are also in use for IBS around the world. Mebeverine is a smooth muscle relaxant with calcium channel blocking actions that is a derivative of beta-phenylethylamine [38, 39]. In a meta-analysis by Poynard *et al.* mebeverine was superior to placebo in terms of global improvement in IBS [35]. Peppermint oil may also have antispasmodic actions [40, 41] but the results with this agent based on a meta-analysis have been equivocal [42]. Cimetropium (an antimuscarinic agent) [43–45], pinaverium (a quaternary ammonium derivative with the properties of a calcium antagonist) [46], and trimebutine (a peripheral opiate agonist) [47–49] have also appeared to be of value in IBS [35]. However, the randomized trials upon which the meta-analyses are based almost all had serious limitations and the results have been judged by others to be at best equivocal [30].

Antidepressants and anxiolytics

Tricyclic antidepressants The tricyclic antidepressants in addition to a peripheral anticholinergic action also have central analgesic and antidepressant actions [50]. A meta-analysis of randomized controlled trials concluded that the tricyclic antidepressants were superior to placebo in IBS with an number needed to treat (NNT) of 3 [51], although the individual trial results and the quality of the trials has been variable [52–56]. Greenbaum *et al.* for example in a study of desipramine 150 mg daily separated diarrhoea from constipation-predominant IBS, and reported that diarrhoea, abdominal pain and depression but not constipation improved with active drug therapy, compared with atropine or placebo [52]. Ritchie & Truelove also reported that abdominal pain and diarrhoea but not constipation or bloating improved with a combination of nortryptiline 30 mg and fluphenazine 1.5 mg [53]. Drossman *et al.* in the largest trial to date reported that desipramine in female patients tended to be superior to placebo in the intention-to-treat analysis (responder rate 60% *vs* 47%), and in subgroup analyses was better in

those with no depression and in those with diarrhoea [57].

Although not all trials used a low dose, there is limited evidence that starting at a low dose can be efficacious [51]. These drugs potentially may aggravate constipation although based on the trial evidence it is still unclear whether this class of agents is best in diarrhoea-predominant IBS.

Side-effects limit this class of drugs; one in three or four develop side-effects, with one in 22 being potentially serious; up to 40% discontinue or change drug because of intolerance [50]. Patient concerns about taking a centrally acting agent also limit the applicability of this drug class in IBS.

Selective serotonin reuptake inhibitors (SSRIs) Few trials have been published in full with the serotonin reuptake inhibitors in IBS. Anecdotal reports suggest that this therapeutic class may be useful in IBS; theoretically, SSRIs may be of most benefit in constipation-predominant IBS as they accelerate orocaecal transit time [58, 59]. The SSRIs also have less side-effects than the tricyclics which makes them potentially attractive. However, the randomized trials have reported conflicting results [60, 61] and the positive study had no placebo control arm [60]; further trials are required to establish the place of this class of agents in IBS.

Anti-anxiety agents Benzodiazepines have been reported to have a small benefit over placebo in IBS but the evidence is very weak [62], and it is generally recommended that they be avoided because of habituation and interaction with other drugs including alcohol. Newer anxiolytic agents such as buspirone have not been tested in IBS, although they may have some role in functional dyspepsia (which often overlaps with IBS) because of their effects on relaxing the gastric fundus [63].

Laxatives

Stimulant laxatives Stimulant laxatives include bisacodyl, senna, phenolphthalein, danthron and ricinoleic acid. These agents are often used by patients with IBS who have severe constipation but no trials have evaluated their efficacy. Indeed, the efficacy of stimulant laxatives in simple constipation is limited based on the available evidence [64]. Furthermore, this class of agents can induce abdominal pain. The theoretical risk of colonic myenteric plexus damage with over the counter stimulant laxatives may not occur in practice with currently available agents [65].

Osmotic laxatives Osmotic laxatives include lactulose, sorbitol and milk of magnesia. These have sometimes been recommended as first line treatment for patients with constipation-predominant IBS who fail to respond to dietary fibre and fibre supplements [15] but this class of agents can also induce abdominal cramps and exacerbate diarrhoea, and in clinical practice seem to be poorly tolerated [1]. Polyethylene glycol (PEG) solutions may be better tolerated in IBS with constipation because less bloating is induced [1], although no randomized controlled trials have tested PEG in the syndrome.

Stool softeners and suppositories There is no evidence that stool softeners or wetting agents such as ducosate are of value in IBS. Indeed, these are slow to work and can induce side-effects including diarrhoea and anorexia [65]. Suppositories or enemas sometimes can be useful for bowel retraining in patients with severe constipation associated with IBS, particularly if there are pelvic floor abnormalities contributing to the symptoms [11], although again randomized controlled trial evidence is lacking.

Antidiarrhoeals

Opioid agonists Loperamide is a butyramide derivative and similar in structure to diphenoxylate but does not have opioid activity at standard doses; it also has a more prolonged duration of action and more rapid onset of action than codeine or diphenoxylate [15]. This class of drugs works by inhibiting intestinal secretion and increasing fluid and electrolyte absorption because of prolongation of intestinal transit time. Loperamide is superior to placebo in improvement of diarrhoea but not abdominal pain in IBS [66–69] as confirmed by a meta-analysis of controlled trials of good quality [30]. Urgency and borborygmi may also be improved. Combining loperamide with simethicone (which is a surfactant, and may modulate gas handling) is superior to loperamide alone in acute diarrhoea but has not been tested in IBS. There are no trials of diphenoxylate, which has opioid activity and is a derivative of pethidine, in IBS. Codeine phosphate has a particular problem of dependence when used long-term and therefore should generally be avoided in IBS.

Bile salt sequestering agents

Cholestyramine and colestipol are bile salt sequestering agents. There is limited evidence that a subset of patients with IBS and diarrhoea have spillover of bile salts from the terminal ileum into the colon, which theoretically makes bile salt sequestering agents attractive [70]. However, this class of agents has not been subjected to randomized controlled trials in IBS.

Serotonergic agonists and antagonists

5HT$_4$-receptor agonists Serotonin type 4 agonists are prokinetic drugs. 5HT$_4$ receptors are located on enterochromaffin cells, enterocytes, smooth muscle cells as well as neurones. Release of serotonin from enterochromaffin cells is one of the initiators of peristalsis, via 5HT$_4$ receptors on the primary afferents [71, 72].

The major 5HT$_4$ agonist now available for IBS is tegaserod, which is an aminoguanidine indole derivative of serotonin and is classified as a partial 5HT$_4$ agonist based on studies in guinea pig ileum [71, 72]. The drug increases co-ordinated intestinal motor function, accelerating small bowel and colonic transit as well as gastric emptying, depending on the patient population and dose used. It also stimulates water and chloride secretion, and may have visceral analgesic actions at least in animal models [72].

The efficacy of this agent has been tested in IBS in four large phase III randomized controlled trials [71–73]. A therapeutic gain over placebo in terms of global symptom relief of 5% to 15% has been observed, which is considered clinically significant albeit modest (NNT = 10). The trials enrolled largely females and the efficacy in males remains unclear. The drug does appear to be well tolerated with mild transient diarrhoea and headaches being the main side-effects. Although some concerns were raised initially about a small numerical increase in abdominal surgeries and particularly cholecystectomies in patients in the tegaserod *vs* placebo arms, based on the available evidence it appears unlikely this drug increases the risk of acute surgical episodes.

Another 5HT$_4$-receptor agonist is prucalopride, a benzofurancarboxamide, but its future is unclear because of concerns about possible carcinogenicity in animals as well as cardiac effects [72, 74]. Cisapride, a 5HT$_4$-receptor agonist which also has 5HT$_3$-receptor antagonist activity, has very limited availability because of cardiac toxicity; this problem is considered to be unrelated to 5HT$_4$-receptor agonism (although there are 5HT$_4$-receptors in the atrium) but is due to the benzamide activity of cisapride which blocks cardiac I_{Kr} channels and can result in QT prolongation.

5HT$_3$-receptor antagonists There has been major interest in serotonin type III receptor antagonists in diarrhoea–predominant irritable bowel syndrome; this class of agents slows colonic transit, relaxes the left colon in humans and results in reduced perception of volume although not pressure thresholds with balloon distension in the rectum [75]. Alosetron is 10 times more potent than ondansetron in terms of 5HT$_3$-receptor antagonism [72]. In clinical trials in females, alosetron was efficacious in diarrhoea-predominant IBS compared with placebo [76–78] and mebeverine [79], with approximately a 12–17% global therapeutic gain.

In November 2000, after the FDA had received 49 reports of ischaemic colitis and 21 of severe constipation related to the drug that had led to 44 hospital admissions, 10 surgical interventions and three deaths, the drug was voluntarily withdrawn [80]. In all, seven deaths have been reported from the drug [80]. Unfortunately, ischaemic colitis secondary to alosetron is unpredictable. Approximately one third of patients will experience constipation on the drug and the risk of ischaemic colitis is possibly as high as 1 in 350, with very severe constipation occurring in about 1 in 1000. In June 2002, the FDA issued a new drug application permitting marketing, albeit starting at a lower dose (1 mg daily rather than twice daily), although a lower dose has not been tested in phase III trials for efficacy [80]. The drug is absolutely contra-indicated in constipation-associated IBS. Cilansetron, another 5HT$_3$-receptor antagonist, is in phase III trials [72].

Miscellaneous drugs for IBS

Domperidone, a dopamine receptor antagonist and upper gastrointestinal tract prokinetic, appears not to be efficacious in IBS based on limited trial evidence [81]. While β-adrenergic pathways modulate colonic motor function, β-adrenoceptor blockade with atenolol or timolol has not been shown to be of value in small trials in IBS [82, 83].

There is an interest in the antiepileptic agents which may also modulate colonic smooth muscle and visceral sensation. Diphenylhydantoin was disappointing in IBS in one trial [84]. Gabapentin derivatives are currently being tested. Octreotide, the somatostatin analogue, reduces gastrointestinal tract motility as well as secretion and sensation, and may be of some therapeutic value in severe IBS but is impractical to use [1, 85].

Gonadotrophin releasing hormone analogues such as leuprolide reduced the synthesis of follicle stimulating hormone and luteinizing hormone as well as the synthesis of gonadotrophins with continuous administration. Leuprolide has significant adverse events but in small trials appeared to have some benefit in terms of severe gastrointestinal complaints, although how many of these patients had IBS remains uncertain and methodological limitations of the trials make interpretation difficult [86, 87].

Challenges in the design of future clinical trials in IBS

There is general agreement that a global assessment of patient symptoms remains the most useful primary end point in clinical trials in IBS, and standard symptom criteria should be used to identify patients for inclusion

[1, 72]. This is because the disease presents as a symptom complex, usually with multiple symptoms. There is as yet no agreed other objective marker that can replace symptom evaluation [2, 3]. However, this approach has a number of limitations. In particular, almost certainly a heterogeneous group of patients will be included in clinical trials even applying the most current symptom-based criteria, which may in turn obscure drug efficacy. Indeed, the most successful clinical trials in recent years have targeted subsets of IBS (e.g. alosetron in diarrhoea-predominant IBS and tegaserod in constipation-predominant IBS) [1, 72].

The application of physiological tests to try and define more homogeneous subgroups of IBS patients for clinical trials remains a paradigm that as yet lacks adequate confirmation [7, 8]. This has been limited in part because of the invasive nature of many of the physiological tests, which precludes utilization of them in large clinical trials. For example, visceral hypersensitivity is best tested with a barostat balloon placed in the rectum or colon, but is an impractical tool outside of small Phase I or Phase IIa clinical studies with new compounds. Although visceral hypersensitivity is a documented abnormality in the majority of patients with IBS, the effects of drugs considered to be likely to modulate pain has been relatively modest in terms of altering sensory thresholds [8]. As yet no change in sensory threshold has been defined that will predict therapeutic response in subsequent Phase III clinical studies.

There are other unresolved methodological issues. For example, how often pelvic-floor dysfunction negatively biases the results of studies in constipation-predominant IBS remains unknown, and the utility of colonic transit evaluation in terms of predicting treatment response is similarly poorly defined. More work is needed to identify clinically relevant physiological subsets of IBS and the challenge remains to develop simple tests that will have wide utility in phase III trials.

New therapeutic directions

A number of other serotonin agonists and antagonists are currently in various phases of testing for the functional gastrointestinal disorders including IBS [72]. There is also interest in combination therapies, such as a $5HT_4$-receptor agonist plus a delta-opiate antagonist, in order to enhance the peristaltic response with prokinetic therapy. Cholecystokinin (CCK_1) antagonists such as loxiglumide and dexloxiglumide may be of value for constipation-predominant IBS and are currently in Phase III testing [88]. A potential limitation of all the cholecystokinin antagonists is induction of gallbladder stasis and therefore possibly cholelithiasis, although whether this will be an important clinical problem remains unknown.

Visceral analgesics including opioid agonists such as asimadoline and tachykinin antagonists remain under consideration [89, 90]. Corticotrophin releasing factor (CRF)-1 antagonists and neurotrophic factor receptor agonists are also under initial testing. Blockade of n-methyl-d-aspartate (NMDA) type glutamate receptors remains of interest, and work is underway testing drugs that may modulate the NMDA receptor–somatostatin pathways.

Other targets potentially include the chloride (CFTR) channel and peptide hormones such as guanylin. Anti-inflammatory agents including probiotics and nonabsorbable antibiotics are being evaluated [91–93]. Antibiotics may provide temporary relief in IBS theoretically because they suppress normal bowel flora and reduce gas production, but their place is unclear presently [92, 93]. Other agents under testing include the α-adrenoceptor agonists in diarrhoea-predominant IBS, as they can relax fasting colonic tone and increase compliance [94].

Conclusions

The treatment of IBS remains challenging. While some have dismissed this disorder as being merely an unpleasant, indeed unimportant, condition, there is increasing evidence that IBS is a real disease that impacts significantly on the quality of life of a number of people and deserves serious attention. As a better understanding of the pathophysiology emerges, and as more information about neuronal targets in the nervous system and gut wall are identified, it appears likely that more effective therapies will become available for this condition in the relatively near future.

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