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Meta-analysis: the treatment of irritable bowel syndrome

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SUMMARY

To evaluate therapies available for the treatment of irritable bowel syndrome, and provide consensus recommendations for their use, a total of 51 double-blind clinical trials using bulking agents, prokinetics, antispasmodics, alosetron, tegaserod and antidepressants were selected. The quality of studies was assessed using 5-point scale. Meta-analyses were performed on all studies, and on 'high-quality studies'.The efficacy of fibre in the global irritable bowel syndrome symptoms relief (OR: 1.9; 95% CI:1.5–2.4) was lost after exclusion of low-quality trials (OR: 1.4; 95% CI: 1.0–2.0, $P = 0.06$). When excluding the low-quality trials, an improvement of global irritable bowel syndrome symptoms with all antispasmodics (OR: 2.1; 95% CI:1.8–2.9) was maintained only for octylonium bromide, but on the basis of only two studies. Antidepressants were effective (OR: 2.6, 95% CI: 1.9–3.5), even after exclusion of low-quality studies (OR: 1.9, 95% CI: 1.3–2.7). Alosetron (OR: 2.2; 95% CI: 1.9–2.6) and tegaserod (OR: 1.4; 95% CI: 1.2–1.5) showed a significant effect in women. We recommend the use of tegaserod for women with irritable bowel syndrome with constipation and alosetron for women with severe irritable bowel syndrome with diarrhoea. Antidepressants can be beneficial for irritable bowel syndrome with diarrhoea patients with severe symptoms. Loperamide can be recommended in painless diarrhoea. Evidence is weak to recommend the use of bulking agents in the treatment of irritable bowel syndrome with constipation.

INTRODUCTION

Irritable bowel syndrome (IBS) is a common gastrointestinal (GI) disorder characterized by recurrent abdominal pain/discomfort, bloating and stool irregularities (constipation and/or diarrhoea). IBS can be classified on the basis of the primary bowel symptom, so there is IBS with constipation (IBS-C), IBS with diarrhoea (IBS-D) and IBS with alternating symptoms of constipation and diarrhoea (IBS-A).

The IBS is estimated to affect 10–15% of the Western population, although rates vary according to the criteria being used.[1] IBS, like many other poorly understood disorders, is viewed as a multifactorial disorder (Figure 1). Symptoms and clinical outcomes may depend on the interaction of several pathogenetic factors including genetics,[2–4] early life events,[5] postinflammatory changes after GI infections,[6] psychosocial impact[7] and food.[8]

Despite low rates of health care-seeking behaviour, IBS accounts for 28% of gastroenterology practice[9] and 12% of primary care caseloads.[10] IBS has major economic impact, both in terms of health care utilization, as well as absenteeism and reduced quality of life in patients not seeking care. The need for effective treatments to combat the multiple symptoms of IBS is thus a matter of considerable interest and importance.

The aim of the present review was to evaluate therapies available for the treatment of IBS, and provide

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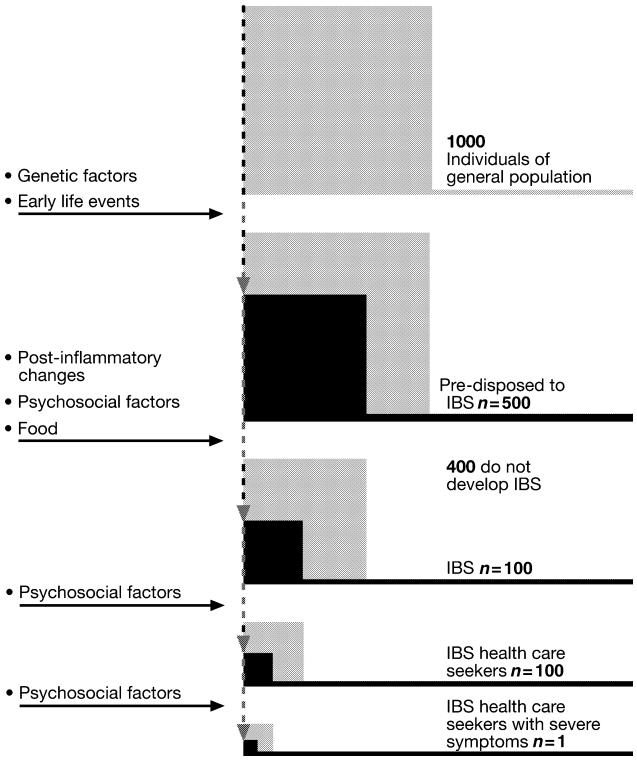

Figure 1. Epidemiology of irritable bowel syndrome (IBS) and factors influencing health care seeking.

consensus recommendations for their use. We focused mainly on pharmacotherapy, but the efficacy of non-drug options such as exclusion diet, probiotics and psychotherapy in the treatment of IBS is also discussed.

GENERAL TREATMENT APPROACH

The IBS is a complex disorder encompassing a wide profile of symptoms. Several pathophysiological mechanisms are involved in producing each symptom. A major problem regarding the treatment of IBS is that there is no well-defined drug target, mainly because of the involvement of multiple receptors or mediators. Additionally, IBS is a clinical condition defined by symptom-based diagnostic criteria and the multitude of symptoms limits the efficacy of many IBS drugs because they target just one or two contributing mechanisms.[11]

The general treatment approach in IBS is to alleviate the symptoms of abdominal pain/discomfort and altered bowel transit (constipation and/or diarrhoea) as well as their consequences such as bloating and anal incontinence.

The approach adopted depends on the intensity of symptoms, the patient's need for health care, and the degree of psychosocial comorbidities (Table 1).[11] Initial treatment is directed towards education, reassurance, dietary/lifestyle modification (if not already attempted independently by the patient), as well as appropriate pharmacotherapy. Patients should be reassured that IBS is a real medical disorder, but typically does not lead to life-threatening disease or physical impairment.[12, 13] Short-term medication should be prescribed during exacerbations of IBS symptoms.

A proportion of patients (approximately 10%) frequently experience symptoms and attend secondary care services (Figure 1). Psychological disturbances may or may not be present (Table 1).[11] Traditionally, treatment is mainly based on conventional pharmacotherapy targeted at the specific predominant symptom.

A small proportion of patients (approximately 1%) have severe and refractory symptoms and are referred to tertiary care centres (Table 1, Figure 1). In these cases, tailored pharmacotherapy of symptoms and, if required, psychological support is recommended.[14]

PHARMACOTHERAPY

The IBS symptoms may arise from disturbed functions of the brain ('top-down' model), the intestine ('bottom-up' model) and neurological links between intestine and brain. Therefore, a large number of treatment targets are available, and therapeutic attempts have been made at all levels of the brain-gut axis.

We review the pharmacotherapy of IBS from three angles. The first part deals with conventional IBS drugs, widely used in the past and whose efficacy remains unproven. In the second part, newly marketed drugs

Table 1. Characteristics of irritable bowel syndrome (IBS) health care seekers depend on symptom severity (adapted from[10])

	Symptom severity		
Characteristics	Mild	Moderate	Severe
Symptom frequency	Occasional	Frequent	Daily/ persistent
Psychological difficulties	Not typical	May be present	Typical
Health care centres consulted	Primary	Secondary	Tertiary
Rates of health care use	Low	Moderate	High

with proven efficacy are reviewed. The third part of this chapter covers developmental compounds which are potential candidates of new IBS drugs and whose efficacy remains to be proven.

We conducted a literature search on bulking agents, standard gastro-prokinetics, smooth muscle relaxants, alosetron, tegaserod and antidepressants. All published English-language placebo-controlled studies were identified by electronic search of MEDLINE database (1966–2004) using the key words 'irritable', 'functional' and 'spastic' adjacent to 'bowel'. Abstracts, studies not published in full and book chapters were excluded. The quality of studies was assessed using 5-point scale [double-blind study (yes: 1, no: 0), sufficient number of subjects (yes: 1, no: 0), crossover (0) or parallel design (1), adequate definition of IBS symptoms (yes: 1, no: 0), and presence (1)/absence (0) of intention-to-treat statistical analysis]. We performed two types of meta-analyses: first including all studies, and the second one including only 'high-quality studies', identified by quality score 3 or more. Although the score of 3 is insufficient to assure a high study quality, we did not exclude these studies; had we done so, practically no studies would have remained. Thus, with respect to these drugs, the results of our meta-analysis given in Figure 2 could be considered too broad. Our evidence recommendations for the treatment of IBS are given in Table 2.

Conventional drugs

Bulking agents.

1. *Mechanism of action*: Up to 82% of IBS subjects with constipation have delayed small bowel transit,[15, 16] colonic transit[17] or orocaecal transit.[18] The most frequent changes in the small bowel motility in IBS patients with constipation include decreased duration of the migrating motor complex (MMC)[19] and decreased amplitude of clustered contractions.[20] The most frequent alteration of colonic motility include a decreased number of high amplitude propagated contractions (HAPC) and an increased number of colonic phasic contractions.[21]

Acceleration of colonic or oroanal transit have been postulated as a mechanism by which bulking agents relieve constipation. A few studies have evaluated the effect of fibre on the GI transit but the results are conflicting. Some studies showed an effect of fibre on the colonic contractile activity[22, 23] while others have not.[24]

2. *Clinical evidence*: Bulking agents have traditionally been a mainstay in the treatment of IBS with constipation. While there is little doubt that these agents improve stool consistency, their overall effectiveness in IBS is controversial (Figure 2a).[23, 25–36] In our meta-analysis, five of 13 placebo-controlled studies reported a benefit of fibre treatment in the relief of global IBS symptoms, with resulting odds ratio (OR) of global symptom relief of 1.9 [95% confidence interval (CI): 1.5–2.4] (Figure 2a). However, after exclusion of low-quality trials, this effect does not reach statistical significance [OR of global symptom relief 1.4 (95% CI: 1.0–2.0, $P = 0.06$)]. This result is comparable with a recent meta-analysis, so far published only in the abstract form.[37]

Another meta-analysis[38] showed a benefit of fibre treatment in the relief of global IBS symptoms (relative risk: 1.33, 95% CI: 1.2–1.5). However, when IBS symptoms were analysed separately, fibre was shown to be ineffective in the relief of abdominal pain in IBS patients.[38] Supplemental bran may even be worse than a normal diet and aggravate symptoms such as pain and bloating.[24] Abnormal bacterial fermentation of fibre,[39] the absence of normal methanogenic flora[40] and disturbed gas handling[41] may induce bloating and abdominal pain during treatment with bulking agents. For these reasons, the use of bulking agents in IBS cannot be recommended except as adjuvants (Table 2). Their use can be recommended in painless constipation.

Antidiarrhoeal agents.

1. *Mechanism of action*: The types of colonic motility patterns in IBS subjects with diarrhoea include increased numbers of HAPC and decreased 'long spike' bursts of activity.[42–44] These alterations are associated with increased small bowel and colonic transit in some studies,[45] but not in others.[15, 46] The best known antidiarrhoeal drug, loperamide, is a synthetic opioid. It decreases intestinal transit, and also enhances intestinal water and ion absorption, as well as anal sphincter tone at rest.[47–49] These actions seem to explain the improvement in diarrhoea, urgency, and faecal soiling observed in patients with IBS-D.[47–52]

2. *Clinical evidence*: There is excellent evidence for the antidiarrhoeal effect of loperamide in IBS-D.[49–51] In each study, loperamide decreased stool frequency and increased stool consistency. However, loperamide does not improve pain in IBS patients and has been shown to

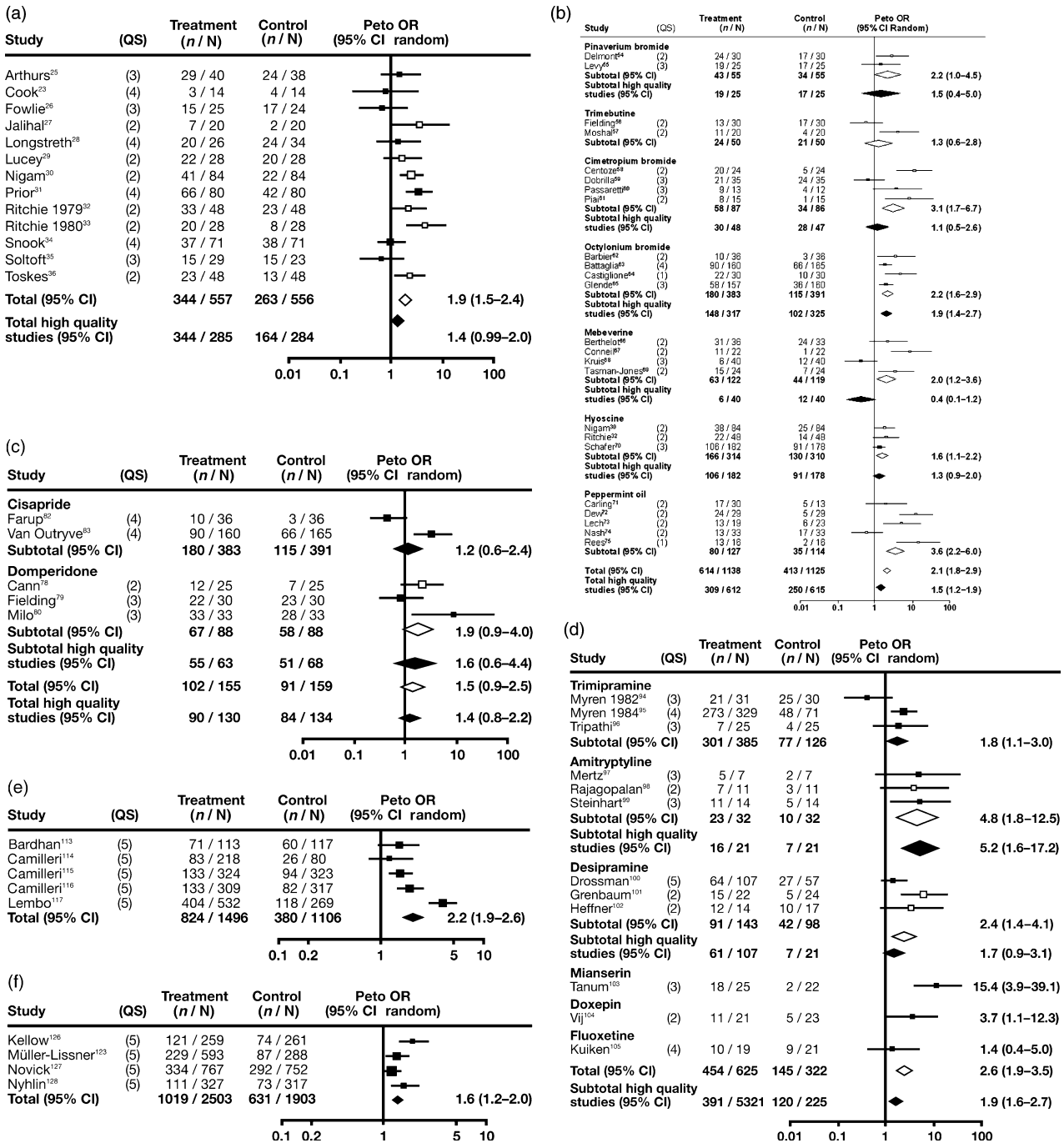

Figure 2. Effects of irritable bowel syndrome (IBS) treatments on overall improvement in gastrointestinal symptoms. The odds ratio and associated 95% confidence interval (CI) for each study are plotted on a logarithmic scale. The box sizes are proportional to the study's weight in the analysis, based on the study size and variance. The diamond box represents the point estimate and 95% CI for the pooled data. The open boxes represent low quality studies (quality score <3), the closed boxes represent high quality studies (quality score >3). The open diamond boxes represent the point estimate of all studies (high-quality and low-quality studies). The closed diamond boxes represent the point estimate of high-quality studies only. Quality score (QS): double-blind study (yes: 1, no: 0), sufficient number of subjects (yes: 1, no: 0), crossover (0) or parallel design (1), adequate definition of IBS symptoms (yes: 1, no: 0), and presence (1)/absence (0) of intention-to-treat statistical analysis.
(a) bulking agents, (b) antispasmodics, (c) prokinetics, (d) antidepressants, (e) alosetron, (f) tegaserod.

Table 2. Efficacy of agents and drugs currently used in the treatment of irritable bowel syndrome (IBS)

	Grades of recommendation
Stimulant laxatives	D
Bulking agents	C
Loperamide	C/A*
Smooth muscle relaxants	C
Peppermint oil	D
Prokinetic agents	D
Antidepressants	B
Benzodiazepines	D
Tegaserod	A†
Alosetron	A‡

A, consistent results from high quality randomized-controlled trials (RCT); B, inconsistent results from high quality RCTs or consistent results from inadequately controlled clinical trials; C, inconsistent results from inadequately controlled clinical trials or poor quality cohort studies; D, unfounded expert opinion or clinical studies of very low quality.
*In painless diarrhoea.
†In women with IBS with constipation (IBS-C).
‡In women with severe IBS with diarrhoea (IBS-D) who failed to respond to conventional therapy.

increase nightly abdominal pain.[51] Thus, loperamide is recommended in patients with painless diarrhoea or to reduce postprandial urgency or as a means of improving control at times of anticipated stress or other colonic stimuli (e.g. exercise, social gatherings). Since loperamide does not cross the blood–brain barrier, it is generally preferred to other opiates such as diphenoxylate, codeine or other narcotics.

Antispasmodics.

1. *Mechanisms of action*: Currently available antispasmodics can be classified in three major subclasses: antimuscarinics (e.g. cimetropium, mebeverine); smooth muscle relaxants (papaverine-like agents) and calcium-channel blockers (e.g. pinaverium, peppermint oil). This distinction is, however, arbitrary, because of mixed pharmacological properties of these agents. Antispasmodics are believed to reduce pain associated with IBS through inhibition of contractile pathways in the muscle wall. Since the clinical evidence supporting the use of antispasmodics in the treatment of IBS is weak, we considered as irrelevant to present their mechanism of action in further details.

2. *Clinical evidence*: The role of smooth muscle relaxants in the treatment of IBS is bedevilled with methodological problems.[53] According to Figure 2b, 12 of the 24 studies which satisfy at least some quality criteria were negative. Some smooth muscle relaxants such as pinaverium bromide[54, 55] and trimebutine[56, 57] were found to be ineffective in the treatment of IBS (Figure 2b). Several other smooth muscle relaxants such as cimetropium bromide,[58–61] octylonium bromide,[62–65] mebeverine,[66–69] hyoscine[30, 32, 70] and peppermint oil[71–75] were reported to yield positive results (Figure 2b), but on the basis of trials which are hardly conclusive. Indeed, when excluding the low-quality trials from meta-analysis, only octylonium bromide appears to be effective in relieving global IBS symptoms, but on the basis of only two studies.[63, 65] The heterogeneity of trials, the differing spectrum of patients' symptoms and efficacy measures, the low number of patients included and high number of drop-outs during follow-up (up to 60%) render the judgement on the therapeutic value of antispasmodics in IBS impossible. In the case of peppermint oil, which on the basis of Figure 2b appears to be effective, another meta-analysis using the same data came to a negative result.[76] Therefore, we disagree with Poynard *et al*. who concluded on the basis of his meta-analysis that smooth-muscle relaxants as a class are effective drugs in IBS.[77] In fact, the treatment of IBS with smooth muscle relaxants highlights the pitfalls and limits of meta-analyses. In addition to the questions remaining regarding efficacy, antispasmodics can provoke and aggravate constipation.

Prokinetics.

1. *Mechanism of action*: The class prokinetics comprises a number of structurally unrelated compounds that share the same pharmacological activity of stimulating GI motility. Blockade of dopaminergic inhibitory transmission at the D_2-receptors has been regarded as the main mechanism of prokinetic effect of domperidone.[78–80] Cisapride, a 5-hydroxytryptamine (serotonin, 5-HT_3) antagonist/5-HT_4 agonist is believed to exert its prokinetic activity via acetylcholine-release from the myenteric plexus.[81]

2. *Clinical evidence*: Standard prokinetic agents such as domperidone[76–78] and cisapride[80, 81] were previously used for treatment of IBS with constipation. Today, these agents cannot be recommended because they were found to be ineffective for IBS[82, 83] (Figure 2c). In addition, cisapride has been withdrawn from the market in the USA and Germany, among others, for its cardiac toxicity.[84]

Antidepressants.

1. *Mechanism of action*: The mechanism by which antidepressants exert their action is not fully understood. Because of their complex pharmacological properties (both central and peripheral), antidepressants may exert their action at more than one site of the brain-gut axis.

A higher percentage of IBS health care seekers (40–60%) than healthy controls (<25%) present with panic disorders, anxiety and depression.[87] In addition, visceral perception is mediated at a cortical level and may therefore be influenced by cognitive and psychosocial factors. Studies using cerebral imaging methods showed that in response to noxious colonic stimulation, IBS patients activated the prefrontal cortex responsible for increased attention to this stimulation, thus amplifying pain perception instead of activating descending inhibitory pathways.[88, 89] This mechanism may explain the greater pain reporting of patients with psychosocial difficulties. Thus, the beneficial effect of antidepressants in the treatment of IBS may be, in part, explained by their psychotropic properties.[14]

In addition, antidepressants seem to have neuromodulatory and analgesic properties.[14, 90] These drugs were also shown to alter GI transit, independently on their mood effects. For example, imipramine prolonged oroceacal and whole gut transit times,[91] probably by a mechanism related to its anticholinergic properties. On the other side, serotonin re-uptake inhibitors such as paroxetine reduced oroceacal transit times with no effect on the whole gut times.[92]

2. *Clinical evidence*: Tricyclic antidepressants given at low doses were found to be effective in alleviating chronic – even severe – abdominal pain in IBS patients. In a meta-analysis of 11 studies using antidepressants, a favourable effect of these drugs was calculated (summary OR for global IBS symptoms improvement = 4.2, 95% CI: 2.3–7.9).[93] Our meta-analysis of 12 placebo-controlled studies also found a positive effect (OR: 2.6, 95% CI: 1.9–3.5; Figure 2d).[94–105] However, the studies with antidepressants, while technically better designed than those with smooth muscle relaxants, are still riddled with problems of design and size (Figure 2d).[93] For this reason, a guarded recommendation for the use of antidepressants is given (Table 2). Because of their severe side-effects, antidepressants should only be given to patients with severe IBS symptoms, i.e. patients with daily or persistent pain.[106] Also, it seems that the beneficial effect of tricyclic antidepressants is limited to patients with predominant abdominal pain and diarrhoea; constipation is a frequent side-effect of these drugs.[91] Benzodiazepines and other antianxiolytic drugs are frequently given to IBS patients but without any evidence coming from a controlled clinical trial.[106]

Newly developed drugs

Serotoninergic agents.

General aspects of serotoninergic drugs: The most important neurotransmitter involved in the pathogenesis of IBS is serotonin (5-HT); 95% of this neurotransmitter is located in the GI tract. Enterochromaffin (EC) cells, along with neurones, mast cells and smooth-muscle cells are major serotonin stores. EC cells release 5-HT in response to increases in interluminal pressure or chemical stimuli. Intrinsic primary afferent neurones (IPANS) express numerous 5-HT receptors, of which 5-HT_{1P}, 5-HT_3 and 5-HT_4 are thought to be most important in the pathogenesis of IBS.[107] Activated 5-HT_{1P} is pivotal to the initiation of the peristaltic reflex while 5-HT_3 and 5-HT_4 are now understood to modulate the process.[107]

The role of the serotonin reuptake transporter (SERT) in the pathogenesis of IBS through 5-HT inactivation is the focus of much current research and early findings indicate that SERT mRNA and immunoreactivity is altered in patients with IBS.[108]

5-HT_3 antagonists.

1. *Mechanism of action*: Antagonism of 5-HT_3 receptors in the sensory apparatus reduces visceral pain whereas 5-HT_3 inhibition in the motor apparatus retards colonic transit and enhances small intestinal absorption.[109] In IBS-D patients and healthy controls, alosetron delays colonic transit,[110] probably by increasing of number and propagation length of HAPC.[111] These mechanisms are responsible for a decrease in stool frequency and firming of stool consistency.[111] In addition, alosetron modulates visceral sensitivity by a central mechanism. A placebo-controlled study in IBS subjects showed a decrease in brain activity in response to aversive rectal stimuli after 3-week treatment with alosetron.[112]

2. *Clinical evidence*: Alosetron, a selective 5-HT_3 antagonist, is more effective than placebo in inducing adequate relief of abdominal pain and discomfort, and improvement in bowel frequency, consistency, and

urgency in women with IBS with diarrhoea[113–117] (Figure 2e). This drug was withdrawn in the USA (2000) because of side-effects of severe constipation, ischaemic colitis and bowel perforation.[118] It was recently re-approved by the FDA following patient petition for use under a restricted prescribing programme in women with severe IBS with diarrhoea who have failed to respond to conventional therapy.[119]

Moreover, the relationship between alosetron and ischaemic colitis has been recently challenged. It has been shown that untreated IBS patients have a higher risk of developing ischaemic colitis.[120] On the other side, it cannot be excluded that some patients with silent ischaemic colitis are labelled as presenting IBS.

5-HT_4 agonists.

1. *Mechanism of action*: Stimulation of 5-HT_4 receptors results in the release of neurotransmitters, such as acetylcholine and calcitonin gene-related petide (CGRP) from enteric neurones which, in turn, modulate the peristaltic reflex.[121] Tegaserod, a selective partial 5-HT_4 agonist, acts on multiple levels. Both *in vitro* and *in vivo*, tegaserod activates GI motility by binding to enteric cholinergic neurones.[121] In placebo-controlled studies with healthy subjects, as well as in studies with IBS with constipation patients, tegaserod led to accelerated orocaecal transit,[122] and increased the frequency of bowel movements and the softness of stools.[123] In addition, tegaserod modulates visceral sensitivity by enhancing transmitter release on IPANS. In animal studies[124] as well as in studies with healthy humans,[125] tegaserod reduces visceral afferent firing and abdominal contractions in response to noxious rectal distension.

2. *Clinical evidence*: Tegaserod has been tested in several large, double-blind, controlled clinical trials using the Rome criteria for IBS to enrol patients[123, 126–128] (Figure 2f). In each trial, a statistically significant effect on constipation, abdominal pain/discomfort, bloating and global relief was demonstrated in women (OR: 1.4, 95% CI: 1.2–1.5; Figure 2f). The difference in symptom relief between placebo and tegaserod was about 10–15%, mainly because of a high placebo response in these trials[129] mirroring that seen in other trials of IBS drugs.[130] In common with the patterns seen in clinical practice, relatively few men were enrolled in the tegaserod trials, meaning no conclusions can be made regarding the efficacy of tegaserod in men. For this reason, tegaserod is registered for use only in women, but this is a statistical rather then a clinical problem. A minor drawback to tegaserod treatment is related to side-effects. As expected from its pharmacodynamic action, tegaserod may provoke and aggravate diarrhoea, but is generally transient and self-limiting, typically resolves with continued therapy and other side-effects are rare.[131, 132] The safety and efficacy profile of tegaserod was also demonstrated in patients with non-diarrhoea IBS[126, 128] and safety was demonstrated in patients with IBS with diarrhoea,[131] although not recommended for use in this subtype.

In contrast to prokinetics such as cisapride, no clinically relevant changes in blood pressure, pulse rate, and electrocardiograph intervals (QRS or QTc) were reported with tegaserod in doses of up to 100 mg/day.[133] Overall, tegaserod is presently the best available drug for the treatment of IBS with constipation. The recommended dose of tegaserod is 6 mg b.d. With this dose, the favourable effect observed during the first weeks is maintained in subsequent 3 months of treatment.[129]

Developmental drugs

Many substances, including serotonin (5-HT), substance P, cholecystokinin (CCK), CGRP, neurotrophins, cytokines, and others, are potential participants in the transmission of painful and non-painful sensations.[134]

The drugs interfering with these mediators or their target receptors are promising candidates to treat patients with IBS. However, their clinical efficacy remains to be shown.

Serotoninergic agents

5-HT_3 antagonists.

1. *Mechanism of action*: Cilansetron is a new 5-HT_3 antagonist, acting on vagal mucosal afferent terminals,[135] with resulting decreased GI motility and secretion. In a placebo-controlled study with healthy subjects, cilansetron augmented meal-stimulated and neostigmine-stimulated phasic motility of the sigmoid colon.[136] Cilansetron appears also effective in reducing of abdominal pain, at least in animal studies.[137]

2. *Clinical evidence*: Cilansetron is being evaluated in phase III trials, but currently, most publications appear in abstract form only. In recent large placebo-controlled studies it was demonstrated that up to 60% of patients with IBS-D receiving cilansetron experience a relief of abdominal pain/discomfort and abnormal bowel habits including diarrhoea and urgency.[138] A subset analysis

of data from two double-blind placebo controlled studies demonstrated that unlike alosetron, cilasetron is also effective in males with IBS-D.[139]

As expected, the side-effects of cilansetron are similar to those occurring with other 5-HT_3 antagonists (see 5-HT_3 antagonist). Constipation is the main adverse effect occurring in up to 8% of subjects.[138, 139] In addition, the concerns persist regarding a potential risk of developing ischaemic colitis in patients treated with cilansetron.[138] The approval of cilansetron for both men and women with IBS-D is currently pending in the USA and Europe.

5-HT_4 agonists.

1. *Mechanism of action*: As discussed previously in detail, stimulation of 5-HT_4 receptors results in the release of neurotransmitters, such as acetylcholine and CGRP from enteric neurones which, in turn, modulate the peristaltic reflex.[121]

2. *Clinical evidence*: Prucalopride, a prokinetic agent with 5-HT_4 agonist effects, has shown promising results in the treatment of IBS with constipation.[140–142] For the time being, further studies have been suspended because of concerns about a carcinogenic effect in animals.

5-HT_4 antagonists.

1. *Mechanism of action*: The 5-HT_4 receptor antagonists are thought to antagonize both the ability of serotonin to sensitize the peristaltic reflex and 5-HT-induced defecation, at least in animal studies.[143]

One study with IBS patients showed that piboserod may have antidiarrhoeal and antinociceptive properties.[144] However, in healthy subjects, piboserod did not alter gastric emptying, small-bowel transit or colonic sensation or motor activity.[145] Thus, the effect of 5-HT_4 antagonists, sulamserod and piboserod, on GI functions is debatable.

2. *Clinical evidence*: Presently, there is no study directly evaluating the effect of 5-HT_4 antagonists on the IBS symptoms.

Neutrophins.

1. *Mechanism of action*: Neutrophins (NTs), such as brain-derived neurotrophic factor (BDNF) or neutrophin (NT3, NT4) accelerate intestinal transit by directly modulating neurotransmitter synthesis and increasing neuronal excitability.[146]

Studies in healthy subjects have shown that recombinant human NTs accelerate colonic transit and increase stool frequency.[147] Further studies are needed to elucidate the precise mechanism by which NTs influence smooth muscle contractility and/or enteric nerve function in the human GI tract.[146]

2. *Clinical evidence*: No clinical studies were conducted to date to evaluate the therapeutic potential of NTs in IBS.

Tachykinin receptor antagonists.

1. *Mechanism of action*: Tachykinin receptor antagonists may, theoretically, be visceral analgesics as well as antispasmodics.[148]

The neurokinin 1 (NK1) and NK3 receptors do not appear to play significant roles in normal GI functions, but both may be involved in defensive or pathological processes. Interactions between NK1 receptors and enteric non-adrenergic, non-cholinergic motorneurones suggest the role of this receptor in disrupted colonic motility. NK1 receptors may have additional influences on intestinal mucosal inflammatory or 'irritant' processes.[149] In animal studies, the NK1 receptor antagonist CJ-11974 showed a weak trend towards increased pressure thresholds for discomfort following repetitive sigmoid distension.[150]

Similarly, NK3 receptor antagonists as talnetant appear to inhibit intestinal nociception via a 'peripheral' mechanism that may be intestine-specific.[151]

Experimental data indicate a role for tachykinin NK2 receptors in the regulation of intestinal motor functions (both excitatory and inhibitory), secretions, inflammation and visceral sensitivity.[152] NK2 receptor antagonists reduce the hyper-responsiveness that occurs following intestinal inflammation or application of stressful stimuli to animals.

In healthy volunteers, the selective NK2 antagonist nepadutant reduced the motility-stimulating effects and IBS-like symptoms triggered by intravenous infusion of neurokinin A.[153] Thus, the blockade of peripheral tachykinin NK2 receptors could be considered as a possible mechanism for decreasing the painful symptoms and altered bowel habits of IBS patients.

2. *Clinical evidence*: For the time being, the clinical data on the role of tachykinin receptor antagonists in IBS patients are lacking.

Somatostatin analogues.

1. *Mechanism of action*: The hypothesis on abnormal activation of brain modulating pain centres such as the thalamus and the anterior cingulate cortex in IBS

patients has stimulated the development of novel pharmacological agents targeting visceral nociception.[108] Somatostatin analogues may be useful for pain and severe diarrhoea in IBS by modulating the anterior cingulate cortex, locus coeruleus, amygdala, and the spinal dorsal horn sensory afferents.[108] A treatment response to somatostatin in IBS patients may involve multiple components, such as analgesic, antihyperalgesic effects, as well as effects on the attention and emotional aspects of chronic pain and discomfort.[154–157] The peripheral effect of somatostatin in IBS with diarrhoea may be mediated via inhibition of the exaggerated release of serotonin from enteroendocrine cells that has been demonstrated in this subgroup of patients with IBS.[158]

The peripherally administered somatostatin analogue octreotide has been reported to slow intestinal transit in IBS subjects with diarrhoea.[159] In addition, in IBS subjects but not controls, octreotide increased rectal perception threshold for discomfort.[160] However, the parenteral administration of octreotide is impractical, and adequate clinical trials have not yet been performed.

2. *Clinical evidence*: The clinical studies using somatostatin analogues in the treatment of IBS are not yet available.

Adrenergic modulators.

1. *Mechanism of action*: Increased sympathetic activity and decreased parasympathetic activity[161] have been described in IBS patients. Alteration of sympathetic modulation of visceral sensitivity may lead to increased perception of gut stimuli.[162] Parasympathetic colonic dysregulation may lead to an increase or decrease in the frequency of HAPC in the colon.[43] This may play a role in diarrhoea and in slow-transit constipation, thereby determining the predominant bowel habit pattern in IBS.[163]

Several studies assessed the effect of adrenergic agonists in IBS in order to evaluate the role of autonomic nervous system activity in IBS. α2-Adrenergic agonists such as clonidine or lidamidine may act on α-2-adrenoreceptors and influence transmission of sensory information and pain.[164] In uncontrolled trials with healthy volunteers, clonidine increased colonic compliance, delayed small bowel transit and reduced colonic tone and sensitivity to distension.[164, 165]

2. *Clinical evidence*: In a recent double-blind, placebo-controlled trial in patients with IBS-D, clonidine led to improvement of abdominal discomfort and stool consistency.[166] However, with respect to relief of IBS symptoms, lidamidine, another α2-agonist, was not superior to placebo in two placebo-controlled clinical trials.[167, 168]

Neostigmine, an acetylcholinesterase inhibitor, improved gas transit and abdominal symptoms, and intestinal propulsion in IBS patients with intestinal gas retention.[169] However, side-effects with cholinesterase inhibitors are common and cardiac toxicity may be severe, including fatal arrhythmias.[170]

Thus, further clinical trials are needed to evaluate the role of parasympathomimetic agents in the treatment of patients with abdominal complaints related to gas retention.

NON-DRUG OPTIONS

Diet

Elimination diet.

1. *Mechanism of action*: Two-thirds of patients perceive their IBS symptoms as food-related.[8] Postprandial worsening of symptoms[171] as well as intolerance to one or more nutrients[172] are commonly described by IBS patients. Several pathological mechanisms may be responsible for this intolerance, such as visceral hypersensitivity,[173, 174] motility disturbances,[175] sugar malabsorption,[176–178] gas-handling disturbances[41, 179] and abnormal colonic fermentation.[39, 40] However, anxiety or depression greatly affect the reporting of food-related symptoms.[8, 180] This speaks, at present, against a major role of food intolerance in the pathogenesis of IBS.

2. *Clinical evidence*: Elimination diets in IBS have yielded conflicting results.[181] Identifying offending dietary substances, e.g. lactose, caffeine, fatty foods, alcohol, gas-producing foods, sorbitol, etc. can help some patients[182] but overly zealous dietary restrictions are harmful, as patients may begin a process of dietary elimination that can lead to severely unbalanced nutrition or an obsessive preoccupation with diet.

Probiotics.

1. *Mechanism of action*: The rationale for the use of probiotics in IBS is its association with infectious diarrhoea. It is generally accepted that IBS-like symptoms are highly prevalent in the months after cure from infectious enteritis, in particular associated after travel to tropical countries. About 7–30% of patients with infectious diarrhoea can develop IBS.[6, 183–185]

Inflammatory infiltration of the intestinal mucosa was observed in IBS subjects after infectious gastroenteritis[6, 186] as well as in other IBS patients.[187] Among the possible mechanisms of probiotic therapy is the promotion of the endogenous defence barrier of the gut. These include normalization of increased intestinal permeability and altered gut microecology as well as improvement of the intestine immunological barrier.

2. *Clinical evidence*: Some probiotics, including acidophilus or bifidus milk, were reported to relieve constipation in an uncontrolled study with a small number of patients.[188] In a randomized, placebo-controlled study, probiotics containing *Saccharomyces boulardii* decreased functional diarrhoea but did not influence other IBS symptoms.[189] Several recent, double-blind placebo-controlled studies showed no effect of probiotic preparations on symptoms or bowel habit in IBS-D[190] or IBS-C subjects.[191] In other studies, probiotics were more efficient than placebo in relieving IBS symptoms.[192–194] However, these studies suffer from methodological inadequacies, including a small number of patients, low compliance and poor statistical analysis. Thus, there is not enough clinical evidence to recommend the use of probiotics in the treatment of IBS.

Psychotherapy.

1. *Mechanism of action*: Psychological factors such as stressful or traumatic life events are reported by up to 60% of IBS patients, and are associated with the first onset of symptoms or with symptom exacerbation[7, 195] (Figure 1). Harmful events such as abuse, neglect or loss of a parent have been described in IBS patients[196, 197] and, to a certain degree, also in animals models.[198] The aggregation of IBS in families of patients with IBS might also be due to learned responses which are transmitted in early childhood.[3] These responses may imply a tendency towards anxiety, depression and somatization.[196]

Thus, it has been suggested that reducing the severity of psychological distress by will alleviate the symptoms of IBS. Psychotherapy, such as cognitive-behavioural therapy,[199] dynamic/interpersonal psychotherapy, hypnotherapy,[200] and stress management[201] may reduce autonomic arousal and anxiety and thus reduce the frequency and severity of symptoms.

There are a number of pathophysiological studies directly evaluating the effect of psychotherapy on GI motility or visceral sensitivity. Most of these studies are related to hypnotherapy. Some controlled studies with IBS patients reported reductions in fasting colonic motility[202] or improvements in abnormal sensory perception in IBS patients[203, 204] with hypnotherapy compared with no treatment or supportive psychotherapy. However, others failed to find such an effect and attributed the improvement of IBS symptoms to reduction in psychological distress and somatization by psychotherapy.[205]

2. *Clinical evidence*: There have been numerous trials of psychological treatment in IBS. Many suffer of methodological inadequacies.[206] The main problem of these studies are the absence of a true control group and lack of adequate blinding, leading to a bias assessment.[206]

For example, hypnotherapy was reported to improve IBS symptoms compared with supportive psychotherapy[207], symptom-monitoring wait-list condition[208] or no treatment.[209] However, some measures such as the therapist contact time or degree of attention to symptoms are lower with these therapeutic procedures than with hypnotherapy. Thus, given the generous placebo response that accompanies trials of functional bowel disorders,[130] the absence of adequate control groups may account for the favourable effect obtained with psychotherapy.[206] Accordingly, in a adequately controlled trial in IBS subjects comparing cognitive behaviour and relaxation therapy to standard care alone showed a reduction in anxiety, depression, social functioning scale and bowel symptoms, with, however, no difference between the three approaches.[210] In addition, similar therapies have been successfully used in organic disorders such as breast cancer.[211] Thus, this type of therapy might simply modify illness behaviour, thus improving the handling of the disorder by the patient. Moreover, while some therapies such as cognitive behaviour therapy, appear efficacious in IBS patients, they are not cost-effective.[212] In conclusion, the role for psychotherapy in IBS has not been established.[206]

CONCLUSION

Despite welcome improvements in trial design and robustness of studies for the newer therapeutic agents for IBS, evaluation of traditional treatments is hampered by poor methodology and inconclusive findings. Many of the treatments currently used in IBS are of dubious efficacy.

The results of our meta-analysis are summarized in the Table 2. We give a grade A evidence-based recommendation for the use of tegaserod for IBS with constipation

in women and alosetron for women with severe IBS with diarrhoea who have failed on conventional therapy. Antidepressants are recommended for IBS with diarrhoea patients with severe refractory symptoms. Loperamide can be recommended in patients with painless diarrhoea.

There is not enough evidence to recommend the use of bulking agents in the treatment of constipation, except as adjuvants in patients with painless constipation. Most trials with antispasmodics were methodologically flawed, and the clinical evidence supporting their use is weak. We do not recommend the use of stimulating laxatives, peppermint oil, prokinetic agents or benzodiazepines in the treatment of IBS.

Elimination diet cannot be recommended except in patients with proven food intolerance. Current studies do not support the routine use of probiotics in IBS patients and large, placebo-controlled trials need to be performed. Finally, the role for psychotherapy in IBS is not established.

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