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REVIEW

Treatment of abdominal pain in irritable bowel syndrome

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Abstract Functional abdominal pain in the context of irritable bowel syndrome (IBS) is a challenging problem for primary care physicians, gastroenterologists and pain specialists. We review the evidence for the current and future non-pharmacological and pharmacological treatment options targeting the central nervous system and the gastrointestinal tract. Cognitive interventions such as cognitive behavioral therapy and hypnotherapy have demonstrated excellent results in IBS patients, but the limited availability and labor-intensive nature limit their routine use in daily practice. In patients who are refractory to first-line therapy, tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors are both effective to obtain symptomatic relief, but only TCAs have been shown to improve abdominal pain in meta-analyses. A diet low in fermentable carbohydrates and polyols (FODMAP) seems effective in subgroups of patients to reduce abdominal pain, bloating, and to improve the stool pattern. The evidence for fiber is limited and only isphagula may be somewhat beneficial. The efficacy of probiotics is difficult to interpret since several strains in different quantities have been used across studies. Antispasmodics, including peppermint oil, are still considered the first-line treatment for abdominal pain in IBS. Second-line therapies for diarrhea-predominant IBS include the non-absorbable antibiotic rifaximin and the $5HT_3$ antagonists alosetron and ramosetron, although the use of the former is restricted because of the rare risk of ischemic colitis. In laxative-resistant, constipation-predominant IBS, the chloride-secretion stimulating drugs lubiprostone and linaclotide, a guanylate cyclase C agonist that also has direct analgesic effects, reduce abdominal pain and improve the stool pattern.

Keywords Irritable bowel syndrome · Visceral pain · Visceral hypersensitivity · Functional pain

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Introduction

Functional abdominal pain, i.e., pain in the absence of an organic, metabolic, or systemic abnormality likely to explain the symptoms, is a highly prevalent and challenging clinical problem for general practitioners, gastroenterologists, and pain specialists. Recurrent functional abdominal pain or discomfort is the predominant symptom and the main diagnostic criterion for irritable bowel syndrome (IBS), accompanied by a change in bowel habit [1]. Depending on the predominant stool pattern, IBS is categorized as a diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), mixed-pattern (IBS-M), or unsubtyped (IBS-U) phenotype. Besides IBS, functional abdominal pain can be a presenting symptom in epigastric pain syndrome [2], a subtype of functional dyspepsia, when the pain is centered in the epigastric region, or functional abdominal pain syndrome (FAPS) if the abdominal pain is not related to food intake or defecation [3]. We focused on the treatment of functional abdominal pain in the context of IBS in adults, since this is the most common presentation in daily clinical practice.

Irritable bowel syndrome is highly prevalent, may profoundly impair quality of life, and is costly to society. IBS affects 5–15 % of the general population [4–7], with a female gender predilection [8, 9]. Although it has no impact on mortality [10], patients with IBS have a similar or worse health-related quality of life compared to chronic

organic diseases like diabetes mellitus and end-stage renal disease [11, 12]. Moreover, functional gastrointestinal disorders cause considerable direct health-care costs and indirect costs like absenteeism [13], and represent a major part of the work load of primary care physicians and gastroenterologists [14]. Diagnosis of IBS is based on the Rome III symptom criteria in the absence of alarm features, although a strategy of exclusion of organic disease is often adopted in clinical practice [1, 15].

Although the etiology and pathophysiology of IBS is still incompletely understood, significant progress has been made in the last decade. A complex interaction between altered intestinal motility [16], the intestinal microbiota [17], impaired mucosal barrier function [18, 19], low-grade inflammatory changes in the gastrointestinal wall [20], and altered functioning of the neurohumoral communication system between the brain and the gut, the so-called brain-gut axis [21–23], has been implicated in the pathogenesis of pain in IBS. Visceral hypersensitivity, defined as a decreased pain threshold to stimuli like balloon distension, can result from altered peripheral and/or central pain processing pathways and is present in a significant proportion of patients with IBS and other functional gastrointestinal disorders [24]. Patients with visceral hypersensitivity more often present with severe abdominal pain, although the correlation between pain thresholds and reported symptoms is far from perfect [25, 26]. Like other functional, i.e., symptom criteria-based, gastrointestinal disorders, IBS most likely represents a heterogeneous disorder with different pathophysiologic mechanisms, which complicates the development of effective treatments.

Methods

A literature search was performed using PubMed and Medline databases with combinations of the following keywords: 'irritable bowel syndrome', 'visceral pain', 'abdominal pain', 'treatment', 'psychological therapy', 'hypnotherapy', 'cognitive behavioral therapy', 'antidepressant', 'nutrition', 'FODMAP', 'anti-spasmodic', 'spasmolytic drugs', 'peppermint oil', 'fiber', 'probiotics', 'antibiotics', 'rifaximin', '$5HT_3$ antagonists', 'alosetron', 'ondansetron', ramosetron', '$5HT_4$ agonists', 'lubiprostone', 'chloride channel activators', 'guanylate cyclase-C agonists', and 'linaclotide'. The search was restricted to controlled studies in adults, published in English. The highest level of evidence was prioritized. Meta-analyses and randomized controlled trials (RCTs) were preferentially included when available. Reference lists of the original studies, meta-analyses, and systematic reviews were searched for relevant studies. Conference abstracts were included for the new and emerging drugs section.

Results

An overview of the pharmacological and non-pharmacological treatment options, targeting primarily the central nervous system or the gastrointestinal tract, is given in Fig. 1. The main pharmacological therapeutic classes with target dosages and approximate number needed to treat (NNT) for individual drugs are summarized in Table 1.

Treatments targeting the CNS

Non-pharmacological treatment

Patient–physician relationship The first step toward a successful treatment is a positive diagnosis and attitude, explaining IBS as a real, established disorder and providing the patient with a plausible and comprehensible disease model since misconceptions among patients are common [27]. Besides part of 'good clinical practice', establishing a positive patient-physician relationship also reduces the number of return visits and improves long-term outcome [28, 29], although this has not been confirmed in RCTs due to the nature of the intervention. This strategy contrasts with the often encountered negative attitude towards the patient, claiming 'everything is fine and nothing abnormal has been found', which may lead to 'medical shopping' and unnecessary follow-up investigations.

Education Patient information can also be formalized in educational programs. A recent randomized study by Labus et al. [30] compared the effect of five weekly, 2-h sessions in small groups of patients, led by a gastroenterologist and a therapist, to a waiting-list control group. The psycho-educational program of this 'IBS school' decreased the overall symptom severity, and improved the IBS-related quality of life and several psychological factors including depression, all persisting at the 3-month follow-up visit. Previous studies indicated the superiority of this multidisciplinary educational approach compared to written information [31]. Interestingly, a short nurse-based version was found to be equivalent to a multidisciplinary longer course [32], increasing the applicability in daily practice.

Psychological interventions Several psychological interventions, such as cognitive behavioral therapy (CBT) and hypnotherapy, have demonstrated clinical efficacy and are recommended in guidelines and treatment recommendations [4, 33]. Psychological and behavioral interventions are mainly used in the treatment of patients with abdominal pain refractory to medical therapy and in the case of psychiatric comorbidity, which is present in a significant proportion of patients, especially in tertiary care referral centers [34].

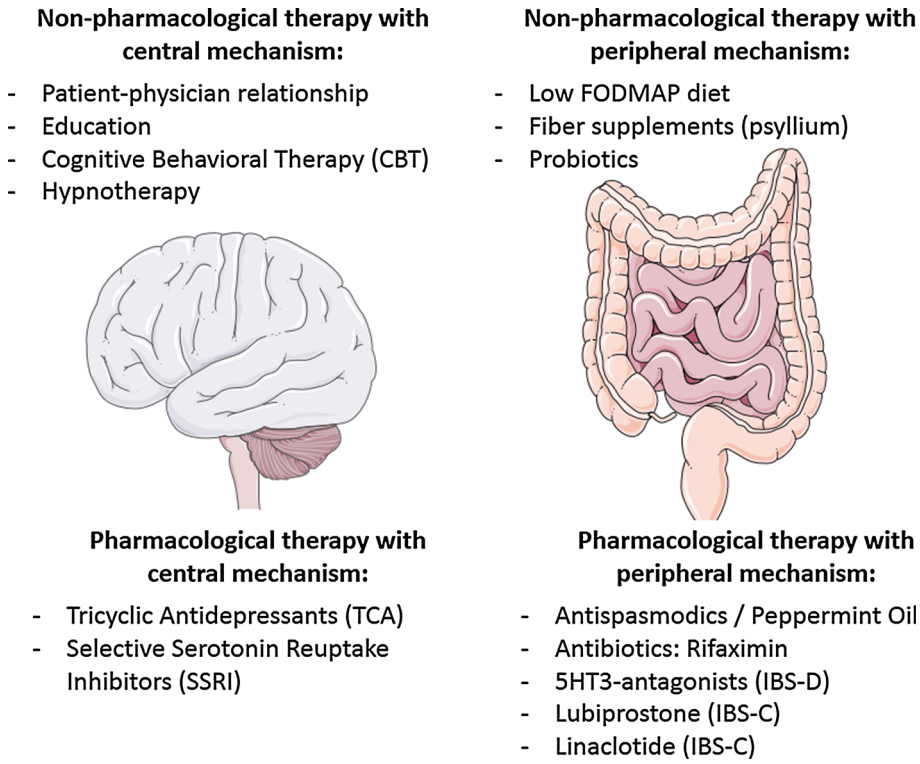

Fig. 1 Overview of pharmacological and non-pharmacological treatment options in irritable bowel syndrome

Cognitive behavioral therapy (CBT), aiming to break the vicious cycle between avoidance behavior, symptom severity, and functional impairment, is the most extensively studied psychological intervention in IBS. CBT has been demonstrated to reduce IBS-related symptoms in several well-performed trials [35, 36] and meta-analyses [37, 38]. The most recent meta-analysis of seven CBT studies with a total of 491 patients showed significant improvement of pain (or general IBS symptoms if pain was not mentioned) in 57 % of patients in the CBT group vs. 39 % in the placebo group ($p < 0.01$). The relative risk (RR) for persistent pain was 0.60 (95 % confidence interval (CI) 0.42–0.87) [38]. However, CBT is labor-intensive, expensive, not readily available in most areas, and subject to long waiting lists in specialized centers, which hampers its use in clinical practice. In an attempt to increase the accessibility, Lackner et al. [36] compared a minimal contact, patient-administered CBT program to a conventional 10-session CBT and a waiting-list control group. Adequate relief of abdominal pain was achieved in a significantly higher proportion of patients in both CBT groups compared to the waiting-list controls (72 % in the minimal contact CBT group and 60.9 % in the conventional CBT group vs. 7.4 % of the waiting-list control). In two recent randomized trials, Ljotsson et al. [39, 40] reported the efficacy, cost-effectiveness, and superiority of an internet-based CBT course specifically designed for IBS patients in comparison to a conventional stress-management program. The minimal contact CBT and internet-based approach could fill in the present need for trained therapists. The optimal protocol and patient selection for CBT warrant further investigation.

Pioneered by the Manchester group [41], gut-directed hypnotherapy improves IBS symptoms (NNT 2; 95 % CI 1.5–7) and quality of life [38]. In the hypnotherapy group, 65 % of patients experienced improvement of pain vs. 25 % in the control group. However, caution is warranted since only 20 patients were available per treatment arm [38]. A recent report of two randomized clinical trials comparing hypnotherapy with supportive therapy in patients refractory to the standard therapy confirmed efficacy in non-specialized hospitals and psychology private practices, although lower efficacy compared to highly specialized centers [42]. The effect was more pronounced for sensory symptoms, such as abdominal pain, than for bowel habit disturbances. The same group recently reported a 69 % patient satisfaction rate, which, surprisingly, was not dependent on improvement of IBS symptoms [43]. The mechanism through which hypnotherapy ameliorates symptoms is still unclear, but several studies reported decreased rectal sensitivity to distension [44, 45]. Like for CBT, the major drawback is the limited availability of qualified therapists and its cost. An ongoing multicenter study in the Netherlands will compare the outcome of individual vs. group hypnotherapy vs. an educational program [46]. If group hypnotherapy turns out to be equally effective, the treatment could be offered by a select number of well-trained specialists to more patients at lower costs.

Table 1 Pharmacological treatment options for IBS

Class	Compound	Target dose	Common or serious side-effects	Comments	NNT
Antidepressants TCA	Amitriptyline	10–75 mg at night	Drowsiness, xerostomia, palpitations, weight gain	Initiate at very low dose at bedtime	4–5 [35, 38, 53]
	Desipramine	10–75 mg at night		Doses usually lower than anti-depressive range	
	Imipramine	10–75 mg at night			
Antidepressants SSRI	Citalopram	10–40 mg o.d.	Nausea, insomnia, agitation, sexual dysfunction	Evidence stronger for general well-being than for abdominal pain	
	Fluoxetine	10–40 mg o.d.			
	Paroxetine	10–50 mg o.d.		Useful for psychiatric comorbidity	
Antispasmodics	Alverine	120–360 mg	Dizziness, blurred vision, xerostomia (anticholinergic drugs)	Low-quality evidence for most compounds in IBS	5 [68]
	Dicyclomine	20–40 mg t.i.d.		Higher quality evidence for otilonium bromide	
	Mebeverine	400–800 mg	Less side effects for musculotropic antispasmodics (otilonium, pinaverium, and mebeverine)		
	Hyoscine derivatives	10 mg			
	Otilonium bromide	40 mg.t.i.d.			
	Pinaverium bromide	50–100 mg t.i.d.			
	Trimebutine	100–200 mg t.i.d.			
	Peppermint oil	187–250 mg t.i.d.	Mint taste, heartburn (less frequent with enteric-coated capsules)		2.5–5 [68, 77]
$5HT_3$ antagonist	Alosetron	0.5–1 mg b.i.d.	Constipation and ischemic colitis (rare)	Approved for females with severe IBS-D under risk management program in USA	10 [80]
	Ramosetron	5 μg o.d.	Constipation	Only approved in Japan, Korea, and Thailand	5–8 [83, 85]
Antibiotics	Rifaximin	550 mg t.i.d.	No antibiotic resistance or *C. difficile* infections reported to date	Treatment for two weeks. Indication and efficacy of retreatment is unclear	11 [90]
Chloride channel activator	Lubiprostone	8 μg b.i.d	Nausea, diarrhea	IBS-C	13 [93]
Guanylate cyclase C agonist	Linaclotide	290 μg o.d.	Diarrhea	IBS-C	3–7 [97–99]

NNT number needed to treat, *TCA* tricyclic antidepressants, *SSRI* selective serotonin reuptake inhibitors, *GI* gastrointestinal, *IBS-D* diarrhea-predominant irritable bowel syndrome, *IBS-C* constipation-predominant irritable bowel syndrome

Pharmacological treatment

Antidepressants Antidepressant drugs have been used as analgesics in chronic pain disorders for decades [47]. Similarly, they are frequently prescribed in functional abdominal pain resistant to non-pharmacological and peripherally-acting therapy. It has been estimated that one in eight IBS patients will at some point be treated with antidepressants [48, 49]. Besides their positive effect on mood for patients with psychiatric comorbidity of depression and anxiety when used in standard doses, they are presumed to be useful in patients with severe and refractory functional abdominal pain without depression, sometimes at lower doses. Proposed mechanisms of action include their central pain-modulatory action [50], improvement of sleep quality, peripheral analgesic effects, and their influence on gastrointestinal motility [51].

Recent meta-analyses reported the efficacy of tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI) in the treatment of IBS-related symptoms [38, 52, 53]. In a meta-analysis of 13 randomized controlled trials (RCT) including 789 patients, the proportion

of patients with persisting symptoms was significantly lower with antidepressant therapy compared to placebo (42 vs. 65 %; RR 0.66) with an NNT of 4 (95 % CI 3–6) [38]. Subgroup analyses showed similar efficacy of TCAs ($n = 575$) and SSRIs ($n = 230$) for overall symptoms. However, a responder analysis for abdominal pain, reported by three studies with TCA and two with SSRI did not reach statistical significance (persisting pain in 49.6 vs. 67.4 % in the antidepressant vs. placebo group; RR 0.66, 95 % CI 0.41–1.06). A recent Cochrane meta-analysis confirmed the superiority of antidepressants over placebo for improvement of global assessment, symptom score, and also for abdominal pain. A subgroup analysis demonstrated a modest superiority of TCAs, but not SSRIs, to placebo in the relief of abdominal pain (RR 1.26; 95 % CI 1.03–1.55; NNT 5) [53].

Interestingly, the largest placebo-controlled trial to date by Drossman and colleagues in 216 patients failed to show a benefit from 12 weeks of desipramine, a TCA, in the intention-to-treat analysis for a composite symptom score and abdominal pain [35]. However, a subgroup analysis limited to those patients with detectable desipramine plasma levels, who supposedly adhered better to the protocol, indicated a significantly better response to desipramine with an NNT of 4.3 for satisfaction with the treatment [35]. A specific analysis for abdominal pain was not reported for this subgroup analysis. A more favorable response was observed in those patients without concomitant depression, suggesting that the beneficial effect was not due to improvement of psychiatric comorbidity. Similarly, symptomatic improvement during treatment with the SSRI citalopram did not correlate with changes in anxiety or depression scores [54].

Interpretation of the outcome of antidepressants in IBS through meta-analyses is complicated by low numbers in most studies, different compounds in different dosages evaluating diverse and often composite endpoints. Moreover, some of the studies report an unexpectedly high efficacy of the active compound [55] or low placebo response rates [56]. Therefore, larger high-quality prospective studies comparing different antidepressants are needed [57]. Notwithstanding these limitations, the available data suggest that both TCA and SSRI are valid treatment options in moderate to severe IBS cases that are refractory to the standard treatment. TCAs appear to be the preferred antidepressant class in patients with pain refractory to antispasmodics as the predominant symptom. The major drawback to starting TCA treatment is the unfavorable side-effect profile, due to its anticholinergic and antihistaminergic properties. The most frequently reported adverse effects are drowsiness, xerostomia, palpitations, and weight gain. Starting at a very low dose (e.g., amitriptyline 10 mg at bedtime), increasing slowly until the effective (25–50 mg) or maximal tolerated dose, reduces the severity of side effects, especially in patients with a high degree of somatization [51]. Along the same line, it is of importance to inform the patient regarding the possible side-effects, the plan to slowly increase the dose with the expectation of a gradual improvement over the course of 4–8 weeks, and the fact that the goal of the treatment is not to treat an underlying depression. In many patients, a dose below the anti-depressant range is sufficient [51]. However, in patients with psychiatric comorbidity, clinicians should feel confident to further increase the dose before stopping the therapy. Others have proposed to associate an antidepressant with a more favorable side-effect profile, such as SSRIs, to a low dose of TCA in the case of psychiatric comorbidity [51], however, supportive data are lacking. Data on the newer, dual serotonin/noradrenalin reuptake inhibitors (SNRI) are very limited. A small open-label study with duloxetine reported decreased pain ratings and increased quality of life [58], but adequate RCTs are needed to determine the added value of SNRIs in the treatment of IBS.

Treatments targeting the gastrointestinal tract

Non-pharmacological treatment

Dietary modification Many patients identify a relationship between ingestion of specific food items and their functional abdominal symptoms. However, demonstrable IgE-mediated food allergies are uncommon and most adverse reactions to food are based on non-immunological 'food intolerance' [59]. In the last several years, a renewed interest in the involvement of specific food constituents, especially gluten and fermentable carbohydrates, has emerged. Biesiekierski et al. [60] were the first to examine the role of gluten in symptom generation in IBS using a blinded placebo-controlled design. Celiac disease was excluded in all 34 included patients with IBS according to Rome III criteria (both constipation- and diarrhea-predominant) who had experienced improvement of symptoms with a gluten-free diet prior to initiation of the study. A gluten-free diet was continued and supplemented by study food items, to which gluten was added in half of the patients in a double-blind fashion. The patients who received the gluten-free supplements experienced significantly less abdominal pain, bloating, and tiredness, and were more satisfied with the general symptom control and stool pattern. This study supported the concept of non-celiac gluten sensitivity. However, in a follow-up study in a similar patient population, the same group failed to demonstrate symptom exacerbations elicited by double-blind gluten introduction in a gluten-free and low-FODMAP diet [61]. FODMAPs (fermentable oligo-, di and

monosaccharides and polyols) are short-chain carbohydrates that are poorly absorbed in the small intestine and can be fermented in the colon, increasing the fecal water content, leading to gas production and symptoms [62]. Clearly, more research is needed on this controversial topic, but these latter data challenge the concept of non-celiac gluten sensitivity. Single-blind administration of FODMAPs induced higher H_2-production, indicating bacterial fermentation, and more symptoms in patients with IBS compared to controls [63]. A diet low in FODMAPs was found to be superior to conventional dietary advice (regular meal pattern, adjusting fiber intake and reducing alcohol and caffeine) in improving abdominal pain (85 vs. 61 % reported improvement, $p = 0.023$) in a non-randomized study in 82 patients diagnosed with IBS according to the NICE criteria (abdominal pain or discomfort, bloating, or change in bowel habit for at least 6 months) [64, 65]. In a recent single-blinded, controlled cross-over study, Halmos et al. [66] compared a low-FODMAP diet to a regular Australian diet in 30 patients with IBS (Rome III definition, 10 IBS-D, 13 IBS-C, 5 IBS-M and 2 IBS-U). The overall symptom score (23 vs. 45 mm on a visual analogue scale (VAS); $p < 0.001$), and the scores for abdominal pain, bloating, and flatulence were significantly lower with the low-FODMAP diet compared to the control diet. A 10-mm lower VAS for the overall symptom score in the low-FODMAP vs. regular Australian diet was observed in 70 % of patients. The maximal effect of the diet was reached after seven days and remained stable until the end of the study two weeks later. Experts have suggested to introduce a general low-FODMAP diet for 6–8 weeks to determine whether the intervention is useful in a certain patient, and then gradually reintroducing certain categories of FODMAPs to avoid over-restriction [62]. Long-term outcomes and safety of low-FODMAP diets remain to be demonstrated. It is also still unclear whether the low FODMAP intervention diet is beneficial to all IBS patients or whether selection, e.g., by hydrogen breath testing, can identify those patients who will benefit most.

Fiber Many physicians advise fiber supplements for abdominal pain and altered bowel habits in IBS in daily practice. Fiber is fermented in the colon with secondary production of short-chain fatty acids (SCFA) and gas [67]. It is probably through SCFA generation that fiber increases the luminal osmotic load, attracting water, and influences the microbiome, resulting in an increased biomass. The net result is an acceleration of colonic transit time. Nevertheless, the benefit of fiber in IBS is not established. A recent Cochrane meta-analysis found no beneficial effect of fiber on abdominal pain, global assessment or general symptoms in IBS [53]. However, the majority of the included studies were old and of poor methodological quality. Ford et al. [68] reported a borderline significant effect when combining 12 studies comparing fiber to placebo with an NNT of 11 (95 % CI 5–100), but the effect was lost when only high-quality studies were included in the analysis. In a subgroup analysis, isphagula (psyllium), a type of soluble fiber, was effective in reducing IBS symptoms with an NNT of 6 (95 % CI 3–50), in contrast to bran, an insoluble fiber [68]. One of the criticisms of the trials evaluating fiber is the fact that most were performed in secondary or tertiary care, prone to selecting patients with the most therapy-resistant symptoms [67]. A recent study, not included in both meta-analyses is a large, well-designed study in primary care IBS patients evaluating a three-month treatment of bran, isphagula, and rice-flour (placebo) [69]. Isphagula was found to be superior to placebo in providing adequate relief of abdominal pain or discomfort at one and two months, but not at three months. Bran improved symptoms only at the three-month time point. This study suffered from 40 % dropouts in all three groups, complicating interpretation of the results. A common adverse effect of fiber supplements or increase in dietary fiber, which may have contributed to the high drop-out rate, is increased flatulence and bloating because the fiber is fermented by the colonic microbial flora. Overall, the effect of fiber in IBS seems limited, but there may be a place for soluble fibers such as isphagula in patients with mild symptoms.

Probiotics Probiotics, live organisms that confer a health benefit to the host, have been hypothesized to improve IBS-related symptoms through effects on visceral hypersensitivity, gastrointestinal motility, intestinal permeability, intestinal immune function, and microbiota [17]. Despite their increasing use, the position of probiotics in the treatment of IBS is still controversial and the magnitude of the effect seems limited. A recent meta-analysis by Moayyedi et al. [70] included 19 RCTs with 1,650 patients and demonstrated improvement of abdominal pain and global IBS symptoms with an NNT of 4 (95 % CI 3–12.5) with different probiotics. In one of the few studies that compared two strains, O'Mahony et al. [71] reported that *Bifidobacterium infantis* was more effective in reducing abdominal pain compared to *Lactobacillus salivarius*. Still, the routine use of probiotics for treatment of pain in IBS is hindered by the fact that it is unclear which strains or combinations are the most beneficial or whether particular symptoms (e.g., bloating) are treated more efficiently by certain strains. This needs to be addressed in larger studies with adequate endpoints and design.

Pharmacological treatment

Antispasmodics and peppermint oil The pathogenesis of functional abdominal pain is complex, but may be partly

related to colonic smooth muscle contractions [72]. A Cochrane meta-analysis for antispasmodics, including 13 RCTs with 1,392 IBS patients, demonstrated efficacy in the improvement of abdominal pain with a pooled RR of 1.32 (95 % CI 1.12–1.55) [53]. For individual spasmolytic agents, only pinaverium bromide and trimebutine reached significance for relief of abdominal pain. Six studies evaluated pinaverium bromide in 158 patients with an RR of 1.57 (95 % CI 1.08–2.26) for improvement of abdominal pain and three studies with a total of 140 patients were available for trimebutine with an RR of 1.32 (95 % CI 1.07–1.64). This meta-analysis found no significant benefit on pain for scopolamine derivates, dicyclomine, otilonium, mebeverine, pirenzepine, and alverine. However, significant heterogeneity among the studies was present and many studies did not mention pain as a separate outcome. Moreover, most of the included trials are old and used variable patient inclusion criteria. It is unclear how the older antispasmodics would perform in patients with IBS according to the Rome III criteria. The meta-analysis by Ford et al. [68] came to similar conclusions, demonstrating an NNT of 5 for relieving IBS symptoms (no specific analysis for pain). In a meta-analysis restricted to high-quality RCTs, only otilonium bromide was found to be superior to placebo in improvement of overall symptoms [73]. A recent high-quality multi-center RCT, not included in the previous meta-analyses, evaluated otilonium bromide for 15 weeks in 356 patients with IBS [74]. The frequency, but not the severity, of abdominal pain was reduced by otilonium bromide. The benefit of otilonium 40 mg t.i.d. was maintained throughout the 10-week treatment-free follow-up period. The adverse effects of the older anticholinergic antispasmodics include dry mouth, dizziness, and blurred vision. These are almost non-existent with the newer musculotropic spasmolytics [75].

Peppermint oil possesses antispasmodic properties through blockade of calcium channels and is often used as first-line therapy for IBS due to its favorable side-effect profile. In the largest RCT of 101 IBS patients in secondary care, 79 % of patients in the peppermint oil arm experienced alleviation of abdominal pain (56 % pain-free) compared to 43 % in the placebo arm (8 % pain-free) ($p < 0.05$) [76]. In a meta-analysis of four older RCTs with 392 patients, the relative risk for persisting symptoms was 0.43 (95 % CI 0.32–0.59) with an NNT of 2.5 (95 % CI 2–3) [68]. A recent meta-analysis of five studies (357 patients) reported improvement of abdominal pain in 57 % of patients with enteric-coated peppermint oil capsules vs. 22 % with placebo (NNT 4) at 2–8 weeks [77].

$5HT_3$ receptor antagonists and $5HT_4$-agonists Serotonin (5HT) plays an important role in gastrointestinal motility and neurotransmission [78]. Alosetron, a $5HT_3$-antagonist with a central and peripheral mode of action, reduces abdominal pain and diarrhea in IBS-D patients. In a systematic review of eight RCTs ($n = 4{,}987$), symptoms persisted in 49 % of patients treated with alosetron, compared to 64 % of patients allocated to placebo (RR 0.70; 95 % CI 0.69–0.90) [79]. A meta-analysis of seven studies specifically reporting the effect on abdominal pain or discomfort demonstrated a superiority of alosetron (RR 1.23; 95 % CI 1.15–1.32) with an NNT of 9.8 [80]. Because of the occurrence of rare complications of ischemic colitis and severe constipation, alosetron is only approved in the USA for women with severe IBS-D under a risk-management plan, and is not available in most other parts of the world. Analysis of the complications in this program ($n = 29{,}072$) demonstrated complication rates of 0.95 and 0.36/1,000 patient years for ischemic colitis and severe constipation, respectively [81]. Ramosetron, another $5HT_3$-antagonist with mainly a peripheral effect, showed a lower incidence of constipation in comparison to alosetron (5 vs. 29 %) and has not been associated with ischemic colitis so far [82]. However, caution is needed since the number of patients in the studies combined is lower compared to alosetron. In a phase III study including 539 patients, 46 % of patients reported adequate relief of abdominal pain compared to 33 % with placebo (RR 1.39; 95 % CI 1.12–1.71), which is similar to alosetron [83]. In a Korean study in 343 male IBS-D patients treated with mebeverine, an antispasmodic, or ramosetron had similar response rates for relief of abdominal pain or discomfort (35 and 40 % for mebeverine and ramosetron, respectively) [84]. The number of adverse events was comparable in both groups [84]. Fukudo et al. [85] recently reported increased response rates with ramosetron compared to placebo for improvement of stool consistency [primary endpoint, 50.3 vs. 19.6 %, NNT 3.3 (95 % 2.4–4.9)], relief of overall IBS symptoms (31.3 vs. 9.5 %), and relief of abdominal pain (32 vs. 10.1 %) in 296 male patients with IBS-D. Ramosetron is currently only approved for male IBS-D patients in Japan, Korea, and Thailand. Ondansetron, one of the first generation and widely available $5HT_3$ antagonists, significantly improved stool consistency and urgency in a recent placebo-controlled crossover trial, but did not affect the pain scores [86].

The $5HT_4$-receptor agonist tegaserod was shown to be effective in IBS-C, but was withdrawn from most markets due to a potential imbalance of cardiovascular adverse events compared to placebo. Prucalopride, a new $5HT_4$-agonist with a more favorable side-effect profile [87], is approved for chronic constipation, but trials in IBS-C are eagerly awaited. Other $5HT_4$-agonists like velusetrag and naronapride are currently under evaluation.

Antibiotics: rifaximin Antibiotics have been used to treat IBS patients with suspicion of small intestinal bacterial

overgrowth (SIBO) with varying results [88, 89]. Because of the lack of validated tests to determine the presence of SIBO and contradictory reports in the literature, focus has now largely shifted to the role of altered microbiota in the pathogenesis of symptoms and its modulation by antibiotics. Rifaximin is a broad-spectrum, poorly-absorbed antibiotic that has been evaluated for IBS. Pimentel et al. [90] reported the results of two phase III trials including 1,258 patients with IBS without constipation treated with rifaximin 550 mg t.i.d. for two weeks and followed up for an additional 10 weeks. Significantly more patients met the primary endpoint of adequate relief of global IBS symptoms (41 vs. 32 %; $p < 0.0001$) and relief of abdominal pain (44 vs. 35 %; $p = 0.003$) with rifaximin compared to placebo, and the therapeutic effects persisted until the end of the 12-week follow-up period, i.e., 10 weeks after the treatment. Concerns have been raised regarding the induction of antimicrobial resistance and *C. difficile* infections, but this has not been reported so far. A small retrospective study indicated that retreatment is possible with favorable outcome [91]. The mechanism of action of the treatment (SIBO vs. colonic microbiota) and appropriate patient selection is a matter for future research.

Chloride channel activators and guanylate cyclase-C agonists In patients with IBS-C, normalization of the stool pattern is the primary goal of the treatment in order to reduce functional abdominal pain. First-line therapy includes dietary modulation, fiber, and osmotic laxatives, although evidence for pain reduction by the latter is limited [92]. Recently, chloride-secretagogues lubiprostone and linaclotide have become available for the treatment of IBS-C. Lubiprostone stimulates type 2 chloride-channels in the gastrointestinal tract, leading to increased fecal water content. The combined results of two large phase III trials ($n = 1{,}171$) demonstrated a modest efficacy for overall response (17.9 vs. 10.1 %, $p = 0.001$) [93]. Improvement of abdominal pain and discomfort scores was significantly better with lubiprostone 8 μg b.i.d. for 12 weeks. A post-hoc analysis demonstrated improved response rates in those patients with more severe abdominal pain at baseline [94]. The most common adverse effect was nausea (10–25 %), which was self-limited in most patients [95].

Linaclotide is a minimally absorbed guanylate cyclase (GC)-C agonist, ultimately activating the apical cystic fibrosis transmembrane conductance regulator (CFTR) chloride-channel through the production of cyclic guanosine-3′5′-monophosphate (cGMP). In addition, animal studies showed that linaclotide also has visceral analgesic effects, mediated by the extracellular release of cGMP, inhibiting nociceptors [96]. To date, two large phase III trials are published in full [97, 98]. In the first study of 804 patients, the Food and Drug Administration (FDA) combined endpoint for IBS-C, which consists of a 30 % reduction in severity of the worst daily abdominal pain combined with an increase of at least one complete spontaneous bowel movement per week during at least six of the first 12 weeks of the treatment, was met by 33.7 % of patients receiving 290 μg of linaclotide once daily, compared to 13.9 % in the placebo group (NNT 5.1; 95 % CI 3.9–7.1) [98]. Restricting the analysis to the pain criterion, 48.9 % of patients treated with linaclotide were responders vs. 34.5 % of patients in the placebo group (NNT 7; 95 % CI 4.7, 13.1). The second study, evaluating 800 patients, reported similar results and demonstrated partial relapse of symptoms during a randomized four-week withdrawal period after 12 weeks of treatment, but not to levels worse than baseline [97]. A meta-analysis of both trials looking specifically at patients who had severe abdominal pain (severity score $\geq$7/10; $n = 376$) at inclusion, confirmed the efficacy of linaclotide in these severely afflicted patients: 61 % of patients reported adequate relief at week 12 of active treatment compared to 30 % with placebo ($p < 0.0001$) [99]. As expected from the mechanism of action, the most common adverse event was diarrhea in about 20 % of patients in both studies, leading to discontinuation of the study in 5 % of patients [97, 98].

Emerging and possible future therapeutic options

Several compounds are currently under evaluation aiming specifically to reduce pain in IBS by interfering with nociceptive stimuli like low-grade inflammation (e.g., adsorbents, mast cell blockers, anti-histaminergic drugs), neurotransmitters (e.g., adsorbents, serotonin synthesis inhibitors) and receptors (e.g., neurokinin receptor antagonists) involved in visceral nociception.

AST-120 is a carbon-based adsorbent that is thought to absorb low-molecular components like neuroactive agents (serotonin, histamine, tyramine), bacterial components like lipopolysaccharide, and bile acids in the intestinal lumen, several of which are thought to be involved in the pathogenesis of IBS. In a multi-center, international RCT, a treatment response, defined as more than a 50 % reduction in the days with abdominal pain in the past two weeks, was achieved in 26.8 % of patients with AST 120 compared to 10.2 % with placebo at week 4 ($p = 0.029$) [100]. However, this difference was lost at eight weeks due to an increasing placebo response. The treatment was well-tolerated and safe, justifying its further evaluation.

Peripherally-acting K-opioid agonists are attractive treatment options for visceral pain in IBS due to their likely favorable side-effect profile. Asimadoline was not effective when administered in an on-demand approach to female IBS patients [101]. In a phase II study evaluating a

maintenance treatment in 596 patients with IBS, pain scores significantly improved in IBS-D ($n = 104$) only [102]. CR665 (or JNJ-38488502) is another peripheral K-agonist with selective analgesic effect on visceral pain, but has not yet been tested in IBS patients [103, 104].

LX-1031, a poorly-absorbable peripheral inhibitor of serotonin synthesis, increased the proportion of patients with adequate relief of pain at one week, but not at the following weeks in a four-week phase II trial in 155 patients with non-constipating IBS; it also showed a favorable adverse event profile [105]. Larger follow-up trials are awaited.

Blockers of the tachykinergic neurotransmitter system are promising new tools in the treatment of IBS. Tachykinins, a family of neuropeptides including substance P, and neurokinin (NK) A and B are important mediators of gastrointestinal motility and nociception. Of the three NK receptors (NK1–3), especially the NK2 receptor has been shown to be involved in the induction of colonic contractions and colonic hypersensitivity [106, 107]. The neurokinin (NK)1 antagonist AV608 decreased pain ratings and reduced anxiety and negative affect in 13 female IBS patients [108]. However, further development of this molecule in clinical experiments was halted because of safety concerns, but the study provided proof of concept that blocking of the NK1 receptors may be effective in the treatment of pain and anxiety-related symptoms in some IBS patients [109]. DNK333, a blocker of the NK1, 2, and 3 receptor, was superior to placebo in adequate relief of abdominal pain/discomfort in the pooled analysis of two phase II trials without major side effects [110]. Ibodutant, a selective antagonist of the NK2 receptor with very low penetration in the brain, was evaluated in a placebo-controlled phase II study in 559 IBS-D patients comparing placebo, 1, 3, and 10 mg daily. In the overall population, a trend toward increased response with escalating ibodutant doses was shown with best efficacy for the 10-mg dose (27.5 % with placebo vs. 39.6 % with ibodutant 10 mg, $p = 0.032$, NS after correction for multiple testing). In a pre-specified analysis by gender, a clear dose–response effect was shown in females, with ibodutant 10 mg demonstrating the highest efficacy and statistically significant superiority over placebo in females (24.4 % response rate with placebo vs. 46.8 % with ibodutant 10 mg; $p = 0.003$, significant after correction for multiple testing) [111]. Phase III studies with ibodutant 10 mg in women with IBS-D are planned in Europe and in the USA.

Low-grade inflammatory changes in the gastrointestinal wall, dominated by increased numbers of mast cells and eosinophils, have been implicated in the pathophysiology of IBS [20]. Release of mast-cell products may contribute to the development of visceral hypersensitivity. The mast cell stabilizer ketotifen increased the discomfort threshold to rectal distension in IBS patients with visceral hypersensitivity [112]. Moreover, abdominal pain ratings and quality of life improved with ketotifen. However, the release of tryptase and histamine from rectal biopsies was unaltered by the treatment, which led to the hypothesis that other properties of ketotifen, e.g., H_1-receptor antagonism, may be of importance. In a follow-up study, the H_1-receptor antagonist ebastine significantly decreased abdominal pain over the course of 12 weeks with recurrence of symptoms during a withdrawal period of two -weeks [113]. At the end of the 12-week treatment, 46 % of patients treated with ebastine had at least considerable relief of symptoms compared to 12 % with placebo ($p = 0.01$).

Along the same line, the anti-inflammatory agent mesalazine has been evaluated in IBS in small studies with variable results [114, 115]. A larger, multi-center study powered to draw conclusions on clinical efficacy is currently ongoing [116].

Conclusion

The treatment of chronic functional abdominal pain in IBS patients is a challenging task for gastroenterologists, pain specialists, and general practitioners. What is currently labeled as IBS probably consists of a group of conditions with different underlying pathophysiological mechanisms. This heterogeneity, the absence of hard outcome measures, and high placebo response rates in a group of disorders known to be influenced by neuropsychological state complicate drug development and interpretation of study results. This is why it is of primary importance to try to link the outcome of a clinical trial to pathophysiological mechanisms, e.g., visceral hypersensitivity, low-grade inflammation, anxiety related dysfunction, etc. The ultimate goal of this strategy would be to predict the best treatment for the individual patient.

Until recently, the role of food intake and specific food constituents was largely neglected in IBS care. Several diets, in many cases not based on evidence, have appeared in the lay press and filled the unmet need of dietary advice felt by our patients. Only recently, blinded placebo-controlled trials for specific diets have been started in functional gastrointestinal disorders, and this should be further encouraged. Although several peripheral, gastrointestinal targets for treatment have been identified, the role of the psyche should not be overlooked in functional gastrointestinal disorders. Well-designed trials have demonstrated the efficacy of hypnotherapy, cognitive behavioral therapy, and educational programs. Unfortunately, in most countries these treatments have not found their way into regular clinical practice. Several reasons can account for this: the

tendency of and ease for physicians to use pharmacological therapies, the lack of reimbursement in certain areas, the limited amount of trained therapists, and the stigma of psychological therapy. We are convinced that the future of functional gastroenterology should be a multi-disciplinary one with teams consisting of primary care physicians, gastroenterologists, pain specialists, psychologists or psychiatric specialists, nutritionists, and others.

Although many of the older trials (and consequently also the meta-analyses of these trials) for older treatments like anti-spasmodics are of questionable quality, new possible future therapies for IBS are emerging at a fast pace. Moreover, the functional gastrointestinal research community has finally entered the era of well-designed, adequately powered, large clinical trials with predetermined, validated end-points in order to achieve approval by the regulatory authorities around the globe. This is an exciting period for functional bowel disorders with innovative, well-studied molecules entering daily practice and new evidence for older treatments like psychotherapy and nutrition-based treatments.

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