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Romanian Guidelines for Nonpharmacological Therapy of IBS

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ABSTRACT

Background & Aims: The nonpharmacological therapy in irritable bowel syndrome (IBS) is expanding rapidly. Practitioners and medical educators need to be aware of progress and changes in knowledge of this topic. The Romanian Society of Neurogastroenterology aimed to create guidelines based on best evidence on the use of nonpharmacological therapy in IBS.

Methods: A group of experts was constituted. This was divided in eleven subgroups dedicated to eleven categories of nonpharmacological therapy. The subgroups searched the literature and formulated statements and recommendations. These were submitted to vote in order to obtain consensus.

Results: The outcome of this activity is represented by the guidelines of the Romanian Society of Neurogastroenterology, presented in this paper. The recommendations are seen as complementary to the pharmacological therapy and are not intended to recommend avoiding pharmacological drugs.

Conclusions: These guidelines were elaborated by a Delphi process and represent a useful tool for physicians managing patients with IBS.

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Key words: acupuncture – alternative and complementary therapy – diet – FODMAP – irritable bowel syndrome – physical activity – probiotics.

Abbreviations: BAT: body awareness therapy; CBT: cognitive behavioral therapy; GFD: gluten free diet; FMT: fecal material transplantation; FODMAP: fermentable oligo, di, monosaccharides, and polyols; IBS: irritable bowel syndrome; IBS-C: IBS with constipation; IBS-D: IBS with diarrhea; IBS-M: mixed type IBS; IBS-SSS: IBS severity scoring system; LFD: low FODMAP diet; mNICE: modified NICE diet (small frequent meals, avoid trigger foods, and avoid excess alcohol and caffeine); PMO: peppermint oil; QoL: quality of life; RCT: randomized control trial; SCFA: short-chain fatty acids; TCM: traditional Chinese medicine.

INTRODUCTION

Irritable Bowel Disease (IBS) is a chronic condition, frequently present in many gastroenterological patients. Management of these patients may be difficult and there is no single pharmacological and/or non-pharmacological treatment applicable to all patients.

The Romanian Society of Neurogastroenterology decided to develop own specific guidelines for non-pharmacological therapy of IBS due to the worldwide expansion of these therapies which are present also now in Romania. Large differences seem to exist between offered non-pharmacological therapies in different countries depending on culture, tradition and availability. We felt that our practitioners should benefit from an evidence-based document to indicate what is useful or not in the therapy of IBS. Of course, we are not overlooking the pharmacological therapy, but the focus of these guidelines for the medical practitioner is limited to the non-pharmacological alternatives, a topic that has been rarely a subject of a specific guideline.

METHODS

The Romanian Society of Neurogastroenterology identified a group of experts in the fields of IBS and nutrition. The group included gastroenterologists, general practitioners, internists, and pharmacists. From this expert group, 11 subgroups were

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created, according to the previous interests of participants, in order to propose statements and recommendations on different aspects of the topic. Using a Delphi-type approach, statements and recommendations were proposed, based on evidence-based data, obtained from a comprehensive literature search. However, included in this manuscript had to be limited to an acceptable length of the manuscript.

The statements and recommendations put to the vote in order to obtain consensus on the degree of evidence and level of recommendation. All were submitted to a vote by the participants for consensus. All the group membersvoted for all the subjects, and consensus was obtained when >80% of respondents agreed with the items. We used the GRADE system scoring to assess the strength of evidence (Table I).

Table I. Grading of the degree of evidence

Degree of evidence	Identification	Meaning
High	A	High-quality studies available; very trustworthy.
Moderate	B	Several studies available, at least one of high quality, others with limitations; trustworthy.
Low	C	No high-quality studies but several studies with limitations available; not very trustworthy.
Very low	D	No evidence available, only expert opinion; use with caution.

The strength of the recommendation was considered strong or weak according also to GRADE. For voting, each statement was presented together with the summary of available evidence. The entire panel indicated the degree of agreement for the statements and recommendations using a 6-point Likert scale from: agree strongly (A+), to disagree strongly (D+), with intermediate points A, A-, D-, D. Connection between contributors was kept via email.

LOW FODMAP DIET

Frequently, IBS patients may report that some foods exacerbate symptoms and therefore several of them attempt use exclusion diets. Some of these foods (cereals, fruits, vegetables, and dairy products) contain fermentable oligo, di, monosaccharides, and polyols (FODMAPs), related with pain occurrence in IBS [1]. FODMAPs are poorly absorbed in the intestine and have an osmotic action. They also represent a substrate for bacterial fermentation, resulting in the accumulation of gas and water in the intestinal lumen and colonic distension. These changes generate symptoms in patients with visceral hypersensitivity, including IBS patients [2]. Therefore, a low FODMAP diet (LFD) is expected to improve IBS symptoms [3].

A low FODMAP diet implies <3 g/day oligosaccharides, and <1 g/day polyols [4] and consists of three phases: the elimination phase (4 to 6 weeks), the reintroduction phase (6-12 weeks), and the personalized phase. First foods containing FODMAPs are eliminated from the daily diet. If symptoms fail to improve, patients should stop the diet and other alternatives should be offered. Afterwards, FODMAPs are gradually reintroduced in the diet to identify which foods determine symptoms' recurrence, therefore allowing a personalized LFD, that can be followed for a longer period [5, 6]. A dietitian should follow the patients through all these phases.

Gut hormones play an important role in IBS pathogenesis. Patients with IBS have a low density of gut endocrine cells, most probably related with diet and microbiota. By-products resulting from bacterial fermentation of nutrients determine a low differentiation of gut stem cells toward endocrine cells, and secondary a low secretion of gut hormones. These hormones are part of the gut-brain axis and contribute to gut motility, visceral sensitivity, and secretion. Hence, a decreased density of endocrine cells will generate gut dysmotility, visceral hypersensitivity, abnormal secretion, and finally gastrointestinal symptoms [7]. Following an LFD, the density of colonic endocrine cells tends to normalize, in parallel with symptoms improvement [8].

Statement 1.1. Low FODMAP diet improves overall IBS symptoms in majority of patients with IBS. *(Quality of evidence: C; agreement: 97.2%.)*

Statement 1.2. Low FODMAP diet is more efficient, compared to traditional dietary advice, on abdominal pain, diarrhoea, bloating and urgency symptoms. *(Quality of evidence: C; agreement: 100%).*

Short-term effects of a low FODMAP diet

Several randomized controlled trials (RCT) evaluated the efficacy of the elimination phase of LFD in IBS patients. A low FODMAP diet was used for 3 to 6 weeks, and was compared to habitual diet [9], traditional dietary advice [10, 11], moderate FODMAP diet [4], modified NICE guideline recommended diet [12], high FODMAP diet [1], sham diet [13] or placebo [3]. Most studies included small numbers of patients, and given the abundance of available information on FODMAPs, the blinding was difficult to achieve. In addition, 5 meta-analyses confirmed the efficacy of LFD on IBS symptoms [5], especially on abdominal pain and bloating, but the evidence was appreciated as of low quality.

A low FODMAP diet was compared with a usual diet in a randomized control trial (RCT) which included IBS patients with bloating or diarrhea as main symptoms. Adequate symptom control was observed in 68% of patients on LFD compared to 23% on usual diet (p=0.005). Bloating, abdominal pain, urgency and borborygmi improved after LFD. However, stool consistency and frequency were not influenced [9]. In a crossover trial LFD was compared witha a typical Australian diet. During the LFD the overall gastrointestinal symptom score (assessed using a visual analogue scale) was lower compared with the score during typical diet (22.8 mm vs. 44.9 mm, p<0.001). Bloating, pain, flatulence, stool consistency also improved, and in IBS with diarrhea (IBS-D) fecal frequency significantly decreased [4]. Another RCT compared LFD with sham diet, with or without probiotics and concluded that LFD determined an adequate relief of symptoms and significantly reduced symptoms score compared with placebo [13].

Traditional dietary advice is the first-line recommendation of the British Dietetic Association in IBS [14], and consists of regular meals, chewing foods properly, avoiding large meals, caffeine, alcohol, fatty foods, spices, soft drinks, insoluble fibers, beans, cabbage, and onions. In other countries, a modified

NICE diet (mNICE: small frequent meals, avoid trigger foods, and avoid excess alcohol and caffeine) is firstly recommended [7]. Following traditional dietary advice or mNICE diet, some FODMAPs are clearly excluded. Some studies that compared LFD with traditional dietary advice [10-12, 15, 16], reported a similar efficacy between these dietary interventions [10, 12, 16]. Other studies reported a greater improvement of symptoms following LFD [11, 15]. Low FODMAPs and mNICE diets showed similar efficacy on global IBS with diarrhoea (IBS-D) symptoms. However, LFD improved abdominal pain in 51% of patients, compared to 23% (p=0.008) in mNICE diet group, and determined a greater reduction in average daily scores of abdominal pain, bloating, consistency, frequency, and urgency [12]. A balanced Mediterranean diet (characterized by distribution of calories and FODMAP intake over the 24 h period to prevent excessive FODMAP intake at once) was not inferior to LFD and was preferred by patients [16].

Statement 1.3. In IBS patients who respond to a low FODMAP diet - elimination phase, a personalized low FODMAP diet in the following months can have a favorable effect on symptoms severity (abdominal pain and distention). *(Quality of evidence: D; agreement: 100%)*

Long-term effects of a low FODMAP diet

Studies reported that at long-term follow-up (> 6 months) 50-70% of patients on LFD had a satisfactory relief of symptoms [17-21]. Patients reintroduced one FODMAP subgroup per week and followed reappearance of symptoms in order to identify triggering foods, that should be avoided. Based on personal tolerance, an "adapted"/ "personalized" diet was followed. At 3-month follow-up pain frequency and severity decreased, abdominal distention diminished, IBS severity scoring system (IBS-SSS) showed mild disease in most cases and also IBS quality of life (QoL) increased. The favorable effects on symptoms and on IBS-QoL were maintained at 6-month follow-up [18]. Triggering foods for IBS symptomatology were hazelnuts and chocolate [19], fructans and free fructose containing foods [22]. In a retrospective analyses, wheat, dairy products and onions were avoided by patients following long-term modified LFD [21]. However, following a LFD for a longer time was more expensive than a habitual diet and also may impair social relationships influencing eating out with family/friends [22].

Statement 1.4. A personalized Low FODMAP diet administered for long periods of time is safe and does not produce significant changes in nutritional composition (decrease in calories, fibers and micronutrients). *(Quality of evidence: D; agreement: 77.7%)*

This statement was accepted even if the agreement was 77.7% instead of 80%, without a second voting round. According to this, we formulated following recommendations:

Recommendation 1.1. A low FODMAP diet may be offered to IBS patients to improve abdominal pain, bloating and/or diarrhea, for a minimum of 4 weeks (elimination phase). If no symptom improvement occurs within 4 weeks, the diet should be stopped. *(Quality of evidence: C, strength of recommendation: weak; agreement: 100%)*

Recommendation 1.2. In IBS patients where symptoms improved during the elimination phase, we recommend gradual reintroduction of FODMAPs (during the next 3 months) to identify triggers, followed by a personalized diet. *(Quality of evidence: C, strength of recommendation: weak; agreement: 100%.)*

Recommendation 1.3. A probiotic may be added to Low FODMAP diet. (*Quality of evidence: C; strength of recommendation: weak; agreement: 97.2%)*

Low FODMAPs diet and the effects on health

FODMAPs may have favorable effects on colonic health through the prebiotic action of oligosaccharides and the anti-inflammatory properties of short-chain fatty acids (SCFAs) [23]. However, there may be some concerns regarding the long-term effects of LFD on colonic health secondary to microbiota and by-products changes.

After the elimination phase of an LFD Staudacher et al. [9] reported the decrease of the concentration and proportion of *Bifidobacteria*, a butyrate producer with immunomodulatory effects, which is inversely related with IBS symptoms. Another study reported a decrease of *Actinobacteria*, *Bifidobacterium*, and *Faecalibacterium prausnitzii*. In addition, fecal SCFAs and n-butyric acid decreased [3]. However, one trial showed that the concomitant administration of the probiotic VSL#3 to LFD increased the abundance of *Bifidobacterium* species [13]. If further studies confirm this finding, the issue of microbiota alteration might be overcome by probiotic supplementation. Other concerns are related to the risk of insufficient energy and fiber intake, as reported by some RCTs [10-12]. Among micronutrients, calcium intake was significantly lower on LFD compared with a habitual diet [9]. However, in the reintroduction and later in the personalized phases, the majority of FODMAPs are reintroduced and the energy and fiber intake increased to pre-diet levels [18, 22].

DIETARY FIBERS

There is a long history of using fibers, starting from the Ancient Greece where bran was used for constipation up to the present days where fibers are modelling intestinal microbiota. The positive effects of dietary fibers are numerous and act in different diseases. They could decrease the risk and mortality of cardiovascular diseases, obesity, colonic diseases diabetes mellitus and they may reduce the risk of cancer correlated with age, etc.

As defined by AACC, dietary fibers are the edible parts of plants or their extracts, or analogous carbohydrates that are resistant to digestion and absorption in the human small intestine and undergo complete or partial fermentation in the large intestine [24]. Another simplified way to define dietary fibers: only dietary components that reach the colon without being absorbed in a healthy human gut [25]. Dietary fiber classification is presented in Table II [26].

Other classifications take into account not only the water solubility but also the fermentability, viscosity and gel formation. From this point of view, dietary fibers can be divided in insoluble and poorly fermented (wheat bran), soluble non viscous, readily fermented (inulina) and soluble viscous gel forming non fermented (psyllium) [28].

Table II. Classification of dietary fibers

1. Water insoluble (*cellulose, hemicelluloses, lignins*)
- *Celluloses*: found in all plant cell walls (wheat bran, peels of apples, pears) without effect on gastric empty or glucose absorption
- *Hemicelluloses*: insoluble in water but soluble in alkaline medium; are found in whole grain and decrease colonic transit time
- *Lignins*: non-carbohydrate polymers of aromatic alcohols are found in cereal grains, potatoes and increase stool bulk and frequency of stool
2. Water soluble (*pectins, gums, muccilages, beta-glucan*)
- *Pectins*: mixture of colloidal polysaccharides, found in bananas, apples and orange and delays gastric emptying
- *Gums*: found in oatmeal, legumes (GUAR, locust bean), improving the glucose metabolism and without effects on gastrointestinal function. Are frequent used as food additives; they form viscous solutions preventing aggregation of the small particles of the dispersed phase
- *Muccilages*: are polysaccharides from plant cells (psyllium, seeds, sea weed) and prevents desiccation of the seed endosperm. Normalizes colonic transit.
- *Beta-glucans*: found in barley mushrooms, yeasts, grains, oats, vitamins, minerals etc. Increases stool bulk and frequency of bowel movement.
- *Soluble fibers (psyllium)*: are easy fermentable by gut bacteria increasing butyrate which gives energy for colonic mucosa and acts as an anti-inflammatory agent, changing the composition of microbiome, resulting in the improvement of symptoms in IBS [27].

The readily fermented fibers can lead to rapid gas formation. Poorly fermented and non-fermented fibers determine less flatulence.

Statement 2.1. Some dietary fibers may act as prebiotics. *(Quality of evidence: A, agreement: 100%.)*

Dietary fibers may can act as prebiotic agents and influence the composition of the intestinal microbiome, altering the proportions of bacterial species and promoting the development of beneficial bacteria such as Lactobacilli and *Bifidobacteria*.

Fermentation of dietary fibers increases the levels of butyrate, which has anti-inflammatory properties, lowering the colonic inflammation by inducing T-cell apoptosis and suppressing interferon-γ mediated inflammation [29].

Inulin is the most studied soluble non viscous fiber acting as a prebiotic. It is usually associated with probiotics in synbiotic supplements

The attempts to modulate the gut microbiome using prebiotics, probiotics and synbiotics are based on observations that IBS may develop after an enteral infection, the small intestinal bacterial overgrowth may have symptoms similar to those of IBS and that the colonic microbiome may be altered in patients with IBS. The use of prebiotics results in specific changes in the composition and activity of bacterial populations in the microbiome. Synbiotics, which are a mixture of prebiotics and probiotics, may have a synergistic action that promotes the development of beneficial bacterial species [30].

Statement 2.2. The quantity of fibers used in IBS vary widely based on the type (characteristics) of fibers, manufacturer and if they are associated with dietary supplements or medication. *(Quality of evidence: B, agreement: 97.2%.)*

The American Academy of Nutrition and Dietetics, recommends 25 g of fiber per day for women and 38 g of fibers per day for men, whether they have IBS or not. Fibers are administrated to normalize the stool, to reduce abdominal pain, bloating and finally to improve the global symptoms of IBS. Higher intakes of dietary fibers can be associated with the aggravation of symptoms in IBS.

There are not enough data to answer how safe is long duration use of high quantity fibers and if they can be used without adverse effects. However, fibers seem to be good in the long term for elderly, well tolerated and without side effects compared to pharmaceutical drugs (suppositories, enemas etc) [31].

Moreover, in the adult population, the use of dietary fibers decreases the risk of cardiovascular diseases, colonic diseases and different types of cancer and normalize glycaemia and reduces LDL-cholesterol.

Statement 2.3. The quantity of fibers used in IBS vary widely based on the type (characteristics) of fibers, manufacturer and if they are associated with dietary supplements or medication. *(Quality of evidence: B, agreement: 97.2%.)*

The role of fibers in IBS is still a subject of debate, with many questions which still remain unanswered. Fibers are recommended not only for the improvement of symptoms but also to increase the quality of life in patients with IBS. A review and meta-analysis conducted by the American College of Gastroenterology on the management of IBS, identified 15 RCT, involving 946 patients [30]. This review showed a statistically significant effect for fiber versus placebo. Insoluble fiber exacerbated pain and bloating in IBS and had no evident efficacy. On the other hand, soluble fibers can be recommended in the treatment of IBS to improve symptoms. The Canadian Association of Gastroenterology recommended psyllium for improving IBS symptoms and recommended against wheat bran supplementation based on a systematic review and meta-analysis of 15 RCT [32].

The evidence suggests that only soluble fibers (ispaghula, husk, psyllium) and not insoluble fibers (wheat bran) had favorable effects in IBS treatment. The addition of linseed relieves constipation, abdominal pain and bloating. In a randomized trial in primary care patients with IBS, psyllium administration reported a significant reduction in the severity of symptoms. In contrast, bran showed no clinical benefits and most of the patients did not tolerate it [33].

Since the majority of IBS patients report the generation or worsening of symptoms after food ingestion, there has been a great interest in the dietary and supplemental management of IBS patients.

Recommendation 2.1. Soluble fibers are recommended for overall symptom improvement in patients with mild to moderate IBS symptoms, especially in type IBS-C. *(Quality of evidence: B, level of recommendation: weak; agreement: 100%.)*

The mechanism of action of soluble fibers also depends on other physical characteristics, such as fermentability, viscosity and binding capacity. Due to the fact that soluble and insoluble

fibers frequently coexist and of the physiologic gut responses that do not depend only on solubility, it is difficult to examine separately the effect of the two fibers categories.

The role of fibers in the management of patients with IBS is controversial. A Cochrane systematic review that included 12 studies did not find any beneficial effect of bulking agents on abdominal pain, global assessment and symptom score [34]. On the other hand, in a review which analyzed the effect of different fibers on intestinal motility and fecal weight, all fiber types shortened transit time in patients with prolonged gut transit time. However, less fermentable fibers contributed most for increasing fecal weight [35]. In a systematic review and meta-analysis including 14 RCTs, soluble fibers have been found to be beneficial in the global symptom improvement of IBS [27].

Recommendation 2.2. Soluble fibres are well tolerated, have a low cost and therefore represent a reasonable first-line treatment in IBS. *(Quality of evidence: B,level of recommendation: weak, agreement: 97.2%.)*

The availability, low cost and good tolerability make soluble fibers a recommended first-line therapy for IBS patients with mild to moderate symptoms, in conjunction with medical therapy, although the evidence to support the beneficial effect is moderate. In comparison to insoluble fibers, bloating, flatulence and abdominal distention seem to be less prominent for soluble fibers [32].

Statement 2.4. Insoluble fibers do not have any benefits in improving symptoms of IBS compared with placebo and cannot be recommended for the management of IBS. In some cases, these fibers can exacerbate abdominal pain and bloating. *(Quality of evidence: A, agreement: 100%.)*

Dietary fiber supplementation remains a cornerstone of IBS management, although its optimal use is controversial [36]. Inadequate fibers consumption may contribute to constipation in patients with IBS with predominant constipation. Increasing dietary fibers intake is a traditional first-line treatment for patients with IBS, but insoluble fibers, such as bran, can exacerbate abdominal pain and bloating [37].

Fiber treatment may be beneficial in IBS patients with constipation (relative risk: 1.56; 95%CI: 1.21–2.02), but there was no evidence that fibers were effective in the relief of abdominal pain in IBS. Soluble and insoluble fibers, separately, had different effects on global IBS symptoms. Soluble fibers (psyllium, ispaghula, calcium polycarbophil) showed significant improvement (relative risk: 1.55; 95%CI: 1.35–1.78), whereas insoluble fibers (corn, wheat bran), in some cases, worsened the clinical outcome, but there was no significant difference compared with placebo (relative risk: 0.89; 95%CI: 0.72–1.11) [38].

In a recent meta-analysis, among the 12 studies that randomized insoluble fibers, nine used wheat bran, and one each used corn fibers, vegetable fibers, and cereal/fruit fibers. There was a broad range of doses administered for the fiber group, from 4.1 to 40 g/day. The duration of therapy ranged from 3 to 16 weeks. On the basis of the results of this meta-analysis the conclusion was that insoluble fibers do not have any beneficial effects in IBS [39].

GLUTEN FREE DIET

In respect to the common use of gluten free diet (GFD) in IBS and of the spread consumption of gluten-free food in normal, population, our literature search lead to the following conclusions:

Recommendation 3.1. No recommendation can be made regarding the gluten-free diet in patients with IBS. *(Quality of evidence: C, strength of recommendation: weak; agreement: 94.4%.)*

The effect of GFD in IBS patients' outcome was studied in four RCTs and three prospective trials. The pain improved in 75-83% of cases at 4-6 weeks of GFD, compared to 25-38% in placebo [40-42] especially in those with presence of anti-gliadin antibodies [40]. The IBS- symptoms severity score improved > 50 points in 71% of patients, after 6 weeks of GFD [43] and in 67%, 34% or 49% respectively, after 3, 4 or 6 months of GFD [44-46]. The reintroduction of gluten after 4 weeks (gluten wash-out period), produced the worsening of the overall symptoms in 59% of the "gluten group" vs 33% of the "placebo group" [42]. The pain occured within the first week after gluten reintroduction [42], as proved in another RCT, which reported 68% pain in gluten-free patients compared to 40% in the placebo group [47].

The GFD improved or normalized the stool frequency in RCT [48] and two prospective trials [40-46]. Also, bloating and stool consistency improved after GFD, especially in with HLA-DQ2/8- positive subjects [41-43] and worsened after gluten reintroduction [42, 43].

The QoL parameters, anxiety and depression scores, fatigue impact score, and Short Form-36 results [43] and the tiredness improved under GFD [42, 47].

One prospective study assessed the balanced diet, the FOODMAP diet and GFD, on the same number of patients. Although all diets improved the pain, bloating or quality of life, the balanced diet was preferred by 86% of patients, while the GFD in only 11% [16].

One meta-analysis, which included 11 trials (the above three prospective and six RCT, plus studies with functional disorders in pediatric population and one retrospective study), considered that gluten might contribute to the occurrence of gastrointestinal symptoms in patients with IBS, without indicating the GFD as a routine recommendation [49].

Recommendation 3.2. The assessment of HLA DQ2/8 for GFD in IBS-D is not recommended. *(Quality of evidence: C; strength of recommendation: weak; agreement: 100%.)*

There is no influence of HLA DQ2/8 status on the response of IBS symptoms severity score to GFD in one RCT and two prospective trials [43, 44, 47]. The presence of HLA DQ2/8 had a sensitivity of only 25% and specificity of 52% from GFD

responders in a prospective study [44]. However, in these patients the bloating decreased, and the depression score and vitality score improved, compared to HLA DQ2/8 negative patients [43]. In patients with IBS-D, diarrhea was resolved more frequently in HLA DQ2–positive patients with celiac disease–associated IgG antibodies [46, 48] or in IgG and IgA positive anti-gliadin patients [40] However, more data are needed for a final conclusion.

LACTOSE FREE DIET

The prevalence of both IBS and lactase deficiency in the general population is high; therefore, the number of people suffering from both conditions simultaneously or independently is significant. IBS patients often complain of lactose or milk intolerance and usually it is a self-reported intolerance. In a meta-analysis that included 9,041 IBS patients tested with hydrogen breath test, the prevalence of malabsorption was 56% (95%CI: 43-69%) in South Asia, 50% (95CI: 43%-56%) in Europe, and 21% (95%CI: 14-29%) in USA [32]. Several studies, most of them non-RCTs, have been conducted to assess the prevalence of lactose malabsorption and to correlate the symptoms with objective findings on hydrogen breath test. Several other case-control studies showed that was no significant differences in lactose malabsorption prevalence between IBS patients and controls. Vernia et al. [50] compared the prevalence of lactose malabsorption in patients diagnosed with IBS (503 patients fulfilled the Rome criteria for IBS) with that in patients with self-reported milk intolerance (336 patients). The lactose absorption was assessed objectively by the hydrogen breath test. They found a high prevalence in both conditions: 66.9% of the subjects with IBS tested positive and 71.4% of the subjects with self-reported milk intolerance tested positive. They concluded that there was a significant overlap between the two conditions.

Vernia et al. [51] also conducted another case-control study analyzing the hydrogen breath test results following a load of lactose in IBS patients with self-reported milk intolerance. The control group was represented by patients diagnosed with IBS without self-reported milk intolerance. The conclusion of the study was that self-reported milk intolerance does not help in identifying lactose malabsorbers. Yang et al. [52] compared lactose absorption between IBS-D patients and healthy controls and also found that self-reported lactose intolerance was not associated with a positive hydrogen breath test. Gupta et al. [53] found that patients with IBS are more likely to report symptoms following lactose ingestion, but the level of breathed hydrogen was similar to that in healthy controls. Only one study found that patients with the IBS-D have a higher incidence of lactose intolerance. However, the study involved only 25 patients and 25 controls [54]. Varjú et al. [55] performed a meta-analysis and found that lactose intolerance, but not lactose malabsorption assessed by the hydrogen breath test, was more frequent among patients with IBS compared with healthy controls.

The objective studies performed using the hydrogen breath test have found a discrepancy between the prevalence of symptoms of lactose intolerance and positive test results. There was also little evidence to suggest that objective lactase deficiency was more common among IBS patients compared with healthy controls. After lactose ingestion, IBS patients reported more symptoms, but breath testing did not yield a significantly higher percentage of positive results.

According to the available data we have formulated the following recommendations:

Recommendation 4.1. We do not recommend routine testing with a lactose hydrogen breath test in IBS patients to exclude lactose malabsorption. *(Quality of evidence: A; strength of recommendation: strong; agreement: 100%.)*

Recommendation 4.2. We do not recommend a routine lactose-free diet in IBS patients. *(Quality of evidence: C; strength of recommendation: weak; agreement: 100%.)*

Several studies, all non-RCTs, have investigated the role of lactose-free diet or low lactose diet in IBS patients. All four studies included patients with IBS and positive lactose hydrogen breath tests, and assessed gastrointestinal symptom scores at baseline and after a variable period of a lactose-free diet [56-59]. All studies concluded that there was no improvement in gastrointestinal symptoms after a lactose-free diet or low lactose diet (<9g/day), except one small study of 16 patients [56]. Patients with IBS did not respond better to an exclusively low lactose diet (< 9 g/day). However, the intake of lactose is restricted in all individuals who are following a low FODMAP diet.

Recommendation 4.3. We suggest starting a trial of milk-free diet rather than a lactose-free diet in IBS patients with a self-reported milk intolerance with a negative lactose hydrogen breath test. (*Quality of evidence: D; strength of recommendation: weak; agreement: 94.2%.)*

Patients usually report "milk intolerance" rather than lactose intolerance per se. A subgroup of patients may be intolerant to other substances than lactose that are regularly found in milk (for example, the protein beta-casein) [60]. Further research is needed, and a possible way to resolve the issue could be to perform a RCT to compare the response to a lactose-free vs milk-free diet in patients with IBS and self-reported milk intolerance.

Recommendation 4.4. We do not recommend lactase enzyme supplementation in IBS patients. *(Quality of evidence: D; strength of recommendation: weak; agreement: 100%.)*

A double-blind, cross-over study, performed by Lisker et al. [61], compared the response of the patients with confirmed lactose malabsorption to lactase and placebo and they found no correlation between symptom severity and treatment with lactase. Another study assessed the response of lactase-deficient patients with IBS to acidophilus milk with that of regular milk. The rationale was that acidophilus milk could supply the gut with additional bacterial flora as well as providing bacterial lactase. The study showed that lactase-deficient patients were as intolerant to acidophilus milk as to unaltered milk [62].

These studies showed that lactase supplementation in IBS patients with objective lactase deficiency did not improve symptoms, which follows the results of the studies conducted using hydrogen breath testing.

These studies showed that lactase deficiency is not responsible for symptoms associated with IBS, which follows the results of the studies conducted using hydrogen breath testing.

PEPPERMINT OIL

Peppermint oil (PMO) is obtained from the aerial parts of peppermint plant (*Mentha* x *piperita L.*) and contains L-menthol as main component and active ingredient [63]. It is an essential oil that exhibits several physiological effects within the gastrointestinal tract, including intestinal smooth muscle relaxation via calcium channels blockade, visceral antinociception via modulation of transient receptor potential channels, 5-hydroxytryptamine antagonism, modulation of histaminergic and cholinergic receptors, kappa opioid agonist activity, and antimicrobial and anti-inflammatory effects [64]. Therefore, PMO may improve IBS symptoms by targeting gastrointestinal motility, visceral hypersensitivity, the gut microbiota and the immune system [65].

There is evidence indicating benefits of PMO in the treatment of IBS, especially for patients with abdominal pain. A recent systematic review and meta-analysis of 12 RCTs in 835 patients with IBS showed that PMO compared to placebo significantly improved global IBS symptoms (RR of improvement 2.39, 95%CI: 1.93-2.97, p<0.001) and abdominal pain (RR of improvement 1.78, 95%CI: 1.43-2.20, p<0.001) [66]. A later systematic review and network meta-analysis compared the efficacy of PMO, soluble fiber, antispasmodic drugs, and central neuromodulators in IBS. Peppermint oil was ranked first for efficacy, when using as endpoint the failure to improve global IBS symptoms after 4 to 12 weeks of treatment (RR 0.63, 95%CI: 0.48-0.83). Nevertheless, some RCTs included in the study lack of methodological rigor, suggesting uncertainty on the findings [67].

With regard to the dosage of PMO for the treatment of IBS, most trials have tested the effects of 0.2-0.4 mL (187 to 500 mg), administered two or three times daily, for 2 to 8 weeks [68]. Indeed, the European Medicines Agency has recently approved PMO for the symptomatic relief of minor spasms of the gastrointestinal tract, flatulence and abdominal pain, especially in patients with IBS and recommends to adult patients a daily dose of 0.6-1.2 ml, divided in two or three times a day [69].

Relating to the safety of PMO, only a few adverse events have been reported during its use for IBS in short-term clinical trials. In the recent systematic review and meta-analysis conducted by Alammar et al. [66], the most common adverse event of oral PMO therapy in IBS was heartburn. However, this tended to be mild and transient and was also not significantly different in the IBS subjects using PMO versus placebo.

Gastro-esophageal reflux symptoms associated with PMO administration may be due to its effects as a relaxant of the lower esophageal sphincter [70]. These adverse events may be avoided by the enteric coating of PMO formulations, which facilitates delivery with sustained release to the lower gastrointestinal tract, and therefore prevents or reduces heartburn as well as improving PMO efficacy [68]. In fact, in a 4-week RCT [71], a triple enteric coated formulation of 90 mg PMO, taken two times a day, was reported to be effective at improving IBS symptoms in patients with mixed type IBS (IBS-M) or IBS-D (n=72). At trial completion, there was a 40% decrease in the total IBS symptom score in the PMO group compared to baseline, superior to the 24.3% reduction observed with placebo (p=0.024). Moreover, the study showed PMO to be safe and well tolerated [71]. In contrast, in a more recent double-blind RCT on 190 patients with IBS, neither small-intestinal release PMO (182 mg/day) nor ileocolonic release PMO (182 mg/day) led to a statistically significant reduction in abdominal pain or increase in overall relief, after 8 weeks of treatment [72]. This is while it was hypothesized that the ileocolonic release formulation may ensure an increased efficacy of treatment due to a more targeted colonic antinociceptive effect. Nevertheless, the small-intestinal release PMO was superior to a placebo in improving secondary outcomes of abdominal pain, discomfort, and IBS symptom severity. Furthermore, there was a higher incidence of adverse effects in both PMO-treated groups compared to placebo but were all mild and transient [72].

Recommendation 5.1. We recommend peppermint oil to improve overall symptoms, as well as abdominal pain in IBS patients. *(Quality of evidence: B; strength of recommendation: strong; agreement: 97.2%)*

HERBAL THERAPY

There are only a few good quality published placebo controlled, randomized, double-blind clinical trials investigating the effect of various herbal therapies in the management of IBS [73]. The majority of them questioned the role of traditional Chinese medicine (TCM) or a multiherbal combination STW 5 (bitter candytuft, chamomile flower, peppermint leaves, caraway fruit, liquorice root, lemon balm leaves, celandine herbs, angelica root, and milk thistle fruit), in observational studies.

The last published systematic review regarding the use of herbal therapy to improve the symptoms in IBS evaluated 6,395 patients with IBS from 72 RCTs using the Rome criteria or Chinese National criteria for the diagnosis. The research concluded that the TCM combined with conventional Western medicine improved IBS symptoms compared with Western medicine alone RRs of 1.22 (95%CI: 1.14–1.30) [74]. The authors underlined the low quality of the included trial, the differences among treatment duration and the lack of follow-up in most studies.

The multiherbal drug combination STW 5 has been questioned for IBS management with favorable results [75], but the outcomes were assessed using a non-standardized original questionnaire without possibility of evidence replication. A systematic review including 27 studies showed that the STW 5 had no clear benefit in IBS [76].

A recent published systematic review and meta-analysis of 21 studies evaluating the efficacy and safety of acupuncture

combined with TCM in irritable bowel syndrome with diarrhea management, support that intervention might be effective and safe. Acupuncture combined with TCM might result in more favorable improvements compared with the control group (RR: 1.29; 95%CI: 1.24-1.35; p=0.03) [77]. A meta-analysis of 11 studies using data from 906 participants showed a significant improvement in overall clinical efficacy of TCM compared with cisapride and mosapride in patients with IBS with constipation (OR=4; 95%CI: 2.74-5.84; p<0.00001) [78].

A small, short duration placebo-controlled, randomized controlled study in 120 patients with mild to moderately severe IBS, using IBS-SSS showed that a combination of curcumin and fennel essential oil improved symptoms and the QoL in the patients with IBS compared with a placebo (50.05 ± 28.85% vs 26.12 ± 30.62%, p<0.001) [79].

The heterogenous underlying pathophysiology of IBS is probably the main cause of the limited evidence obtained in IBS therapeutic trials with herbal compounds also with no clear chemical mechanism [80]. The evidence for herbal treatments derives from studies with compounds that are not regulated, and the amount of 'active ingredient' may vary among the different products. The lack of reliable information about the efficacy, using frequently non-standardized original questionnaire for outcomes' assessment and no international accepted criteria for diagnosis, without possibility of evidence replication, are the main limitations of the published studies in this field. The use of both single or compound preparations, the issues of herbal product quality and the use of personalized therapy in TCM performed in the Chinese population, limit further the studies' results and interpretations [78]. Despite the reported data coming from one study with good quality methodology [81] the result might not be used for clear recommendation in the Western population.

The consensus group concluded that even if some herbal therapies may have an effect on IBS symptoms and they have a good safe profile, there is insufficient evidence for any particular herbal product recommendations at least in our area.

Irritable bowel syndrome patients frequently use herbal therapy as first line therapy. However, there are limited scientific based data related to its efficiency. self-indication and self-administration.

Statement 6.1. Based on current data we do not recommend the use of herbal therapies for IBS. *(Quality of evidence: D; strength of recommendation: weak; agreement: 94.4%.)*

PROBIOTICS

Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [82]. In the last decade, the use of probiotics in IBS has been intensively studied due to evidence that this functional gastrointestinal disorder might have an underlying microbial pathogenesis. There are studies showing differences in the composition of intestinal microbiota in IBS patients compared with healthy controls as well as unique microbial signatures associated with the severity of IBS symptoms [83, 84].

In IBS, probiotics may act by restoring intestinal dysbiosis, normalizing gut dysmotility, enhancing intestinal barrier function, reducing visceral hypersensitivity, downregulating low-grade mucosal inflammation and immune activation, and improving gut-brain communication [85]. Based on these mechanisms of the action of probiotics, numerous clinical trials have been conducted to assess their efficacy in the management of IBS. Interesting results are reported by a recent RCT, in which IBS patients treated with a probiotic formulation containing a mixture of spores from five *Bacillus* spp. (n=30) showed improvements in the severity of symptoms, quality of life, and rectal sensation to the same degree as the patients treated with rifaximin followed by a low FODMAP diet (n=30) [86].

Furthermore, several systematic reviews and meta-analyses have indicated a beneficial effect of probiotics over placebo on IBS symptoms. The meta-analysis of 53 RCTs involving 5,545 patients, conducted by Ford et al. [87], reported that some particular combination probiotics, most of which contained different species of *Lactobacillus*, determined a lower incidence of persistence of IBS symptoms (RR: 0.79, 95%CI 0.68-0.91] and reduced scores for flatulence (SMD: 0.29, 95%CI: −0.51 to −0.07) but not for bloating.

A further meta-analysis of 35 RCTs in 3,452 patients, published by Niu et al. [88], showed a reduced risk of persistent IBS symptoms (RR: 0.79, 95%CI: 0.70-0.89) as well as a reduction in scores for abdominal pain (SMD: −0.25, 95%CI: −0.36 to −0.14), bloating (SMD: −0.15, 95%CIL −0.27 to −0.03), and flatulence (SMD: −0.20, 95%CI: −0.35 to −0.05), with multi-strain probiotics containing one or both of the bacteria from the *Lactobacillus* and *Bifidobacterium* genera.

Moreover, the recent meta-analysis of 59 RCTs including 6,761 patients, conducted by Li et al. [89], found probiotics to reduce global IBS symptoms scores (SMD: −1.8, 95%CI: −0.30 to −0.06). However, in contrast to Ford et al. [87] and Niu et al. [88], Li et al. [89] suggested that single probiotics may be more effective than combination probiotics in IBS symptom alleviation.

Despite the promising findings of the meta-analyses previously described [87-89], it remains difficult to draw a determinate conclusion on the efficacy of probiotics in IBS treatment and this point is also highlighted by the authors of these studies. There is difficulty in the interpretation of data due to evidence of publication bias and great heterogeneity between compared trials, in terms of individual strains or combinations of strains used, dose, duration of treatment, end points and outcomes reported, and statistical analyses.

Considering that the effects of probiotics are strain-specific and dose-specific [90], further studies are warranted to establish which probiotic strains are most efficient for IBS treatment and the conditions for their intake, such as formulations, dosage, and duration. Research should provide particular attention to the duration of treatment. In many trials, the duration of the probiotic intervention varies from 4 to 16 weeks. The systematic review of 11 RCTs published by Dale et al. [91] suggested that probiotics have a delayed effect in the alleviation of IBS symptoms and require an intervention period lasting at least 8 weeks. Indeed, the long-term effects of probiotic therapy in IBS are unclear and should be addressed in future studies. Likewise, many of the trials on probiotics use in IBS conducted to date include a relatively small sample

size. Therefore, further studies that are well-designed and have a large sample size are required.

Finally, the findings regarding the safety of probiotics in IBS are limited and conflicting. In fact, it has been acknowledged that safety outcomes are inconsistently assessed and reported in probiotic intervention studies [92]. In IBS, the incidence of adverse events was not significantly greater among patients treated with probiotics than among those assigned to placebo, according to both the meta-analysis by Ford et al. [87] (RR: 1.09, 95%CI: 0.91-1.29) and the meta-analysis by Li et al. [89] (RR: 1.07, 95%CI: 0.92-1.24). In contrast, the meta-analysis conducted by Niu et al. [88] reported a higher incidence of any adverse event in patients who received probiotics versus those who received placebo (RR: 1.21, 95%CI: 1.02-1.44). These results suggest more evidence is required concerning the safety of probiotics in IBS.

Recommendation 7.1. In patients with IBS, we recommend the use of probiotics as an alternative therapy in trials of limited duration. *(Quality of evidence: B; strength of recommendation: weak; agreement: 97.2%.)*

PHYSICAL EXERCISE

The data presented so far in the literature indicate that the promotion of physical activity in the general population can help prevent the occurrence of IBS [93]. Exercise is proven beneficial for health because it reduces the risk of cardiovascular disease, endocrine disorders and lowers levels of anxiety and depression [94]. Regular physical activity can help relieve constipation, promote bowel movements and improve bloating [95]. Patients experiences with the effects of physical activity on IBS symptoms are not really known. This knowledge is required to enable adequate support from health professionals. In some patient groups it is difficult to motivate patients to change their lifestyle [96]. Physical activity counteracts the effects of stress [97]. Compared to physically active people (1 hour / week), those with sedentary physical activity (<1 hour / week) were 1.27 times more likely to have IBS [98]. There was a significant difference in improving the IBS-SSS score between the physical activity group and the control group. Here is a review of main physical activities and their possible effects on IBS symptoms.

Walking and cycling: a moderate increase in physical activity within 12 weeks, 20-60 min/day of moderate to vigorous physical activity, 3-5 days a week, may improve symptoms and can be effective against constipation.

Aerobic exercise may improve: constipation, abdominal pain, abdominal distension, depression and anxiety. A low-to-moderate intensity exercise training attenuated symptoms in sedentary IBS patients. Symptom improvement might have been associated with a reversal of the ratio of anti-inflammatory/proinflammatory cytokines and blood redox homeostasis, suggesting that a low to moderate intensity exercise training program may have immune and redox-modulating functions [99]. Thus, aerobic exercise appears to be a simple, acceptable, effective, feasible and eligible treatment approach for patients with IBS.

Swimming and running/jogging were studied; at a 12-week follow-up compared to baseline, the symptoms were significantly lower in the physical activity group. However, the IBS-SSS score was also significantly lower in those with physical activity [100]. Constipation symptoms were significantly better in the mountaineering group than in the control group in a study comparing the effects of hiking in patients with IBS [101]. Baduanjin qigong exercise is a type of traditional Chinese fitness exercise that involves the following 4 parts: mood relaxation, breathing adjustment, organ regulation and shape readjustment. The overall efficiency, symptoms and stool characteristics were significantly better in Baduanjin qigong active elderly IBS patients with constipation (IBS-C) [102]. Yoga has similar positive effects on IBS symptoms such as walking. Physiotherapy is a useful resource when discussing physical activity. Patients with depression needed the active support of a physiotherapist to overcome their own resistance in order to participate in an exercise intervention.

Body awareness therapy (BAT™) consists of simple structured movement exercises, based on human anatomical and physiological conditions to achieve optimal movement dynamics. BAT™ exercises aim to help the body find its natural posture, thus facilitating the circulatory, muscular, nervous and respiratory systems to regain their natural function. BAT™ is used to treat various stress and pain conditions in all Nordic countries, as well as in Scotland, Switzerland, Austria, the Netherlands, Spain and Turkey [103]. Posture, breathing and muscle tension, along with the function and mobility of the internal organs are affected by body-mind training. It is assumed that body-mind therapies work through a physiological transformation achieved through the autonomic nervous system.

Recommendation 8.1. Physical exercise may be useful in IBS. Regular exercise can help manage some symptoms in IBS and can be a primary treatment in IBS-C. *(Quality of evidence: C; strength of recommendation: low; agreement: 97.2%.)*

ACUPUNCTURE

A meta-analysis by Zheng et al. [105] analyzed 41 RCTs (3,440 subjects) for the assessment of acupuncture efficacy in IBS. The results show no significant difference between acupuncture and sham on IBS symptoms and QoL (SMD: 0.18, 95%CI: −0.26 to 0.63, p=0.42; SMD:−0.10, 95%CI: −0.31 to 0.11, p=0.35) [105]. Further, the study demonstrated that acupuncture was more effective compared with western medicine in alleviating IBS symptomatology (RR: 1.17, 95%CI: 1.12-1.23, I2= 0%, p<0.00001), and the positive effect lasted about 3 months [105]. From 8 RCTs which compared acupuncture with sham acupuncture, 3 RCT concluded show a significant benefit of acupuncture in treating abdominal pain, discomfort, and stool frequency [105]. A meta-analysis performed by Chao et al. [106] analyzed 6 RCT about the effectiveness of acupuncture in IBS [106]. The results showed that the relative risk for clinical improvement with acupuncture was 1.75 (95%CI: 1.24-2.46, p=0.001) and the authors

concluded that acupuncture had statistically significant positive effects in the reduction of IBS symptoms [106]. A study by Wu et al. [107] conducted an overview of systematic reviews and a network of meta-analysis in order to evaluate the comparative effectiveness of acupuncture and related therapies. A total of 2,141 IBS patients from 27 RCT were included in the study and the results demonstrated that both classic acupuncture using metallic needles and electro-acupuncture were superior in improving IBS symptomatology compared to other therapies. The authors concluded that IBS patients with no response to first-line conventional therapies or antidepressant agents may consider acupuncture as an alternative [107].

Recommendation 9.1. There is not enough evidence to recommend acupuncture as therapy of IBS. *(Quality of evidence: D; strength of recommendation: low; agreement: 100%.)*

There is no consensus yet in respect to the role of acupuncture in IBS. Most trials were of poor quality because the results were heterogeneous and were obtained from interventions and control groups. It should also be taken into account that so far, all RCTs did not analyse the long-term effects of acupuncture on IBS evolution [105-113]. Another major limit of most RCT is represented by the fact that the level of the therapist training is not mentioned nor the acupuncture points or technique. The majority of RCTs did not mention any information about the effects of acupuncture on the IBS subtype. We also mention that most studies report that adverse events are rare and include local bleeding and local pain [114, 115]. Extremely rare, serious complications can include nerve injury and infections [114, 115]. Finally, it cannot be ruled if acupuncture is effective in IBS, and more high-quality studies are required.

PSYCHOLOGICAL THERAPIES

Psychotherapy is frequently used in IBS, mainly in patients with severe symptoms or with important pathogenic contribution of psychosocial factors.

Statement 10.1. Psychological therapies are useful in IBS. *(Quality of evidence: B; agreement: 100%.)*

IBS is thought to result from the interaction between biological, psychological, and social factors [116]. Early life events, psychological distress, and negative coping style may play essential roles in the pathogenesis of IBS. The use of maladaptive coping strategies positively correlates with symptom severity and degree of anxiety and depression among patients [117].

The lack of a universally effective medical treatment has led to various psychological treatments recommended in patients who do not respond to medical therapy. Psychotherapy options contain psychoeducation, cognitive-behavioral therapy (CBT), psychodynamic psychotherapy, hypnotherapy, mindfulness, relaxation therapy.

The effect of psychological interventions in IBS was studied in 41 RCTs containing 4072 adult participants, with a minimum duration of therapy of 4 weeks and a minimum duration of follow-up of 4 weeks. These RCTs compared different psychological therapies with each other or with a control intervention [116, 118].

The psychological interventions with the highest efficacy included cognitive-behavioral therapy with two different approaches: the self-administered and minimal contact approach (RR: 0.61; 95%CI: 0.45-0.83, p=0.66), or face-to-face approach (RR: 0.62; 95%CI: 0.48-0.80, P score 0.65) and also included gut-directed hypnotherapy (RR: 0.67; 95%CI: 0.49 to 0.91, p=0.57) [116].

A trial showed a reduction of 50% of digestive symptoms, anxiety, and depression in the cognitive behavioral therapy (CBT) group [119]. Another RCT demonstrated a 42% decrease in gastrointestinal symptoms in patients with IBS treated using an online CBT program compared to the control group [120].

After 15 and 18 months, the follow-up revealed the same positive results in the psychological intervention group [121]. Another study compared standard CBT with home-based CBT with minimal therapist contact and also with education and found improvement in gastrointestinal symptoms in 61% patients from the minimal contact CBT group, 55% patients from the CBT group, and 44.8% patients from the education group [121]. At six months after the end of treatment, there was a significant difference between minimal contact CBT (58.4%) and education (44.8%) regarding digestive symptom improvement [122]. This trial showed similar efficacy of minimal contact CBT and standard CBT; therefore, this kind of psychotherapy could be delivered online or by telephone, most probably in a more cost-effective manner.

Gut-directed hypnotherapy (both as an individual or group approach) has been demonstrated to produce a reduction in IBS symptoms ($p<0.05$) [123]. It seems to be superior to medication and has a long-term effect. 60.8% of patients treated with hypnotherapy improved vs. 40.9% treated with standard medical treatment with the effect lasting over 15 months (54.3% of gut-related hypnotherapy patients and 25.0% of controls improved [124]. It also has a positive effect on the quality of life, somatic and psychological symptoms. In a RCT published in 2019, the improvement of symptoms was 40.8% in the individual hypnotherapy group, 33.2% in the group hypnotherapy group and 16.7% in the control group at three months. Hypnotherapy was more effective than control at three months (p=0.0240) and 12 months (p=0.0185). Group hypnotherapy was non-inferior to individual hypnotherapy [125].

Among trials recruiting only patients with refractory symptoms, CBT and gut-directed hypnotherapy were more efficacious than either education and/or support or routine care, and CBT via the telephone, contingency management, CBT via the internet, and dynamic psychotherapy were all superior to routine care [116].

Recommendation 10.1. Psychotherapy should be considered for people with IBS who do not respond to pharmacological treatments after 12 months and who develop a refractory IBS. *(Quality of evidence: C; strength of recommendation: low; agreement: 97.2%.)*

Recommendation 10.2. Psychotherapy cannot be recommended routinely in patients with IBS. It should be indicated in individual cases (with refractory symptoms and/or psychiatric comorbidities) but remains subject to the availability of appropriate resources and expertise. *(Quality of evidence: B; strength of recommendation: strong; agreement: 100%)*

FECAL MATERIAL TRANSPLANTATION

The use of fecal material transplantation (FMT) has been considered for IBS, since the role of dysbiosis in this setting was highly investigated [84, 126-128]. Even though the latest published RCT identified FMT as an effective treatment for IBS, regardless of the IBS subtype, it also highlighted the importance of using a well-defined donor and adequate quantity of transplant as main prerequisites for successful FMT [129]. The results of several RCTs currently available [129-135] are conflicting and difficult to compare due to several differences among the trials: size of patient cohorts, prior patient treatment, type of donors used, amount of the transplants, route of administration. Moreover, inconsistent results from RCTs could also be due to other factors, such as the placebo effect, considering prior stated relative placebo responses for IBS symptom severity of 41.4% and for quality of life between 20% and 125% [136]. A recent meta-analysis including all available RCTs on FMT and also single-arm trials identified crude placebo response rates in RCTs comparable to the response to FMT in single-arm trials. This finding suggests that better outcomes of FMT from single-arm trials would be mainly in the context of a placebo effect [137]. Consequently, current evidence from RCTs and meta-analyses [137, 138] does not provide a solid ground for an overall clinical benefit in using FMT for global IBS symptoms. It is still uncertain whether FMT is efficacious in IBS, especially considering discrepant results among RCTs in subgroup analysis. Further high-quality clinical trials are needed, including an appropriate control for FMT and also a better characterization of microbiota profile at baseline.

Recommendation 11.1. FMT should not be routinely used for IBS and should currently be limited to the research setting for this indication. *(Quality of evidence: C; strength of recommendation: low; agreement: 97.2%.)*

DISCUSSION

Irritable bowel syndrome is characterized by chronic abdominal pain associated with changes in the frequency and consistency of stools, without organic involvement according to present Rome IV definition. A recent multicenter worldwide rigorous study gave a very low prevalence of 1.5% (1.3-1.7) for IBS using strict definition. However, prevalence for non-specific functional bowel disorders is quite high: 16.0 (15.5-16.5) [130]. The pathophysiology of IBS is not fully known, the disease being considered multifactorial. This aspect makes the present treatments unsatisfactory for all patients, the management of symptoms being sometimes difficult. In addition, this condition leads to high costs, absenteeism from work and an unsatisfactory quality of life [140].

Along with drug therapy, non-pharmacological therapy can play an important role in the management of these patients and this paper attemps to to guide the medical practitioners in this regard. The LOW FODMAP diet recommends reducing or excluding fermentable foods that can influence pain in IBS, due to reduced absorption and osmotic action [3]. This diet could be tested in patients and if the exclusion does not improve symptoms, it can be stopped [5, 6]. Although there is a low quality of evidence, there were five meta-analysis, which highlighted the effectiveness of LFD in relieving symptoms [5]. However, there are also studies linking LFD with a decrease in the concentration of *Bifidobacteria*, insufficient energy intake and a decrease in calcium intake, which means this diet should not be recommended for all IBS patients [3, 9-13]

Fibers have been used for long time in the diet of patients. Recent data are more subtle in the recommendations. It is recognized that insoluble fibers may cause an increase in pain intensity and excessing bloating in IBS, unlike soluble fibers, which can be recommended in the treatment of this condition [32,33]. Sometimes, however, it is difficult to separate soluble and insoluble fibers because they frequently coexist naturally in food components [34].

Regarding the GFD there are some prospective studies, the results of which oppose for the reduction of pain in a significant percentage, up to 83%, if the diet is maintained for 4-6 weeks and the reintroduction of gluten worsened the symptoms in a significant percentage [40, 42, 44]. However, there is some reluctance on the part of patients to accept this diet [16]; only 11% of the patients studied accepted GFD, 86% preferring a balanced diet, but there is also a meta-analysis which, although recognizing the role of gluten as a possible cause of symptoms does not indicate this regimen as a permanent recommendation [49].

Another chapter discussed in the literature is the lactose-free diet in IBS; there is generally a discrepancy between patients‘ self-reported lactose intolerance and the positive results of confirmatory tests. Some meta-analyses have discordant results regarding the prevalence of lactose malabsorption and IBS on different continents [32]. If, however, the prevalence of lactose malabsorption was compared in patients diagnosed with IBS, to self-reported patients with milk intolerance, a high prevalence was found in both situations (66.9% IBS and 71.4% self-reported) [50]. There are some studies that have not shown any improvement in IBS symptoms after a low-lactose or lactose-free diet [56]. It is necessary to differentiate between ‚self-reported milk intolerance‘ and actual lactose intolerance, as there are other products in milk that may cause malabsorption [60).

Peppermint oil was studied in patients with IBS symptoms. A meta-analysis of 12 studies and 835 patients showed improvement in IBS symptoms and pain syndrome in the PMO group compared with placebo [66], attempting a comparison between PMO, soluble fiber, antispasmodics and central neuromodulators, but without a methodological rigor of comparative calculations [67]. The EMA also approved the use of PMOs to relieve IBS symptoms, minor spasms, flatulence and pain; no significant side effects have been reported with the use of PMO.

Herbal therapy has limited evidence for IBS treatment efficacy, mainly due to heterogeneous pathophysiology and also due to the amount of active substances which is not standardized between different products [80].

The use of probiotics may have a beneficial effect, proven in some meta-analysis, but there are some contradictory issues related to the safety of their use, with an inconsistent assessment and safety reporting between different studies [92]. However, probiotics can restore intestinal dysbiosis, normalize intestinal dysmotility, and help improve intestinal barrier function, reduce mucosal inflammation, and reduce visceral hypersensitivity [86].

Exercise may be useful in the management of IBS [93, 94]. In addition, physical activity reduces the effects of stress [97], but no excessive physical effort is indicated, and exercise programs should be customized, depending on age and pathology.

Acupuncture can be used as an alternative in patients with IBS without a response to conventional first-line therapies, or to antidepressants [107], but there is no consensus on the role of acupuncture in IBS [105-113].

In the treatment of IBS, psychotherapy is quite often used. There are psychological methods with greater effectiveness, such as cognitive-behavioral therapy [116]. Some studies indicate an improvement in digestive symptoms as well as anxiety and depression by up to 50% [119].

Starting from the role of dysbiosis in the pathophysiology of IBS, FMT was also tested. There are contradictory studies [129-135], which are also difficult to compare, and the results are generally inconsistent, so that current evidence and meta-analysis do not provide a solid ground for the clinical benefit of FMT. [137, 138].

CONCLUSIONS

There are several non-pharmacological therapeutic alternatives for IBS. They can be used alone or associated with pharmacological therapy. As, in general, the quality of evidence and the levels of recommendation are variable, these therapeutic interventions should be individualized.

Conflicts of interest: None to declare.

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