Guidelines on the management of irritable bowel syndrome

In memory of Professor Witold Bartnik

Anna Pietrzak[1,2], Barbara Skrzydło-Radomańska[3], Agata Mulak[4], Michał Lipiński[5], Ewa Małecka-Panas[6], Jarosław Reguła[1,2], Grażyna Rydzewska[5,7]

[1]Department of Oncological Gastroenterology, Maria Sklodowska-Curie Memorial Cancer Center, Institute of Oncology, Warsaw, Poland
[2]Department of Gastroenterology, Hepatology and Clinical Oncology, Centre of Postgraduate Medical Education, Warsaw, Poland
[3]Department of Gastroenterology, Medical University of Lublin, Lublin, Poland
[4]Department of Gastroenterology and Hepatology, Wroclaw Medical University, Wroclaw, Poland
[5]Department of Internal Medicine and Gastroenterology with Inflammatory Bowel Disease Subdivision, Central Clinical Hospital of the Ministry of the Interior, Warsaw, Poland
[6]Department of Digestive Tract Diseases, Medical University of Lodz, Lodz, Poland
[7]Department of the Prevention of Alimentary Tract Diseases, Faculty of Medicine and Health Science, Jan Kochanowski University, Kielce, Poland

Gastroenterology Rev 2018; 13 (4): 259–288
DOI: https://doi.org/10.5114/pg.2018.78343

Key words: irritable bowel syndrome, IBS, recommendations, guidelines, IBS treatment, diastolic drugs, antidepressants, rifaximin α, loperamide, macrogols.

Address for correspondence: Anna Pietrzak, Department of Oncological Gastroenterology, Maria Sklodowska-Curie Memorial Cancer Center, Institute of Oncology, 5 Roentgena St, 02-781 Warsaw, Poland, phone: +48 22 546 23 28, e-mail: anpietrzak@gmail.com

Abstract

These guidelines constitute an update of the previous "Recommendations on the management of irritable bowel syndrome" issued in 2008. They have been developed by a Task Force organized by the Governing Board of the Polish Society of Gastroenterology. They discuss, with particular emphasis on new scientific data covering papers published since 2008, the aetiology, epidemiology, clinical presentation, diagnostic principles and criteria for the diagnosis, and recommendations for the treatment of irritable bowel syndrome (IBS). The English-language acronym for the syndrome (IBS) has become popular in medical and popular scientific language. It is also widely recognized by patients who identify with this diagnosis. Therefore, in the discussed guidelines, this is what we will use.

1. Methodology of the guidelines

These guidelines constitute an update of the previous "Recommendations on the management of irritable bowel syndrome" issued in 2008 [1]. They have been developed by a Task Force organized by the Governing Board of the Polish Society of Gastroenterology. They discuss, with particular emphasis on new scientific data covering papers published since 2008, the aetiology, epidemiology, clinical presentation, diagnostic principles and criteria for the diagnosis, and recommendations for the treatment of irritable bowel syndrome (IBS). The English-language acronym for the syndrome (IBS) has become popular in medical and popular scientific language. It is also widely recognized by patients who identify with this diagnosis. Therefore, in the discussed guidelines, this is what we will use.

1.1. Scope and aim of the guidelines

1.1.1. Aim

The general aim of these guidelines is to determine the optimal diagnostic treatment for people with suspected IBS and to determine the most effective treatment for IBS patients. We expect that the use of these guidelines will translate into a greater awareness of the disease with, at the same time, reduction of the financial outlay on differential diagnoses, as well as having an impact on the appropriate treatment of various forms of IBS.

1.1.2. Health questions covered by the guidelines

The guidelines precisely outline the health problems of irritable bowel syndrome:

- What is the aetiology of IBS in the light of the latest scientific evidence?
- Has the epidemiology of IBS changed in recent years, after taking into account the latest diagnostic criteria?
- What are the clinical manifestations (symptoms) of IBS?
- What are the diagnostic criteria of IBS?
- What kind of differential diagnosis should be taken into consideration?
- How should patients with irritable bowel syndrome be managed (recommendations for lifestyle modifications, diets, supplements and therapeutic recommendations, and how to monitor treatment)?

1.1.3. Target population of patients to whom the guidelines apply

The guidelines apply to the management of adult patients (over 18 years old) of both sexes with symptoms suggestive of IBS and in whom the diagnosis can be made on the basis of the criteria, regardless of the form or severity of the symptoms. In addition, the recommendations regarding IBS treatment also include patients with post-infectious IBS and with co-existing small intestine bacterial overgrowth (SIBO) and symptomatic uncomplicated diverticular disease (SUDD), in whom the so-called overlap syndromes IBS/SIBO and IBS/SUDD have been diagnosed.

1.2. How the guidelines were created

The source data were searched for in the electronic databases PubMed, NCBI, Cochrane Library, ResearchGate, Google Scholar, as well as in the recommendations and guidelines published on the websites of international scientific societies (American, British, European: AGA, ACG, USNGC, NICE, UEG).

Only original (optimally prospective, randomized, controlled and double-blind) studies were used to prepare the guidelines, and in the absence of such studies, lower-grade evidence studies, up to observational and retrospective studies, excluding case series and case reports, as well as systematic reviews and meta-analyses, were used. Studies published in languages other than Polish and English were excluded. The guidelines were developed in accordance with the recommendations of the Medical Technology Protection Agency (Polish: *Agencja Ochrony Technologii Medycznych i Taryfikacji*). AGREE II (Advancing Guideline Development, Reporting and Evaluation in healthcare, version II) methodology and the GRADE (Grading of Recommendations Assessment, Development and Evaluation) recommendation evaluation system were used to assess and describe a given recommendation. Questions regarding the treatment of patients were developed in accordance with the PICO (Patient Intervention Comparison Outcome) protocol [2, 3].

Recommendations were allocated a strength of recommendation with an additional assessment of the evidence level (discussed in Tables I and II). The method of making final decisions involved the Delphi voting system [4]. In addition, the acceptance of each recommendation was rated by a panel of experts on a 5-point scale (A-E) (agreement level – rating scale, Table III).

Each recommendation was discussed on the basis of the scientific evidence used in its creation (the connection between the guidelines and the scientific data).

If in the vote 80% or more of the voters chose categories A or B, then the degree of compliance (agreement level) of the experts is high; if below 80%, it is low.

The guidelines are provided with questionnaires to facilitate the diagnosis of IBS and monitoring of treatment as well as treatment algorithms to facilitate rapid therapeutic decisions.

Table I. Determination of strength of the recommendation according to GRADE [2, 3]

Strength of recommendation	
Strong	Benefits clearly outweigh risks and burden or vice versa. Usually stated as: "we recommend"
Weak	Benefits closely balanced with risks and burden. Usually stated as: "we suggest"

Table II. Determination of strength of the recommendation according to GRADE [2, 3]

Evidence level (quality of evidence)	
High	One or more well-designed and well-executed randomized controlled trials (RCTs) that yield consistent and directly applicable results. This level also means that further research is very unlikely to change our confidence in the estimate of effect.
Moderate	RCTs with important limitations (i.e., biased assessment of the treatment effect, large loss to follow-up, lack of blinding, unexplained heterogeneity), indirect evidence originating from similar (but not identical) populations of interest, and RCTs with a very small number of participants or observed events. In addition, evidence from well-designed controlled trials without randomization, from well-designed cohort or case-control analytic studies, and from multiple time series with or without intervention is in this category. This level also means that further research will probably have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Observational studies would typically be rated as low quality because of the risk for bias. This level also means that further research is very likely to have an important impact on our confidence in the estimate of effect and will probably change the estimate.
Very low	Evidence is conflicting, of poor quality, or lacking, and hence the balance of benefits and harms cannot be determined. Any estimate of effect is very uncertain as evidence is either unavailable or does not permit a conclusion.

1.2.1. Recommendation interpretation

A graphic interpretation of the recommendations is presented below.

Each recommendation has three categories of information: strength of recommendation, quality of evidence, and rating scale of experts' voting.

– strength of recommendation according to GRADE (strong or weak)
– quality of evidence according to GRADE (high, moderate, low, very low)
– agreement level (rating scale)

Table III. Scale determining the agreement level (rating scale) for the recommendations used in the vote [2]

Category	Agreement level
A	Full acceptance
B	Acceptance with certain reservations
C	Acceptance with serious reservations
D	Rejection with certain reservations
E	Full rejection

Example

Recommendation 1

We recommend using Rome IV Criteria to diagnose IBS.

Recommendation: strong; quality of evidence: moderate.

RECOMMENDATION: On this basis, practitioners will know if they should/may (strong recommendation), or if they may consider using, but do not have to (weak recommendation) use the drug.

QUALITY OF EVIDENCE: On this basis, doctors will know what quality of scientific research is behind the strength of recommendation.

AGREEMENT LEVEL: Strength of recommendation and evidence level which are subject to voting for agreement level.

Voting:

A – %; B – %; C – %; D – %; E – % ← percentage of experts voting for the recommendation (according to Table III).

Agreement level: ← If in the vote 80% or more of the voters chose categories A or B, then the degree of compliance of the experts is high; if below 80%, it is low.

2. Epidemiology

Statement 1

Irritable bowel syndrome is a common disease occurring at all geographical latitudes. The prevalence of IBS in the global population is estimated at 11%. The prevalence of IBS in women is about twice as high as in men. Half of patients report their first symptoms before the age of 35.

Discussion

The incidence of IBS in the world population has been estimated at 11% in total, taking into account the following: Manning criteria 1978, Rome I (1989), Rome II (1999) and Rome III (2006) diagnostic criteria [5]. The prevalence of IBS among women is 14% (95% CI: 11.0–16.0), and among men 8.9% (95% CI: 7.3–10.5). Half of the patients report the first symptoms of irritable bowel syndrome before the age of 35, and the prevalence of IBS in this group is 25% higher than in patients over 50 years of age [1, 5, 6]. A study conducted among students aged 18 to 30 showed an incidence of IBS of 24% [7]. Morbidity in the Northern Hemisphere is estimated at about 10%, and the incidence rates differ depending on the criteria for diagnosis and are 9.1% (according to Manning criteria), 6.7% (Rome I), 7.8% (Rome II) and 9.1% (Rome III) [1, 8].

Statement 2

The average incidence of IBS varies considerably with respect to individual continents and individual countries.

Discussion

The average prevalence of irritable bowel syndrome shows significant differences for individual continents – from 17.5% (95% CI: 16.9–18.2) in Latin America, through 9.6% (95% CI: 9.5–9.8) in Asia, 7.1% (95% CI: 8.0–8.3) in North America/Europe/Australia/New Zealand, to 5.8% (95% CI: 5.6–6.0) in the Middle East and Africa. These differences are even more significant in individual countries and range from 1.1% in France and Iran, to 35.5% in Mexico [8].

Statement 3

The introduction of Rome IV diagnostic criteria affects the frequency of diagnosis of IBS and may change the indicators in further epidemiological studies.

Discussion

Following the announcement of the Rome IV diagnostic criteria, a trial study in a total of 5,931 patients in the United States, Canada and the United Kingdom diagnosed IBS based on these criteria in 5.7% of this group (95% CI: 97.1% (96.6–97.6)), when the same diagnosis according to Rome III criteria was 10.7% ($p < 0.0001$). However, among all functional gastrointestinal disorders diagnosed in 843 patients, the diagnosis of irritable bowel syndrome according to Rome IV criteria constituted 52.4% [9–11]. In the study by Aziz *et al.* in 2018, 85% of patients diagnosed with IBS according to Rome III criteria met the Rome IV criteria for this diagnosis, more often women – with a worse quality of life, a greater severity of pain, abdominal distension, fatigue and somatization [6]. The population of patients with IBS diagnosed on the basis of Rome IV criteria probably reflects those with more severe symptoms, greater psychological and personality disorders and a lower quality of life [12].

Statement 4

The familial occurrence of IBS and studies in twins confirm the involvement of genetic factors in this disease.

Discussion

Genetic studies in familial IBS indicate changes in genetic polymorphisms associated with the regulation of the serotonergic system [13]. In adopted children whose biological parents were diagnosed with IBS, the OR of the occurrence of the disease in the Swedish study was 1.67 (95% CI: 1.06–2.62), but only 0.88 (95% CI: 0.48–1.63) in the case of diagnosis of IBS in the adoptive parents [14]. The studies also deal with the interaction of genetic and environmental factors and the role of epigenetic mechanisms [15].

Statement 5

Post-infectious irritable bowel syndrome (PI-IBS) develops in 8–31% of patients who have had an acute infectious episode of gastrointestinal inflammation. The incidence of IBS after acute gastroenteritis is 7 times higher than without an infectious episode.

Discussion

The prevalence of IBS after gastrointestinal infection is 7 times higher than without infection (median 9.8% (IQR: 4.0–13.3) vs. 1.2% in the control group (IQR: 0.4–1.8), $p = 0.01$, pooled OR is 7.3 (95% CI: 4.7–11.1), $p = 0.41$ [16, 17]. The prevalence of IBS within 12 months of intestinal infection is 10.1% (95% CI: 7.2–14.1), and over 12 months from an infectious episode – 14.5% (95% CI: 7.7–25.5). The risk of developing IBS is 4.2 times higher in patients who have had gastro-intestinal infection in the last year than in those who have

not (95% CI: 3.1–5.7) and 2–3 times higher in those whose infectious episode was more than 12 months ago (95% CI: 1.8–3.0) [18]. Also among patients with enteritis caused by protozoa or parasites, up to 41.9% developed IBS. The risk of developing IBS after infection is significantly higher in women (OR = 2.2), especially those treated with antibiotics (OR = 1.7), in women with anxiety (OR = 2), depression (OR = 1.5), somatization (OR = 4.1), neuroticism (OR = 3.3) and clinical indicators of increased intestinal inflammation [18]. It should be remembered that *Clostridium difficile* infection can also cause PI-IBS – 25% as shown in studies, in which the mixed bowel habits form (52%) and diarrhoea-predominant form (40%) of IBS are dominant [19].

3. Aetiopathogenesis

Statement 6

In the multifactorial pathogenesis of IBS a key role is played by disorders of gut-brain interactions (DGBI). The intestinal microbiota is an essential element of these interactions, and its dysregulation directly affects the other pathogenic mechanisms of IBS.

Discussion

Apart from disorders of the intestinal microbiota, or dysbiosis, the main pathogenic factors of IBS include abnormal gastrointestinal motility, visceral hypersensitivity, impaired immune function of the intestinal mucosa and dysregulation at the level of the central nervous system [20]. Neuronal, endocrine and immune mechanisms modified by the intestinal microbiota participate in the regulation of gut-brain interactions [21, 22]. The higher incidence of IBS in women is determined by gender-related differences with regard to these mechanisms [23]. One of the major neurotransmitters of the gut-brain axis is serotonin, synthesized in the intestines by enterochromatophilic cells [24]. Interactions of pathophysiological and psychosocial factors, together with genetic and environmental determinants, affect the development and expression of IBS symptoms. In the pathogenesis of IBS, peripheral factors play a key role in the majority of patients, whereas the contribution of central factors (psychiatric disorders, traumatic experiences) is associated with greater severity of symptoms [20].

Statement 7

Activation of the immune system of the intestinal mucosa associated with dysbiosis, diet, stress and endogenous factors results in increased permeability of the intestinal barrier and the induction of motor-sensory functions of the gastrointestinal tract.

Discussion

Activation of the intestinal mucosal immune system associated with micro-inflammation is considered to be the main pathogenic agent of the post-infectious form of IBS (PI-IBS) [18]. In biopsies involving the submucosal membrane in patients with PI-IBS, an increase in the number of T lymphocytes, macrophages, mast cells and enterochromatophilic cells as well as an increase in the expression of pro-inflammatory cytokines was demonstrated in patients with PI-IBS. In addition, in patients with IBS (not only PI-IBS) there was an increase in the expression of proinflammatory cytokines in the serum [25, 26]. Endogenous factors that influence the activation of the immune system and disturbance of the intestinal barrier include serotonin, histamine and bile acids [27, 28].

Statement 8

In patients with IBS there are qualitative and quantitative changes in the composition of the gut microbiota, which has significant therapeutic implications. SIBO plays a special role in the pathogenesis of intestinal symptoms.

Discussion

The intestinal microbiota plays a key role in the regulation of gut-brain interactions [21]. Changes in the composition of the microbiota in patients with IBS include a reduction in the number of bacteria of the genera *Lactobacillus* and *Bifidobacterium*, an increase in the number of *Streptococcus*, *Escherichia coli*, *Clostridium* spp. and changes in the proportion between *Firmicutes* and *Bacteroidetes*, to the detriment of the latter [29]. In addition, in patients with IBS, the risk of SIBO is about 5 times higher compared to the control group (OR = 4.7, 95% CI: 3.1–1.2) [30]. However, attention is drawn to the large diversity of data on the incidence of SIBO resulting from, among other factors, the diagnostic method used. SIBO in the course of IBS is more common in women and in patients with diarrhoea and increased abdominal distension [31]. The composition and functioning of the gut microbiota depend on many dietary and endogenous factors [29, 32].

Statement 9

Disturbed motor activity of the gastrointestinal tract and visceral hypersensitivity are typical but not completely specific features of IBS.

Discussion

A characteristic feature of IBS is the impaired motor-sensory reactivity of the colon to various stimuli (e.g. stress, rectal distension, meals or cholecystokinin). Dis-

turbances in motor function are not limited to the large intestine, as in IBS patients differences in postprandial changes in motor activity of the small intestine have also been demonstrated [33]. Visceral hypersensitivity may be the result of impaired generation, transmission and analysis of sensory stimuli, as well as an abnormal response to these stimuli with weakening of central pain-inhibition processes [32]. An association between the hypersensitivity of the sensory nerve endings in the intestinal wall with increased production of neurotransmitters (serotonin, substance P) and the release of inflammatory mediators from mast cells has been demonstrated [33]. An important endogenous factor modulating motor, sensory and secretory functions of the intestine is bile acids [27]. Bile acid absorption disorders occur in up to 1/3 of patients with diarrhoea-predominant IBS [34].

Statement 10

Central nervous system disorders occurring in patients with IBS may cause increased reactivity to stress stimuli and influence the severity of symptoms.

Discussion

Research on the central nervous system (CNS) using modern imaging techniques has revealed neuro-functional and neuro-structural differences in the brain of IBS patients compared to healthy individuals [35, 36]. Among other differences, changes in the activity of the brain centres associated with the perception of visceral stimuli and the regulation of emotions have been found [35]. Clinical observations confirm that in 50–80% of patients with IBS there is a clear relationship between stress and the occurrence and severity of symptoms [37]. Central nervous system disorders are also associated with dysregulation of the autonomic nervous system, which may explain the occurrence of a wide spectrum of parenteral symptoms in patients with IBS, such as headache, back pain, fibromyalgia, sleep disorders, chronic fatigue syndrome or anxiety-depressive disorders [38].

Statement 11

Genetic factors are important in the pathogenesis of IBS.

Discussion

The results of genetic tests in patients with IBS indicate that a role is played by gene polymorphisms associated with the serotoninergic system, the integrity of the intestinal barrier, the regulation of neuronal and immunological functions and the regulation of the synthesis, absorption and secretion of bile acids [13, 15]. Epigenetic mechanisms influencing gene expression are also significant [15].

Statement 12

Dietary factors, with particular emphasis on poorly absorbed, easily fermentable oligo-, di-, monosaccharides and polyols (FODMAPs), may influence the occurrence and severity of IBS symptoms.

Discussion

The consumption of poorly absorbed, easily fermentable short-chain carbohydrates and polyols, i.e. FODMAPs, intensifies bacterial fermentation processes [39]. Stress is also placed on the close relationship between diet and the intestinal microbiota and the role of the metabolites produced by it, such as short-chain fatty acids, which affect bowel function and a number of regulatory processes in the gut-brain axis [40, 41]. Analyzing the relationship between IBS and hypersensitivity to gluten, it is indicated that other components of cereals contribute to the induction of intestinal symptoms [42]. In the pathogenesis of IBS, the role of food allergy has not been confirmed [31].

Statement 13

Psychosocial factors and coexisting psychiatric disorders have a significant impact on the course and results of IBS treatment.

Discussion

Psychosocial factors are an integral part of the biopsychosocial model of the pathogenesis of functional disorders of the gastrointestinal tract [20]. These factors include chronic stress, in particular of high severity, as in traumatic experience, the experience of physical or sexual violence and adaptive disorders. In addition, 20–60% of IBS patients have depressive-anxiety disorders [43, 44]. Often, somatization and neuroticism are also observed in this group of patients. Psychosocial factors and co-existing psychiatric disorders affect the patient's perception of the disease, the feelings of discomfort, seeking medical help, as well as the results of treatment [37].

4. Symptoms, differential diagnosis and diagnostic criteria

Recommendation 1

We recommend diagnosis of irritable bowel syndrome based on the Rome IV diagnostic criteria. **Recommendation: strong, quality of evidence: moderate**.

Vote

A – 85.7%; B – 14.3%; C – 0%; D – 0%; E – 0%.

Agreement level: high.

Discussion

Irritable bowel syndrome is a chronic disease that belongs to the group of gut-brain interaction disorders (formerly known as functional) in which recurrent abdominal pain is associated with defaecation, a change in bowel habit or a change in stool consistency. The diagnosis of IBS should be based on the Rome IV criteria, which are presented in Table IV [20].

Comparing the current Rome IV criteria to the previously applied Rome III criteria, it is worth emphasizing that, among others, the word "discomfort" has been removed, justifying this by the lack of its specificity and the ambiguity of this wording.

In recent reports, it is increasingly noted that IBS should also be considered in patients who report bloating/flatulence, as well as in those with a shorter duration of symptoms than those defined in the Rome IV criteria [45, 46].

It is worth noting that patients with IBS often have symptoms other than those affecting the digestive system, such as drowsiness, headaches and back pain in the lumbar region, nocturia, frequent and urgent urination, and in women also menstrual disorders and dyspareunia. These symptoms are not of diagnostic significance, although they may interfere with the clinical picture of the disease and cause diagnostic difficulties [47, 48].

Recommendation 2

There are four main subtypes of IBS: constipation-predominant (IBS-C), diarrhoea-predominant (IBS-D), mixed bowel habits (IBS-M) and unclassified (IBS-U). We recommend the use of these subtypes. **Recommendation: strong, quality of evidence: high**.

Vote

A – 100%; B – 0%; C – 0%; D – 0%; E – 0%.

Agreement level: high.

Discussion

In differentiating between the subtypes, the Bristol Stool Formulation Scale is used (without the use of laxatives or anti-diarrhoeal agents) in relation only to abnormal stools, not all stools as before. This is due to the fact that many patients with IBS have periods when the stool is properly formed and should not be taken into account when assessing the predominant type of bowel movement.

Table IV. Irritable bowel syndrome – Rome IV criteria [45]

Recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with 2 or more of the following*:
1. Related to defecation and/or 2. Associated with a change in frequency of stool and/or 3. Associated with a change in form (appearance) of stool
*Criterion should be fulfilled for the last 3 months with symptom onset over 6 months prior to diagnosis.

According to the Rome IV criteria, IBS with diarrhoea occurring in over 25% of bowel movements is types 6 and 7, and that with less than 25% of bowel movements affected is types 1 and 2. Irritable bowel syndrome with constipation is diagnosed when more than 25% of bowel movements are of types 1 and 2 according to the Bristol Stool Formation scale, and at the same time less than 25% of bowel movements are of types 6 and 7. It should be noted here that in clinical practice, in order to differentiate between IBS-D and IBS-C, it is sufficient that the patient reports abnormal bowel movements usually of types 6 and 7 for IBS-D or types 1 and 2 for IBS-C. IBS with mixed bowel habits is diagnosed when the patient reports that more than 25% of bowel movements are of types 6 and 7 and at the same time more than 25% of bowel movements are of types 1 and 2. Other cases of IBS are classified as the unclassified form (less than 25% of bowel movements are types 6 and 7 and types 1 and 2) [45]. In these guidelines, we use two nomenclatures: the one introduced in 2016 and binding from that time, and the previous, distinctive subtype non-constipation IBS to which they belong according to the new nomenclature: diarrhoea-predominant IBS, mixed bowel habits IBS and unclassified IBS. This is related to the studies assessed in the guidelines, in which the definitions are different.

Recommendation 3

We recommend that the diagnosis of IBS should be based on clinical symptoms. There are no confirmatory diagnostic tests. **Recommendation: weak, quality of evidence: moderate**.

Vote

A – 85.7%; B – 14.3%; C – 0%; D – 0%; E – 0%.

Agreement level: high.

Discussion

The diagnosis of IBS should be preceded by the reliable collection of a medical history, physical examination, the implementation of the necessary laboratory tests (reduced to a minimum) as well as in justified situations (described below) by the performance of a colonoscopy. The basic laboratory tests necessary for the diagnosis of IBS include a full blood count since anaemia or leukocytosis requires further diagnosis [45]. The meta-analyses performed have confirmed the usefulness of serum C-reactive protein (CRP) and faecal calprotectin in situations requiring differentiation between IBS without constipation and inflammatory bowel disease (IBD) [49]. If the inflammatory parameters are only slightly elevated and the probability of IBD is low, it is recommended to repeat the tests (CRP and calprotectin) before performing colonoscopy [50].

In justified clinical cases, thyroid-stimulating hormone (TSH) testing is also recommended [45]. Serological tests for coeliac disease (IgA antibodies against tissue transglutaminase and total IgA) are particularly recommended for IBS-D and IBS-M not responding to empirical therapy [45]. In the case of elevated levels of anti-tTG in the IgA class, it is recommended to perform gastroscopy with biopsies from the duodenum for histopathological assessment [51]. In the differentiation of diarrhoea, microbiological and parasitological stool examinations may be considered depending on the clinical picture [45].

Due to the frequent coexistence of SIBO in patients with IBS (especially in the diarrhoea-predominant form and with extensive bloating), breath testing for SIBO should be included in the diagnostics [30]. In justified cases, abdominal ultrasound may be indicated as a complement to the physical examination.

Recommendation 4

We recommend that colonoscopy in IBS diagnosis should be offered only in justified cases (e.g. with co-existing alarming symptoms. **Recommendation: strong, quality of evidence: high**.

Vote

A – 71.4%; B – 28.6%; C – 0%; D – 0%; E – 0%.
Agreement level: high.

Discussion

Colonoscopy and fibrosigmoidoscopy are not recommended for patients under 50 years of age with suspicion of IBS without alarming symptoms [52]. Colonoscopy is recommended in patients with alarming symptoms and symptoms of organic diseases (listed in Table V) to exclude organic disease and in people over 50 as a test for colorectal cancer [53, 54].

In the case of a colonoscopic examination in patients with IBS-D, especially women over 50 years old, it is recommended to take biopsies from the right and left colon in search of microscopic inflammation [55].

The suggested diagnostic algorithm for patients with suspected IBS is shown in Figure 1.

Table V. Risk factors for organic disease and alarming symptoms

- Age > 50 years
- Family history for colon cancer, celiac disease, inflammatory bowel diseases
- Recent treatment with antibiotics
- Stays in regions of endemic occurrence of infectious or parasitic diseases
- Short duration of symptoms
- Occurrence of symptoms at night
- Unintentional weight loss
- Fever
- Bleeding from the lower gastrointestinal tract; blood in the stool
- Abdominal tumour or mass
- Ascites
- Anaemia
- Leukocytosis

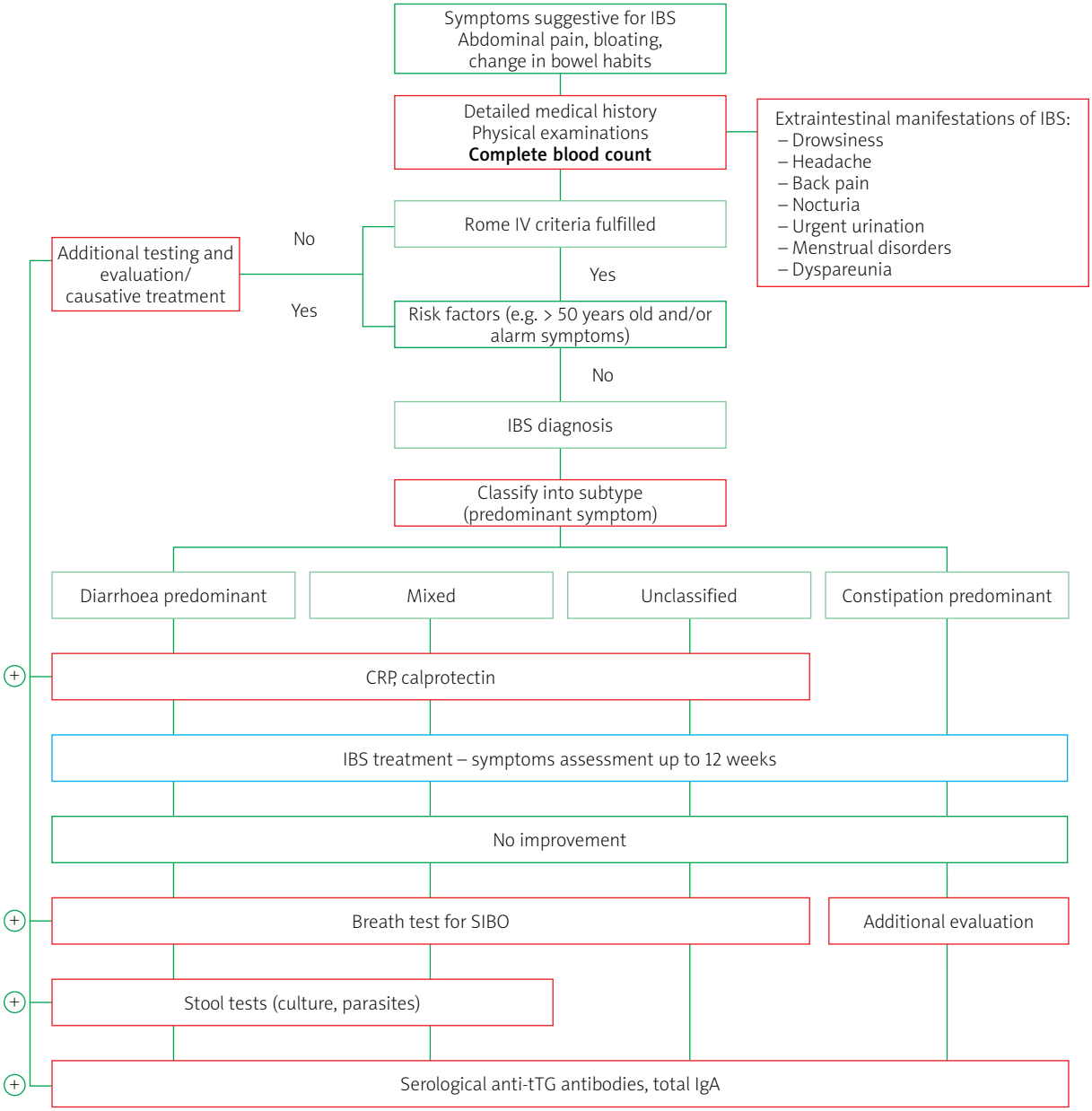

Figure 1. Proposed diagnostic algorithm for diagnose of IBS
IBS – irritable bowel syndrome, SIBO – small intestine bacterial overgrowth, anti-tTG – anti-transglutaminase antibodies.

5. Non-pharmacological management

5.1. Exercise and psychological therapies

Recommendation 5

We suggest moderate physical exercise of various forms (including yoga) in order to maintain fitness and reduce the overall symptoms of IBS. Recommendation: weak, quality of evidence: very low.

In order to reduce the overall symptoms of IBS, we suggest a reasonable supervised (physician, dietitian, trainer) weight-loss programme to achieve a normal BMI. **Recommendation: weak, quality of evidence: very low.**

We suggest: independent exercise sessions, participation in support groups, patient organisations, associations, clubs or psychological consultations in order to develop optimal ways of coping with stress, which may translate into a reduction in overall IBS symptoms. **Recommendation: weak, quality of evidence: very low.**

Vote

A – 71.4%; B – 14.3%; C – 0%; D – 14.3%; E – 0%.

Agreement level: high.

Discussion

Mental balance, the ability to cope with stress, as well as physical activity and fitness, remain key elements in maintaining physical and mental health. Based on research in various fields of medicine, bearing in mind the overall pro-health effect, it should be assumed that they also bring added benefits to the treatment of patients with IBS [56].

In the analysis of the efficacy of various forms of exercise in the reduction of IBS symptoms, four prospective randomized controlled trials were taken into account, which included 310 patients, and one observational study evaluating the long-term effects in the same group of patients (39 people, mean follow-up time 5.2 years). The patients had individual consultations with the selection of appropriate exercises, or exercises with a physiotherapist or a recommended walking and running time over 12 weeks to 24 months [57–60]. Due to the significant heterogeneity of the studies, the total therapeutic effect cannot be estimated (various presentations of results, differently defined endpoints). The Daley *et al.* study showed a significant improvement in the quality of life and a reduction in the severity of constipation, but not of other symptoms of IBS, while in the others there was a statistically significant reduction in total IBS symptoms. It was found that the beneficial effect of exercise lasts, on average, for 5 years and concerns primarily the quality of life, and selected intestinal and parenteral IBS symptoms [58].

The results of numerous observational studies have shown that people who are overweight and obese are more likely to have IBS symptoms, and weight loss leads to a reduction in their severity. The latest studies of obese patients prior to bariatric surgery (observation of 1,542 patients) show that the prevalence of IBS in this group is up to three times higher than in the general population and ranges between 13.3% and 30% [61–66]. Only one study dealt with the effects of a weight-loss programme in relation to IBS symptoms. With a statistically significant reduction in body weight, there was also a statistically significant reduction in the severity of overall IBS symptoms, and after analysis of individual symptoms, also each of them except for pain [65].

A limitation of the research on physical activity and weight reduction is the low or very low percentage of patients implementing the recommendations, which adversely affects the final results assessing the efficacy of such treatments (about 18% to 28%) [58, 65].

As noted earlier, psychosocial factors and co-existing mental disorders have a significant impact on the course and results of IBS treatment. Therefore, the number of studies and analyses devoted to this issue is not surprising. Their biggest drawback is the variety of methods and evaluation systems used, and objective difficulties in conducting the studies with a placebo, which does not allow for a uniform analysis. Most studies have dealt with the assessment of cognitive-behavioural therapy (22 studies) [67–70]. Other methods of psychotherapy included hypnosis, classical psychotherapy, relaxation therapies, mindfulness training and methods developed for self-healing. They included over 2,300 patients. The results differed considerably, however, although they favoured psychotherapy, and in 22/40 studies they did not reach statistical significance. The four meta-analyses and statistical reviews available to date (2009, 2014, 2016 and 2017) showed a statistically significant improvement in intestinal symptoms and mental health in the case of combined therapies, and individually in the case of cognitive-behavioural therapy, hypnosis and complex psychotherapy. However, the authors emphasize the absolute necessity of a critical interpretation of results due to significant discrepancies in the methodology and results [67–70].

Acupuncture also deserves a mention. Its efficacy, including long-term, has been investigated by over twenty original studies (some of them with randomization and control groups) and a Cochrane meta-analysis, which included more than two thousand patients [71]. In all the studies, a high proportion of responses in the placebo group was noted, and although the results were more favourable for the study group, no statistically significant difference was found between the groups.

5.2. Diets

Recommendation 6

In order to reduce the overall symptoms, we suggest a temporary (6-week) diet with a low content of poorly absorbed, easily fermentable oligo-, di-, monosaccharides and polyols (the low-FODMAP diet). Due to the fact that there is insufficient evidence, we do not recommend repeating the diet. **Recommendation: weak, quality of evidence: very low.**

We do not recommend the use of a gluten-free diet. **Recommendation: weak, quality of evidence: very low.**

We do not recommend the use of an elimination diet based on the concentration of antibodies against individual nutrients. **Recommendation: weak, quality of evidence: very low.**

In the case of patients benefiting from an elimination diet, individual dietary modifications based on the patient's experience are suggested. **Recommendation: weak, quality of evidence: very low.**

Vote

A – 85.7%; B – 14.3%; C – 0%; D – 0%; E – 0%.

Agreement level: high.

Discussion

Taking into account the symptoms reported by patients (up to 80% of respondents say the occurrence of symptoms is dependent on their current diet) and the available test results, it can be assumed that diet is important in the occurrence of symptoms of irritable bowel syndrome. In the largest NutriNet-Sante Cohort report so far, published in 2018, covering 33,343 people, it was shown that the symptoms of IBS are dependent on diet, and, what is more, it is a "dose-dependent" effect, i.e. the more highly processed products there are in the diet, the greater the severity of symptoms [72]. So far, most studies have been concerned with the efficacy of the low-FODMAP diet, a diet low in fermenting oligo-, di- and monosaccharides, and polyols, and a gluten-free diet. The efficacy of the first is seen in the reduction of fermentation, and thus regulation of passage, the reduction of stool volume and gas production. In people without coeliac disease, there may be so-called non-coeliac gluten sensitivity; hence there attempts to treat it with a gluten-free diet. Single studies assessed the efficacy of a diet selected individually based on the presence of antibodies to specific food products as well as diets with restrictions (milk, sugars, meat) or supplements (vegetables, fruits) of individual products. All the assessed diets were introduced temporarily (2–12 weeks), and the effects of re-introduction of the diet were not assessed, even if it was proven that the symptoms recurred after being challenged with previously eliminated ingredients (3 studies, 82 patients) [73–75]. As in the case of other non-pharmacological interventions, in the case of diets the main drawback of the studies is their heterogeneous methodology (end points, evaluated scales). In total, 12 randomized controlled trials (734 subjects) and two systematic reviews and meta-analyses were included to assess the effectiveness of the low-FODMAP diet [39, 76–86]. These studies differed significantly in methodology. Five compared a diet to a lack of recommendations or a diet rich in FODMAP [78, 79, 83, 85, 86]. The others (2 studies) compared a diet to other diets recommended in IBS, or to other interventions (4 studies: two with supplementation of probiotics, one with exercises and one with hypnosis). The efficacy of a diet in the absence of dietary recommendations was assessed in 113 people and demonstrated a statistically significant effect of the low-FODMAP diet (OR = 3.15, 95% CI: 1.68–5.94, p = 0.0004, OR range 2.67–3.43, number needed to treat [NNT] = 2). Other studies comparing the low-FODMAP diet to other interventions showed no statistically significant differences between the interventions (studies on 396 patients, OR = 1.18, 95% CI: 0.85–1.63, p = 0.042; OR range ± 0.1). This means that the efficacy of the low-FODMAP diet was comparable to other dietary recommendations, probiotic supplementation, hypnosis or yoga, which again confirms the significant effect of any intervention in this group of patients (which should not be confused with placebo; in this case even a simulated intervention provides patients with more interest shown and more time consumed than in standard care).

In three randomized controlled trials on the effectiveness of a gluten-free diet, it has not been shown to be superior to placebo and should therefore not be recommended in patients with IBS [87–89].

5.3. Fibre supplementation

Recommendation 7

In order to reduce the overall symptoms, we recommend using a diet rich in soluble fibre in all types of IBS. Due to the nature of the disease, the diet should be used long-term. **Recommendation: strong, quality of evidence: moderate.**

The dose of fibre has not been clearly defined. We suggest using 10–25 g fibre daily. **Recommendation: weak, quality of evidence: low.**

Due to the proven lack of efficacy, we do not recommend the use of insoluble fibre, which may additionally exacerbate pain and abdominal distension. **Recommendation: strong, quality of evidence: moderate.**

Vote

A – 100%; B – 0%; C – 0%; D – 0%; E – 0%.

Agreement level: high.

Discussion

The effect of fibre on intestinal symptoms has been under evaluation for many years. Until recently, the interpretation of inconsistent results caused researchers difficulty. On the one hand, patients pointed to the effect of supplementation, while on the other hand, previous studies showed no statistically significant differences between the study groups (RR for inefficacy 0.9, 95% CI: 0.79–1.03). It should be emphasized that of 15 randomized trials, conducted on almost 1,000 patients, the majority were carried out in the 1970s or 80s and did not take into account the type of fibre used [90–102]. However, for several years we have known that the efficacy of fibre depends on its structure, and it has now been proven that only soluble fibre is effective (in contrast to the previously recommended insoluble fibre). So far, only one study (2009) devoid of risk of error has dealt with a comparison between the two [100]. In this study (as in other studies in which the intervention concerns the modification of broadly understood lifestyle, diet, and physical activity), a serious limitation is the number of people who do not comply with the

recommendations (ultimately the study was completed on average by 60% of the group randomized to individual arms), which significantly affects the ITT and PP analysis results. While after 3 months of treatment in the analysis of PP, 52% of patients using fibre compared to 32% in the placebo group showed improvement (p = 0.02, NNT = 5), in the ITT analysis it was only 31% of patients (compared with 19% in the placebo group (p = 0.05, NNT = 8.8). However, summing up, if patients are willing to follow the recommendations, soluble fibre supplementation brings significant therapeutic benefits. It is also worth noting that in the available meta-analyses it was found that insoluble fibre increased abdominal distension, pain and constipation.

In the analysed studies, the average dose was 10 g, and from studies assessing the efficacy of fibre in other indications it is known that 25 g/day is optimal and such a range of doses should be recommended. In most studies, supplementation was used for months; thus, taking into account the potential mechanisms of action of plant fibres (a laxative effect through increasing stool volume, acceleration of peristalsis and stimulation of the colon mucosa, interaction with the intestinal microbiota and the immune system as well as the nervous and neuroendocrine system) they should be used long term [88, 89, 95]. Typical sources of soluble fibre (suggested) include fresh vegetables and fruit, plantains (psyllium (ispaghula) – *Plantago lanceolata*, *Plantago ovata*), oat bran and ready-made supplements. Sources of insoluble fibre (not recommended) are: wheat bran, grains, nuts, beans and grains as well as cruciferous and root vegetables. Many natural products contain both types of fibre.

5.4. Peppermint oil

Recommendation 8

We recommend using selected peppermint oil preparations to reduce overall symptoms. **Recommendation: strong, quality of evidence: moderate.**

We suggest using a preparation containing peppermint oil at a dose of 180–225 mg twice a day. **Recommendation: weak, quality of evidence: very low.**

So far, the minimum, optimal or maximum duration of use of peppermint oil has not been determined. Based on available studies, we suggest using the preparation for 2 to 12 weeks. The efficacy and safety of longer-term use must be confirmed by tests. **Recommendation: weak, quality of evidence: very low.**

Vote

A – 57.1%; B – 42.9%; C – 0%; D – 0%; E – 0%.

Agreement level: high.

Discussion

Eight prospective studies (including 6 with randomization and a control group) and 3 systematic reviews (meta-analyses) were included in the analysis to evaluate the efficacy of peppermint oil [103–110]. A total of 567 patients were evaluated and it was found that the use of peppermint oil showed a statistically significant benefit in reducing the overall symptoms of IBS (OR = –2.22; 95% CI: 1.65–2.99, p < 0.0001; OR range in the studies 1.64–4.87: NNT = 3 range: 1.8–6.4).

In the study by Alam *et al.* it was demonstrated that intestinal symptoms recur after discontinuation of the preparation, which, in the absence of studies on safety and efficacy of the preparation (the longest period of administration was 12 weeks), should be taken into account when formulating permanent recommendations for patients [110].

It must be stipulated that efficacy studies concerned specific oil preparations (hence their high heterogeneity) and cannot be extrapolated to all available forms of mint and mint products. Due to the different formulations and preparation methods available in Poland, the optimal dose cannot be determined. The dose used in the aforementioned studies was 180–225 mg, which is a large dose.

Peppermint oil is a relatively safe preparation. No significant adverse reactions were observed, but heartburn was more frequently reported than in the placebo group [104, 108]. The mechanism of action of the preparation is complex and includes relaxation of smooth muscle (by blocking calcium channels or a direct effect on the intestinal nervous system), modulation of visceral sensation (a transient change of cation channel potentials), antibacterial and anti-inflammatory effects as well as modulation of psychosocial disorders.

5.5. Other herbal products

Recommendation 9

There is not sufficient evidence to make a recommendation regarding STW 5. Taking into consideration mode of action and efficacy in other indications, this product can be helpful in defined clinical situations. **Recommendation: weak, quality of evidence: very low.**

Vote

A – 57.1%; B– 42.9%; C – 0%; D – 0%; E – 0%.

Agreement level: high.

Discussion

To date, reports on the efficacy of STW 5 and cannabinoids in relieving IBS symptoms come from case reports, non-interventional and observational studies. One prospective randomized trial evaluating the effica-

cy of STW 5 has been published (203 patients, assessment after 4 weeks, statistically significant efficacy, but assessed using a non-standardized original questionnaire, no possibility of evidence replication), and two studies assessing cannabinoids (102 patients, no statistically significant efficacy proven) [111]. At this stage, there is insufficient evidence to recommend the use of STW-5 or cannabinoids to treat the symptoms of IBS. Nevertheless, considering the observational studies as well as the efficacy of the STW-5 in other functional disorders, it seems that it may be helpful, at least partially, in alleviating symptoms.

In addition, it should be mentioned that so far two cannabinoid assessments including 102 patients have been published. There was no statistically significant difference in efficacy between treatment group and placebo; thus, there is insufficient evidence to recommend cannabinoids to treat the symptoms of IBS [112].

5.6. Probiotics

Recommendation 10

We suggest using certain strains or a combination of probiotic strains tested for their efficacy in IBS, rather than probiotics as a group, to reduce overall symptoms of IBS as well as bloating and diarrhoea in patients with IBS. **Recommendation: weak, quality of evidence: very low.**

The probiotics with expected beneficial effects in patients with IBS and known levels of bacteria per dose are listed in Table VI. **Recommendation: weak, quality of evidence: moderate.**

At this stage, it is not possible to determine the efficacy of individual strains included in combined preparations or the efficacy of other configurations (blends) of the aforementioned strains. **Recommendation: weak, quality of evidence: very low.**

Vote

A – 57.1%; B – 28.6%; C– 14.3%; D – 0%; E – 0%.

Agreement level: high.

Discussion

Many trials have shown that efficacy of probiotics is strain-dependent. Therefore, in this analysis, although probiotics in general were also considered, we focused on certain preparations and specific blends, the efficacy of which was assessed in prospective, randomized and controlled trials. A total of 55 studies (over 6,000 patients) assessing probiotics in IBS were included. Of these, 15 assessed the effect of probiotics in general, 18 assessed the effect of selected, specific blends (a repeatable composition), and 22 assessed the efficacy of individual strains. Most studies dealt with *L. plantarum* 299v (3) and *S. boulardii* (3) and particular combinations of probiotics (Table VI, bottom)

Table VI. Probiotics (single strains and combined preparations) with a likely beneficial effect on IBS symptoms taken into account in the analysis [113–165]

Monostrains:
– *Bifidobacterium bifidum MIMBb75*
– *Bifidobacterium infantis* 35624
– *Bifidobacterium lactis*
– *Escherichia coli DSM17252*
– *Lactobacillus acidophilus SDC 2012, 2013*
– *Lactobacillus plantarum 299v*
Stains tested in selected populations, or an effect covering only a part of symptoms:
– *Bacillus coagulans* GBI-30, 6086
– *Bifidobacterium animalis*
– *Saccharomyces boulardii* CNCM I-745
Blends:
– Combined preparation: *Lactobacillus rhamnosus NCIMB 30174*, *L. plantarum NCIMB 30173*, *L. acidophilus NCIMB* and *Enterococcus faecium NCIMB 30176*
– Combined preparation: *Lactobacillus animalis* subsp. *lactis* BB-12, *L. acidophilus* LA-5, *L. delbrueckii* subsp. *bulgaricus* LBY-27 and *Streptococcus thermophilus* STY-31; *Bifidobacterium animalis* DN-173 010 in fermented milk (together with *Streptococcus thermophilus* and *Lactobacillus bulgaricus*)
– Combined preparation: *Lactobacillus rhamnosus* GG, *L. rhamnosus* LC705, *Propionibacterium freudenreichii* subsp. *shermanii* JS DSM 7067 and *Bifidobacterium animalis* subsp. *lactis* Bb12 DSM 15954
– Combined preparation *Pediococcus acidilactici* CECT 7483, *Lactobacillus plantarum* CECT 7484 and *L. plantarum* CECT 7485
– Combined preparation: *Streptococcus thermophilus* DSM24731, *Bifidobacterium longum* DSM24736, *Bifidobacterium breve* DSM24732, *Bifidobacterium infantis* DSM24737, *Lactobacillus acidophilus* DSM24735, *Lactobacillus plantarum* DSM24730, *Lactobacillus paracasei* DSM24733 and *Lactobacillus delbrueckii* ssp. *bulgaricus* DSM24734

Table VII. Discussion of studies evaluating single strains of probiotics included in the analysis [113–165]

Author, year	No. of patients	Probiotic	Main results	Discussion
Niedzielin, 2001	40	*L. plantarum*	Statistically significant improvement	Improvement in 100% of study group and in 55% of placebo group (non-repeatable result)
Niv, 2005	93	*L. reuteri*	No significance	
O'Mahony, 2005	77	*B. infantis*	Improvement all symptoms without number of stools	VAS scale, comparison vs other probiotic
Whorwell, 2006	362	*B. infantis*	Statistically significant improvement	Study only in women, original system of evaluation of efficacy, only one of three doses (10^8 effective, smaller and larger – no)
Guyonnet, 2007	274	*B. animalis*	Only an improvement in quality of life	Only IBS-C
Sinn, 2008	40	*L. acidophilus*	Significant reduction in severity of pain	No efficacy in remaining symptoms
Agrawal, 2009	34	*B. lactis*	Significant improvement in overall symptoms and quality of life	
Enck, 2009	298	*E. coli*	Statistically significant improvement	Original efficacy evaluation scale Only abstract in English
Choi, 2011	67	*S. boulardii*	Statistically significant improvement only in quality of life	No other parameters underwent statistically significant improvement
Guglielmetti, 2011	122	*B. bifidum*	Statistically significant improvement in overall symptoms and quality of life	
Kruis, 2011	120	*E. coli Nissle*	Statistically significant improvement only after 10 and 11 weeks (not after end of study)	The scale is not validated for IBS, the highest statistical significance in the subgroup with previous gastrointestinal infection or after antibiotic treatment
Kabir, 2011	35	*S. boulardii*	No significance	
Ducrotte, 2012	214	*L. plantarum*	Reduction in severity of pain and abdominal distension	Original scale, separation of severity and frequency of symptoms
Stevenson, 2014	65	*L. plantarum*	No significance	
Rogha, 2014	56	*B. coagulans*	Significant improvement in overall symptoms	Above all, reduction in severity of pain
Abbas, 2014	72	*S. boulardii*	Significant improvement in the quality of life	No significance in assessment using IBS-SSS questionnaire
Pineton, 2015	179	*S. cerevisiae*	Reduction in intensity of pain	Original, unvalidated assessment scale
Thijssen, 2016	80	*L. casei*	No significance	A 30% reduction in integrated scale of symptoms was evaluated (original, unvalidated)
Spiller, 2016	379	*S. cerevisiae*	No significance	
Lyra, 2016	340	*L. acidophilus*	No significant difference between groups	Improvement statistically significant in all groups; including placebo
Pinto-Sanchez, 2017	44	*B. longum*	Reduction in depression, improvement in some aspects of quality of life	Only in 3 points from the entire questionnaire significant improvement, study aimed at psychiatric evaluation, without improvement in the intensity of anger
Ringel-Kulka, 2017	275	*B. infantis*	Significant improvement in probiotic group and placebo	No significant differences between probiotic and placebo. Study based on volunteers with symptoms
Cremon, 2018	40	*L .paracasei*	No significance	
Shin, 2018	48	*L. gasseri*	Significant improvement in quality of life	Other symptoms were not evaluated

(4). The others were evaluated in individual studies [113–165]. The vast majority of studies had different endpoints, and the majority evaluated only selected aspects, e.g. quality of life, pain, abdominal circumference as a surrogate of bloating, etc., which does not allow for a coherent analysis. With these endpoints, in 13/22 studies an improvement of at least one parameter was found; the others did not show any significant difference (there is a critical discussion of the studies in Table VII). Studies using generally available, widely used scales showed no advantage of probiotics in general or individual strains over a placebo. On the other hand, patented blends of strains showed statistical efficacy also based on the most frequent scales, but so far 13 of these studies have been published, and most of them concerned single preparations. .

In conclusion, it should be emphasized that the efficacy of probiotics cannot be assessed in general, and the efficacy of specific preparations remains controversial. The results of the studies are close to the borderline of statistical significance, which, considering the potential significant side effects of the group (including, for example, reports of sepsis in critically ill patients), should lead to the prudent prescription of these preparations.

6. Treatment and monitoring

6.1. Drugs used in all forms of IBS

6.1.1. Antispasmodics

Recommendation 11

We suggest using certain antispasmodics, the efficacy of which in IBS has been confirmed, such as hyoscine and drotaverine (and some unavailable in Poland: otilonium, cimetropium and pinaverium bromides, and dicyclomine) rather than antispasmodics as a group.
Recommendation: weak, quality of evidence: very low.

Vote

A – 28.6%; B – 57.1%; C – 0%; D – 14.3%; E – 0%.
Agreement level: high.

Discussion

Antispasmodic drugs are a very large and heterogeneous group of preparations. Therefore, their combined analysis in a given indication is burdened with a high risk of error resulting not only from different methodologies or endpoints of various studies, but above all from different mechanisms of action of individual drugs, and thus expected other results. The available studies, evaluating the effects of 13 various formulations, are subject to a significant risk of error resulting from heterogeneity. An assessment of the efficacy of individual drugs is also difficult due to the usually single studies dedicated to one preparation, typically carried out on a small number of patients.

In total, 18 studies (2,237 patients) were included in randomized trials that demonstrated the efficacy of antispasmodics in reducing overall IBS symptoms. The RR for inefficacy was 0.65 (95% CI: 0.56–0.76); NNT = 5 (95% CI: 4–8) [166–185]. Nine studies (630 people) did not show any efficacy of the preparations tested in reducing complaints (detailed discussion in Table VIII). Other studies that did not meet the criteria for inclusion in the analysis (observational, without randomization or control groups) assessed not the improvement in the symptoms of the disease, but the quality of life of the patients. In one of them, a statistically significant improvement in the quality of life of patients treated with mebeverine was demonstrated. The advantage of the study was that it was multi-centre, the number of patients included was large (607 people), and it had a precisely defined endpoint based on a validated questionnaire [186]. It should be noted, however, that mebeverine has not been shown to be advantageous in the relief of IBS symptoms in general in randomised placebo-controlled trials, as confirmed by three meta-analyses and systematic reviews.

Antispasmodics, despite being an extremely heterogeneous group, with various mechanisms of action, in

Table VIII. Studies evaluating the efficacy of antispasmodic drugs included in the analysis. Preparations, the efficacy of which in the alleviation of IBS symptoms was confirmed in RCT, have been highlighted in bold type [166–185]

Preparation	No. of studies	No. of patients	RR	95%CI	NNT	95% CI
Hyoscine	3	426	0.63	0.51–0.78	3	2–25
Drotaverine	2	150	0.31	0.19–0.50	2	2–3
Otilonium	5	791	0.70	0.54–0.0	5	4–11
Pinaverium	4	615	0.56	0.38–0.82	4	3–6
Cimetropium	3	158	0.38	0.20–0.71	3	2–12.5
Dicyclomine	1	97	0.65	0.45–0.95	4	2–25
Mebeverine	6	351	1.18	0.93–1.50	–	–
Trimebutine	2	172	Evaluation not possible, one study assessed the improvement in an original unvalidated scale, the second assessed only the quality of life. Neither achieved statistical significance. There was no statistical significance between the groups			
Alverine	1	107	1.07	0.84–1.37	–	–

general constitute a group of relatively safe drugs. Although side effects occur statistically significantly more often than in the control group, they mainly include dry mouth, dizziness and blurred vision, and no severe complications have been observed after their use.

6.1.2. Antidepressants

Recommendation 12

In order to improve the overall symptoms of IBS, we recommend the use of tricyclic antidepressants (TCAs). **Recommendation: strong, quality of evidence: high.**

In order to improve the overall symptoms of IBS, we suggest the use of selective serotonin reuptake inhibitors (SSRIs). **Recommendation: weak, quality of evidence: low.**

We suggest using the drugs in the smallest effective doses for 4–12 weeks, although the maximum duration of drug use (regarding their efficacy and safety) has not been clearly defined. If treatment brings additional benefits, it can be used for longer. **Recommendation: weak, quality of evidence: very low.**

Vote

A – 71.4%; B – 14.3%; C – 0%; D – 14.3%; E – 0%.

Agreement level: high.

Discussion

Functional gastrointestinal tract disorders have been considered for several years as a manifestation of disorders of interactions of the brain-gut-microbiota axis. Abnormalities leading to the occurrence of abdominal symptoms include disturbances of nerve conduction which result in hypersensitivity to stimuli and a hyper-reactive neuronal response. In patients with IBS, emotional disorders often occur (mood disorders, depression, anger, somatisation). For this reason, centrally acting drugs are of great interest in the treatment of this group of patients. The majority of studies deal with tricyclic antidepressants (TCAs) and serotonin reuptake inhibitors (SSRIs).

Sixteen randomized trials (1,009 patients) were included in the analysis; 10 dealt with TCAs (618 patients), 6 with SSRIs (305 subjects), and one dealt with drugs from both groups (51 people) [187–200]. Only 4 studies had a low risk of errors [190, 199–201].

TCAs were shown to reduce the severity of overall IBS symptoms (RR = 0.65, 95% CI: 0.55–0.77, NNT = 4; 95% CI = 3.5–7). In the case of SSRIs, the RR was 0.68 (95% CI: 0.51–0.91) and NNT = 5 (95% CI: 3–16.5). The greatest reduction in symptoms concerned pain. This is most likely due to the complex, central and peripheral mode of action of those drugs.

The studies were conducted for various drugs, from both groups. Therefore, it is not possible to formulate unambiguous recommendations as to the dosage and duration of treatment. Ideally, drugs should be used that have been tested and shown to be effective in this indication, i.e. amitriptyline, doxepin, desipramine, fluoxetine, imipramine, paroxetine, trimipramine (citalopram: controversial efficacy; paroxetine: not efficacious; duloxetine: not studied in this indication) [192, 195,196, 198, 199]. We suggest using medications up to 12 weeks, with the proviso that an effect appears after a dozen or so days of use. Patients should be aware of possible side effects, which are significantly more frequent than in the placebo group – most frequently a dry mouth.

6.2. Drugs used in non-constipation IBS (with predominant diarrhoea and/or mixed bowel habit and/or unclassified IBS)

6.2.1. Rifaximin α

Recommendation 13

In the following types of IBS, in order to reduce the overall symptoms and to reduce abdominal bloating and/or diarrhoea, we recommend a 14-day course of rifaximin α: with predominant diarrhoea, with mixed bowel habit and unclassified. **Recommendation: strong, quality of evidence: high.**

In the case of the first and second recurrence, in patients who have benefited from rifaximin α therapy, we recommend repeated treatment in the same pattern. The minimum interval between cycles has not been clearly defined; we recommend a 4-week interval between successive cycles. **Recommendation: strong, quality of evidence: high.**

Vote

A – 100%; B – 0%; C – 0%; D – 0%; E – 0%.

Agreement level: high.

Discussion

Six prospective randomized controlled trials were included in the analysis of rifaximin α efficacy, including 2,439 patients with non-constipated IBS, and one systematic review and meta-analysis (based on 5 studies) [202–206]. A statistically significant benefit of rifaximin α in treatment of the overall symptoms of irritable bowel syndrome was demonstrated (OR = 1.48, 95% CI: 1.26–1.74, $p < 0.0001$, range of OR from 1.38 to 4.8 in various studies, NNT = 11) and in the treatment of bloating (OR = 1.42, 95% CI: 1.20–1.68, $p < 0.0001$). There was no heterogeneity between the studies, and the meta-analysis showed a low risk of bias errors. Old-

er people and women were shown to have a better response to treatment. A dose-dependent effect was also observed.

The largest studies confirming the efficacy of rifaximin α in the treatment of symptoms (TARGET 1 and 2) and in the treatment of recurrence of symptoms in patients who responded to initial treatment (TARGET 3) were conducted using a dose of 1650 mg (3 tablets of 550 mg three times a day) [205, 206]. There are 200 mg tablets available in Poland; hence the dose of 1600 mg per day (4 × 400 mg) is treated as an equivalent dose and this should be used. Although subject to an expected lower efficacy, it is permitted to use a dose of 1200 mg/day (3 × 200 mg). In the case of two consecutive relapses (TARGET 3), rifaximin α was statistically significantly more effective than placebo in the reduction of symptoms (38.1% vs. 31.5%, $p = 0.03$), in particular pain [206]. Treated patients also had a significantly lower risk of relapse and a more stable response to therapy. Therefore in the case of symptoms recurrences rifaximin α should be used in the cyclic regimen with 4-week intervals.

Rifaximin α is the only known eubiotic that restores the normal composition of intestinal microbiota in the direct (antibacterial) mechanism and indirect – by modulating microbiota. It does not affect the general composition of the bacterial flora, but mainly affects harmful bacteria (*Clostridium, Peptostreptococcaceae* and *Escherichia*). 14-day treatment increases the number of bacteria such as *Bifidobacterium, Lactobacillus* and bacteria with anti-inflammatory properties such as *Faecalibacterium prausnitzii*. Rifaximin α has anti-inflammatory activity acting on the pregnane-X receptor, immunomodulatory activity (stimulation of anti-inflammatory and inhibition of proinflammatory cytokines), reduces pathological permeability of enterocytes and restore intestinal barrier tightness. All these mechanisms play an important role in the treatment of irritable bowel syndrome [207–209].

In cases of post-infectious IBS, IBS /SUDD and IBS/SIBO (positive breath test) overlap syndromes, SIBO, we recommend using rifaximin α in the scheme as for the irritable bowel syndrome.

Rifaximin α is not absorbed from the gastrointestinal tract. The safety profile of the drug is comparable to a placebo, no significant side effects have been observed, nor is there an increase in resistance to rifaximin α or cross-resistance to other antibiotics or any increased risk of *C. difficile* infection [210–212].

6.3. Drugs used only in constipation-predominant IBS

6.3.1. Macrogols (preparations of polyethylene glycol – PEG)

Recommendation 14

We suggest using polyethylene glycol preparations to decrease the severity of constipation in patients with constipation-predominant IBS. These drugs do not decrease the overall IBS symptoms. **Recommendation: weak, quality of evidence: low.**

Vote

A – 85.7%; B – 14.3%; C – 0%; D – 0%; E – 0%.

Agreement level: high.

Discussion

Macrogols non-absorbable from digestive tract, which are osmotically active substances that are not absorbed in the gastrointestinal tract, are undoubtedly effective as laxatives, as evidenced by the fact that they have dominated the method of bowel preparation for colonoscopy. However, in the form of IBS with predominant constipation, their efficacy has not been proven, although up to now only two prospective randomized trials (181 people) have dealt with this issue [213, 214]. Although an increase in the number of bowel movements was demonstrated, this is comparable to the placebo group and the severity of other symptoms also did not differ between the groups. It is difficult to interpret these data, bearing in mind the excellent laxative effect of the preparations. Perhaps this is related to the general profile of this group of patients. In 2017, the results of the multi-centre, prospective study "CHRO.CO.DI.T.E" were published, which included 878 patients with various forms of functional constipation (idiopathic, IBS-C, others) [215]. Of this group, 31.3% had IBS with predominant constipation. It turned out that the subgroup of patients with IBS had statistically significantly more severe symptoms, a worse quality of life and more symptoms of other functional diseases (dyspepsia, GERD, but also depression and anger), more specialist consultations (psychiatric, gynaecological) and more diagnostic tests (including manometry and defaecography). Perhaps this group of patients is more demanding when it comes to management, and even reducing the intensity of one symptom (in this case constipation) does not lead to an improvement that is noticeable for the patient.

Nevertheless, macrogols, used as an aid only in reducing the severity of constipation, also in the group of patients with IBS, may remain a valuable alternative.

6.4. Drugs used only in diarrhoea-predominant IBS

6.4.1. Loperamide

Recommendation 15

We suggest the use of loperamide to decrease severity of diarrhoea in patients with diarrhoea-predominant IBS. The drug does not decrease overall symptoms of IBS. **Recommendation: weak, quality of evidence: very low.**

Vote

A – 85.7%; B – 14.3%; C – 0%; D – 0%; E – 0%.

Agreement level: high.

Discussion

To date, only three randomized trials have been published that assess the efficacy of loperamide in the treatment of diarrhoea-predominant IBS, all from the last century [216–218]. In 171 patients, the efficacy of loperamide was not demonstrated in alleviating the overall symptoms associated with IBS (RR = 0.42, 95% CI: 0.14–1.42), but in all the studies a statistically significant difference between the groups ($p < 0.001$) in alleviation of diarrhoea was achieved, and in this indication, conditionally, the drug may be prescribed.

Drugs available in Poland together with evidence of their effectiveness are presented in Table IX.

6.5. Drugs with proven effectiveness not available in Poland

This section discusses briefly, maintaining the existing uniform format publication, drugs tested for effectiveness in various forms of IBS and registered in other countries, but by the time of issuing of these recommendations are not available in Poland. Experts participating in the preparation of recommendations have no experience with these drugs, and for obvious reasons, cannot take the recommendation of individual preparations. Consequently, the conclusions of scientific research on the discussed drugs will be presented only in the form of statements, together with the quality of evidence arising from the quality of analysis. They are currently not subject to expert voting on the agreement level. As the registration of individual drugs in Poland, after an analysis published since the current recommendations of scientific research, we will update these guidelines, if necessary, in the form of short annexes regarding the safety and effectiveness of individual preparations.

6.5.1. Linaclotide

Statement 14

In constipation-predominant IBS linaclotide reduces overall symptoms. **Quality of evidence: high.**

Discussion

Linaclotide is a guanylate cyclase-C agonist found in the cell membrane (from the side of the intestinal lumen). It works by activating chloride channels, which increases the secretion of fluids and electrolytes and accelerates intestinal transit. Therefore, it is only of use in patients with IBS with predominant constipation. Additionally, it has been shown that activation of guanyl cyclase-C leads to the cyclic release of guanosine monophosphate, which inhibits nociceptors, leading to a reduction in the pain response.

The efficacy in improving the frequency of bowel movements and stool consistency and the safety of linaclotide were evaluated in four randomized, placebo-controlled trials with low risk of bias conducted on 2,867 patients [219–222]. They showed a statistically significant benefit of using the drug (RR = 0.81, 95% CI: 0.77–0.85, NNT = 6, 95% CI: 5–8). In all the studies,

Table IX. Drugs used in management of IBS available in Poland

IBS type	Drug	Efficacy				Quality of evidence	Recommendation
		Pain	Bloating	Diarrhoea	Constipation		
All	Antispasmodics (hyoscine, drotaverine)	+	+	+	+	Very low	Weak
	TCAs	+	+	+	+	High	Strong
	SSRI	+	+	+	+	Low	Weak
Diarrhoea predominant, mixed, unclassified	Rifaximin α	+	+	+	+	High	Strong
Constipation predominant	PEG	–	–	–	+	Low	Weak
Diarrhoea predominant	Loperamide	–	–	+	–	Very low	Weak

TCAs – tricyclic antidepressants, SSRI – selective serotonin re-uptake inhibitors, PEG – polyethylene glycol.

a reduction in pain severity was also demonstrated in patients treated with linaclotide.

The effective dose of the drug was determined to be 290 µg/day, though up to now there have not been any studies assessing the safety and efficacy of its long-term use or re-treatment in the case of relapses. For this reason, we recommend a 6-month course of treatment, with the manufacturer's proviso that in the absence of improvement after 4 weeks of use, the indications for use should be re-evaluated.

6.5.2. Plecanatide

Statement 15

In constipation-predominant IBS plecanatide reduces overall symptoms. **Quality of evidence: moderate.**

Discussion

Plecanatide is another guanylate cyclase-C agonist. Its action is similar to linaclotide, with the difference that activation of the drug depends on pH. In irritable bowel syndrome, the preparation is only used in patients with predominant constipation.

The efficacy and safety of plecanatide in this subgroup of patients were evaluated in 3 randomized and placebo-controlled studies conducted on 2,612 patients. The drug was effective in regulating bowel movements and improving stool consistency (RR = 0.88, 95% CI: 0.84–0.92, NNT = 10, 95% CI: 8–14) [223, 224]. The effect of the drug in the treatment of other IBS symptoms is negligible.

The effective dose of the drug was determined to be 3 mg/day, but up to now there have not been any studies assessing the safety and efficacy of its long-term use or repeated treatment in the case of relapses. For this reason, a 12-week course of treatment is recommended.

The main side effect of both guanylate cyclase-C agonists is diarrhoea.

6.5.3. Lubiprostone

Statement 16

In constipation-predominant IBS, lubiprostone reduces overall symptoms. **Quality of evidence: moderate.**

Discussion

Lubiprostone, a prostaglandin 1 derivative, is an activator of type 2 intestinal chloride channels. It works by increasing the secretion of sodium chloride and water by enterocytes and colonocytes, which results in the acceleration of intestinal transit – hence its use only in patients with IBS with predominant constipation.

The efficacy and safety of lubiprostone were assessed in 6 randomized and placebo-controlled studies conducted on 1,399 patients (two studies were a continuation of previous analyses in the same study group) [225–229]. It was shown to have a statistically significant advantage over placebo in the treatment of constipation in patients with this type of IBS (RR = 0.91, 95% CI: 0.87–0.95, NNT = 12.5 (95% CI: 8–25). Fukudo *et al*. reported that lubiprostone also improves quality of life, and Chang *et al.* found in their study that it also reduces pain and abdominal distension [227, 228].

The effective dose of the drug was determined to be 24 µg twice a day. To date, one study evaluating the safety and efficacy of its long-term use has been published [229]. In the group of patients initially included in the phase III study, lubiprostone was used for an average of 9–13 months, the effect of the drug persisted throughout its duration of administration and no significant adverse effects were observed.

6.5.4. Alosetron

Statement 17

In women with diarrhoea-predominant IBS alosetron reduces overall symptoms. **Quality of evidence: low.**

Discussion

Alosetron is a selective 5-HT_3 receptor antagonist. It inhibits colonic secretion and motility, and by means of central and peripheral mechanisms, it reduces the level of visceral sensation thus bringing about improvement in patients with diarrhoea-predominant IBS. Due to its serious side effects (severe constipation and acute colonic ischaemia), it was temporarily withdrawn from circulation. After a few years, the drug was reintroduced onto the market with severe limitations and the indications for its use were significantly narrowed down and tightened (risk assessment and mitigation strategy). Currently (with the awareness of potential side effects), it is recommended only in women with "severe IBS with predominant diarrhoea, which causes their exclusion from life" [230]. This is because almost all of the studies evaluating the efficacy of alosetron (8 studies, 4,987 patients) recruited exclusively or almost exclusively women [230–237]. Only one study was conducted exclusively in men [237].

A statistically significant effect of alosetron in the reduction of overall symptoms was demonstrated in patients with constipation-predominant IBS (RR = 0.79, 95% CI: 0.69–0.90, NNT = 7.5, 95% CI: 5–16).

The minimum effective dose of the drug was determined to be 0.5 mg twice a day. Due to safety concerns, the method of its use has been clearly defined, thus: if constipation occurs, the drug should be discontinued until it disappears. It can be re-introduced at the re-

duced dose (once daily). If the symptoms are not sufficiently controlled after 4 weeks of use, the dose may be increased to 1 mg a day. If the symptoms do not disappear after 4 weeks, the medication should be discontinued.

6.5.5. Eluxadoline

Statement 18

In diarrhoea-predominant IBS eluxadoline reduces overall symptoms. **Quality of evidence: moderate.**

Discussion

Eluxadoline is a μ- and κ-opioid receptor agonist and δ-opioid receptor antagonist that acts locally on the intestinal nervous system. It thus reduces diarrhoea in patients with diarrhoea-predominant IBS, without causing the adverse reactions typical of opioids. The efficacy and safety of eluxadoline were evaluated in three randomized and placebo-controlled trials conducted on 3,235 patients [238, 239]. They showed a significant advantage of eluxadoline over a placebo in the treatment of diarrhoea (RR = 0.91, 95% CI: 0.85–0.97, NNT = 12.5, 95% CI: 8–33). For the treatment of other symptoms, the effect was not so pronounced, though it was still noticeable.

The effective dose of the drug was determined to be 100 mg twice a day. So far, the safety of the medicine has been assessed during a 26–52 week course of treatment. While the preparation is well tolerated, it can be used long term. However, it should be noted that in people with a history of cholecystectomy, pancreatitis, alcohol abuse, or severe disease of the liver or the sphincter of Oddi, the drug should not be used due to the risk of acute pancreatitis. This warning should be given to all patients in whom administration of the drug is planned.

6.6. Drugs with proven inefficacy in all forms of IBS

6.6.1. Mesalazine

Recommendation 16

We recommend against mesalazine for improvement of overall symptoms of IBS due to proven lack of efficacy in this indication. **Recommendation: strong, quality of evidence: high.**

Vote

A – 100%; B – 0%; C – 0%; D – 0%; E – 0%.
Agreement level: high.

Discussion

Four randomized trials and a control group evaluating the efficacy of mesalazine in alleviating IBS symptoms were included in the analysis of the recommendation. A total of 484 patients were included in the study [240–242]. In all, it was proven that mesalazine is no better than placebo in reducing IBS symptoms. This was also true for patients with only diarrhoea-predominant IBS and post-infective IBS. For this reason, we do not recommend the use of mesalazine in patients with IBS.

6.7. Experimental treatment and new research areas

6.7.1. Faecal microbiota transplantation (FMT)

Recommendation 17

There is not enough evidence to make unambiguous recommendations concerning FMT. We do not recommend the use of FMT in IBS. **Recommendation: weak, quality of evidence: very low.**

Vote

A – 71.4%; B – 14.3%; C – 14.3%; D – 0%; E – 0%.
Agreement level: high.

Discussion

The quality of evidence regarding the efficacy of FMT is more or less distributed half and half. Earlier studies (but conducted in small groups of patients, with concerns regarding the methodology of the procedure itself or the conducting of the study) have not shown the advantage of FMT over a placebo in this group of patients. Two randomized controlled trials in 2018 using validated endpoint assessment methods once again obtained opposite results [243, 244]. In the first (83 patients), a fresh or frozen suspension was administered enterally. A statistically significant response was achieved after 3 months (regardless of the type of suspension). In the second study, which included 52 patients, the suspension was administered in capsules (after freezing). The single dose of microbiota was about 40% lower, but the capsules were administered for 12 days. The results of this analysis are quite different; in this group, the placebo achieved a statistically significant advantage over FMT. Therefore, after analysing both studies, the OR was 0.96 (95% CI: 0.54–1.71, $p = 0.78$).

It should also be taken into account that so far we do not have research assessing the long-term safety of FMT. In the case of research on the use of FMT in IBS, the balance of benefits and harms should be evaluated very critically. It is a new method for now and it is not known what the long-term consequences may be. FMT is, perhaps, an irreversible interference in the microbiota and microbiome. We are not able to predict the effects of such a modification measured even between generations. Possible potential links between microbio-

ta transplantation and infections, autoimmune diseases and cancer are still unknown, but it appears from individual reports that they are not impossible.

Therefore, at this stage, in IBS, a disease, although chronic, without progressive, life-threatening complications, we should apply extreme caution when undertaking this type of experiment.

Due to the significant discrepancies between the study results, and unproved safety profile at this stage, we do not recommend FMT as a method of IBS treatment.

6.8. Treatment monitoring and assessment of response to treatment

Recommendation 18

Various widely available scales can be used to monitor the efficacy of IBS treatment, although the heterogeneity of scales in the available studies (IBS-GAI, IBS-SSS, GSRS, IBS-QOL, FBDSI) is noteworthy. Due to the objectification of the data obtained, we suggest using scales (they will be quoted in the supplement). **Recommendation: weak; quality of evidence: very low.**

Vote

A – 42.9%; B –42.9%; C – 0%; D – 14.3%; E – 0%.

Agreement level: high.

Discussion

The most difficult part of managing IBS patients is monitoring the efficacy of treatment. Since, as has been repeatedly emphasized, this is a chronic condition, which in itself has periods of exacerbation and remission of symptoms, patients will repeatedly come to consultations, each time reporting their symptoms in a different way. In the case of subjective assessment scales, the evaluation of efficacy is de facto left to the patient (this can change the assessment result in up to half of the cases). From the point of view of supervision and assessment of the efficacy of the procedure, it is worth introducing validated questionnaires to assess the increasing/decreasing severity of symptoms in this group of patients, which enables conclusions to be drawn and further recommendations to be made.

We suggest using the simplest, most widespread and, above all, widely available questionnaires proposed in Figures 2 and 3.

The proposed algorithm for the management of patients with diagnosed IBS is shown in Figure 4.

1) How strong is the pain today?

No pain Very severe

..... (result) × 1 = _____

2) Have you ever been diagnosed with a functional disorder (e.g. IBS)?

Yes = 1

No = 0

..... (result) × 106 = _____

3) How many times have you been to a doctor because of IBS symptoms in the last 6 months?

..... visits

..... (result) × 11 = _____

Please add up the number of points obtained in each answer. Interpretation: mild IBS: < 37 points, moderate IBS: 37–110 points, severe IBS: > 110 points.

Figure 2. Functional bowel disorder severity index (FBDSI)

How severe is your pain?

0 100

No pain | Not very severe | Quite severe | Severe | Very severe

If currently in pain, how severe is your pain?

0 100

No pain | Not very severe | Quite severe | Severe | Very severe

If you currently have abdominal distension, how severe is it?

0 100

No pain | Not very severe | Quite severe | Severe | Very severe

How satisfied are you with your bowel habits?

0 100

Very happy | Quite happy | Unhappy | Very unhappy

How much does your IBS affect your life in general?

0 100

Not at all | Not much | Quite a lot | Completely

The patient indicates the severity of the symptom on the scale (answer to the question). Then the results obtained are totalled. Interpretation: mild IBS: 75–174 points, moderate IBS: 175–299 points, severe IBS: ≥ 300 points. Improvement is demonstrated by a reduction in the severity of symptoms by a minimum of 50 points during the following assessment (performed depending on the doctor's recommendations, which results from the treatment).

Figure 3. IBS Symptoms Severity Score: IBS-SSS

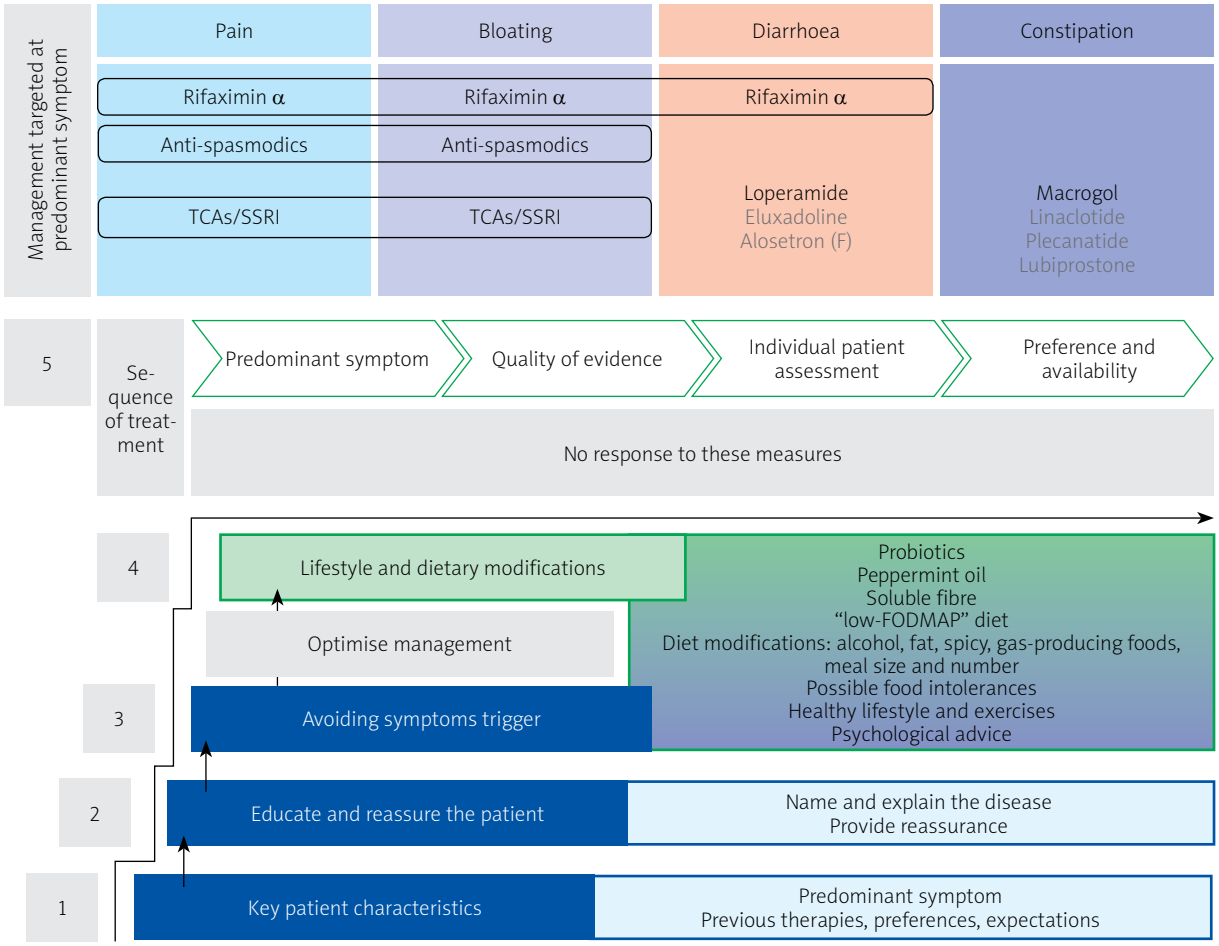

Figure 4. Proposed management algorithm for IBS. Step-up strategy (from the easiest modifications to combined pharmacotherapy)

TCAs – tricyclic antidepressants, SSRI – selective serotonin re-uptake inhibitors, F – females, medications listed in light grey – unavailable in Poland. First follow-up after 4–8 weeks, then every 3–6 months.

References

1. Bartnik W, Chojnacki J, Paradowski L, et al. Rekomendacje diagnostyczno-terapeutyczne w zespole jelita nadwrażliwego. Gastroenterol Klin 2009; 1: 9-17.
2. Brouwers M, Kho M, Browman G, et al.; the AGREE Next Steps Consortium. AGREE II: advancing guideline development, reporting and evaluation in healthcare. CMAJ 2010; 182: E839-42.
3. Guyatt G, Oxman A, Akl A, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary findings tables. J Clin Epidemiol 2011; 64: 383-94.
4. Dalkey N, Helmer O. An experimental application of the DELPHI method to the use of experts. Manag Sci 1963; 9: 458-67.
5. Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. Clin Epidemiol 2014; 7: 71-80.
6. Aziz I, Tornblom H, Palsson O, et al. How the change in IBS Criteria from Rome III to Rome IV impacts on clinical characteristics and key pathophysiological factors. Am J Gastroenterol 2018; Doi: 10.1038/s41395-018-0074-z [Epub ahead of print].
7. Gwee K, Ghoshal U, Chen M. Irritable bowel syndrome in Asia: pathogenesis, natural history, epidemiology and management. J Gastroenterol Hepatol 2018; 33: 99-110.
8. Canon M, Ruiz A, Rondon M, Alvarado J. Prevalence of irritable bowel syndrome and health related quality of life in adults aged 18 to 30 years in a Colombian University: an electronic survey. Ann Gastroenterol 2017; 30: 67-75.
9. Sperber A, Dumitrascu D, Fukudo S, et al. The global prevalence of IBS in adults remains elusive due to the heterogeneity of studies: a Rome Foundation working team literature review. Gut 2017; 66: 1075-82.
10. Palsson O, Whitehead W, vanTilburg M, et al. Development and validation of the Rome IV Diagnostic Questionnaire for adults. Gastroenterology 2016; 150: 1481-91.
11. Palsson O, vanTilburg M, Simren M, et al. Mo1642 population prevalence of Rome IV and Rome III irritable bowel syndrome (IBS) in the United States (US), Canada and the United Kingdom (UK). Gastroenterology 2016; 150 Suppl. 1: S739-40.

12. Vork L, Weerts Z, Mujagic J, et al. Rome III vs Rome IV criteria for irritable bowel syndrome: a comparison of clinical characteristics in a large cohort study. Neurogastroenterol Motil 2018; Doi: 10.1111/nmo.13189.
13. Saito YA. The role of genetics in IBS. Gastroenterol Clin North Am 2011; 40: 45-67.
14. Waehrens R, Zoller B, Sundguist J, et al. A Swedish national adoption study of risk of irritable bowel syndrome (IBS). BMJ Open Gastroenterol 2017; 214: e000156.
15. Gazouli M, Wouters M, Kapu-Pojskic L, et al. Lessons learned – resolving the enigma of genetic factors in IBS. Nat Rev Gastroenterol Hepatol 2016; 13: 77-87.
16. Wouters M, vanWanrooy S, Nguyen A, et al. Psychological comorbidity increases the risk for postinfectious IBS by enhanced susceptibility to develop infectious gastroenteritis. Gut 2016; 65: 1279-88.
17. Halvorson H, Schlett C, Riddle M. Postinfectious irritable bowel syndrome: a meta-analysis. Am J Gastroenterol 2006; 101: 1894-9.
18. Klem F, Wadhwa A, Prokop L, et al. Prevalence, risk factors and outcomes of irritable bowel syndrome after infectious enteritis: a systematic review and meta-analysis. Gastroenterology 2017; 152: 1042-54.
19. Wadhwa A, AlNahhas M, Dierkhishing R, et al. High risk of postinfectious irritable bowel syndrome in patients with Clostridium difficile infection. Alimentary Pharmacol Ther 2016; 44: 576-82.
20. Drossman D. Functional gastrointestinal disorders: history, pathophysiology, clinical features, and Rome IV. Gastroenterology 2016; 150: 1262-79.
21. Mayer E, Savidge T, Shulman R. Brain-gut microbiome interactions and functional bowel disorders. Gastroenterology 2014; 146: 1500-12.
22. El-Salhy M. Recent developments in the pathophysiology of irritable bowel syndrome. World J Gastroenterol 2015; 21: 7621-36.
23. Houghton L, Heitkemper M, Crowell M, et al. Age, gender, and women's health and the patient. Gastroenterology 2016; 150: 1332-43.
24. Crowell M. Role of serotonin in the pathophysiology of irritable bowel syndrome. Br J Pharmacol 2004; 141: 1285-93.
25. Ohman L, Isaksson S, Lindmark A, et al. T-cell activation in patients with irritable bowel syndrome. Am J Gastroenterol 2009; 104: 1205-12.
26. Liebregts T, Adam B, Bredack C, et al. Immune activation in patients with irritable bowel syndrome. Gastroenterology 2007; 132: 913-20.
27. Barbara G, Cremon C, De Giorgio R, et al. Mechanisms underlying visceral hypersensitivity in irritable bowel syndrome. Curr Gastroenterol Rep 2011; 13: 308-15.
28. Camilleri M, Lasch K, Zhou W. Irritable bowel syndrome: methods, mechanisms, and pathophysiology. The confluence of increased permeability, inflammation, and pain in irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol 2012; 303: G775-85.
29. Simrén M, Barbara G, Flint H, et al. Intestinal microbiota in functional bowel disorders: a Rome foundation report. Gut 2013; 62: 159-76.
30. Chen B, Kim J, Zhang Y, et al. Prevalence and predictors of small intestinal bacterial overgrowth in irritable bowel syndrome: a systematic review and meta-analysis. J Gastroenterol 2018; doi: 10.1007/s00535-018-1476-9.
31. Sachdeva S, Rawat A, Reddy R, Puri A. Small intestinal bacterial overgrowth (SIBO) and irritable bowel syndrome: frequency and predictors. J Gastroenterol Hepatol 2011; 26 (Suppl. 3): 135-8.
32. Barbara G, Feinle-Bisset C, Ghoshal U, et al. The intestinal microenvironment and functional gastrointestinal disorders. Gastroenterology 2016; 150: 1305-18.
33. Boeckxstaens G, Camilleri M, Sifrim D, et al. Fundamentals of neurogastroenterology: physiology/motility – sensation. Gastroenterology 2016; 150: 1292-304.
34. Slattery S, Niaz O, Aziz Q, et al. Systematic review with meta-analysis: the prevalence of bile acid malabsorption in the irritable bowel syndrome with diarrhoea. Aliment Pharmacol Ther 2015; 42: 3-11.
35. Tillisch K, Labus J. Advances in imaging the brain-gut axis: functional gastrointestinal disorders. Gastroenterology 2011; 140: 407-11.
36. Weaver K, Sherwin L, Walitt B, et al. Neuroimaging the brain-gut axis in patients with irritable bowel syndrome. World J Gastrointest Pharmacol Ther 2016; 7: 320-33.
37. Qin H, Cheng C, Tang X, Bian Z. Impact of psychological stress on irritable bowel syndrome. World J Gastroenterol 2014; 20: 14126-31.
38. Van Oudenhove L, Levy R, Crowell M, et al. Biopsychosocial aspects of functional gastrointestinal disorders: how central and environmental processes contribute to the development and expression of functional gastrointestinal disorders. Gastroenterology 2016; 150: 1355-67.
39. Halmos E, Power V, Shepherd S, et al. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. Gastroenterology 2014; 146: 67-75.
40. Tana C, Umesaki Y, Imaoka A, et al. Altered profiles of intestinal microbiota and organic acids may be the origin of symptoms in irritable bowel syndrome. Neurogastroenterol Motil 2010; 22: 512-9.
41. Mulak A, Paradowski L. Interakcje jelitowo-mózgowe – nowe aspekty patogenetyczne. Terapia 2017; 1: 8-12.
42. Biesiekierski J, Peters S, Newnham E, et al. No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates. Gastroenterology 2013; 145: 320-8.
43. Folks D. The interface of psychiatry and irritable bowel syndrome. Curr Psychiatry Rep 2004; 6: 210-5.
44. Lee C, Doo E, Choi J, et al. The increased level of depression and anxiety in irritable bowel syndrome patients compared with healthy controls: systematic review and meta-analysis. J Neurogastroenterol Motil 2017; 23: 349-62.
45. Lacy B, Mearin F, Chang L, et al. Bowel disorders. Gastroenterology 2016; 150: 1393-407.
46. Wu J, Chan A, Chan Y, et al. The current treatment landscape of irritable bowel syndrome in adults in Hong Kong: consensus statements. Hong Kong Med J 2017; 23: 641-7.
47. Vandvik P, Lydersen S, Farup P. Prevalence, comorbidity and impact of irritable bowel syndrome in Norway. Scand J Gastroenterol 2006; 41: 650-6.

48. Vandvik P, Wilhelmsen I, Ihlebaek C, et al. Comorbidity of irritable bowel syndrome in general practice: a striking feature with clinical implications. Aliment Pharmacol Ther 2004; 20: 1195-203.
49. Menees S, Kurlander J, Goel A, et al. Meta-analysis of the utility of common serum and fecal biomarkers in adults with IBS. Gastroenterology 2014; 146: S194.
50. Waugh N, Cummins E, Royle P, et al. Faecal calprotectin testing for differentiating amongst inflammatory and noninflammatory bowel diseases: systematic review and economic evaluation. Health Technol Assess 2013; 17: 1-211.
51. Moayyedi P, Mearin F, Azpiroz F, et al. Irritable bowel syndrome diagnosis and management: a simplified algorithm for clinical practice. Unit Eur Gastroenterol J 2017; 5: 773-88.
52. Song K, Jung H, Kim H, et al. Clinical practice guidelines for irritable bowel syndrome in Korea, 2017 Revised Edition. J Neurogastroenterol Motility 2018; 24: 197-215.
53. Black T, Manolakis C, Di Palma J. "Red flag" evaluation yield in irritable bowel syndrome. J Gastrointest Liver Dis 2012; 21: 153-6.
54. Robertson D, Kaminski M, Bretthauer M. Effectiveness, training and quality assurance of colonoscopy screening for colorectal cancer. Gut 2015; 64: 982-90.
55. Limsui D, Pardi D, Camilleri M, et al. Symptomatic overlap between irritable bowel syndrome and microscopic colitis. Inflamm Bowel Dis 2007; 13: 175-81.
56. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015–2020 Dietary Guidelines for Americans. 8th Edition. December 2015. Available at: http://health.gov/dietaryguidelines/2015/guidelines/.
57. Villoria A, Serra J, Azpiroz F, et al. Physical activity and intestinal gas clearance in patients with bloating. Am J Gastroenterol 2006; 101: 2552-7.
58. Daley AJ, Grimmett C, Roberts L, et al. The effects of exercise upon symptoms and quality of life in patients diagnosed with irritable bowel syndrome: a randomised controlled trial. Int J Sports Med 2008; 29: 778-82.
59. Johannesson E, Simren M, Strid H, et al. Physical activity improves symptoms in irritable bowel syndrome: a randomized controlled trial. Am J Gastroenterol 2011; 106: 915-22.
60. Johannesson E, Ringstrom G, Abrahamsson H, et al. Intervention to increase physical activity in irritable bowel syndrome shows long-term positive effects. World J Gastroenterol 2015; 21: 600-8.
61. Levy R, Linde J, Feld K, et al. The association of gastrointestinal symptoms with weight, diet and exercise in weight-loos program participants. Clin Gastroenterol Hepatol 2005; 10: 992-6.
62. Sadik R, Bjornson E, Simren M. The relationship between symptoms, body mass index, gastrointestinal transit and stool frequency in patients with irritable bowel syndrome. Eur J Gastroenterol Hepatol 2010; 22: 102-8.
63. Schneck AS, Anty R, Tran A, et al. Increased prevalence of irritable bowel syndrome in a cohort of french morbidly obese patients candidate for bariatric surgery. Obes Surg 2016; 26: 1525-30.
64. Aasbrenn M, Hogestol I, Eribe I, et al. Prevalence and predictors of irritable bowel syndrome in patients with morbid obesity: a cross-sectional study. BMC Obesity 2017; 4: 1-8.
65. Aasbrenn M, Lydersen S, Farup P. A conservative weight loss intervention relieves bowel symptoms in morbidly obese subjects with irritable bowel syndrome: a prospective cohort study. J Obes 2018; 2018: 3732753.
66. Maleki B, Tartibian B, Mooren F, et al. Low-to-moderate intensity aerobic exercise training modulates irritable bowel syndrome through antioxidative and inflammatory mechanisms in women: results of a randomized controlled trial. Cytokine 2018; 102: 18-25.
67. Zijdenbos I, de Wit N, van der Heijden G, et al. Psychological treatments for the management of irritable bowel syndrome. Cochrane Database Syst Rev 2009; 21: CD006442.
68. Ford AC, Quigley EM, Lacy BE, et al. Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: systematic review and meta-analysis. Am J Gastroenterol 2014; 109: 1350-65.
69. Laird K, Tanner-Smith E, Russell A, et al. Short-term and long-term efficacy of psychological therapies for irritable bowel syndrome: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2016; 14: 937-47.
70. Laird K, Tanner-Smith E, Russell A, et al. Comparative efficacy of psychological therapies for improving mental health and daily functioning in irritable bowel syndrome: a systematic review and meta-analysis. Clin Psychol Rev 2017; 51: 142-52.
71. Manheimer E, Wieland L, Cheng K, et al. Acupuncture for irritable bowel syndrome: systematic review and meta-analysis. Am J Gastroenterol 2012; 107: 835-48.
72. Schnabel L, Buscail C, Sabate J, et al. Association between ultra-processed food consumption and functional gastrointestinal disorders: results from the French NutriNet-Santé Cohort. Am J Gastroenterol 2018; 113: 1217-28.
73. Atkinson W, Sheldon TA, Shaath N, et al. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. Gut 2004; 53: 1459-64.
74. Ali A, Weiss TR, McKee D, et al. Efficacy of individualised diets in patients with irritable bowel syndrome: a randomised controlled trial. BMJ Open Gastroenterol 2017; 4: e000164.
75. Buscail C, Sabate J, Bouchoucha M, et al. Association between self-reported vegetarian diet and the irritable bowel syndrome in the French NutriNet cohort. PLoS One 2017; 12: e0183039.
76. Eswaran SL, Chey WD, Han-Markey T, et al. A randomized controlled trial comparing the low FODMAP diet vs. modified NICE guidelines in US adults with IBS-D. Am J Gastroenterol 2016; 111: 1824-32.
77. Bohn L, Storsrud S, Liljebo T, et al. Diet low in FODMAPs reduces symptoms of irritable bowel syndrome as well as traditional dietary advice: a randomized controlled trial. Gastroenterology 2015; 149: 1399-e2.
78. McIntosh K, Reed DE, Schneider T, et al. FODMAPs alter symptoms and the metabolome of patients with IBS: a randomised controlled trial. Gut 2017; 66: 1241-51.
79. Staudacher HM, Lomer MC, Anderson JL, et al. Fermentable carbohydrate restriction reduces luminal bifidobacteria and gastrointestinal symptoms in patients with irritable bowel syndrome. J Nutr 2012; 142: 1510-8.
80. Staudacher HM, Lomer MCE, Farquharson FM, et al. Diet low in FODMAPs reduces symptoms in patients with irritable

bowel syndrome and probiotic restores Bifidobacterium species: a randomized controlled trial. Gastroenterology 2017; 153: 936-47.
81. Hustoft TN, Hausken T, Ystad SO, et al. Effects of varying dietary content of fermentable short-chain carbohydrates on symptoms, fecal microenvironment, and cytokine profiles in patients with irritable bowel syndrome. Neurogastroenterol Motil 2017; 29: https://doi.org/10.1111/nmo.
82. Krogsgaard LR, Lyngesen M, Bytzer P. Systematic review: quality of trials on the symptomatic effects of the low FODMAP diet for irritable bowel syndrome. Aliment Pharmacol Ther 2017; 45: 1506-13.
83. Halmos EP, Christophersen CT, Bird AR, et al. Diets that differ in their FODMAP content alter the colonic luminal microenvironment. Gut 2015; 64: 93-100.
84. Bennet SMP, Bohn L, Storsrud S, et al. Multivariate modelling of faecal bacterial profiles of patients with IBS predicts responsiveness to a diet low in FODMAPs. Gut 2017; https://doi.org/10.1136/gutjnl-2016-313128.
85. Shepherd S, Parker F, Muir J, Gibson P. Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomized placebo-controlled evidence. Clin Gastroenterol Hepatol 2008; 6: 765-71.
86. Laatikainen R, Koskenpato J, Hongisto S, et al. Randomised clinical trial: low-FODMAP rye bread vs. regular rye bread to relieve the symptoms of irritable bowel syndrome. Aliment Pharmacol Ther 2016; 44: 460-70.
87. Shahbazkhani B, Sadeghi A, Malekzadeh R, et al. Non-celiac gluten sensitivity has narrowed the spectrum of irritable bowel syndrome: a double blind randomized placebo-controlled trial. Nutrients 2015; 7: 4542-54.
88. Soltoft J, Krag B, Gudmand-Hoyer E, et al. A double-blind trial of the effect of wheat bran on symptoms of irritable bowel syndrome. Lancet 1976; 307: 270-2.
89. Manning AP, Heaton KW, Harvey RF, et al. Wheat fibre and irritable bowel syndrome: a controlled trial. Lancet 1977; 310: 417-8.
90. Ritchie JA, Truelove SC. Treatment of irritable bowel syndrome with lorazepam, hyoscine butylbromide, and ispaghula husk. BMJ 1979; 278: 376-8.
91. Longstreth GF, Fox DD, Youkeles L, et al. Psyllium therapy in the irritable bowel syndrome: a double-blind trial. Ann Intern Med 1981; 95: 53-6.
92. Arthurs Y, Fielding JF. Double blind trial of ispaghula/poloxamer in the irritable bowel syndrome. Ir Med J 1983; 76: 253.
93. Nigam P, Kapoor KK, Rastog CK, et al. Different therapeutic regimens in irritable bowel syndrome. J Assoc Physicians India 1984; 32: 1041-4.
94. Kruis W, Weinzierl M, Schussler P, et al. Comparison of the therapeutic effects of wheat bran, mebeverine and placebo in patients with the irritable bowel syndrome. Digestion 1986; 34: 196-201.
95. Lucey MR, Clark ML, Lowndes JO, et al. Is bran efficacious in irritable bowel syndrome? A double blind placebo controlled crossover study. Gut 1987; 28: 221-5.
96. Prior A, Whorwell P. Double blind study of ispaghula in irritable bowel syndrome. Gut 1987; 28: 1510-3.
97. Jalihal A, Kurian G. Ispaghula therapy in irritable bowel syndrome: improvement in overall well-being is related to reduction in bowel dissatisfaction. J Gastroenterol Hepatol 1990; 5: 507-13.
98. Fowlie S, Eastwood MA, Prescott R. Irritable bowel syndrome: assessment of psychological disturbance and its influence on the response to fibre supplementation. J Psychosom Res 1992; 36: 175-80.
99. Rees G, Davies J, Thompson R, et al. Randomised-controlled trial of a fibre supplement on the symptoms of irritable bowel syndrome. J R Soc Health 2005; 125: 30-4.
100. Bijkerk CJ, de Wit NJ, Muris JW, et al. Soluble or insoluble fibre in irritable bowel syndrome in primary care? Randomised placebo controlled trial. BMJ 2009; 339: b3154.
101. Cockerell KM, Watkins AS, Reeves LB, et al. Effects of linseeds on the symptoms of irritable bowel syndrome: a pilot randomised controlled trial. J Hum Nutr Diet 2012; 25: 435-43.
102. Kamiya T, Shikano M, Tanaka M, et al. Therapeutic effects of biobran, modified arabinoxylan rice bran, in improving symptoms of diarrhea predominant or mixed type irritable bowel syndrome: a pilot, randomized controlled study. Evid Based Complement Altern Med 2014; 2014: 828137.
103. Cash BD, Epstein MS, Shah SM. A novel delivery system of peppermint oil is an effective therapy for irritable bowel syndrome symptoms. Dig Dis Sci 2016; 61: 560-71.
104. Mosaffa-Jahromi M, Lankarani KB, Pasalar M, et al. Efficacy and safety of enteric coated capsules of anise oil to treat irritable bowel syndrome. J Ethnopharmacol 2016; 194: 937-46.
105. Lech Y, Olesen KM, Hey H, et al. Treatment of irritable bowel syndrome with peppermint oil. A double-blind investigation with a placebo. Ugeskr Laege 1988; 150: 2388-9.
106. Liu JH, Chen GH, Yeh HZ, et al. Enteric-coated peppermint-oil capsules in the treatment of irritable bowel syndrome: a prospective, randomized trial. J Gastroenterol 1997; 32: 765-8.
107. Cappello G, Spezzaferro M, Grossi L, et al. Peppermint oil (Mintoil) in the treatment of irritable bowel syndrome: a prospective double blind placebo-controlled randomized trial. Dig Liver Dis 2007; 39: 530-6.
108. Capanni M, Surrenti E, Biagini M, et al. Efficacy of peppermint oil in the treatment of irritable bowel syndrome: a randomized, controlled trial. Gazz Med Ital 2005; 164: 119-26.
109. Merat S, Khalili S, Mostajabi P, et al. The effect of enteric-coated, delayed-release peppermint oil on irritable bowel syndrome. Dig Dis Sci 2010; 55: 1385-90.
110. Alam M, Roy P, Miah A, et al. Efficacy of Peppermint oil in diarrhea predominant IBS – a double blind randomized placebo-controlled study. Mymensingh Med J 2013; 22: 27-30.
111. Ottillinger B, Storr M, Malfertheiner P, Allescher HD. STW 5 (Iberogast®): a safe and effective standard in the treatment of functional gastrointestinal disorders. Wien Med Wochenschr 2013; 163: 65-72.
112. Wong B, Camilleri M, Eckert D, et al. Randomized pharmacodynamic and pharmacogenetic trial of dronabinol effects on colon transit in irritable bowel syndrome-diarrhea. Neurogastroenterol Motil 2012; 24: 358-e169.
113. Kabir MA, Ishaque SM, Ali MS, et al. Role of Saccharomyces boulardii in diarrhea predominant irritable bowel syndrome. Mymensingh Med J 2011; 20: 397-401.
114. Ko SJ, Han G, Kim SK, et al. Effect of Korean herbal medicine combined with a probiotic mixture on diarrhea-dominant ir-

ritable bowel syndrome: a double-blind, randomized, placebo-controlled trial. Evid Based Complement Altern Med 2013; 2013: 824605.
115. Stevenson C, Blaauw R, Fredericks E, et al. Randomized clinical trial: effect of Lactobacillus plantarum 299 v on symptoms of irritable bowel syndrome. Nutrition 2014; 30: 1151-7.
116. Sisson G, Ayis S, Sherwood RA, et al. Randomised clinical trial: a liquid multi-strain probiotic vs. placebo in the irritable bowel syndrome – a 12 week double-blind study. Aliment Pharmacol Ther 2014; 40: 51-62.
117. Jafari E, Vahedi H, Merat S, et al. Therapeutic effects, tolerability and safety of a multi-strain probiotic in Iranian adults with irritable bowel syndrome and bloating. Arch Iran Med 2014; 17: 466-70.
118. Ludidi S, Jonkers DM, Koning CJ, et al. Randomized clinical trial on the effect of a multispecies probiotic on visceroperception in hypersensitive IBS patients. Neurogastroenterol Motil 2014; 26: 705-14.
119. Yoon JS, Sohn W, Lee OY, et al. Effect of multispecies probiotics on irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. J Gastroenterol Hepatol 2014; 29: 52-9.
120. Abbas Z, Yakoob J, Jafri W, et al. Cytokine and clinical response to Saccharomyces boulardii therapy in diarrhea-dominant irritable bowel syndrome: a randomized trial. Eur J Gastroenterol Hepatol 2014; 26: 630-9.
121. Lorenzo-Zuniga V, Llop E, Suarez C, et al. I.31, a new combination of probiotics, improves irritable bowel syndrome-related quality of life. World J Gastroenterol 2014; 20: 8709-16.
122. Pineton de Chambrun G, Neut C, Chau A, et al. A randomized clinical trial of Saccharomyces cerevisiae versus placebo in the irritable bowel syndrome. Dig Liver Dis 2015; 47: 119-24.
123. Wong RK, Yang C, Song GH, et al. Melatonin regulation as a possible mechanism for probiotic (VSL#3) in irritable bowel syndrome: a randomized double-blinded placebo study. Dig Dis Sci 2015; 60: 186-94.
124. Yoon H, Park YS, Lee DH, et al. Effect of administering a multispecies probiotic mixture on the changes in fecal microbiota and symptoms of irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. J Clin Biochem Nutr 2015; 57: 129-34.
125. Thijssen AY, Clemens CH, Vankerckhoven V, et al. Efficacy of Lactobacillus casei Shirota for patients with irritable bowel syndrome. Eur J Gastroenterol Hepatol 2016; 28: 8-14.
126. Spiller R, Pelerin F, Cayzeele Decherf A, et al. Randomized double blind placebo-controlled trial of Saccharomyces cerevisiae CNCM I-3856 in irritable bowel syndrome: improvement in abdominal pain and bloating in those with predominant constipation. U Eur Gastroenterol J 2016; 4: 353-62.
127. Hod K, Sperber AD, Ron Y, et al. A double-blind, placebo-controlled study to assess the effect of a probiotic mixture on symptoms and inflammatory markers in women with diarrhea-predominant IBS. Neurogastroenterol Motil 2017; 29 https://doi.org/10.1111/nmo.
128. Pinto-Sanchez MI, Hall GB, Ghajar K, et al. Probiotic Bifidobacterium longum NCC3001 reduces depression scores and alters brain activity: a pilot study in patients with irritable bowel syndrome. Gastroenterology 2017; 153: 448-59.
129. Lyra A, Hillila M, Huttunen T, et al. Irritable bowel syndrome symptom severity improves equally with probiotic and placebo. World J Gastroenterol 2016; 22: 10631-42.
130. Gade J, Thorn P. Paraghurt for patients with irritable bowel syndrome. Scand J Prim Health Care 1989; 7: 23-6.
131. Nobaek S, Johansson ML, Molin G, et al. Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. Am J Gastroenterol 2000; 95: 1231-8.
132. Niedzielin K, Kordecki H, Birkenfeld B. A controlled, double blind, randomized study on the efficacy of Lactobacillus plantarum 299V in patients with irritable bowel syndrome. Eur J Gastroenterol Hepatol 2001; 13: 1143-7.
133. Kim HJ, Camilleri M, McKinzie S, et al. A randomized controlled trial of a probiotic, VSL#3, on gut transit and symptoms in diarrhea-predominant irritable bowel syndrome. Aliment Pharmacol Ther 2003; 17: 895-904.
134. Kajander K, Hatakka K, Poussa T, et al. A probiotic mixture alleviates symptoms in irritable bowel syndrome patients: a controlled 6-month intervention. Aliment Pharmacol Ther 2005; 22: 387-94.
135. Kim HJ, Vazquez Roque MI, Camilleri M, et al. A randomized controlled trial of a probiotic combination VSL#3 and placebo in irritable bowel syndrome with bloating. Neurogastroenterol Motil 2005; 17: 687-96.
136. Niv E, Naftali T, Hallak R, et al. The efficacy of Lactobacillus reuteri ATCC 55730 in the treatment of patients with irritable bowel syndrome – a double blind, placebo-controlled, randomized study. Clin Nutr 2005; 24: 925-31.
137. O'Mahony L, McCarthy J, Kelly P, et al. Lactobacillus and Bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. Gastroenterology 2005; 128: 541-51.
138. Kim YG, Moon JT, Lee KM, et al. The effects of probiotics on symptoms of irritable bowel syndrome. Korean J Gastroenterol 2006; 47: 413-9.
139. Simren M, Syrous A, Lindh A, et al. Effects of Lactobacillus Plantarum 299V on symptoms and rectal sensitivity in patients with irritable bowel syndrome (IBS) – a randomized double blind controlled trial. Gastroenterology 2006; 130: A600.
140. Whorwell PJ, Altringer L, Morel J, et al. Efficacy of an encapsulated probiotic Bifidobacterium infantis 35624 in women with irritable bowel syndrome. Am J Gastroenterol 2006; 101: 1581-90.
141. Guyonnet D, Chassany O, Ducrotte P, et al. Effect of a fermented milk containing Bifidobacterium animalis DN-173 010 on the health-related quality of life and symptoms in irritable bowel syndrome in adults in primary care: a multicentre, randomized, double blind, controlled trial. Aliment Pharmacol Ther 2007; 26: 475-86.
142. Drouault-Holowacz S, Bieuvelet S, Burckel A, et al. A double blind randomized controlled trial of a probiotic combination in 100 patients with irritable bowel syndrome. Gastroenterol Clin Biol 2008; 32: 147-52.
143. Enck P, Zimmerman K, Menke G, et al. A mixture of Escherichia coli (DSM 17252) and Enterococcus faecalis (DSM 16440) for treatment of the irritable bowel syndrome – a ran-

domized controlled trial with primary care physicians. Neurogastroenterol Motil 2008; 20: 1103-9.
144. Kajander K, Myllyluoma E, Rajilic-Stojanovic M, et al. Clinical trial: multispecies probiotic supplementation alleviates the symptoms of irritable bowel syndrome and stabilizes intestinal microbiota. Aliment Pharmacol Ther 2008; 27: 48-57.
145. Sinn DH, Song JH, Kim HJ, et al. Therapeutic effect of Lactobacillus acidophilus -SDC 2012, 2013 in patients with irritable bowel syndrome. Dig Dis Sci 2008; 53: 2714-8.
146. Zeng J, Li YQ, Zuo XL, et al. Clinical trial: effect of active lactic acid bacteria on mucosal barrier function in patients with diarrhea predominant irritable bowel syndrome. Aliment Pharmacol Ther 2008; 28: 994-1002.
147. Agrawal A, Houghton LA, Morris J, et al. Clinical trial: the effects of a fermented milk product containing Bifidobacterium lactis DN-173 010 on abdominal distension and gastrointestinal transit in irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2009; 29: 104-14.
148. Enck P, Zimmerman K, Menke G, et al. Randomized controlled treatment trial of irritable bowel syndrome with a probiotic E. coli preparation (DSM17252) compared to placebo. Z Gastroenterol 2009; 47: 209-14.
149. Hong KS, Kang HW, Im JP, et al. Effect of probiotics on symptoms in Korean adults with irritable bowel syndrome. Gut Liver 2009; 3: 101-7.
150. Williams EA, Stimpson J, Wang D, et al. Clinical trial: a multistrain probiotic preparation significantly reduces symptoms of irritable bowel syndrome in a double-blind placebo-controlled study. Aliment Pharmacol Ther 2009; 29: 97-103.
151. Simren M, Ohman L, Olsson J, et al. Clinical trial: the effects of a fermented milk containing three probiotic bacteria in patients with irritable bowel syndrome – a randomized, double-blind, controlled study. Aliment Pharmacol Ther 2010; 31: 218-27.
152. Choi CH, Jo SY, Park HJ, et al. A randomized, double-blind, placebo-controlled multicenter trial of Saccharomyces boulardii in irritable bowel syndrome: Effect on quality of life. J Clin Gastroenterol 2011; 45: 679-83.
153. Guglielmetti S, Mora D, Gschwender M, et al. Randomised clinical trial: Bifidobacterium bifidum MIMBb75 significantly alleviates irritable bowel syndrome and improves quality of life – a double-blind, placebo controlled study. Aliment Pharmacol Ther 2011; 33: 1123-32.
154. Michail S, Kenche H. Gut microbiota is not modified by randomized, double-blind, placebo-controlled trial of VSL#3 in diarrhea predominant irritable bowel syndrome. Probiotics Antimicrob Proteins 2011; 3: 1-7.
155. Ringel-Kulka T, Palsson OS, Maier D, et al. Probiotic bacteria Lactobacillus acidophilus NCFM and Bifidobacterium lactis Bi-07 versus placebo for the symptoms of bloating in patients with functional bowel disorders: a double-blind study. J Clin Gastroenterol 2011; 45: 518-25.
156. Sondergaard B, Olsson J, Ohlson K, et al. Effects of probiotic fermented milk on symptoms and intestinal flora in patients with irritable bowel syndrome: a randomized, placebo-controlled trial. Scand J Gastroenterol 2011; 46: 663-72.
157. Cha BK, Jung SM, Choi CH, et al. The effect of a multispecies probiotic mixture on the symptoms and fecal microbiota in diarrhea-dominant irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. J Clin Gastroenterol 2012; 46: 220-7.
158. Cui S, Hu Y. Multistrain probiotic preparation significantly reduces symptoms of irritable bowel syndrome in a double-blind placebo-controlled study. Int J Clin Exp Med 2012; 5: 238-44.
159. Dapoigny M, Piche T, Ducrotte P, et al. Efficacy and safety profile of LCR35 complete freeze-dried culture in irritable bowel syndrome: a randomized, double-blind study. World J Gastroenterol 2012; 18: 2067-75.
160. Ducrotte P, Sawant P, Jayanthi V. Clinical trial: Lactobacillus plantarum 299v (DSM 9843) improves symptoms of irritable bowel syndrome. World J Gastroenterol 2012; 18: 4012-8.
161. Farup PG, Jacobsen M, Ligaarden SC, et al. Probiotics, symptoms, and gut microbiota: What are the relations? A randomized controlled trial in subjects with irritable bowel syndrome. Gastroenterol Res Pract 2012; 2012: 214102.
162. Kruis W, Chrubasik S, Boehm S, et al. A double-blind placebo-controlled trial to study therapeutic effects of probiotic Escherichia coli Nissle 1917 in subgroups of patients with irritable bowel syndrome. Int J Colorectal Dis 2012; 27: 467-74.
163. Begtrup LM, de Muckadell OB, Kjeldsen J, et al. Long-term treatment with probiotics in primary care patients with irritable bowel syndrome – a randomised, double-blind, placebo controlled trial. Scand J Gastroenterol 2013; 48: 1127-35.
164. Roberts LM, McCahon D, Holder R, et al. A randomised controlled trial of a probiotic 'functional food' in the management of irritable bowel syndrome. BMC Gastroenterol 2013; 13: 45.
165. Rai RR, Dwivedi M, Kumar N. Efficacy and safety of drotaverine hydrochloride in irritable bowel syndrome: a randomized double-blind placebo-controlled study. Saudi J Gastroenterol 2014; 20: 378-82.
166. Zheng L, Lai Y, Lu W, et al. Pinaverium reduces symptoms of irritable bowel syndrome in a multi-center, randomized controlled trial. Clin Gastroenterol Hepatol 2015; 13: 1285-92.
167. Misra SC, Pandey RM. Efficacy of drotaverine in irritable bowel syndrome: a double blind, randomized, placebo-controlled clinical trial. Am J Gastroenterol 2000; 95: 2544.
168. Schafer VE, Ewe K. The treatment of irritable colon. Efficacy and tolerance of buscopan plus, buscopan, paracetamol and placebo in ambulatory patients with irritable colon. Fortschr Med 1990; 108: 488-92.
169. Centonze V, Imbibo BP, Campanozzi F, et al. Oral cimetropium bromide, a new antimuscarinic drug, for long-term treatment of irritable bowel syndrome. Am J Gastroenterol 1988; 83: 1262-6.
170. Dobrilla G, Imbibo BP, Piazzi L, et al. Long term treatment of irritable bowel syndrome with cimetropium bromide: a double blind placebo controlled clinical trial. Gut 1990; 31: 355-8.
171. Passaretti S, Guslandi M, Imbibo BP, et al. Effects of cimetropium bromide on gastrointestinal transit time in patients with irritable bowel syndrome. Aliment Pharmacol Ther 1989; 3: 267-76.
172. Levy C, Charbonnier A, Cachin M. Pinaverium bromide and functional colonic disease (double-blind study). Sem Hop Ther 1977; 53: 372-4.

173. Virat J, Hueber D. Colopathy pain and dicetel. Prat Med 1987; 43: 32-4.
174. Fielding JF. Double blind trial of trimebutine in the irritable bowel syndrome. Ir Med J 1980; 73: 377-9.
175. Ghidini O, Saponati G, Intrieri L. Single drug treatment for irritable colon: rociverine versus trimebutine maleate. Curr Ther Res Clin Exp 1986; 39: 541-8.
176. Moshal MG, Herron M. A clinical trial of trimebutine (Mebutin) in spastic colon. J Int Med Res 1979; 7: 231-4.
177. Glende M, Morselli-Labate AM, Battaglia G, et al. Extended analysis of a double blind, placebo-controlled, 15-week study with otilinium bromide in irritable bowel syndrome. Eur J Gastroenterol Hepatol 2002; 14: 1331-8.
178. Gilvarry J, Kenny A, Fielding JF. The non-effect of pirenzipine in dietary resistant irritable bowel syndrome. Ir J Med Sci 1989; 158: 262.
179. Mitchell SA, Mee AS, Smith GD, et al. Alverine citrate fails to relieve the symptoms of irritable bowel syndrome: results of a double-blind, randomized, placebo-controlled trial. Aliment Pharmacol Ther 2002; 16: 1187-95.
180. Piai G, Mazzacca G. Prifinium bromide in the treatment of the irritable colon syndrome. Gastroenterology 1979; 77: 500-2.
181. Page JG, Dirnberger GM. Treatment of the irritable bowel syndrome with Bentyl (dicyclomine hydrochloride). J Clin Gastroenterol 1981; 3: 153-6.
182. Baldi F, Corinaldesi R, Ferrarini F, et al. Clinical and functional evaluation of octilonium bromide in the treatment of irritable bowel syndrome: a double-blind controlled trial. Clin Trials J 1983; 20: 77-88.
183. Castiglione F, Daniele B, Mazzacca G. Therapeutic strategy for the irritable bowel syndrome. Ital J Gastroenterol 1991; 23: 53-5.
184. Clave P, Acalovschi M, Triantafillidis JK, et al. Randomised clinical trial: otilonium bromide improves frequency of abdominal pain, severity of distention and time to relapse in patients with irritable bowel syndrome. Aliment Pharmacol Ther 2011; 34: 432-42.
185. Hou X, Chen S, Zhang Y, et al. Quality of life in patients with irritable bowel syndrome assessed using IBS-QoL measure after 4 and 8 weeks of treatment with mebeverine hydrochloride or pinaverinum bromide: results of an international prospective observational cohort study in Poland, Egypt, Mexico and China. Clin Drug Investig 2014; 34: 783-93.
186. Agger JL, Schroder A, Gormsen LK, et al. Imipramine versus placebo for multiple functional somatic syndromes (STreSS-3): a double-blind, randomised study. Lancet Psychiatry 2017; 4: 378-88.
187. Myren J, Groth H, Larssen SE, et al. The effect of trimipramine in patients with the irritable bowel syndrome: a double-blind study. Scand J Gastroenterol 1982; 17: 871-5.
188. Vij JC, Jiloha RC, Kumar N, et al. Effect of antidepressant drug (doxepin) on irritable bowel syndrome patients. Indian J Psychiatry 1991; 33: 243-6.
189. Drossman DA, Toner BB, Whitehead WE, et al. Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders. Gastroenterology 2003; 125: 19-31.
190. Kuiken SD, Tytgat GNJ, Boeckxstaens GEE. The selective serotonin reuptake inhibitor fluoxetine does not change rectal sensitivity and symptoms in patients with irritable bowel syndrome: a double-blind, randomized, placebo-controlled study. Clin Gastroenterol Hepatol 2003; 1: 219-28.
191. Tabas G, Beaves M, Wang J, et al. Paroxetine to treat irritable bowel syndrome not responding to high fiber diet: a double-blind placebo controlled trial. Am J Gastroenterol 2004; 99: 914-20.
192. Vahedi H, Merat S, Momtahen S, et al. Clinical trial: the effect of amitriptyline in patients with diarrhea-predominant irritable bowel syndrome. Aliment Pharmacol Ther 2008; 27: 678-84.
193. Vahedi H, Merat S, Rashidioon A, et al. The effect of fluoxetine in patients with pain and constipation-predominant irritable bowel syndrome: a double-blind randomized-controlled study. Aliment Pharmacol Ther 2005; 22: 381-5.
194. Tack J, Broekaert D, Fischler B, et al. A controlled crossover study of the selective serotonin reuptake inhibitor citalopram in irritable bowel syndrome. Gut 2006; 55: 1095-103.
195. Talley NJ, Kellow JE, Boyce P, et al. Antidepressant therapy (imipramine and citalopram) for irritable bowel syndrome: a double-blind, randomized, placebo-controlled trial. Dig Dis Sci 2008; 53: 108-15.
196. Abdul-Baki H, El Hajj II, ElZahabi L, et al. A randomized controlled trial of imipramine in patients with irritable bowel syndrome. World J Gastroenterol 2009; 15: 3636-42.
197. Masand PS, Pae CU, Krulewicz S, et al. A double-blind, randomized, placebo-controlled trial of paroxetine controlled-release in irritable bowel syndrome. Psychosomatics 2009; 50: 78-86.
198. Ladabaum U, Sharabidze A, Levin TR, et al. Citalopram is not effective therapy for nondepressed patients with irritable bowel syndrome. Clin Gastroenterol Hepatol 2010; 8: 42-8.
199. Ghadir MR, Habibinejad H, Heidari A, et al. Doxepin is more effective than nortriptyline and placebo for the treatment of diarrhea-predominant irritable bowel syndrome: a randomized triple-blind placebo-controlled trial. Tehran Univ Med J 2011; 69: 352-8.
200. Sharara A, Aoun E, Abdul-Baki H, et al. A randomized double blind placebo controlled trial of rifaximin in patients with abdominal bloating and flatulence. Am J Gastroenterol 2006; 101: 326-33.
201. Heefner JD, Wilder RM, Wilson ID. Irritable colon and depression. Psychosomatics 1978; 19: 540-7.
202. Pimentel M, Park S, Mirocha J, et al. The effect of a nonabsorbed oral antibiotic (rifaximin) on the symptoms of the irritable bowel syndrome: a randomized trial. Ann Intern Med 2006; 145: 557-63.
203. Lembo A, Ferreira S, Ringel N, et al. Rifaximin for the treatment of diarrhea-associated irritable bowel syndrome: short term treatment leading to long term sustained response. Gastroenterology 2008; 134: P-255 (T1390).
204. Pimentel M, Lembo A, Chey W, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med 2011; 363: 22-32.
205. Lembo A, Pimentel M, Rao S, et al. Repeat treatment with rifaximin is safe and effective in patients with diarrhea-predominant irritable bowel syndrome. Gastroenterology 2016; 151: 1113-21.

206. Menees S, Maneerattannaporn M, Kim H, Chey W. The efficacy and safety of rifaximin for irritable bowel syndrome: a systematic review and meta-analysis. Am J Gastroenterol 2012; 107: 28-35.
207. Bianchi M, Festa V, Moretti A, et al. Meta-analysis: long-term therapy with rifaximin in the management of uncomplicated diverticular disease. Aliment Pharmacol Ther 2011; 33: 902-10.
208. Chen B, Kim J, Zhang Y, Du L. Prevalence and predictors of small intestinal bacterial overgrowth in irritable bowel syndrome: a systematic review and meta-analysis. J Gastroenterol 2018; 53: 807-18.
209. Schoenfeld P, Pimentel M, Chang L, et al. Safety and tolerability of rifaximin for the treatment of irritable bowel syndrome without constipation: a pooled analysis of randomised, double-blind, placebo-controlled trials. Aliment Pharmacol Ther 2014; 39: 1161-8.
210. Acosta A, Camilleri M, Shin A, et al. Effects of rifaximin on transit, permeability, fecal microbiome, and organic acid excretion in irritable bowel syndrome. Clin Transl Gastroenterol 2016; 7: e173.
211. Bruzzese E, Pesce M, Sarelli G, Guarino A. Pharmacokinetic drug evaluation of rifaximin for treatment of diarrhea-predominant irritable bowel syndrome. Expert Opin Drug Metab Toxicol 2018; 14: 753-60.
212. Chapman RW, Stanghellini V, Geraint M, et al. Randomized clinical trial: Macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. Am J Gastroenterol 2013; 108: 1508-15.
213. Awad RA, Camacho S. A randomized, double-blind, placebo-controlled trial of polyethylene glycol effects on fasting and postprandial rectal sensitivity and symptoms in hypersensitive constipation-predominant irritable bowel syndrome. Colorectal Dis 2010; 12: 1131-8.
214. Bellini M, Usai-Satta P, Bove A, et al. Chronic constipation diagnosis and treatment evaluation: the "CHRO.CO.DI.T.E." study. BMC Gastroenterol 2017; 17: 11.
215. Hovdenak N. Loperamide treatment of the irritable bowel syndrome. Scand J Gastroenterol 1987; 130: 81-4.
216. Lavo B, Stenstam M, Nielsen AL. Loperamide in treatment of irritable bowel syndrome – a double-blind placebo controlled study. Scand J Gastroenterol 1987; 130: 77-80.
217. Efskind PS, Bernklev T, Vatn MH. A double-blind placebo-controlled trial with loperamide in irritable bowel syndrome. Scand J Gastroenterol 1996; 31: 463-8.
218. Yang Y, Fang JY, Guo X, et al. Efficacy and safety of linaclotide in patients with IBS-C: results from a phase 3, randomized, double-blind, placebo-controlled trial in China and other regions. Gastroenterology 2016; 150: S741.
219. Johnston JM, Kurtz CB, MacDougall JE, et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome and constipation. Gastroenterology 2010; 139: 1877-86.
220. Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. Am J Gastroenterol 2012; 107: 1702-12.
221. Rao S, Lembo AJ, Shiff SJ, et al. 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. Am J Gastroenterol 2012; 107: 1714-24.
222. Brenner DM, Fogel R, Dorn SD, et al. Efficacy, safety, and tolerability of plecanatide in patients with irritable bowel syndrome with constipation: results of two phase 3 randomized clinical trials. Am J Gastroenterol 2018; 113: 735-45.
223. Miner P, De Luca R, La Portilla M, et al. Plecanatide, a novel urogunaylin analog: a 12-week randomized, double-blind, placebo-controlled, dose ranging trial to evaluate efficacy and safety in patients with irritable bowel syndrome with constipation (IBS-C). Am J Gastroenterol 2014; 109: S541.
224. Drossman DA, Chey WD, Johanson JF, et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome – results of two randomized, placebo-controlled studies. Aliment Pharmacol Ther 2009; 29: 329-41.
225. Johanson JF, Drossman DA, Panas R, et al. Clinical trial: phase 2 study of lubiprostone for irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2008; 27: 685-96.
226. Cryer B, Drossman DA, Chey WD, et al. Analysis of nausea in clinical studies of lubiprostone for the treatment of constipation disorders. Dig Dis Sci 2017; 62: 3568-78.
227. Fukudo S, Hongo M, Kaneko H, Ueno R. Efficacy and safety of oral lubiprostone in constipated patients with or without irritable bowel syndrome: a randomized, placebo-controlled and dose-finding study. Neurogastroenterol Motil 2011; 23: 544-e205.
228. Chang L, Chey W, Drossman D, et al. Effects of baseline abdominal pain and bloating on response to lubiprostone in patients with irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2016; 44: 1114-22.
229. Miller DP, Alfredson T, Cook SF, et al. Incidence of colonic ischemia, hospitalized complications of constipation, and bowel surgery in relation to use of alosetron hydrochloride. Am J Gastroenterol 2003; 98: 1117-22.
230. Camilleri M, Mayer EA, Drossman DA, et al. Improvement in pain and bowel function in female irritable bowel patients with alosetron, a 5-HT 3 receptor antagonist. Aliment Pharmacol Ther 1999; 13: 1149-59.
231. Camilleri M, Northcutt AR, Kong S, et al. Efficacy and safety of alosetron in women with irritable bowel syndrome: a randomised, placebo-controlled trial. Lancet 2000; 355: 1035-40.
232. Camilleri M, Chey WY, Mayer EA, et al. A randomized controlled clinical trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant irritable bowel syndrome. Arch Intern Med 2001; 161: 1733-40.
233. Bardhan KD, Bodemar G, Geldof H, et al. A double-blind, randomized, placebo-controlled dose-ranging study to evaluate the efficacy of alosetron in the treatment of irritable bowel syndrome. Aliment Pharmacol Ther 2000; 14: 23-34.
234. Lembo T, Wright RA, Lotronex Investigator T, et al. Alosetron controls bowel urgency and provides global symptom improvement in women with diarrhea-predominant irritable bowel syndrome. Am J Gastroenterol 2001; 96: 2662-70.
235. Chey WD, Chey WY, Heath AT, et al. Long-term safety and efficacy of alosetron in women with severe diarrhea-predominant irritable bowel syndrome. Am J Gastroenterol 2004; 99: 2195-203.

236. Chang L, Ameen VZ, Dukes GE, et al. A dose-ranging, phase II study of the efficacy and safety of alosetron in men with diarrhea-predominant IBS. Am J Gastroenterol 2005; 100: 115-23.
237. Lembo AJ, Lacy BE, Zuckerman MJ, et al. Eluxadoline for irritable bowel syndrome with diarrhea. N Engl J Med 2016; 374: 242-53.
238. Dove LS, Lembo A, Randall CW, et al. Eluxadoline benefits patients with irritable bowel syndrome with diarrhea in a phase 2 study. Gastroenterology 2013; 145: 329-38.e1.
239. Barbara G, Cremon C, Annese V, et al. Randomised controlled trial of mesalazine in IBS. Gut 2016; 65: 82-90.
240. Lam C, Tan W, Leighton M, et al. A mechanistic multicentre, parallel group, randomised placebo-controlled trial of mesalazine for the treatment of IBS with diarrhoea (IBS-D). Gut 2016; 65: 91-9.
241. Aron J, Lin M, Yu J, et al. Mesalamine granules 1500 mg once daily for 12 weeks provides adequate relief of IBS symptoms in irritable bowel syndrome with diarrhea: results from a phase 2 trial. Am J Gastroenterol 2012; 107: S711-2.
242. Halkjær S, Christensen A, Lo B, et al. Faecal microbiota transplantation alters gut microbiota in patients with irritable bowel syndrome: results from a randomised, double-blind placebo-controlled study. Gut 2018 Jul 6. pii: gutjnl-2018-316434. doi: 10.1136/gutjnl-2018-316434.
243. Johnsen P, Hilpüsch F, Cavanagh J, et al. Faecal microbiota transplantation versus placebo for moderate-to-severe irritable bowel syndrome: a double-blind, randomised, placebo-controlled, parallel-group, single-centre trial. Lancet Gastroenterol Hepatol 2018; 3: 17-24.
244. Miller LE. Study design considerations for irritable bowel syndrome clinical trials. Ann Gastroenterol 2014; 27: 338-45.

Received: 1.09.2018
Accepted: 9.09.2018