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Irritable bowel syndrome – diagnostic and therapeutic recommendations considering the place of antispasmodics

Zespół jelita nadwrażliwego – rekomendacje diagnostyczno-terapeutyczne, miejsce leków rozkurczowych

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Abstract

Irritable bowel syndrome is a common and recurrent disease occurring at all geographical latitudes. The prevalence in the northern hemisphere is estimated at 11%, with more women affected than men (2:1). The symptoms usually develop in the third or fourth decade of life. The aetiology of the disease is complex and not fully explained. Genetic factors, gastrointestinal motor dysfunction, visceral hypersensitivity, psychological stress and intestinal infections are believed to contribute to the etiopathogenesis. Irritable bowel syndrome reduces life quality and work productivity as well as is a considerable financial burden for both health care system and patients themselves. Despite its arduous course, it does not lead to the development of a serious disease with excessive mortality. Irritable bowel syndrome is characterised by recurrent abdominal pain related to defecation, change in bowel habits and/or stool consistency. The diagnosis of irritable bowel syndrome is currently based on the Rome IV diagnostic criteria published in 2016. These criteria are the latest update of the diagnostic criteria for gastrointestinal functional disorders now defined as disorders of gut–brain interaction. Irritable bowel syndrome is currently defined as abdominal pain that has occurred on average at least 1 day per week during the previous 3 months, which meets at least 2 of 3 criteria: 1) is related to bowel movement, 2) is related to a change in stool frequency, 3) is related to a change in stool consistency. The paper presents the main changes introduced in the Rome IV criteria, their rationale and implications for clinical practice.

Keywords: irritable bowel syndrome, diagnosis, Rome IV criteria, treatment, adults

Streszczenie

Zespół jelita nadwrażliwego to częsta i nawracająca choroba, która występuje na wszystkich szerokościach geograficznych. Na półkuli północnej chorobowość jest oceniana na około 11%, z liczbową przewagą kobiet nad mężczyznami (2:1). Objawy zespołu rozwijają się najczęściej w trzeciej lub czwartej dekadzie życia. Przyczyna choroby jest złożona i nie do końca wyjaśniona. Wśród czynników etiopatogenetycznych wymienia się czynniki genetyczne, zaburzenia motoryki przewodu pokarmowego, nadwrażliwość trzewną, stres psychologiczny oraz zakażenia jelitowe. Zespół jelita nadwrażliwego obniża jakość życia, utrudnia pracę zawodową i generuje duże wydatki z funduszy przeznaczonych na ochronę zdrowia; stanowi też poważne obciążenie finansowe dla samych pacjentów. Mimo uciążliwego przebiegu nie prowadzi jednak do rozwoju poważnej choroby z nadmierną umieralnością. Jest to zespół chorobowy przebiegający z nawracającymi bólami brzucha związanymi z defekacją, zmianą rytmu wypróżnień i/lub zmianą konsystencji stolca. Aktualnie rozpoznanie zespołu jelita nadwrażliwego powinno się opierać na Kryteriach Rzymskich IV, opublikowanych w maju 2016 roku. Stanowią one najnowszą aktualizację kryteriów diagnostycznych zaburzeń czynnościowych układu pokarmowego, określanych zgodnie z nową definicją jako zaburzenia interakcji jelitowo-mózgowych. Obecnie zespół jelita nadwrażliwego definiuje się jako ból brzucha występujący średnio przez co najmniej 1 dzień w tygodniu przez ostatnie 3 miesiące, który spełnia co najmniej 2 z 3 kryteriów – jest związany z: 1) defekacją, 2) zmianą częstości wypróżnień, 3) zmianą konsystencji stolca. W pracy przedstawiono ważniejsze zmiany wprowadzone w Kryteriach Rzymskich IV wraz z uzasadnieniem i omówiono znaczenie nowych kryteriów w praktyce klinicznej.

Słowa kluczowe: zespół jelita drażliwego, rozpoznawanie, Kryteria Rzymskie IV, leczenie, dorośli

BACKGROUND AND EPIDEMIOLOGY

Irritable bowel syndrome (IBS) is a disease occurring at all geographical latitudes. The disease affects 11% of the population globally[1]. It is diagnosed twice as often in women than in men, considering the Manning criteria (1978), the Rome I criteria (1978), the Rome II criteria (1999) and the Rome III criteria (2006) altogether[2]. IBS affects 14% of females and 8.9% of males. Half of patients report their first symptoms before the age of 35 years, and the prevalence of IBS in this group is 25% higher than in patients over 50 years of age[1,3]. A study among students aged 18 to 30 years showed IBS incidence of 24%[1,3].

IBS is a troublesome condition reducing life quality and work productivity as well as generating considerable expenses[1,3]. Despite its arduous course, it does not lead to the development of a serious disease. IBS is diagnosed based on chronic symptoms in the absence of detectable abnormalities. It belongs to the group of brain–gut axis disorders. Recurrent abdominal pain is associated with bowel movement, changes in the frequency or consistency of stool. The diagnosis is based on the Rome IV criteria, which require that recurrent abdominal pain has occurred on average at least 1 day per week during the previous 3 months – with the onset of symptoms at least 6 months before the diagnosis[1–5]. The introduction of the Rome IV criteria contributed to IBS diagnostic rates and may change the rates in further epidemiological studies.

ETIOPATHOGENESIS

Familial occurrence of IBS and studies in twins confirm the involvement of genetic factors in the disorder. Genetic studies in familial IBS indicate genetic polymorphisms associated with the regulation of the serotonergic system[6,7], intestinal barrier integrity, regulation of immune and neural function as well as synthesis, absorption and secretion of bile acids[8].

About 8–31% of patients after an episode of acute infectious gastroenteritis develop post-infectious IBS (PI-IBS). The incidence of IBS is 7 times higher in patients with previous acute infectious gastroenteritis than those with no history of the infectious episode. The prevalence of IBS within 12 months of bowel infection is 10.1%. PI-IBS may be also associated with *Clostridium difficile* infection (in 25% of patients), with mixed (52%) and diarrhoea-predominant IBS (40%) being the most common forms[9,10].

The etiopathogenesis is multifactorial, with impaired gut–brain interactions and intestinal microbiota being the primary element, which triggers other pathogenetic mechanisms of IBS: gastrointestinal motor dysfunction, visceral hypersensitivity, mucosal immune dysfunction, and central nervous system (CNS) dysregulation[8,11]. Neuronal, immune and endocrine mechanisms modified by gut microbiota are involved in the modulation of the gut–brain interactions[12,13]. The higher incidence of IBS in females is determined by gender-related differences in these mechanisms[8]. Serotonin, which is synthesised in the intestines by enterochromatophilic cells, belongs to the primary neurotransmitters of the brain–gut axis[8].

Intestinal mucosal immune activation in response to dysbiosis, poor diet, stress and endogenous factors increases intestinal barrier permeability and induces gastrointestinal sensory-motor dysfunction. Activation of the intestinal mucosal immune system associated with microinflammation is considered to be the primary pathogenic factor of PI-IBS[8,14]. In biopsies involving the submucosal membrane in PI-IBS patients showed increased counts of T cells, macrophages, mast cells and enterochromatophilic cells as well as increased expression of pro-inflammatory cytokines compared to healthy controls[11,15]. Serotonin, histamine and bile acids are endogenous factors contributing to immune activation and intestinal barrier dysfunction as well as modulating sensory and motor functions[11,15,16].

Patients with IBS present with disturbances in the quantitative and qualitative composition of gut microbiota, modified by endogenous factors and diet, which has significant therapeutic implications. Small intestinal bacterial overgrowth (SIBO) plays a special role in the pathogenesis of intestinal symptoms.

Changes in the composition of microbiota include a reduced number of *Lactobacillus* and *Bifidobacterium*, an increased number of *Streptococcus*, *Escherichia coli*, *Clostridium* spp. and altered *Firmicutes*/*Bacteroidetes* ratio (to the detriment of the latter). Furthermore, the risk of SIBO is 5 times higher in IBS patients compared to controls[17,18]. SIBO is more common in females and patients with diarrhoea and increased flatulence. Positive lactulose hydrogen breath test, which is defined as a double peak on the breath hydrogen expiration after lactulose administration, is found in about 65% of adults and 56% of children with IBS[18]. Increased incidence of SIBO was detected in 50% of patients treated with proton pump inhibitors (PPI) and in 6% of healthy controls. Although a positive test is a reasonable indication for antibiotic therapy, none of the conventional antibiotics, except for rifaximin, which is considered an appropriate treatment option in all types of IBS, are recommended for long-term treatment of IBS[19,20].

Impaired colonic motor-sensory response to different stimuli (stress, rectal distension or meal) is a characteristic feature of IBS. Motor dysfunctions are seen in both large and small bowel[21].

Visceral hypersensitivity may result from impaired generation, transmission and analysis of sensory stimuli as well as an incorrect response to these stimuli, with impaired central pain inhibition[22]. A relationship was demonstrated between hypersensitive sensory endings of nerve fibres in the intestinal wall and an increased production of neurotransmitters (serotonin, substance P) and a release of inflammatory mediators from mast cells[21].

CNS dysfunction in patients with IBS may increase reactivity to stress stimuli and contribute to symptom severity. Studies using modern imaging techniques have shown

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neurofunctional and neurostructural differences in the brains of IBS patients compared to healthy individuals[23,24]. An impaired activity of the brain centres associated with the perception of visceral stimuli and emotion regulation was found in IBS patients.

Clinical observations have confirmed a relationship between stress and the severity of symptoms in 50–80% of IBS patients[25]. CNS disorders are associated with autonomic nervous system dysregulation, which may explain a variety of extraintestinal manifestations in patients with IBS, such as headaches and back pain, fibromyalgia, sleep disorders, chronic fatigue syndrome as well as anxiety and depression disorders[26].

Dietary factors, poorly absorbable and easily fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs) may contribute to the development and severity of IBS symptoms. Consumption of FODMAPs increases bacterial fermentation[27]. Also, a close relationship between diet and gut microbiota and its metabolites, such as short-chain fatty acids, which affect intestinal function and numerous regulatory brain–gut axis processes, is emphasised[27,28]. Studies investigating the relationship between IBS and hypersensitivity to gluten indicate the involvement of other grain components in inducing intestinal symptoms[29]. Three randomised, controlled studies demonstrated no benefit of gluten-free diet over placebo; therefore, it should not be recommended in IBS patients[30–32].

There is no evidence to support the role of food allergy in the pathogenesis of IBS[18]. Up to 80% of patients notice a relationship between symptoms and diet used. This is a dose-dependent effect – e.g. an increased amount of highly processed food products translates into an increased symptom severity[33]. It is suggested to temporarily (for a period of 6 weeks) use a low FODMAP diet to alleviate the symptoms. This helps limit fermentation, regulates passage as well as reduces stool and gas volume[34,35].

Furthermore, 20–60% of IBS patients develop anxiety-depressive disorders[36,37]. Somatisation and neuroticism are also relatively common. Patients with IBS often report extraintestinal symptoms, such as somnolence, frequent headaches and lumbar pain, nocturia, frequent and urgent urination as well as menstrual disorders and dyspareunia in the case of women[38]. Overlapping mental disorders have an impact on the perception of the disease and symptoms as well as on the search for medical help and treatment outcomes. They can also distort the clinical picture and cause diagnostic difficulties[36–38].

SYMPTOMS AND DIAGNOSIS, INCLUDING DIFFERENTIAL DIAGNOSIS

The concept of IBS being a diagnosis of exclusion is no loner valid.

The diagnosis is based on thorough medical history, physical examination and meeting the Rome IV criteria. Additional investigations should be limited to the minimum. Colonoscopy should be used only in justified cases (described later in the article).

IBS has been classified into four main types: constipation-predominant irritable bowel syndrome (IBS-C), diarrhoea-predominant irritable bowel syndrome (IBS-D), irritable bowel syndrome with mixed bowel habits (IBS-M) and unsubtyped irritable bowel syndrome (IBS-U).

The diagnosis should be based on clinical manifestations. There are no confirmatory diagnostic tests.

Complete blood cell count is the primary laboratory test used in the diagnosis of IBS (anaemia and elevated leukocyte counts require further diagnosis)[39]. Also, serum C-reactive protein (CRP) and stool calprotectin were found useful in patients requiring differential diagnosis of non-constipation IBS and inflammatory bowel disease (IBD)[40]. In the case of slightly elevated inflammatory markers and a low risk of IBD, repeated testing for CRP and calprotectin is recommended before a decision is made to perform colonoscopy[41]. Thyrotropin testing is also recommended in justified clinical cases[39]. Serological tests for coeliac disease (tissue transglutaminase IgA and total IgA) are particularly recommended for IBS-D and IBS-M not responding to empirical therapy[39]. In the case of elevated levels of IgA anti-tTG, it is recommended to perform gastroscopy with biopsies from the duodenum for histopathological assessment[42]. Microbiological and parasitological stool examinations may be considered in the differentiation of diarrhoea, depending on the clinical picture[39].

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

Colonoscopy should be limited to justified cases (e.g. in patients with overlapping alarming symptoms and risk factors for organic disease as well as patients over 50 years of age to test for colorectal cancer). Colonoscopy and fibrosigmoidoscopy are not recommended for patients under 50 years of age suspected of IBS, but without alarming symptoms[43,44]. In the case of a colonoscopic examination in patients with IBS-D, especially women over 50 years of age, it is recommended to collect biopsies from the right and left colon in search of microinflammation[42].

Risk factors for organic disease and alarming symptoms:

- age >50 years;
- family history of colon cancer, coeliac disease, inflammatory bowel diseases;
- recent antibiotic therapy;
- stays in regions of endemic occurrence of infectious or parasitic diseases;
- short duration of symptoms;
- occurrence of symptoms at night;
- unintentional weight loss;
- fever or subfebrile status;
- bleeding from the lower gastrointestinal tract or blood in the stool;

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- palpable abdominal resistance;
- ascites;
- anaemia;
- leukocytosis.

TREATMENT OF DIFFERENT FORMS OF IBS

Since there is no causative treatment, the therapy used should target the predominant symptom.

Non-pharmacological treatment strategy: physical exercise and psychological support

Different forms of moderate physical exercise (e.g. yoga) are recommended to maintain physical fitness and alleviate IBS symptoms. Mental balance, the ability to cope with stress as well as physical activity remain key elements in maintaining physical and mental health[45]. Patients are recommended to train on their own, participate in support groups, organisations or associations, or psychological consultations aimed to develop optimal stress coping strategies. Overweight and obese individuals are more likely to develop IBS symptoms, whereas weight loss leads to improvement. The latest studies in obese patients scheduled for a bariatric surgery (1,542 patients) have shown that the prevalence of IBS in this group is up to three times higher compared to the general population, and ranges between 13.3% and 30%[46–49]. Only one study focused on the effects of weight loss on IBS symptoms. A statistically significant reduction in body weight was correlated with a statistically significant reduction in the severity of overall IBS symptoms as well as individual IBS symptoms, except for pain[50].

Diet

As already mentioned, a temporary low FODMAP diet (6 weeks) is recommended to alleviate the symptoms. Repeating the diet is not recommended due to the lack of sufficient evidence. An elimination diet based on the levels of antibodies against individual nutrients is also not recommended. In the case of patients benefiting from an elimination diet, individual dietary modifications based on the individual patient's experience are suggested[51,52].
The diet should be used long-term due to the nature of the disease. The dose of fibre has not been clearly determined; an intake of 10–25 g per day and avoiding insoluble fibre (increased flatulence) are suggested. Sources of (recommended) soluble fibre include fresh vegetables and fruit, plantains (*Plantago afra*, *Plantago lanceolata*, *Plantago ovata*), oat bran and ready-made supplements. Sources of insoluble (not recommended) fibre include wheat bran, grains, nuts, beans, cruciferous and root vegetables[53,54].

Treatment with herbal preparations

The use of peppermint oil results in a statistically significant reduction of symptoms. Alam et al. demonstrated that intestinal symptoms recur after discontinuation of the preparation, which, in the absence of studies on its safety and efficacy (the longest period of administration was 12 weeks), should be taken into account when formulating permanent recommendations for patients[55]. It was found that heartburn was more common in the groups receiving the oil compared to patients on placebo[56,57].
It should be noted that efficacy studies used specific oil preparations, and thus 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 aforementioned studies used high doses, i.e. 180–225 mg[58].

Pharmacotherapy in diarrhoea-predominant IBS

Loperamide is recommended to reduce the severity of diarrhoea in patients with diarrhoea-predominant IBS. However, the drug does not reduce overall IBS symptoms.
Although no efficacy of loperamide in alleviating the overall symptoms of IBS was demonstrated in a study in 171 patients, statistically significant reduction of diarrhoea was found in all studies and the drug may be conditionally prescribed in this indication.
A 14-day rifaximin therapy is recommended to reduce overall symptoms in all forms of IBS. In the case of two episodes of recurrence in patients who have benefited from rifaximin therapy, repeated treatment according to the same regimen and with at least 4-week intervals is recommended[59,60]. A dose of 1,200 mg (3 × 400 mg) is authorised in Poland. Rifaximin is the only known eubiotic that restores the normal composition of intestinal microbiota via a direct (antibacterial) mechanism and by modulating microbiota. It has no adverse effects on the general composition of bacterial flora, but its action is limited to harmful bacteria. A 14-day therapy increases the number of *Bifidobacterium* and *Lactobacillus* as well as bacteria with anti-inflammatory properties. Rifaximin has immunomodulatory activity (stimulation of anti-inflammatory and inhibition of proinflammatory cytokines), reduces the pathological permeability of enterocytes and restores the tightness of intestinal barrier[17,61].

Pharmacotherapy in constipation-predominant IBS

Macrogols, osmotically active substances that are not absorbed in the gastrointestinal tract, are successfully used as laxatives; however, they do not reduce the overall IBS symptoms. Other options include metoclopramide (treatment for up to 7 days), trimebutine (a modulator of gastrointestinal motility), 5-HT_4 receptor agonists, tegaserod, prucalopride, and itopride[62].

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Probiotics in the treatment of IBS

The wide variety of probiotic bacteria and their doses makes optimal treatment with probiotics difficult. At this stage, it is not possible to determine the efficacy of the individual strains included in combined preparations or the efficacy of other configurations (mixtures) of strains. The efficacy of specific preparations remains controversial. The results of research are on the verge of statistical significance, which, due to potentially significant adverse effects (there are reports of sepsis in critically ill patients), should lead to careful prescription of these preparations[62,63].

Antidepressants

Tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI) are recommended to improve the overall symptoms of IBS.

The drugs should be used at the lowest effective doses for 4–12 weeks, although the maximum duration of therapy (based on its efficacy and safety) has not been clearly defined. If the therapy brings additional benefits, it may be used for a longer period. Antidepressants inhibit the reuptake of neurotransmitters (which leads to patient's mood improvement), exhibit analgesic activity, inhibit afferent pain transmission and have antispasmodic effects associated with anticholinergic activity (amitriptyline and doxepin), which is used in IBS-D[64,65]. SSRI may bring relief in IBS-C (increased levels of serotonin stimulate peristalsis). They are used for 6–12 months until improvement is noted, and then are gradually discontinued[64,66–69].

Pharmacotherapy in all forms of IBS – antispasmodics

Since it is impossible to eliminate the cause of IBS, only symptomatic treatment is used. Patients with IBS usually suffer from abdominal cramping; therefore the therapy is usually based on antispasmodics. Antispasmodics are a very large and heterogeneous group of drugs with varying mechanisms of action.

An assessment of the efficacy of individual drugs is difficult due to the sparsity of studies dedicated to specific preparations, which usually use small sample sizes and heterogeneous methodology (endpoints, assessed scales).

Antispasmodics, which act either directly on the smooth muscles or indirectly via the cholinergic system, were and still are the basic pharmacotherapy in IBS. A total of 18 studies (2,237 patients) were included in randomised trials showing the efficacy of antispasmodics in reducing overall IBS symptoms. The relative risk (RR) for inefficacy was 0.65 (95% confidence interval, CI: 0.56–0.76), and the number needed to treat (NNT) was 5 (95% CI: 4–8)[70–73].

Other studies that failed to meet the inclusion criteria (observational, without randomisation or a control group) assessed patients' quality of life rather symptom improvement. One of these studies demonstrated statistically significant improvement in the quality of life in patients treated with mebeverine. However, mebeverine showed no benefits over placebo in reducing overall IBS symptoms[74].

Among the many antispasmodics with different mechanisms of action (hyoscine, drotaverine, mebeverine, trimebutine), the native alverine at a new, increased dose of 120 mg concentrated in one capsule is the answer to the needs of IBS patients. The chemical structure and the pharmacological form of the drug were modified to maximise its potency. The efficacy of alverine in alleviating IBS symptoms was confirmed in randomised placebo-controlled trials[75–77].

Alverine inhibits bowel peristalsis, has smooth muscle relaxing activity, and shows anticholinergic activity. It shows a multidirectional action by inhibiting the activity of the phosphodiesterase enzyme (it increases cAMP levels), which blocks calcium channels and reduces Ca^{2+} inflow, improving intestinal motor function. Alverine binds to serotonin receptors ($5HT_1$ receptor antagonist)[78], which generates antinociceptive effects, and reduces visceral pain. As a selective $5HT_1$ receptor inhibitor, alverine citrate inhibits serotonin-induced rectal hypersensitivity[79,80]. Serotonin modulates motor and secretory functions as well as visceral sensation by acting on different 5-HT subtypes ($5\text{-}HT_1$, $5\text{-}HT_3$, $5\text{-}HT_4$). Since 5-HT antagonists slow down the passage, reduce colorectal muscle tone and visceral sensations, they are used in IBS-D.

Furthermore, since alverine shows no atropine-like activity, it is not contraindicated in patients with glaucoma or prostate hypertrophy. It is well-absorbed in the gastrointestinal tract, and undergoes rapid transformation into pharmacologically active metabolites. The peak therapeutic effect is achieved within 0.5–1.5 hours, and the duration of action is 3–4 hours[76,77].

Preclinical pharmacological studies showed beneficial effects of alverine on intestinal motor function and sensitivity[79–81]. In their randomised, double-blinded, placebo-controlled trial using the Rome Committee's criteria, Wittmann et al. demonstrated significantly higher efficacy of alverine citrate and simethicone over placebo in alleviating abdominal pain and discomfort in IBS patients[82,83]. In their meta-analysis assessing the efficacy of antispasmodics (alverine), Poynard et al. showed an over 50% improvement in abdominal pain[84].

What should the antispasmodic treatment strategy look like? Should it be on-demand or continuous treatment? Based on randomised studies, Ducrotte et al. showed better on-demand treatment outcomes[85].

Another question arises: is it better to use alverine citrate in monotherapy or in combination with an antiflatulent agent? Due to the complexity of symptoms and their varying severity, associated with individual predispositions of each patient, it seems that the use of monotherapy, which allows for dosage adjustment depending on the dominant symptoms, would be a better solution.

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The psychogenic component of the symptoms distorts the assessment of IBS pharmacotherapy. The observed therapeutic effect of placebo translates into difficulties demonstrating a statistically significant advantage of pharmacological agents. However, Mitchell et al. showed better treatment outcomes for alverine vs. placebo in their randomised study. Symptom resolution was observed in more than half of patients in the alverine group. The study shows that alverine should be used as first-line therapy in IBS[76]. Similar conclusions were drawn by Patel et al. in their meta-analysis[86].

The proposed step-up treatment algorithm for IBS patients is as follows:

- pain – rifaximin, antispasmodics and antidepressants;
- flatulence – rifaximin, antispasmodics and antidepressants;
- diarrhoea – loperamide, antispasmodics;
- constipation – macrogols, antispasmodics.

CONCLUSIONS

IBS is a chronic functional gastrointestinal disease, which manifests in abdominal pain and an abnormal rhythm of bowel movement. Although the causes of IBS are not fully understood, a group of risk factors have been identified. The development of the syndrome is not directly related to organic (intestinal damage) or biochemical factors (metabolic disorders). Also, there is no therapy that would allow for cure in IBS patients. The treatment involves symptom elimination and preventing recurrence. In addition to diet, pharmacotherapy also plays an important role in the treatment of different IBS symptoms. The drugs used help reduce pain, restore normal rhythm of bowel movement, and control factors (including mental ones) that are likely to increase the symptoms. The disease has periods of exacerbations and remissions. Patients attend multiple consultations, and each time they report their symptoms slightly differently, which makes treatment monitoring difficult. They learn to cope with their symptoms and try to lead a normal life. Prognosis is good: despite the long-term course of the disease in some cases, it does not progress or lead to cachexia.

The new approach to gastrointestinal dysfunctions as impaired gut–brain interactions is associated with advances in neurogastroenterology. Many studies from the last decade on the epidemiology, pathogenesis, symptomatology, diagnosis and treatment of functional disorders have provided rationale for the changes introduced in the Rome IV criteria. Another update, which will be available in a few years and will take into account further advances in neurogastroenterology, will verify the accuracy and usefulness of the current criteria.

Conflict of interest

The author does not report any financial or personal connections with other persons or organisations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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