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IRRITABLE BOWEL SYNDROME

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Irritable Bowel Syndrome

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Resumo

A síndrome do intestino irritável é um distúrbio gastrointestinal funcional, que pode afetar todos os membros da sociedade, independentemente da idade, sexo, raça ou estrato socioeconómico. Devido à sua elevada prevalência e natureza crónica, representa um encargo económico significativo. De facto, estes doentes apresentam uma alteração relevante da sua qualidade de vida, o que limita a sua produtividade laboral e atividades de vida diárias, sobretudo quando está associada a outros distúrbios, tais como ansiedade e depressão.

O diagnóstico da síndrome do intestino irritável depende de critérios diagnósticos baseados em sintomas, com resultados normais num número limitado de testes complementares que excluem outros diagnósticos possíveis. A etiologia desta doença não está completamente estabelecida. No entanto, a evidência sugere que se trata de um distúrbio multifatorial com vários mecanismos diferentes que têm sido implicados como responsáveis pelos sintomas. Visto que a estratégia terapêutica é geralmente baseada nos sintomas predominantes e sua severidade, é importante reconhecer os mecanismos subjacentes para aliviar com sucesso a dor visceral e a alteração dos hábitos intestinais.

O objetivo desta revisão literária é realçar a importância desta doença e explorar a fisiopatologia e opções terapêuticas disponíveis para a síndrome do intestino irritável, tendo em conta a evidência mais recente, desde os novos critérios Rome IV até ao novo arsenal farmacológico.

Palavras-chave

Síndrome do intestino irritável, Revisão, Critérios Rome

Abstract

The irritable bowel syndrome is a functional gastrointestinal disorder, which can affect all members of society, regardless of age, sex, race or socioeconomic status. Because of its high prevalence and chronic nature, it represents a significant economic burden. In fact, these patients have a significant impairment of their quality of life, which limits their work productivity and daily social activities, especially when it is associated with other disorders, such as anxiety and depression.

The diagnosis of irritable bowel syndrome relies on symptom-based diagnostic criteria with normal results on a limited number of complementary tests that rule out other possible diagnoses. The aetiology of this condition is incompletely established. However, evidence suggests that it is a multifactorial disorder with several different mechanisms that have been implicated as responsible for the symptoms. Since the treatment strategy is usually based on predominant symptoms and their severity, it is important to recognise the underlying mechanisms in order to successfully relief the visceral pain and altered bowel habits.

The aim of this literature review is to highlight the importance of this condition and explore the pathophysiology and treatment options of irritable bowel syndrome, taking into account the most recent evidence, from the new Roma IV criteria to the new drug armamentarium.

Key words

Irritable bowel syndrome, Review, Rome criteria

Lista de abreviaturas

BSFS – Bristol Stool Form Scale

CRP – C-Reactive Protein

DBPCCT – Double-Blind Placebo-Controlled Clinical Trial

ENS – Enteric Nervous System

FODMAPs – Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols

GI – Gastrointestinal

5-HT – Serotonin

IBS – Irritable Bowel Syndrome

IBS-C – Irritable Bowel Syndrome with constipation-associated symptoms

IBS-D – Irritable Bowel Syndrome with diarrhea-associated symptoms

IBS-M – Irritable Bowel Syndrome with mixed bowel habits

IBS-U – Irritable Bowel Syndrome Unclassified

MA – Meta-Analysis

RCT – Randomized Clinical Trial

SSRIs – Selective Serotonin Reuptake Inhibitors

TCAs – Tricyclic Antidepressants

TNF-α – Tumour Necrosis Factor α

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1. Introduction

Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder which can affect all members of society, regardless of age, sex, race or socioeconomic status [1]. Because of its chronic nature and impairment of quality of life, this condition represents a significant economic burden and these patients are more likely to resort to health services and to require time off work [2]. Traditionally labelled as a functional gastrointestinal (GI) disorder without evident structural or pathological changes, new insights suggest a disturbed GI physiology with impairment of GI motor function, visceral sensation and secretion, all of them potential therapeutic targets to improve symptoms and quality of life of these patients.

The aim of this literature review is to highlight the importance of this condition and explore the pathophysiology and treatment options of irritable bowel syndrome, taking into account the most recent evidence, from the new Roma IV criteria to the new drug armamentarium. For this purpose, online search of PUBMED was carried out, considering articles with no more than 10 years. The inclusion criteria were: being published in English language and being a systematic revision, a meta-analyse, a case-control study, a cohort study or a guideline. The exclusion criteria were: being published in other languages and being a case report.

2. Epidemiology

The worldwide estimated prevalence of IBS is 11,2% and vary based on the geographic region, age, gender and diagnostic criteria [3].

The prevalence of IBS is higher in younger age groups from 26-55 years [4] and in women, who appear to have more frequent and severe IBS symptoms during menses due to low ovarian hormone levels, which are associated with a decreased sensory threshold to rectal distension. Additionally, symptoms vary between genders with women reporting more commonly symptoms of constipation (IBS-C) and men having more diarrhea-associated symptoms (IBS-D) [5]. Constipation symptoms are also more frequent in older patients, most likely because these patients show more comorbidities and less mobility [6].

There is little information about subtype-specific prevalence, because patients with IBS vary over time in terms of symptoms, switching subtype [4]. However, some studies suggest IBS with mixed bowel habits (IBS-M) as being the most common [6].

2.1 Association between IBS and other disorders

IBS is commonly associated with other functional, somatoform and mental disorders [7]. In more than 20% of the cases, there is an overlap of IBS with functional gastrointestinal disorders of the upper gastrointestinal system - particularly functional dyspepsia and gastroesophageal reflux disease - and of the lower gastrointestinal system - such as diarrhoea, incontinence, pelvic floor dyssynergia and constipation [8]. Psychiatric comorbidities are present in approximately 50% of IBS patients and include depressive symptoms, anxiety and eating disorders [7].

IBS patients appear to have an increase of the incidence rate of other diseases, including stroke, osteoarthritis and infections, probably because these patients are hypervigilant in detecting somatic symptoms [9].

2.2 Post-infectious IBS

A strong association between gastrointestinal infections and the development of IBS has been established [10]. Around 1 in 9 patients exposed to infectious enteritis may develop IBS, at a rate 4 times higher than non-exposed individuals. The greatest risk is associated with protozoal and bacterial infections, with viral infections having a lower risk of development of IBS. The severity of the acute gastroenteritis increases the risk of developing IBS [11,12] but symptoms usually decrease over time [12].

3. Pathophysiology

IBS is a functional gastrointestinal disorder without evident structural or pathological changes; still there is evidence of a disturbed gastrointestinal physiology, because gastrointestinal motor function, visceral sensation and secretion are altered [13]. Evidence suggests that it is a multifactorial disorder with several different underlying mechanisms responsible for the symptoms reported by the patients. In IBS, the epithelial barrier, gut microbiota, food antigens and bile acids give rise to abnormal responses in the main regulators of sensorial and motor functions, such as the hypothalamus-pituitary-adrenal axis, the immune system, the brain-gut axis and the Enteric Nervous System (ENS) [14]. In addition, it is well-recognized the association of psychological factors, particularly anxiety and depression, and the development of IBS, with the corticotropin-releasing factor being one of the key mediators between the two [15].

3.1 Epithelial barrier

Intestinal barrier dysfunction has been proven to have a pathogenic role in IBS and is considered an early event in the course of this disorder [16]. Increased intestinal permeability can be triggered by different factors, such as stress, food allergies, bile acids, infections and dysbiosis, genetic and epigenetic factors. This mechanism is associated with low-grade inflammation, visceral hypersensitivity and pain, with evidence suggesting that increased levels of mast cell mediators may be involved in increased epithelial permeability [15,17].

3.2 Bile acids

It has been suggested that one of the mechanisms for symptom generation in patients with IBS-D is the increased bile acid exposure at the colon. Among patients with IBS, faecal bile acid levels are higher in patients with IBS-D and lower in patients with IBS-C [18]. Approximately 25% of patients with IBS-D have excessive levels of total faecal bile acids [19], both because of bile acid absorption and synthesis dysregulation [20].

The increased levels of total faecal bile acids in patients with IBS-D are associated with increased concentrations of serum 7α-hydroxy-4-cholesten-3-one (C4), being a potential non-invasive test for bile acid malabsorption in IBS [21,22].

3.3 Immune response

Evidence suggests that systemic or intestinal immune activation has a role in the pathophysiology of IBS shown both by increased infiltration of inflammatory cells (T cells and mast cells) and increased humoral activity (higher density of activated B lymphocytes and plasma cells and a higher local production of Immunoglobulin G) in the mucosa of small and large intestine of some patients with IBS, findings positively associated with the number of bowel movements per day and stool form, but not with the intensity and frequency of abdominal pain. [23]. Mast cells are a key component in inducing and maintaining a low-grade immune activation. Peripherally elevated cytokine levels like Tumour Necrosis Factor α (TNF-α) and toll-like receptor activity of patients with IBS demonstrates the immune dysfunction present in these patients [13,24].

3.4 Neuroimmune interactions

The ENS is sometimes called the “second brain” because of the diversity of neuronal cell types and complex, integrated circuits that permit the ENS to autonomously regulate many processes in the bowel [25]. IBS patients have a higher density of mucosal nerve fibers and increased nerve outgrowth with functional and structural alterations in the ENS that might be responsible for the visceral hypersensitivity [26]. Also, the release of pro-inflammatory mediators by persistently activated immune cells such as mast cells are crucial in the mechanisms underlying abdominal pain and dysmotility in IBS patients [27,28].

3.5 Serotonin metabolism

Serotonin (5-HT) is an important neurotransmitter present in the brain and the ENS. Up to 90% of the total body serotonin is produced by the enteroendocrine cells present in the gastrointestinal tract and regulates intestinal motor and secretory functions. 5-HT can make the bowel contract or relax, depending on the activation of cholinergic excitatory neurons – mediated by 5-HT_3 or 5-HT_4 receptors – or nitric oxide inhibitory enteric motor neurons, mediated by 5-HT_4, 5-HT_{1A} or 5-HT_{1D} receptors. Serotonin is also a potent intestinal secretagogue [29,30].

Patients with IBS, regardless of bowel habit, have a higher colonic mucosa 5-HT availability, which was associated with mucosal mast cell infiltration, suggesting that the immune activation can lead to 5-HT release. The increased colonic 5-HT release was correlated with the severity of abdominal pain [31].

3.6 Microbiota

The dysbiosis of microbiota in IBS has been recognized by the Roma Foundation Working Team as a plausible contributing factor to this condition [32]. IBS symptom severity has been associated with a distinct faecal microbiota signature and patients with severe IBS have lower microbial richness and exhaled methane, as well as reduced presence of Methanobacteriales and Prevotella enterotype, but increased presence of Bacteroides enterotype [33].

Diet plays a major role in the pathogenesis of IBS [34] and it can rapidly change the intestinal microbiota, affecting the abundance of specific microbial groups [35]. In fact, dietary intolerance is common in patients with IBS and symptoms can be triggered by dairy products, grains and fat [36].

The dysbiosis of microbiota present in some individuals with IBS results in abnormal levels of intestinal fermentation. The colonic pH was reported to be significantly lower in patients with IBS,

compared to healthy controls, which suggests a higher proportion of colonic fermentation [37]. In these patients, the presence of Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols (FODMAPs) can induce IBS symptoms, because these products increase the intraluminal osmotic pressure and provide a substrate for bacterial fermentation, resulting in gas production, abdominal distension and abdominal pain [34]. In addition, the overproduction of gas can lead to faster colonic transit in patients with IBS-D, due to the increased sensitivity to the augment of intestinal volume [38].

3.7 Brain and behaviour

One of the key mechanisms in the development of IBS is believed to be a dysregulation of the axis between the brain and the gut as a consequence of peripheral and central mechanisms [39]. The brain, through the hypothalamus-pituitary-adrenal axis and the autonomic nervous system, can influence intestinal motility, fluid secretion, intestinal epithelial permeability, immune function and gut microbiota [14].

On the one hand, central mechanisms are based on depression, anxiety and somatisation [39]. Patients with IBS have reported a higher prevalence of somatisation, compared with controls without IBS, which can be partly explained by the increased levels of depression and anxiety that lead to a greater awareness of any physical symptoms [40]. Stressful life events may alter the central processing of afferent stimuli and have been directly associated with neuroticism and higher rates of functional bowel disorders [41].

On the other hand, peripheral mechanisms are characterized by changes in intestinal motility and secretion, as well as visceral hypersensitivity [39]. These peripheral changes can influence brain structure and function [14]. Alterations in the volume of grey matter were identified in patients with IBS and may be linked with the increased sensitivity to somatic and visceral stimuli, as well as an increase in emotional arousal [42]. In fact, epidemiological evidence suggests that, in about half of the patients, the gastrointestinal symptoms arise first and then the mood disorders become apparent [41].

3.8 Genetic and epigenetic data

IBS has familial aggregation and higher concordance between monozygotic twins compared to dizygotic twins, which demonstrates that genetic factors play a role [43]. Polymorphisms and variants of several genes involved in neuronal signal transduction, immune response and intestinal

barrier, as well as mutations in genes encoding proteins involving the serotonergic system and bile acid synthesis regulation, have been associated with IBS [22,44].

Although only a few studies have been performed, miRNA studies have linked target genes to increased gut permeability, visceral sensitivity and colonic motility [14].

4. Diagnosis

4.1 Diagnostic criteria

The diagnosis of IBS relies on symptom-based diagnostic criteria with normal results on a limited number of complementary tests that rule out other possible diagnoses [14]. These criteria were first established in 1978, the Manning criteria [45], but the current gold standard criteria for the diagnosis of IBS are the Rome IV criteria [Table I], updated in 2016 [1]. When these criteria are present and alarm features are absent, only a limited number of laboratory tests are recommended without any need to perform invasive investigations. Currently, there is no valid biomarker for IBS [46].

In the new Rome IV criteria, “discomfort” was eliminated from the criteria because it is non-specific and has different meanings in different languages. Now pain related to bowel movements is required, rather than just improving with bowel movements, because, in some cases, pain can worsen after bowel movements [47]. Furthermore, the frequency of abdominal pain was increased from 3 days per month to 1 day per week on average [48].

IBS is classified into 3 main subtypes, according to the predominant disorder in bowel habits: IBS-C, IBS-D and IBS-M. IBS-C is characterized by more than 25% of bowel movements with Bristol Stool Form Scale (BSFS) types 1 or 2 and less than 25% of bowel movements with BSFS types 6 or 7 while in IBS-D, more than 25% of bowel movements with BSFS are types 6 or 7 and less than 25% of bowel movements with BSFS types 1 or 2. IBS-M is characterized by more than 25% of bowel movements with both BSFS types 1 or 2 and types 6 or 7 and patients who meet the criteria for IBS but whose bowel habits cannot be classified in any of the above subtypes are considered IBS Unclassified (IBS-U).

4.2 Clinical features

Abdominal pain must be present anywhere throughout the abdomen, but it is more common in the lower quadrants; the absence of this feature excludes the diagnosis of IBS. Abdominal pain is

associated with abnormal bowel habit, such as diarrhoea, constipation or alternating diarrhoea and constipation [1].

Abnormal stool frequency (more than 3 bowel movements per day or less than 3 bowel movements per week), abnormal stool form in the BSFS (types 1-2 or 6-7), excessive straining during defecation, urgency, feelings of incomplete evacuation and mucus with bowel movements are common symptoms but are not specific of IBS [14]. The same applies to abdominal bloating and abdominal distension that are present in most IBS patients [1].

4.3 Physical examination

Physical examination should be performed in every patient evaluated for IBS since it helps to exclude organic causes for the symptoms [1], although abdominal examination rarely gives information to support a specific diagnosis. Digital rectal examination can exclude rectal cancer and can identify patients with dyssynergic defecation, which has to be ruled out in patients with constipation. Perianal inspection is also an important part of the physical examination to exclude perianal fistulas and other relevant anal pathology. The absence of objective findings on physical examination supports a diagnosis of IBS [14].

4.4 Laboratory tests

At the time there is not sufficient evidence to recommend which laboratory tests should be used for the diagnostic work-up of patients with IBS. It is important to perform limited laboratory studies, starting with a complete blood count [14]. C-Reactive Protein (CRP) or faecal calprotectin must be measured, because normal levels help exclude IBD in patients with non-constipated symptoms of IBS [49].

In the clinical suspicion of thyroid disease, a thyroid profile should be performed. Serologic tests for celiac disease should be used to exclude this condition in patients with symptoms of IBS-D and IBS-M [1,50]. Other differential diagnoses include bile-acid induced diarrhoea and carbohydrate malabsorption. Furthermore, stool analysis for bacteria, parasites and ova may be considered to detect gastrointestinal infections in patients with diarrhoea [1].

Colonoscopy is indicated in the presence of alarm features and persistent diarrhoea, in the suspicion of IBD and in cases of a family history of colorectal cancer [1]. In patients with watery diarrhea if symptoms are not controlled by empiric treatment, biopsies of the colon might be required to exclude microscopic colitis [51].

All described biomarkers were not superior to symptom-based criteria for the diagnosis of IBS [52]. Serum biomarkers such as antibodies to a bacterial toxin produced by *Campylobacter jejuni* called cytolethal distending toxin B and vinculin have been studied and permit the distinction between IBS and non-IBS subjects with high specificity but low sensitivity [53].

5. Managment

The first step after the diagnosis of IBS is explaining the natural history of the disease and providing reassurance that it is a benign condition. Establishing of a good rapport with a patient is an essential step in the management of this condition, making sure the patient feels heard as well as validating their symptoms. A trust relationship between a doctor and his patient will lead to a more effective treatment [1].

The heterogeneity of IBS complicates the development of an algorithm to all patients, even within individual IBS subtypes. Management of IBS involves an integrated approach [54] and treatment options include establishment of an effective patient–provider relationship, education, reassurance, nutritional interventions, drug therapy and psychological therapy. [8] In fact, patients that received information about the course of the disease, disease-related diet and lifestyle, medications and check-ups had their quality of life improved [55].

Treatment strategy should be based on predominant symptoms and their severity [8]. For mild symptoms, reassurance, education and dietary modifications are probably enough. For moderate symptoms, more specific actions are recommended, such as identification and alteration of exacerbating factors, psychological therapy and pharmacological therapy aimed at the predominant symptoms. For severe symptoms, behaviour changes and psychopharmacologic agents should be used [54].

The current pharmacological therapies used in IBS aim to relief predominant problematic bowel habits and visceral pain [Table II]. However, new therapies are emerging regarding manipulation of the intestinal microbiota [14].

5.1 Dietary modifications

Food ingestion is one of the most common precipitants of symptoms in IBS [56] and most food-related IBS symptoms seem to represent food intolerance, a physiological reaction to food allergens not associated with an immune response [57]. In some patients, a food and symptom diary can help

patients determine which foods trigger symptoms, for instance lactose and fructose intolerance can increase IBS symptoms [54].

Evidence suggests there is an exaggerated motor response to food, especially lipids, in the small intestine of patients with IBS. Food-related symptoms can be mediated by products of the digestion, 5-HT and gut microbiota [14]. Some of the most reported exacerbating products include vegetables, wheat and fruits [58]. Complementing the dietary changes, it is important that IBS patients exercise and reduce stress and sleep deprivation [1].

Fiber and fiber-based supplements accelerate colon transit and facilitate stool passage, resulting in an increased stool frequency, which can be helpful in patients with IBS-C [8]. Soluble fibers have symptomatic benefits in IBS. However, insoluble fibres may exacerbate IBS symptoms, including bloating, abdominal pain and distension [59].

A diet low in FODMAPs is one of the major options of treatment in IBS [Table III] [14], with a symptomatic improvement in about 70% of the patients. This diet strategy effectively reduces functional gastrointestinal symptoms such as bloating, abdominal pain, urgency, stool frequency and consistency [60]. It is suggested that a low-FODMAP diet should be used as first line treatment in combination with other methods. Still the safety of this diet needs to be monitored regarding long-term consequences, such as the possibility of malnutrition [61].

Despite the absence of immunological, serological and histological markers of celiac disease, gluten ingestion can also be responsible for IBS symptoms in some patients, altering bowel barrier functions in patients with IBS-D [62]. However, wheat contains high levels of fructan, a polysaccharide, which might explain the benefits of a gluten-free diet that can also be achieved with a low-FODMAPs diet. In fact, a diet both low in FODMAPs and gluten-free did not have additional benefits compared with a low-FODMAPs diet alone, demonstrating there is no benefit in avoiding gluten [63].

5.2 Antispasmodic drugs

In some patients with IBS, pain is mediated through colonic smooth muscle spasm [14]. Different studies have demonstrated that antispasmodic therapy improves IBS symptoms like abdominal pain and stool consistency. Butylscopolamine, due to its ability to antagonize the binding of acetylcholine to the muscarinic receptor at the neuromuscular junction, leads to smooth muscle relaxation [64]. However, due to anti-muscarinic adverse effects such as constipation, it should not be used in patients with IBS-C [65]. Pinaverium, a selective calcium channel blocker of gastrointestinal smooth muscle cells, is one of the most commonly used IBS medications, with evidence proving it reduces

abdominal pain and improves stool consistency in 4 weeks [66]. Peppermint oil also inhibits smooth muscle contraction through calcium channel blockade and has been proven to reduce IBS symptoms, being a safe and effective treatment for IBS [67]. Mebeverine, a spasmolytic without atropine-like side effects, has high efficacy for abdominal pain and reduction in daily defecation frequency, as well as an improvement in global wellbeing, with good tolerability with minor complications [68,69].

5.3 Laxatives and motility accelerants

In patients with constipation, simple laxatives are a suitable therapeutic option due to their relative safety, low cost and availability [70]. However, lactulose is often poorly tolerated by IBS patients because of worsening of bloating and pain; therefore, it is not recommended [14].

Linaclotide and lubiprostone are novel drugs that increase fluid secretion into the gastrointestinal tract and accelerate gastrointestinal transit [71]. Linaclotide is a minimally absorbed peptide guanylate cyclase C receptor agonist that should be used as second line therapy, in patients with IBS-C after the failure of laxatives [14]. Besides its laxative effect, linaclotide also reduces colonic nociception and abdominal pain [72-74]. Lubiprostone causes secretion of fluid and electrolytes in the small bowel, through the activation of chloride channels [75]. Two randomized trials revealed the significant improvement of IBS-C symptoms with lubiprostone, without major side effects [76].

5.4 Antidiarrheals

Loperamide, a μ-opioid receptor agonist, frequently used as first line therapy in IBS-D, slows peristalsis and increases fluid reabsorption, improving stool consistency, urgency and pain [77,78]. Eluxadoline is a new oral agent with peripherally acting mixed μ-opioid receptor agonist–δ-opioid receptor antagonist and κ-opioid receptor agonist that slows GI motility and decreases visceral hypersensitivity [79]. Reports of severe pancreatitis and sphincter of Oddi dysfunction, particularly in patients without a gallbladder or those who abuse alcohol, led to the contraindication of eluxadoline in these groups of patients [80].

5-HT_3 receptor antagonists are effective in patients with IBS-D, both slowing colonic transit through the inhibition of peristaltic reflex [81] and modulating visceral nociception [30]. Alosetron significantly improved abnormal bowel function and relieved pain and discomfort on IBS-D, but was withdrawn due to reports of severe constipation in around 25% of patients and ischemic colitis [82]. Ondansetron leads to significant improvements in stool consistency, though abdominal pain was not reduced. It has been used widely for over 25 years without a single report of ischaemic colitis [83].

In patients with IBS-D, an increased exposure of the ileal mucosa to bile acids leads to an excessive secretory response [84]. In fact, treatment with colestipol in these patients had a positive symptomatic response [85]. Additionally, there is evidence that colestyramine is effective in patients with functional chronic watery diarrhea [86].

5.5 Manipulation of the microbiota

Disruption of gut microbiota homeostasis has been proven to contribute to the pathophysiology of IBS. Thereby, antibiotics and probiotics may improve IBS symptoms by restoring balance to the gut microbiota [87].

The non-absorbable, non-systemic antibiotic, rifaximin, appears to play a role in modulation of the gut microbiota and in local micro-inflammation [14]. Rifaximin was associated with significant relief of IBS symptoms such as bloating, abdominal pain and loose or watery stools, in patients without constipation [88].

Probiotics are attenuated bacteria or bacterial products that are beneficial to the host. Although there are some inconsistencies in different studies, there is enough evidence to suggest their efficacy in reducing IBS symptoms, such as bloating, abdominal pain and flatulence [89]. *Lactobacillus plantarum* had the most evidence in favour to their use [90].

5.6 Antidepressants

There is evidence to recommend the use of low-dose antidepressants, such as tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs) for reducing abdominal pain in IBS, especially in patients who maintain symptoms after nutritional interventions and antispasmodic therapy [65]. In a recent meta-analysis, TCAs showed to improve the global symptoms of IBS, while there was no strong evidence to confirm the effectiveness of SSRIs in the treatment of IBS [91]. These medications are generally well tolerated. However, TCAs have adverse effects that need to be considered, for instance constipation, dry mouth, drowsiness and fatigue. Therefore TCAs are particularly successful in patients with IBS-D, but less helpful in patients with IBS-C [14].

5.7 Psychotherapy

Patients who do not respond to pharmacological therapy after 12 months should be referred to cognitive-behavioural therapy or other psychological therapies [14]. Gut-directed hypnotherapy seems to have a durable efficacy in reducing IBS symptoms [92]. Additionally, there is promising evidence of the feasibility and efficacy of a mindfulness intervention for reducing IBS symptom severity and symptoms of stress, lasting 6 months after the intervention [93]. Lastly, psycho-educational group intervention appears to be a cost-effective option in modulating IBS symptoms and improving the patients' quality of life [94].

6. New therapies

In patients with IBS-C, plecanatide is a promising therapeutic option. It is a peptide guanylate cyclase C receptor agonist that, in a phase 3 clinical trial, led to a significant reduction of IBS symptoms [95]. Another novel agent is tenapanor, an inhibitor of the gastrointestinal sodium/hydrogen exchanger NHE3. It increases intestinal fluid volume and transit, leading to an improvement of constipation, bloating and pain in a phase 2 clinical trial [96].

In patients with IBS-D, a bile acid sequestrant, colesevelam, has been evaluated. A clinical trial demonstrated that colesevelam increases the delivery of bile acids to stool, improving stool consistency, and increases hepatic bile acid synthesis, avoiding steatorrhea in these patients [97]. Also, Farnesoid X-activated receptor agonists can reduce hepatic bile acid. Of these, obeticholic acid was shown to decreased bile acid synthesis and improved stool form and symptoms of diarrhoea in patients with bile acid diarrhea [98], but trials in IBS are missing. Another drug also being evaluated for IBS-D is ebastine, an antagonist of histamine receptor H1 [99].

Lastly, although faecal microbiota transplantation was thought to be a potential therapeutic option, current evidence suggests there is no improvement in global IBS symptoms after faecal microbiota transplantation [100] .

Table I - Rome IV criteria for IBS
Patient has recurrent abdominal pain (≥1 day per week, on average, in the precious 3 months), with an onset ≥6 months before the diagnosis Abdominal pain is associated with at least two of the following three symptoms: - Pain related to defecation - Change in frequency of stool - Change in form/appearance of stool
No alarm features are present: - Unintended weight loss (>10% in 3 months) - Presence of blood in the stools - Symptoms that awaken the patient in the night - Fever in association with the bowel symptoms - Family history of colorectal cancer, inflammatory bowel disease or celiac disease - New onset of IBS symptoms after 50 years of age - Recent change in bowel habits - Palpable abdominal mass or lymphadenopathy - Evidence of iron-deficiency anaemia - Positive test for faecal occult blood

Table II - Therapeutic options for IBS based on predominant symptom							
Symptom	Therapy	Agent	Dose	Target	Type of study	Results	References
Diarrhea	Opioid agonists	Loperamide	2 to 4 mg when necessary up to 16mg/day	μ-opioid receptor	DBPCCT	Improvement of stool consistency, pain and urgency, decreasing frequency of defecation	[77,78]
	Diet	Low FODMAPs	Not applicable	Lumen and gut microbiota	RCT	Improvement of bloating, abdominal pain, urgency, stool frequency and consistency	[60,61]
	Bile acid sequestrants	Cholestyramine Colestipol	4g tid (up to 24g/day) 2g qd-bid	Bile acids	RCT	Reduction of stool frequency	[86]
	Probiotics	Multiple products available		Gut microbiota	MA	Improvement of bloating, abdominal pain and flatulence	[89,90]
	Antibiotics	Rifaximin	400mg tid, 14 days	Gut microbiota	DBPCCT	Significant relief of bloating, abdominal pain and loose or watery stools	[88]
	5-HT_3 antagonists	Ondansetron	4-8mg tid	5-HT_3 receptor	RCT, MA	Relief of loose stools, frequency and urgency	[82,83]
	Mixed opioid agonists/ antagonists	Eluxadoline	100mg bid	μ-opioid, δ-opioid and κ-opioid receptors	RCT	Delay of GI motility and reduction visceral hypersensitivity	[79]
Constipation	Soluble fiber	Psyllium	Up to 30g/day in divided doses	Unclear	MA	Improvement of global IBS-C symptoms, increasing stool frequency	[59]
	Motility accelerants	Linaclotide	290μg qd	Guanylate Cyclase C	DBPCCT, RCT	Laxative effect, reduction of colonic nociception and abdominal pain	[73,74]

		Lubiprostone	8µg bid	Chloride channel	RCT	Increased stool frequency, improvement of stool consistency and reduction of abdominal pain and bloating	[76]
Abdominal pain	Smooth muscle antispasmodics	Pinaverium	100mg bid	Calcium channel	DBPCCT	Relief of abdominal pain and improvement of stool consistency	[66]
		Mebeverine	200mg bid	Anticholinergic (mechanism of action is not known)	MA, RCT	Improvement of global wellbeing, with reduction of abdominal pain and daily defecation frequency	[68,69]
		Peppermint oil	Enteric-coated capsules, 250-750mg, bid-tid	Calcium channel	MA	Improvement of global IBS symptoms, specially abdominal pain	[67]
	Tricyclic antidepressants	Desipramine Amitriptyline	25-100mg qhs 10-50mg qhs	Mostly serotonin and noradrenaline transporters	MA	Improvement of global IBS symptoms, specially abdominal pain	[91]
	Selective serotonin reuptake inhibitors	Paroxetine Sertraline Citalopram	10-40mg qd 25-100mg qd 10-40mg qd	Presynaptic serotonin receptor	MA	Improvement of global IBS symptoms, specially abdominal pain	[70]
	Motility accelerants	Linaclotide	290µg qd	Guanylate Cyclase C	DBPCCT, RCT	Laxative effect, reduction of colonic nociception and abdominal pain	[73,74]
		Lubiprostone	8µg bid	Chloride channel	RCT	Increased stool frequency, improvement of stool consistency and reduction of abdominal pain and bloating	[76]

DBPCCT: Double-Blind Placebo-Controlled Clinical Trial, MA: Meta-Analysis, RCT: Randomized Clinical Trial

Table III - Foods with high- and low-FODMAPs content
Foods with high-FODMAPs content: - Wheat, rye, barley - Cabbage, cauliflower, onion, garlic, asparagus - Beans, lentils, peas - Mushrooms - Milk and dairy products - Honey, corn syrup, artificial sweeteners - Apples, pears, watermelon, stone fruits (mango, peach, nectarines, plums, cherries)
Foods with low-FODMAPs content: - Vegetables: cucumber, carrot, corn, eggplant, lettuce, leafy greens, pumpkin, potato, squash, tomato, zucchini - Fruits: banana, grapes, grapefruit, kiwi, lemon, lime, orange, passion fruit, pineapple, tangerine - Protein: beef, chicken, canned tuna, egg, fish, lamb, pork, shellfish, turkey, cold cuts, nuts, seeds - Dairy and non-dairy alternatives: lactose-free milk, cream cheese, cheddar cheese, parmesan, mozzarella, almond milk, rice milk - Grains: products made with wheat-free grains and flours, rice, quinoa - Beverages: water, coffee, tea

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