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Irritable Bowel Syndrome (IBS) Clinical Review

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Abstract – Irritable bowel syndrome (IBS) is a chronic and recurrent functional gastrointestinal disorder that influences 9-23% of the population across the world. Patients with IBS are regularly referred to gastroenterology, go through different examinations, take different drugs, take time off work and have a low quality of life. The pathophysiology of IBS isn't yet totally comprehended and it seems to be multifactorial. Numerous pathogenetic factors, and not all necessarily present in every patient, can assume a significant part, discomfort or abdominal pain relieved by defecation, associated with an adjustment of stool form, is a typical clinical sign of IBS. Numerous variables, like emotional stress and eating, may intensify the manifestations. A timely diagnosis of IBS is significant with the goal that treatment which will give sufficient indicative alleviation (diarrhea, constipation, pain and bloating) can be presented. The finding of IBS isn't affirmed by a particular test or underlying irregularity. It is made utilizing rules dependent on clinical symptoms like Rome criteria, except if the symptoms are believed to be atypical. Today the Rome Criteria IV is the current gold standard for the determinations of IBS. Treatment of patients with IBS requires many approaches. A few patients react well to non-pharmacological treatment, while others likewise require pharmacological treatment. This review will give a summary of pathophysiology, symptomatic standards and therapies for IBS.

Keywords – Irritable Bowel Syndrome, Pathogenesis, Diagnosis, Rome Criteria, Therapy.

I. INTRODUCTION

Irritable bowel syndrome (IBS) is a persistent, chronic, relapsing and the most prevalent functional problem of the gastrointestinal tract. This disease is described by abdominal pain, bloating, and changes in bowel habits that lack a known structural or anatomic explanation [1-3]. Throughout the long term, the unexplained gastrointestinal symptoms of IBS have been described in different terms, including mucous colitis, spastic colitis, nervous colon, and irritable colon [4]. The symptoms of IBS show up and disappear over the long time, and are regularly connected with other functional gastrointestinal diseases and non-gastrointestinal somatic pain disorders [5]. Patients with IBS are frequently referred to gastroenterology, go through different examinations, take various medicines, get some much-needed rest work and have a low quality of life. Notwithstanding, there is countless patients that don't report to the specialist's office or look for clinical attention [6,7]. The main instance of IBS was portrayed by Osler in 1982 as 'mucosal colitis'. Patients complained of abdominal pain and in the fundamental were hysterical, hypochondriacs people or depressed. The term 'irritable colon' first showed up in the clinical writing when it was used by Jordan and Kiefer to describe a colonic Musculo neural disorder present in 30% of gastroenterology outpatients. In spite of the huge number of studies that endeavor to clarify IBS, the disease keeps on introducing as a challenge in the 21st century [8].

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1. Epidemiology

IBS is a chronic and debilitating functional gastrointestinal problem that influences 9-23% of the population across the world [7]. women are two to multiple times bound to create IBS than men [9]. Age-related onset of IBS symptoms occurred predominantly in patients younger than 45 years however prevalence rose again in the elderly [10]. Numerous cases develop in early childhood [11]. The development of symptoms in individuals older than 40 years doesn't exclude IBS however should incite a nearer look for an underlying organic etiology [7]. The prevalence changes according to country and criteria used to define IBS. The impacts of socioeconomic status have not been well described [9,12]. The role of various cultural impacts and varying health care-seeking behaviors is unclear [11,12].

2. Pathogenesis

Regardless of its high prevalence, the pathophysiology of IBS isn't yet totally comprehended and seems to be multifactorial [4-6,13,14]. Many pathogenetic factors (Table 1), in different combinations, and not all necessarily present in each patient, can play a significant role [15]. It is unclear which among these variables is the trigger or how these conditions unite to start IBS.

Table 1. Factors potentially involved in pathogenesis of irritable bowel syndrome [15].

1.	Genetic predisposition.
2.	Altered intestinal motility.
3.	Intestinal hypersensitivity.
4.	Psychological distress and disorders.
5.	Enteric infection/contamination.
6.	Altered gut microbiota.
7.	Food intolerance.

2.1 Genetic predisposition

The impact of hereditary predisposition in the development of IBS has been well-researched. A positive family history for IBS is available in 33% of patients [15]. Having a parent with IBS is a more prominent predictive factor for IBS than having a twin with IBS, which shows that environmental factors may assume a larger part than hereditary ones [16].

Various studies have explored the conceivable part of gene polymorphisms coding for mitigating and favorable to provocative interleukins, alpha 2 adrenergic receptors, serotonin (SERT) and cholecystokinin (CCK) receptors [17]. There is a significant relationship between SERT polymorphisms and IBS symptom severity, despite the fact that their conceivable direct causal role stays to be demonstrated. Moreover, the current discoveries don't uphold a relationship of SERT with IBS or its clinical presentation as far as bowel habit predominance [18]. Traditionally, IBS has been conceptualized as a state of altered intestinal motility (prompting diarrhea or constipation), intestinal hypersensitivity (prompting abdominal discomfort or pain), and psychopathology [7,19].

2.2 Altered intestinal motility

In patients with IBS, environmental stress or strong emotion by means of the brain- gut axis can prompt dysmotility all through the small and large intestine. Patients with IBS have a significantly more noteworthy motility reaction to stressors when compared with ordinary subjects [20,21]. Small bowel dysmotility shows as speed up meal transit in patients prone to diarrhea and in postponed meal transit in patients prone to constipation. Likewise, patients display more shorter intervals between migratory motor complexes (predominantly interdigestive small bowel motor pattern). Colonic dysmotility in IBS shows as varieties in slow wave frequency and a blunted, late-peaking, postprandial reaction of spike potentials. Patients who are prone to diarrhea show these adjustments to a more noteworthy degree than patients who are prone to constipation [22].

Serotonin, acting especially through receptors, plays a critical part in the control of gastrointestinal motility. It has been seen observed that plasma serotonin concentrations are decreased in IBS patients with constipation, however brought up in those with diarrhea. There has been extensive interest in these receptors as conceivable therapeutic targets for IBS, with agonists or antagonists at the serotonin receptor [23-25].

2.3 Intestinal hypersensitivity

Intestinal hypersensitivity is a multifactorial cycle that may happen inside the peripheral or central sensory systems and plays a key part in the etiology of IBS [25].

This specific hypersensitization happens because of stimulation of different receptors of visceral afferent nerve fibers in the gut wall, set off by gut distention or bloating, and is a potential clarification for IBS symptoms. The increased sensitivity of the colon could be impacted by a psychological tendency to report pain and urgency, instead of increased neurosensory sensitivity [26,27].

2.4 Psychopathology

There is a reasonable increased prevalence of current psychological distress among patients who seek for medical care for IBS. Symptoms of anxiety, depression, paranoia and global psychological symptoms are normally experienced in these patients. A study has proposed that patients with IBS may have suicidal ideation and/or suicidal attempts because of their bowel symptoms. Several studies have exhibited more significant levels of physical abuse among IBS patients compared with patients in other medical clinics [7].

Patients with IBS who don't present for care generally have a normal psychological profile, albeit some studies show expanded psychosocial distress of intermediate severity [28]. Limbic system abnormalities, as exhibited by positron emission tomography, have been portrayed in patients with IBS [29].

Koloski et al directed a 12-year longitudinal, prospective, population-based concentrate on the brain gut axis and inferred that the central nervous system and gut react bidirectionally in functional gastrointestinal disorders [30]. psychological problems can influence the brain-gut axis, advancing the arrival of corticotropin-releasing hormone, which can impact mood, digestive motility, visceral sensitivity and inflammatory pathways by means of neuroendocrine and autonomic outflows [31]. Stress in IBS patients expands the levels of pro-inflammatory interleukins, activating both the hypothalamic-autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis and therefore builds the serological adreno-cortico-tropic hormone and cortisol levels [32].

2.5 Enteric infection/inflammation

Enteric inflammation has been noted in certain patients with IBS after prolonged infectious enteritis (postinfectious IBS) [15]. In patients with Giardia lamblia disease the predominance of IBS was 46.1% up to 3 years after exposure, compared with 14% in controls [33]. The mechanisms that cause postinfectious IBS are known however could include residual inflammation or persistent changes for mucosal immunocytes, enterochromaffin and mast cells, enteric nerves, and the gastrointestinal microbiota [7]. vomiting during initial enteric infection may decrease the risk of postinfectious IBS, potentially by diminishing the pathogen load in the distal gastrointestinal tract [34].

2.6 Changed gut microbiota

Differences in the bacterial composition of the gut and also decreased fecal microbial diversity in IBS patients, comparative with healthy people, have suggested a causative role in the onset and maintenance of IBS [35]. The microbiota is modified in IBS and such modifications may add to the pathogenesis of the problem through, for instance, expanded penetrability, an altered immune profile, consequences for gut–brain axis and regulation of gut neuromuscular function [36]. Lactobacilli and bifidobacterial were discovered to be diminished in IBS patients, and their activities were discovered to be vigorously compromised [15]. Moreover, there is proof that probiotics can influence intestinal fermentation and stabilizing out microbiotia, normalizing the relationship among pro and anti-inflammatory cytokines. This outcome beneficially affects intestinal inflammation, penetrability and visceral sensitivity [37].

2.7 Food intolerance

Patients with IBS will in general report that their symptoms are frequently exacerbated by specific food varieties. The traditional IgE mediated food hyper allergy doesn't appear to assume a significant part in IBS [38]. As of late, it has been seen that the ingestion of gluten causes abdominal discomfort and IBS-like symptoms in subjects without a determination of celiac disease (gluten sensitivity). Undoubtedly, the gluten, as other notable variables, alters the intestinal permeability, activating the enteric and autonomous nervous systems and producing of the typical symptoms of IBS [39,40].

II. Clinical Manifestations

Discomfort and abdominal pain relieved by defecation, associated with a difference in stool structure, is a typical clinical manifestation of IBS [4]. Many factors, as emotional stress, and eating, may exacerbate the pain. Patients with IBS complain of altered bowel habits, ranging from the diarrhea, constipation, or alternating the diarrhea and constipation; up to 33% of patients will move beginning with one assembling then onto the following.

Patients with IBS and constipation may experience a sensation of incomplete evacuation and periods of constipation can last from days to months, alternating with the diarrhea or normal bowel function [41]. Bloating or a feeling of abdominal distension are very frequent complaints in IBS and may be associated with the diagnostic criteria for IBS on the future. Most adults sign of IBS and ought to be part both of the symptom complex and of the outcome extents of drug trials [42]. Most adults with the condition, experience episodes of symptom exacerbation, followed by periods of remission.

IBS is much of the time similarly associated with other digestive symptoms as dysphagia, dyspepsia, nausea and non-cardiac chest pain. Comorbidity with other functional gastrointestinal disorders (FGIDs) is high and can be achieved by shared visceral hypersensitivity pathophysiological mechanisms [4,5]. Fibromyalgia, chronic fatigue syndrome, temporomandibular joint issue and chronic pelvic pain are nongastrointestinal disorders with an especially recorded relationship with IBS [4]. In like manner consistently related are psychiatric disorders including major depression, anxiety and somatoform disorders [43]. These comorbidities are associated with a more significant need to search for clinical attention, a worse prognosis, and a higher rate of anxiety and depression, all of which add to a reduced quality of life [44]. It is basic to see these results as a part of the IBS symptomatology and avoid unnecessary additional specialists' examinations.

1. Diagnosis

A convenient determination of IBS is significant with the goal that treatment which will give satisfactory symptomatic relief (from diarrhea, constipation, pain and flatulence) can be presented. Research demonstrates that many primary care providers are unaware of the diagnostic criteria for IBS and that these patients are regularly referred to expert gastroenterologists for additional analytic testing [45]. However, most of patients can be overseen adequately by doctors in the primary care setting at a lower cost [46]. However, when making a diagnosis, thought ought to be given to the way that the symptoms of IBS are like those of organic disorders and can coexist with organic disease.

The principal attempt at building up a diagnostic criteria that would define IBS dates back to 1970 by Manning and associates [47]. Following this, more consideration was paid to this functional digestive disorder, such that in Rome, a Rome Foundation was shaped which assumed an urgent part in making a diagnostic criteria and operationalizing the spread of new information in the field of all functional gastrointestinal problems. The Rome I standards was published in 1990, Rome II criteria in 1999 and Rome III criteria in 2006. Rome IV standards is a summary of the information aggregated since Rome III was published 10 years ago [48-50]. The improvement of the Rome IV standards (Table 2) occurred over a six-year time period including the contribution from more than 100 specialists worldwide [51]. Albeit the Rome diagnostic criteria for IBS are broadly utilized in clinical trials, there is acknowledgment that they are not regularly utilized in clinical practice [52].

It is essential to request that the patient explain the circumstance, severity and area of their pain or discomfort, and whether this is generalized abdominal pain. Four bowel patterns might be seen with IBS, and these remain in the Rome IV classification [53].

- IBS-D (diarrhea predominant)
- IBS-C (constipation predominant)

Table 2. Rome IV Criteria for Diagnosing IBS [51]

Recurrent abdominal pain at any rate 1 day/week over the last 3 months, with in any event two of the following criteria:
• Related to defecation
• Associated with an alteration in frequency of stool
• Associated with a change in form (appearance) of stool the criteria ought to be met throughout the previous 3 months and the symptoms begin at least 6 months before diagnosis.

- IBS-M (mixed diarrhea and constipation)
- IBS-U (unclassified; the symptoms can't be categorized into one of the above three subtypes)

Patients may encounter a change starting with one IBS subtype then onto the next with time. In patients who meet the diagnostic criteria for IBS, other digestive related diseases ought to be avoided, and the following investigations be attempted: blood count, biochemical and inflammatory markers and immunological tests for celiac disease. The following investigations in such patients are unnecessary: ultrasound checking of the abdomen, recto sigmoidoscopy or colonoscopy or irrography, thyroid and parathyroid analysis, stool analysis (parasites, microscopic organisms, specifically Clostridium difficile toxin, and potentially Giardia antigen, occult bleeding test Lactose intolerance). The choice to embrace further examinations is reliant upon the presence of other risk factors or alarming symptoms (Table 3) [11]. For individuals under 50 years, that meet the criteria for IBS, there ought to be no further gut assessment if the accompanying highlights

are absent: weight loss, hypochromic anemia and additionally family background of certain GI illness.

In patients with IBS-D, a differential diagnostic that incorporates the accompanying ought to be thought of: microscopic colitis, ulcerative colitis, Crohn's sickness, celiac disease, Giardiasis, lactose malabsorption, tropical sprue, bacterial small bowel contamination, malabsorption of bile salts and colorectal cancer.

III. The Recommendation For Clinical Praxis

While deciding IBS treatment, one should initially determine which type of IBS is it, or which are the prevailing symptoms and signs. Today, there are different gatherings of medications for the treatment of IBS. In any case, regardless of the positive therapeutic effects, some medications have their limits in the view on not having the option to be utilized for long time, or they have contra-indications or side-effects. Nonetheless, this ought not discourage specialists, particularly those of primary medical services, when choosing to begin with IBS treatment. Treatment should start slowly utilizing a non-pharmacological treatment as per IBS type. For the situation where a non-pharmacological treatment doesn't lead to improvement, a pharmacological treatment ought to be added. Start treatment with one, perhaps two medicaments (most normally added to the IBS-C antispasmodics). Treatment ought to be begun with a medicament that has the most involvement with clinical practice. Notwithstanding various studies that have thought about various therapeutic choices, an ideal IBS treatment algorithm can't yet be formed.

Prior to commencing with treatment, the patient ought to be instructed and made aware of the nature of IBS. In addition to other things, patients ought to be educated about the typical recurrence of intestinal emptying, which goes from three times each day to three times each week. Treatment of patients with IBS requires many approaches. Treatment is on an individual basis and dependent on the dominant symptoms. Not all patients react to a similar treatment. Specific consideration ought to be paid to disaggrevating factors in IBS like nutrition, stress, and psychological factors. some patients react well to nonpharmacological treatment, while others require pharmacological treatment.

1. Non-pharmacological treatment

Expanded physical activity improves side effects in IBS-C. Truly active patients with IBS-C will confront less symptom deterioration compared to inactive patients. Physical activity ought to be utilized as a primary treatment modality in IBS-C. Nonetheless, excessive exercise isn't recommended [54]. An increment in active work in IBS-C patients adds to speeding up transit through the colon and lessening bloating [55]. The relationship among nourishment and its impact relies upon the type of IBS; a similar dietary counsel can't be applied to all IBS patients. It is suggested that patients keep a diet diary where they can record which food varieties lead to manifestations. Patients with IBS regularly express that specific food types exasperate their manifestations, for example caffeine, dairy products and cereals, and artificial sweeteners [56].

Table 3. Alert manifestations that recommend natural intestinal disease [11]

• A change in bowel habit to looser or potentially more continuous stools enduring for over about six weeks in an individual aged.
• Family history of bowel or ovarian disease.
• Rectal bleeding.
• Rectal masses.
• Abdominal masses.
• Anemia.
• Raised inflammatory markers.

Table 4. Clinical Guidelines for changing healthful admission in IBS patients [11]

• Eat regular meals and permit sufficient time for them.
• Drink at least 8 glasses of liquids, especially water or other non-caffeinated drinks during the day. Restrict Coffee or tea to 3 cups each day.
• When it hasn't prompted an improvement, limit the admission of high-fiber food sources (like whole meal flour and breads, cereals high in wheat, and entire grains like brown rice).
• Reduce the intake of "resistant starch".
• Limit the intake of fresh fruits product to 3 portions each day (a proximately is roughly 80 g).
• Reduce the intake of alcohol and fizzy drinks.
• In IBS-D stay away from the sugar Sorbitol,
• In instances of bulging or flatulence oats might be useful.

In certain patients, the admission of gluten exacerbates symptoms, with no evidence of celiac disease, which is related with hypersensitivity to gluten, and it is encouraged to stop it.

Volta et al [57], assessed current proof and recommended that patients with gluten/wheat sensitivity might be a subset of those with IBS, moreover, in certain patients with IBS, fats and lactose can be aggravating factors because of the presence of intolerance or sensitivity to fat and lactose [58]. In the previous few years, an eating regimen low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) has been embraced by patients with IBS, especially those with IBS-D or patients who have manifestations of bloating [59]. National Institute for Health and Care Excellence Gave proposals for modifying nutritional intake in IBS (Table 4) [11]. In situations where an exacting eating regimen has not brought about an attractive result, pharmacological treatment is suggested.

2. Therapeutic approach

Prior to discussing therapeutic options, it is valuable to remember that a strong doctor-patient relationship will be the establishment for compelling treatment and practical expectations [60]. specifically, during the first clinical interview is somewhat attentive listening and a detailed explanation of natural history, pathophysiology, and diagnostic and therapeutic strategies underlying that IBS is a kind condition with no connection with the development of severity of disease or decrease of life expectancy. [61,62].

The therapeutic approach of IBS may comprise of both non-pharmacological treatments and pharmacotherapy and ought to be founded on common symptomatology.

Way of life changes, for example, stress decrease and expanded physical activity appear to be valuable to improve GI symptoms in IBS, as announced by a randomized clinical trial [63]. considering the overall positive wellbeing impacts of structured physical activity, it ought to be supported in IBS patients.

Dietary modifications address an important first-line remedial choice. IBS patients frequently associate their symptoms, for example, bloating and abdominal pain with eating a meal and up to 90% of subjects reduce food intake to diminish or improve postprandial symptoms.[64] regardless of the low pervasiveness and the absence of relationship between actual food hypersensitivities and IBS [65] food intolerance or sensitivities are regularly reported. The role of lactose restriction in IBS symptoms is questionable. as announced in a 5-year follow-up study, up to 85% of IBS patients with lactose malabsorption refer symptoms alleviation after lactose restriction,[66] albeit the last alone is by insufficient for effective symptom remission.[67] an expanded dietary fiber consumption, particularly soluble fiber like psyllium or ispaghula, is a potential treatment alternative in IBS-c patients with an unassuming impact in diminishing worldwide iBS symptoms,[68] while insoluble fiber (bran) could prompt a deteriorating of IBS symptoms, for example, flatulence and abdominal pain.[69].

Non-celiac gluten sensitivity (NcGS) is a new clinical substance without diagnostic biomarkers. [70,71] in some IBS patients it could prompt intensification of symptoms (abdominal pain, bloating, tiredness and changed stool consistency) subsequent to ingesting gluten despite the fact that without celiac disease, [72,73] however this impact is by all accounts identified with ineffectively absorbable carbohydrates rather than gluten itself,[74] so further investigations are fundamental. Fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FOdmaPs) are incompletely absorbed carbs found in foods as wheat, onions, a few products of the vegetables and fruits, sorbitol, and some dairy which cause increased water secretion and fermentation.[75] dietary FOdmaPs limitation could prompt decreased flatulence and symptoms relief in some IBS patients.[76] However, there is no strong evidence for its prevalence over other dietary regimens and a recent comparative effectiveness study on 75 patients has detailed improved IBS side effects both in a low-FOdmaP diet and in a standardized traditional iBS diet, with similar results.[77] in sensitized individuals, the ingested nickel (Ni) may induce GI manifestations like those experienced in IBS (nausea, pyrosis, meteorism, abdominal pain, diarrhea, and constipation), notwithstanding typical systematic cutaneous lesions. This clinical picture is known as systemic Ni hypersensitivity syndrome (SNaS).[78] albeit in the literature there is no broad understanding about the efficacy of a dietary treatment,[79] a few studies have affirmed improvement of dermatitis on Ni free or a low Ni diet for a minimum of about a month (up to a limit of 6 months).[80] in an interesting investigation, showing a high pervasiveness of Ni allergy in patients with IBS,[81] the authors discovered objective evidence that people starting a Ni dietary avoidance had a significant clinical response in their IBS symptoms, affirming the connection among IBS and Ni sensitivity. Besides, low Ni diet permitted numerous food sources normally stayed away from in a low-FOdmaP diet.

The pharmacological treatment should consider the prevalent symptoms and test each drug in turn with a predefined time point for viability assessment and measurement change. Treatment objectives ought to be reasonable, imparted to the patient and focused to diminish specific symptoms. Transitory suspension of treatment could be helpful to assess on the off chance that it is as yet required.

2.1. Pharmacotherapy for IBS-D

Loperamide is an synthetic peripheral μ-narcotic receptor agonist frequently utilized as first decision with IBS-D to inhibit peristalsis, prolong transit and decrease fecal volume [82] On the other hand it isn't effective on the decrease of other IBS-d symptoms like abdominal pain or bloating.[83] it very well may be utilized either for intermittent or chronic diarrhea as it doesn't cross the blood brain barrier and is less liable to addiction.[82] Since 33% of patients with IBS-d have bile acid diarrhea, numerous gastroenterologists incline toward bile acid sequestrants, for example, cholestyramine, colesevelam and colestipol.[84] for this situation, small pilot studies improved stool passage and stool consistency[85,86]

albeit thorough, randomized preliminaries are attractive. Utilizing these medications, the most well-known unfavorable impact is constipation however beginning with a low dose and step by step expanding it is possible to keep away from this result.

As of now referenced 5-HT impacts GI transit and visceral sensation through 5-HT3 and 5-HT4 receptors. 5-HT3 receptor antagonists, initially produced for chemotherapy-prompted nausea and vomiting, additionally cause constipation [87] aldosterone, an highly selective 5-HT3 antagonists, is accessible under limited permit in the United States for women with extreme IBS-d to calm pain and diminish stool recurrence and rectal urgency[88] hence , this drug should not be used in ischemic colitis and dose dependent constipation [89] Other 5-HT3 antagonists (ondansetron and ramosetron) likewise appear to be powerful in IBS-d patients decreasing urgency and average stool frequency [90,91]

Eluxadoline, a mixed μ-receptor agonist/δ-opioid receptor antagonists recently approved in the US for IBS-d [92], the most widely recognized unfavorable occasions were constipation, nausea and abdominal pain, while uncommon results were sphincter of Oddi dysfunction or self-limited pancreatitis.[88] Hence, this drug ought not be utilized in patients with bile channel obstruction, pancreatitis, severe liver impairment or severe constipation.

rifaximin, a nonabsorbable antibiotic recently approved by the Food and drug administration (FDA) for the treatment of IBS-D, showed significantly alleviation of global IBS symptoms and bloating following 14 days of treatment and during the initial 4 weeks of follow-up.[93] The efficacy, compared to placebo, continued as long as 10 weeks albeit a slow loss of side effect response was noted.

With this drug, a recurrence of symptoms can be retreated with superior efficacy compared to placebo.[94] Nausea is the most common side effect reported.

2.2. Pharmacotherapy for IBS-C

Taking into account that most patients with IBS-c have a typical transit time,[95] fiber supplementation and bulking agents are frequently utilized as first line treatment in this unique circumstance. In a meta-analysis soluble fiber (psyllium and ispaghula) showed modest improvement in global IBS symptoms [91] though, since they can exacerbate IBS symptoms (particularly flatulence and abdominal) [92] insoluble fiber (bran) ought to be avoided, fiber dosage ought to be titrated gradually to a total daily intake of 30g.

Polyethylene glycol (PeG) is an osmotic laxative utilized either as first-line in IBS-C or as second-line when treatment with fiber and bulking agents fails. Clinical preliminaries showed improvements for stool frequency and stool consistency yet not on abdominal pain or bloating.[96] PeG is typical very much tolerated however can cause dose dependent bloating, gas and loose stools.

Prucalopride, a highly selective 5-HT4 agonists, is approved in Europe for symptomatic therapy of patients with chronic constipation as second-or third-line after purgatives failure. as opposed to nonselective 5-HT4 agonists (cisapride, removed due to heart arrhythmias;[97] tegaserod limited being used due to ischemic cardiovascular events [98]), it has not been related with adverse cardiovascular events. [98,99] Large, multicenter randomized controlled preliminaries (rcTs) have shown the efficacy and safety of prucalopride in chronic idiopathic constipation,[100] and its term effects,[101] yet no preliminary has been published with regards to IBS-c.

Lubiprostone is a selective type 2 chloride-channel (ClC-2) activator that stimulate intestinal fluid secretion, acting as a stool lubricant and facilitating its evacuation. This drug has been approved in USA and Switzerland (8 mg twice every day) for treatment in women with IBS-c with evidence of higher overall response compared and placebo.[102] Possible adverse effects impacts are nausea and diarrhea, more frequent at higher dosage (8% with an 8-µg portion and 33%with a 24-µg dose) and away from food.

Linaclotide is a new type of intestinal secretagogue that goes about as a guanylate cyclase-c agonist expanding cyclic guanosine monophosphate production. The result is an expanded intestinal chloride secretion through the cystic fibrosis transmembrane controller. In IBS-C, at the dose of 290 µg day by day, linaclotide improves stool frequency and consistency, ease of defecation and abdominal pain, discomfort and bloating.[103]

The maximum benefit happens within a week of treatment commencement for stool frequency, while for abdominal pain and bloating it might take 8 to 12 weeks. The most side effect is the diarrhea.

2.3. Pharmacotherapy for abdominal pain

Antispasmodics (dicycylomine, otilonium, mebeverine) are utilized in all IBS subtypes to treat symptoms like abdominal pain and spasm. as they reduce GI contractility, these drugs are useful for postprandial symptoms related to exaggerated gastrocolic reflex. The mechanism of action incorporates either anticholinergic or calcium channel blocking properties and the efficacy is superior than placebo treatment for the anticipation of intermittent IBS symptoms.[78] Peppermint oil is another compound with antispasmodic properties for global improvement of IBS symptoms and abdominal pain.[78] Heartburn and reflux symptoms are the most frequent adverse effects[104] The actions of trimebutine [3,4,5-trimethoxybenzoic corrosive 2-(dimethylamino)- 2-phenylbutylester] on the GI tract are mediated by means of (i) an agonist impact on peripheral µ, k and δ narcotic receptors and (ii) release of Gi peptides like motilin and modulation of the release of different peptides, including vasoactive intestinal peptide, gastrin and glucagon. Trimebutine speeds up gastric emptying, induces premature phase of the migrating motor complex in the intestine and modulates the contractile activity of the colon. Trimebutine has additionally been appeared to diminish reflexes induced by distension of the gut lumen in animals and it might subsequently adjust visceral sensitivity.

clinically, trimebutine has proved effective in the therapy of both acute and chronic abdominal pain in patients with functional bowel problems, particularly IBS, at doses going from 300 to 600 mg/day.[105] centrally acting agents, for example, antidepressants are a therapeutic alternative because of their impact on pain perception, mood, and motility, acting on dysregulation of the brain-gut axis.

Both tricyclics antidepressants (Tcas) and selective serotonin reuptake inhibitors (SSRIs) showed adequacy in treating IBS symptoms,[105] while few information are accessible for particular norepinephrine reuptake inhibitors (SNris).[106]

The decision of various kind of antidepressant could be tended to by the stool habit, the presence of insomnia, or comorbid anxiety taking advantage of side effects. For example, as Tcas can cause constipation, they may be valuable in IBS-d patients. Besides, likewise patients with an insomnia, anorexia, or weight reduction may discover advantage with Tcas. Then again, SSris might be a superior decision for IBS-c patients due to their prokinetic impacts and for IBS subjects with significant anxiety. Beginning with the lower dose and gradually expanding it if a sufficient reaction isn't seen, is viewed as a wise approach.[107] Taking into account the role of the gut-brain axis, immune, neural, and endocrine pathways in the pathogenesis of IBS, the conceivable valuable impact of benzodiazepines (BZD) in this axis ought to be thought of BZd receptor modulators can be useful, particularly in the diarrhea of the bowels prevailing type of IBS, by influencing the inflammatory, neural, and psychologic pathways. Nonetheless, discussions still exist.[108], a summary of treatment options based on dominant IBS symptom is shown in Table 5.

Table 5: summary of treatment options based on dominant IBS symptom

a. Diarrhea

Narcotic agonist: loperamide (2-4 mg/d, up to 16 mg/d) Bile acid sequestrants
• cholestyramine (9 g bid-tid)

• colestipol (2 g qd-bid) • colesevelam (625 mg qd-bid) 5-HT3 receptor adversaries:
• alosetron (0.5-1 mg bid)
• ondansetron (4-8 mg tid)
• ramosetron 5 mg qd
• Mixed narcotic agonists/antagonists: eluxadoline (100 mg bid) anti-microbials: rifaximin (550 mg tid for 14 d)

b. Constipation

Type 2 chloride-channel activator: lubiprostone (8 µg bid)
Guanylate cyclase-c agonist: linaclotide (290 µg qd)

c. Abdominal pain

antispasmodics: • dicyclomine (10-20 mg qid • otilonium (40-80 mg bid-tid) • mebeverine (135 mg tid)
Peppermint oil: 250-750 mg, bid-tid Tricyclic antidepressants: • desipramine (25-100 mg/d)
• amitriptyline (10-50 mg/d) Selective serotonin reuptake inhibitor: • paroxetine (10-40 mg/d) • sertraline (25-100 mg/d

2.4. Different medicines

Since the role of gut microbiota in the pathogenesis of IBS is a relevant topic, probiotics are generally utilized in this context.[109] Multiple mechanisms may prompt benefit [110] and a meta-analysis including 43 clinical preliminaries showed that different probiotic products had efficacy on global IBS symptoms, pain, bloating and flatulence.[111]

A case control study, a group has shown that a mix of L-tryptophan, inulin, angelica, vegetal charcoal, group and probiotics (Lactobacillus sporogenes, Lactobacillus acidophilus, Streptococcus thermophilus), in a cohort of patients with IBS decreased significantly abdominal pain, abdominal distension and constipation [112]

These advantageous impacts could be clarified through the modulation of several activities. Its peculiarity resides in the impact on serotonin (5-HT) production, because of the essential amino acid tryptophan. Serotonin has a key role in the pathogenesis of IBS in light of the fact that while in the GI tract impacts the peristaltic activity, it is likewise included as a neurotransmitter in the central nervous system and is notable its implication in platelet aggregation.

The way that probiotics give off an impression of being safe contribute to their wide use. The biopsychosocial model portrays the collaboration among psychosocial and physiological factors related with IBS. It clarifies how the early life factors like genetic predisposition and social learnings, the psychological factors related with life stress, and the gut pathophysiology like dysmotility, visceral hypersensitivity and brain-gut interactions, connect each other impacting GI symptomatology, patient reaction and illness outcome.[113] Psychological treatments give another option or adjunctive therapy for IBS patients and are predominantly cognitive behavioral treatment (cBT), psychodynamic psychotherapy, relaxation treatment, care and gut-directed hypnotherapy. Psychological interventions might be marginally better than usual care toward the end of treatment,[114] and a meta-analysis considering 32 separate preliminaries showed that cBT, hypnotherapy, multicomponent psychotherapy and dynamic psychotherapy were all effective treatments for IBS.[106] in spite of this, poor patient and clinician acceptance of the requirement for treatment, the expenses and the span of the actual treatment could restrict the reception of these treatments in clinical practice.

Integral and elective treatments are regularly utilized by numerous IBS patients notwithstanding the absence of evidence.[115] Some of these medicines have been summed up in Cochrane surveys. acupuncture was no greater than sham acupuncture therapy in improving symptoms or quality of life,[116] while Chinese herbal therapy has showed efficacy in alleviating IBS symptoms.[117] However, further investigations are attractive with satisfactory control groups and validated study endpoints.

IV. Prognosis

In many patients with IBS symptoms persists however they don't decline, while the rest may encounter deteriorating or complete resolution. Components that may add to a poor prognosis include:

- Uncertainty or uncertainty concerning the impact of medicinal treatment.
- Damage to the gut because of existing symptoms.
- Long standing IBS.
- Chronic stress exposure.
- Comorbidity of psychiatric diseases.

V. Conclusion

IBS is a typical issue with a significant effect on personal satisfaction and medical care costs. in spite of new Rome IV symptom-based criteria have been recently affirmed, IBS stays a significant test both for diagnosis and treatment. A valuable clinical methodology ought to think about a mix of the analytic measures (with clinical history and actual assessment), a predetermined number of demonstrative tests, and a careful follow-up. For most patients, when symptomatic models are satisfied and alert side effects are missing, the requirement for demonstrative tests ought to be negligible. The remedial methodology of IBS may comprise of both non-pharmacological treatments and pharmacotherapy, recalling that a strong doctor patient relationship is central for successful treatment and reasonable assumptions. as the treatment ought to be founded on prevalent symptomatology, a several IBS-specific agents showed efficacy in randomized controlled preliminaries, albeit further examinations are attractive to more readily customize the treatment and provide the most significant benefit.

Conflict Of Interest

All authors declare no conflicts of interest.

Authors Contribution

Authors have equally participated and shared every item of the work.

References

[1] Sinagra, Emanuele, Claudia Romano, and Mario Cottone. "Psychopharmacological treatment and psychological interventions in irritable bowel syndrome." Gastroenterology Research and Practice 2012 (2012).

[2] Belcaro, G., et al. "Supplementation with a lecithin-based delivery form of Boswellia serrata extract (Casperome®) controls symptoms of mild irritable bowel syndrome." Eur Rev Med Pharmacol Sci 21.9 (2017): 2249-54. [3]. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. JAMA 2015;313(9):949-58.

[4] Soares, Rosa Leonôra Salerno. "Irritable bowel syndrome, food intolerance and non-celiac gluten sensitivity. A new clinical challenge." Arquivos de gastroenterologia 55.4 (2018): 417-422. [5]. Noddin, Laura, Michael Callahan, and Brian E. Lacy. "Irritable bowel syndrome and functional dyspepsia: different diseases or a single disorder with different manifestations?" Medscape General Medicine 7.3 (2005): 17.

[6] Scalera, A., and C. Loguercio. "Focus on irritable bowel syndrome." Eur Rev Med Pharmacol Sci 16.9 (2012): 1155-71.

[7] Saha, Lekha. "Irritable bowel syndrome: pathogenesis, diagnosis, treatment, and evidence-based medicine." World Journal of Gastroenterology: WJG 20.22 (2014): 6759.

[8] Hoveyda, Nourieh, et al. "A systematic review and meta-analysis: probiotics in the treatment of irritable bowel syndrome." BMC gastroenterology 9.1 (2009): 1-11.

[9] Canavan, Caroline, Joe West, and Timothy Card. "The epidemiology of irritable bowel syndrome." Clinical epidemiology 6 (2014): 71.

[10] Grundmann, Oliver, and Saunjoo L. Yoon. "Irritable bowel syndrome: Epidemiology, diagnosis and treatment: An update for health-care practitioners." Journal of gastroenterology and hepatology 25.4 (2010): 691-699.

[11] Excellence, Care. "Developing NICE Guidelines: The Manual [Internet]." (2015).

[12] Lovell, Rebecca M., and Alexander C. Ford. "Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis." Clinical gastroenterology and hepatology10.7 (2012): 712-721. [13]. Houghton, L. A., et al. "Increased platelet depleted plasma 5-hydroxytryptamine concentration following meal ingestion in symptomatic female subjects with diarrhoea predominant irritable bowel syndrome." Gut 52.5 (2003): 663-670.

[14] van der Veek, Patrick PJ, et al. "Testing a biobehavioral model of irritable bowel syndrome." European journal of gastroenterology & hepatology 22.4 (2010): 412-419.

[15] Bellini, Massimo, et al. "Irritable bowel syndrome: a disease still searching for pathogenesis, diagnosis and therapy." World journal of gastroenterology: WJG 20.27 (2014): 8807.

[16] Mohammed, Imtiyaz, et al. "Genetic influences in irritable bowel syndrome: a twin study." American Journal of Gastroenterology 100.6 (2005): 1340-1344.

[17] Park, Moo-In, and Michael Camilleri. "Genetics and genotypes in irritable bowel syndrome: implications for diagnosis and treatment." Gastroenterology Clinics 34.2 (2005): 305-317. [18]. Colucci, Rocchina, et al. "Influence of the serotonin transporter 5HTTLPR polymorphism on symptom severity in irritable bowel syndrome." PLoS One 8.2 (2013): e54831.

[19] Chumpitazi, Bruno P., and Robert J. Shulman. "Underlying molecular and cellular mechanisms in childhood irritable bowel syndrome." Molecular and cellular pediatrics 3.1 (2016): 1-9.

[20] Zeevenhooven, Judith, Ilan JN Koppen, and Marc A. Benninga. "The new Rome IV criteria for functional gastrointestinal disorders in infants and toddlers." Pediatric gastroenterology, hepatology & nutrition 20.1 (2017): 1.

[21] Posserud, Iris, Amanda Ersryd, and Magnus Simrén. "Functional findings in irritable bowel syndrome." World Journal of Gastroenterology: WJG 12.18 (2006): 2830.

[22] Radovanovic-Dinic, Biljana, et al. "Irritable bowel syndrome-from etiopathogenesis to therapy." Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 162.1 (2018): 1-9.

[23] De Ponti, F. "Pharmacology of serotonin: what a clinician should know." Gut 53.10 (2004): 1520-1535.

[24] Mayer, Emeran A., and Sylvie Bradesi. "Alosetron and irritable bowel syndrome." Expert opinion on pharmacotherapy 4.11 (2003): 2089-2098.

[25] Farzaei, Mohammad H., et al. "The role of visceral hypersensitivity in irritable bowel syndrome: pharmacological targets and novel treatments." Journal of Neuro gastroenterology and Motility 22.4 (2016): 558.

[26] Dorn, Spencer D., et al. "Increased colonic pain sensitivity in irritable bowel syndrome is the result of an increased tendency to report pain rather than increased neurosensory sensitivity." Gut 56.9 (2007): 1202-1209.

[27] Nozu, Tsukasa, et al. "Repetitive rectal painful distention induces rectal hypersensitivity in patients with irritable bowel syndrome." Journal of gastroenterology 41.3 (2006): 217-222. [28]. Mertz, H. "Role of the brain and sensory pathways in gastrointestinal sensory disorders in humans." Gut 51. suppl 1 (2002): i29-i33.

[29] Bonaz, B., et al. "Central processing of rectal pain in patients with irritable bowel syndrome: an fMRI study." The American journal of gastroenterology 97.3 (2002): 654-661.

[30] Koloski NA, Jones M, Kalantar J, Weltman M, Zaguirre J, Talley NJ. The brain-gut pathway in functional gastrointestinal disorders is bidirectional: a 12-year prospective population-based study. Gut 2012;61(9):1284-90.

[31] Stasi, Cristina, et al. "Altered neuro-endocrine–immune pathways in the irritable bowel syndrome: the top-down and the bottom-up model." Journal of gastroenterology 47.11 (2012): 1177-1185.

[32] Dinan, Timothy G., et al. "Hypothalamic-pituitary-gut axis dysregulation in irritable bowel syndrome: plasma cytokines as a potential biomarker?" Gastroenterology 130.2 (2006): 304-311. [33]. Hanevik, Kurt, et al. "Irritable bowel syndrome and chronic fatigue 6 years after giardia infection: a controlled prospective cohort study." Clinical Infectious Diseases59.10 (2014): 1394-1400.

[34] Patel, Shaileshkumar R., et al. "Levels of interleukins 2, 6, 8, and 10 in patients with irritable bowel syndrome." Indian Journal of Pathology and Microbiology 60.3 (2017): 385.

[35] Guinane, Caitriona M., and Paul D. Cotter. "Role of the gut microbiota in health and chronic gastrointestinal disease: understanding a hidden metabolic organ." Therapeutic advances in gastroenterology 6.4 (2013): 295-308.

[36] Hyland, Niall P., Eamonn MM Quigley, and Elizabeth Brint. "Microbiota-host interactions in irritable bowel syndrome: epithelial barrier, immune regulation and brain-gut interactions." World journal of gastroenterology: WJG 20.27 (2014): 8859.

[37] Hyland, Niall P., Eamonn MM Quigley, and Elizabeth Brint. "Microbiota-host interactions in irritable bowel syndrome: epithelial barrier, immune regulation and brain-gut interactions." World journal of gastroenterology: WJG 20.27 (2014): 8859.

[38] Atkinson, W., et al. "Food elimination based on IgG antibodies in irritable bowel syndrome: a randomized controlled trial." Gut 53.10 (2004): 1459-1464.

[39] Elli, Luca, et al. "Diagnosis of gluten related disorders: Celiac disease, wheat allergy and non-celiac gluten sensitivity." World journal of gastroenterology: WJG 21.23 (2015): 7110.

[40] Biesiekierski, Jessica R., 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 145.2 (2013): 320-328.

[41] Seo, A. Young, Nayoung Kim, and Dong Hyun Oh. "Abdominal bloating: pathophysiology and treatment." Journal of neuro gastroenterology and motility 19.4 (2013): 433.

[42] Layer, Peter, et al. "Tegaserod in the treatment of irritable bowel syndrome (IBS) with constipation as the prime symptom." Therapeutics and Clinical Risk Management 3.1 (2007): 107. [43]. Bonavita, Vincenzo, and Roberto De Simone. "Towards a definition of comorbidity in the light of clinical complexity." Neurological Sciences 29.1 (2008): 99-102.

[44] Gralnek, Ian M., et al. "The impact of irritable bowel syndrome on health-related quality of life." Gastroenterology119.3 (2000): 654-660.

[45] Hungin, A. P. S., et al. "Systematic review: the perceptions, diagnosis and management of irritable bowel syndrome in primary care–a Rome Foundation working team report." Alimentary pharmacology & therapeutics 40.10 (2014): 1133-1145.

[46] Soubieres, Anet, et al. "Burden of irritable bowel syndrome in an increasingly cost-aware National Health Service." Frontline gastroenterology 6.4 (2015): 246-251.

[47] Sunderland, Rhian. "Irritable bowel syndrome in adults: symptoms, treatment and management." Nursing Standard31.26 (2017).

[48] Drossman, D. A., et al. "Identification of sub-groups of functional gastrointestinal disorders." Gastroenterology international 3.4 (1990): 159-172.

[49] Thompson, W. G., et al. "Functional bowel disorders and functional abdominal pain." Gut 45. suppl 2 (1999): II43-II47.

[50] Drossman, Douglas A. "The functional gastrointestinal disorders and the Rome III process." gastroenterology130.5 (2006): 1377-1390.

[51] Schmulson, Max J., and Douglas A. Drossman. "What is new in Rome IV." Journal of neuro gastroenterology and motility 23.2 (2017): 151.

[52] Lacy, Brian E., et al. "Bowel disorders." Gastroenterology150.6 (2016): 1393-1407. [53] Simren, Magnus, Olafur S. Palsson, and William E. Whitehead. "Update on Rome IV criteria for colorectal disorders: implications for clinical practice." Current gastroenterology reports 19.4 (2017): 15.

[54] Johannesson, Elisabet, et al. "Physical activity improves symptoms in irritable bowel syndrome: a randomized controlled trial." American Journal of Gastroenterology106.5 (2011): 915-922.

[55] Iovino, Paola, et al. "Bloating and functional gastro-intestinal disorders: where are we and where are we going?" World Journal of Gastroenterology: WJG 20.39 (2014): 14407. [56] Spiller R, Aziz Q, Creed F Emmanuel A, Houghton L, Hungin P, Jones R, Kumar D, Rubin G, Trudgill N, Whorwell P. Guidelines on the irritable bowel syndrome: mechanisms and practical management. Gut 2007;56(12):1770-98.

[57] Volta, Umberto, et al. "Dietary triggers in irritable bowel syndrome: is there a role for gluten?" Journal of Neuro gastroenterology and Motility 22.4 (2016): 547.

[58] Catassi, Carlo, et al. "Non-celiac gluten sensitivity: the new frontier of gluten related disorders." Nutrients 5.10 (2013): 3839-3853. A, Castillejo G, Ciacci C, Cristofori F, Dolinsek J, Francavilla R, Elli L, Green P, Holtmeier W, Koehler P, Koletzko S, Meinhold C, Sanders D, Schumann M, Schuppan D, Ullrich R, Vécsei A, Volta U, Zevallos V, Sapone A, Fasano A. Nonceliac gluten sensitivity: the new frontier of gluten related disorders. Nutrients 2013;5(10):3839-53.

[59] Magge, Suma, and Anthony Lembo. "Low-FODMAP diet for treatment of irritable bowel syndrome." Gastroenterology & hepatology 8.11 (2012): 739.

[60] Saha, Lekha. "Irritable bowel syndrome: pathogenesis, diagnosis, treatment, and evidence-based medicine." World Journal of Gastroenterology: WJG 20.22 (2014): 6759.

[61] Owens, Dorothy M., Daniel K. Nelson, and Nicholas J. Talley. "The irritable bowel syndrome: long-term prognosis and the physician-patient interaction." Annals of Internal Medicine 122.2 (1995): 107-112.

[62] Drossman, Douglas A. "Diagnosing and treating patients with refractory functional gastrointestinal disorders." Annals of internal medicine 123.9 (1995): 688-697.

[63] Saha, Lekha. "Irritable bowel syndrome: pathogenesis, diagnosis, treatment, and evidence-based medicine." World Journal of Gastroenterology: WJG 20.22 (2014): 6759.

[64] Hayes, Paula A., Marianne H. Fraher, and Eamonn MM Quigley. "Irritable bowel syndrome: the role of food in pathogenesis and management." Gastroenterology & hepatology 10.3 (2014): 164.

[65] Park, M-I., and Michael Camilleri. "Is there a role of food allergy in irritable bowel syndrome and functional dyspepsia? A systematic review." Neuro gastroenterology & Motility 18.8 (2006): 595-607.

[66] Böhmer, Clarisse JM, and Hans ARE Tuynman. "The effect of a lactose-restricted diet in patients with a positive lactose tolerance test, earlier diagnosed as irritable bowel syndrome: a 5-year follow-up study." European journal of gastroenterology & hepatology 13.8 (2001): 941-944. [67]. Deng, Yanyong, et al. "Lactose intolerance in adults: biological mechanism and dietary management." Nutrients7.9 (2015): 8020-8035.

[68] Ford, Alexander C., et al. "American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation." Official journal of the American College of Gastroenterology| ACG 109 (2014): S2-S26. [69].

Bijkerk cJ, de Wit NJ, muris JW, Whorwell PJ, Knottnerus Ja, Hoes AW. Soluble or insoluble fibre in irritable bowel syndrome in primary care? randomized placebo-controlled trial. BmJ 2009;339: b3154.

[70] Vasagar, Brintha, et al. "World epidemiology of non-celiac gluten sensitivity." Minerva gastroenterologica e dietologica63.1 (2017): 5-15.

[71] Caio, Giacomo, et al. "Pathophysiology of non-celiac gluten sensitivity: where are we now?" Minerva gastroenterologica e dietologica 63.1 (2016): 16-21.

[72] Biesiekierski, Jessica R., et al. "Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial." American Journal of Gastroenterology 106.3 (2011): 508-514.

[73] Vazquez–Roque, Maria I., et al. "A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: effects on bowel frequency and intestinal function." Gastroenterology 144.5 (2013): 903-911.

[74] Biesiekierski, Jessica R., 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 145.2 (2013): 320-328.

[75] Murray, Kathryn, et al. "Differential effects of FODMAPs (fermentable oligo-, di-, mono-saccharides and polyols) on small and large intestinal contents in healthy subjects shown by MRI." The American journal of gastroenterology109.1 (2014): 110.

[76] Halmos, Emma P., et al. "A diet low in FODMAPs reduces symptoms of irritable bowel syndrome." Gastroenterology146.1 (2014): 67-75.

[77] Böhn, Lena, et al. "Diet low in FODMAPs reduces symptoms of irritable bowel syndrome as well as traditional dietary advice: a randomized controlled trial." Gastroenterology 149.6 (2015): 1399-1407.

[78] Falagiani, Paolo, et al. "Systemic nickel allergy syndrome (SNAS): A review." Rev Port Imunoalergologia 16.2 (2008): 135-47.

[79] Pizzutelli, S. "Systemic nickel hypersensitivity and diet: myth or reality?" European annals of allergy and clinical immunology 43.1 (2011): 5.

[80] Veien, N. K., and T. Menné. "Nickel contact allergy and a nickel-restricted diet." Seminars in dermatology. Vol. 9. No. 3. 1990.

[81] Rizzi, Angela, et al. "Irritable bowel syndrome and nickel allergy: what is the role of the low nickel diet?" Journal of neuro gastroenterology and motility 23.1 (2017): 101.

[82] Chey, William D., Jacob Kurlander, and Shanti Eswaran. "Irritable bowel syndrome: a clinical review." Jama 313.9 (2015): 949-958.

[83] Almquist, Ellinor, Hans Törnblom, and Magnus Simren. "Practical management of irritable bowel syndrome: a clinical review." Minerva gastroenterologica e dietologica62.1 (2015): 30-48.

[84]. Slattery, S. A., et al. "Systematic review with meta-analysis: the prevalence of bile acid malabsorption in the irritable bowel syndrome with diarrhoea." Alimentary pharmacology & therapeutics 42.1 (2015): 3-11.

[85] Wong, Banny S., et al. "Increased bile acid biosynthesis is associated with irritable bowel syndrome with diarrhea." Clinical gastroenterology and hepatology 10.9 (2012): 1009-1015. [86]. Bajor, Antal, et al. "Increased colonic bile acid exposure: a relevant factor for symptoms and treatment in IBS." Gut64.1 (2015): 84-92.

[87] Spiller, Robin C. "Targeting the 5-HT3 receptor in the treatment of irritable bowel syndrome." Current opinion in pharmacology 11.1 (2011): 68-74.

[88] Camilleri, Michael, and Guy Boeckxstaens. "Dietary and pharmacological treatment of abdominal pain in IBS." Gut66.5 (2017): 966-974.

[89] Chang, Lin, Kenneth Tong, and Vanessa Ameen. "Ischemic colitis and complications of constipation associated with the use of alosetron under a risk management plan: clinical characteristics, outcomes, and incidences." American Journal of Gastroenterology 105.4 (2010): 866-875.

[90] Garsed, Klara, et al. "A randomized trial of ondansetron for the treatment of irritable bowel syndrome with diarrhoea." Gut 63.10 (2014): 1617-1625.

[91] Matsueda, Kei, et al. "A randomized, double-blind, placebo-controlled clinical trial of the effectiveness of the novel serotonin type 3 receptor antagonist ramosetron in both male and female Japanese patients with diarrhea-predominant irritable bowel syndrome." Scandinavian journal of gastroenterology 43.10 (2008): 1202-1211.

[92] Wade, P. R., et al. "Modulation of gastrointestinal function by MuDelta, a mixed μ opioid receptor agonist/μ opioid receptor antagonist." British journal of pharmacology 167.5 (2012): 1111-1125.

[93] Pimentel, Mark, et al. "Rifaximin therapy for patients with irritable bowel syndrome without constipation." New England journal of medicine 364.1 (2011): 22-32.

[94] Lembo, Anthony, et al. "Repeat treatment with rifaximin is safe and effective in patients with diarrhea-predominant irritable bowel syndrome." Gastroenterology 151.6 (2016): 1113-1121. [95]. Törnblom, Hans, et al. "Colonic transit time and IBS symptoms: what's the link?" American Journal of Gastroenterology 107.5 (2012): 754-760.

[96] Chapman, R. W., et al. "Randomized clinical trial: macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome." American Journal of Gastroenterology 108.9 (2013): 1508-1515.

[97] Quigley, Eamonn MM. "Cisapride: what can we learn from the rise and fall of a prokinetic?" Journal of digestive diseases 12.3 (2011): 147-156.

[98] Tack, Jan, et al. "Systematic review: cardiovascular safety profile of 5-HT 4 agonists developed for gastrointestinal disorders." Alimentary pharmacology & therapeutics 35.7 (2012): 745-767.

[99] Camilleri, Michael, et al. "A placebo-controlled trial of prucalopride for severe chronic constipation." New England Journal of Medicine 358.22 (2008): 2344-2354.

[100] Tack, J., et al. "Effect of prucalopride on symptoms of chronic constipation." Neuro gastroenterology & Motility 26.1 (2014): 21-27.

[101] Camilleri, M., et al. "Clinical trial: the efficacy of open-label prucalopride treatment in patients with chronic constipation–follow-up of patients from the pivotal studies." Alimentary pharmacology & therapeutics 32.9 (2010): 1113-1123.

[102] Drossman, D. A., et al. "Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome–results of two randomized, placebo-controlled studies." Alimentary pharmacology & therapeutics 29.3 (2009): 329-341.

[103] Simrén, Magnus, and Jan Tack. "New treatments and therapeutic targets for IBS and other functional bowel disorders." Nature Reviews Gastroenterology & Hepatology15.10 (2018): 589-605.

[104] Khanna, Reena, John K. MacDonald, and Barrett G. Levesque. "Peppermint oil for the treatment of irritable bowel syndrome: a systematic review and meta-analysis." Journal of clinical gastroenterology 48.6 (2014): 505-512.

[105] Delvaux, M., and D. Wingate. "Trimebutine: mechanism of action, effects on gastrointestinal function and clinical results." Journal of international medical research 25.5 (1997): 225-246.

[106] Ford, Alexander C., et al. "Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: systematic review and meta-analysis." American Journal of Gastroenterology 109.9 (2014): 1350-1365.

[107] Dekel, Roy, Douglas A. Drossman, and Ami D. Sperber. "The use of psychotropic drugs in irritable bowel syndrome." Expert opinion on investigational drugs 22.3 (2013): 329-339.

[108] Salari, Pooneh, and Mohammad Abdollahi. "Systematic review of modulators of benzodiazepine receptors in irritable bowel syndrome: is there hope?" World journal of gastroenterology: WJG 17.38 (2011): 4251.

[109] Simrén, Magnus, et al. "Intestinal microbiota in functional bowel disorders: a Rome foundation report." Gut 62.1 (2013): 159-176.

[110] Borowiec, Anna M., and Richard N. Fedorak. "The role of probiotics in management of irritable bowel syndrome." Current gastroenterology reports 9.5 (2007): 393-400.

[111] Ford, Alexander C., et al. "Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis." American journal of gastroenterology 109.10 (2014): 1547-1561.

[112] Astegiano, M., et al. "Treatment of irritable bowel syndrome. A case control experience." Minerva gastroenterologica e dietologica 52.4 (2006): 359-363.

[113] Tanaka, Yukari, et al. "Biopsychosocial model of irritable bowel syndrome." Journal of neuro gastro enterology and motility 17.2 (2011): 131.

[114] Zijdenbos, Ingeborg L., et al. "Psychological treatments for the management of irritable bowel syndrome." Cochrane Database of Systematic Reviews 1 (2009).

[115] Hussain, Zahra, and E. M. M. Quigley. "Systematic review: complementary and alternative medicine in the irritable bowel syndrome." Alimentary pharmacology & therapeutics23.4 (2006): 465-471.

[116] Ma, Xiao-Peng, et al. "Acupuncture-moxibustion in treating irritable bowel syndrome: how does it work?" World journal of gastroenterology: WJG 20.20 (2014): 6044.

[117] Liu, Jian Ping, et al. "Herbal medicines for treatment of irritable bowel syndrome." Cochrane Database of Systematic Reviews 1 (2006).