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Potential causes and present pharmacotherapy of irritable bowel syndrome (IBS): an overview

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Introduction

Irritable bowel syndrome (IBS), a functional bowel disorder associated with alterations of stool habits, seriously affects social life, health-being, regular daily activities and diets of affected subjects [1,2]. It is one the most frequent gastroenterological (GI) diseases in the industrialized world [1]. As a functional disorder, IBS typically lacks histopathological, biochemical or visual differences to healthy individuals. The severity of IBS strongly varies and limits the quality of life [3]. Often, a variety of symptoms occur, consisting of abdominal pain, bloating, nausea, an irregular but more frequent urge to defecate, and an altered stool consistency (sometimes switching between softer and harder stool forms) [2,4,5]. After a bowel movement, IBS sufferers lack the feeling of complete emptying [4]. Among the symptoms, abdominal pain is the most frustrating and found in almost all IBS patients [3,6,7]. According to a questionnaire of people diagnosed with IBS, respondents suffered from IBS symptoms on average for 16.6 years with 57% reporting their symptoms daily and 16% responded to have experienced symptoms even for 21–30 years [8]. Eighty percent of respondents were taking some form of treatment during the completion of the questionnaire [8]. For the diagnosis of IBS, the Rome III criteria for functional GI disorders were introduced after revision of Rome II criteria [9]. Rome I criteria were little useful to capture all IBS patients [10]. Although Rome III criteria were introduced several years ago, authors in a recent systematic review reported that the new criteria were still poorly adopted and utilized [11]. Previously, the exclusion of any organic disease was sufficient for considering IBS; however, a diagnosis of IBS, based on exclusion of organic pathology alone, is no longer valid according to current definitions [12]. To diagnose a functional bowel disorder like IBS, symptoms need to persist for more than 6 months, such as: alternating constipation, diarrhea, abdominal pain, and bowel irregularities. “Red flags”, i.e. alarm symptoms that include weight loss, anemia, nocturnal symptoms, fecal blood, disorders of malabsorption and thyroid function should be assessed and in case they are present, testing for organic causes is warranted [13]. The most common symptoms, i.e. diarrhea, constipation, pain perception or an alternation between diarrhea and constipation, are used to divide IBS into subgroups. IBS is thus categorized into IBS-C (constipation-

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predominant), IBS-D (diarrhea-predominant), IBS-M (mixed type), and IBS-U (unsubtyped) [9].

Epidemiology and risk factors

IBS is a disorder that varies depending on its regional location. It occurs in the Western world in 10 to 20% of the population, depending on the diagnostic criteria used [14]. In North America, prevalence estimates range from 10 to15% [15], and are 11.1% in Australia [16]. A meta-analysis of studies on IBS epidemiology estimates a global prevalence of 11.2% [17]. Compared with the Western countries, Southeast Asia and especially China have low prevalences of IBS, which lie between 5 and 7% [18,19]. Apparently, India has the lowest prevalence of IBS (4.2%) [20].

Risk factors of IBS are manifold, such as depression, war experiences with malnutrition, and various infectious epidemics that trigger gastroenteritis episodes [21-23]. A bacterial gastroenteritis has been shown to be a major independent risk factor for the development of IBS [24]. Additionally, an expired infectious gastroenteritis in combination with stress is believed to potentiate IBS [21]. Anxiety associated with GI symptoms exaggerates symptoms of IBS-D [23]. In a population-based study, a significant association between IBS and sexual, emotional or verbal abuse as well as between IBS and abuse in childhood or adulthood has been found [25]. Stressful moments like exams, a birth weight of less than 1500 grams, early traumatic events in childhood, and a strict childhood deprivation can support the development of IBS [23,26]. A family history of IBS, being of female gender and a hysterectomy also pose important risk factors [27,28]. Thus, IBS of the constipation and pain subtype were more common in hysterectomy patients than in controls [29].

Potential causes of IBS

Functional GI diseases, such as IBS, have multifactorial pathophysiologies and are not fully explored. For IBS to develop, cellular and molecular processes could occur individually or in combination. For instance, following a preceding inflammation, lymphocytes and cytokines are increased in the intestinal mucosa of patients with IBS [30,31]. Other likely causes include visceral hypersensitivity and abnormal intestinal motility. Some of the possible causes of IBS are discussed in the following sections.

Disturbances in the intestinal bacterial colonization

The bowel of the fetus is not yet colonized by bacteria. Only by the birth process, first bacteria, fungi and protozoa can orally reach the newborn and colonize the intestine. An individual microbial intestinal balance that stabilizes over time is thus created in every single human being [32]. During this time, variations in the composition of the bacterial strains may have been already formed and the basis for the development of IBS could have been laid [32]. Through daily food intake, we regularly select different bacterial populations in our intestinal flora, which in turn can affect physiological GI functions. This complex bacterial system makes up the so-called microbiome which consists of about 100 trillion bacteria [32]. There is now good indication that fecal microbiota and organic acids are altered in IBS patients [33,34]. GI infections may induce a change in the bacterial

colonization of a normal intestinal flora and as this change continues, it may contribute to the development of IBS. IBS could be therefore triggered either by an expired pathogenic infection or by bacterial products that affect the motility and secretion of the gut, or even the brain [35-37]. It is recognized that a change in the bacterial lawn of *E. coli*, *Lactobacilli* and *Bifidobacteria* is present in the IBS diarrhea-type [32]. Scanu et al. suggested that *Mycobacterium avium ssp. paratuberculosis*, a pathogen that causes chronic watery diarrhea and inflammatory bowel reactions, plays a critical role in the development of IBS [38]. In this small cohort study, infection with *Mycobacterium avium ssp. paratuberculosis* was detected in about 75% of IBS patients as compared to 15% of healthy people. The probability of having IBS was 17x higher in infected than in non-infected subjects [38].

SIBO - “Small intestinal bacterial overgrowth”

As indicated by the term, SIBO occurs in the upper part of the small bowel and can be caused by dysmotility, altered gastric acid secretion, blind or afferent loops, and partial obstruction [39]. The question whether SIBO plays a role in IBS is not quite clear. A small clinical study of 162 IBS patients did not attest SIBO an important role in IBS, although it was found that slightly increased counts of small-bowel bacteria were more common in the IBS group [40]. A review on studies using different diagnostic methods for investigating the prevalence of SIBO in IBS patients, concludes that, although the frequency of SIBO in IBS varied from 4 to 78%, SIBO was higher in IBS patients than in controls [41]. Therefore, an association between SIBO and IBS seems likely, or in other words, there may be a high likelihood of yet not diagnosed SIBO in patients with IBS.

Gut-brain axis

The central nervous system (CNS) affects all the features of the GI tract, such as bowel movements, the perception of intestinal pain, and the illness behavior. A derangement along the intestinal brain-axis, e.g. by increase of the HPA axis activity, can, therefore, cause changes in the CNS, which could lead to IBS symptoms [42,43]. A malfunction of the GI tract may also occur at the level of the enteric nervous system and contribute to IBS [44]. A dysregulation in brain areas may then cause altered processing in the CNS and eventually lead to an abnormal perception of visceral pain. For instance, rectosigmoid distension in IBS patients caused greater activation of the amygdala, rostroventral anterior cingulate cortex, and dorsomedial frontal cortical regions than in healthy individuals [45]. Additionally, the emotional modulation of the neural responses to visceral stimuli may be distorted in people with IBS [46]. Therefore, the daily thinking, feeling and acting may be constantly influenced by visceral pain, in a way that many activities are consistently avoided and solitude and tranquility are preferred [23].

Diet as a possible cause of IBS

Intake of certain foodstuff and irregular or improper eating habits represent additional potential triggers of IBS [47,48]. A survey suggested that IBS may be associated with a higher consumption of canned food, processed meat, legumes, whole cereals, confectionary, fruit compotes and herbal tea [48]. Fast food, fried foods, food irritants that can be found in cow’s milk, eggs, wheat, soy, nuts, citrus fruits, fish, marine fish and chocolate, can interfere with the movements of the intestine and result in symptoms such as constipation, diarrhea

and flatulence [49,50]. The motility of the small intestine can be reduced by a high fat diet and soluble fiber [49]. As to food intolerance or allergies, a recent review concluded that no convincing data exist to link these with IBS [51]. Rather, certain food items rich in poorly absorbed short-chain carbohydrates (FODMAPs) and insoluble fibers may trigger IBS symptoms [51].

The role of mast cells in the etiology of IBS

Mast cells can secrete mediators, such as histamine, serotonin, cytokines, arachidonic acid derivatives as well as tryptases and proteases. Through the release of these mediators, primary afferent neurons respond with increased excitability. Barbara et al. found that infiltration of the colon with mast cells and the release of mediators in proximity to mucosal innervation likely contributes to abdominal pain perception in IBS patients [52]. In particular, serotonin has been shown to act locally at nerve endings and to contribute to the sensation of intestinal pain [53]. Mast cell infiltration may come about as a reaction to expired earlier moments of stress, which may affect the frequency and severity of the perceived pain [54]. The facts i) that mast cells lie in close proximity to nerve endings, ii) that their mediators released have sensorimotor function, iii) that their activation produces IBS-like symptoms and iv) that mast cell stabilizers, such as sodium cromoglycate, show good efficacy in alleviating symptoms in IBS patients suggest that mast cells could be causative of IBS symptoms [54].

Pharmacotherapy of IBS

The pharmacological therapy is the most common form of therapy for IBS and medication is based on individual symptoms. Substances mentioned here are already in use, still in clinical evaluation or have been withdrawn from the market due to serious side effects.

Pharmacotherapy of IBS-C

IBS-C is characterized by predominance of constipation associated with abdominal pain, which is relieved by defecation. Lumpy stools occur in ≥25% and loose or watery stools in <25% of bowel movements [9]. Bloating and abdominal pain are more common in IBS-C than IBS-D patients [55]. For symptomatic relief of discomfort in IBS-C, prokinetic and laxative agents (e.g., macrogol, bisacodyl and lactulose) are used.

Linaclotide, a guanylate cyclase-C agonist, has various effects on digestion and effectively improves abdominal pain and bowel symptoms. It simultaneously reduces stool consistency and increases the frequency of bowel movements. The most common side effect is diarrhea, which is the reason why around 5% of patients have discontinued treatment during phase III trials [56].

Lubiprostone activates a voltage-gated chloride ion channel that promotes the transport of chloride ions across the intestinal epithelium. It thereby enhances fluid secretion and accelerates stool frequency. It also reduces abdominal pain and is regarded as a good treatment option due to its limited side effects (diarrhea and dizziness) [57].

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Tegaserod (Zelmac®) is a selective and partial 5-HT_4 receptor agonist that reduces visceral sensitivity and stimulates the secretion of chloride from epithelial cells. It has been shown to reduce discomfort and pain in IBS [58,59]. Although long-term safety of *tegaserod* was investigated in a prospective study, from which it was suggested that treatment was safe over a 12-month period (despite serious adverse events in 4.4% of patients) [60], the drug has been taken from the market in 2007 [61].

Prucalopride is also a 5-HT_4 receptor agonist and is active in severe chronic constipation [62]. It has been shown to accelerate colonic transit time [63]. As a rare side effect, *prucalopride* may produce cardiovascular events [64]. However, the drug does not lead to prolongation of the QT-interval, which occurs frequently with 5-HT_4 agonists [65]. Due to insufficient data, *prucalopride* is currently only indicated for women with IBS [66]. Another prokinetic agent, *pumosetrag*, is a partial 5-HT_3 receptor agonist. Positive effects of the drug on IBS-C were reported by the company in a phase II proof-of-concept trial [67].

Cisapride is a 5-HT_4 receptor agonist and a 5-HT_3 receptor antagonist with prokinetic effects in the stomach, thereby accelerating gastric emptying. It was taken from the market for producing non-rhythmic cardiac output [68,69]. In spite of this action, it is still available in third world countries and via internet, although no obvious benefit for IBS has been demonstrated [70].

Velusetrag is another 5-HT_4 receptor agonist and also acts as a prokinetic agent. According to a placebo-controlled and dose-response study, it is efficacious and well tolerated in patients with chronic idiopathic constipation [71].

Pharmacotherapy of IBS-D

IBS-D, the diarrhea-predominant subtype of IBS, is characterized by loose (mushy) or watery stools occurring in ≥25% and by hard or lumpy stools in <25% of bowel movements [9]. IBS-D patients do not report on upper GI symptoms as often as people with IBS-C do [55].

Loperamide, a μ-opioid receptor agonist, decreases gastric emptying, delays intestinal transit, relaxes the segmental colonic spasm and acts against diarrhea, while stool frequency is reduced [72]. An increase in nocturnal pain after loperamide intake, however, has been observed in IBS patients [73]. *Loperamide* may be used in the treatment of adults with IBS-D [74].

Alosetron is a 5-HT_3 receptor antagonist and is effective in female IBS patients with predominant diarrhea or alternating constipation and diarrhea [75]. It is a therapeutic agent with limited use and only available for IBS-D (and for women only). It improves pain and discomfort but is an absolute no-go for the therapeutic use in IBS-C [74].

Crofelemer binds to the CFTR channel (cystic fibrosis transmembrane conductance regulator) and reduces chloride ion secretion in the intestinal epithelium. It provides some visceral analgesic effects and improves stool consistency in symptomatic diarrhea [76]. In one trial of IBS-D patients, *crofelemer* failed to improve stool consistency after a treatment

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of 12 weeks; however, a significant increase in pain-free days was noted in female patients [77].

Clonidine is an agonist at presynaptic α_2-receptors and inhibits sympathetic efferent outflow. Agonists of α_2-adrenergic receptors were found to modulate colorectal sensation and motility in humans suggesting that they may be of use for the treatment of IBS [78]. However, in a prospective, placebo-controlled study in women with urge-predominant fecal incontinence, symptom severity and bowel symptoms (stool consistency or frequency) were unaffected by treatment with *clonidine*, although a slightly improved fecal continence were seen in the patients with diarrhea [79].

Solabegron is a selective β_3-adrenergic agonist and still in the developmental phase. It hardly affects GI transit time but seems to have an influence on pain [80]. It also decreases hyperexcitability of enteric neurons, which is the basis for its beneficial effects in IBS [81].

Octreotide is a somatostatin-2 receptor agonist and is commonly used for the treatment of growth hormone-induced tumors. In IBS patients, *octreotide* increases thresholds of visceral perception without changing the muscular tone of the colon [82]. In a study of long-term treatment in 46 non-constipated IBS patients, *octreotide* improved stool consistency and increased first sensation threshold but had no effect on abdominal pain [83].

The benefit of antidepressant therapy, especially that of IBS-D, was recognized nearly fifty years ago [84]. Tricyclic antidepressants such as *amitriptyline* are applied in low doses and they are usually well tolerated [84-86]. In IBS patients, a*mitriptyline* may also significantly reduce brain activation during rectal pain in combination with stress conditions [87].

Treatment of pain in IBS

For the therapy of pain in IBS, neurokinin receptor antagonists, selective serotonin reuptake inhibitors (SSRIs) and glutamatergic excitation inhibitors have been used [84,85,88]. In case of unresponsiveness to these agents, *benzodiazepines* provide certain benefit (especially in IBS-D). They are believed to affect the inflammatory, neural, and psychological pathways. The use of *benzodiazepines* in IBS, however, this is still a controversial issue [89]. Regarding sensory threshold and pain, *pregabalin*, a second generation $\alpha_2\delta$-ligand, showed significant improvement in a trial of 26 IBS patients. Larger trials are warranted to prove the efficacy and safety of the drug before recommendation [90]. *Melatonin* was able to significantly attenuate abdominal and rectal pain sensitivity in IBS patients with sleep disturbances [91]. Interestingly, sleep disturbances did not improve by melatonin treatment indicating that the benefit from melatonin was independent of sleep behavior [91].

Fluoxetine and *citalopram* are serotonin reuptake inhibitors (SSRIs) widely used in IBS treatment. *Fluoxetine* reduces abdominal pain and discomfort in IBS-C and decreases sense of bloating [88], while the benefit of *citalopram* on relieving IBS symptoms has been described as modest at the most [92].

Symptoms of abdominal pain may ease when treated with antispasmodics. A meta-review, which analyzed 22 trials in 1778 IBS patients, revealed clear beneficial effects of antispasmodics over placebo; however, consistent evidence of efficacy were only shown for

otilonium and *hyoscine* [93]. Another widely used smooth muscle-relaxing agent in IBS, *mebeverine, is well* tolerated with no significant adverse reactions, but its efficacy in IBS have not yet been firmly proved [94].

Probiotics and antibiotics

Probiotics are live microorganisms intended to provide benefit for the consumer. They are used as non-digestible food ingredients that positively affect the host by enhancing the growth of certain strains of bacteria in the colon [32,95]. Probiotics are thought to interfere with inflammatory responses in the gut, enhance the barrier function or reduce visceral hypersensitivity, and favor a balanced composition of bacteria in the intestines. This may lead to an improvement of symptoms and increased psychological well-being [96,97]. In a clinical trial with 362 female primary care IBS patients, *Bifidobacterium infantis* improved global IBS symptoms by more than 20% [98]. Also, after a four week-treatment of IBS patients with *Lactobacillus acidophilus*, abdominal pain or discomfort were reduced by more than 20%, as compared to placebo [99]. However, in a recent randomized, double-blind, placebo-controlled trial, in which IBS patients received a probiotic mixture of *Lactobacillus paracasei ssp paracasei* F19, *Lactobacillus acidophilus* La5 and *Bifidobacterium* Bb12 over six months, no differences in GI symptoms were noticed between the cohorts [100]. Although health-related quality of life improved in the IBS group, it did not statistically differ from the placebo group [100].

Abdominal pain occurs when there is a reduced ability to emit gas. Antibiotics have been long used to relieve symptoms of IBS, probably because antibiotics interfere with small intestinal bacterial overgrowth and, therefore, reduce gas production [101]. Amongst them, *rifaximin* conferred significant relief of global IBS symptoms, such as bloating and abdominal pain, in two phase III double-blind and placebo-controlled trials with non-constipated IBS patients (TARGET 1 and TARGET 2) [102]. A small study showed that *metronidazole* provided benefit for IBS patients without affecting rectosigmoid motility [103]. In a double-blind, placebo-controlled trial, *neomycin* improved constipation in IBS-C [104]. The improvement was dependent on the production and elimination of methane as determined by breath test [104]. A meta-analysis on the use of antibiotics confirmed their beneficial effects in IBS; however, the authors of the study noted that routine use of antibiotics in IBS is not yet recommended due to the lack of pathophysiological explanation [105].

Anti-allergic and anti-inflammatory pharmacotherapy

Sodium cromoglycate is a drug from the group of mast cell stabilizers, which inhibits the release of mediators, such as histamine, serotonin and leukotrienes. According to an older study, it can improve persistent diarrhea by 40% [106]. Since the study was performed in a low sample size, newer data are warranted. *Ketotifen* is an H_1-blocker, thus exerting antihistaminic effects. It has been shown to reduce the sensitivity in the gut and to improve quality of life in patients with IBS [107]. In a prospective study, *mesalazine* (*5-aminosalicylic acid*) provided benefit in IBS-D patients with regard to days of discomfort and bowel movement satisfaction [108]. A larger randomized placebo-controlled study could not confirm whether patients with IBS-D benefit from a treatment with *mesalazine* [109].

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Possibilities of new pharmacotherapies for IBS: the endocannabinoid system

In traditional medicine (especially in Asia), extracts of *Cannabis sativa*, were used to treat inflammation and diarrhea. During the past decade, the existence of a so-called endocannabinoid system, which encompasses the cannabinoid receptors and their endogenous ligands, was described. Its possible purpose in the GI tract is to maintain homeostasis [110]. Active ingredients of *Cannabis*, such as Δ^9-tetrahydrocannabinol (THC) and cannabidiol, may be candidates for pharmacological intervention in IBS. The THC-derivative *dronabinol* is currently in use for the treatment of people with AIDS and cancer to increase appetite [111]. Activation of cannabinoid receptors in enteric neurons attenuate the hyperexcitability in the gut [112] and slows exaggerated contractions during intestinal inflammation [113]. In a retrospective study, Crohn's disease patients reported improvement of their disease and a reduction in the required conventional pharmacotherapy after treatment with *cannabis* [114]. Cannabinoids may be, therefore, useful for the treatment of inflammatory processes and motility disturbances of the GI tract, a situation that also applies for IBS.

Dronabinol has been already used in trials with IBS patients. When taken orally, it is metabolized by about 90 to 95%, which means only 10 to 20% of the oral dose actually reaches the systemic circulation [115]. *Dronabinol* was effective in reducing fasting colonic motility in IBS patients with diarrhea or alternating [116]. In another trial, *dronabinol* was without effect on gut transit with only a modest delay in colonic transit in subjects with a CNR1 rs806378 single nucleotide polymorphism, indicating that the group of IBS patients that might benefit from *dronabinol* remains to be determined [117].

Additional and alternative therapies

One way of meeting the challenge of IBS treatment is the use of herbal medicine. For instance, the intake of essential oils, such as peppermint oil (*Menta piperita*), may reduce stool frequency and could represent an adjunctive therapy to IBS-D with little side effects [118]. Traditional Chinese Medicine (TCM) may represent an alternative form of IBS therapy. TCM applies empiric diagnostics approaches, such as the pulse and tongue diagnosis, for IBS [119]. Alternative forms of IBS treatment can achieve good therapeutic results and can, in some cases, be almost as effective as conventional therapy. According to a study by Chedid et al., herbal therapy was equivalent to *rifaximin* in the treatment of small intestinal bacterial overgrowth [120]. In a TCM study of 60 individuals suffering from IBS, symptoms improved in 43 subjects [121]. In 11 subjects, an apparent improvement was noted whereas in 6 subjects, no improvement was observed [121]. IBS patients may also experience some benefit from acupuncture [122]. However, data are still inconclusive whether acupuncture is more effective than sham acupuncture or other therapies in alleviating IBS symptoms [123]. A cognitive behavioral therapy for IBS patients may be also helpful, for instance, a "gut-focused hypnosis" has been reported to improve quality of life and scores for anxiety and depression in IBS [124]. Because of the involvement of intestinal dysbiosis, fecal transplantation has been discussed as a future option for the treatment of IBS [125].

Conclusion

It is broadly accepted that IBS is a multifactorial disease and influenced by numerous mechanisms. Causes of IBS are multifold, leading to a complex of symptoms that requires different pharmacological treatments as well as supportive and alternative treatment options. The past years has seen an increase in effective pharmacotherapeutics. However, treatment of symptoms associated with IBS using conventional pharmacotherapy may cause dissatisfaction of patients and health care professionals alike. Most likely, the multifactorial etiology of the disease and its variety of cardinal symptoms warrant a broad and individual set of therapeutics. Considering that IBS is one of the most expensive health care management-related GI diseases in some countries, the introduction of new therapeutics is urgently awaited.

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