

Introduction

About 30% to 40% of adults claim to have frequent indigestion, and over 50 million visits are made annually to ambulatory care facilities for symptoms related to the digestive system. IBS is present in patients with symptoms of chronic abdominal pain and altered bowel habits but no identifiable organic etiology. IBS has a prevalence of 1% to 20% worldwide, although up to 75% affected individuals never seek care. Diagnosing IBS can be challenging due to the nonspecific nature of symptoms, overlapping upper and lower abdominal symptoms, and the frequent presence of somatic and psychological comorbidities. Up to 80% of IBS patients identify food as a possible trigger for their symptoms, so they increasingly ask for dietary and behavioral counseling. Moderate-severe IBS is estimated

to account for around 60% of all IBS cases and has been shown to impose a considerable burden on patients. It is estimated that IBS-C accounts for around 30% of IBS cases. The economic burden of IBS in the US is estimated at \$28 billion annually, a portion of these costs may be related to unnecessary and high-frequency tests, although few studies have assessed the factors underlying frequent tests and procedures among patients with IBS. 32% of IBS-C patients suffer depression as their condition almost every day in the previous month. If main IBS symptom is constipation, linaclotide and lubiprostone are two drugs that are recommended by the American College of Gastroenterology (ACG). Sexual dysfunction is positively associated with perceived GI symptom severity and HRQoL.

Figure 1. Summary of the available treatment options for mitigating the severity of IBS symptoms [1]. Major demerit of probiotics is that most have a short lifespan and thus repeated doses are necessary. Prebiotics may serve as an alternative treatment as they provide the metabolizable substrates for growth of specific bacteria and hence can alter the microbiota. Xifaxan® was approved by the US FDA in 2015 for the treatment of IBS-D in adults. EnteraGam®, is also approved by the US FDA for use in patients with chronic loose and frequent stools including IBS-D and IBD under physician supervision.

Methodology: Research conducted a year-round comprehensive literature search, which included technical newsletters, newspapers, journals, and many other sources. The present

study was started at the beginning of 2018. PubMed, ALTAVISTA, Embase, Scopus, Web of Science, and the Cochrane Central Register were thoroughly searched. The keywords were used to search for different publishers' journals such as Elsevier, Springer, Willey Online Library, and Wolters Kluwer which were extensively followed.

Results and Discussion:

A. Conventional Treatments

Due to disappointing results with conventional IBS treatments, complementary and alternative medicines are becoming attractive options for many patients [2-6]. Up to 50% of patients declared that they used some form of CAM for their GI symptoms, ranging from biologically active compounds to mind–body interventions [7-15]. CAM alone and in conjunction with pharmacological treatments as an integrative approach to manage patients with IBS and improve their QoL [9], [16-18]. Prokinetics are not specific to IBS and increase gastrointestinal motility in general by acting via dopamine and 5-HT₃ receptors as antagonists or 5-HT₄ receptors as agonists [19-27]. Along with prokinetics, treatment revolves around the use of therapies which are not specifically approved/not truly effective for treating IBS-C, such as laxatives, antispasmodics, gastric relaxants, or central neuromodulators and bulking agents (e.g. dietary fibers) [28-36]. Novartis has agreed to continue to supply Zelnorm® (Tegaserod maleate) for use in emergency situations, due to an increased cardiovascular risk [37,38]. Alosetron hydrochloride (Lotronex), voluntarily withdrawn in November 2000 by GlaxoSmithKline, but put back on the market, is the only medication approved for the treatment of severe IBS-D in women who have inadequately responded to conventional therapy [39-43]. However, no studies have evaluated the efficacy of alosetron using the new FDA composite endpoint which requires improvement in both abdominal pain

and diarrhea [44,45]. Fecal calprotectin, an indicator of colonic inflammation, is associated with non-constipated IBS. It can be a useful biomarker for measuring the effect of rifaximin therapy. In non-constipated IBS without documented small intestinal bacterial overgrowth (SIBO), Xifaxan® (rifaximin) treatment is associated with acceleration of colonic transit and changes in microbial richness. On the other hand, another antibiotic, neomycin has been shown to improve global IBS symptoms by 50%. Nonetheless, unlike rifaximin, neomycin had adverse effects and induced rapid bacterial resistance or *Clostridium difficile* infection [46]. Additionally, patients with IBS may experience a range of altered bowel habits, including diarrhea, constipation or alternating constipation and diarrhea. Besides that, digestive symptoms such as dyspepsia, dysphagia, non-cardiac chest pain and nausea are also frequently encountered in patients with IBS. On the other hand, IBS also showed comorbidity with other functional gastrointestinal disorders and association with non-gastrointestinal disorders such as chronic pelvic pain, temporomandibular joint disorder, fibromyalgia and chronic fatigue syndrome. Studies have demonstrated that EnteraGam® is safe and improves GI symptoms (e.g., chronic loose and frequent stools, abdominal discomfort, bloating, and urgency). Approximately 25%-50% of orally administered IgG survives digestion in the stomach and small intestine [47]. Eluxadoline (mixed μ -opioid receptor agonist– δ -opioid receptor antagonist and κ -opioid receptor agonist) appears safe and effective for treating IBS-D symptoms in patients with an intact gallbladder reporting inadequate relief with prior loperamide use. It has the potential to impact HRQoL in patients with IBS-D via improvement of the burdensome symptoms of IBS-D, including abdominal pain, diarrhea, and urgency [48].

B. Alternative Approaches

A mixture of dried powdered slippery elm bark, lactulose, oat bran, and licorice root significantly improved both bowel habit and IBS symptoms in patients with IBS-C [49]. More than 95% of patients rated artichoke leaf extract as better than or at least equal to previous therapies administered for their symptoms, and the tolerability was very good [50]. Probiotics may be useful in the management of IBS; however, dose and specific bacterial strain are important [51]. Enteric-coated peppermint oil is a safe and effective therapy for the relief of abdominal pain and global symptoms and in adults with IBS. Menthacarin, the primary component blocks Ca²⁺ channels and causing the relaxation of intestinal smooth muscle tissue [52-60]. STW 5 is a liquid formulation of nine herbs (*Iberis amara totalis recens*, *Angelicae radix*, *Cardui mariae fructus*, *Chelidonii herba*, *Liquiritiae radix*, *Matricariae flos*, *Melissae folium*, *Carvi fructus* and *Menthae piperitae folium*) used in clinical practice in Germany for more than 50 years, acts beneficially on abdominal symptom clusters as well as on individual GI symptoms in adults and children with efficacy, tolerability, reduced children school absenteeism [61-70]. Turmeric (*Curcuma longa*) or Java ginger (*Curcuma xanthorrhiza*) or curcumin, a biologically active phytochemical or combination with fennel oil was found to be beneficial, improved patient QoL (due to myorelaxant effect towards the intestinal muscle, involves not only the cholinergic receptors, but also L type Calcium channels) but not statistically significant in IBS symptoms (compared with placebo) [50], [71-80]. Enzymes comprise the endocannabinoid system in intestinal pain and motility in IBS is also claimed [81] but no significant difference found with dronabinol/nabilone (synthetic compounds containing cannabinoids found in the marijuana plant) [82-86]. *Aloe Vera* found to be improved QoL with insignificant/no severity symptom reduction in several studies [87-94] and studies show its carcinogenic potential in

the colon [90], [95-98], nephrotoxicity and hepatotoxicity [95], [99-104] which surely demands very limited use unless necessary. *Zingier officinale* also showed limited potential in symptom management [105-108]. Mixture of *Boswellia carterii*, *Zingiber officinale*, and *Achillea millefolium* improved QoL in men but not in women [109]. Although, an earlier study with *Mentha longifolia*, *Cyperus rotundus* and *Zingiber officinale* combination showed significant improvements after 8-weeks of treatment [110]. Alkhatib, 2019 reported that Carob (*Ceratonia siliqua* L.) aqueous extract can be used successfully to ameliorate the symptoms of IBS [111]. CAM for IBS include hypnosis, acupuncture, cognitive behavior therapy, yoga, probiotics, meditation, and herbal medicine [12], [19], [50], [112,113]. Yan et.al, 2019 and Wu et.al, 2019 and few other studies reported efficiency and safety of acupuncture alone or combined with Moxibustion or other CHM in IBS [12], [114-126]. Like *Zingier officinale* and *Curcuma longa*, *Fumaria officinalis*, *Hypericum perforatum*, *Plantago psyllium* and Carmint (*Mentha spicata*, *Melissa officinalis*, *Coriandrum sativum*) do not have significant efficacy or at least similar efficacy as placebo is also reported [50]. CHM like Sishen Wan, Ma Zi Ren Wan, CCH1 (patented, modified herb formula), Hemp seed pill, Jianpi Tiaogan Wenshen Recipe (JTWR), Chinese Medicine syndrome-differentiation therapy, Yun-chang capsule, plantain-senna granule (CPSG), Tongxie Yaofang (TXYF) Granule, Changjishu soft elastic capsule, Tongyouqing and many more showed potentials in IBS [127]. The emerging role of brain-gut therapies in IBS are visible. Cognitive behavioral therapy (CBT) and gut-directed hypnosis are the primary behavioral interventions that are introduced to patients with gastrointestinal conditions [128]. IBS involves dysregulation of the brain-gut axis and psychological processes play an important role in the development and maintenance of the disorder [129]. Gut-focused hypnotherapy was

found to be effective in primary and secondary care [130-133], but only small changes were found in intestinal microbiota composition [134]. CBT-IE for IBS includes exposure to abdominal sensations in addition to psychoeducation, self-monitoring, cognitive restructuring, attention training, and in vivo exposure, which are often used in traditional CBT [135]. Home-based version of CBT produced significant and sustained gastrointestinal symptom improvement for patients with IBS compared with education [136]. Both web/phone-delivered CBT and home/clinic-based CBT was found to be effective than usual treatment in refractory IBS, resulted in substantial and enduring relief of multiple symptoms [137,138]. Although significant for both outcomes, the statistical analysis revealed CBT interventions have a greater effect on alleviating IBS symptoms severity rather than on reducing psychological distress [139]. It has recently been found that many patients with IBS have poor dietary habits, with irregular meal intake and high intake of cereals, sweets, and soft drinks, and a low intake of vegetables, fruits, and fish, with correlations between the intake of soft drinks and gastrointestinal (GI) symptoms. According to Britain's National Institute for Health and Care Excellence (NICE) guidelines for dietary and lifestyle advice, dietary and nutritional perspectives should be considered in administering appropriate advice to IBS patients [140]. Emotional stress exacerbates IBS symptoms, and mind-body interventions may be beneficial. Exercise (yoga, walking/aerobic physical activity, Tai Ji, mountaineering, and Baduanjin qigong activity) is potentially a feasible and effective treatment for IBS patients [141]. Yoga improved sleep, increased visceral sensitivity and reduced abdominal pain in teens [142], adolescents and young adults [143], women [144] and postmenopausal women [145]. Patients with IBS might benefit from yoga and a low-FODMAP diet, as both groups showed a reduction in gastrointestinal symptoms [146].

Low-FODMAPs, ketogenic gluten-free diets are considered therapeutic [147-151]. However, there are gaps in implementation of the low FODMAP diet in clinical practice, as well as long-term safety and efficacy [152]. A low FODMAP diet is only recommended as a second line treatment guided by qualified clinicians with specialized training [153]. Dietary sources fibers include oats, psyllium, ispaghula, nuts and seeds, some fruit and vegetables and pectins. An increase in fiber has often been suggested as an initial treatment for IBS [154]. There is strong evidence to support three mechanisms of action: a) Augmentation of small intestinal water b). Increased colonic fermentation c). Immune modulation [155]. However, water-insoluble fiber does not improve IBS symptoms, consuming soluble fiber improves overall IBS symptoms [156].

Conclusion

IBS is associated with diverse pathophysiologic mechanisms. These mechanisms include increased abnormal colonic motility or transit, intestinal or colorectal sensation, increased colonic bile acid concentration, and superficial colonic mucosal inflammation, as well as epithelial barrier dysfunction, neurohormonal up-regulation, and activation of secretory processes in the epithelial layer. Abdominal pain/discomfort, bloating/distension, urgency, incomplete evacuation, straining, passage of gas, bowel habit satisfaction, overall assessment of IBS symptoms, and change in severity of symptoms, and stool consistency matters during investigation and treatment interventions. Novel approaches to treatment include lifestyle modification, changes in diet, probiotics, and pharmacotherapy directed to the motility, sensation, and intraluminal milieu of patients with IBS. Ramosetron is a promising agent in development. For IBS with constipation, traditional laxatives have failed to demonstrate significant benefit. However, lubiprostone, linaclotide, and plecanatide have demonstrated improvement of IBS with constipation in large, placebo-controlled trials.

Tenapanor, a sodium/hydrogen exchanger 3 inhibitor, appears to be a promising treatment option in the pipeline. There are multiple pharmacologic agents with a variety of mechanisms that have demonstrated efficacy in IBS with diarrhea and constipation. There are no established pharmacologic agents for IBS with a mixed bowel pattern. CAM treatments for IBS are also person-specific and cannot be generalized in most cases. CAM along with conventional treatments should weigh risk benefit issues

Future Recommendation

Current drug options including antispasmodic, antidiarrheals, rifaximin, antidepressants, Laxatives and motility accelerants are limited by barely ideal efficacy or side-effect [157]. CD4+ T-cells from IBS-D patients exhibit immune activation, but this did not appear to correlate with psychological stress measurements or changing symptoms over time. It can be said that CD4+ T-cell cytokines and gut homing reveals immune activation in IBS and is largely confined to IBS-D patients but requires further investigation [158]. Probiotics is a safety choice to improve the overall symptoms for IBS patient. The human gut microbiome is genetically diverse, expressing approximately 150-times more genes than the human host. Since it is agreed that the majority of the bacteria commonly identified in the microbiome cannot be routinely cultured using traditional laboratory techniques (80% or greater) [159]. Probiotic supplements are thought to improve IBS symptoms through manipulation of the gut microbiota, but the exact mechanisms of probiotics in the human body are not fully understood [160].

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Abbreviation

Irritable Bowel Syndrome (IBS); Interoceptive Exposure-based CBT program (CBT-IE); Fermentable Oligo-, Di-, Mono-saccharides And Polyols (FODMAP); Complementary and Alternative Medicine (CAM)

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