Life Sciences 212 (2018) 176–181

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Updated review of current pharmacological and non-pharmacological management of irritable bowel syndrome

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ARTICLE INFO

Keywords:
IBS
Irritable bowel syndrome
Constipation
Diarrhea
Diet
Pharmacological agents
IBS-C
IBS-D
Pathophysiology

ABSTRACT

Irritable bowel syndrome (IBS) is a functional disorder of the gastrointestinal tract that is usually associated with chronic abdominal pain and altered bowel habits. The two spectra of the disease include constipation-predominant IBS and Diarrhea-predominant IBS. Earlier it was thought to be an unexplained brain-gut disorder, but of late, various underlying causes suggesting primary gut disturbance have been identified. The initial management primarily includes the non-pharmacological measures such as dietary modifications, increasing physical activity, and psychological therapy. Pharmacological management is adjunct to non-pharmacological management, and the drug is chosen based on the predominant symptom of bowel habit whether constipation or diarrhea. In this review, we aim to update the readers on the currently available management options in the treatment of IBS – both pharmacological and non-pharmacological options. Further, for the various pharmacological treatments, we summarize the clinical pharmacology, indications, contraindications, adverse effects and use in pregnancy.

1. Introduction

Irritable bowel syndrome (IBS) is defined as a functional disorder affecting the gastrointestinal tract usually associated with chronic abdominal pain and altered bowel habits [1].

1.1. Pathophysiology

Pathophysiology of IBS is unclear, earlier it was thought to be an unexplained brain-gut disorder, but of late, various underlying causes suggesting primary gut disturbance have been identified [2]. Underlying mechanisms that could lead to IBS include post-infectious changes, chronic infections and disturbances in the intestinal microbiota, genetic factors like SCN5A mutation, low-grade mucosal inflammation, immune activation, altered intestinal permeability, disordered bile salt metabolism especially in 10–20% of cases with diarrhea and abnormal serotonin metabolism [3].

One theory suggests that disease begins in the gut. In genetically predisposed population infections or other environmental antigens like foods alter microbiome and promote increased permeability of intestine [3,4]. This leads to an inflammatory response with T-helper-2 cells promoting recruitment of mast cells that degranulate [5]. These changes induce gut visceral hypersensitivity and secondary motor abnormalities, and cytokine and intestinal T-cell responses via peripheral mechanisms, which causes increased anxiety and other non-gastrointestinal symptoms, such as fatigue and generalized pains [6]. Another theory suggests that IBS is thought to be caused by primary abnormalities of the stress pathway, which lead to alteration in gut permeability and sets off an immune activation cascade that results in IBS [7]. Other mechanisms such as abnormal bile acid metabolism can lead to IBS and diarrhea [3,8], or methanogenic flora after infection, with methane gas slowing intestinal transit [9], or learned behavioral responses, leading to pelvic floor dysfunction and constipation which can lead to IBS and constipation [3].

1.2. Diagnosis

The diagnosis of IBS is given by the Rome IV criteria which is given by at least six months prior onset of symptoms before diagnosis and it is characterized by recurrent abdominal pain or discomfort, 1 day per week in the last three months which is associated with 2 or more of the following criteria namely symptom improvement with defecation, onset associated with a change in stool frequency or onset associated with change in appearance/form of the stool [10]. IBS is the most prevalent

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https://doi.org/10.1016/j.lfs.2018.10.001
Received 13 September 2018; Received in revised form 27 September 2018; Accepted 1 October 2018
Available online 02 October 2018
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form of functional gastrointestinal disorders, and it accounts for 25–50% of all referrals to a gastroenterologist in the USA [11]. The Prevalence in North America is estimated to be anywhere between 5 and 10% while the global prevalence is estimated to be around 11% [12,13]. IBS is clinically classified into a number of subtypes based on the reported predominant bowel habit on days with abnormal bowel movements where the bowel habits are recorded based on the Bristol stool form scale (BSFS) [14]. The various sub-types of IBS and their clinical criteria are as follows:

- IBS with predominant constipation (IBS-C): > 25% of bowel movements with BSFS types 1 or 2 and < 25% with BSFS types 6 or 7
- IBS with predominant diarrhea (IBS-D): > 25% of bowel movements with BSFS types 6 or 7 and < 25% with BSFS types 1 or 2
- IBS with mixed bowel habits (IBS-M): > 25% of bowel movements with BSFS types 1 or 2 and > 25% with BSFS types 1 or 2
- IBS unclassified (IBS-U): Patients who meet the diagnostic criteria for IBS but unable to be accurately categorized in one of the groups mentioned above.

This review is aimed at summarizing the various pharmacological and non-pharmacological management measures that are available currently in the treatment of IBS. For the various pharmacological treatments, we summarize the clinical pharmacology, indications, contraindications, adverse effects and use in pregnancy. Table 1 gives a summary of the recently approved drugs for the treatment of IBS.

2. Review methodology

We searched for studies in electronic databases such as PubMed, MEDLINE, Embase, Scopus, Google Scholar and Cochrane database based on the article titles, abstracts contents, and relevance in the field of IBS. Information regarding medications used in the treatment of IBS was also accessed from regulatory websites like the US Food and Drug Administration (FDA), European Medicines Agency (EMA) and Clinicaltrials.gov. Additional relevant studies were manually searched for and added. The "keywords" as mentioned above were used to retrieve relevant articles. Pertinent literature published in major English-language journals for the last 25 years, describing the treatment of patients with IBS was reviewed.

3. Non-pharmacological management

Non-pharmacological treatment is the initial therapy that is offered especially in patients who do not have symptoms that are not severe enough to impair quality of life. A good doctor-patient relationship combined with the reassurance that though IBS is a chronic disease, it does not increase the risk of malignancy plays an important role in treatment [15].

3.1. Dietary modifications

Patients with symptoms of IBS should be counseled to avoid gas-producing foods like beans, onions, carrots, bananas, celery, prunes, apricots, Brussel sprouts, wheat germ, pretzels, bagels and likewise as the visceral hypersensitivity would result in exaggerated discomfort [16]. Patients with known lactose intolerance should be placed on a lactose-free diet. Similarly, those patients who have persistent bloating despite avoiding gas-producing foods should be placed on an empirical trial of a lactose-free diet [17]. IBS patients should also be put on a diet low in fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs) which includes avoidance of honey, high-fructose corn syrup, apples, pears, cherries, mangoes or wheat [18]. The patient is initially asked to eliminate all FODMAPs for six to eight weeks till symptom resolution and then reintroduce foods high in fermentable carbohydrates in order to determine the tolerance to individual fermentable carbohydrates [18].

A randomized, single-blind cross-over trial with 30 IBS patients and 8 controls demonstrated a significant overall reduction in gastrointestinal symptoms when assigned to a 21 day trial of a diet low in FODMAP when compared to moderate FODMAP [19]. A randomized controlled trial (RCT) of 92 patients showed that 40–50% of patients reported adequate relief of their IBS-D symptoms with the low FODMAP diet or a diet based on modified National Institute for Health and Care Excellence guidelines (mNICE) guidelines. When compared to mNICE diet, patients in low FODMAP diet had significantly greater improvement in individual IBS symptoms, particularly pain and bloating [20]. A gluten-free diet may also be beneficial for IBS-D patients, but it is the associated reduction in fructan that causes the symptomatic relief and not the reduced gluten [21]. Though dietary modifications have shown tremendous improvements in symptoms of IBS, the role of routine food allergy testing in IBS has not been well studied and hence remains unclear [22]. A meta-analysis of 6 RCTs by Schumann et al. concluded that yoga might be a feasible and safe adjunctive treatment for people with IBS. Beneficial effects of yoga were seen on GI symptoms like decreased bowel movements, quality of life, and anxiety when compared with no treatment [23].

3.2. Physical activity

Exercise is proven to be beneficial to health as it reduces the risk of cardiovascular diseases, endocrine disorders, improves bone and muscle conditioning, and decreases the levels of anxiety and depression [24]. The results of an RCT with 75 IBS patients demonstrated that a moderately increased physical activity over a period of 12 weeks reduced the symptoms related to IBS [25].

3.3. Psychological therapy

Since several psychological and central processing mechanisms like visceral hypersensitivity, visceral anxiety (hypervigilance to bowel symptoms leading to avoidance of situations where IBS symptoms occur) and central processing deficits have been attributed in the pathophysiology of IBS, psychological treatments targeting such cognitive processes are believed to help improve symptoms in IBS patients [26]. Moreover, patients with IBS also have increased rates of anxiety,

Table 1
Recently approved drugs for use in IBS.

Generic name	Brand name	Mechanism of action	Indication	Dose	Pregnancy category
Lubiprostone	Amitiza	Chloride channel activator	IBS-C	8 μg BD	C
Linaclotide	Linzess	Guanylate cyclase-C agonist	IBS-C	290 μg OD	C
Plecanatide	Trulance	Guanylate cyclase-C agonist	IBS-C	3 mg OD	C
Eluxadoline	Viberzi	mu-opioid receptor agonist	IBS-D	75–100 mg BD	C
Rifaximin	Xifaxan	Anti-microbial: inhibits bacterial RNA synthesis	IBS-D	550 mg TID	C
Alosetron	Lotronex	5HT3 receptor antagonist	IBS-D	1 mg BD	C

IBS-C: irritable bowel syndrome – constipation predominant; IBS-D: irritable bowel syndrome – diarrhea predominant; OD – once daily; BD – twice daily: TID – thrice daily.

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