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Management and current treatment of irritable bowel syndrome

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SUMMARY

Treatment of patients with irritable bowel syndrome (IBS) should be individualised on the basis of patient's symptoms and needs. The management of IBS starts with its safe diagnosis based on the patient's symptoms and a limited work-up for exclusion of organic diseases. The physician should always try to establish a good therapeutic relationship with the patient, explain the benign nature of IBS, and clarify potential triggering factors for IBS exacerbations. Dietary and lifestyle changes may help a very small number of IBS patients with mild symptoms, while high-fiber diets or supplements are recommended only for patients with severe constipation. Loperamide is the drug of choice for episodes of diarrhea and/or urgency, while smooth muscle relaxants may be used for IBS exacerbations with abdominal pain, bloating and/or distention. Antidepressants are currently used for the treatment of diarrhea- or abdominal pain-predominant IBS patients who are refractory to other forms of drug therapy, while psychological therapies may help refractory IBS cases, but their availability is rather limited, their cost high, and their efficacy unproven. In the future, novel agents, which have resulted from the better understanding of IBS pathophysiology, may prove to be more effective and safe therapeutic options for our IBS patients.

Key words: Irritable bowel syndrome, diet, fiber, loperamide, smooth muscle relaxants, antidepressants

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Irritable Bowel Syndrome (IBS) is a common chronic disorder of unknown etiology characterized by episodes of abdominal pain or discomfort accompanied by alterations in bowel habits.[1] Currently, several pathophysiologic mechanisms are considered to contribute to IBS. The main mechanisms, which are not mutually exclusive, include alterations in bowel motility and transit, enhanced visceral perception, and psychosocial distress.[2] IBS diagnosis can safely be based on the patient's symptoms and a limited work-up for exclusion of other organic diseases[3,4]. The recently formalized "Rome II" criteria have been widely accepted as the gold standard for IBS diagnosis in clinical trials and have also improved the diagnosis of IBS in clinical practice[3,5]. It should be noted, however, that, in clinical practice, the Rome II criteria have relatively low specificity, which can be improved by the exclusion of other organic diseases[2,6], and relatively low sensitivity for IBS patients with atypical presentations, such as those with painless diarrhea or atypical bloating[2,7,8]. As with every other functional disorder, accurate diagnosis is a prerequisite for the safe management of patients with IBS symptoms.

Effective management of patients with IBS depends on the type and severity of their symptoms, the degree of pathophysiologic changes, and the possible involvement of phychosocial factors. IBS patients can be divided into those with predominance of diarrhea, predominance of constipation, or predominance of abdominal pain and bloating[9]. However, such a classification of IBS patients based only on the type of presenting symptoms does not take into account severity of symptoms. Fortunately, approximately 70% of IBS patients usually have only mild symptoms and are treated by general physicians, 25% of them have moderate symptoms and visit gastroenterologists, and only 5% of cases have severe and frequent symtpoms not responding to initial therapeutic trials and require extensive work-up in specialized centers[10]. This review focuses on the current therapeutic options available

in clinical practice for the management of IBS patients (Table 1).

1. GENERAL APPROACH

Any physician who treats a patient presenting with IBS symptoms should carefully assess the patient's symptoms and medical history, perform a thorough physical examination, and order some initial investigations in order to exclude organic disorders. The usual initial diagnostic work-up of a potential IBS patient without alarming symptoms includes full blood count, erythrocyte sedimentation rate, routine biochemistry tests, stool examination for occult blood and signoidoscopy or total colonoscopy in patients over 40-45 years of age or with a family history positive for colon neoplasms. In particular in patients presenting with diarrhea, stool examination for ova and parasites and rectal biopsies may also be added[2,4].

When the IBS diagnosis is confirmed, the attendant physician should try to establish a therapeutic relationship with the patient. In particular, the physician should try to undestand the patient's thoughts about his/her problems and the patient's main concerns, explain the nature of IBS and reassure the patient about the benign course of this disorder, set realistic therapeutic targets, and involve the patient in the treatment[10]. The explanation for the benign nature of IBS and the patient's reassurance seem to be very important for the effective management of any patient with IBS[11]. As in any other chronic disorder, it is also of great help for the physician to clarify the immediate reasons for every patient's visit, which may differ from time to time and may be associated with several triggering factors, such as new environmental stressful events, new drugs, dietary changes, new personal concerns, depression, or even secondary gain.

The significance of an effective therapeutic relationship between the physician and the IBS patient is supported by the high proportion of such patients who experience remission of their symptoms after their first visit and appropriate reassurance[12] or by the high placebo response rates (30-88%) reported in IBS clinical trials (placebo effect)[10]. The high probability of a placebo effect complicates the evaluation of the efficacy of several therapeutic options for IBS patients and supports the concerns for evaluation of data only from properly designed, randomized, double-blind, placebo-controlled trials before safe conclusions can be drawn.

2. CONVENTIONAL THERAPIES

2.1. Diet - Fiber

Dietary factors have not been consistently found to be associated with development of IBS symptoms, although many patients frequently attribute their symptoms to certain foods[13]. Food digestion might trigger IBS symptoms through its effect on intestinal motility and such a phenomenon probably explains the postprandial exacerbation of symptoms in a proportion of IBS patients[14]. Moreover, individual intolerance to certain dietary factors, such as lactose and fructose, is well recognised and cannot be readily excluded in the majority of cases[15-18]. In addition, excessive caffeine has been associated with some symptoms in IBS patients[16]. Thus, al-

Table 1. Current therapies in the management of irritable bowel syndrome (IBS).

Therapy	IBS symptom	Efficacy
A. Therapeutic relationship	Non-specific	Most probable
B. Diet		
Exclusion diets	Non-specific	Doubtful
Fiber	Constipation	Possible*
C. Drugs		
Antidiarrheal (loperamide)	Diarrhea-Urgency	Satisfactory in acute phase
Smooth muscle relaxants	Abdominal pain	Possible
Prokinetics	Constipation	Not documended
Antidepressants –tricyclic– SSRIs**	Diarrhea-Pain	Most probable
	Constipation-Pain	Not documended
D. Psychological approach	Stressful factors	Possible

*Possible when fiber is administered in high quantities, but it may aggravate other IBS symptoms

**SSRIs: selective serotonin re-uptake inhibitors.

though very restricted dietary recommendations are rather ineffective, many patients seem to benefit from restriction of fatty foods, legumes, alcohol and caffeine[13,16]. In addition, lactose free diets may help particularly Greek patients or others living in areas with common lactose intolerance[19-22].

Fiber has been suggested as offering some benefit to patients with constipation-predominant, but not with other forms of IBS. Several pathophysiologic mechanisms have been proposed for the beneficial effect of fiber in IBS patients with constipation, such as: 1) decrease of colonic or oroanal transit time that may improve bowel habbits[23], 2) decrease of intracolonic pressure that may reduce abdominal pain[24], and 3) reduction of intracolonic bile salts concentrations that may be associated with reduced colonic intracontactile activity[25]. Despite all these potentially beneficial pathophysiologic effects of fiber, its overall clinical efficacy remains doubtful, even in patients with constipation-predominant IBS. Bran or corn supplements were not found to be superior to placebo in the symptomatic relief of IBS patients[2] and were sometimes reported to exacerbate symptoms[26]. It is currently believed that IBS patients have a relatively low pain threshold for intraluminal colonic distention and that increase in dietary fiber may exacerbate their symptoms due to the subsequent increase of bowel gas produced by the bacterial fermentation of fiber[27].

In practice, bloating is a very frequent complaint of IBS patients who receive fiber supplements. Use of fiber supplements associated with production of less bowel gas (such as psyllion) may be tolerated better than the usual fiber-bran supplements. Although the beneficial effect of fiber on the overall symptoms of IBS is currently questioned, the consumption of sufficient quantities of fiber (>20-30 g daily) undoubtedly results in significant improvement of constipation regardless of its effect on other symptoms[23]. Recently, the general recommendations for high fiber diets to every IBS patient were reconsidered and it was suggested that the role of fiber in several sugroups of IBS patients should be evaluated in properly designed trials[13]. For the time being, the management of patients with constipation-predominant IBS may start with relatively low doses of fiber that will increase gradually and will be discontinued in case of worsening of symptoms[2].

2.2. Drug therapies

2.2.1. Antidiarrheal agents

Antidiarrheal agents are certainly used in the management of patients with diarrhea-predominant IBS. Loperamide (2-4 mg for 2-4 times daily), a synthetic opiod, is the most commonly used antidiarrheal agent. Loperamide is preferred over other opiods, such as diphenoxylate, which may induce several atropine-associated side efects that might be dangerous, particulalry in older patients. Moreover, loperamide is also prefered over other opiods, such as diphenoxylate and codeine, since it is the only agent of this group that does not transverse the blood-brain barrier. Data has shown that loperamide decreases intestinal transit, increases intestinal water and ion absorption and increases resting anal sphincter tone[28]. These pathophysiologic data explain the beneficial effect of loperamide in the treatment of patients with diarrhea, urgency, and/or incontinence[29]. Loperamide has also been shown to help patients with fecal soiling that is associated with internal anal sphincter dysfunction[30]. The major adverse effect of loperamide, which is common to all antidiarrheal agents, is the induction of constipation that may lead to a vicious circle in IBS patients with alternate symptoms of diarrhea and constipation.

Cholestyramine has also been used in the treatment of patients with diarrhea-predominant IBS, because of its capacity to bind bile salts that were considered to be responsible for the induction of diarrhea in some cases[31]. However, it has been shown that rapid ileal transit is associated with bile salt malabsorption and increased quantities of bile salts in the stool and therefore loperamide represents the most reasonable initial treatment of IBS patients with diarrhea, even if bile salt malabsorption is suspected[32]. In contrast, cholestyramine may be the treatment of choice for non-IBS patients with painless diarrhea due to bile salts malabsorption[33].

2.2.2. Smooth muscle relaxants

In many countries, including Greece, smooth muscle relaxants are the most commonly used agents for the management of pain in IBS patients. A variety of agents belong to this category and they may be classified into anticholinergic-antimouscarinic agents (mebeverine, cimetropium bromide), peripheral opiate antagonists (trimebutine), or calcium-channel antagonists (pinaverium bromide, octylonium bromide).

Although smooth muscle relaxants are widely used, their efficacy in IBS is not widely accepted[2]. The major problem in the evaluation of the efficacy of smooth muscle relaxants is the poor methodology in many of the IBS trials with such agents (absence or poor randomization, high placebo effects, small numbers of patients, high drop out rates, high heterogeneity, short follow-up)[34]. Moreover, only a few of these individual studies have shown a

significant benefit from treatment with a smooth muscle relaxant over placebo. However, a meta-analysis of studies available up to the mid-nineties suggested that treatment of IBS patients with smooth muscle relaxants is superior to placebo achieving more frequent improvement in overall symptoms (62% vs 35%, P<0.01) and control of abdominal pain (64% vs 45%, P<0.01)[35]. In particular in the latter meta-analysis, 5 drugs were found to be more efficacius than placebo: cimetropium bromide, pinaverium bromide, octylonium bromide, trimebutine, and mebeverine[35]. A more recent meta-analysis including 23 trials, in which 1888 IBS patients were treated with one of the above 5 agents or hyoscine butyl-bromide, showed similar results in favor of smooth muscle relaxants, although the benefit was relatively smaller than that observed in the first meta-analysis (global improvement: 56% in the drug therapy group vs 38% in the placebo group, P<0.001; improvement of abdominal pain: 53 % vs 42% respectively, P<0.001)[36]. Another systemic review including only the studies of at least two weeks duration with the best methodology and design also showed that smooth muscle relaxants may be superior to placebo in IBS patients for abdominal pain relief [68% (23%-87%) vs 31% (22%-66%) respectively][37].

In current clinical practice, smooth muscle relaxants are used for the management of IBS symptoms, such as abdominal pain or bloating, that cannot usually be controlled with any other drug therapy[2,16]. It seems that smooth muscle relaxants may be relatively beneficial when used for IBS exacerbations presenting with acute attacks of abdominal pain[16], but their effects probably decrease with long-term continuous use[2].

2.2.3. Prokinetic agents

Data relating the use of prokinetic agents in the management of IBS patients is very limited. Prokinetics could help in the management of patients with constipation-predominant IBS. Cicapride is a 5-hydroxytryptamine (serotonin or 5-HT) type 4 receptor (5-HT_4) agonist and 5-HT type 3 receptor (5-HT_3) antagonist that may also enhance the release of achetylocholine from the cholinergic neurons. In one study, cicapride was found to help patients with constipation-predominant IBS, but to worsen IBS patients with diarrhea-predominant IBS[38]. However, cicapride does not seem to be effective in patients with severe and persistent constipation[39]. Given the restricted efficacy and the potential cardiac adverse events, cicapride is not currently used in the management of IBS patients. The use of dopamine antagonists (domperidone, metoclopramide) had poor results and adverse events relating to the central nervous system, while macrolides (erythromycin) have not been tested in IBS patients to date. Thus, prokinetic agents do not seem to have a role in the management of patients with IBS.

2.2.4. Psychotropic agents

Antidepressant agents are potentially useful drugs in the management of IBS because of their anticholinergic and analgesic properties and/or their effects on serotonin receptors (selective serotonin re-uptake inhibitors or SSRIs)[16,40,41]. Moreover, the beneficial effects of antidepressants on depression or panic attacks, which are often observed in patients with severe IBS symptoms[42], may have a beneficial effect on the management of IBS symptoms as well[40].

Tricyclic antidepressants (amitriptyline, imipramine, desimipramin) are agents that are used for the management of IBS patients with severe and refractory symptoms of diarrhea and/or abdominal pain[13,43]. These agents seem to offer the greatest benefit to IBS patients with associated depression and/or panic symptoms[13,43], but they do not help and may worsen patients with constipation-predominant IBS, probably due to their anticholinergic effects[32]. The effects of tricyclic antidepressants on IBS symptoms are usually observed sooner and with relatively lower doses than with drugs used in the treatment of depression[13]. Since treatment with antidepressants means long-term therapy, such agents are currently used only for the management of IBS patients with severe and refractory or frequently relapsing symptoms that have previously failed to respond to other forms of drug therapy and impair the patient's quality of life[2].

The newer antidepressants SSRIs (fluoxetine, paroxetine, sertraline) are currently used in the management of IBS patients due to their rare side effects[13,44] and despite their unproven benefit. In fact, there is no good data to support the efficacy of SSRIs in the treatment of IBS and only a few uncontrolled studies have suggested that these agents may have a similar efficacy with tricyclic antidepressants[13,40]. It has also been suggested that SSRIs may be superior to tricyclic antidepressants in the treatment of patients with constipation-predominant IBS, since they may cause diarrhea[32]. The role of SSRIs in the management of IBS is currently under evaluation in prospective clinical trials[2].

Whenever treatment with antidepressants is administered, a 2-3-month period is required before a therapeutic benefit can be excluded. If therapy is effective, it should continue for at least 3-12 months[13,45]. Common causes for therapy failure include poor compliance and inadequate dosage of the antidepressant agent[45]. Com-

pliance to antidepressant therapy may be improved by giving giving comprehensive information to the patient about the central analgesic role of these drugs and the relation of IBS symptoms to depression and other psychological symptoms[45].

Benzodiazelines have also been tried in some IBS patients with stress or anxiety symptoms that may be associated with exacerbation of the intestinal symptoms. However, data from the very few trials of benzodiazepines in IBS were not so encouraging[46]. Because of absence of data on efficacy and their frequent side effects, the use of benzodiazepines cannot be recommended for the treatment of IBS patients.

3. PSYCHOLOGICAL THERAPIES

Psychological therapies have been tried for the treatment of IBS patients with unremitting symptoms that are usually refractory to any type of drug therapy, impair patients' daily functioning and are associated with psycological stress[13]. Forms of psychological therapies that have been used with IBS patients include relaxation therapy, biofeedback, hypnosis, cognitive behavioural therapy, and dynamic psychotherapy[13,16].

The efficacy of psychological therapies in IBS has not been established mainly due to methodological problems in the reported trials[47]. In addition, there is no data to support the superiority of one form of psychological therapy over others. Recent data suggested that the combination of multicomponent behavioral therapy plus drug therapy may be superior to drug therapy alone in the management of IBS patients[48]. Psychological approaches seem to help mainly IBS patients with abdominal pain and diarrhea rather than those with constipation[2]. Besides predominance of diarrhea, other factors which have been associated with a higher probability of a favorable response to psychological therapies include a) relationship of exacerbations of IBS to stressful events, b) intermittent instead of constant abdominal pain, and c) age less than 50 years[13,49]. Another major drawback for psychological therapies is their very limited availability in routine clinical practice. Psychological therapies are, therefore, restricted to only the IBS patients most difficult to treat and their application depends on cost, and patient's and physician's preferences, but mostly on the availability of therapy.

4. CONCLUSIONS

IBS is a complex disorder with pathophysiologic and psychological abnormalities. Treatment of patients with IBS should be individualized on the basis of each patient's symptoms and needs. Management of IBS starts with the confirmation of IBS diagnosis based on symptoms and limited tests for exclusion of organic disorders. The establishment of a good therapeutic relationship, reassurance of a benign prognosis and clarification of potential triggering factors for IBS exacerbations are particularly important for the successful management of these patients. Dietary and lifestyle changes may help a very few IBS patients with mild symptoms. High-fiber diets or supplements are recommended only for patients with severe constipation. Unfortunately, the efficacy of drug therapy on IBS symptoms is rather limited. Loperamide is the drug of choice for episodes of diarrhea and/or urgency, while smooth muscle relaxants may be used for IBS exacerbations with abdominal pain, bloating and/or distention. Antidepressants are currently used for the treatment of diarrhea- or abdominal pain-predominant IBS patients who are refractory to other forms of drug therapy. Psychological therapies may help refractory IBS cases, but their availability is limited, their cost high, and their efficacy unproven. Recently, there has been a significant improvement in our understanding of the pathophysiologic abnormalities of IBS and of their significance, which has led to the development[50-52] and trial of many novel therapies[53-55]. Although it may be difficult for a single agent to control all abnormalities observed in IBS, we hope that the development of all these novel agents will finally result in more effective and safe therapeutic options for our IBS patients.

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