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# Do We Know How to Manage Irritable Bowel Syndrome?

**Anton Emmanuel (Consultant Gastroenterologist; University College Hospital London)**
Correspondence to: Anton Emmanuel a.emmanuel@ucl.ac.uk

## ABSTRACT

Symptoms related to irritable bowel syndrome (IBS) represent the most common cause of presentation to gastroenterologists, but also result in a significant burden at the primary care level. Despite its high prevalence, diagnosis and management in these patients remains frustrating for both patients and health care professionals. This is due to the lack of an identifiable organic cause, specific diagnostic marker, but also a universally agreed treatment algorithm. This article reviews some of the challenges we have with patients with 'refractory' IBS and how to manage it today by providing an outlook of approaches that may help to overcome them in the near future.

**Key Words**: biofeedback; prokinetic; laxatives; hypnotherapy; psychotherapy; FODMAPS

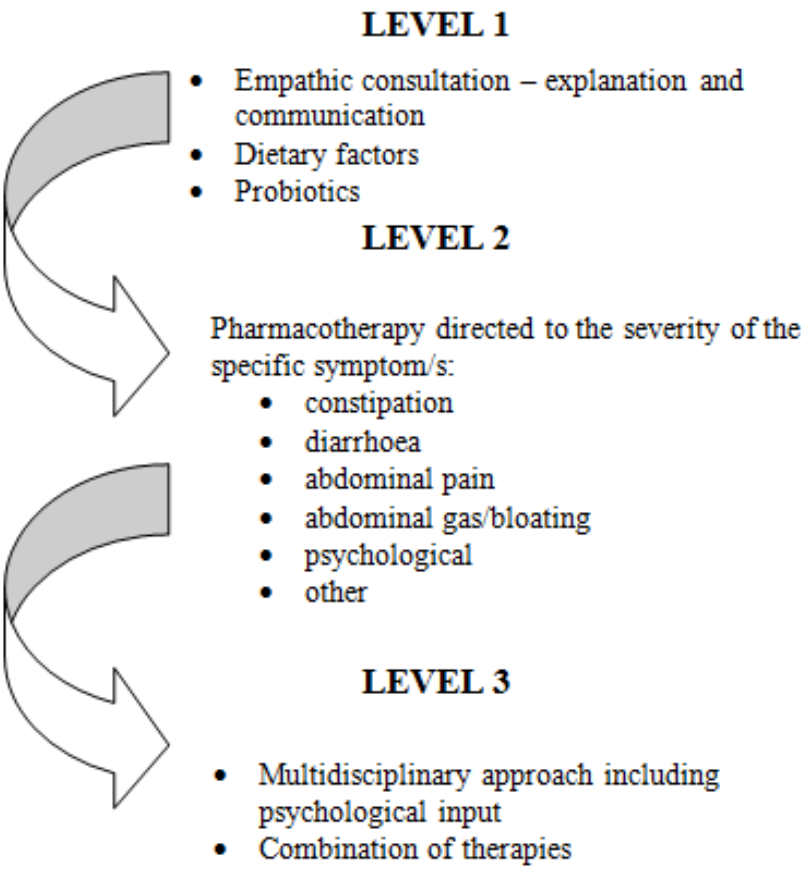
## Introduction

IBS is classified as a functional gastrointestinal disorder, referring to the chronicity and recurrent nature of symptoms which have no obvious structural or biochemical basis[1]. It is a chronic condition including symptoms of abdominal pain or discomfort temporally related to disordered bowel habit. Most patients with IBS experience symptoms that are reasonably short-lived but that trouble them on an intermittent basis. However, some patients develop chronic and severe symptoms that are difficult to treat[2]. Such patients respond poorly to several pharmacological interventions, who continue to seek medical aid or further diagnostic procedures, or those who are incapacitated by their symptoms. Patients may experience medical staff's reluctance to treat them, the tendency to over-generalise them or unfortunately, a clear rejection, which may lead them to "doctor shopping" with health-care over-utilization, or to seeking relief in alternative and complementary medicine.

Patients with IBS, especially when refractory, experience a chronic illness that affects their daily quality of life including diminished physical, social and emotional well being[1,3-4]. IBS is a major cause of absenteeism from work, which is a reflection of symptom severity and impact as opposed to work avoidance[5]. Patients, especially those with more severe symptoms, are characterised by higher levels of anxiety, neuroticism and a tendency towards pain catastrophising[6].

IBS has been aetio-pathogenically classified as being related to motility, visceral hypersensitivity, brain-gut dysfunction, alterations in inflammation, central processing, genetics, dietary factors and neurotransmitters[7,8] (Figure 1).

**Figure 1: Level of treatments and management in IBS**




## Symptoms

In the absence of a specific diagnostic test and with the heterogeneity of such patients, the diagnosis remains clinical. The three cardinal features of IBS are:

- Abdominal pain or discomfort
- Disordered bowel habit with diarrhoea or constipation, or alternating diarrhoea and constipation.
- A temporal relationship between bowel dysfunction and pain.

Abdominal bloating (a subjective sensation) or distension (an objective sign) are frequent but not invariable. Many patients also experience extra-colonic features. (NICE) guidelines recommend that healthcare professionals should consider assessment for IBS if the person reports having had any of the above symptoms for at least 6 months or if any alarm features (unplanned weight loss, rectal bleeding, family history of cancer, abdominal mass, anaemia) are present[2].

# Treatment

## Introduction

A key initial aspect of successful management is to offer an explanatory model individually directed according to the patient's particular symptoms, beliefs and anxieties. Symptoms occur variably in patients with IBS, therefore, the most vital first step in managing these patients, is to obtain a comprehensive history. Simple validated instruments such as the Bristol Stool Form scale[9] and symptom diaries[6] have an established complementary role in this process. Symptom pattern helps categorise in to particular subgroups (constipation (IBS-C), diarrhoea (IBS-D), mixed (M) or un-subtype (U)); this is important as it serves as a guide when choosing therapies aimed at improving altered bowel habits in IBS patients. From clinical experience it is often evident that the information about bowel habits, i.e. stool frequency and consistency, differs between retrospectively recalled information (i.e. taking patient history during a visit) and prospectively collected diary data. The severity of IBS symptoms and the influence of IBS-related and extra-intestinal symptoms on daily life is also of importance when determining the optimal therapeutic approach, and this can be assessed (albeit more often in trials than clinical practice) with the IBS symptom severity score (IBS-SSS)[6].

One treatment model to arise out of the extensive, if somewhat patchy, IBS-literature base is to subdivide treatment options into three levels (Figure 1). All IBS patients are assumed to benefit from the treatment options in level 1, regardless of symptom severity and psychological co-morbidity. The recommendations in treatment level 2 may benefit patients with moderate symptom severity, for example with an IBS-SSS score >175, or with frequent counselling despite seemingly mild symptoms. Treatment level 3 is aimed in patients with abdominal pain predominance, severe IBS symptoms in general (IBS-SSS>300), a complex situation with several extra-intestinal complaints or a difficult psychosocial situation that may include psychiatric illness or drug-dependence.

## Treatment Level 1

### Empathic consultation: explanation and communication

It is important to work with the patient to help them develop an understanding about the factors causing their symptoms and the complexity in treating them. From the beginning, the patient needs to know that no single therapy has been shown to change the long-time course in IBS and an explanation that treatment is intended to decrease specific symptoms rather than curing the disease is important. An explanatory model that encompasses the trigger factors and pathophysiological mechanisms can be key to forward progress in these patients.

Some patients express concerns about their disorder and believe that their symptoms signify something dangerous or life threatening[3]. Information from the health care professional is essential to complement the occasionally erroneous publicly available information on IBS. If available, a structured patient group education, an "IBS school", has been found to be superior to written information to enhance knowledge of IBS and improve GI symptoms and GI-specific anxiety in IBS

patients, even though the cost-effectiveness of this kind of education remains to be investigated[10].

## Dietary factors

According to NICE guidelines[2] diet and nutrition should be considered in patients with IBS. These include advice to:

- have regular meals and take time to eat
- avoid missing meals or leaving long gaps between eating
- drink at least eight cups of fluid per day, especially water or other non-caffeinated drinks
- restrict tea and coffee to three cups per day
- reduce intake of alcohol and fizzy drinks
- limit intake of high fibre food and reduce intake of 'resistant starch'
- limit fruit to three portions a day
- restrict Sorbitol if patients have IBS-D and if patients have wind/bloating they may find it helpful to eat oats.

About two out of three patients with IBS experience worsening of gastrointestinal symptoms related to food intake[11]. However, there is no convincing evidence that food allergy is the mechanism underlying symptom deterioration. Even though the mechanisms underlying adverse food reactions in IBS are not fully understood, and the evidence supporting the effectiveness of dietary interventions is weak, dietary advice has the highest treatment priority in the perception of patients[12] and should be considered in the management process. Treatment-refractory patients are occasionally on unusual and unhelpful diets, and a dietary history can help rationalise as a generalised lifestyle option.

Several patients with IBS have used exclusion of the foods from their diet that provokes their symptoms[11]. There is no evidence to support use of food allergy test-panels of any kind in adults with IBS, except for transglutaminase antibodies to exclude coeliac disease. As for lactose intolerance, most patients have tried dietary avoidance without benefit by the time of presentation[2]. Intake of artificial sweeteners like mannitol and sorbitol in chewing gums, soft drinks and candy, may also be of importance for gas related symptoms. Moreover, emerging evidence suggests that reduced intake of fermentable carbohydrates (FODMAPs - fermentable oligosaccharides, disaccharides, monosaccharides and polyols) might be helpful for subgroups of IBS patients[13]. This diet has both reduced osmotic and fermentable content, and unsurprisingly, is most effective in improving diarrhoea and bloating symptoms. Based on physiological studies, reduced intake of fat may be indicated in IBS patients with food related symptoms, especially abdominal pain, gas and bloating, as well as urgency and diarrhoea. Additionally, NICE guidelines have suggested that health care professionals need to review the fibre intake of people with IBS by adjusting (usually reducing it) in conjunction to monitoring symptoms. Patients with IBS should also be discouraged from eating insoluble fibre (i.e. bran), however if one was to increase their fibre intake, it should be fibre such as ispaghulla powder or foods high in soluble fibre (i.e. oats) [2].

## Probiotics

The use of probiotics in IBS appears to be safe and may be of benefit in some individuals. NICE have suggested that patients take the product for at least 4 weeks while monitoring the effect and take the dose recommended by the manufacturer[2]. However, probiotics are rather complex agents, in that different strains can elaborate various mediators that present several properties on different organisms. Thus, the therapeutic activity of one strain can be completely different from that of another.

Recent meta-analyses suggest that the majority of probiotic therapies tested show a trend to be effective in IBS[14]. Publication bias, of course limits what can be concluded from this wide range of mostly short-term studies on a variety of agents. Of the individual IBS symptoms reported as an outcome, the effects on abdominal pain and bloating after probiotic treatment are most convincing and of the individual bacteria, *Bifidobacterium infantis* 35624 has shown to be effective in well-designed clinical trials[15]. To date it is not possible to give specific strain recommendations, based on the lack of comparative trials, and insufficient data to recommend certain probiotics to different patient groups.

## Treatment Level 2

At this level of treatment, pharmacotherapy is directed towards the nature and severity of specific symptoms. It is recommended that one drug or treatment is adjusted at a time, with a predefined time point for evaluation. A state of mutual understanding that the pharmacological agent may help for the specific symptom/s of concern should be reached, but if it does not, it should be stopped. It is also important from time to time to give advice to temporarily stop a treatment in order to evaluate if it is still needed.

## Constipation

Patients with IBS-C, usually have a normal transit time[16]. Thus, fibre supplementation and bulking agents (Table 1) rather than stimulant laxatives or prokinetics are used as first-line treatment options for patients with IBS-C. However, the evidence supporting the use of bulking agents and fibre supplementation is relatively weak[17].

In order to avoid common side effects like bloating, flatulence and intensified abdominal discomfort and pain, a gradual dose-titration is recommended on an empirical basis as during the initial evaluation of symptoms, a symptom diary may help to evaluate effects of the treatment regimen. A trial with osmotic laxatives like polyethylene glycol (PEG) or lactulose is indicated to ease passage of stool even if formal trials in IBS are lacking[2]. From a clinical point of view, it is reasonable that PEG will affect bowel habits in IBS-C in a similar way as in patients with chronic idiopathic constipation as shown in a recent meta-analysis[18].

## Table 1: Treatment options by symptom

| Symptoms | Pharmacological Treatments | Non-Pharmacological Treatments |
|---|---|---|
| **Constipation** | • ***Bulking agents*** (psyllium, methylcellulose and calcium polycarbophil): mainly in patients who can't consume adequate dietary fibre<br>• ***Colonic stimulants*** (senna, bisacodyl) are best used on an as required basis, generally having an effect within 12 weeks of ingestion<br>• ***Osmotic agents****:* are useful in patients with slow transit and dose titratable with generally good efficacy<br>• ***Lactulose, Sodium picosulphate*** *-:* often results in flatulence and bloating; the inorganic salts are usually more effective<br>• ***Stool softener****:* usually best as adjunctive agents in combination with one of the above.<br>• ***Suppositories and enemas****:* best used in patients with frequent frustrated urge to open their bowel where rectal evacuation is the problem.<br>• ***PEG*** - polyethylene glycol<br>• **Lubiprostone** - a chloride channel activator<br>• **Prucalopride** - a selective, high-affinity $5HT_4$ receptor agonist<br>• **Linaclotide** – a guanylate cyclase activator | • Explanation and reassurance of symptoms<br>• Lifestyle changes (diet & exercise)<br>• Biofeedback therapy<br>• Probiotics<br>• Prokinetcs<br>• Contraindications medication<br>• Psychological intervention (i.e. CBT or hypnotherapy).<br>• Neuromodulation (sacral nerve stimulation). |
| **Diarrhoea** | • ***Anti-diarrhoeal agents***: Loperamide, diphenoxylate and codeine phosphate.<br>• **Serotonin ($5\text{-}HT_3$) receptor antagonists** (Alosetron, cilansetron, ramosetron). | • Explanation and reassurance of symptoms.<br>• Lifestyle changes (Diet, exercise).<br>• Biofeedback therapy<br>• Probiotics<br>• Contraindications medication<br>• Psychological intervention (i.e. CBT, hypnotherapy). |
| **Abdominal Pain** | • **Antimuscarinics** (e.g. dicycloverine, hyoscine)<br>• **Antispasmodics** (e.g. mebeverine, alverine, peppermint oil)<br>• **Tricyclic antidepressants (TCAs)**<br>• **Linaclotide** – a guanylate cyclase activator | • Explanation and reassurance of symptoms.<br>• Lifestyle changes (Diet, exercise).<br>• Probiotics<br>• Psychological intervention (i.e. CBT, hypnotherapy)<br>• Pain management therapy |
| **Abdominal gas and bloating** | • **Probiotics** | • Explanation and reassurance of symptoms.<br>• Lifestyle changes (Diet, exercise).<br>• Psychological intervention (i.e. CBT, hypnotherapy).<br>• Contraindications medication |

Linaclotide is a novel 14-amino acid peptide that is minimally absorbed and has been shown to reduce measures of intestinal pain and increase fluid secretion and transit in IBS-C[19]. Interestingly, beside the effect on secretion, linaclotide also have antinociceptive effects with improvement of abdominal pain, discomfort and bloating, which of course is favourable for IBS patients. Prucalopride is a selective, high-affinity $5HT_4$ agonist authorized for symptomatic treatment of females with chronic constipation in whom laxatives fail to provide adequate relief based upon the results from large trials [20]. However, no formal trials in IBS-C exist so far, but it can be expected that the drug would be useful also in subsets of IBS-C patients, as

the overlap between IBS-C, functional constipation and chronic idiopathic constipation is substantial.

Patients with refractory IBS, a repeat analysis of the symptom pattern may be performed, and in selected cases where difficult rectal passage of stool is the predominant symptom, assessment of pelvic floor function can be done, and evaluate if biofeedback (a gut-focussed behavioural therapy) is indicated.

### Diarrhoea

Anti-diarrhoeal agents include loperamide, diphenoxylate and codeine phosphate. Both loperamide and diphenoxylate inhibit peristalsis and gut secretion. Loperamide is the first choice for intermittent or chronic use in patients with IBS-D, with a dose-range of 2-16 mg/day[2]. The drug has neither mood related nor anticholindergic effects, but it should not be expected to decrease other IBS symptoms such as abdominal pain or bloating[21]. Codeine phosphate is not favoured due to the potential for dependence and its potential to induce dysphoria[16].

It has been suggested that some patients with diarrhoea who do not respond to loperamide treatment, may have bile acid malabsorption and that their symptoms are more responsive to the bile-acid binding agent cholestyramine than to loperamide[22]. Especially in IBS patients with nocturnal diarrhoea and in those with an acute onset of their IBS symptoms after a gastroenteritis (post-infectious IBS) a trial period with a bile-acid binding agent is indicated, as well as in patients with more severe diarrhoeal symptoms not responding to loperamide[22].

Recently, the focus has been on single receptor targets, especially serotonin (5-HT) receptors in the gut, since they influence motor, sensory and secretory responses to food and have shown to reduce pain and retard transit in patients with diarrhoea. 5-$HT_3$ antagonists have shown efficacy in IBS-D patients[23]. Unfortunately side effects, mainly ischemic colitis, have stopped further development of drugs from this class or led to withdrawal [23] – but the widely available anti-emetic, ondansetron, may be an option. Any 5-$HT_3$ antagonist needs to be discontinued promptly if constipation develops.

### Abdominal pain

Antimuscarinics attenuate the heightened baseline and postprandial contractility that may underlie functional pain and diarrhoea. Meta-analysis trials have found that the efficacy of these agents have minor advantages over placebo[24]. Only two of these drugs are licensed in the UK (mebeverine and hyoscine) and they have a modest effect on pain but no benefit on other IBS symptoms. However, they are well tolerated and can be used on an as-required basis. Peppermint oil is an over-the-counter drug non-specific smooth muscle relaxant. It is a safe and cheap alternative to the more traditional antispasmodics, and perhaps just as effective[17].

Tricyclic antidepressants (TCAs) have an analgesic effect on the gut, in addition to their prime action on mood and anxiety. The most commonly used agents are amitriptyline and nortriptyline, started at a low dose (5-10mg) which should be

taken once at night and reviewed regularly. The dose can be increased if needed (usually not exceeding 30 mg)[2]. Low dose TCAs seem to have greater efficacy than selective serotonin re-uptake inhibitors (SSRIs)[25]. It has been suggested that SSRIs may be beneficial in treating IBS-C, with tricyclic favoured for IBS-D[12]. Patients need to be informed about the frequent anti-cholinergic side effects (dry mouth, constipation, drowsiness and fatigue) and also that there is a lag period of 2-4 weeks for response. Whether switching from one agent to another in refractory cases has not been studied.

### Abdominal gas and bloating

For the moment, dietary advice, as stated under treatment level 1 is probably the most effective recommendation for these symptoms. Some probiotics may also have a positive effect, but no systematic advice about this is possible at the moment. Since visceral sensory function may be involved as a pathophysiologic mechanism, a trial with a TCA may be considered.

### Psychological

A wide range of psychological treatments have been studied in patients with refractory IBS. The most evaluated therapies in IBS are cognitive behavioural therapy (CBT), dynamic psychotherapy, hypnotherapy and relaxation therapy[2]. All forms of psychological therapy seem more effective than usual care to improve global symptom severity, and there is emerging cost-effectiveness data[25]. Table 2 summarises the evidence for different modalities of psychological therapy and the patient subtypes most responsive. The nature of such treatment, is to be 'gut focused' because general CBT and relaxation therapies are not more effective than standard care[25].

**Table 2: Psychological therapies and their possible utility**

| Therapy | Mode of action | Patient selection |
|---|---|---|
| **Relaxation therapy** | Progressive muscle relaxation and meditation for stress relief | • Especially useful in diarrhoea-predominance and when there is psychological co-morbidity |
| **Hypnotherapy** | Induce deep relaxation and alter gut autonomic tone | • Especially helpful to relieve symptoms of constipation, pain and flatulence and when there is anxiety |
| **Cognitive behavioural therapy (CBT)** | Identify symptom triggers and learn to respond appropriately | • Abdominal pain, bloating and flatulence most responsive<br>• Least helpful when depression prominent |
| **Psychodynamic interpersonal therapy** | Improve understanding of link between emotions and bowel symptoms | • Especially effective when there has been a history of abuse<br>• Least effective in chronic pain, constipation or depression |

### Other

It has been suggested that some reviews of Chinese herbal medicines/plant preparations have a positive effect on the control of IBS symptoms, but scientific evidence is limited and not sufficient to make clinical recommendations[26].

Biofeedback is a gut-directed behavioural therapy for functional constipation. It is a learning strategy based on operant conditioning and is effective for patients with both slow transit and evacuation dysfunction. 'Gut-directed hypnotherapy' (GDH) is centred on the use of hypnotic induction, using progressive relaxation and other techniques and imagery directed towards control and normalization of gut function. Randomised controlled trials show significant efficacy in patients with IBS, extending to the long term[27].

### Treatment Level 3

Psychiatric co-morbidities and extra-intestinal symptoms are present in a significant proportion of IBS sufferers[2]. In some of these patients, use of multiple drugs may have become a part of the problem, especially analgesics and laxatives. The presence of drug-dependency (especially opioid analgesics) needs separate specific withdrawal interventions besides the regular IBS treatment.

The multidisciplinary approach is critical to success in this patient group. Some of these patients need combinations of pharmacological treatment alternatives in order to control the severe symptoms, but a key goal is to avoid opioid analgesics, since this will worsen the situation. Another key advantage of the multidisciplinary approach is that such organized, health care continuity avoids "doctor-shopping".

## Conclusion

Patients with IBS are sometimes a challenging group of patients who undergo several fruitless cycles of investigation and who respond poorly to current treatment modalities. In addition to ongoing support a range of treatment modalities are required. The frequent extra-intestinal symptoms and related diagnoses such as fibromyalgia, chronic headache, insomnia, anxiety and mood disorders may need to be addressed as part of a multidisciplinary approach. Clinical trials are not always helpful in this situation since entry to these studies usually requires patients to have no co-morbidity, which is quite the opposite of the situation in many patients. When managing these patients, it is important to include an explanatory model individually targeted towards the patient's particular symptoms, beliefs and concerns. Subsequently treatment should be tailored to cardinal symptoms.

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