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The Management of Irritable Bowel Syndrome

A Position Paper of the Neurogastroenterology and Motility Section of the Israeli Gastroenterology Association

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Abstract: Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction with symptoms including abdominal pain associated with a change in stool form or frequency. IBS global prevalence is around 4% and its impact on patient's quality of life and social functioning is substantial. Multidisciplinary working teams of the Israeli Society of Neurogastroenterology and Motility evaluated all validated approaches to IBS management. The aim was to develop a national, evidence-based position document on IBS management for general practitioners and adult and pediatric gastroenterologists. This position document comprehensively reviewed therapeutic options, including patient education (including specific national communities), dietary modifications (particularly the low FODMAP diet), antispasmodic drugs, probiotics, antibiotics (eg, rifaximin), secretagogues (eg, linaclotide), neuromodulators, psychological therapies (including cognitive behavioral therapy and gut-directed hypnotherapy), and complementary medicine approaches. The importance of establishing a positive physician-patient communication with a therapeutic partnership, including an empathic approach and implementation of the bio-psycho-social model, was also strongly emphasized. A structured treatment algorithm incorporating multiple therapeutic tools that are locally available was developed as well. We hope that this position paper will provide a practical and updated tool for the management of IBS in Israel and in other countries as well.

Key Words: irritable bowel syndrome, FODMAP, neuromodulation, psychotherapy, functional gastrointestinal disorders, treatment algorithm

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Irritable bowel syndrome (IBS) is the most studied disorder of gut-brain interaction (DGBI). In clinical practice, DGBI are responsible for up to a third of all referrals to gastroenterology clinics and to about one-tenth of all primary care referrals. DGBI affects the entire gastrointestinal system, from swallowing difficulties to defecation disorders. IBS's main clinical features include abdominal pain associated with a change in stool form or frequency. According to the Rome Foundation Global Epidemiology Study, the global prevalence of IBS is 4.1%[1] This extensive multinational survey, which encompassed 26 countries, found a pooled prevalence of 5.2% among females, compared with 2.9% in males. According to the data of the study, the pooled prevalence of IBS was 3.2% (4.9% among females, compared with 1.6% in males).[2]

The pathophysiology of IBS is not completely understood, and the proposed underlying mechanisms are disordered communication between the gut and the brain (due to altered pain-gatekeeper function), visceral hypersensitivity, impaired central processing[3] genetics, dysbiosis and disturbed mucosal and immune function.[4]

The significance and centrality of DGBI's stem from their high prevalence and their substantial human and economic impact. IBS patients report significant impairment in almost every aspect of quality of life that has been examined: self-esteem, body image, sleep, sexual function, concentration, eating habits, recreational activities, and social and occupational functioning. Moreover, the chronic nature of the disorder often leads to numerous medical tests (mostly unnecessary) that burden the health care system with patient load and costs.[5] Therefore, developing effective treatments for IBS is of paramount medical, human, and economic importance.

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The authors declare that they have nothing to disclose

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It should also be acknowledged that pelvic floor dysfunction, although a distinct entity, frequently overlaps with IBS and may contribute to symptoms such as constipation, incomplete evacuation, and abdominal discomfort. Awareness of this overlap is important when evaluating patients with refractory or atypical symptoms.

Unfortunately, the belief that "IBS has no effective treatment" and that patients must "learn to live with it" remains prevalent among many physicians. This approach frustrates both patients, who are left without hope, and physicians, who feel powerless when treating these patients. It is important to emphasize that while IBS treatment does not cure IBS or eliminate all types of symptoms, physicians may find validated, available tools to alleviate patient suffering. It is our hope that physicians and other health care providers find in this position document practical and evidence-based approaches for their IBS patients. Finally, we hope that this position paper will increase patient and provider satisfaction and reduce provider burnout.

APPROACHING PATIENTS WITH IBS

Many physicians characterize IBS treatment in negative terms, such as "difficult" or "frustrating," largely because of the lack of an effective approach and/or therapeutic tools. Even more concerning is the projection of physician frustration onto patients, who become labeled as "challenging" at best, or more commonly as "difficult," "problematic," "frustrating," or even "crazy." Much of this negativity can be changed through better familiarity with validated new therapeutic schemes and management of expectations between physicians and patients. While IBS is indeed a chronic remittent disorder, and most patients will continue to experience symptoms, there are several therapeutic tools available to improve patients' symptoms and quality of life and ability to control their symptoms and illness. In our experience, when improvement of symptoms, daily functioning and quality of life are presented as the goals of treatment, rather than "total cure," many patients are happy to participate in such a therapeutic partnership.[6]

The therapeutic approach to IBS should be based on the bio-psycho-social model, where biological/pathophysiological, personal, environmental, and emotional factors are recognized as inseparable components in understanding the patient's clinical presentation.

In addition, a strong physician-patient relationship is achieved by creating a therapeutic strategy in which the physician and the patient are partners, with the physician providing professional guidance.[7,8] Essential components for any successful therapeutic session include:

1. Listening: Empathic listening to the patient using mirroring behavior can help to establish a strong therapeutic relationship. Indeed, mirroring builds trust and enhances communication in a more comfortable environment.
2. Explaining: One of the first steps in any therapeutic approach should include patient education about IBS clinical presentation, pathophysiologic mechanisms, and natural history. Empathic interviewing, with explanations and discussion of the above points, can improve patients' quality of life and symptoms, reduce health care visits, and enhance adherence to treatment. The physician should explain how disordered bidirectional communication between the gut and the brain can lead to symptoms through motility disorders of the gastrointestinal tract, visceral hypersensitivity, and altered central information processing. It is important to emphasize the chronic and remittent nature of IBS (periods of flare-ups and remission) and its benign nature.
3. Understanding the timing of the current consultation: Since IBS is a chronic condition, it is important to understand why the patient is seeking help at this particular time. Often, it relates to specific concerns or fears (eg, serious illness, malignancy, etc.), theories about etiology (eg, food allergies/intolerances, infections, etc.), or personal circumstances (eg, starting a new job, beginning a relationship, fear of symptom interference with functioning). These concerns are often intensified through social media. Addressing these concerns is crucial for optimal care. Questions such as "What brought you here today?," "Which is your most bothersome symptom?," "What do you think is causing your symptoms?," "What concerns you most?," and "How do you think I can help?" can help establish a strong physician-patient relationship.
4. Emphasizing emotional factors: Explaining the importance of emotional state in relation to symptoms is crucial, as many patients tend to minimize or deny the connection between their symptoms and emotional states such as depression, anxiety, and somatization. While it is important not to label IBS as a psychiatric disorder and to legitimize the symptoms and suffering, it is essential to emphasize that emotional states such as anxiety can exacerbate symptoms, creating a vicious cycle, where symptoms increase anxiety and anxiety worsens symptoms.
5. Managing patient's expectations about the treatment: It is crucial to explain that the main aims of treatment are to improve quality of life and reduce symptoms because, unfortunately, chronic illnesses such as IBS can be brought under control but not cured. In this respect, it is helpful to mention that the goal of treatment in well-recognized chronic diseases, such as diabetes mellitus and hypertension, is to bring them under control rather than to cure them. In this regard, it is advisable to agree upon several achievable goals and to evaluate progress during follow-up meetings.
6. Maintaining therapeutic continuity: Patients need to feel that their physician is "always there for them." Knowing that help is available, when needed, often reduces symptoms and anxiety. Modern communication options (telephone/virtual/online) facilitate therapeutic continuity without overburdening clinical practice.

Since IBS is multidimensional in pathophysiological terms, the therapeutic process involves trial and error and the combination of different therapeutic approaches. In recent years, a practical approach called the "Multidimensional Clinical Profile" (MDCP) has been developed by the Rome Foundation for classifying patients along different dimensions. Through patient characterization, MDCP can assist us to select specific treatment plans as in personalized medicine.[9] This approach applies to all DGBI including IBS, and defines each patient based on various axes. In IBS, for example:

(a) Formal diagnosis of IBS according to the Rome IV diagnostic criteria.
(b) Additional information defining subtypes (eg, diarrhea or constipation predominant IBS).
(c) The personal impact of IBS on patient functioning.
(d) Psychosocial factors involved (eg, depression, anxiety, and somatization disorder).
(e) Physiological impairments and biomarkers (eg, abnormal laboratory or manometry findings).

To demonstrate and illustrate this approach, we selected 2 cases with IBS that represent 2 opposite ends of the severity spectrum. Note that numerous other manifestations may exist, leading to different MDCP characterizations:

Example 1. A 24-year-old female patient with:
- IBS with diarrhea (IBS-D).
- Mild impact on quality of life and daily functioning.
- Anxiety about symptoms due to family history (her aunt died of colon cancer with similar symptoms).
- No specific biomarkers.

MDCP-patient characterization and treatment plane:
- IBS is characterized by mild severity (low impact).
- Treatment can likely focus on education and reassurance.
- Medical therapy is not necessarily required.

Example 2. A 57-year-old patient with:
- IBS with functional dyspepsia and functional heartburn.
- Frequent, intermittent pain episodes unrelated to meals or exercise.
- Unable to work and withdrawn from social life.
- Somatic disorder according to DSM-5.
- Negative work-up (esophageal manometry and pH study, gastric emptying test).

MDCP-patient characterization and treatment plan:
- IBS is characterized by high severity (high impact), with coexisting functional dyspepsia and functional heartburn.
- Treatment: A comprehensive therapeutic plan, combining education, reassurance, pharmacological therapy, nonpharmacological interventions, psychological therapy, and other modalities.

Finally, the MDCP model facilitates an effective therapeutic approach based on a thorough understanding of all aspects affecting the patient's illness experience. With experience, evaluation becomes intuitive without requiring a detailed analysis of each dimension.

NUTRITIONAL INTERVENTIONS IN IBS

Most IBS patients attribute at least some of their symptoms to dietary factors. However, until recently, there was a significant lack of uniform evidence-based dietary guidelines. In recent years, a substantial body of knowledge has accumulated, establishing the role of nutritional interventions in treatment.

Several general principles underpin all individual nutritional interventions:

(a) While general nutritional guidelines can and should serve as a therapeutic framework, there is no substitute for a personalized nutritional approach. A comprehensive evaluation of dietary history that includes past experiences and identification of food intolerances, combined with an individualized treatment plan, particularly when developed by an experienced clinical dietitian, will increase the likelihood of success.[10]
(b) "How we eat" is as important as "what we eat." Proper eating behaviors include correct distribution of mealtimes throughout the day, eating slowly while seated, thorough chewing, and avoiding large meals late at night, can significantly improve symptom control.[11]
(c) Recommendations, such as avoiding spicy foods, reducing consumption of alcohol, caffeine, and dietary fat, or limiting industrialized and processed foods, have supporting evidence in the literature and a place in nutritional treatment for IBS patients.[12–16]
(d) Naturopathic diets and diets based on IgG antibody levels in blood lack sufficient evidence-based scientific support.[11,17]
(e) Nonceliac patients who report IBS-like symptoms that improve with gluten avoidance are considered to have nonceliac gluten sensitivity (NCGS). The underlying mechanism remains unclear, and the 2 main hypotheses are incomplete gluten breakdown leading to an innate immune system reaction and that gluten avoidance results in a parallel reduction in the consumption of fructans and agglutinins that may cause symptoms. In the absence of clear-cut biomarkers to diagnose NCGS, the diagnosis is based on patient reporting only.[18,19] Gluten avoidance in healthy nonceliac individuals can lead to harmful changes in the composition and function of the microbiome.[20,21]

The main evidence-based approaches for treating IBS with dietetic modifications are the following:

Low FODMAP Diet

FODMAPs (Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols) are carbohydrates that are poorly digested and absorbed in the small intestine. Consequently, those carbohydrates undergo digestion and fermentation by colonic bacteria that generate IBS symptoms through 3 main mechanisms:

1. Increase in luminal osmolarity is responsible for a shift of water into the lumen of the colon resulting in diarrhea.[22]
2. Excessive intestinal gas production that results in bloating and abdominal distension.[23]
3. Microbiome changes, known as dysbiosis, are characterized by a change in the composition of the microbiome, potentiating a decrease in anti-inflammatory bacterial strains.[24]

Several comprehensive papers from 2016 to 2018, including meta-analyses, controlled studies, and prospective cohort studies, found that within 3 to 6 weeks, a low FODMAP diet improves stool frequency and consistency, reduces abdominal pain, bloating, and diarrhea in IBS patients.[11,25,26] Evidence for long-term efficacy is more limited. However, a study from 2020 of 120 IBS patients on a low FODMAP diet showed maintained symptom improvement at 3 and even 6 months after food reintroduction.[27] In a recent primary care setting—randomized controlled trial (RCT) that enrolled 460 IBS patients found that a self-management FODMAP—lowering smartphone application was superior to otilonium bromide in alleviating IBS symptoms.[28]

On the basis of current published data, this dietary approach is recommended for IBS patients with diarrhea (IBS-D) or with diarrhea and constipation (IBS-M).

The restrictive hard-to-follow nature of the low FODMAP diet, the risk of dysbiosis and the need for personalization have led to several "softer" therapeutic approaches:

(a) "Top Up"–Starting with loose dietary restrictions while monitoring symptoms, and then gradually increasing restrictions until reaching the classic low FODMAP diet.
(b) "Top Down"—Beginning with the classic low FODMAP diet, then gradually reintroducing foods based on symptom response.[29]
(c) "Gentle FODMAP"—Less restrictive guidelines as in "Top Up" allowing higher FODMAPs consumption, which may be more suitable for special populations such as those with eating disorders, pregnant women, or children.[30]

The process of eliminating FODMAP-rich foods and gradually reintroducing them is complex and requires personalization. English-language resources about implementing this diet are readily available online (eg, www.monashfodmap.com, www.myginutrition.com). However, the likelihood of success and adherence for a long period are significantly lower without guidance from an experienced clinical dietitian.[10]

Increasing dietary fiber intake is a common practice in IBS treatment, though evidence for its efficacy in symptom reduction remains uncertain. A literature review of 17 interventional IBS studies showed no significant overall efficacy of fiber intake, though the data were analyzed without distinguishing between IBS types or specific symptoms. However, 2 additional meta-analyses found that intake of soluble fiber was beneficial for symptom improvement, while insoluble fiber proved ineffective.[31,32]

In our experience, adding soluble fiber may improve stool frequency and consistency in IBS patients with constipation (IBS-C) without exacerbating other symptoms.

The Mediterranean Diet (MedDiet)

The MedDiet is characterized by high intake of vegetables, fruits, nuts, legumes, whole grains, fish, and olive oil and moderate consumption of red wine. MedDiet is associated with numerous health benefits, supported by a substantial body of observational and interventional studies. MedDiet has been linked to a reduced risk of several chronic diseases, including heart disease, dyslipidemia, and high blood pressure. In IBS, a randomized controlled trial found that adherence to a MedDiet led to significant improvements of symptoms (83% compared with 37% in the control group).[33] In another study, it was found that the MedDiet can promote a beneficial effect on gut microbiota and can improve IBS symptoms and quality of life.[34] However, certain components of this diet (maybe those rich in FODMAP) might exacerbate symptoms in IBS patients, suggesting the need for personalized dietary modifications.[35]

In summary, a personalized MedDiet appears to be a reasonable therapeutic option for IBS.

In conclusion, dietary intervention constitutes an essential component of IBS treatment. A comprehensive dietary assessment, including both nutritional and behavioral aspects, can provide valuable insights and contribute to improved medical care. Early collaboration and consistent messaging between the physician and dietitian will create therapeutic synergy and enhance the likelihood of success.

Highlights:

- "How we eat" is as important as "what we eat." Proper eating behavior significantly impacts IBS symptoms.
- The low FODMAP diet is effective and recommended for IBS patients with diarrhea (IBS-D) or mixed type (IBS-M). The process of eliminating and reintroducing FODMAP-rich foods is complex and requires personalization.
- For IBS patients with constipation (IBS-C), adding soluble dietary fiber may improve stool frequency and consistency.
- A personalized Mediterranean diet (MedDiet) appears to be a reasonable therapeutic option in IBS.
- While general nutritional guidelines can and should serve as a therapeutic framework, there is no substitute for a personalized nutritional approach by an experienced clinical dietitian.

Treatment With Probiotics, Antibiotics, and Fecal Transplantastion in IBS

The gastrointestinal microbiota composition plays a key role in IBS pathogenesis.[36] Dysbiotic microbiome changes increase intestinal permeability, promote microinflammation, reduce pain thresholds, and alter intestinal motility.[37] In IBS, the microbiome composition typically shows an increase in proinflammatory bacteria (eg, Enterobacteriaceae) and a decrease in beneficial bacteria (eg, Lactobacillus and Bifidobacterium).[38] Consequently, microbiome manipulation has emerged as a therapeutic target in IBS.

Probiotics

Probiotics contain bacteria intended to optimize the gut microbiome composition and to improve IBS-related symptoms. Probiotics are investigated as single-strain and as combined multistrain preparations. The assumptions that a high number of different strains will increase the chances of success through their broader spectrum of activity or synergistic effects increased the use of multistrain preparations. However, 2 reviews did not find convincing evidence that these assumptions are valid. According to these reviews, in most cases, single strains were equivalent to multistrains. Consequently, it was concluded that the selection of an appropriate probiotic preparation should be based on evidence-based efficacy rather than on the number of strains. In IBS, one controlled clinical trial with De Simone Formulation (previously known as VSL#3), a multistrain preparation, was tested in 48 patients.[39] After 8 weeks of treatment, the only improved symptom was bloating. Vivomixx, another multistrain product, was readily available in Israel. In another controlled clinical trial, Bio-25, a multistrain preparation (Supherb, Israel), was tested in 107 women with IBS. After 8 weeks, BIO-25 showed no greater efficacy than placebo.[40] Despite the results of these 2 clinical trials, one meta-analysis, comparing various probiotics versus placebo found improvements in IBS symptoms such as abdominal pain, bloating, distension, and diarrhea, along with high safety profiles.[41] International gastroenterology associations, including the Canadian[42] American[43] and Korean[44] associations, recommend probiotics for treating IBS with diarrhea (IBS-D), while other associations do not support their use[45]

In conclusion, the debate over probiotic use in IBS remains unresolved, and more high-quality randomized controlled trials (RCTs) are needed. Nevertheless, given the high safety profile of probiotics, an empirical treatment trial may be warranted, particularly in patients with diarrhea, distension and bloating. Currently in Israel, evidence does not support recommending any specific preparation.

Antibiotics–Rifaximin

Rifaximin is a nonabsorbable, broad-spectrum antibiotic with high gastrointestinal selectivity and an excellent safety profile. The rationale behind its use is that rifaximin may manipulate the microbiome composition within the gut and, through that, improve IBS symptoms. In 2 multicenter controlled studies (TARGET 1 and TARGET 2), 1258 IBS patients without constipation received either rifaximin 550 mg 3 times daily or placebo for 14 days. A significant reduction in symptoms (particularly bloating and diarrhea) was observed 30 days after treatment completion in the treatment group versus placebo (40.7% vs. 31.7%, $P < 0.001$)[46] with no significant side effects. A follow-up study (TARGET 3), with 1074 patients who responded to rifaximin were recruited. In 64% of responders, improvement was temporary, with decreased response beginning 1-week post-treatment. Patients who lost response were randomized to rifaximin retreatment or placebo. Rifaximin retreatment showed clinical improvement compared with placebo (OR = 1.57; 95% CI: 1.22-2.01) (NNT = 10.2),[46] indicating that retreatment is a viable option. In addition, in clinical practice, some providers use prolonged low-dose "maintenance" treatment, though this approach lacks research support.

In Israel, rifaximin (marketed as 200 mg tablets) is currently registered for treating hepatic encephalopathy and symptomatic, uncomplicated diverticular disease (SUDD) and not for IBS. This presents certain barriers, as treatment involves taking multiple pills and carries a significant patient cost that is not reimbursed by public health services.

In summary, treatment with rifaximin is a short-term, safe option that, despite its costs, is generally well accepted by most patients. However, it should be noted that efficacy over placebo is modest, evidence is lacking for IBS with constipation (IBS-C), and response, when achieved, is short-lived.

Fecal Transplantation

Fecal transplantation involves transferring fecal materials from a healthy donor into the intestine of a sick individual. As for rifaximin, the rationale behind its use is to ameliorate the microbiome composition within the gut and by that to improve IBS symptoms. Studies of fecal transplantation in IBS patients have yielded conflicting results. In one RCT involving 55 IBS-D patients, 50 to 80 g of fecal material were transplanted through colonoscopy, with 28 patients receiving placebo treatment. After 3 months, significant improvement was observed in the treatment group versus placebo (65% vs. 43%, $P = 0.049$)[47] However, other studies, including 2 recent meta-analyses, failed to demonstrate superiority over placebo treatment.[48,49]

While fecal transplant is being investigated for various conditions and diseases, in Israel, it is currently approved only for treating recurrent Clostridium difficile infection. Its use in IBS remains investigational and is not included in any international treatment guidelines.

SYMPTOMATIC TREATMENT

Symptomatic treatment aims to alleviate dominant symptoms. Treatment may be chronic (eg, for constipation or chronic diarrhea) or episodic (eg, for abdominal pain). In our experience, these medications are primarily prescribed for flare-ups. While some medications (eg, peppermint oil and polyethylene glycol 3350) have strong evidence to support their use, others have weak supporting evidence (eg, papaverine) despite extensive clinical experience. Notably, the American College of Gastroenterology guidelines do not include these medications in their current recommendations (except for peppermint oil).[50] This decision has 3 reasons:

1. Many, if not most, of these medications are not available in the US.
2. Older medications rely on studies of lesser quality than currently required for drug approval.
3. The standard primary endpoint in recent IBS drug studies is global symptom improvement rather than improvement of a specific symptom. Symptomatic medications rarely achieve global improvement as they only target specific symptoms or mechanisms.

Despite these limitations, we believe these medications have a place in IBS treatment, and therefore, we included them in our recommendations.

In IBS, the main symptoms requiring treatment are:
Abdominal pain (with or without bloating and abdominal distension).
Constipation.
Diarrhea.

Each of the main symptoms has appropriate treatments (Table 1), and combinations of several treatments are possible when more than one symptom predominates.

IBS With Pain (With or Without Bloating and Abdominal Distension)

Chronic, remittent abdominal pain is the most important symptom and diagnostic criteria for IBS.

Pain is typically:
Spastic in nature.
Associated with a bowel movement, a change in stool form or frequency.
Concentrated in the left lower quadrant.
More common in morning hours and after meals.
Often accompanied by urgency (sometimes to the point of incontinence), bloating, and abdominal distension.

Symptomatic medications primarily work by alleviating spastic pain, originating in the gastrointestinal tract (antispasmodic medications). Enteric-coated peppermint oil (Colpermin, Tillots Pharma, Switzerland) is the most common symptomatic medication whose mechanism of action is relaxation of smooth muscles. Evidence from clinical trials supports its beneficial effects on pain and bloating in IBS. Consequently, colpermin is considered as first line treatment in various IBS guidelines[42,51] Gaspan (Schwabe Pharma, Italy) is another peppermint oil-based antispasmodic medication that includes caraway also. However, Gaspan has not been evaluated in an RCT enrolling IBS patients and controls, and for that reason, is not included in our recommendations.

TABLE 1. Symptomatic Treatments for IBS

Main indication and class of drugs	Generic (brand) name	Max daily dosage	Adverse effects	Comments
Abdominal pain+bloating				
Antispasmodic	Peppermint oil (Colpermin)	1-2 pills, 3 times a day	Heartburn, headache, anal burning	First line drug treatment
Antispasmodic - Anticholinergic	Dicyclomine (Notensyl)	10-20 mg, 3 times a day	Dry mouth, blurred vision, weakness, and nausea	Spasmomen is not available in Israel
	Otilonium bromide, (Spasmomen)	40 mg, 3 times a day		
Antispasmodic - Ca^{++} blocker	Papaverine (Papaverine)	80 mg, 3 times a day	Weakness, changes in blood pressure, and heart rate	Close to meals
	Mebeverine (Colotal)	135 mg, 3 times a day		Before meals
Combined benzodiazepine+smooth muscle relaxant	Chlordiazepoxide+Clidinium Bromide (Librax, Bralix, Librocol)	1 pill, 3 times a day	Dry mouth, constipation, and sleepiness	Attention: Driving skills
		1 pill, 3 times a day		Tolerance and dependence in long-term use
Combined smooth muscle relaxants+pain killers that include codeine	Paracetamol+ Papaverine+Codeine+ Atropine (Spasmalgin)			
Diarrhea				
Opioid receptor agonists	Loperamide (Imodium, Loperid, Rekamide, Lopi-care, Stopit)	2-16 mg a day	Abdominal pain and nausea	
Bile acid sequestrants	Cholestyramine (Colestid Colestipol, Chol-Less, Questran)	4-6 g, 1-2 times a day	Abdominal pain and flatulence	Short-term trial
Coating substances and prebiotics	Gelsectan	1-2 capsules, 1-2 times a day	None	Currently not available in Israel
Serotonin receptor 5-HT3 antagonists	Ondansetron (Zofran· Odatron)	4-8 mg a day	Fatigue and headache	
Constipation				
Osmotic laxatives	Polyethylene Glycol 3350 (Normalax, Regulax Peglax)	17 g, once daily (can be titrated up as needed)	Diarrhea, abdominal pain, bloating	Powder, no global effect
Prokinetics with a global effect			Diarrhea	Not available
	Lubiprostone (Amitiza)	8 mcg, 2 times a day	Diarrhea	Not available
	Linaclotide (Constella or Linzess)	290 mcg, once a day		

Additional antispasmodic medications utilizing calcium channel blockade, anticholinergic activity, or combinations thereof, are also available for IBS patients suffering mainly from abdominal pain. Anticholinergic medications with evidence-based benefits include dicyclomine (Notensil, CTS, Israel) and included otilonium bromide (Spasmomen, Menarini, Italy) that was recently withdrawn from the market in Israel.[52] Besides dicyclomine, there are several other antispasmodic medications available in Israel.

Despite relying on lower-quality evidence, they remain widely used. These preparations may contain:

- Single active ingredients:
  Mebeverine.
  Papaverine.
- Combined multiple active ingredients:
  Combination of atropine, paracetamol, codeine, and papaverine (Spasmalgin, Sam-On, Israel).
  A combination of clidinium bromide and chlordiazepoxide (Librax, Meda Pharm, Portugal; Bralix, Remedica, Cyprus; Librocol, Switzerland) that contains a benzodiazepine, making it particularly suitable when tension and anxiety exacerbate abdominal pain. However, benzodiazepines should be used with caution due to their sedative effects, and for short periods to decrease the risk for tolerance and dependence.

IBS With Bloating and Abdominal Distension

Although bloating and abdominal distension are not part of the formal diagnostic criteria for IBS, they are among the most prevalent and distressing symptoms reported by patients and frequently represent a primary reason for seeking medical care. Therefore, targeted treatment of bloating and abdominal distension is clinically relevant in the management of IBS.

Bloating and abdominal distension are common and troublesome IBS-related symptoms that are particularly resistant to treatment. Abdominal distension is an objective visible sign of increased abdominal girth. Bloating is a feeling of abdominal fullness and discomfort. The pathophysiology of bloating and abdominal distension is multifactorial and involves visceral hypersensitivity, abdomino-phrenic dyssynergia, intestinal dysmotility, and dysbiosis. Treatment may include dietary modifications (eg, lactose-limiting diet and low FODMAP diet), probiotics, antispasmodics (eg, otilonium bromide, peppermint oil), rifaximin, secretagogues (eg, linaclotide), neuromodulators (eg, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and buspirone), and plethysmography-based biofeedback. Moreover, cognitive behavioral therapy and gut-directed hypnotherapy can be used in cases of functional bloating associated with IBS.

Specific treatments for excess gas, such as digestive enzymes or activated charcoal, have not been tested in IBS, and in our experience, their efficacy is very limited.

IBS With Diarrhea (IBS-D)

Several classes of medications may be used to treat IBS with diarrhea:

Loperamide (Imodium, Loperid, Rekamide, Lopi-care, Stopit) is a medication of the opioid receptor agonist class used to decrease the frequency of diarrhea. It binds to the opiate receptor in the gut, reducing propulsive peristalsis and increases intestinal transit time, reducing daily fecal volume, increases fecal viscosity and bulk density, and diminishes the loss of fluid and electrolytes. This medication is among the most common medications used in IBS-D. Small studies have demonstrated its efficacy in reducing bowel movement frequency in IBS-D. However, loperamide does not affect other IBS symptoms such as abdominal pain and therefore cannot serve as monotherapy.[42] It can be used for targeted treatment during exacerbations or when continence is crucial (such as during long public transportation rides).

Bile acid sequestrants are a group of resins used to bind bile acids and prevent their reabsorption through the mechanism of enterohepatic circulation. Consequently, bile acid sequestrants are used in the treatment of chronic diarrhea due to bile acid malabsorption. A proportion of IBS-D patients have bile acid malabsorption, particularly those with previous intestinal surgery or cholecystectomy. Because a lack of a simple method to diagnose bile acid malabsorption and because treatment is safe and response is rapid, a short empirical trial (1 to 2 wk) is reasonable, especially when other diarrhea treatments have failed.[53] These patients may benefit from bile sequestrants such as cholestyramine (eg, Colestipol, Chol-Less, Colestid, Questran).

Coating substances and prebiotic substances contain combinations of herbal extracts rich in xyloglucans and xylo-oligosaccharides. Such a product is available in Israel under the name of Gelsectan (Lapidot Medical, Israel). Clinical indications include diarrhea, abdominal pain, and bloating in adult patients with IBS. The 2 proposed mechanisms of action are the formation of a protective coating over intestinal surfaces (restoring disordered intestinal permeability) and promoting the proliferation of bacteria that control normal intestinal function.[54] Studies in IBS-D have shown improvement in stool consistency and frequency, as well as pain and bloating sensations.[55] Again, given the rapid response and excellent safety profile, a short empirical trial for IBS-D is reasonable.

Serotonin receptor (5-HT3) antagonists such as ondansetron (Zofran, Odatron), primarily used as an antiemetic, were also found to improve diarrhea. The proposed mechanism involves alterations in gastrointestinal neural pathways, including pain transmission. In one controlled study in patients with IBS-D, ondansetron 4 mg, significantly improved urgency (within 1 wk), bowel movement frequency, stool consistency and bloating.[52] A multicenter European RCT that evaluated the role of ondansetron in IBS-D confirmed that ondansetron improves stool consistency and urgency but showed a minor effect on pain.[56] It should be mentioned that this study was closed early due to slow recruitment (20% of the target).

Eluxadoline (Viberzi) is an opioid receptor agonist to μ and κ and an antagonist to δ. Eluxadoline is an effective medication that is not available in Israel (reviewed in chapter 8: medications that are not available in Israel).

IBS With Constipation

Laxative treatment is often necessary in IBS-C. However, most studied preparations show improvement in the number of bowel movements without improvement in pain or bloating (no global improvement). Therefore, treatment of IBS-C cannot rely solely on laxatives and typically needs to combine additional therapeutic measures to achieve global improvement. While the market offers many laxatives, most have not been tested in IBS, making their efficacy difficult to establish. Among laxatives that were

TABLE 2. Neuromodulators for IBS

Main class of drugs	Generic (brand) name	May improve	Max daily dosage	Adverse effects: class effects and specific SE	Comments
Tricyclic antidepressants (TCAs)	Nortriptyline (Nortylin)	Pain, diarrhea	150 mg	All: Anticholinergic AE as sedation, constipation, urinary retention, dry mouth, dizziness, arrhythmia and QT elongation, weight gain, anxiety	Starting: 10-25 mg with gradual increase. Maximum effect after 4-6 wk
	Amitriptyline (Elatrolet, Elatrol)	Pain, diarrhea	150 mg		
	Desipramine (Deprexan, Chlomipramine)	Pain, diarrhea or incomplete evacuation	150 mg		
	Doxepin (Gilex)	Pain	75 mg		
Serotonin-noradrenaline reuptake inhibitors (SNRIs)	Venlafaxine (Effexor, Venla, Viepax)	Pain	300 mg	All: Headache, sleep disorders, nausea, agitation Venlafaxine: may cause hypertension	Starting: 25 mg with gradual increase. Maximum effect after 4-6 wk
	Duloxetine (Cymbalta Yentreve)	Pain	90 mg		
	Milnacipran (Ixel)	Pain	100 mg		
Selective serotonin reuptake inhibitors (SSRIs)	Paroxetine (Paxxet Parotin, Seroxat)	Constipation, anxiety	50 mg	All: Weakness, dizziness, diarrhea, dry mouth, sleep disorders, nausea, agitation Paroxetine: Vomiting Fluoxetine: headache, confusion	No analgesic effect
	Fluoxetine (Prozac, Flutine, Prizma)	Pain, constipation, anxiety, distension	40 mg		
	Escitalopram (Cipralex, Esto, Escitalopram Teva) 10-15 mg	Pain, constipation, anxiety, bloating	20 mg		
Other neuromodulators	Sulpiride (Modal)	Pain, vomiting	100 mg	Hyperprolactinemia, dyskinesia Dizziness, dry mouth, weight gain Constipation, weight gain, dizziness, dry mouth Weakness, dizziness, sleepiness Vertigo, dizziness, headache Dystonia, Akathisia	
	Pregabalin (Lyrica)	Pain, distension, diarrhea	300 mg		
	Mirtazapine (miro, remeron)	Pain, nausea, vomiting, anxiety, diarrhea, dyspepsia	45 mg		
	Gabapentin (Gabapentin, Neurontin)		600 mg		
	Buspirone (Sorbon)	Pain, diarrhea, bloating	60 mg		
	Olanzapine (Zyprexa)	Pain, dyspepsia, anxiety	10 mg		
	Quetiapine (Seroquel)	Nausea, vomiting	100 mg		
	Bupropion (Wellbutrin)	Complementary	300 mg		
		Complementary			

tested in IBS, polyethylene glycol 3350 (PEG) is the most studied medication (Normalax, Taro, Israel; Peglax, Neopharm, Israel). PEG is an osmotic laxative that works by drawing water into the intestinal lumen, thus softening stool. PEG treatment was found to increase bowel movement frequency and decreased straining but did not improve pain or bloating.[57] Other commonly used osmotic laxatives, such as magnesium or lactulose, have been less studied in IBS but may have similar efficacy.

Prokinetic medications that have been shown to improve constipation in IBS-C also have demonstrated an effect on pain, bloating, and distension. Lubiprostone (eg, Amitiza) or Linaclotide (eg, Constella or Linzess) were found to achieve global improvement in patients with IBS-C. Lubiprostone and linaclotide are not available in Israel and are reviewed in chapter 8.

Highlights:

- Symptomatic treatment of IBS targets dominant symptoms and not all IBS-related symptoms. Consequently, symptomatic treatment usually does not achieve global improvement, and it is most appropriate for mild-moderate IBS. Symptomatic treatment of IBS can be recommended as adjunctive treatment to neuromodulation in severe cases of IBS or for patients who decline neuromodulation.
- A wide range of antispasmodic preparations is available to alleviate abdominal pain in IBS.
- Available treatments for diarrhea (eg, Loperamide) and constipation (eg, PEG preparations) effectively target these specific symptoms (monotherapy) but do not affect concurrent symptoms (such as pain or bloating) and, as a result, do not provide global improvement.
- Other preparations commonly used in clinical practice (bismuth, digestive enzymes, and gas-reducing preparations) lack solid evidence of efficacy in IBS, so they are not discussed in detail in this position paper.

NEUROMODULATION

Neuromodulators are a central therapeutic tool for patients with moderate to severe IBS. Because these medications were primarily developed for psychiatric disorders, we prefer and recommend the use of the term "neuromodulation" as it reduces stigma and better reflects the mechanism of action: modulation of central and peripheral hypersensitivity by controlling neurotransmitters levels (serotonin, noradrenaline, and dopamine) in both the central nervous system (CNS) and the enteric nervous system (ENS).

The rationale for neuromodulation in IBS is multifaceted:

(a) Neuromodulators effectively manage neuropathic pain across various medical conditions, some similar to IBS (eg, fibromyalgia) and others different (eg, diabetic neuropathy or postherpetic pain).
(b) Neuromodulators may improve gastrointestinal dysmotility (eg, tricyclic antidepressants slow intestinal motility, reducing bowel movements in IBS-D or IBS-M and serotonin reuptake inhibitors increase the number of bowel movements in IBS-C).
(c) Neuromodulators can help manage concurrent psychiatric conditions, a common phenomenon in severe IBS.

It should be noted that most evidence for neuromodulators in DGBI, including IBS, comes from small studies, some uncontrolled. Nevertheless, the cumulative data and clinical experience of the panel working teams suggest positive outcomes for neuromodulators, warranting their inclusion in our therapeutic arsenal.

The main studied classes of neuromodulators include:

Tricyclic antidepressants (TCAs).
Selective serotonin reuptake inhibitors (SSRIs).
Serotonin noradrenaline reuptake inhibitors (SNRIs).

While neuromodulators are not registered in Israel for IBS treatment, we believe this should not preclude their appropriate use. However, since psychiatric conditions can result in severe morbidity and even mortality, when severe anxiety, major depression, or other significant mental disorders are suspected, the patient should be referred to psychiatric consultation and monitoring. Commonly used neuromodulators appear in Table 2.

The strongest evidence supports tricyclic antidepressants (TCAs). Meta-analyses and reviews have found these medications effective, with a number needed to treat (NNT) of ~6.[58] TCAs are "multitasking" neuromodulators as they can interact with almost 7 receptors. As a result, TCAs have a stronger analgesic effect compared with other antidepressant classes that target 1 or 2 receptors only. TCA's additional receptor affinities include, among others, the muscarinic-1 receptor (has anticholinergic side effects), the alpha1 adrenergic and the histamine (H1) receptors.[59,60] The combination of pain reduction and decreased bowel movements makes these the drugs of choice for IBS-D or IBS-M. Treatment typically begins with low doses (10 mg at bedtime), with dose titration based on tolerance and response, with maximum effect achieved after 4 to 6 weeks. Consequently, 3 to 4 weeks of treatment should be attempted before increasing again the dose (to a maximum of 100 mg if needed). However, high doses are rarely necessary, with clinical effect typically achieved at 25 to 50 mg.[59,60]

In case of intolerance, dosing can be decreased, or another TCA may be prescribed. In one RCT, 463 patients with IBS (primary care setting) were randomly allocated to titrated low-dose amitriptyline (10 to 30 mg daily) or placebo.[61] Results showed that titrated low-dose amitriptyline was superior to placebo (lower IBS symptom severity scores and significantly more considerable or complete relief of IBS symptoms, odds ratio 1.88) in primary care across multiple outcomes, and was safe and well tolerated.

TCAs may be combined with antispasmodics in patients with both episodic and persistent symptoms, as above. Primary side effects are anticholinergic and antihistaminic but are usually minimal at low doses.

Commonly used TCAs include:

Nortriptyline (Nortylin).
Amitriptyline (Elatrolet, Elatrol).
Desipramine (Deprexan, Desipramine).
Doxepin (Gilex).

Serotonin noradrenaline reuptake inhibitors (SNRIs) are particularly effective due to their combined noradrenergic analgesic and serotonergic promotility effects. To note that this class of drugs are indicated for pain reduction even without psychiatric comorbidity (eg, duloxetine for diabetic neuropathy). SNRI's typically do not cause constipation and are therefore optimal for patients with IBS-C. Treatment should begin at the lowest available dosage.[60]

Commonly used drugs include:

Duloxetine (Cymbalta, Yentreve).
Venlafaxine (Effexor, Venla, Viepax).
Milnacipran (Ixel).

Selective serotonin reuptake inhibitors (SSRIs) improve IBS symptoms and general well-being, though their impact on pain is lower than TCAs or SNRIs. SSRIs do not cause constipation (and may occasionally cause diarrhea as a side effect), making them suitable for IBS with constipation, particularly when anxiety is a significant component.[52]
Among the different SSRI's those that demonstrated efficacy in IBS included:
Paroxetine (Paxet).
Fluoxetine (Prozac, Flutine).
Esi/Citalopram (Cipralex, Esto).
Additional neuromodulators:
Sulpiride (Modal) is a well-known antipsychotic that has been used in low doses for treating gastrointestinal symptoms. While no studies have specifically examined it in IBS, it is the only neuromodulator drug registered in Israel for functional gastrointestinal disorders. Sulpiride has antiemetic effects and is recommended when IBS combines with functional dyspepsia and upper gastrointestinal complaints. The drug has anticholinergic effects that may worsen constipation, and there is a possibility of hyperprolactinemia or tardive dyskinesia, though these complications are rare at the low doses typically used for functional disorders. Hence, our recommendation is to use sulpiride in low doses and for short periods.
Pregabalin (Lyrica) is a calcium channel α2δ ligand and an anticonvulsant drug used in the treatment of neuropathic pain, fibromyalgia and anxiety, among others. In addition, pregabalin modifies visceral hypersensitivity and improves symptoms in patients with IBS-D.[62]
Mirtazapine (Remeron, Miro) is a tetracyclic antidepressant that increases the release of serotonin and norepinephrine in the CNS and inhibits the H1 receptor of histamine. Mirtazapine proved to achieve a global effect in IBD-D that is accompanied by depression and anxiety. In a randomized, placebo-controlled trial, it was found that mirtazapine significantly improved early satiation, quality of life, gastrointestinal- specific anxiety, nutrient tolerance, and weight loss in patients with functional dyspepsia.[63] Other potential uses include treatment of chronic nausea/vomiting.
The medical literature mentions other drug classes for DGBI and IBS. However, there are no specific studies of these drugs in IBS, and therefore, they are not discussed in detail in this position paper.
Quetiapine (Seroquel) is an atypical antipsychotic drug.
Buspirone (Sorbon) is a serotonergic agonist.

Practical Aspects of Treatment

Neuromodulation treatment of IBS faces 2 main challenges:

1. Physician-related: There is a clear underutilization due to a lack of expertise and concerns about the treatment itself or patient reactions. Position papers like this aim to address these challenges.
2. Patient-related: A low treatment compliance due to fears of addiction, dependency, stigma, or adverse effects. In addition, patients are afraid that neuromodulation treatment will invalidate their physical symptoms and suffering, sending them a hidden message that "it's all in their head" or implying they suffer from a mental disorder. When we discuss neuromodulation with our patients, to improve their adherence, these concerns must be proactively addressed. We suggest emphasizing the following points:

- Neuromodulation is a symptomatic gastrointestinal treatment, not a psychiatric treatment. Dosages are significantly lower than those used for psychiatric indications and prescribing neuromodulators does not imply the patient has a psychiatric condition. However, treatment can reduce anxiety and distress that often accompany and exacerbate symptoms in IBS. It is important to explain that medications can have multiple indications (use Aspirin as an example: originally for fever and pain, now primarily for ischemic heart disease and stroke prevention).
- The treatment does not cause dependency or addiction, so discontinuation is always possible if needed.
- At low dosages, side effects are relatively mild (dose-dependent), short-term and reversible.
- To decrease side effects and to increase adherence, start with the lowest available dosage (or half) and increase gradually. Explain that the therapeutic effect appears after 4 to 6 weeks and that side effects, if any, typically appear in the first week and resolve quickly. Duration of treatment is flexible and is usually around 6 to 12 months. The decision on discontinuation is based on clinical signs and made collaboratively with the patient.
- If necessary, medications from different classes can be combined at low dosages to increase efficacy (eg, combining a TCA with an SSRI in an IBS patient with constipation and significant anxiety). However, when physicians feel they lack expertise or when significant psychiatric comorbidity exists (eg, severe depression and anxiety), professional psychiatric consultation is recommended to support both the patient and the physician. Furthermore, neuromodulation can augment other therapies, especially behavioral therapy, as discussed below.

In conclusion, neuromodulator therapy is a significant component of the treatment of medium/severe IBS, and it is desirable that every physician treating these patients acquire skill and experience for the benefit of their patients. Treatment with these drugs is generally safe and the main challenge is to present it to the patient in a manner designed to increase adherence.

Highlights:

- Neuromodulation is a crucial component in treating moderate/severe IBS. We hope that this position paper will help physicians treating IBS patients to use neuromodulators more frequently.
- IBS neuromodulation uses lower dosages than psychiatric treatment, does not require a psychiatric diagnosis, and primarily targets pain rather than psychiatric disorders. Improvement in psychiatric comorbidity, if present, is a secondary benefit.
- TCAs are first-line treatment for IBS-D.
- SNRIs are preferred for IBS-C but can also be used in IBS-D.
- The main challenge is to successfully mediate neuromodulators to our patients.
- A detailed explanation and a strong physician-patient relationships increases patient's compliance and adherence.
- Neuromodulators can be combined with other neuromodulators, and with brain–gut behavior therapy as part of treatment augmentation.

BRAIN–GUT BEHAVIOR THERAPY (BGBT)

IBS involves disordered gut-brain interaction (DGBI) and frequently coincides with psychological comorbidities (primarily depression, anxiety, somatization, and trauma history).[64,65] Whether psychological comorbidities precede or follow IBS, they are closely related to the IBS course and severity. Therefore, incorporating various psychological and cognitive behavioral therapies (CBTs) into IBS treatment.[42,43] These treatment modalities are now known as brain–gut behavior therapies (BGBTs). Recently, a Rome Foundation Working Team composed of world authorities in the field, published a paper on BGBTs. In it, the authors presented an overarching approach to the incorporation of psychotherapy into treatment plans, including the modalities themselves, selecting patients, explaining the treatment and its rationale, tailoring the treatment to the patient, and the integration of BGBTs into personalized treatment plans as monotherapy or as augmented therapy.[66]

Although psychological treatments and CBT possess a favorable safety profile and have no physical side effects, patients may avoid trying them for various reasons: fear of social stigma, desire to find a yet unidentified structural reason or the "root cause" of their symptoms, disbelief in the DGBI model and concern with a functional rather than a structural disorder, as the main mechanism through which psychological therapy would invalidate their physical suffering. However, when IBS is presented not as a psychiatric disorder but as a physical condition, exacerbated by emotional state, with them being trapped in a "vicious cycle," where symptoms exacerbate the emotional state and the emotional state exacerbates symptoms, patients become open to discuss these aspects of IBS and agree to try psychological treatments. On top of these obstacles, psychological treatments and CBT are costly, as reimbursed services availability is quite limited. Furthermore, prescribing and administering them requires both patient and provider education which is time consuming. There are no guidelines about when and how to incorporate psychotherapy into treatment plans. Generally, good candidates include patients who acknowledge the DGBI biopsychosocial model, are open to talk-based therapy, have psychiatric comorbidity, those expressing an interest in nonpharmaceutical approaches, or when medications are ineffective.

Several BGBTs have been found to be effective in IBS.[67] A meta-analysis published in 2020 showed that CBT and gut-directed hypnotherapy are more effective and sustainable compared with other interventions.[68] Below we review the recommended therapies.[42,43]

CBT is one of the most common and best studied BGBT. CBT is a focused, short-term therapy (typically up to 10 sessions) aimed at improving coping abilities and solving problems. The goal is to recognize (cognitive) and change (behavior) false and distressing beliefs (maladaptive cognitions), sometimes due to the exaggerated importance that is attached to them. During treatment, patients learn to practice relaxation techniques, and to modify unconscious and maladaptive thought patterns that impair effective coping. Through psychoeducation where they are taught how to develop copping skills (to confront stress) and through gradual exposure to stress, patients learn how to eradicate avoidance, "safe" and anxious behaviors.[69] Data shows that in IBS patients treated successfully with CBT, the number needed to treat (NNT) was 4, which is comparable to treatment with an antidepressant.[58] A 2-year study that compared telephone-based and online CBT to standard care (without CBT), in resistant IBS, showed a significant improvement in symptoms and social functioning in the CBT groups.[70] CBT is particularly helpful when there is a need to change avoidance behaviors such as a fear of leaving the house or of entering "scary" locations (busy supermarkets, public toilets, or malls), avoiding relationships or work, and spending excessive time on the toilet (as in obsessive compulsive disorder), among others.

More recently, CBT was shown to improve avoidant restricting food intake disorder in patients with IBS and other DGBI conditions, where the fear of GI symptoms leads to excessive food avoidance.[71]

Gut-directed hypnotherapy (GDH) is another effective therapeutic method for various conditions involving mind-body interaction. Treatment typically involves 6 to 12 sessions, during which patients undergo relaxation, receive hypnotic suggestions targeting symptom relief and acquire tools for symptom management and coping. For example, a patient who suffers from abdominal pain would receive suggestions about abdominal warmth pain relief. A constipated patient receives suggestions involving movement (like thinking of the waterflow in a river) and normal elimination, while an IBS-D about building a dam and being continent. GDH involves no discomfort and, when conducted by a certified therapist, it is very safe. In Israel, practicing hypnotherapy requires both formal training and a Ministry of Health certification and licensing available only to psychologists, physicians, or dentists. Numerous studies have demonstrated hypnotherapy's efficacy in improving gastrointestinal symptoms and overall well-being, establishing it as an effective, clinically validated treatment in IBS.[72] Meta-analyses of various studies (some heterogeneous and of limited quality due to challenges in creating blinded controls for psychotherapy) found an NNT of 4to 5 for hypnotherapy.[58] Another recent meta-analysis found that GDH may improve global symptoms of IBS. In particular, it improved pain symptoms compared with other standard IBS interventions. GDH delivered in groups was effective at reducing global IBS symptoms compared with standard interventions.[73] Long-term follow-up studies have shown benefits persisting for at least 5 years.[74,75] GDH for IBS in Israel is available at some gastroenterology departments. In addition, the Israeli Society of Hypnosis website (https://www.hypno.co.il/therapists) provides a therapist directory.

Medical psychology involves short-term intervention (~10 sessions) focusing on physical illness and integrating mind-body interactions into treatment. Medical psychology incorporates various therapeutic approaches, drawing from CBT, hypnosis (GDH) and psychodynamic psychology. Medical psychology has been shown to be equally effective compared with antidepressants, particularly in patients with a history of trauma.[76] It is available through some health maintenance organizations (HMOs) and hospitals and covered, at least in part, by the HMOs or by a private insurance. Psychodynamic psychological treatment has an excellent NNT of 4[58] but, due to its longer duration is more expensive than other BGBTs.

Mindfulness meditation is a type of meditation in which patients focus on being intensely aware of what they are sensing and feeling in the current experience (now), devoid of interpretation or judgment. Practicing mindfulness involves breathing techniques, guided imagery, and other

practices to relax the body and mind and help reduce stress and anxiety. The method integrates yoga, group discussion, and individual practice to enhance inner awareness and environmental mindfulness.

Research has shown that mindfulness-based stress reduction (MBSR), an 8-week structured intensive course, significantly reduced gastrointestinal and concurrent symptoms in IBS patients by 71%.[77] MBSR is not reimbursed by HMOs and is available at various private institutes throughout Israel.

In conclusion, many IBS patients experience psychological comorbidities, and BGBTs can serve as a complementary or central treatment tool that can be combined with neuromodulators or symptomatic treatments. While various approaches have proven effective for IBS, the main challenge remains guiding patients toward accepting this treatment path. When patients shift their perspective from purely "physical" medicine to a "mind-body" medicine, the likelihood of persistence and improvement increase significantly.

Highlights:

- Psychological comorbidities frequently coincide with IBS.
- CBT and hypnotherapy are the most studied and effective psychotherapies used in IBS [now known as brain–gut behavior therapies (BGBTs)].
- BGBTs are safe and can be easily and successfully combined with dietary interventions, neuromodulators or symptomatic treatments (augmentation approach).
- BGBTs are offered by some HMOs and hospitals. However, in Israel, treatment has limited availability and a high cost (for the patient).

COMPLEMENTARY MEDICINE TREATMENT

The limitations of conventional IBS treatments led about one half of patients to seek advice from complementary medicine (CM) providers.[78] CM includes herbal medicine, nutritional supplements, and touch therapies (eg, acupuncture, reflexology, and massage).

Herbal medicines and nutritional supplements–A review of the literature revealed ~70 preparations containing one or more herbal plants that have been evaluated in IBS. The following is a list of the most studied herbal preparations:

1. Aloe vera was tested in several controlled double-blind studies and demonstrated a short-term reduction in IBS symptoms in both IBS-C and IBS-D. However, loss of a therapeutic effect was observed after only 3 months of treatment.[79]
2. Curcumin, the active ingredient of turmeric, was evaluated in 3 double-blind randomized studies in IBS. In a meta-analysis based on these 3 studies, curcumin was not more effective than a placebo in reducing IBS symptoms.[80,81]
3. Padma lax is a Tibetan formula containing 15 minerals and medicinal herbs. A randomized double-blind study at Hadassah Hospital, Israel, showed that compared with placebo, Padma lax improved stool consistency, reduced abdominal bloating and pain, and enhanced quality of life.[81–83] Results showed that this formula is safe and effective in IBS with and without constipation.
4. STW 5 (Iberogast) is an herbal formula containing alcoholic extracts from 9 plants. A randomized double-blind study demonstrated a global improvement of IBS symptoms, including reduction of abdominal pain after 4 weeks.[82,83] No significant adverse effects were noted. This formula is marketed in Europe but not in Israel.
5. Traditional Chinese medicine (TCM) was evaluated in several studies that treated patients with IBS. In TCM, a personally tailored combination of medicinal herbs is selected for each patient. For research purposes, this approach makes treatment standardization almost impossible. In addition, 3 randomized double-blind studies in IBS, showed inconclusive results. In the first study, 161 patients with IBS were treated with a combination of 20 medicinal herbs (Chinese herbal medicine). Results showed an advantage over placebo in improving IBS symptoms. However, there were no significant differences in outcome between the personally tailored treatment and a standard herbal combination.[82,83] In another study, a 4-ingredient traditional Chinese formula (Tong-Xie-Yao-Fang) showed symptomatic improvement in IBS-D and there were no significant side effects. In the third study that examined a modified Tong-Xie-Yao-Fang (11 herbs) formula, in IBS-D, there was no improvement in symptoms or quality of life compared with placebo[82,84]

In summary, several studies with herbal medicines and nutritional supplements showed a trend toward improvement in IBS. However, because of a lack of uniformity across studies (variation in herbal combinations and in control group preparations), the very limited number of studies for most preparations and the possibility of publishing bias favoring positive results, a definitive conclusion regarding herbal medicines and nutritional supplements cannot be drawn. There is a need for more RCT's of a higher quality before we can recommend herbal medicines and nutritional supplements for IBS.

In addition, in studies with herbal medicines and nutritional supplements, safety aspects were not thoroughly tested, and despite the very few reported significant adverse effects, caution is warranted.

Chinese acupuncture is an important component of CM and touch therapy (that includes various interventions such as acupuncture, reflexology and massage). After that, a diagnosis is made according to the principles of CM, and the patient receives a customized therapy. This individualized approach (as for herbal medicine), makes treatment standardization almost impossible and a definitive conclusion and recommendation for IBS is difficult to reach.

1. Chinese acupuncture: Several RCT's treated IBS patients with Chinese acupuncture. Two review studies and a meta-analysis comparing acupuncture to placebo acupuncture (nonmeridian points or superficial acupuncture) found no significant difference in symptom severity or quality of life.[85,86] Studies comparing acupuncture to standard care showed a symptomatic improvement in acupuncture patients; however, due to a lack of blinding, a definitive conclusion and recommendation for IBS cannot be drawn. Again, these studies were classified as low-quality studies.[85,86] A systematic review from 2018 examined various acupuncture techniques including acupuncture alone, moxibustion (burning moxa cones over acupuncture points) and electro-acupuncture found a high risk of bias that prevents reaching definitive conclusions.[87] Nevertheless, authors found that the most promising approach in IBS was the combination of acupuncture with the Chinese herb Geshanxiaoyao.[87] A recent systemic review and meta-analysis found that acupuncture, as compared with

conventional treatment, improved quality of life and reduced symptoms severity in patients with IBS.[88] However, acupuncture was not associated with abdominal pain reduction.

In summary, while herbal medicine, nutritional supplements and acupuncture may improve IBS symptoms, current evidence does not support unequivocal recommendations. Additional high-quality RCT's are needed to clarify their efficacy in IBS patients.[85] This position paper aligns with treatment guidelines from both the Canadian Gastroenterology Association and the British National Institute for Health Care (NICE guidelines), which currently do not recommend herbal treatments or acupuncture for IBS patients.[42] Nevertheless, given the growing patient demand for complementary treatments, their reported satisfaction with these approaches, and the possibility of quality-of-life improvements, these treatments cannot be entirely dismissed. We recommend that they should be acknowledged through informed discussion with patients and careful consideration of their use. Please refer to Table 3 that summarizes complementary medicine treatments.

Highlights:

- There are more than a few studies that used herbal medicine, nutritional supplements or acupuncture for IBS and reported a beneficial treatment response.
- Studies that used herbal medicine, nutritional supplements and acupuncture in IBS were of poor quality, and therefore a valid conclusion regarding treatments cannot be drawn at this stage.
- The safety of herbal medicine treatment has not been thoroughly tested, necessitating caution in using these preparations.
- At this stage, and as for acupuncture, there is insufficient established evidence to recommend massage or reflexology for IBS.
- Additional high-quality RCTs are needed to clarify the efficacy of herbal medicine, nutritional supplements and touch therapies in IBS.

DRUGS FOR IBS THAT ARE NOT AVAILABLE IN ISRAEL

Several effective drugs for IBS that are available in the American, European, and Far East markets are still missing in Israel (Table 4). This is particularly unfortunate given the clear need for effective global IBS treatment options. However, these drugs can still be recommended and imported through specialized private pharmacies. Limitations are significant patient's cost of therapy as these drugs are not reimbursed at all and the requirement to complete an application form, presented to the Ministry of Health. Given the drug's effectiveness, we consider it important to discuss these drugs and their specific indications, noting that import barriers can be overcome.

Drugs are for IBS-C:

Lubiprostone (Amitiza) is a prostaglandin analog that activates type 2 chloride channels, located in the lining of the intestine. Channel activation facilitates the movement of chloride ions, and then sodium ions and water into the gut lumen. This flow of water and electrolytes softens the stool, increases peristalsis and improves symptoms such as pain, straining, and bloating. Efficacy was demonstrated in 2 studies, including 1154 IBS-C patients. Approximately 75% of patients treated with lubiprostone report an increase in bowel movement frequency and of spontaneous bowel movements (without laxatives) within 24 hours of treatment initiation.[89–91] The drug shows a good safety profile with main side effects being nausea, abdominal pain, and diarrhea.

Linaclotide (Constella, Linzess) and Plecanatide (Trulance) are agonists of guanylate cyclase-C (GC-C) receptors, a membrane protein located in the lining of the intestine. Activation of GC-C receptors results in increased intracellular cyclic adenosine monophosphate (cGMP) levels and activation of the cystic fibrosis transmembrane conductance regulator (CFTR). Activation of this membrane protein results in the transfer of chloride ions, bicarbonate, and water into the gut lumen. Efficacy was demonstrated in 2 randomized phase 3 studies including 1299 IBS-C patients. Patients treated with linaclotide report an increase in bowel movement frequency and of spontaneous bowel movements (without laxatives) within 24 hours of treatment initiation. In addition, linaclotide significantly improved abdominal pain, discomfort and bloating and showed excellent safety profile with main side effects being diarrhea.[92–94] Plecanatide was tested in 2 phase 3 studies (2189 IBS-C patients), demonstrating significant improvement in frequency of bowel movements and concurrent symptoms: abdominal pain, discomfort, and bloating.[50] Common side effects included diarrhea and headache.

Tenapanor (Ibsrela, Xphozah) is a sodium-proton exchanger isoform 3 (NHE3) inhibitor. NHE3 inhibition decreases sodium-hydrogen exchange through cell membranes and increases luminal sodium concentration and then water content within the lumen. Efficacy was demonstrated in a randomized phase 3 study (606 patients) showing improved peristalsis, increased spontaneous bowel movements, and reduced abdominal pain severity.[95] Effects were noted within 1 week of treatment initiation. Except for diarrhea, safety was excellent, including elderly patients and it is probably safe during pregnancy as well.

Drugs for IBS-D

TABLE 3. Complementary Medicine Treatments for IBS

Treatment	Recommendation	Dosage
Aloe vera	May be beneficial in the short-term reduction of symptoms	
STW5 (Iberogast)	May be beneficial for abdominal pain	20 drops 3 times a day
Padma lax	May benefit IBS-C	1-2 pills a day
Curcumin	Not established as reducing IBS symptoms	
Chinese herbal medicine Tong-Xie-Yao-Fang	May benefit IBS-D	
Massage, reflexology	Not established as reducing IBS symptoms	
Acupuncture	Not established as reducing abdominal pain	

TABLE 4. Drugs for IBS That Are Not Available in Israel

Generic name	Trade name	Indication	Max daily dosage	Main side effects
Lubiprostone	Amitiza	IBS-C	8 mcg×2	Nausea, abdominal pain, and diarrhea
Linaclotide	Constella, Linzess	IBC-C	290 mcg	Diarrhea, abdominal pain
Plecanatide	Trulance	IBC-C	3 mg	Diarrhea, headache
Tenapanor	Ibsrela, Xphozah	IBC-C	50 mg×2	Diarrhea
Alosetron	Lotronex	IBS-D	2 mg	Constipation
Ramosetron	Ibset, Irribow, Nasea	IBS-D	5 mcg	Constipation
Eluxadoline	Viberzi	IBS-D	100 mg×2	Constipation, nausea

Alosetron (Lotronex) is a selective 5-hydroxytryptamine-3 receptor (5-HT3) antagonist used for the management of severe IBS-D in females only. Alosetron was withdrawn from the market in 2000 owing to the occurrence of ischemic colitis but was reintroduced in 2002 with restricted availability and use. Efficacy was demonstrated in at least 2 randomized phase 3 studies that included 647 and 745 female patients with IBS-D.[96,97] Alosetron reduced symptom severity and increased quality of life. Since its withdrawal, usage is limited to women with severe IBS-D because of the risk for ischemic colitis. These strict prescribing guidelines (2002) were relaxed slightly in 2016. Constipation is the most common side effect (up to 30% of patients).

Ramosetron (Irribow, Ibset, Nasea) is another 5-hydroxytryptamine-3 receptor (5-HT3) antagonist indicated for the treatment of nausea, vomiting and IBS-D in both genders. Ramosetron is only licensed for use in Japan and selected Southeast Asian countries (eg, India). Ramosetron reduced diarrhea severity and quality of life. In addition, it improved abdominal pain and bloating. Ramosetron has a better safety profile than alosetron and its main side effect is constipation.[98]

Eluxadoline (Viberzi) is an opioid receptor agonist to μ and κ and an antagonist to δ. Activation of μ receptors reduces secretions, slows motility, prolongs intestinal transit time, and increases water absorption. Activation of κ receptors reduces abdominal pain. Inhibition of δ receptors reduces constipation (caused by μ receptor activation) and synergistically with μ activation, both reduce abdominal pain. Efficacy was demonstrated in 2 randomized phase 3 studies (2400 patients) showing a global effect on IBS, including reduction in abdominal pain, diarrhea, and bloating. Its main side effects are constipation and nausea.[99–101] Eluxadoline is contraindicated in patients with liver cirrhosis, postcholecystectomy, history of pancreatitis/pancreatic disease, biliary tract disease, and alcohol consumers (more than 3 alcoholic drinks daily).

Highlights:
- Several effective IBS drugs that are available in the American, European, and Far East markets are still missing in Israel.
- The medical community should advocate for importing and marketing these medications in Israel.
- Lubiprostone and linaclotide are the most effective and safest for IBS-C treatment.
- Eluxadoline is an effective and safe treatment for IBS-D.
- Alosetron is reserved for women with resistant IBS-D.

MEDICAL CANNABIS FOR IBS

We considered that a brief discussion of this topic is warranted since primary care physicians and gastroenterologists are asked to recommend medical cannabis for IBS. Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most studied phytocannabinoids. The use of medical cannabis for a variety of medical purposes is growing worldwide. The evidence from medical trials supports its use in chronic pain, multiple sclerosis, epilepsy, anorexia and in nausea and vomiting induced by chemotherapy.

Research has demonstrated that the endocannabinoid system neuromodulates the gastrointestinal system.[102] In one study CBD receptors were found on neurons that control visceral pain suggesting that CBD may be of a therapeutic value in IBS.[103] However, only a limited number of studies assessed the effects of medical cannabis on IBS symptoms. Two studies that evaluated the effect of dronabinol (synthetic THC) in IBS-D found inconsistent results. In one study, 5 mg of dronabinol improved diarrhea severity in IBS-D, while the other showed no significant effects.[104,105]

In summary, there is insufficient evidence to recommend the use of medical cannabis in IBS. One should also bear in mind the risk of using an addictive substance in a chronic condition that mainly affects young people. There is a need to conduct prospective controlled studies to examine the effectiveness of CBD and THC as a treatment for IBS.

THE MULTICULTURAL DIMENSION OF IBS TREATMENT–CLINICAL INSIGHTS FROM ISRAEL'S DIVERSE SOCIETY

Israel's multicultural landscape presents unique challenges and opportunities in the clinical management of IBS. The country's diverse population encompasses a rich tapestry of cultural backgrounds, including Russian-speaking Jews, Ethiopian Jews, Arab communities (Muslim, Christian, and Druze), and Bedouins, each with distinct cultural practices and health beliefs. This diversity is further layered with religious and social complexities that significantly impact health care delivery and patient outcomes.

The ultraorthodox Jewish community serves as a compelling example of the importance of culturally tailored health care approaches. Clinicians treating IBS patients from this community must develop culturally sensitive strategies that honor their values, traditions, and social structures. Health care providers need familiarity with strict religious guidelines that govern daily activities, including dietary laws that may intersect with IBS management recommendations.

The social context of ultraorthodox families—often characterized by large household sizes, potential financial constraints, and strong community expectations—can contribute to emotional distress that may exacerbate IBS symptoms. Effective communication strategies incorporate

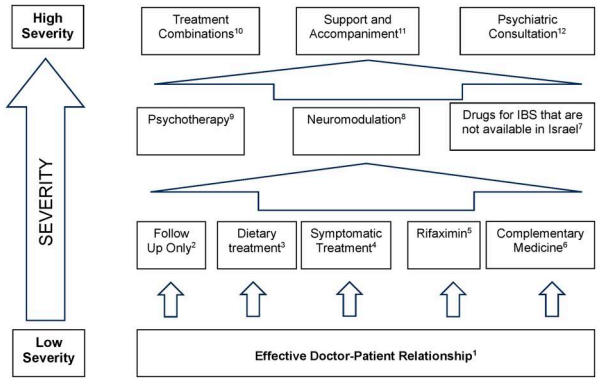

FIGURE 1. Treatment pyramid for IBS. Explanations for the treatment pyramid: (1) A therapeutic doctor-patient relationship includes: empathy, IBS as a definitive diagnosis, not a "diagnosis of exclusion," giving the patient a biological explanation of symptoms (visceral hypersensitivity), describing the benign chronic course (with remissions and flares), understanding patients' concerns (fear of malignancy, food allergies, and functional difficulties), investigating psychosocial factors affecting course, aligning treatment expectations (quality of life improvement vs. "cure") and maintaining therapeutic continuity. (2) The "as needed" follow-up option is appropriate after giving a detailed explanation of disorder nature. This is suitable for mild IBS (eg, symptoms during exam periods or a few days monthly). (3) Dietary treatment is the first-line choice for extended chronic complaints. It is recommended that the evaluation be performed by an experienced dietician and that any individual approach will be based on low FODMAP diet principles. (4) Symptomatic treatment is focused on the dominant complaint (constipation/diarrhea/pain). This kind of treatment can be chronic (eg, treating constipation or chronic diarrhea) or episodic (eg, antispasmodic treatment for pain episodes) and can be combined with other therapeutic options as needed. (5) Rifaximin is an effective IBS treatment, particularly for IBS-D and bloating. Of note, for good but short-term responders, consider retreatment with the same dosage or consider extending the duration of treatment (4-8 wk) at low doses (400-800 mg/d). (6) Complementary medicine includes herbal medicine, nutritional supplements, and acupuncture may improve IBS symptoms; however, evidence-based data in support of these treatments is very limited. (7) Evidence-based, effective drugs for IBS that are not available in Israel are to be considered as second-line treatment but and can be imported and tested for a defined period of time. (8) Neuromodulators are recommended for moderate to severe IBS. These drugs are effective in reducing IBS symptoms and can provide relief for concurrent psychological comorbidities. (9) BGBT can be a stand-alone treatment (especially for medication-averse patients) or combined with other mentioned treatments. (10) Treatment combinations (augmentation) are recommended for refractory and severe cases. We may combine treatments such as diet, rifaximin, psychotherapy, symptomatic treatment, neuromodulation, hypnosis, and more. (11) Support and continuity of care are essential even when treatments fail and maintaining physician support remains crucial. (12) Psychiatric consultation is relevant when symptom's intensity and quality-of-life impairment increase and whenever patient danger-safety issues are raised (eg, suicide ideation). Gaining patient acceptance for psychiatric consultation is a major challenge. In severe IBS cases, there is a higher incidence and significance of psychiatric comorbidity. As a rule, and at any point, psychiatric consultation should be considered.

religious texts, values, and metaphors to establish trust and enhance treatment adherence.

Mental health aspects of IBS management require particular sensitivity, as psychological issues often carry significant stigma within the ultraorthodox community. Many patients consult with rabbinical authorities before pursuing psychological treatments or therapies. Consequently, successful IBS management programs in Israel have found that collaborating with respected rabbis can create valuable bridges between conventional medical approaches and religious life, improving treatment acceptance and outcomes.

This culturally informed approach to IBS management exemplifies how health care delivery in Israel must adapt to meet the needs of its diverse population, recognizing that effective treatment extends beyond medical interventions to encompass cultural understanding and respect.

SUMMARY AND CONCLUSIONS

IBS is a highly prevalent chronic disorder that significantly impairs quality of life. This position paper presents the diverse therapeutic options currently available in Israel and abroad to improve symptoms and quality of life of IBS patients.

While IBS treatment is not perfect and remains primarily symptomatic and palliative in nature, we have numerous diverse tools to help manage this syndrome. Effective treatment invariably builds upon a strong physician-patient relationship, application of the bio-psycho-social model framework and on top, we may add any of the various treatments discussed in this document, used individually or in combination.

Differences between the therapeutic hierarchy proposed in Figure 1 and recommendations from other professional societies reflect variations in health care systems, drug availability, cost considerations, and real-world clinical practice. In Israel, rifaximin is often used earlier in the treatment course for IBS-D due to clinical experience, patient preference, cost and its favorable safety profile, despite its modest effect size. Neuromodulators are generally reserved for patients with more severe symptoms or higher disease impact in order to reduce stigma and improve adherence. Although brain–gut behavioral therapies may be used as first-line or stand-alone treatments, their placement as second-line options in the treatment pyramid reflects limited availability, reimbursement issues, and patient-related barriers rather than lack of efficacy. Figure 1 summarizes the various treatments reviewed in this position paper and presents the recommended therapeutic hierarchy for IBS.

We hope this document will enrich the medical community's knowledge about available therapeutic tools in IBS and will serve as a call to action for regulatory bodies, HMOs and pharmaceutical companies to address gaps in bringing new IBS medications to Israel for our patients' benefit.

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