Updates on treatment of irritable bowel syndrome

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Abstract

Irritable bowel syndrome (IBS) is a highly prevalent gastrointestinal disorder characterized by abdominal pain and discomfort in association with altered bowel habits. It is estimated to affect 10%-15% of the Western population, and has a large impact on quality of life and indirect costs incurred as a result of absenteeism from work. IBS can be classified according to the predominant bowel symptoms: IBS with constipation predominant (IBS-C), IBS with diarrhea predominant features (IBS-D), and IBS with alternating symptoms of diarrhea and constipation (IBS-A). While the exact pathophysiology of IBS is unclear, dysregulation within the brain-gut axis and interactions between genetics and psychosocial factors, post-inflammatory changes, and motor and sensory dysfunction all likely play a role.

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders affecting Western countries, with rates estimated as high as 10%-15% in the general population[1-3]. IBS is a heterogeneous condition broadly characterized by recurrent abdominal pain and discomfort with altered bowel habits and no detectable structural abnormalities[1]. In addition to constipation and/or diarrhea, frequently reported symptoms include abdominal pain and cramps, flatulence, fecal urgency, straining, a sense of incomplete evacuation and relief of pain or discomfort upon defecation. IBS can be classified according to the predominant bowel symptoms: IBS with constipation predominant features (IBS-C), IBS with diarrhea predominant features (IBS-D), and IBS with alternating symptoms of diarrhea and constipation (IBS-A). While the exact pathophysiology of IBS is unclear, dysregulation within the brain-gut axis and interactions between genetics[4,5], psychosocial factors[6,7], post-inflammatory changes[7-10], and motor[11] and sensory dysfunction[12] all likely play a role.

While only a fraction of IBS patients seek medical care[13], this condition accounts for up to 20% of all referrals to gastroenterologists[14]. IBS has widespread economic ramifications in terms of both healthcare utilization and indirect costs incurred as a result of absenteeism from work[15,16]. Moreover, IBS is a cause of substantial morbidity and is associated with a lower health care-related quality of life[17]. It is clear that effective drugs for IBS are greatly needed.

GENERAL TREATMENT APPROACH

IBS is a chronic, recurring condition with a wide range of symptoms. Therefore, the general goal of treatment...
is to alleviate the symptoms of abdominal pain, altered bowel transit (diarrhea or constipation) and any associated symptoms such as bloating and fecal incontinence. The treatment approach should be individualized, and will depend on the intensity of symptoms and the degree of other comorbid conditions. As with other functional medical disorders, the cornerstone of successful management revolves around establishing an effective patient-physician relationship. The physician should be non-judgmental, listen actively to determine the patient’s needs and concerns, and encourage the patient to participate in their medical care. Well-established physician relationships and positive interactions with health care providers have been shown to be associated with fewer IBS-related follow-up visits and a lower utilization of health care resources.

The majority of IBS patients are successfully managed in the primary care setting. These patients typically have mild symptoms and respond well to dietary and lifestyle modifications, education, and reassurance about their disease. Gut-directed medical therapy (anticholinergics, antispasmodics and newer IBS-specific agents) is used more frequently in patients with moderate to severe symptoms and is occasionally accompanied by the use of low dose tricyclic antidepressants (TCAs) and/or other psychiatric medications. The most severe, and smallest percentage of IBS cases, are often refractory to standard treatment and are likely to be seen at tertiary specialty centers. These patients will often require mental health providers, psychotropic medications, and may need frequent appointments with primary care providers to offer ongoing support throughout treatment.

In all cases of IBS, it is important to establish realistic and consistent treatment goals. Patients should be aware that a single drug is not likely to eradicate all symptoms, and that time, patience, and “trial and error” use of medications will be required. Additionally, physicians should educate patients about their diagnosis and provide reassurance that though this condition is a real medical disorder, it is a benign process that portends a normal life expectancy. In a long-term prognostic study of IBS, Owens and colleagues found that less than 10% of IBS patients developed an organic gastrointestinal disease, and that patients with IBS had survival rates not different from expected. Misconceptions about the causes, diagnosis and treatment of IBS are common among patients. In a recent questionnaire-based study of 636 IBS patients, 80% believed their condition developed as a result of anxiety, nearly two-thirds believed diet was responsible for IBS, and one in seven patients believed that IBS leads to cancer. Education about the possible mechanisms of IBS may dispel some of these misconceptions and it will help lay a foundation for the use of pharmacologic interventions if needed.

Physicians should be aware of other comorbidities that may worsen symptoms, and as with all chronic conditions, a detailed history about environmental stressors, social or emotional disturbances, impaired daily functioning, and underlying psychiatric conditions should be collected. This may help determine why the patient is seeking medical care and it could help uncover any potential hidden agendas.

### PHARMACEUTICAL THERAPIES

#### Serotonin axis

Serotonin (5-hydroxytryptophan) is the most important neurotransmitter (NT) in the pathogenesis of IBS. It is a paracrine signaling molecule found extensively throughout the gastrointestinal tract (approximately 90% of all body stores) that modulates key functions such as motility, sensation, blood flow, and secretion. Serotonin is stored primarily in enterochromaffin cells (90%) and in neurons of the enteric motor system (10%). Its release is triggered by luminal distension and chemical signals, and it binds to receptors located on enteric motor neurons, peripheral afferents, and within central nervous system domains that control appetite, mood and sexual function. The majority of serotonin receptors are G protein-coupled, with the exception of the 5-HT3 receptor, which is a ligand-gated ion channel. 5-HT3 and 5-HT4 appear to be the most important NTs in IBS. 5-HT3 receptors modulate visceral pain, aid in peristalsis, and its receptors within the CNS appear to influence the emotional component of visceral stimulation. 5-HT1 is important in gastric emptying, colonic secretions, facilitating the peristaltic reflex, and it contracts or relaxes smooth muscle depending upon its location within the alimentary tract. Serotonin levels and its activity on receptors are in part regulated by the serotonin reuptake transporter (SERT). Costes et al recently demonstrated that patients with IBS have decreased levels of SERT mRNA and protein expression in intestinal epithelial cells when compared to healthy volunteers. Furthermore, polymorphisms within the SERT promoter region have been shown to be associated with the IBS-D phenotype, and findings from a recent study suggest that their existence may influence the response to a 5-HT3 antagonist in female IBS-D patients. While the exact role of serotonin signaling in the pathophysiology of IBS remains to be fully elucidated, pharmacotherapy directed at modulating its activity has proven to be an effective way of treating many IBS symptoms.

#### 5-HT3 antagonists

Antagonism of the 5-HT3 receptor results in slower small bowel and colonic transit times, a reduction in intestinal secretion, increased stool firmness, and an increase in colonic compliance. There is also data suggesting that antagonism of this receptor in the amygdala, dorsal pons and ventral striatum may be responsible for perceived improvement in visceral pain, though the exact mechanism is unclear.

Alosetron is a selective 5-HT3 receptor antagonist initially approved by the Food and Drug Administration (FDA) in 2000 for use in female patients with IBS-D who failed in conservative treatment. Approval of this medication was based on several large randomized controlled-trials that found alosetron (1 mg. po twice daily) was more effective than placebo in controlling abdominal pain and discomfort in IBS-D. Alosetron was associated with a statistically significant decrease in the percentage of days with urgency, and it led to firmer stools and a decrease in stool frequency. Clinical improvement was noted throughout the treatment
period and usually occurred within 1-4 wk of therapy; symptoms returned to baseline following discontinuation of the medication. The most frequently reported adverse event was mild to moderate constipation which was self-limited and responded well to cessation of therapy. A meta-analysis by Cremolini in 2003 examined six randomized controlled-trials of alosetron and calculated a combined odds ratio of 1.8 for the adequate relief of pain [95% confidence interval (95% CI), 1.57-2.10] and the NNT of 7 patients in order to compare its relieving effect with placebo (95% CI, 5.74-9.43)[54].

In late 2000, alosetron was withdrawn from the U.S. market over concerns regarding side-effects of severe constipation (approximately 70 cases), ischemic colitis (approximately 50 cases), and bowel perforation[45,46]. Following substantial public pressure, it was re-introduced into the U.S. market in 2002 under a restricted prescribing program and further post-marketing studies are currently underway. In a recent placebo-controlled study, Krause and colleagues examined the safety and efficacy of alosetron at varying doses, and found that one of 250 patients developed self-limited ischemic colitis (0.5 mg daily)[47]. In a systematic review of post-marketing surveillance data, Chang and colleagues estimated the rate of ischemic colitis to be 1.1 per 1000 patients. All cases of documented ischemic colitis were reversible and no long-term sequelae were noted[48]. These data suggest that the rate of adverse events is relatively low and that alosetron is a well-tolerated, effective medication that should be considered in the treatment of IBS-D. There are ongoing studies of alosetron in men.

Cilansetron is another 5-HT4 antagonist that has been used for treatment for men and women with IBS-D. Its mechanism of action is similar to alosetron and it has comparable bioavailability and metabolism. Two large phase III trials have shown that cilansetron is similar in efficacy to alosetron, but concerns over ischemic colitis and severe constipation led to the FDA denying approval in 2005[48-51].

Ramosetron is a potent 5-HT3 receptor antagonist that is effective in relieving chemotherapy-induced nausea and vomiting, and is currently being developed for IBS-D[52,53]. Preliminary pharmacokinetic data suggest that it has a greater affinity, slower dissociation, and stronger antagonism at the 5-HT3 receptor than either alosetron or cilansetron[54]. It also appears to be superior to both of these medications in inhibiting stress-induced defecation and stress-induced changes in colonic transit rates in rats[52,53]. Data in human use are not available but can be anticipated in the near future.

5-HT4 agonists
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Mixed 5-HT3 agonist/5-HT4 antagonist
Renzapride is a mixed agent that has shown promise for patients with IBS-C and with IBS-A. It is a full agonist of the 5-HT3 receptor and an antagonist of the 5-HT4 receptor. In a dose-ranging efficacy trial by Camilleri and colleagues, a statistically significant linear dose response to renzapride was observed for colonic transit and ascending colonic emptying time, but not for gastric emptying or small bowel transit time[70]. No clinical or laboratory adverse

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Tegaserod is a 5-HT4 agonist that was initially approved by the FDA for use in female patients with IBS-C, and in men and women under the age of 65 with chronic idiopathic constipation. It stimulates intestinal secretion of water and chloride and decreases the nociceptive response to rectal distension[56]. Several large, randomized-trials have shown that tegaserod has a significant impact on a patient’s overall assessment of global relief, and that it statistically improves abdominal pain and bloating[59-62]. A 2004 Cochrane meta-analysis supported these results by concluding that tegaserod was associated with improvement in global relief of GI symptoms [relative risk (RR), 1.17; 95% CI, 1.08-1.27] and that it improved bowel consistency and frequency[63]. The primary side-effect of tegaserod is diarrhea (NNH of 20 patients), but it is usually transient and resolves with ongoing treatment[63,64]. Long-term use of tegaserod appears to be efficacious and re-treatment response rates appear to be similar to initial treatment[63,64]. Recent data regarding the effect of tegaserod in men have shown that it accelerates colonic transit time, but improvement in bowel symptoms failed to reach statistical significance[65]. In March 2007, Novartis voluntarily removed tegaserod from the U.S. and Canadian market as an FDA safety analysis of pooled data from 12 clinical trials demonstrated a statistical increase in the incidence of myocardial infarction, stroke and unstable angina. In July 2007, tegaserod was re-introduced to the U.S. market, but under a restricted investigational new drug (IND) protocol which limits its use to treatment of IBS-C and chronic idiopathic constipation in women under 55 years of age who meet specific guidelines. It continues to remain off market for general use.

Pruclolapride is a new agent in a class of medications known as benzofurans. It is an agonist at the 5-HT3 receptor, and data have suggested that it enhances GI transit in patients with functional constipation compared to placebo[66]. However, the clinical development of this drug remains unclear at this time based on the reported cases of intestinal carcinogenicity in animals[66].

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events occurred during this study. In a dose-escalating pilot study of 17 patients, renzapride (2 mg twice daily) reduced overall gastrointestinal transit time and abdominal pain, increased the number of pain-free days and improved stool consistency. Adverse events were similar in drug and placebo groups. Further studies are underway.

Octreotide is a somatostatin analogue, works by activating somatostatin type-2 receptors and has been shown to reduce visceral sensitivity in response to rectal distension. In healthy volunteers and in small numbers of IBS-D patients, octreotide administered in a 50 mg bolus was shown to prolong orocecal transit times and inhibit small bowel transit times. While these results suggest that octreotide may have benefits in patients with IBS-D, its intravenous preparation precludes daily use, and to date, no studies with oral somatostatin analogues exist for the treatment of IBS.

Opioid agents
Opioid receptors are found throughout the enteric nervous system and on nociceptive pathways that conduct pain to the central nervous system. Altered bowel transit and visceral hypersensitivity are important components in IBS pathophysiology and peripherally-acting opioid receptors may be effective drug targets. Alvimopan is a peripherally acting μ-opioid antagonist that is effective in treatment of post-operative ileus. In a study of 74 healthy volunteers, it normalized colonic transit delays induced by the administration of codeine, and alone was shown to accelerate colonic transit.

The κ-opioid agonist, asimadoline, exerts nociceptive properties on the GI tract at least in part by blocking μ-receptor channels. It has been shown to decrease colonic tone during fasting and decrease colonic pain at low levels of distension. In a study of 20 IBS-C patients, asimadoline was shown to be effective in decreasing pain perception from colonic distension without affecting colonic compliance or tone.

More recently, a randomized, placebo-controlled trial by Szarka and colleagues showed that asimadoline (up to 1 mg four times daily) did not statistically improve abdominal pain when taken on an “as needed basis” compared to placebo. Further studies are needed to determine the efficacy of this medication.

CRH receptor antagonists
Corticotropin-releasing hormone (CRH) is a key mediator that regulates changes in colonic motility, visceral hypersensitivity, and autonomic function in response to stress. Corticotropin-releasing hormone stimulates colonic motility and inhibits gastric emptying. Distension of the colon also activates CRH pathways in the brain, providing a plausible rationale for why visceral stimulation is perceived as anxiety or stress in some patients with IBS. Fukudo and colleagues demonstrated that administration of intravenous CRH was associated with exaggeration of colonic motility and increased ACTH secretion in IBS patients compared to healthy controls. More recently, α-Helical CRH (a non-selective CRH receptor antagonist) has been shown to significantly reduce abdominal pain and anxiety ratings induced by electrical stimulation of the rectum of IBS patients, but not of controls. Two CRH receptors appear important in the pathogenesis of IBS. Stimulation of the CRH-1 receptor is anxiogenic and associated with pro-inflammatory states, while CRH-2 receptors are involved in the inhibition of gastric emptying. CRH-1 antagonists are currently under development for clinical use in IBS.

Chloride channel activators
Lubiprostone is a member of a new class of bicyclic fatty-acid derivatives known as prostones, and was approved by the FDA in 2006 for the treatment of chronic constipation. It acts on type-2 chloride channels located on the apical side of gastrointestinal epithelial cells, and increases secretion of electrolyte-rich fluid into the small intestine, promoting increased motility. Several studies have shown that in
patients with chronic constipation, lubiprostone is effective in improving the spontaneous bowel movement and is associated with less bloating, straining and abdominal discomfort\textsuperscript{[99,100]}. The role of lubiprostone in IBS-C has recently been evaluated in a randomized, double-blinded placebo-controlled trial of approximately 200 patients\textsuperscript{[101]}. The results of this study showed an overall improvement in abdominal symptoms and bowel movement when compared to placebo and the most frequently reported side-effect was mild to moderate nausea. To date, no serious adverse events have been noted in clinical trials\textsuperscript{[100,102]}. Sucampo Pharmaceuticals submitted a supplemental New Drug Application to the FDA in September 2007 requesting approval for the use of lubiprostone in IBS-C. A decision is expected sometime in early 2008.

**CCK antagonists**

Cholecystokinin (CCK) is a neuropeptide released by duodenal and jejunal enterochromaffin cells that stimulates secretion of pancreatic enzymes and decreases gastric emptying in response to dietary fat. CCK1 receptors are distributed within enteric neurons and vagal afferents, and antagonism at this receptor has been postulated to stimulate gut motility in patients with IBS-C. A recent double-blinded study found that the CCK antagonist, dexloxiglumide (200 mg three times daily) had no significant effect on satisfactory relief of IBS, and that it did not alter transit times in IBS-C\textsuperscript{[103]}. Furthermore, two large phase III clinical studies of 1,400 women with IBS-C found no statistical improvement in the symptoms of abdominal pain, discomfort or altered bowel habits when compared to placebo\textsuperscript{[100]}. As a result, Forest Laboratories have discontinued development of this drug, though Rotta Research is pursuing additional placebo-controlled studies in Europe.

**Neurokinin antagonists**

Substance P and neurokinin A are excitatory co-transmitters of cholinergic enteric neurons that have been well-linked to the pathophysiology of several neurologic and psychiatric disorders. Their receptors, neurokinin 1 (NK1) and NK2, play important roles in nociception and smooth muscle contraction, and the regulation of visceral sensitivity and mucosal inflammatory processes\textsuperscript{[104-107]}. Clinical data is currently deficient. However, in one study of healthy volunteers using the selective NK2 antagonist nepatudant (MEN11420), IBS-like symptoms triggered by the infusion of neurokinin A were reduced\textsuperscript{[108]}. Saredutant (SR48968), another NK2 antagonist, is also being developed for the treatment of IBS, but clinical results are not yet available.

**Antidepressants**

Antidepressants are frequently prescribed by gastroenterologists for the treatment of IBS\textsuperscript{[109]}. Their mechanism in IBS is not completely understood, but has been postulated to relate to an ability to modulate central and peripheral pain perception\textsuperscript{[110,111]}, improve underlying psychiatric conditions, and possibly improve gut motility through modification of neurotransmitter activity\textsuperscript{[112,113]}. Unfortunately, randomized-controlled trials to date have largely been hindered by poor study design and methodological flaws, making it difficult to judge the therapeutic value of these agents\textsuperscript{[114-116]}. Most studies provide little evidence that antidepressants are superior to placebo in improving specific IBS-related symptoms, but some do suggest that overall global well-being may be improved. In a recent meta-analysis evaluating 12 randomized-controlled trials, Jackson and colleagues concluded that tricyclic antidepressants are effective in improving global IBS symptoms (OR, 4.2; 95% CI, 2.3-7.9), and calculated an NNT of only 3 in order to see an effect\textsuperscript{[117]}. Fewer studies have been conducted with SSRIs. In one randomized-controlled trial comparing paroxetine (10-40 mg/d) to placebo, patients treated with the SSRI reported a significant improvement in overall well-being, but did not experience improvement in abdominal pain\textsuperscript{[118]}. Other studies with paroxetine have shown an improvement in abdominal pain and discomfort, and suggest that further studies with this class of medication are needed\textsuperscript{[119,120]}. While certain subgroups of IBS patients (particularly those with psychiatric comorbidities such as depression or anxiety) will likely benefit from the use of antidepressants, their use in other patients (particularly the elderly) should be met with caution as side-effects are common. Furthermore, the anticholinergic nature of some of these medications limits their use in patients with IBS-C. Antidepressants should not be used to relieve the target symptoms of IBS, and their use will not likely alter GI motility or physiology. Instead, antidepressants should be used as an adjunct in patients with moderate to severe IBS to help improve overall quality of life, well-being, and patient satisfaction with treatment.

**Antispasmodics**

Antispasmodic agents are believed to work in IBS based on their ability to decrease intestinal smooth muscle activity. There are two broad categories of antispasmodic agents: anticholinergics/antimuscarinic agents (e.g. hyoscyamine, dicyclomine, cimetropium) and direct smooth muscle relaxing agents (e.g. mebeverine, pinaverine, octolynon bromide). Most studies of smooth muscle relaxants have been hindered by poor study design, high drop-out rates, and low patient enrollment which have made assessment of their therapeutic value in IBS difficult\textsuperscript{[112-114]}. In a recent meta-analysis, only octolynon bromide was found to have some benefit after excluding poor quality studies\textsuperscript{[112]}. In a review of anticholinergic drugs, Schoenfield and colleagues found similar problems with study design, and based on the poor quality of trials and marginal data, concluded that any benefit observed with these agents was likely due to placebo effect\textsuperscript{[125]}. Additionally, their substantial side-effect profile makes these agents a suboptimal choice for IBS therapy.

**Antidiarrheals**

Loperamide is one of the most frequently used drugs for IBS-D. It is a synthetic opioid that decreases intestinal transit, and increases intestinal water and ion absorption. Several RCTs have provided a good evidence that loperamide decreases stool frequency and improves stool...
consistency in IBS-D. Loperamide does not appear to improve abdominal pain and should only be considered in cases of painless diarrhea.

**Benzodiazepines**

Dextofisopam is a 2, 3 benzodiazepine that has been used outside of the U.S. for treatment of anxiety and autonomic and stress-related disorders. Unlike typical benzodiazepines which bind GABA receptors, dextofisopam binds 2, 3 benzodiazepine receptors. Results from a 12-wk placebo-controlled phase II b trial showed that dextofisopam (200 mg twice daily) was associated with longer periods of overall relief from IBS symptoms than placebo during the treatment period (57% vs 43%). Stool frequency and consistency were also improved. Further trials are underway.

**Antibiotics**

Small intestinal bacterial overgrowth (SIBO) has been proposed to be common in patients with IBS. Using lactulose breath tests (LBT), Pimental and colleagues showed that 78% of IBS patients had SIBO and that eradication with a seven-day course of neomycin was associated with a significant reduction in symptoms. However, these results are somewhat controversial, as both the accuracy of the LBT and its ability to gauge treatment response has been questioned. More recently, Posserud and colleagues conducted a study of 162 IBS patients using cultures of jejunal aspirates to detect SIBO. They found that higher bacterial counts were present in IBS patients compared to placebo (43% vs 12%), but this finding was not related to small intestinal motility. Furthermore, using a standard definition of SIBO (≥ 10³ bacteria/mL), there was no difference between IBS patients and healthy controls. Further research is needed in this area, including a better evaluation of the long-term effects of SIBO eradication.

**NON-PHARMACEUTICAL THERAPY**

**Bulking agents**

The use of fiber and bulking agents remains a mainstay of therapy for patients with IBS-C, though their efficacy is controversial. The proposed mechanism for fiber is a decrease in intra-colonic pressures and an acceleration of oroanal transit. Decrease in intra-colonic pressures and an acceleration of oroanal transit is controversial. The proposed mechanism for fiber is a decrease in intra-colonic pressures and an acceleration of oroanal transit. Decrease in intra-colonic pressures and an acceleration of oroanal transit is controversial. The proposed mechanism for fiber is a decrease in intra-colonic pressures and an acceleration of oroanal transit. Decrease in intra-colonic pressures and an acceleration of oroanal transit is controversial. The proposed mechanism for fiber is a decrease in intra-colonic pressures and an acceleration of oroanal transit. Decrease in intra-colonic pressures and an acceleration of oroanal transit is controversial. The proposed mechanism for fiber is a decrease in intra-colonic pressures and an acceleration of oroanal transit. Decrease in intra-colonic pressures and an acceleration of oroanal transit is controversial. The proposed mechanism for fiber is a decrease in intra-colonic pressures and an acceleration of oroanal transit. Decrease in intra-colonic pressures and an acceleration of oroanal transit is controversial. The proposed mechanism for fiber is a decrease in intra-colonic pressures and an acceleration of oroanal transit.

**Probiotics**

The presence of low-grade inflammation and immune activation in some patients with IBS suggests that alterations in indigenous gut flora may play an important role in this disorder. Probiotics may work by helping restore both qualitative (i.e. depleted bifidobacteria species) and quantitative (i.e. small intestinal bacterial overgrowth) alterations in intestinal flora. Lactobacilli and bifidobacteria are two of the most frequently studied probiotics, and several trials have shown that their use is associated with improvement in IBS symptoms. Niedzielin and colleagues demonstrated a complete resolution of abdominal pain in patients who took L. plantarum compared to approximately 50% of placebo control. Other studies have shown that L. plantarum is associated with a decrease in bloating and may reduce global IBS symptom index scores. Post-infectious IBS may lead to abnormal immune activation and a persistent inflammatory state. The bifidobacterial species may be beneficial in this subset of IBS as it appears to possess immune-modulating activity through an ability to alter levels of IL-10 and IL-12.

To date, most studies assessing the efficacy of probiotics have been small, and it has been difficult to compare results across studies largely because of non-standardized formulations of probiotics. Nonetheless, data suggests that probiotics may be beneficial, and a good safety profile makes them a reasonable choice for IBS.

**Diet**

Two-thirds of IBS patients believe that their disorder is related to diet. They often complain of postprandial worsening of symptoms, and are intolerant to certain foods. Visceral hypersensitivity, motility disorders, gas-handling disturbances, and abnormal carbohydrate absorption are abnormalities that may explain some of these findings. However, presence of underlying psychological issues also affects the diet-related symptoms. In a recent pilot study of 20 IBS patients, Drisko and colleagues found that elimination and rotation diets based on the results of IgG and IgE food and mold panels led to a substantial improvement in stool frequency, abdominal pain, and quality-of-life scores. These results were sustained at the one year follow-up. Previous studies on elimination diets have produced more conflicting results, showing an effectiveness rate ranging from 15% to 71%. Nonetheless, dietary modification may be an option for patients who fail in the standard therapy.

**CONCLUSION**

The complex nature of IBS continues to pose a significant
treatment challenge for patients and practitioners. Traditional medications such as antispasmodics, bulking agents, and antidepressants are frequently prescribed for IBS. But, they are seldom efficacious in patients with advanced symptoms. Fortunately, the recent efforts of basic scientists and clinician investigators have elucidated many of the neurotransmitters, effectors and neuroenteric interactions involved in the pathophysiology of IBS, and have led to the development of several new and promising therapeutic agents. Over the past years, the serotonergic medications, tegaserod and alosetron, have been proven to significantly improve patients’ overall quality of life and effectively manage many of the motor and sensory abnormalities in IBS. With more progress made in our understanding of IBS and more data obtained from phase III trials, we can expect to see several other classes of medications, such as CCK antagonists, NK antagonists, CRH antagonists, opioid-receptor agents and chloride channel activators, in the near future.

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