Pharmacologic and Complementary and Alternative Medicine Therapies for Irritable Bowel Syndrome

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Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterized by episodic abdominal pain or discomfort in association with altered bowel habits (diarrhea and/or constipation). Other gastrointestinal symptoms, such as bloating and flatulence, are also common. A variety of factors are believed to play a role in the development of IBS symptoms, including altered bowel motility, visceral hypersensitivity, psychosocial stressors, altered brain-gut interactions, immune activation/low grade inflammation, alterations in the gut microbiome, and genetic factors. In the absence of biomarkers that can distinguish between IBS subgroups on the basis of pathophysiology, treatment of this condition is predicated upon a patient’s most bothersome symptoms. In clinical trials, effective therapies have only offered a therapeutic gain over placebos of 7-15%. Evidence based therapies for the global symptoms of constipation predominant IBS (IBS-C) include lubiprostone and tegaserod; evidence based therapies for the global symptoms of diarrhea predominant IBS (IBS-D) include the probiotic Bifidobacter infantis, the nonabsorbable antibiotic rifaximin, and alosetron. Additionally, there is persuasive evidence to suggest that selected antispasmodics and antidepressants are of benefit for the treatment of abdominal pain in IBS patients. Finally, several emerging therapies with novel mechanisms of action are in development. Complementary and alternative medicine therapies including probiotics, herbal therapies and acupuncture are gaining popularity among IBS sufferers, although concerns regarding manufacturing standards and the paucity of high quality efficacy and safety data remain.

Key Words: Serotonin; Chloride secretagogues; Antibiotics; Antidepressants; Probiotics

INTRODUCTION

The irritable bowel syndrome (IBS) is a chronic functional gastrointestinal (GI) disorder characterized by the presence of episodic abdominal pain or discomfort in association with altered bowel habits (diarrhea and/or constipation) and other GI symptoms such as bloating and flatulence. By definition, these symptoms should be occurring in the absence of identifiable structural or biochemical abnormalities.1

IBS is the most common diagnosis rendered by gastroenterologists affecting 10-20% of the US adult population.2 Data on the prevalence of IBS based upon geographic region can be found in Table 1. Though IBS affects both men and women and any age group, IBS is more commonly diagnosed in women and younger individuals.3,4 The burden of illness associated with IBS, in terms of quality of life, work productivity and health resource utilization, is considerable.5,6

PATHOPHYSIOLOGY OF IBS

It is likely that IBS, the diagnosis of which is currently predicated exclusively upon the presence of characteristic symptoms, is comprised of a number of different disease states for which we currently lack reliable biomarkers. A variety of factors are believed to play a role in the development of the IBS symptoms including altered bowel motility, visceral hypersensitivity, psychosocial stressors, altered brain-gut interactions, low grade inflammation, alterations in the gut microbiome, and genetic factors.7-10 A leading hypothesis holds that an interaction of one or more of these etiologic factors is responsible for the frequently complex and heterogeneous symptoms of IBS.

Alterations in rectal, colonic and small bowel motility have been reported and may be associated with characteristic IBS
symptoms in some patients. A number of studies have reported accelerated small bowel and colon transit as well as exaggerated bowel motility patterns in those with diarrhea predominant IBS (IBS-D).1-14 Likewise, several studies have report delayed bowel transit in those with constipation predominant IBS (IBS-C).1-13 Visceral hypersensitivity to mechanical distension can often be identified in IBS patients.15-18 Unfortunately, visceral hypersensitivity does not occur commonly enough to be considered a biomarker of IBS.19 There is recent evidence to suggest central dysregulation of emotional arousal and pain modulation in IBS.20,21 Psychological distress is not only a common comorbidity in IBS patients, but also a factor which amplifies IBS symptoms and perhaps plays a direct role in the pathogenesis of IBS.22,23 Alterations in a key neurotransmitters such as serotonin, which play a role in sensation, secretion, absorption and motility of the GI tract have been identified in IBS patients.24 A number of studies have reported increased serotonergic activity in IBS-D and decreased serotonergic activity in IBS-C.25-27 Post-infectious IBS (PI-IBS) which as the name implies occurs following an infectious gastroenteritis, is a well established entity believed to arise from deranged immune activation leading to persistent low grade inflammation and alterations in the gut microbiome.28 PI-IBS has been reported following a variety of acute infections including bacteria, viruses and parasites.29-31 Recent studies suggest that some individuals are genetically predisposed to developing PI-IBS, with individuals demonstrating an increased pro-inflammatory and/or decreased anti-inflammatory cytokine response to infection.32,33 There is a growing body of evidence to suggest that alterations in the microbiome may play a role in the development of IBS symptoms. The greatest attention has been placed on the possible role of small intestinal bacterial overgrowth (SIBO) in the pathogenesis of IBS symptoms, particularly bloating and diarrhea.34-37 Further, early studies utilizing gene cloning and sequencing techniques as well as polymerase chain reaction have demonstrated differences in the microbiome in IBS patients when compared to healthy controls.38,39 More recent studies have combined sophisticated molecular techniques with more traditional culture to associate specific bacterial strains with the symptoms of IBS-D.40-42 The role of genetic factors in the development of IBS has grown from early familial aggregation studies43 to more recent reports concerning genetic polymorphisms involving genes targeting proinflammatory cytokines, the serotonin reuptake transporter, tryptophan hydroxylase, sodium ion channel proteins and the alpha 2A adrenergic receptor.

An interesting clinical observation which might have implications with regard to pathogenesis is the frequent overlap between IBS symptoms and other GI and non-GI symptoms. For example, Nastaskin et al.44 conducted a systematic review which suggested a strong overlap between IBS and gastroesophageal reflux disease that exceeds the expected individual presence of each condition. Recently, Ford et al.45 reported the results from a systematic review that reported an 8-fold increase in prevalence of IBS amongst people with dyspepsia compared to the general population. Although some have reported that overlapping upper and lower GI symptoms tend to occur more commonly in individuals with anxiety,46 the mechanistic explanation which underlies this phenomenon remains unclear. It is attractive to speculate that patients with diffuse upper and lower GI symptoms hallmarked by pain or discomfort may have a centrally driven abnormality in pain processing or perception. There is data to suggest that patients with overlapping GI symptoms have more severe/frequent GI symptoms and worse health related quality of life.47-49

**CURRENT AND EMERGING MEDICAL THERAPIES FOR IBS**

In the absence of biomarkers which can distinguish between IBS subgroups on the basis of pathophysiology, treatment of this condition is predicated upon the patient’s most bothersome symptoms. Though there is some overlap in the therapies offered to the different IBS subgroups, treatment decisions are largely based upon the frequency and severity of constipation, diarrhea, bloating or pain. The American College of Gastroenterology (ACG) recently published an evidence-based monograph on therapies for IBS.50 A summary of the criteria used in this monograph to judge the therapies for IBS is provided in Table 2. Summaries of the recommendations from this monograph for IBS-C and IBS-D can be found in Tables 3 and 4.

**IBS-C**

1. **Fiber supplements**

Dietary fiber supplements consist of non-digestible carbohydrates that increase stool bulk and water content resulting
in decreased stool consistency and increased stool frequency.\textsuperscript{46} Commercially available fiber supplements include psyllium, ispaghula husk, bran (wheat and corn), methylcellulose, calcium polycarbophil, and partially hydrolyzed guar gum (PHGG). An evidence-based systematic review on the effectiveness of fiber supplements in the management of IBS conducted by the ACG IBS task force concluded that psyllium hydrophilic mucillliod (ispaghula husk) is moderately effective in the treatment of IBS (Grade 2C, Table 1).\textsuperscript{47} The task force added that wheat bran or corn bran is no more effective than placebo in relief of the global IBS symptoms. A recent randomized, controlled trial corroborated these results.\textsuperscript{48} Collectively, the data suggest that psyllium may improve constipation symptoms such as stool frequency and consistency in patients with IBS-C and perhaps mixed type IBS (IBS-M). Bran does not appear to offer symptomatic benefit and the effect of other available fiber supplements remains largely unknown. Potential adverse effects of fiber supplements may include bloating, abdominal distention and flatulence.

\textbf{2. Laxatives}

Laxatives are commonly used as a treatment for patients with IBS-C. In addition, some IBS-M patients report extended periods with small, hard bowel movements or no bowel movement followed by periods with loose stools. Such patients are often constipated and may benefit from laxative therapies. Traditional laxative therapies include osmotic agents, stimulants, and stool softeners. Only the osmotic laxative, polyethylene glycol (PEG), has been assessed in a randomized trial which enrolled 28 post-pubertal adolescent IBS-C patients.\textsuperscript{50} Patients were randomized to receive 4 weeks of PEG or PEG and the 5-HT4 agonist, tegaserod. In the group that received PEG alone, there was a significant increase in mean bowel movement frequency compared to baseline (2.07 to 5.04 weekly bowel movements, p<0.05) but no change in abdominal pain. The group that received both

\begin{table}[h!]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Grade of recommendation/description} & \textbf{Benefit vs risk and burdens} & \textbf{Methodological quality of supporting evidence} & \textbf{Implications} \\
\hline
1A. Strong recommendation, high-quality evidence & Benefits clearly outweigh risk and burdens, or vice versa & RCTs without important limitations or overwhelming evidence from observational studies & Strong recommendation, can apply to most patients in most circumstances. Further evidence is unlikely to change the level of confidence in the estimate of effect \\
\hline
1B. Strong recommendation, moderate-quality evidence & Benefits clearly outweigh risk and burdens, or vice versa & RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies & Strong recommendation, can apply to most patients in most circumstances. Higher quality evidence may change the level of confidence in the estimate of effect \\
\hline
1C. Strong recommendation, low-quality or very low-quality evidence & Benefits clearly outweigh risks and burdens, or vice versa & Observational studies or case series & Strong recommendation can apply to most patients in most circumstances. Higher quality evidence is very likely to change the level of confidence in the estimate of effect \\
\hline
2A. Weak recommendation, high-quality evidence & Benefits closely balanced with risks and burdens & RCTs without important limitations or overwhelming evidence from observational studies & Weak recommendation, best action may differ depending on circumstances or patients’ or societal values. Further evidence is unlikely to change the level of confidence in the estimate of effect \\
\hline
2B. Weak recommendation, moderate-quality evidence & Benefits closely balanced with risks and burdens & RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies & Weak recommendation, best action may differ depending on circumstances or patients’ or societal values. Higher quality evidence may well change evidence the level of confidence in the estimate of effect \\
\hline
2C. Weak recommendation, low-quality or very low-quality evidence & Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced & Observational studies or case series & Very weak recommendation; other alternatives may be equally reasonable. Higher quality evidence is likely to change the level of confidence in the estimate of effect \\
\hline
\end{tabular}
\caption{Grading Recommendations from the ACG Evidence-Based IBS Monograph\textsuperscript{47}}
\end{table}
PEG and tegaserod enjoyed improvements in bowel movement frequency and pain \(p<0.05\). Other commonly used laxative therapies have thus far, not been adequately studied as a treatment for IBS-C. Though further studies assessing the efficacy of laxative therapies for IBS-C are clearly needed, the relative safety, availability, and low cost of these drugs make their continued use as a treatment for constipation related complaints in IBS patients quite likely.

### 3. Prokinetic agents

Prokinetics are a diverse group of compounds which exert effects on GI motility, secretion, and sensation. Most prokinetic agents which have been developed for the treatment of IBS have focused on serotonin. Of the 14 different serotonin receptor subtypes which have been identified, 5-HT4, 5-HT3, and 5-HT1a receptors have the greatest evidence supporting a role in GI and colonic function and sensation. In the GI tract, 5-HT4 receptors are found on enteric neurons and smooth muscle cells. Stimulation of 5-HT4 receptors leads to acetylcholine release and prokinetic effects.51,52 A number of 5-HT4 agonists have been developed as potential treatments for patients with IBS-C. Tegaserod is a selective 5-HT4 receptor partial agonist which has been found to be more effective than placebo for global IBS symptoms as well as abdominal pain and constipation in multiple short- and long-term studies of women with IBS-C and IBS-M from around the world.53-59 In 2007, a review of the clinical trials database by the manufacturer revealed an increased incidence of cardiovascular and cerebrovascular events in the tegaserod treatment group compared to the placebo group. This analysis specifically revealed a total of 13 cardiovascular ischemic events (3 myocardial infarctions, 1 sudden cardiac death, 6 cases of unstable angina and 3 cerebrovascular accidents) in 11,614 patients treated with tegaserod compared with 1 event in the 7,031 patients receiving placebo.60 Although the event rates were quite low (0.1% in the tegaserod group vs 0.01% in the placebo group) the difference was found to be statistically significant \(p=0.02\). The significance and explanation for this discrepancy remains poorly characterized, although there has been speculation that tegaserod may induce platelet aggregation via 5-HT4 receptors on platelets.61 Related to these findings, tegaserod was withdrawn in the many countries, including the US and Canada in 2009. Tegaserod remains available in a small number of countries throughout the world. The most commonly reported side effects included diarrhea, headache and abdominal

### Table 3. Evidence-Based Summary of Medical Therapies for IBS-C Symptoms

| Improvements in symptoms | Grade |
|--------------------------|-------|
| Global symptoms | Pain | Bloating | Stool frequency | Stool consistency |
| Alosetron | + | + | + | + | 2A/1B |
| Antibiotics (rifaximin) | + | + | + | + | 1B* |
| Antidepressants | + | + | + | + | 1B |
| Loperamide | + | + | + | + | 2C |
| Antispasmodics | + | + | + | + | 2C |
| Probiotics (Bifidobacteria/some combos) | + | + | + | + | 2C |
| Fiber (psyllium) | + | + | + | + | 2C |

Adapted from Am J Gastroenterol 2009;104 Suppl 1:S1-S35.47 IBS-C, constipation predominant irritable bowel syndrome; PEG, polyethylene glycol.

*Available in the US only under Emergency IND program.

### Table 4. Evidence-Based Summary of Medical Therapies for IBS-D Symptoms

| Improvements in symptoms | Grade* |
|--------------------------|-------|
| Global symptoms | Pain | Bloating | Stool frequency | Stool consistency |
| Alosetron | + | + | + | + | 2A/1B |
| Antibiotics (rifaximin) | + | + | + | + | 1B* |
| Antidepressants | + | + | + | + | 1B |
| Loperamide | + | + | + | + | 2C |
| Antispasmodics | + | + | + | + | 2C |
| Probiotics (Bifidobacteria/some combos) | + | + | + | + | 2C |
| Fiber (psyllium) | + | + | + | + | 2C |

Adapted from Am J Gastroenterol 2009;104 Suppl 1:S1-S35.47 IBS-D, diarrhea predominant irritable bowel syndrome.

*Positive results from 2 large phase 3 studies published since creation of the ACG document.
pain. Twenty-six cases of possible colonic ischemia were also reported during post-marketing surveillance providing an estimated incidence of 7-8 cases of colonic ischemia per 100,000 patient-years of tegaserod use.62

It is reasonable to hypothesize that other 5-HT4 agonists such as mosapride and prucalopride might offer benefits for IBS-C patients, though to date, this has not been convincingly demonstrated in high quality randomized trials. Pumosetrag is a potent, partial 5-HT4 agonist with prokinetic effects in animals and humans. Work is proceeding in the development of pumosetrag as a treatment for IBS-C. Itopride is a dopaminergic antagonist and cholinesterase inhibitor which exerts effects on upper and lower GI motility and transit in animals. Randomized, placebo controlled trials evaluating itopride in patients with IBS-C are not yet available.63

4. Prosecretory agents

In recent years, a number of agents have been developed which increase intestinal secretion and in this way improve symptoms in patients with IBS-C. Lubiprostone, a chloride type 2 channel activator, is the first such drug to have been approved for the treatment of patients with IBS-C in the US. The efficacy and tolerability of lubiprostone in IBS-C has been assessed in several high quality randomized controlled trials (RCTs). A phase 2, dose-ranging, double-blind, placebo controlled trial was performed in 194 adults with IBS-C (92% female, 83% Caucasian).64 In this study, lubiprostone was superior to placebo with regard to spontaneous bowel movement frequency, stool consistency, straining, constipation severity, bloating and abdominal pain. Two subsequent phase 3 multicenter, double-blind, randomized, placebo-controlled trials further evaluated lubiprostone 8 mcg twice daily in 1,167 patients (92% female) with IBS-C.65 Using a highly rigorous multi-dimensional responder definition designed to minimize the placebo effect, those on lubiprostone were significantly more likely to be responders as those on placebo (18% vs 10%). Further, lubiprostone was significantly more likely than placebo to improve individual IBS symptoms including abdominal pain, stool consistency, straining, constipation severity and quality of life. After a careful review of the literature, the ACG IBS task force concluded that lubiprostone at a dose of 8 mcg twice daily was more effective than placebo in relieving global IBS symptoms in women with IBS-C (Grade 1B).67 The task force commented on the lack of data addressing the efficacy of lubiprostone in men with IBS-C. Lubiprostone 8 mcg twice daily dosed with food was found to be generally well tolerated. The most common side effects at this dose included nausea (8%) and diarrhea (6%). Five percent of IBS-C patients enrolled in the phase III trials withdrew related to side effects. There have been postmarketing reports of dyspnea in a small number of patients prescribed lubiprostone. Lubiprostone is also contraindicated in pregnancy due to fetal demise in guinea pig studies.

Guanylate cyclase-C (GC-C) agonists are another class of prosecretory agents which are being developed for IBS-C. Binding of intestinal GC-C receptors stimulates production of cyclic guanosine monophosphate (cGMP) which activates the cystic fibrosis transmembrane conductance regulator (CFTR) channel leading to intestinal chloride secretion. Linaclotide is a locally acting synthetic 14-amino acid peptide which avidly binds GC-C receptors. Linaclotide has been shown to improve symptoms in patients with chronic constipation.66,67 The most common side effect reported with linaclotide has been diarrhea which in most cases has been mild to moderate in severity and self limited in duration. More recently, two phase III randomized, controlled trials which enrolled over 1,600 patients with IBS-C found linaclotide 266 μg was superior to placebo for constipation-related complaints and abdominal pain for up to 26 weeks.68

Plecanatide is another orally administered GC-C agonist. A recently completed phase IIa study reported that oral plecanatide given at doses of 0.3, 1.0, 3.0, and 9.0 mg once daily for 14 days improved stool frequency, straining, and abdominal discomfort in patients with chronic constipation. Plecanatide treatment led to no diarrhea and no severe adverse events.69 To date, there are no data on the efficacy of plecanatide in IBS patients.

5. Bile acid modulators

Bile acids can alter intestinal and colonic motility and secretion. Recent work has utilized specific bile acid analogs or drugs which alter bile acid reabsorption as novel therapies for IBS-C. The main results from a trial which evaluated the effects of chenodeoxycholic acid (CDCA) on colonic transit and clinical parameters in female IBS-C patients were recently reported. CDCA significantly accelerated overall colonic transit and improved clinical outcomes including stool frequency, stool consistency and facilitated the passage of stool. The most common side effect with CDCA was abdominal cramping/pain which was reported by over 40% of patients vs none with placebo.70

A3309 is a novel small molecule which inhibits ileal bile acid transporters. In so doing, A3309 results in greater delivery of bile acids to the right colon with consequent effects on motility, transit and secretion. A3309 has been shown to accelerate colon transit in animals and humans.61 Top line data from a randomized, placebo-controlled phase Ib II dose range study in 190 patients with chronic constipation were recently reported. A3309 once daily at doses of 5, 10, and 15 mg/day showed dose dependent effects on the primary outcome of weekly spontaneous bowel movements as well as a number of other constipation related secondary outcomes. A3309 failed to show significant effects on abdominal pain in this trial but results may have been confounded by low baseline levels of abdominal pain. The most common side effect with A3309 was dose dependent diarrhea.71 Studies of A3309 in IBS-C patients are not yet available.
IBS-D

1. Antidiarrheals

Antidiarrheals are perhaps the most commonly employed agents used in the treatment of IBS-D. Only loperamide has been evaluated in RCTs for the treatment of IBS.\textsuperscript{70-75} Although limited by significant methodological flaws, in aggregate these studies demonstrate improvements in stool consistency, stool form and urgency amongst IBS-D patients. The effect of loperamide on abdominal pain has been less consistent. The systematic review conducted ACG IBS task force concluded that loperamide was helpful for diarrhea related symptoms such as stool frequency and consistency but no more effective than placebo at reducing abdominal pain, bloating or global symptoms in IBS patients. The task force added that safety and tolerability data on loperamide remains lacking.\textsuperscript{77} One advantage of loperamide is its peripheral site of action with little penetration of the blood brain barrier and thus, little potential for CNS side effects or habituation.

2. Serotonergic agents

5-HT\textsubscript{3} receptor antagonists slow small bowel transit, decrease intestinal secretion, decrease colonic tone, and delay colonic transit.\textsuperscript{76-79} The best studied 5-HT\textsubscript{3} receptor antagonist in patients with IBS-D is alosetron. Methodologically rigorous, large clinical trials have consistently demonstrated the efficacy of alosetron in relieving IBS symptoms including abdominal pain, diarrhea, and urgency. Alosetron has also been shown to improve quality of life in women with IBS-C and IBS-M.\textsuperscript{80-83} The long-term efficacy and safety of alosetron has also been established in a 48-week placebo-controlled trial.\textsuperscript{84} Alosetron has been assessed in 662 men with IBS-D demonstrating superiority to placebo in providing adequate relief of abdominal pain (53% vs 40%, \(p=0.04\)) and improving stool consistency (\(p<0.001\)).\textsuperscript{85} Due to potential serious side effects including severe constipation and ischemic colitis,\textsuperscript{86} alosetron is currently prescribed in the US through a risk management plan, the details of which can be found in the product label. A recent systematic review and meta-analysis conducted by the ACG IBS task force concluded that alosetron was more effective than placebo at relieving global IBS in men with IBS-D (Grade 2B) and women with IBS-D (Grade 2A). The task force went on to say that the benefits and harms of alosetron were most favorable in women with severe IBS-D who have not responded to conventional medical therapies (Grade 1B).\textsuperscript{47,87}

Ramosetron is another 5-HT\textsubscript{3} receptor antagonist which has recently been evaluated in a double-blind, placebo-controlled Phase II trial in 418 patients with IBS-D from Japan. In this trial, female and male patients with IBS-D were randomized to ramosetron at doses of 1, 5, and 10 \(\mu\)g or placebo given once

![Emerging pharmacological therapies for IBS and mechanisms of action. Blue boxes represent drugs used for IBS-D; Pink boxes represent drugs used for IBS-C; Purple boxes represent drugs used for both IBS subtypes. Adapted from Gastroenterol Clin North Am 2011;40:223-43.](image-url)
daily for 12 weeks. Patients randomized to ramosetron 5 and 10 μg had significantly higher global responder rates than placebo (42.57% and 43.01% vs 26.92%, p=0.027, p=0.026, respectively). Ramosetron also led to significantly greater improvements in relief of abdominal discomfort and/or pain and abnormal bowel habits. Dose-dependent constipation and hard stools were noted but no cases of ischemic colitis or serious complications of constipation were reported. Ramosetron is approved for use in Japan but is not available in US.

Emerging pharmacological therapies for IBS and mechanisms of action are summarized in Fig. 1.

3. Antibiotics

There is now robust data to suggest that treatment with a course of oral antibiotics improves IBS symptoms in the short term. The largest and most rigorously designed studies addressing this issue have utilized the non-absorbable antibiotic rifaximin. Rifaximin is a derivative of rifamycin which is concentrated in the gut lumen with little systemic absorption. This feature makes rifaximin an attractive candidate for the modification of the gut flora as it mitigates some of the concerns regarding resistance and side effects that are more relevant with systemically absorbed antibiotics. Data from two phase 3 trials in 1,260 non-constipation IBS patients demonstrated that rifaximin 550 mg three times daily for 14 days significantly improved global symptoms, as well as individual symptoms including bloating, abdominal pain and stool consistency compared to placebo in a subset of affected patients for up to 3 months. It is quite interesting that a short course of therapy results in clinical benefits which persist well beyond the discontinuation of the antibiotic. It remains unclear whether these clinical benefits are the result of reduction/modification of intestinal or colonic flora or both. Though the precise mechanism of action remains to be determined, the authors of this study proposed several potential explanations for these findings: 1) the effect of rifaximin, by affecting gut bacteria, could reduce the bacterial products that negatively affect the host; 2) the effect on gut flora might alter local mucosal engagement of bacteria such as the immune responses of the host or; 3) the antibiotic alters both the bacteria and host responses. The safety profile during and after treatment with rifaximin was comparable to that observed with placebo. There were no cases of C. difficile associated diarrhea or ischemic colitis reported in the phase 3 trials. Despite these very encouraging results, a number of important questions remain regarding the role of antibiotic therapy in IBS patients. Clinical wisdom and some data suggest that an unclear proportion of rifaximin responders will develop recurrent IBS symptoms over time. Neither the proportion of patients who will relapse or the duration of clinical response beyond 10 weeks of therapy is currently known. Further, the optimal management strategy for patients who experience symptom relapse is also unknown at present. Studies to clarify these questions are currently being developed and will clarify the optimal means by which to utilize antibiotic therapy in IBS patients.

4. Other emerging therapies for IBS-D

A number of other compounds with a variety of mechanisms of action are in various stages of development for patients with IBS-D. Some examples include kappa opioid agonists such as asimadoline, orally administered, non-absorbable, carbon-based adsorbent such as AST-120, corticotropin releasing factor (CRF) antagonists such as pexacerfont and GW876008, chloride secretion inhibitors such as detofisopam, and atypical benzodiazepines such as LX-1031.

ABDOMINAL PAIN/DISCOMFORT

1. Antispasmodics

Antispasmodics remain a mainstay of therapy for IBS. Antispasmodics encompass a diverse group of drug classes including antimuscarinics, smooth muscle relaxants, anticholinergics and unique agents such as pinaverium, an ammonium derivative with calcium channel blocking properties, and trimetubine, a peripheral opiate agonist. Although antispasmodics remain among the most commonly prescribed drugs for IBS, the clinical evidence supporting their use is limited. Given the lack of high quality studies addressing the efficacy of specific antispasmodic agents in IBS, this drug class has been largely assessed through systematic reviews and meta-analyses. The ACG IBS task force recently performed a comprehensive evidence-based systematic review and meta-analysis which concluded that the antispasmodics hyoscine, cimetropium, and pinaverium provided short-term relief of abdominal pain/discomfort in IBS patients. The task force added that evidence for long-term efficacy, safety and tolerability was limited. The available evidence and clinical experience suggest that antispasmodics are most effective in IBS patients with crampy abdominal pain and diarrhea. Clinical wisdom (non-evidence based) suggests that antispasmodics are most effective in patients with intermittent, meal related symptoms. Patients with continuous pain rarely improve with this form of therapy. The anticholinergic properties of these agents can be associated with the development of significant side effects including dry mouth, dizziness, blurry vision, confusion (particularly in the elderly), urinary retention and constipation. The use of these agents should be avoided in the elderly.

2. Psychotropic agents

The three major classes of psychotropic agents employed in the treatment of IBS include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs). Psychotropics possess a variety of peripheral and central effects which make them attractive candidate treatments for IBS. These effects include...
modulation of pain perception, mood stabilization, treatment of coexistent psychiatric disorders, and possible direct effects on GI motility and secretion. Indeed recent systematic reviews and meta-analyses have found these agents to be more effective than placebo in the treatment of overall symptoms and abdominal pain in IBS patients.\textsuperscript{83,84} On the other hand, the effects of psychotropic agents on bowel symptoms in IBS patients have been less robust and less consistent than the benefits reported for global symptoms and abdominal pain/discomfort.

TCAs are the best studied class of psychotropic agents in the treatment of IBS. In a recent systematic review by the ACG IBS task force, the pooled data from 9 RCTs totaling 575 patients demonstrated the superiority of TCAs over placebo in the treatment of IBS with a number needed to treat (NNT) of 4.\textsuperscript{79} The most common side effects of TCAs result from their anticholinergic properties, including constipation, tachycardia, urinary retention, and xerostomia. Patients may also encounter central side effects including insomnia, agitation, and nightmares. The secondary amine TCAs (desipramine, nortriptyline) tend to be better tolerated than tertiary amine TCAs (amitriptyline, imipramine) given their decreased anticholinergic properties. Based upon the available evidence, it seems reasonable to conclude that TCAs are more effective than placebo in relieving global symptoms and abdominal pain in IBS. Given the potential for side effects, TCAs are most appropriate for IBS patients with persistent, moderate to severe symptoms predominated by abdominal pain and loose stools. To minimize side effects, TCAs should be started at a low dose (10-25 mg) and slowly titrated up as needed to achieve symptom control.

Given the important peripheral and central roles of serotonin in gut function and sensation, there has been growing interest in the use of SSRIs for IBS. As a treatment for IBS, SSRIs offer potential advantages over TCAs including anxiolytic effects and arguably, a more favorable side effect profile. In the systematic review and meta-analysis conducted by the ACG IBS task force, pooled data from 5 RCTs totaling 230 patients demonstrated the superiority of SSRIs over placebo in the treatment of IBS with an NNT of 3.5.\textsuperscript{47} The task force concluded that SSRIs were more effective than placebo in relieving global symptoms and abdominal pain in IBS, although limited data exists regarding their safety and tolerability. In contrast to TCAs, SSRIs are likely to increase small bowel and colonic transit.\textsuperscript{109} Therefore, it has been argued that SSRIs might be better suited for patients with IBS-C. From the limited evidence available, it seems reasonable to conclude that SSRIs may offer benefits in IBS subtypes with a tendency toward constipation and those with coexistent anxiety disorders.

The unique dual effect of SNRIs on serotonin and norepinephrine has made this class of psychotropic agents attractive for potential use in IBS. At the present time, use of these agents is largely based upon evidence from small observational or translational studies. There is a single open-label study assessing the efficacy of duloxetine in 15 adults with IBS.\textsuperscript{111} Although duloxetine was associated with significant improvements in abdominal pain, loose stools, anxiety and quality of life; nearly 50% dropped out of the study due to side effects. Venlafaxine has been shown to increase colonic compliance, decrease colonic tone and reduce sensation of colonic distention in healthy adults.\textsuperscript{112} Large, methodologically rigorous, randomized trials to elucidate the clinical benefits and tolerability of SNRIs in IBS patients are eagerly awaited.

**COMPLEMENTARY AND ALTERNATIVE MEDICINE THERAPIES**

The term “complementary and alternative medicine” (CAM) refers to treatment practices which are not currently considered an integral part of conventional allopathic medical practice. Treatments are considered as “complementary” when used in addition to conventional therapies and as “alternative” when used instead of conventional therapies.\textsuperscript{74} A number of factors are likely fueling the increasing interest in CAM therapies for IBS. First, traditional medical therapies for IBS offer marginal efficacy with therapeutic gains over placebo of 7-15%. Further, in many countries including the US, prescription medication insurance coverage for IBS and other “quality of life” conditions is decreasing. Finally, perhaps related to concerns regarding the safety of prescription medications, there appears to be a growing desire amongst patients for more holistic and “natural” treatment options. A population based survey in 1,409 subjects from the UK indicated that over 50% of IBS patients used CAM treatments\textsuperscript{113} while another prospective 6-month study from a large HMO in the US found that 35% of patients with functional GI diseases use CAM.\textsuperscript{114} The following section will focus on the evidence addressing the efficacy of CAM therapies for IBS.

1. **Probiotics**

Probiotics are live microorganisms which when taken in sufficient quantities, confer a health benefit. Probiotics are distinguished from prebiotics (substrates which encourage the growth of probiotic organisms), synbiotics (a combination of a prebiotic and probiotic), or postbiotics (isolated bacterial components). Probiotics may offer benefits to IBS patients through a number of mechanisms including modification of gut mucosal barrier function, the luminal microbiome, the mucosal immune system, visceral sensation as well as alterations in fermentation and production of bacteriocins or substances with neurotransmitter properties.\textsuperscript{115} Though numerous RCTs have evaluated the efficacy of probiotics in IBS patients, most suffer from serious methodological flaws.\textsuperscript{116} In a recent systematic review, Brenner and colleagues reported that of 16 RCTs evaluating probiotics in the treatment of IBS, *Bifidobacterium infantis* (B. infantis) 35624 was the only one which provided significant improvements in IBS symptoms in appropriately designed, albeit short...
term, studies. In the study by O’Mahoney et al., IBS patients were randomized to receive B. infantis 35624, Lactobacillus salivarius (L. salivarius) UCC4331, or placebo. Patients randomized to B. infantis 35624 experienced a greater reduction in symptom scores for abdominal pain/discomfort, bloating/distention, and bowel movement difficulty compared to placebo. This study also reported normalization of peripheral blood mononuclear cell cytokine levels in IBS patients with B. infantis 35624 but not with L. salivarius UCC4331 suggesting a possible anti-inflammatory effect. The second study by Whorwell et al. was a dose-ranging study which found that B. infantis 35624 at a dose of 10^8 CFU/mL was significantly more likely than placebo to improve the primary outcome of abdominal pain/discomfort (p=0.023) as well as global IBS symptoms (p=0.014) at 4 weeks. The greatest benefits were observed in IBS-D patients. Somewhat surprisingly, a higher dose of B. infantis 35624 (10^10 CFU/mL) was no more effective than placebo though concerns have been raised over the bioavailability/formulation of this dose. It is logical to hypothesize that other single and multi-strain probiotics will offer benefits to the symptoms of IBS. Further, large, methodologically rigorous randomized, controlled trials will be necessary to clarify this important issue.

2. Herbal therapies

One of the most extensively studied herbal therapies for IBS is “Tong xie yao fang (TXYF).” A systematic review of 12 randomized trials which included 1,125 IBS patients found that TXYF was more effective than control treatments (relative risk [RR], 1.35; 95% confidence interval [CI], 1.21 to 1.50; p<0.05). Unfortunately, the quality of the included studies was poor and as such, any conclusions drawn from this systematic review must be viewed with extreme caution.

Peppermint oil is extracted from Mentha piperita Linnaeus plant which possesses Ca^2+-channel blocking activity and thus, leads to smooth muscle relaxation. Previous meta-analyses and systematic reviews which assessed the efficacy of peppermint oil in IBS patients included small studies with significant methodological flaws. These analyses found that peppermint oil was more efficacious than placebo for the treatment of IBS (odds ratio [OR], 2.7; 95% CI, 1.56 to 4.76) but the poor quality of the included studies cast doubt on the validity of these results. A meta-analysis by Ford et al. which included more recent, higher quality studies (three studies with 345 patients) reported that peppermint oil was less likely to be associated with persistent IBS symptoms than placebo (RR, 0.40; 95% CI, 0.29 to 0.55). No statistically significant heterogeneity was noted in this analysis (I^2=22.0%, p=0.28). One study showed that peppermint oil improved generic quality of life using SF-36 as well as IBS symptoms.

Traditional Chinese herbal therapies have been evaluated in IBS patients. In one of the higher quality studies, 116 patients were randomized to receive either a standardized traditional Chinese herbal formula, an herbal combination formulated for each individual IBS patient based on her/his specific IBS symptoms, or placebo which looked and smelled like the test preparations. After 16 weeks, patients receiving either of the herbal formulations reported significantly greater improvements in their symptoms than placebo (42% vs 16%, p<0.05). A recent Cochrane review which assessed over 70 different herbal therapies for IBS identified 75 trials which enrolled almost 8,000 participants. Only three of the trials were felt to be of high methodological quality. Over ninety percent of the trials were performed in China. Another recent well designed, randomized trial found that St. John’s Wort was actually less likely than placebo to improve IBS symptoms. This study should remind providers that all herbal therapies for IBS are not created equally and that further well designed, appropriately powered trials are needed.

3. Acupuncture

Acupuncture is a traditional CAM technique that has been practiced in many far Eastern countries for thousands of years. Some have speculated that acupuncture, through effects on motility, visceral sensation, and/or brain-gut interactions, might be beneficial for IBS. There have been at least 4 double blind, sham controlled trials which have assessed the efficacy of acupuncture in IBS patients. To date, none has provided compelling evidence that acupuncture is superior to sham acupuncture as a treatment for IBS. In one of the best designed trials by Lembo et al., 230 IBS patients were randomized to 5 groups: waitlist control, acupuncture with limited interaction, acupuncture with augmented interaction, sham acupuncture with limited interaction, and sham acupuncture with augmented interaction. There was no statistically significant difference in the proportion of responders receiving acupuncture versus sham acupuncture. Further, for the secondary endpoints, there were no differences in responder rates for adequate relief of IBS, IBS QOL, and IBS-symptom severity scale. Interestingly, both the acupuncture and sham acupuncture led to a significantly greater proportion of responders for the primary and many of the secondary outcomes as compared to the waitlist control group.

The explanations for these results remain unclear but possible explanations include confounding by inadequacies in power, study methodology, and a reliable sham acupuncture control. In addition, one wonders whether the benefits of real and sham acupuncture over “usual care” are the consequence of the interaction between the CAM provider and patient. At present, it is reasonable to conclude that the available evidence has not identified a clear clinical benefit of acupuncture over sham acupuncture. However, at least a third of patients who receive acupuncture will experience substantial benefit in their IBS symptoms with a very low likelihood of side effects when compared to continuing usual care.
SUMMARY

The heterogeneity of pathogenesis and clinical phenotypes provides an explanation for the marginal therapeutic gains offered by treatments found to be more effective than placebo in clinical trials. Traditional therapies have focused on modulating motility/transit and visceral sensation. As our understanding of the pathogenesis of symptoms in IBS patients has improved, so too has the number of novel therapies being developed for IBS. The popularity of CAM therapies is rapidly increasing. Though some high quality trials have recently been published, further data on the efficacy and safety of CAM therapies is greatly needed. Ironically, the way forward for the treatment of IBS is likely to lie in our growing understanding of pathogenesis with the consequent development of reliable biomarkers which offer predictive value in terms of the success of specific therapies. Until that time, it is unlikely that any therapy will address more than a subgroup of the total population of IBS sufferers.

CONFLICTS OF INTEREST

Dr. Saad and Maneerattanaporn declare no potential conflicts of interest. Dr. Chey is a consultant for Albireo, Ironwood, Johnson and Johnson, Movetis, Prometheus, Salix, and Takeda.

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