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. **(Gut Liver 2011;5:253-266)**

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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

Table 1. Epidemiologic Data for IBS by Geographic Region

Location	Prevalence (%)	% IBS subtype (C:D:A)	Gender (F:M)
North America[134]	17–20*	27.1–29.4:27.1–33.9:26.3[135-137]	1:1–2:1
European Union[138]	4[†]	16:21:63	2:1
Asia[139,140]	2.9-15.6	No systematic evaluation has been reported	1:1–1.5:1

IBS, irritable bowel syndrome.
*Manning criteria; [†] Rome II criteria.

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).[11-14] Likewise, several studies have report delayed bowel transit in those with constipation predominant IBS (IBS-C).[11,13] 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 co-morbidity 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.[34,35] 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.[36,37] More recent studies have combined sophisticated molecular techniques with more traditional culture to associate specific bacterial strains with the symptoms of IBS-D.[38,39] The role of genetic factors in the development of IBS has grown from early familial aggregation studies[40] 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.[41] 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.[42] 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,[43] 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.[44-46]

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.[47] 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

Table 2. Grading Recommendations from the ACG Evidence-Based IBS Monograph[47]

Grade of recommendation/ description	Benefit vs risk and burdens	Methodological quality of supporting evidence	Implications
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
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
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
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
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
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

ACG, American College of Gastroenterology; IBS, irritable bowel syndrome; RCT, randomized controlled trial.

in decreased stool consistency and increased stool frequency.[48] 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 mucilliod (ispaghula husk) is moderately effective in the treatment of IBS (Grade 2C, Table 1).[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.[49] 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.

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.[50] Patients were randomized to receive 4 weeks of PEG or PEG and the 5-HT$_4$ 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

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

	Improvements in symptoms					Grade
	Global symptoms	Pain	Bloating	Stool frequency	Stool consistency	
Lubiprostone	+	+			+	1B
Antidepressants	+	+				1B
Tegaserod*	+	±	+	+	+	2A
Fiber (psyllium)				+	+	2C
Laxatives (PEG)				+		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)						Insufficient evidence

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.

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, $5-HT_{1p}$, $5-HT_3$ and $5-HT_4$ receptors have the greatest evidence supporting a role in GI and colonic function and sensation. In the GI tract, $5-HT_4$ receptors are found on enteric neurons and smooth muscle cells. Stimulation of $5-HT_4$ receptors leads to acetylcholine release and prokinetic effects.[51,52] A number of $5-HT_4$ agonists have been developed as potential treatments for patients with IBS-C. Tegaserod is a selective $5-HT_4$ 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 $5-HT_4$ 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

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-HT$_4$ 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-HT$_3$ 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).[47] 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.[63] Top line data from a randomized, placebo-controlled phase IIb 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.[72-75] 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.[47] 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$_3$ receptor antagonists slow small bowel transit, decrease intestinal secretion, decrease colonic tone, and delay colonic transit.[76-79] The best studied 5-HT$_3$ 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 IBC-D and IBS-M.[80-83] The long-term efficacy and safety of alosetron has also been established in a 48-week placebo-controlled trial.[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).[85] Due to potential serious side effects including severe constipation and ischemic colitis,[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).[47,87]

Ramosetron is another 5-HT$_3$ 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 μg or placebo given once
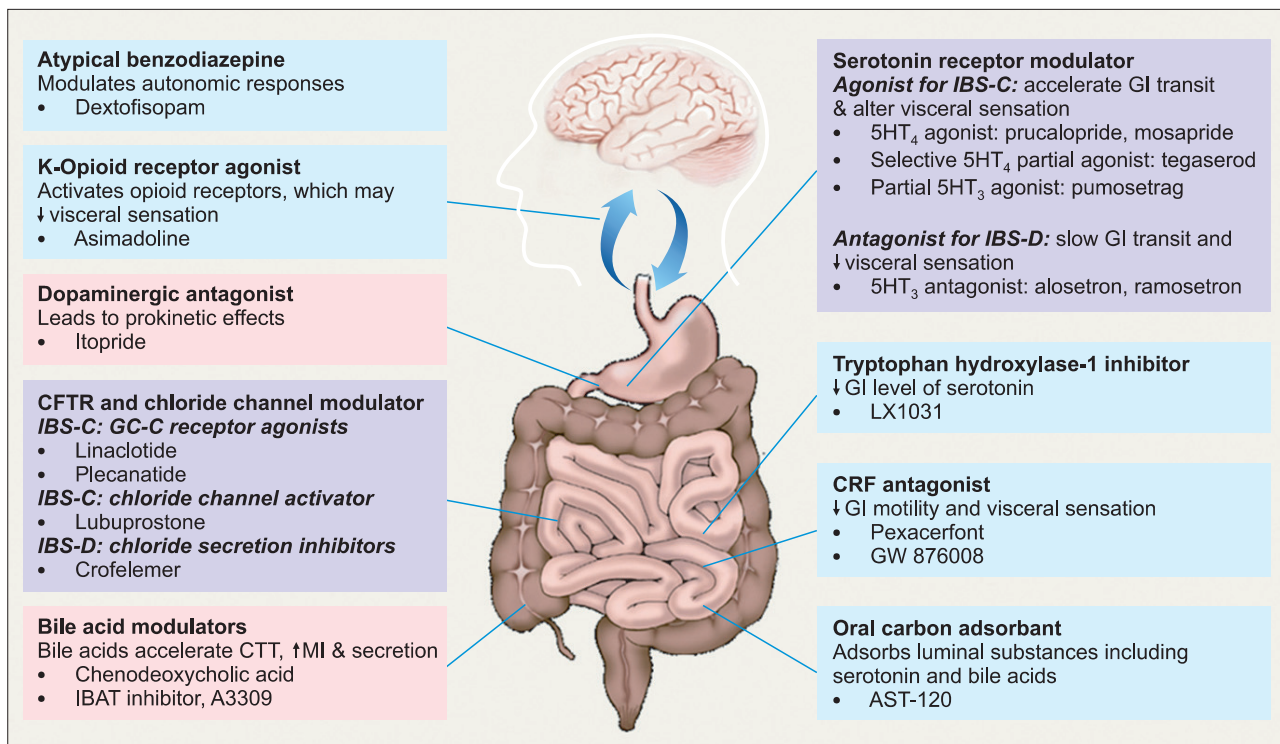

Fig. 1. Emerging pharmacological therapies for IBS and mechanisms of action. Blue boxes represent drugs used for IBS-D; Pink boxes represent drugs used for IBS-C; Purple boxes represent drugs used for both IBS subtypes. Adapted from Gastroenterol Clin North Am 2011;40:223-43.[63]
IBS, irritable bowel syndrome; κ-Opioid, kappa opioid; GI, gastrointestinal; GC-C, guanylate cyclase; CFTR, cystic fibrosis transmembrane conductance regulator; CRF-1R, corticotropin releasing factor receptor type1; IBAT, ileal bile acid transporter; CTT, colonic transit time; MI, motility index.

daily for 12 weeks.[88] 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.[89-91] The largest and most rigorously designed studies addressing this issue have utilized the non-absorbable antibiotic rifaximin.[90-92] 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.[91] Despite these very encouraging results, a number of important questions remain regarding the role of antibiotic therapy in IBS patients.[93] Clinical wisdom and some data suggest that an unclear proportion of rifaximin responders will develop recurrent IBS symptoms over time.[94] 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.[63] Some examples include kappa opioid agonists such as asimadoline,[95,96] orally administered, non-absorbable, carbon-based adsorbent such as AST-120,[97] corticotropin releasing factor (CRF) antagonists such as pexacerfont and GW876008,[98,99] chloride secretion inhibitors such as crofelemer,[100] and atypical benzodiazepines such as detofisopam,[101] and tryptophan hydroxylase inhibitors such as LX-1031.[102]

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 trimebutine, a peripheral opiate agonist.[103] 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.[47,104-106] 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.[47] 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.[107]

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.[108,109] 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.[47] 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.[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.[110] 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.[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.[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.[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[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.[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.[115] Though numerous RCTs have evaluated the efficacy of probiotics in IBS patients, most suffer from serious methodological flaws.[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.[117] 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.[118] 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=0.028) and bowel habit satisfaction (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.[119] 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).[120] 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^{++}-channel blocking activity and thus, leads to smooth muscle relaxation.[121,122] Previous meta-analyses and systematic reviews which assessed the efficacy of peppermint oil in IBS patients included small studies with significant methodological flaws.[123,124] 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.[124] 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).[125] One study showed that peppermint oil improved generic quality of life using SF-36 as well as IBS symptoms.[126]

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).[127] 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.[128] Another recent well designed, randomized trial found that St. John's Wort was actually less likely than placebo to improve IBS symptoms.[129] 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

Acupunture 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.[130-133] 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.,[133] 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

ACKNOWLEDGEMENTS

REFERENCES

1. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology 2006;130:1480-1491.
2. Longstreth GF, Wilson A, Knight K, et al. Irritable bowel syndrome, health care use, and costs: a U.S. managed care perspective. Am J Gastroenterol 2003;98:600-607.
3. Hungin AP, Chang L, Locke GR, Dennis EH, Barghout V. Irritable bowel syndrome in the United States: prevalence, symptom patterns and impact. Aliment Pharmacol Ther 2005;21:1365-1375.
4. Grundmann O, Yoon SL. Irritable bowel syndrome: epidemiology, diagnosis and treatment: an update for health-care practitioners. J Gastroenterol Hepatol 2010;25:691-699.
5. El-Serag HB, Olden K, Bjorkman D. Health-related quality of life among persons with irritable bowel syndrome: a systematic review. Aliment Pharmacol Ther 2002;16:1171-1185.
6. Gralnek IM, Hays RD, Kilbourne A, Naliboff B, Mayer EA. The impact of irritable bowel syndrome on health-related quality of life. Gastroenterology 2000;119:654-660.
7. Crowell MD, Harris L, Jones MP, Chang L. New insights into the pathophysiology of irritable bowel syndrome: implications for future treatments. Curr Gastroenterol Rep 2005;7:272-279.
8. Hasler WL. Traditional thoughts on the pathophysiology of irritable bowel syndrome. Gastroenterol Clin North Am 2011;40:21-43.
9. Ohman L, Simrén M. Pathogenesis of IBS: role of inflammation, immunity and neuroimmune interactions. Nat Rev Gastroenterol Hepatol 2010;7:163-173.
10. Pimentel M, Chang C. Inflammation and microflora. Gastroenterol Clin North Am 2011;40:69-85.
11. Manabe N, Wong BS, Camilleri M, Burton D, McKinzie S, Zinsmeister AR. Lower functional gastrointestinal disorders: evidence of abnormal colonic transit in a 287 patient cohort. Neurogastroenterol Motil 2010;22:293-e82.
12. Deiteren A, Camilleri M, Burton D, McKinzie S, Rao A, Zinsmeister AR. Effect of meal ingestion on ileocolonic and colonic transit in health and irritable bowel syndrome. Dig Dis Sci 2010;55:384-391.
13. Lee OY. Asian motility studies in irritable bowel syndrome. J Neurogastroenterol Motil 2010;16:120-130.
14. Chey WY, Jin HO, Lee MH, Sun SW, Lee KY. Colonic motility abnormality in patients with irritable bowel syndrome exhibiting abdominal pain and diarrhea. Am J Gastroenterol 2001;96:1499-1506.
15. Ritchie J. Pain from distension of the pelvic colon by inflating a balloon in the irritable colon syndrome. Gut 1973;14:125-132.
16. Whitehead WE, Holtkotter B, Enck P, et al. Tolerance for rectosigmoid distention in irritable bowel syndrome. Gastroenterology 1990;98(5 Pt 1):1187-1192.
17. Mertz H, Naliboff B, Munakata J, Niazi N, Mayer EA. Altered rectal perception is a biological marker of patients with irritable bowel syndrome. Gastroenterology 1995;109:40-52.
18. Nozu T, Kudaira M, Kitamori S, Uehara A. Repetitive rectal painful distention induces rectal hypersensitivity in patients with irritable bowel syndrome. J Gastroenterol 2006;41:217-222.
19. Spiller RC. Potential biomarkers. Gastroenterol Clin North Am 2011;40:121-139.
20. Zhou Q, Fillingim RB, Riley JL 3rd, Malarkey WB, Verne GN. Central and peripheral hypersensitivity in the irritable bowel syndrome. Pain 2010;148:454-461.
21. Tillisch K, Mayer EA, Labus JS. Quantitative meta-analysis identifies brain regions activated during rectal distension in irritable bowel syndrome. Gastroenterology 2011;140:91-100.
22. Drossman DA. Do psychosocial factors define symptom severity and patient status in irritable bowel syndrome? Am J Med 1999;107(5A):41S-50S.
23. Ohman L, Simrén M. New insights into the pathogenesis and pathophysiology of irritable bowel syndrome. Dig Liver Dis 2007;39:201-215.
24. Garvin B, Wiley JW. The role of serotonin in irritable bowel syndrome: implications for management. Curr Gastroenterol Rep 2008;10:363-368.
25. Houghton LA, Atkinson W, Whitaker RP, Whorwell PJ, Rimmer MJ. Increased platelet depleted plasma 5-hydroxytryptamine

concentration following meal ingestion in symptomatic female subjects with diarrhoea predominant irritable bowel syndrome. Gut 2003;52:663-670.

26. Dunlop SP, Coleman NS, Blackshaw E, et al. Abnormalities of 5-hydroxytryptamine metabolism in irritable bowel syndrome. Clin Gastroenterol Hepatol 2005;3:349-357.

27. Atkinson W, Lockhart S, Whorwell PJ, Keevil B, Houghton LA. Altered 5-hydroxytryptamine signaling in patients with constipation- and diarrhea-predominant irritable bowel syndrome. Gastroenterology 2006;130:34-43.

28. Thabane M, Marshall JK. Post-infectious irritable bowel syndrome. World J Gastroenterol 2009;15:3591-3596.

29. Halvorson HA, Schlett CD, Riddle MS. Postinfectious irritable bowel syndrome: a meta-analysis. Am J Gastroenterol 2006;101:1894-1899.

30. Marshall JK, Thabane M, Borgaonkar MR, James C. Postinfectious irritable bowel syndrome after a food-borne outbreak of acute gastroenteritis attributed to a viral pathogen. Clin Gastroenterol Hepatol 2007;5:457-460.

31. Soyturk M, Akpinar H, Gurler O, et al. Irritable bowel syndrome in persons who acquired trichinellosis. Am J Gastroenterol 2007;102:1064-1069.

32. Gonsalkorale WM, Perrey C, Pravica V, Whorwell PJ, Hutchinson IV. Interleukin 10 genotypes in irritable bowel syndrome: evidence for an inflammatory component? Gut 2003;52:91-93.

33. van der Veek PP, van den Berg M, de Kroon YE, Verspaget HW, Masclee AA. Role of tumor necrosis factor-alpha and interleukin-10 gene polymorphisms in irritable bowel syndrome. Am J Gastroenterol 2005;100:2510-2516.

34. Lin HC. Small intestinal bacterial overgrowth: a framework for understanding irritable bowel syndrome. JAMA 2004;292:852-858.

35. Ford AC, Spiegel BM, Talley NJ, Moayyedi P. Small intestinal bacterial overgrowth in irritable bowel syndrome: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2009;7:1279-1286.

36. Malinen E, Rinttilä T, Kajander K, et al. Analysis of the fecal microbiota of irritable bowel syndrome patients and healthy controls with real-time PCR. Am J Gastroenterol 2005;100:373-382.

37. Kassinen A, Krogius-Kurikka L, Mäkivuokko H, et al. The fecal microbiota of irritable bowel syndrome patients differs significantly from that of healthy subjects. Gastroenterology 2007;133:24-33.

38. Carroll IM, Chang YH, Park J, Sartor RB, Ringel Y. Luminal and mucosal-associated intestinal microbiota in patients with diarrhea-predominant irritable bowel syndrome. Gut Pathog 2010;2:19.

39. Kerckhoffs AP, Ben-Amor K, Samsom M, et al. Molecular analysis of faecal and duodenal samples reveals significantly higher prevalence and numbers of Pseudomonas aeruginosa in irritable bowel syndrome. J Med Microbiol 2011;60(Pt 2):236-245.

40. Park MI, Camilleri M. Genetics and genotypes in irritable bowel syndrome: implications for diagnosis and treatment. Gastroenterol Clin North Am 2005;34:305-317.

41. Nastaskin I, Mehdikhani E, Conklin J, Park S, Pimentel M. Studying the overlap between IBS and GERD: a systematic review of the literature. Dig Dis Sci 2006;51:2113-2120.

42. Ford AC, Marwaha A, Lim A, Moayyedi P. Systematic review and meta-analysis of the prevalence of irritable bowel syndrome in individuals with dyspepsia. Clin Gastroenterol Hepatol 2010;8:401-409.

43. Lee SY, Lee KJ, Kim SJ, Cho SW. Prevalence and risk factors for overlaps between gastroesophageal reflux disease, dyspepsia, and irritable bowel syndrome: a population-based study. Digestion 2009;79:196-201.

44. Kaji M, Fujiwara Y, Shiba M, et al. Prevalence of overlaps between GERD, FD and IBS and impact on health-related quality of life. J Gastroenterol Hepatol 2010;25:1151-1156.

45. De Vries DR, Van Herwaarden MA, Baron A, Smout AJ, Samsom M. Concomitant functional dyspepsia and irritable bowel syndrome decrease health-related quality of life in gastroesophageal reflux disease. Scand J Gastroenterol 2007;42:951-956.

46. Nojkov B, Rubenstein JH, Adlis SA, et al. The influence of comorbid IBS and psychological distress on outcomes and quality of life following PPI therapy in patients with gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2008;27:473-482.

47. American College of Gastroenterology Task Force on Irritable Bowel Syndrome, Brandt LJ, Chey WD, et al. An evidence-based position statement on the management of irritable bowel syndrome. Am J Gastroenterol 2009;104 Suppl 1:S1-S35.

48. Stevens J, VanSoest PJ, Robertson JB, Levitsky DA. Comparison of the effects of psyllium and wheat bran on gastrointestinal transit time and stool characteristics. J Am Diet Assoc 1988;88:323-326.

49. Bijkerk CJ, de Wit NJ, Muris JW, Whorwell PJ, Knottnerus JA, Hoes AW. Soluble or insoluble fibre in irritable bowel syndrome in primary care? Randomised placebo controlled trial. BMJ 2009;339:b3154.

50. Khoshoo V, Armstead C, Landry L. Effect of a laxative with and without tegaserod in adolescents with constipation predominant irritable bowel syndrome. Aliment Pharmacol Ther 2006;23:191-196.

51. Gershon MD, Tack J. The serotonin signaling system: from basic understanding to drug development for functional GI disorders. Gastroenterology 2007;132:397-414.

52. Degen L, Petrig C, Studer D, Schroller S, Beglinger C. Effect of tegaserod on gut transit in male and female subjects. Neurogastroenterol Motil 2005;17:821-826.

53. Müller-Lissner SA, Fumagalli I, Bardhan KD, et al. Tegaserod, a 5-HT(4) receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. Aliment Pharmacol Ther 2001;15:1655-1666.

54. Novick J, Miner P, Krause R, et al. A randomized, double-blind, placebo-controlled trial of tegaserod in female patients suffering

from irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2002;16:1877-1888.

55. Lefkowitz M, Shi Y, Heggland J, Dunger-Baldauf C, Ruegg P. Tegaserod rapidly improves abdominal pain, bloating and bowel function in patients with C-IBS. Gut 2000;47(Suppl 3):A217.

56. Chey WD, Paré P, Viegas A, Ligozio G, Shetzline MA. Tegaserod for female patients suffering from IBS with mixed bowel habits or constipation: a randomized controlled trial. Am J Gastroenterol 2008;103:1217-1225.

57. Kellow J, Lee OY, Chang FY, et al. An Asia-Pacific, double blind, placebo controlled, randomised study to evaluate the efficacy, safety, and tolerability of tegaserod in patients with irritable bowel syndrome. Gut 2003;52:671-676.

58. Nyhlin H, Bang C, Elsborg L, et al. A double-blind, placebo-controlled, randomized study to evaluate the efficacy, safety and tolerability of tegaserod in patients with irritable bowel syndrome. Scand J Gastroenterol 2004;39:119-126.

59. Tougas G, Snape WJ Jr, Otten MH, et al. Long-term safety of tegaserod in patients with constipation-predominant irritable bowel syndrome. Aliment Pharmacol Ther 2002;16:1701-1708.

60. Thompson CA. Novartis suspends tegaserod sales at FDA's request. Am J Health Syst Pharm 2007;64:1020.

61. Serebruany VL, El Mouelhi M, Pfannkuche HJ, Rose K, Marro M, Angiolillo DJ. Investigations on 5-HT$_4$ receptor expression and effects of tegaserod on human platelet aggregation in vitro. Am J Ther 2010;17:543-552.

62. Schoenfeld P. Review article: the safety profile of tegaserod. Aliment Pharmacol Ther 2004;20 Suppl 7:25-30.

63. Maneerattanaporn M, Chang L, Chey WD. Emerging pharmacological therapies for the irritable bowel syndrome. Gastroenterol Clin North Am 2011;40:223-243.

64. Johanson JF, Drossman DA, Panas R, Wahle A, Ueno R. Clinical trial: phase 2 study of lubiprostone for irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2008;27:685-696.

65. Drossman DA, Chey WD, Johanson JF, et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome--results of two randomized, placebo-controlled studies. Aliment Pharmacol Ther 2009;29:329-341.

66. Lembo AJ, Kurtz CB, Macdougall JE, et al. Efficacy of linaclotide for patients with chronic constipation. Gastroenterology 2010;138:886-895.e1.

67. Lembo A, Schneier H, Lavins BJ, et al. 286 efficacy and safety of once daily linaclotide administered orally for 12-weeks in patients with chronic constipation: results from 2 randomized, double-blind, placebo-controlled phase 3 trials. Gastroenterology 2010;138(5 Suppl 1):S53-S54.

68. Ironwood and Forest announce positive linaclotide results from second phase 3 trial in patients with irritable bowel syndrome with constipation 2010 [Internet]. Forest Laboratories, Inc. & Ironwood Pharmaceuticals, Inc.; 2010 [cited 2010 Dec 2]. Available from: http://www.ironwoodpharma.com/newsPDF/IRWD.FRX.Ph3.MCP-103-302.11.01.10.pdf.

69. Shailubhai K, Talluto C, Comiskey S, Foss J, Joslyn A, Jacob G. Phase II clinical evaluation of SP-304, a guanylate cyclase-C agonist, for treatment of chronic constipation. Am J Gastroenterol 2010;105:S487-S488.

70. Rao AS, Wong BS, Camilleri M, et al. Chenodeoxycholate in females with irritable bowel syndrome-constipation: a pharmacodynamic and pharmacogenetic analysis. Gastroenterology 2010;139:1549-1558, 1558.e1.

71. Chey WD, Camilleri M, Chang L, Rikner L, Graffner H. A3309, an ileal bile acid transport (IBAT/ASBT) inhibitor, significantly improved stool frequency and other constipation-related complaints in adults with chronic constipation: data from an 8-week, randomized, double-blind, placebo-controlled study. Gastroenterology 2011;140(5 Suppl 1):S3.

72. Cann PA, Read NW, Holdsworth CD, Barends D. Role of loperamide and placebo in management of irritable bowel syndrome (IBS). Dig Dis Sci 1984;29:239-247.

73. Hovdenak N. Loperamide treatment of the irritable bowel syndrome. Scand J Gastroenterol Suppl 1987;130:81-84.

74. Lavö B, Stenstam M, Nielsen AL. Loperamide in treatment of irritable bowel syndrome: a double-blind placebo controlled study. Scand J Gastroenterol Suppl 1987;130:77-80.

75. Efskind PS, Bernklev T, Vatn MH. A double-blind placebo-controlled trial with loperamide in irritable bowel syndrome. Scand J Gastroenterol 1996;31:463-468.

76. Talley NJ, Phillips SF, Haddad A, et al. GR 38032F (ondansetron), a selective 5HT3 receptor antagonist, slows colonic transit in healthy man. Dig Dis Sci 1990;35:477-480.

77. Zighelboim J, Talley NJ, Phillips SF, Harmsen WS, Zinsmeister AR. Visceral perception in irritable bowel syndrome. Rectal and gastric responses to distension and serotonin type 3 antagonism. Dig Dis Sci 1995;40:819-827.

78. Delvaux M, Louvel D, Mamet JP, Campos-Oriola R, Frexinos J. Effect of alosetron on responses to colonic distension in patients with irritable bowel syndrome. Aliment Pharmacol Ther 1998;12:849-855.

79. Houghton LA, Foster JM, Whorwell PJ. Alosetron, a 5-HT3 receptor antagonist, delays colonic transit in patients with irritable bowel syndrome and healthy volunteers. Aliment Pharmacol Ther 2000;14:775-782.

80. Camilleri M, Northcutt AR, Kong S, Dukes GE, McSorley D, Mangel AW. Efficacy and safety of alosetron in women with irritable bowel syndrome: a randomised, placebo-controlled trial. Lancet 2000;355:1035-1040.

81. Camilleri M, Chey WY, Mayer EA, et al. A randomized controlled clinical trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant irritable bowel syndrome. Arch Intern Med 2001;161:1733-1740.

82. Watson ME, Lacey L, Kong S, et al. Alosetron improves quality of life in women with diarrhea-predominant irritable bowel syndrome. Am J Gastroenterol 2001;96:455-459.

83. Lembo T, Wright RA, Bagby B, et al. Alosetron controls bowel

urgency and provides global symptom improvement in women with diarrhea-predominant irritable bowel syndrome. Am J Gastroenterol 2001;96:2662-2670.

84. Chey WD, Chey WY, Heath AT, et al. Long-term safety and efficacy of alosetron in women with severe diarrhea-predominant irritable bowel syndrome. Am J Gastroenterol 2004;99:2195-2203.

85. Chang L, Ameen VZ, Dukes GE, McSorley DJ, Carter EG, Mayer EA. A dose-ranging, phase II study of the efficacy and safety of alosetron in men with diarrhea-predominant IBS. Am J Gastroenterol 2005;100:115-123.

86. Chang L, Chey WD, Harris L, Olden K, Surawicz C, Schoenfeld P. Incidence of ischemic colitis and serious complications of constipation among patients using alosetron: systematic review of clinical trials and post-marketing surveillance data. Am J Gastroenterol 2006;101:1069-1079.

87. Ford AC, Brandt LJ, Young C, Chey WD, Foxx-Orenstein AE, Moayyedi P. Efficacy of 5-HT3 antagonists and 5-HT4 agonists in irritable bowel syndrome: systematic review and meta-analysis. Am J Gastroenterol 2009;104:1831-1843.

88. Matsueda K, Harasawa S, Hongo M, Hiwatashi N, Sasaki D. A phase II trial of the novel serotonin type 3 receptor antagonist ramosetron in Japanese male and female patients with diarrhea-predominant irritable bowel syndrome. Digestion 2008;77:225-235.

89. Frissora CL, Cash BD. Review article: the role of antibiotics vs. conventional pharmacotherapy in treating symptoms of irritable bowel syndrome. Aliment Pharmacol Ther 2007;25:1271-1281.

90. Lembo A, Zakko SF, Ferreira NL, et al. T1390 rifaximin for the treatment of diarrhea-associated irritable bowel syndrome: short term treatment leading to long term sustained response. Gastroenterology 2008;134(4 Suppl 1):A545.

91. Pimentel M, Lembo A, Chey WD, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med 2011;364:22-32.

92. Pimentel M, Park S, Mirocha J, Kane SV, Kong Y. The effect of a nonabsorbed oral antibiotic (rifaximin) on the symptoms of the irritable bowel syndrome: a randomized trial. Ann Intern Med 2006;145:557-563.

93. Tack J. Antibiotic therapy for the irritable bowel syndrome. N Engl J Med 2011;364:81-82.

94. Lauritano EC, Gabrielli M, Scarpellini E, et al. Small intestinal bacterial overgrowth recurrence after antibiotic therapy. Am J Gastroenterol 2008;103:2031-2035.

95. Camilleri M. Novel pharmacology: asimadoline, a kappa-opioid agonist, and visceral sensation. Neurogastroenterol Motil 2008;20:971-979.

96. Mangel AW, Bornstein JD, Hamm LR, et al. Clinical trial: asimadoline in the treatment of patients with irritable bowel syndrome. Aliment Pharmacol Ther 2008;28:239-249.

97. Tack JF, Harris MS, Proksch S, Bornstein JD, Miner PB. S1298 AST-120 (spherical carbon adsorbent) improves pain and bloating in a randomized, double-blind, placebo-controlled trial in patients with non-constipating irritable bowel syndrome (IBS). Gastroenterology 2010;138(5 Suppl 1):S223.

98. Sweetser S, Camilleri M, Linker Nord SJ, et al. Do corticotropin releasing factor-1 receptors influence colonic transit and bowel function in women with irritable bowel syndrome? Am J Physiol Gastrointest Liver Physiol 2009;296:G1299-G1306.

99. Dukes GE, Mayer EA, Kelleher DL, Hicks KJ, Boardley RL, Alpers DH. A randomised, double blind, placebo controlled, crossover study to evaluate the efficacy and safety of the CRF1 receptor antagonist GW876008 in irritable bowel syndrome patients. Neurogastroenterol Motil 2009;21(Suppl):84.

100. Mangel AW, Chaturvedi P. Evaluation of crofelemer in the treatment of diarrhea-predominant irritable bowel syndrome patients. Digestion 2008;78:180-186.

101. Leventer SM, Raudibaugh K, Frissora CL, et al. Clinical trial: dextofisopam in the treatment of patients with diarrhoea-predominant or alternating irritable bowel syndrome. Aliment Pharmacol Ther 2008;27:197-206.

102. Brown P, Riff DS, Jackson J, et al. 907 LX1031, a novel locally-acting inhibitor of serotonin (5-HT) synthesis significantly improves symptoms in patients with IBS. Gastroenterology 2010;138(5 Suppl 1):S129.

103. Talley NJ. Pharmacologic therapy for the irritable bowel syndrome. Am J Gastroenterol 2003;98:750-758.

104. Darvish-Damavandi M, Nikfar S, Abdollahi M. A systematic review of efficacy and tolerability of mebeverine in irritable bowel syndrome. World J Gastroenterol 2010;16:547-553.

105. Poynard T, Regimbeau C, Benhamou Y. Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. Aliment Pharmacol Ther 2001;15:355-361.

106. Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. Ann Intern Med 2000;133:136-147.

107. Goulding MR. Inappropriate medication prescribing for elderly ambulatory care patients. Arch Intern Med 2004;164:305-312.

108. Ford AC, Talley NJ, Schoenfeld PS, Quigley EM, Moayyedi P. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. Gut 2009;58:367-378.

109. Lesbros-Pantoflickova D, Michetti P, Fried M, Beglinger C, Blum AL. Meta-analysis: the treatment of irritable bowel syndrome. Aliment Pharmacol Ther 2004;20:1253-1269.

110. Gorard DA, Libby GW, Farthing MJ. Influence of antidepressants on whole gut and orocaecal transit times in health and irritable bowel syndrome. Aliment Pharmacol Ther 1994;8:159-166.

111. Brennan BP, Fogarty KV, Roberts JL, Reynolds KA, Pope HG Jr, Hudson JI. Duloxetine in the treatment of irritable bowel syndrome: an open-label pilot study. Hum Psychopharmacol 2009;24:423-428.

112. Chial HJ, Camilleri M, Ferber I, et al. Effects of venlafaxine, buspirone, and placebo on colonic sensorimotor functions in healthy humans. Clin Gastroenterol Hepatol 2003;1:211-218.

113. Kong SC, Hurlstone DP, Pocock CY, et al. The Incidence of self-prescribed oral complementary and alternative medicine use by patients with gastrointestinal diseases. J Clin Gastroenterol 2005;39:138-141.

114. van Tilburg MA, Palsson OS, Levy RL, et al. Complementary and alternative medicine use and cost in functional bowel disorders: a six month prospective study in a large HMO. BMC Complement Altern Med 2008;8:46.

115. Borowiec AM, Fedorak RN. The role of probiotics in management of irritable bowel syndrome. Curr Gastroenterol Rep 2007;9:393-400.

116. Moayyedi P, Ford AC, Talley NJ, et al. The efficacy of probiotics in the treatment of irritable bowel syndrome: a systematic review. Gut 2010;59:325-332.

117. Brenner DM, Moeller MJ, Chey WD, Schoenfeld PS. The utility of probiotics in the treatment of irritable bowel syndrome: a systematic review. Am J Gastroenterol 2009;104:1033-1049.

118. O'Mahony L, McCarthy J, Kelly P, et al. Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. Gastroenterology 2005;128:541-551.

119. Whorwell PJ, Altringer L, Morel J, et al. Efficacy of an encapsulated probiotic Bifidobacterium infantis 35624 in women with irritable bowel syndrome. Am J Gastroenterol 2006;101:1581-1590.

120. Bian Z, Wu T, Liu L, et al. Effectiveness of the Chinese herbal formula TongXieYaoFang for irritable bowel syndrome: a systematic review. J Altern Complement Med 2006;12:401-407.

121. Hills JM, Aaronson PI. The mechanism of action of peppermint oil on gastrointestinal smooth muscle: an analysis using patch clamp electrophysiology and isolated tissue pharmacology in rabbit and guinea pig. Gastroenterology 1991;101:55-65.

122. Hawthorn M, Ferrante J, Luchowski E, Rutledge A, Wei XY, Triggle DJ. The actions of peppermint oil and menthol on calcium channel dependent processes in intestinal, neuronal and cardiac preparations. Aliment Pharmacol Ther 1988;2:101-118.

123. Pittler MH, Ernst E. Peppermint oil for irritable bowel syndrome: a critical review and metaanalysis. Am J Gastroenterol 1998;93:1131-1135.

124. Spanier JA, Howden CW, Jones MP. A systematic review of alternative therapies in the irritable bowel syndrome. Arch Intern Med 2003;163:265-274.

125. Ford AC, Talley NJ, Spiegel BM, et al. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. BMJ 2008;337:a2313.

126. Merat S, Khalili S, Mostajabi P, Ghorbani A, Ansari R, Malekzadeh R. The effect of enteric-coated, delayed-release peppermint oil on irritable bowel syndrome. Dig Dis Sci 2010;55:1385-1390.

127. Bensoussan A, Talley NJ, Hing M, Menzies R, Guo A, Ngu M. Treatment of irritable bowel syndrome with Chinese herbal medicine: a randomized controlled trial. JAMA 1998;280:1585-1589.

128. Liu JP, Yang M, Liu YX, Wei ML, Grimsgaard S. Herbal medicines for treatment of irritable bowel syndrome. Cochrane Database Syst Rev 2006;(1):CD004116.

129. Saito YA, Rey E, Almazar-Elder AE, et al. A randomized, double-blind, placebo-controlled trial of St John's wort for treating irritable bowel syndrome. Am J Gastroenterol 2010;105:170-177.

130. Fireman Z, Segal A, Kopelman Y, Sternberg A, Carasso R. Acupuncture treatment for irritable bowel syndrome: a double-blind controlled study. Digestion 2001;64:100-103.

131. Forbes A, Jackson S, Walter C, Quraishi S, Jacyna M, Pitcher M. Acupuncture for irritable bowel syndrome: a blinded placebo-controlled trial. World J Gastroenterol 2005;11:4040-4044.

132. Schneider A, Enck P, Streitberger K, et al. Acupuncture treatment in irritable bowel syndrome. Gut 2006;55:649-654.

133. Lembo AJ, Conboy L, Kelley JM, et al. A treatment trial of acupuncture in IBS patients. Am J Gastroenterol 2009;104:1489-1497.

134. Saito YA, Schoenfeld P, Locke GR 3rd. The epidemiology of irritable bowel syndrome in North America: a systematic review. Am J Gastroenterol 2002;97:1910-1915.

135. Talley NJ, Zinsmeister AR, Melton LJ 3rd. Irritable bowel syndrome in a community: symptom subgroups, risk factors, and health care utilization. Am J Epidemiol 1995;142:76-83.

136. Talley NJ, Zinsmeister AR, Van Dyke C, Melton LJ 3rd. Epidemiology of colonic symptoms and the irritable bowel syndrome. Gastroenterology 1991;101:927-934.

137. Guilera M, Balboa A, Mearin F. Bowel habit subtypes and temporal patterns in irritable bowel syndrome: systematic review. Am J Gastroenterol 2005;100:1174-1184.

138. Systematic review on the management of irritable bowel syndrome in the European Union. Eur J Gastroenterol Hepatol 2007;19 Suppl 1:S11-S37.

139. Gwee KA, Bak YT, Ghoshal UC, et al. Asian consensus on irritable bowel syndrome. J Gastroenterol Hepatol 2010;25:1189-1205.

140. Gwee KA, Lu CL, Ghoshal UC. Epidemiology of irritable bowel syndrome in Asia: something old, something new, something borrowed. J Gastroenterol Hepatol 2009;24:1601-1607.