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IRRITABLE BOWEL SYNDROME: A SYSTEMATIC REVIEW

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Irritable bowel syndrome (IBS) is one of the most common conditions that is encountered in general medical practices [1,2]. It has the potential for protean manifestations, but generally is characterized by abdominal pain, bloating, and disturbed defecation. Based upon survey data from the general population, the prevalence of symptoms that are suggestive of IBS is between 14% and 24% in women and from 5% and 19% in men in the United States and Britain [3]. Although it is clear that symptoms that are suggestive of IBS are common, only a quarter of symptomatic patients seek medical advice for their symptoms [4]. Despite this observation, it was estimated that IBS is responsible for approximately 2.4 to 3.5 million physician visits per year and represents 12% of primary care visits and 28% of referrals to gastroenterologists [5].

IBS negatively impacts upon the quality of life (QOL) of affected individuals. Recent studies indicate that the QOL in patients who have IBS in the United States is worse than that of the general U.S. population and is similar to that of patients who have any of several significant medical conditions, including clinical depression [6]. Moreover, patients who have IBS are much more likely to exhibit health care–seeking behaviors that are

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related to gastrointestinal (GI) and non-GI complaints. Consultations for non-GI problems are four times more common in this population compared with patients who do not have IBS [7].

The annual economic consequences of IBS in the United States are substantial. A recent study found that patients who have IBS account for greater health care expenditures than patients who do not have IBS [8]. It was estimated that IBS accounts for approximately $1.7 to $10 billion in annual direct medical costs per year [9]. In addition to costs from physician visits, diagnostic testing, and treatment, women who have IBS are more than twice as likely as women who do not have IBS to undergo abdominal or pelvic surgery [10]. These surgical procedures frequently are performed in a misguided attempt to improve symptoms that are the consequence of IBS. Another $10 to $20 billion in indirect costs as a consequence of work absenteeism and decreased productivity can be attributed to IBS each year [8,11]. IBS represents a leading cause of work absenteeism and is equivalent to the leading cause, the common cold [12].

PATHOPHYSIOLOGY

IBS likely represents the common clinical expression of multiple potential pathophysiologic factors. Potential factors that contribute to IBS include a genetic predisposition to the condition, disturbed central nervous system pain processing and visceral hypersensitivity, mucosal inflammation, abnormal colonic motility, and emotional stress. It is likely, given the degree of variation of IBS symptoms in affected patients, that the etiology of IBS is actually a heterogeneous combination of these factors, as well as other mechanisms that remain to be elucidated.

Genetic Predisposition

It is not uncommon for patients who have suspected IBS to describe similar symptoms, if not the diagnosis, of IBS in family members. This observation gave rise to several studies that evaluated the possible role of a genetic predisposition for IBS. Although these studies do seem to support a genetic contribution to IBS, the basis of this contribution remains unknown. Some investigators hypothesized that differences in inherited patterns of serotonin processing at the neuronal level may play a role [13]. Studies from Olmstead County, Minnesota demonstrated that IBS is more common in patients who have a first degree relative who has IBS symptoms [14,15]. Such observational studies, although interesting, do not help us to understand the relative contribution of "nature versus nurture". Levy and colleagues [16] observed that IBS was more common in monozygotic twins than in dizygotic twins. They also observed that the presence of a parent who had IBS was even more predictive for the subsequent development of IBS, a finding that lends credence to the theory that IBS may have a significant learned or behavioral component.

Altered Motility

For many years, investigators focused on the role of abnormal motility in the pathogenesis of IBS. Numerous motility abnormalities that affect the GI tract have been identified in patients who have IBS. For example, patients who have a predominant symptom of diarrhea seem to have accelerated whole gut and colonic transit times [17–19]. Conversely, patients who have constipation-predominant IBS demonstrate decreased migrating motor complexes compared with controls who did not have IBS [20]. Whether these motility changes are primary or secondary to another potential etiology of IBS remains to be proven. The degree of variability in the observed results and the methodologic limitations of previous trials of colonic motility highlight the need for additional evidence in this area. Currently, motility studies are not recommended for use as diagnostic markers or therapeutic guides for patients who have IBS.

Visceral Hypersensitivity and Brain-gut Interactions

Pain is a central requirement of the definition and diagnosis of IBS. Over the past 20 years, the potential roles of heightened visceral sensation, also referred to as "visceral hypersensitivity," and abnormalities in brain-gut interactions also were implicated in the pathogenesis of IBS. Several investigators have reported a heightened visceral sensation in response to rectal balloon distention in patients who had IBS and other functional GI disorders. In addition, recent work using positron emission tomography scanning and functional MRI identified abnormalities in brain activation in patients who had IBS versus controls [21,22]. Abnormalities have been identified consistently in the activation of the anterior cingulate cortex which likely plays an important role in the development of attention to a painful stimulus, the unpleasantness associated with a painful stimulus, and the attribution of an emotional response to a painful stimulus. The anterior cingulate cortex also plays an important role in the activation of descending inhibitory pathways that help to gate or control the passage of afferent information from the periphery to the brain.

Our understanding of the enteric nervous system and the role that abnormalities in the enteric nervous system may play in patients who have IBS continues to evolve. The enteric nervous system functions semi-autonomously but can be modulated by input from the autonomic nervous system. In this way, the enteric nervous system plays a critical role in modulation of GI motility and secretory function. Evolving evidence has implicated several neuromodulators, including serotonin, in the normal function of the enteric nervous system [23].

Mucosal Inflammation

Gastrointestinal infection with its consequent mucosal inflammation seems to play a role in the etiology of IBS in a subset of patients. Several

groups have reported that up to one third of individuals who suffered with a case of bacterial enteritis go on to develop more chronic GI symptoms. More recent observations suggest that the percentage of patients who develop "postinfectious" IBS probably is substantially less than 33% [24]. Nonetheless, there is doubt that this condition is a real entity. Recent research has identified abnormalities in immune function in a subset of patients with IBS. Most patients who develop IBS after an enteric infection will suffer with diarrhea-predominant symptomatology. In such patients, abnormalities in intestinal permeability, gut transit, and the numbers and function of immune cells have been proposed [24]. It is likely that postinfectious IBS is one of many disorders that leads to chronic inflammation of the GI tract and in this fashion, causes symptoms that are suggestive of IBS.

Emotional Stress

Several groups have determined that psychosocial stress alters GI motor function and sensation [25,26]. In this way, psychosocial stressors likely exacerbate GI symptoms in patients who have functional GI disorders. Anxiety disorders, somatoform disorders, or a history of physical or sexual abuse can be identified in approximately 42% to 61% of patients who have IBS in referral practices [27–29]. In particular, several studies suggested that the presence of somatization is particularly common and likely influences outcomes in patients who have IBS [30,31]. The role of emotional stress as an etiologic factor in the development of IBS symptoms also may be inferred from the effects of psychologic therapies on IBS symptoms (see later discussion).

DIAGNOSIS

For a variety of reasons, clinicians often struggle to arrive at a confident diagnosis of IBS. The differential diagnosis in patients who have symptoms that are suggestive of IBS is broad and there is no reliable biologic marker for this condition. Box 1 chronicles the differential diagnosis for abdominal pain and disturbed defecation [32]. As such, IBS is viewed more often as a "diagnosis of exclusion" than as a primary diagnosis. Over the past 30 years, several groups have attempted to develop symptom-based criteria to guide researchers and clinicians in identifying patients who have IBS. Multiple symptom-based criteria have been developed, including the Manning, Rome I, and Rome II criteria (Table 1) [33–35]. In particular, the Rome I and Rome II criteria, developed by multinational working groups, provide a uniform framework for the selection of patients in diagnostic and therapeutic trials of IBS.

In recent years, the application of these criteria to patients in clinical practice has been encouraged [35,36]. Studies found that the Rome II criteria are specific for IBS and have the advantage of being easier to recall and use than the older Rome I criteria [37]. Recent evidence

Box 1. Differential Diagnosis of Abdominal Pain and Disturbed Defecation

Irritable bowel syndrome
Celiac disease
Inflammatory bowel disease
  Crohn's disease
  Ulcerative colitis
  Proctitis
  Microscopic/collagenous colitis
Infectious
  Bacterial
  Viral
  Protozoal
  Parasitic
  Small intestinal bacterial overgrowth
Endocrinopathy
  Addison's disease
  Hyper/hypothyroidism
  Diabetes mellitus
Malabsorption
  Lactose intolerance
  Celiac disease
  Pancreatic insufficiency
Medications
  Laxatives
  Narcotics
  Antacids
Malignancy
  Colorectal
  Endocrinologic/amine precursor uptake decarboxylation (APUD)
  Metastatic
Diverticular disease
Postoperative
  Postgastrectomy syndromes
  Short gut syndrome
Psychiatric disorders
  Panic disorder
  Somatization disorder
  Depression

Data from Cash BD, Chey WD. Irritable bowel syndrome: an evidence-based management approach. Journal of Clinical Outcomes Management 2002;9(7):410.

suggests, however, that the Rome II criteria may not be as sensitive as the Rome I criteria, largely because of the more restrictive temporal pain requirement that is associated with Rome II [38,39]. For the clinician, this means that patients who fulfill IBS criteria are likely to suffer with IBS. Many patients who do not fulfill the criteria still ultimately end up with a diagnosis of IBS.

TABLE 1.
Symptom-based Criteria for the Diagnosis of Irritable Bowel Syndrome

Manning Criteria	Rome I Criteria	Rome II Criteria
Abdominal pain relieved by defecation	At least 12 weeks of continuous or recurrent symptoms of the following:	At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two of the three features:
Looser stools with the onset of pain	Abdominal pain or discomfort: Relieved with defecation, or Associated with a change in frequency of stool, or Associated with a change in consistency of stool	Relieved with defecation or
More frequent stools with the onset of pain	Two or more of the following, at least on one fourth of occasions or days: Altered stool frequency, or Altered stool form, or Altered stool passage, or Passage of mucus, or Bloating or feeling of abdominal distention	Onset associated with a change in frequency of stool or
Abdominal distension		Onset associated with a change in form (appearance) of stool
Passage of mucus in stools Sensation of incomplete evacuation		

Data from Refs. [34–36].

The Role of Diagnostic Testing

The Rome Committee on Functional Gastrointestinal Disorders and many IBS authorities recommend that selected diagnostic tests be performed as a part of the routine evaluation of patients who have suspected IBS [40,41]. These tests include serum and stool studies and direct colonic visualization by way of colonoscopy in the hopes of excluding important organic GI diseases [42]. Recently, the necessity of performing a standardized series of tests in patients who have suspected IBS was questioned [43].

The performance of a diagnostic test should shift the clinician's estimate of pretest probability of a disease so that s/he may be assured reasonably that the disease being considered is either present or absent (Table 2) [43]. In the case of IBS, diagnostic tests are performed to exclude organic diseases that may have similar presenting symptoms and in so doing, to reassure the clinician and patient that the diagnosis of IBS is correct. Inflammatory bowel disease (IBD), colorectal cancer, systemic hormonal disturbances, enteric infections, and malabsorptive diseases are of greatest concern to the clinician who is faced with a patient who has symptoms that are suggestive of IBS.

A recent systematic review of the English language literature regarding commonly-used diagnostic tests for IBS was performed [43]. This review included clinical trials that were published between 1980 and 2001 that enrolled patients who fulfilled symptom-based criteria for IBS and who underwent diagnostic testing. After applying established criteria for quality and validity of trials about diagnosis [44], six studies fulfilled inclusion criteria [45–50]. A review of these studies suggested that the pretest probability of organic disorders, including colon cancer, IBD, thyroid disease, and lactose malabsorption, was not different between patients who were suspected of having IBS and the general population. When patients fulfilled symptom-based criteria for IBS, performance of commonly-recommended tests, including endoscopic evaluation of the colon, a complete blood cell count, comprehensive serum chemistry panels, stool ova and parasite testing, fecal occult blood testing, thyroid function test screening, and hydrogen breath tests for lactose intolerance, were unlikely to lead to the diagnosis of organic GI diseases. One possible exception was celiac disease, which seemed to be more common in patients who had suspected IBS than in age- and gender-matched controls. This single study was conducted in a referral setting with a homogeneous population. Thus, the results require replication in the United States before recommending routine testing for celiac disease in patients who have suspected IBS. The absence of compelling evidence to pursue a detailed

TABLE 2.
Pretest Probability of Organic Gastrointestinal Disease in Patients Who Meet Symptom-based Criteria for Irritable Bowel Syndrome

Organic GI Disease	Patients who have IBS (Pretest Probability)	General Population (Prevalence)
Colitis/IBD	0.51–0.98%	0.3–1.2%
Colorectal cancer	0–0.51%	4–6%
Gastrointestinal infection	0–1.7%	N/A
Thyroid dysfunction	6%	5–9%
Lactose malabsorption	22–26%	25%

Data from Cash BD, Schoenfeld PS, Chey WD. The utility of diagnostic tests in irritable bowel syndrome patients: a systematic review. Am J Gastroenterol 2002;97:2812–19.

diagnostic evaluation in patients who have suspected IBS does not address the potential "reassurance value" of a negative evaluation. Such a response has been demonstrated with other functional GI conditions, such as dyspepsia [51,52], but has not been shown with IBS.

There is a broad consensus that the presence of "alarm" features of GI symptomatology should prompt an appropriate, complete, and directed evaluation. Such features include the onset of new GI symptoms in patients who are older than age 50; unexplained weight loss; progressive or unrelenting abdominal pain; symptoms that awaken the patient at night; a family history of colon cancer; and stool characteristics, such as fasting diarrhea or large volume diarrhea (greater than 300 mL/d).

The choice of detailed diagnostic testing in those patients with refractory symptoms or alarm features is dictated by the patient's predominant symptoms. Celiac disease antibody testing, with antiendomysial or tissue transglutaminase serum antibody tests may be useful, particularly in patients who have prominent complaints of abdominal bloating and loose stools. In most patients who have suspected IBS based upon symptom-based criteria, the clinician can feel comfortable about proceeding to therapeutic interventions without performing an exhaustive medical evaluation. These recommendations do not negate the need for colorectal cancer screening in all individuals who are older than 50 years.

TREATMENT

There is no single consistently successful therapeutic approach for patients who have IBS. Because IBS typically is a chronic condition, the goals of therapy should focus on patient reassurance, education about the syndrome, and symptom improvement, rather than on disease cure. This is best achieved through a well-developed patient-physician relationship with a clear delineation of realistic goals and expectations. Table 3 presents a general therapeutic approach to IBS and specific agents, depending upon the predominant IBS symptom subtype that is encountered.

Most patients who have IBS (ie, those who have mild symptoms and minimal impairment) can be managed at the primary care level. Fewer than 25% of patients who have IBS have more severe symptoms with significant lifestyle impairment and require management by a gastroenterologist. Finally, approximately 5% of patients who have IBS have such severe and incapacitating symptoms that they require referral to a center with multispecialty capability [4].

Dietary Therapy

Supplemental dietary fiber increases stool weight and decreases colonic transit time. For the last 20 to 25 years, fiber has been considered widely to be the first-line agent for treatment of IBS. Although fiber seems to ameliorate constipation symptoms in some patients, the ability of dietary fiber to alleviate abdominal pain and diarrhea has been disappointing.

TABLE 3.
Serotonergic Agents: Differences Between Alosetron and Tegaserod

	Alosetron	Tegaserod
Mechanism	5-HT_3 antagonist	5-HT_4 agonist
Indication	Women who have IBS and diarrhea	Women who have IBS and constipation
Dosage	1 mg qd to bid	6 mg bid
Therapeutic gain versus placebo	17%	8%
	27%	13%
	12%	5%
	16%	19%
Side effects	Constipation	Diarrhea
	Ischemic colitis	Headache

Data from Refs. [32,76–79,84–87].

Multiple randomized, controlled trials have failed to show any convincing benefit from fiber supplementation for the multiple symptoms of IBS [53–55]. For the most part, these studies reported similar degrees of symptomatic improvement between experimental and control populations. In addition, symptomatic improvement did not correlate to altered colonic motility or changes in stool weight.

Patients who have IBS frequently relate their symptoms to the ingestion of certain foods or food groups. Multiple trials have examined the role of dietary exclusion as a treatment for IBS. A systematic review of the available trials that examined dietary exclusion concluded that such an approach did not seem to benefit most patients who had IBS [56]. The methodology of the included trials varied widely as did the results of individual studies; this may dilute any true treatment effects of such an approach. Major limitations to all of the dietary exclusion trials included the failure to use formal symptom criteria to identify patients who had IBS, serious methodologic flaws, and variable duration of exclusion diets and food challenges. There is no convincing evidence that the routine use of exclusion diets (eg, lactose-reduced or gluten-free diets) consistently benefits patients who have IBS. Nonetheless, if a careful dietary history uncovers the excessive intake of specific foods (eg, fatty foods; caffeine; fruits or other foods that contain poorly-digestible carbohydrates, including lactose, sorbitol or fructose) or if there is a clear association between symptoms and certain foods, then simple dietary advice is inexpensive and harmless and may result in a reduction in symptoms in a subset of patients who have IBS.

Pharmacologic Therapies

In 2002, a systematic review and clinical practice guideline for the management of IBS was published by the American College of Gastroenterology (ACG) [57]. This document largely conformed to evidence-based

medicine criteria for a systemic review [58] and critically assessed and graded the various treatment approaches for IBS. According to this document, traditional therapies, including bulking agents, antidiarrheals, antispasmodics, and behavioral therapy, were believed to be effective for individual IBS symptoms, but have not been shown to improve global IBS symptoms reliably. The presence of serious methodologic flaws complicates the interpretation of data from most of the older studies that evaluated these therapies. Because the quality of clinical trials in IBS has improved in recent years, there is emerging evidence to suggest that some therapies are of benefit to certain subsets of patients who have IBS [59,60]. Based upon the results of high-quality clinical trials, the ACG document reported that alosetron and tegaserod were the only agents that had proven efficacy for the treatment of IBS.

Antidiarrheals and Laxatives

Commonly-used antidiarrheals in the United States include opiate derivatives and cholestyramine. Of the opiate derivatives, loperamide is favored over diphenoxylate in patients who have chronic symptoms because it penetrates the blood–brain barrier poorly and therefore, has little to no potential for addiction.

The only antidiarrheal agent that has been evaluated for IBS is loperamide. Three randomized controlled trials evaluated the use of loperamide for symptom relief in patients who had IBS [61–63]. All of these trials had significant methodologic limitations, including differences in the way patients who had IBS patients were defined, short duration of therapy, and small sample sizes. These trials indicated that although loperamide was an effective treatment for diarrhea, it did not relieve abdominal pain or improve global IBS symptoms consistently.

Osmotic (eg, magnesium citrate, milk of magnesia, sodium phosphate, polyethylene glycol, lactulose, sorbitol) and stimulant (eg, senna, cascara, castor oil, diphenylmethane derivatives, docusate sodium, mineral oil) laxatives are used widely to treat patients who have constipation-predominant IBS. No randomized controlled trials have assessed their effectiveness in these patients.

Antispasmodics

Antispasmodics (eg, anticholinergics, antimuscarinics, calcium channel blockers) are the medications that are prescribed most frequently for patients who have IBS. The rationale for the use of these medications is based upon their ability to relax smooth muscle in the GI tract, and, thus, reduce the contractile response that occurs as a result of stress or a meal. Several reviews reported that antispasmodic medications were more effective than placebo in patients who had IBS [64–66]. The meta-analysis by Poynard and colleagues [64] included 26 studies that examined similar end points, including global assessment, pain, constipation, distention, and

adverse reactions. The investigators determined that antispasmodics were superior to placebo for improving patients' global assessment and pain. This study found these benefits to hold true for medications that contained antimuscarinic, anticholinergic, and calcium channel blocker properties [64]. The U.S. Food and Drug Administration (FDA) has not approved any of the medications that were demonstrated to be more efficacious than placebo. In addition, the investigators pointed out that the studies that were included in their meta-analyses suffered from variable inclusion criteria, study end points, insufficient sample size, and other significant methodologic flaws.

The most commonly-prescribed antispasmodic agents in the United States are hyoscyamine (levsin) and dicyclomine (bentyl). Three small, randomized trials compared the effectiveness of these drugs with placebo in patients who had IBS. All of the studies had significant methodologic flaws; only one study [68] demonstrated a benefit of dicyclomine, 40 mg four times/d, over placebo in a 2-week trial [67–69].

Another meta-analysis reported that peppermint was superior to placebo for improvements in global IBS symptoms, probably because of its calcium channel blocker properties [66]. Although over-the-counter preparations of peppermint are available in the United States, the use of peppermint oil in clinical practice is limited by the development of symptomatic acid reflux in up to one third of treated patients.

Antidepressants

Because of the associations among psychologic distress, abnormalities in visceral sensation, and IBS, antidepressants are a potentially attractive treatment option in patients who have moderate to severe symptoms. A recent meta-analysis reported that tricyclic antidepressants (TCAs) significantly reduced abdominal pain and diarrhea in patients who had diarrhea-predominant IBS [31]. In this meta-analysis, TCAs yielded a number-needed-to-treat (NNT) of three and were effective at dosages that were lower than typically are used to treat depression. The studies that are included in this meta-analysis contained serious methodologic flaws that limit the ability to generalize the results to routine community practice.

The first high-quality randomized controlled trial that compared the efficacy of the TCA, desipramine (norpramin), with placebo sends a mixed message regarding the usefulness of TCAs for patients who have IBS [60]. The intention-to-treat analysis failed to show a statistically significant improvement in a composite symptom scale between the groups who were given desipramine and placebo (60% versus 47%, $P = 0.13$). This was largely due to the patients (28%) who did not complete the trial. The most commonly-cited reason for patient drop-out was adverse drug effects. There also were several patients who had undetectable serum levels of desipramine, despite reporting medical compliance. When these patients were excluded from the analysis, the use of desipramine resulted in a statistically significant benefit compared with placebo (73% versus 49%,

$P = 0.006$, NNT = 4). This trial tells us that patients who can tolerate TCAs are likely to experience symptomatic benefit; however, many patients experience unacceptable side effects. It also confirms previous findings that the risk/benefit ratio that is associated with TCAs is most favorable in patients who have with persistent, moderate to severe symptoms [70].

Few studies have addressed the potential role of selective serotonin reuptake inhibitors (SSRIs) in the treatment of IBS. Despite the lack of evidence, many clinicians routinely use SSRIs in patients who have functional GI complaints, presumably related to their proven efficacy for the treatment of anxiety and depression, beneficial effects on the treatment of somatic pain, and better tolerability when compared with TCAs. Several uncontrolled trials reported some symptomatic benefit from SSRIs in patients who had a variety of functional GI disorders [70–73].

Recent randomized, double-blind trials reported differing effects of venlafaxine (effexor) or fluoxetine (prozac) on colonic sensorimotor function and symptomatology [74,75]. Venlafaxine increased colonic compliance, decreased the gastrocolonic response, and marginally reduced colonic sensation in healthy volunteers [74]. In another trial that involved 40 patients who had IBS, fluoxetine did not significantly alter rectal sensation or reduce abdominal pain or global symptoms compared with placebo [75].

In a third study from the United Kingdom, 257 patients who had severe IBS were randomized to 12 weeks of active treatment with paroxetine (paxil) at a dosage of 20 mg/d, psychotherapy, or usual care by their gastroenterologists or general practitioners [59]. Individual therapies that were contained within the "usual care" were not defined by the investigators, but antidepressant agents and psychotherapy were prohibited in this group during the active treatment part (initial 12 weeks) of the study. At the end of 12 weeks of treatment, the group that was given paroxetine experienced a small, but significant, reduction in the number of days with abdominal pain compared with baseline ($P = 0.014$). Paroxetine also led to small improvements in QOL, that predominantly were related to effects on psychologic distress and social disability due to emotional problems and fatigue. Only 50% of patients in the group that received SSRIs completed the 12-week treatment.

The available data do not send a clear mandate for the use of SSRIs in the treatment of patients who have IBS. It makes intuitive sense that SSRIs are likely to be of most benefit in patients who have comorbid psychiatric illness, but it remains unclear as to whether these agents offer any benefit in the absence of concomitant psychiatric conditions. Further appropriately-designed and adequately-powered studies are necessary to settle this important issue.

Serotonergic Agents

Over the past decade, our understanding of the enteric nervous system, the afferent pathways that are responsible for the sensation of visceral pain, and the cortical centers that are responsible for the processing and perception of peripheral stimuli has expanded rapidly. There is

complex bidirectional communication between the cerebral cortex and the enteric nervous system (so-called "brain–gut interactions") that influences GI function and sensation. In recent years, serotonin was found to be an important neurotransmitter in the enteric nervous system, spinal cord, and brain. Specifically, serotonin type-3 (5-HT_3) receptors and serotonin type-4 (5-HT_4) receptors that are found on visceral sensory neurons and within the enteric nervous system play an important, integrated role in the reflexes that control GI sensation, motility, and secretion [76].

Serotonin Type-3 Receptor Antagonists

The expanding recognition of the role of serotonin in the GI tract led to the development of specific 5-HT_3 receptor antagonists for the treatment of IBS. Several 5-HT_3 receptor antagonists, including ondansetron (zofran), granisetron (kytril), and alosetron (lotronex), are commercially available in the United States. Of the available 5-HT_3 receptor antagonists, alosetron is the most potent antagonist; it is 10 times more potent than ondansetron and is the only agent that is FDA-approved for the treatment of women who have severe IBS and a predominant complaint of diarrhea. Another 5-HT_3 receptor antagonist, cilansetron, is currently in phase III trials within the United States.

Alosetron was developed to address specifically several pathophysiologic factors that are important to IBS. Alosetron has effects on visceral sensation, slows colonic transit, and decreases chloride and water secretion, all of which are potentially attractive features in patients who have IBS and diarrhea. [77,78].

Several large, high-quality, randomized, parallel-group, double-blind 12-week trials assessed the efficacy of alosetron versus placebo in patients who had IBS and a predominant symptom of diarrhea (see Table 3) [77–80]. Alosetron, 1 mg twice daily, improved the primary outcome measures of abdominal pain or discomfort [77–79] and fecal urgency [80]. Stool consistency and frequency also significantly improved with alosetron. The one trial that assessed global IBS symptoms reported a significantly greater improvement with alosetron than with placebo (76% versus 44%, $P < 0.001$) [80]. A fifth randomized trial from Europe compared alosetron to the antispasmodic mebeverine (colofac); alosetron was superior for IBS symptom relief [81]. Another study reported that overall satisfaction with therapy was significantly greater with alosetron than placebo (69% versus 46%, $P < 0.001$) [82].

Between 22% and 39% of patients who had IBS and were randomized to alosetron reported constipation as an adverse event. In the clinical trials, constipation was severe enough to cause the discontinuation of alosetron in 10% of patients. Approximately 1 in 1000 patients who reported constipation developed a serious complication, such as obstruction, perforation, impaction, toxic megacolon, or in a few rare instances, death [83]. In addition, several cases of possible ischemic colitis were reported in the clinical trials. It was estimated that 3 per 1000 patients (95% confidence

interval, 1–4) who were treated with alosetron for 6 months developed ischemic colitis. During the brief time that alosetron was commercially available, the FDA recorded 113 cases of severe constipation and 80 cases of possible ischemic colitis. An explanation for the association between alosetron and ischemic colitis remains elusive. Elderly patients may be more susceptible to adverse events in association with alosetron. To what degree improper patient selection played a role in the development of these serious adverse events remains unclear.

Alosetron was withdrawn voluntarily from the United States marketplace in December 2000; as a result of the public outcry that followed withdrawal of this drug, the availability of further safety data, and development of a detailed risk management plan with the manufacturer, the FDA reapproved alosetron for use in female patients who had severe diarrhea-predominant IBS who failed to respond to conventional therapy. Alosetron should not be used in patients who have any degree of constipation. Health care providers who prescribe alosetron must complete an educational module, use special identifying stickers on prescriptions, fully inform patients of the potential risks that are associated with the use of this medication, and obtain a signed patient-physician agreement stating that the patient understands the risks of taking this medication.

Serotonin Type-4 Agonists

The selective, partial 5-HT_4 agonist, tegaserod (zelnorm), is one of a new class of compounds called the aminoguanidine indoles. Structurally, tegaserod is similar to serotonin, which accounts for its agonist, or stimulatory activity, at the 5-HT_4 receptor. Tegaserod stimulates the release of calcitonin gene-related peptide from enteric neurons and promotes increases in GI peristalsis. It induces chloride and water secretion into the colonic lumen and may exert effects on visceral sensation [84]. Related to these physiologic effects, tegaserod is an attractive candidate medication for patients who have IBS and constipation. Box 2 highlights a comparison of mechanism of action, indication, dosage, side effects, and potential therapeutic gain versus placebo between alosetron and tegaserod.

In several large, well-designed, randomized, parallel-group, placebo-controlled 12-week clinical trials, tegaserod was shown to improve global IBS symptoms and the specific abdominal symptoms, such as pain, bloating, and constipation, that are found in female patients who have IBS and constipation [85–88]. As a consequence of these trials, tegaserod was approved by the FDA for use in women who have IBS and a predominant bowel complaint of constipation.

Largely because of safety concerns with other drugs that affect serotonin receptors, multiple trials that examined the safety of tegaserod were performed. Tegaserod has not been associated with any serious adverse effects or drug interactions. The most common adverse events that are associated with tegaserod are diarrhea and headache. The discontinuation rate because of diarrhea in the large, randomized, controlled trials ranged from 1% to 3%. Tegaserod-associated diarrhea usually occurs within the

Box 2. Symptom-Directed Therapies for Irritable Bowel Syndrome

Overall
- Education and reassurance
- Establishment of a therapeutic patient-physician relationship
- Dietary exclusion/modification aided by dietary and activity diaries

Pain-predominant
- Fiber supplementation (psyllium/ispaghula husk)
- Antispasmodic agents (dicyclomine/hyoscamine)
- Antidepressants (TCA or SSRI)
- Psychologic therapies/relaxation therapy
- Alternative medicine

Constipation-predominant
- Fiber supplementation (psyllium/ispaghula husk)
- Osmotic laxatives (magnesium citrate, milk of magnesia, sodium phosphate, polyethylene glycol, lactulose, sorbitol)
- Stimulant laxatives (senna, cascara, diphenylmethane derivatives, docusate sodium)
- SSRIs
- 5-HT_4 agonist (tegaserod)
- Psychologic therapies/relaxation therapy
- Alternative medicine

Diarrhea-predominant
- Opiate derivatives (diphenoxylate/loperamide)
- TCAs
- 5-HT_3 antagonist (alosetron)
- Bile acid binding resins (cholestyramine)
- Psychologic therapies/relaxation therapy
- Alternative medicine

Data from Refs. [77–80,83–88].

first week of initiating therapy and typically is self-limited. A recently completed trial in 579 patients who had IBS and constipation assessed the safety of tegaserod for 12 months and confirmed results from the 12-week clinical trials [89]. The most common adverse events reported in this trial included diarrhea (10%), headache (8%), abdominal pain (7%), and flatulence (6%).

Behavioral Therapies

Several behavioral-based therapies have been investigated as potential treatment options for IBS. Examples include cognitive-behavioral therapy, interpersonal psychotherapy, group therapy, biofeedback, and hypnosis. Most of these therapies have their basis in relaxation therapy and are directed toward correcting maladaptive coping skills that are believed to engender emotional stress, which may manifest as GI symptoms. Much

like the clinical trials of pharmacologic agents, significant methodologic flaws limited early behavioral therapy research. It was observed, however, that certain subgroups of patients who had IBS responded to behavioral therapy to a greater degree than others. These groups include patients who have intermittent abdominal pain, short symptom duration, personal insight as to the presence of depression or anxiety, and those who have a predominant symptom pattern of pain or diarrhea [37].

Several recent publications that evaluated the use of psychologic therapies in IBS represent significant advances in this body of literature. Palsson and colleagues [90] reported the results of studies that evaluated the role of hypnosis for IBS. These trials found that weekly hypnosis sessions, in combination with self-hypnosis techniques for 12 weeks, improved the symptoms of abdominal pain, bloating, and disturbed defecation, and psychologic parameters by way of somatization and anxiety scores, but did not alter rectal tone and pain threshold. Another study from the United Kingdom confirmed the effectiveness of hypnotherapy in 250 unselected patients who had IBS [91]. This study suggested that male patients who had diarrhea-predominant symptoms may not respond as well to hypnotherapy as other subgroups of patients who have IBS. Another study reported significant improvements in individual IBS symptoms after meditation and relaxation for a period of 3 months [92].

In a recently reported well-designed, randomized clinical trial, Drossman and colleagues [60] reported that cognitive behavioral therapy (CBT) significantly improved symptoms in patients who had moderate to severe IBS compared with education alone. In the intention-to-treat analysis, 70% of the group that underwent CBT responded compared with 37% in the education group ($P < 0.001$, NNT = 3). In this trial, current or recent depression predicted a worse response to CBT or therapy with desipramine.

The aforementioned trial by Creed and colleagues [59] also included a cost-effectiveness analysis that compared individual psychodynamic interpersonal therapy or paroxetine to usual care (not defined) for IBS. At 3 months, no difference in pain severity was observed between the groups that received psychotherapy or usual care. Psychotherapy led to a significant improvement in QOL that predominantly was related to effects on psychologic distress and social disability that were due to emotional problems and fatigue. Over a year, health care costs were less with psychotherapy; this was related largely to a reduction in the number of physician visits. Only patients from tertiary care centers were enrolled in the study; therefore, these patients may not be representative of the overall IBS population.

Although these trials support a role for behavioral therapies in IBS, the real-world effectiveness of such interventions depends upon motivated patients who can see beyond the stigma of pursuing psychotherapy and access to an appropriately-trained therapist. Of equal importance, coverage for mental health care services remains inconsistent among insurance carriers. Finally, most clinicians use antidepressants in combination with psychologic therapies. Trials that are designed to assess the incremental benefit of combined medical and psychologic therapies are awaited eagerly.

Alternative Therapies

Alternative medicine techniques, including acupuncture, probiotic therapy and Chinese herbal medicine, are becoming increasingly popular. Among GI diseases, IBS is the most common reason for the use of these alternative strategies [93]. A recent study from Australia reported that more than 20% of patients who had IBS or functional dyspepsia reported using alternative strategies for their GI complaints [94].

Previous reviews indicate that acupuncture affects the enteric nervous system and can alter GI motility, electrical activity, gastric secretion, and cytoprotection in animals and humans [95]. The proposed mechanism of action in IBS, similar to the pain-modifying qualities of acupuncture, is by way of afferent neural stimulation with consequent effects on the autonomic nervous system through opioid-dependent pathways. A recent study in patients who had IBS found that acupuncture resulted in small, but statistically significant, improvements in the patients' sense of well-being and bloating, but not in stool frequency or pain [96].

Probiotic bacteria may have anti-inflammatory effects on the GI mucosa. Small studies of 4 weeks' duration reported that *Lactobacillus plantarum* was superior to placebo for controlling abdominal pain and flatulence in patients who had IBS [97,98]. More recently, a randomized, controlled trial found that the probiotic supplement, VSL #3 (a powder containing multiple strains of live, freeze-dried lactic acid bacteria made and distributed by VSL Pharmaceuticals), improved bloating, but not global symptoms, pain, urgency, or transit in patients who had diarrhea-predominant IBS [99].

In a well-designed, randomized, controlled trial in Australian patients who had IBS, Chinese herbal medicine (either standardized or individualized) was more effective than placebo in improving GI symptoms and several QOL parameters [100]; however, the active ingredients that were responsible for these observed improvements are unknown. In addition, questions regarding product quality and purity remain. For these and other reasons, despite these promising preliminary results, more carefully designed and rigorously controlled human studies are needed before alternative therapies can be recommended routinely.

SUMMARY

IBS is a prevalent GI disorder of diverse pathophysiology. Recent guidelines have assessed and graded the evidence that supports various diagnostic approaches and therapeutic options for IBS. IBS can be diagnosed confidently through the identification of the appropriate symptoms and the exclusion of alarm features. Younger patients who fulfill symptom-based criteria for IBS and have no alarm features do not need to undergo exhaustive testing to exclude organic diseases. Preliminary evidence suggests that celiac disease may be more prevalent in patients who have suspected IBS, although this needs to be validated in appropriately

designed trials from North America before routine screening can be recommended. After the diagnosis of IBS has been established, management should focus on patient reassurance, education, and amelioration of symptoms. This is best achieved through a well-developed patient-physician relationship with a clear delineation of realistic goals and expectations. Medical therapies that target the predominant symptoms of diarrhea and constipation are appropriate first-line agents. Frequently, multiple therapies need to be tried in a stepwise manner before therapeutic success is achieved. More recently-developed therapies, including the serotonergic agents, that affect function of the enteric nervous system and visceral sensation, offer the possibility of addressing multiple symptoms in patients who have IBS. Psychologic therapies seem to offer benefit in appropriately-selected patients who have IBS. Alternative medicine techniques also may offer benefit to a subset of patients who have IBS; however, additional, adequately powered, well-designed studies in this area are needed.

Key Points

Diagnosis

- In the absence of alarm features, symptom-based criteria are sufficient to make a presumptive diagnosis of IBS—Evidence Level C.
- Serologic evaluations (complete blood counts, routine electrolytes and chemistries, thyroid function studies) cannot be recommended in the absence of alarm features confidently—Evidence Level C.
- Routine use of structural colonic evaluations (barium enema, sigmoidoscopy, colonoscopy, rectal biopsies) cannot be recommended in the absence of alarm features confidently—Evidence Level C.
- Among patients who have IBS with diarrhea, testing for celiac sprue may be considered confidently—Evidence Level C.

Therapy

- Bulking agents and antispasmodics are not more effective than placebo at relieving global IBS symptoms—Evidence Level B.
- Loperamide is not more effective than placebo at relieving global IBS symptoms—Evidence Level B.
- Tricyclic antidepressants are superior to placebo for abdominal pain and global IBS symptom relief—Evidence Level B.
- SSRIs are not more effective than placebo for abdominal pain and global IBS symptom relief—Evidence Level C.
- Tegaserod is more effective than placebo at relieving global IBS symptoms in female patients who have constipation-predominant IBS—Evidence Level A.
- Alosetron is more effective than placebo at relieving global IBS symptoms in female patients who have diarrhea-predominant IBS—Evidence Level A.
- Behavioral therapy is more effective than placebo at relieving global IBS symptoms—Evidence Level B.

References

[1] Longstreth GF, Wolde-Tsadik G. Irritable bowel-type symptoms in HMO examinees: prevalence, demographics and clinical correlates. Dig Dis Sci 1993;38:1581–9.
[2] Mitchell CM, Drossman DA. Survey of the AGA membership relating to patients with functional gastrointestinal disorders. Gastroenterology 1987;92:1282–4.
[3] Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: a technical review for practice guideline development. Gastroenterology 1997;112:2120–37.
[4] Drossman DA, Thompson WG. The irritable bowel syndrome: review and a graduated, multicomponent treatment approach. Ann Intern Med 1992;116:1009–16.
[5] Sandler RS. Epidemiology of irritable bowel syndrome in the United States. Gastroenterology 1990;99:409–15.
[6] Gralnek IM, Hays RD, Kilbourne A, et al. The impact of irritable bowel syndrome on health-related quality of life. Gastroenterology 2000;119:654–60.
[7] Drossman DA, Li Z, Andruzzi E, et al. US householder survey of functional GI disorders: prevalence, sociodemography, and health impact. Dig Dis Sci 1993;38:1569–80.
[8] Leong SA, Barghout V, Birnbaum HG, et al. The economic consequences of irritable bowel syndrome. A US employer perspective. Arch Intern Med 2003;163:929–35.
[9] American Gastroenterological Association. The burden of gastrointestinal diseases. Bethesda (MD): American Gastroenterological Association; 2001.
[10] Hasler WL, Schoenfeld P. Systematic review: abdominal and pelvic surgery in patients with irritable bowel syndrome. Aliment Pharmacol Ther 2003;17(8):997–1005.
[11] Martin R, Barron JJ, Zacker C. Irritable bowel syndrome: toward a cost-effective management approach. Am J Manag Care 2001;7(Suppl 8):S268–75.
[12] Camilleri M, Williams DE. Economic burden of irritable bowel syndrome. Lancet 1992;340:1447–52.
[13] Camilleri M, Atanasova E, Carlson PJ, et al. Serotonin-transporter polymorphism pharmacogenetics in diarrhea-predominant irritable bowel syndrome. Gastroenterology 2002;123(2):425–32.
[14] Locke GR III, Zinsmeister AR, Talley NJ, et al. Familial association in adults with functional gastrointestinal disorders. Mayo Clin Proc 2000;75(9):907–12.
[15] Kalantar JS, Locke GR III, Talley NJ, et al. Is irritable bowel syndrome more likely to be persistent in those with relatives who suffer from gastrointestinal symptoms? A population-based study at three time points. Aliment Pharmacol Ther 2003; 17(11):1389–97.
[16] Levy RL, Jones KR, Whitehead WE, et al. Irritable bowel syndrome in twins: heredity and social learning both contribute to etiology. Gastroenterology 2001;121(4):799–804.
[17] Bazocchi G, Ellis J, Villaneuva-Meyer J, et al. Colonic scintigraphy and manometry in constipation, diarrhea, and inflammatory bowel disease [abstract]. Gastroenterology 1988;94:A29.
[18] Cann PA, Read NW, Brown C, et al. Irritable bowel syndrome. Relationship of disorders in the transit of a single solid meal to symptom patterns. Gut 1983;24:405–11.
[19] Vassallo M, Camilleri M, Phillips SF, et al. Transit through the proximal colon influences stool weight in the irritable bowel syndrome. Gastroenterology 1992;102:102–8.
[20] Bazocchi G, Ellis J, Villaneuva-Meyer J, et al. Postprandial colonic transit and motor activity in chronic constipation. Gastroenterology 1990;98:686–93.
[21] Naliboff BD, Derbyshire SWG, Munakata J, et al. Cerebral activation in irritable bowel syndrome patients and control subjects during rectosigmoid stimulation. Psychosom Med 2001;63:365–75.
[22] Mertz H, Morgan V, Tanner G, et al. Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. Gastroenterol 2000;118:842–8.
[23] Wood JD. Enteric nervous system, serotonin and the irritable bowel syndrome. Curr Opin Gastroenterol 2001;17:91–7.
[24] Spiller RC. Postinfectious irritable bowel syndrome. Gastroenterol 2003;124:1662–71.
[25] Dickhaus B, Mayer EA, Firooz N, et al. Irritable bowel syndrome patients show enhanced modulation of visceral perception by auditory stress. Am J Gastroenterol 2003;98:135–43.

[26] Drossman DA, Lesserman J, Nachman G, et al. Sexual and physical abuse in women with functional or organic gastrointestinal disorders. Ann Intern Med 1990;113: 828–33.
[27] Walker EA, Gelfand AN, Gelfand MD, et al. Medical and psychiatric symptoms in female gastroenterology clinic patients with histories of sexual victimization. Gen Hosp Psychiatry 1995;17:85–92.
[28] Lesserman J, Drossman DA, Li Z, et al. Sexual and physical abuse history in gastroenterology practice: how types of abuse impact health status. Psychosom Med 1996;58:4–15.
[29] Miller AR, North CS, Clouse RE, et al. The association of irritable bowel syndrome and somatization disorder. Ann Clin Psychiatry 2001;13:25–30.
[30] Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? Gastroenterology 2002;122:1140–56.
[31] Jackson JL, O'Malley PG, Tomkins G, et al. Treatment of functional bowel gastrointestinal disorders with antidepressant medications: a meta-analysis. Am J Med 2000; 108:65–72.
[32] Cash BD, Chey WD. Irritable bowel syndrome: an evidence-based management approach. Journal of Clinical Outcomes Management 2002;9(7):409–18.
[33] Manning AP, Thompson WG, Heaton KW, et al. Towards a positive diagnosis of the irritable bowel syndrome. BMJ 1978;2:653–4.
[34] Thompson WG, Doteval G, Drossman DA, et al. Irritable bowel syndrome: guidelines for the diagnosis. Gastroenterology International 1989;2:92–5.
[35] Thompson WG, Longstreth GF, Drossman DA, et al. Functional bowel disorders and functional abdominal pain. Gut 1999;45(Suppl 2):43–7.
[36] Brandt LJ, Locke R, Olden K, et al. An evidence based approach to the diagnosis of irritable bowel syndrome in North America. Am J Gastroenterol 2002;97(Suppl 11): S1–26.
[37] Drossman DA, Camilleri M, Mayer EA, et al. AGA technical review on irritable bowel syndrome. Gastroenterology 2002;123:2108–31.
[38] Vanner SJ, Depew WT, Paterson WG, et al. Predictive value of the Rome criteria for diagnosing the irritable bowel syndrome. Am J Gastroenterol 1999;94:2912–17.
[39] Chey WD, Olden K, Carter E, et al. Utility of the Rome I and Rome II criteria for IBS in US women. Am J Gastroenterol 2002;97:2803–11.
[40] Drossman DA. An integrated approach to the irritable bowel syndrome. Aliment Pharmacol Ther 1999;13(Suppl 2):3–14.
[41] Camilleri M, Prather CM. The irritable bowel syndrome: mechanisms and a practical approach to management. Ann Intern Med 1992;116:1001–8.
[42] American Gastroenterological Association. American Gastroenterological Association medical position statement: irritable bowel syndrome. Gastroenterology 2002;123:2105–7.
[43] Cash BD, Schoenfeld PS, Chey WD. The utility of diagnostic tests in irritable bowel syndrome patients: a systematic review. Am J Gastroenterol 2002;97:2812–9.
[44] Lijmer JG, Mol BW, Heisterkamp S, et al. Empirical evidence of design-related bias in studies of diagnostic tests. JAMA 1999;282:1061–6.
[45] Hamm LR, Sorrells SC, Harding JP, et al. Additional investigations fail to alter the diagnosis of irritable bowel syndrome in subjects fulfilling the Rome criteria. Am J Gastroenterol 1999;94:1279–82.
[46] Tolliver BA, Herrera JL, DiPalma JA. Evaluation of patients who meet clinical criteria for irritable bowel syndrome. Am J Gastroenterol 1994;89:176–8.
[47] MacIntosh DG, Thompson WG, Patel DG, et al. Is rectal biopsy necessary in irritable bowel syndrome? Am J Gastroenterol 1992;87:1407–9.
[48] Francis CY, Duffy JN, Whorwell PJ, et al. Does routine ultrasound enhance diagnostic accuracy in irritable bowel syndrome? Am J Gastroenterol 1996;91:1348–50.
[49] Sanders DS, Carter MJ, Hurlstone DP, et al. Association of adult coeliac disease with irritable bowel syndrome: a case-control study in patients fulfilling the ROME II criteria referred to secondary care. Lancet 2001;358:1504–8.
[50] Pimentel M, Chow EJ, Lin HC. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. Am J Gastroenterol 2000;95:3503–6.

[51] Bytzer P, Hansen JM, Schaffalitzky de Muckadell OB. Empirical H_2-blocker therapy or prompt endoscopy in management of dyspepsia. Lancet 1994;343:811–6.
[52] Lassen AT, Pedersen FM, Bytzer P, et al. *Helicobacter pylori* test-and-eradicate versus prompt endoscopy for management of dyspeptic patients: a randomised trial. Lancet 2000;356(9228):455–60.
[53] Carin PA, Read NW, Holdsworth CD. What is the benefit of coarse wheat bran in patients with irritable bowel syndrome? Gut 1984;24:168–73.
[54] Arffman S, Anderson JR, Hegnhoj J, et al. The effect of coarse wheat bran in the irritable bowel syndrome. A double blind cross-over study. Scand J Gastroenterol 1985;20:295–8.
[55] Lucey MR, Clark ML, Lowndes JO, et al. Is bran efficacious in irritable bowel syndrome? A double-blind placebo controlled cross-over study. Gut 1987;28:221–5.
[56] Niec AM, Frankum B, Talley NJ. Are adverse food reactions linked to irritable bowel syndrome? Am J Gastroenterol 1998;93:2184–90.
[57] Brandt LJ, Locke GR, Olden K, et al. An evidence-based approach to the management of irritable bowel syndrome in North America. American College of Gastroenterology Functional Gastrointestinal Disorders Task Force. Am J Gastroenterol 2002;97(Suppl 11):S1–26.
[58] Schoenfeld P, Chey WD. An evidence-based approach to clinical practice guidelines: diagnosis and treatment of irritable bowel syndrome. Clin Gastroenterol Hepatol 2003;1:322–7.
[59] Creed F, Fernandes L, Guthrie E, et al. The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome. Gastroenterology 2003;124:303–17.
[60] Drossman DA, Toner BB, Whitehead WE, et al. Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders. Gastroenterology 2003;125:19–31.
[61] Cann PA, Read NW, Holdsworth CD, et al. Role of loperamide and placebo in management of irritable bowel syndrome (IBS). Dig Dis Sci 1984;29:239–47.
[62] Hovdenak N. Lopermide treatment of the irritable bowel syndrome. Scand J Gastroenterol Suppl 1987;130:81–4.
[63] Efskind PS, Bernklev T, Vatn MH. A double-blind, placebo controlled trial with loperamide in irritable bowel syndrome. Scand J Gastroenterol 1996;31:463–8.
[64] Poynard T, Naveau S, Mory B, et al. Meta-analysis of smooth muscle relaxers in the treatment of irritable bowel syndrome. Aliment Pharmacol Ther 1994;8:499–510.
[65] Jaiwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. Ann Intern Med 2000;133:136–47.
[66] Pittler MH, Ernst E. Peppermint oil for irritable bowel syndrome: a critical review and metaanalysis. Am J Gastroenterol 1998;93:1131–5.
[67] Wheatley D. Irritable colon syndrome treated with an antispasmodic drug. Practitioner 1976;217:276–80.
[68] Page J, Dirnberger GM. Treatment of the irritable bowel syndrome with bentyl (dicyclomine hydrochloride). J Clin Gastroenterol 1981;3:153–6.
[69] Ritchie JA, Truelove SC. Treatment of irritable bowel syndrome with lorazepam, hyoscine butylbromide, and ispaghula husk. BMJ 1979;10:376–8.
[70] Clouse RE. Antidepressants for irritable bowel syndrome. Gut 2003;52:598–9.
[71] Akehurst R, Kaltenthaler E. Treatment of irritable bowel syndrome: a review of randomised controlled trials. Gut 2001;48:272–82.
[72] Creed FH, Joy R, Guthrie EA. Cost-effective randomised controlled trial of psychotherapy and antidepressants for severe irritable bowel syndrome. Psychosom Med 2000;62:108–9.
[73] Clouse RE. Antidepressants for functional gastrointestinal syndromes. Dig Dis Sci 1994;39(11):2352–63.
[74] 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: 211–8.
[75] Kuiken SD, Tytgat GNJ, Boeckxstaens GEE. The selective serotonin reuptake inhibitor fluoxetine does not change rectal sensitivity and symptoms in patients with irritable

bowel syndrome: a double blind, randomized, placebo-controlled study. Clin Gastroenterol Hepatol 2003;1:219–28.
[76] Gershon M. Roles played by 5-hydroxytryptamine in the physiology of the bowel. Aliment Pharmacol Ther 1999;13:15–30.
[77] 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;161:1733–40.
[78] Camilleri M, Mayer E, Drossman D, et al. Improvement in pain and bowel function in female irritable bowel syndrome patients with alosetron, a $5HT_3$ receptor antagonist. Aliment Pharmacol Ther 1999;13:1149–51.
[79] Camilleri M, Northcutt AR, Kong S, et al. The efficacy and safety of alosetron in female patients with irritable bowel syndrome: a randomized, placebo controlled study. Lancet 2000;355:1035–40.
[80] 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;96:2662–70.
[81] Jones R, Holmann G, Rodrigo L, et al. Alosetron relieves pain and improves bowel function compared with mebeverine in female non-constipated irritable bowel syndrome patients. Aliment Pharmacol Ther 1999;13:1419–27.
[82] Olden K, DeGarmo RG, Jhingran P, et al. Patient satisfaction with alosetron for the treatment of women with diarrhea-predominant irritable bowel syndrome. Am J Gastroe nterol 2002;97:3139–46.
[83] Lotronex tablets: understanding the risks and benefits. Research Triangle Park (NC): GlaxoSmithKline, USA; 2002.
[84] Camilleri M. Review article: tegaserod. Aliment Pharmacol Ther 2001;15:277–89.
[85] Muller-Lissner SA, Fumagalli I, Bardhan KD, et al. Tegaserod, a $5\text{-}HT_4$ receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. Aliment Pharmacol Ther 2001;15:1655–6.
[86] Whorwell PJ, Krumholz S, Muller-Lisner S, et al. Tegaserod has a favorable safety and tolerability profile in patients with constipation-predominant irritable bowel syndrome. Gastroenterology 2000;118:A1204.
[87] 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;16:877–8.
[88] Kellow J, Lee OY, Chang FY, et al. An Asia-Pacific, double blind, placebo controlled, randomized study to evaluate the efficacy, safety, and tolerability of tegaserod in patients with irritable bowel syndrome. Gut 2003;52:671–6.
[89] 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; 16:1701–8.
[90] Palsson OS, Turner MJ, Johnson DA, et al. Hypnosis treatment for severe irritable bowel syndrome: investigation of mechanism and effects on symptoms. Dig Dis Sci 2002;47:2605–14.
[91] Gonsalkorale WM, Houghton LA, Whorwell PJ. Hypnotherapy in irritable bowel syndrome: a large-scale audit of a clinical service with examination of factors influencing responsiveness. Am J Gastroenterol 2002;97:954–61.
[92] Keefer L, Blanchard EB. A one-year follow-up of relaxation response meditation as a treatment for irritable bowel syndrome. Behav Res Ther 2002;40:541–6.
[93] Smart HL, Mayberry JF, Atkinson M. Alternative medicine consultations and remedies in patients with the irritable bowel syndrome. Gut 1986;27(7):826–8.
[94] Koloski NA, Talley NJ, Huskic SS, et al. Predictors of conventional and alternative health care seeking for irritable bowel syndrome and functional dyspepsia. Aliment Pharmacol Ther 2003;17(6):841–51.
[95] Li Y, Tougas G, Chiverton SG, et al. The effect of acupuncture on gastrointestinal function and disorders. Am J Gastroenterol 1992;87:1372–81.
[96] Chan J, Carr I, Mayberry JF. The role of acupuncture in the treatment of irritable bowel syndrome: a pilot study. Hepatogastroenterology 1997;44:1328–30.

[97] Niedzielin K, Kordecki H, Birkenfeld B. A controlled, double-blind, randomized study on the efficacy of *Lactobacillus plantarum* 299V in patients with irritable bowel syndrome. Eur J Gastroenterol Hepatol 2001;13(10):1143–7.
[98] Nobaek S, Johansson ML, Molin G, et al. Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. Am J Gastroenterol 2000;95(5):1231–8.
[99] Kim HJ, Camilleri M, McKinzie S, et al. A randomized controlled trial of a probiotic, VSL#3, on gut transit and symptoms in diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther 2003;17(7):895–904.
[100] Bensoussan A, Talley N, Hing M, et al. Treatment of irritable bowel syndrome with Chinese herbal medicine: a randomized controlled trial. JAMA 1998;280(18):1585–9.

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