Journal of Gastroenterology and Hepatology

JGHF

doi:10.1111/j.1440-1746.2009.06120.x

REVIEW SERIES: ADVANCES IN CLINICAL PRACTICE

Irritable bowel syndrome: Epidemiology, diagnosis and treatment: An update for health-care practitioners

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Key words
functional bowel disorders, inflammatory bowel disease, irritable bowel syndrome.

Accepted for publication 2 September 2009.

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Abstract

Irritable bowel syndrome (IBS), a chronic gastrointestinal disorder, affects from 3–20% of the US population, depending on sociocultural and comorbid factors. IBS is characterized by a symptom complex of abdominal pain and abnormal bowel habits that present as diarrhea or constipation, and general physical weakness in the absence of abnormal morphological, histological or inflammatory markers. The main diagnostic Rome III criteria as established by international professional organizations are based on exclusion criteria and the occurrence and rate of symptoms. Because the pathophysiology and causes of IBS are poorly understood, treatment approaches are mainly focused on symptom management to maintain everyday functioning and improve quality of life for persons with IBS. The mainstay of intervention is pharmacological treatment with antispasmodics and antidiarrheals for diarrhea, prokinetics and high-fiber diets for constipation, and supportive therapy with low-dose antidepressants to normalize gastrointestinal motility. Other interventions include lifestyle and dietary changes, psychotherapy, herbal therapies and acupuncture. The purpose of this review is to critically assess benefits and risks of current treatment approaches as well as promising complementary and alternative therapies.

Introduction

In the last two decades, irritable bowel syndrome (IBS) has gained considerable attention in the health-care field due to its increasingly high prevalence, sometimes debilitating effects and diverse symptom representation.[1] IBS belongs to a group of chronic gastrointestinal (GI) diseases referred to as functional bowel disorders (FBD) as classified by the Rome foundation,[2] an international organization dedicated to research and education in the field of functional GI disorders.

The World Health Organization (WHO) has given IBS its own classification in its 10th revision of the International Classification of Diseases (ICD-10), recognizing the significance of this syndrome.[3] The first diagnostic evaluation of IBS was introduced with the Manning criteria in the 1970s, which utilized a 15-symptom questionnaire to differentiate between IBS and what were then referred to as organic abdominal diseases.[4] Over the past decade, advances have been made in classifying various chronic disease states of FBD to create differential diagnosis criteria as well as exploring new treatments for a group of widespread disorders.

Although a precise definition of IBS is still controversial on the basis of a functional or an organic disorder with symptoms that differentiate it from other FBD, current efforts underline that IBS requires attention from a health-care professional.[1] The purpose of this clinical review is to provide health-care practitioners with an overview of IBS epidemiology, symptoms and diagnostic criteria, and current treatment approaches.

Epidemiology

Assessment of the prevalence of IBS has been complicated by the clarity of assessment criteria to differentiate between various FBD and other chronic GI disorders. The last comprehensive review of the prevalence and epidemiology of IBS in North America, in which five population-based prevalence studies were evaluated, was conducted in 2002.[5] An important factor in diagnosing IBS is the set of criteria utilized, such as the Rome criteria[6] and the Manning questionnaire.[4] In some cases, the two evaluation tools were directly compared in the studies and provided a more diverse dataset, depending on how many scale criteria a person had to meet in order to be diagnosed with IBS.

The range of prevalence was from 3–20%, with most studies between 10% and 15% (mean of all 13 studies was 11.6% with a standard deviation of 4.6%). Interestingly, there is a higher ratio of women who develop IBS compared to men (ratio of 2:1) although there were also differences observed among studies. Age-related onset of IBS symptoms occurred predominantly in patients younger than 45 years but prevalence rose again in the elderly. The subclassification of IBS as either IBS-D (IBS with predominant

diarrhea) with 5.0–5.5%, IBS-C (IBS with predominant constipation) with 5.2–5.4% or IBS-M (IBS with alternating constipation and diarrhea, mixed IBS) with 5.2% was evaluated by two population-based studies.[7,8] Other factors that have a significant impact on the development of IBS are health status, comorbid conditions,[9] diet[10] and mental health.[11,12]

Recent study findings in Korea,[13] Greece,[14] Malaysia,[15] Finland[16] and France[17] showed variations in prevalence of IBS and distribution of the subclassification. In the Korean study, approximately half of the patients diagnosed with IBS first experienced symptoms before the age of 40 years with approximately even distribution between women and men.[13] Although prevalence of IBS was not reported, these researchers evaluated the subtype of IBS and found that more than half of IBS patients suffered from constipation-predominant IBS. A study with young Malaysian adults (mean age 22 ± 1.8 years) showed a prevalence rate of 15.8% with a female-to-male ratio of 1.7:1.[15] Subclassification of IBS also resulted in approximately 75% of patients diagnosed with IBS-C, with much lower IBS-M type occurrence. This outcome is surprising in light of other studies conducted in Asian populations that frequently reported a lower prevalence rate of IBS.[18–20] One reason for this discrepancy might involve diagnostic criteria because use of Manning and Rome I criteria frequently resulted in a lower rate of a positive IBS diagnosis.[1] In a Finnish study, the various diagnostic criteria were compared and applied to an obtained dataset of patients diagnosed with IBS.[16] The prevalence as evaluated by Manning and Rome I and II criteria varied from 5.1–16.2%. Use of the Manning criteria in this study resulted in a significantly higher prevalence rate than the Rome criteria. The reported age of IBS onset was evenly distributed throughout the study population, with a slightly higher prevalence in women than men. It appeared that diarrhea was predominantly observed in this population but no subclassification has been made.

French researchers utilized the Rome I criteria to conclude that prevalence of IBS was 4.0% with a female-to-male ratio of 2.3:1 and equal distribution of IBS-D, IBS-C and IBS-M subclassification throughout the study population.[17] Prevalence of IBS symptoms ranged from 3.2–4.3% between the different age groups; the lowest prevalence was in younger adults 18–24 years of age. In a recent study conducted in Greece, prevalence of IBS was 15.7% based on the Rome II diagnostic criteria.[14] Constipation-predominant IBS was the most common among IBS subtypes, followed by diarrhea-predominant IBS. More women than men were affected, with a ratio of 1.3:1 with reported onset of IBS symptoms.

Other important comorbidity factors that contribute to development of IBS as a functional disorder are depression, anxiety and insomnia, which should be evaluated by health-care providers to derive the differential diagnosis.[11,14] The most common psychiatric disorder associated with IBS is depression, with a prevalence of approximately 30% in IBS patients compared to only 18% in a control population.[11] Anxiety is also commonly encountered as a comorbid condition in IBS, with 16% affected compared to controls at a rate of 6%.[11] There also appears to be a correlation between anxiety and depressive disorders and the severity of IBS symptoms as increases in comorbidity have been found between these diagnoses and worsening of IBS symptoms.[21] Findings regarding association of comorbid conditions including psychiatric disorders with IBS may be strengthened by tightly controlled symptom criteria (e.g. instead of using self-reported diagnosis) with sufficient patient numbers.[22]

The population studies demonstrate the diversity of IBS based on ethnicity, age and culture (e.g. diet, access to health-care providers) and the importance of evaluation criteria that impact choice of therapy.[8,23] Diet, as part of a cultural factor, has been studied in relation to IBS treatment. Simple changes in diet may improve symptoms (most likely reductions in fat consumption that lead to bloating) for some patients, while symptoms actually worsen for others if the diet is rich in fiber, wheat or carbohydrates (specifically diarrhea-predominant IBS).[10,24] As mentioned before, these studies were mainly conducted in small patient populations and larger clinical studies are required to confirm these findings.

Symptoms, differential diagnosis and pathophysiology

Symptoms of IBS have been studied and its criteria have been refined over the past decades, and guidelines for differential diagnosis have been established by various professional societies, including the British Society of Gastroenterology,[25] the American College of Gastroenterology[26] and the American Gastroenterological Association.[27] Diagnostic criteria for IBS are now based on evaluating present symptoms to distinguish it from other GI disorders globally and from FBD, specifically. In general, IBS is characterized as a functional disorder of the GI tract associated with abdominal pain and altered bowel activity but lacking any pathological organic changes. This distinguishes it from inflammatory bowel disease (IBD), which presents with increased phagocyte-specific protein in the feces, in that IBS does not cause inflammation as can be assessed with a differential blood test and fecal markers, observation of ulcers, or other organic damage to the GI tract.[28] Furthermore, the absence of organic pathophysiological changes distinguishes IBS from many other GI disorders such as Crohn's disease, chronic inflammation of the distal GI tract caused by certain *Escherichia coli* strains with high genetic predisposition,[29] and celiac disease which causes gluten-induced auto-inflammatory degeneration of the small intestines.[30]

Despite these differences, diagnosis of IBS is based on symptom representation and a thorough initial evaluation of any organic abnormalities. Symptoms that predominate in IBS are unspecific abdominal pain or discomfort that recurs infrequent bowel movements with periods of increased or decreased activity, alleviation of pain and discomfort with defecation, and onset of symptoms with changes in stool frequency and appearance. These are the symptoms most frequently employed in making a differential diagnosis in conjunction with the Rome II and new Rome III criteria.[9]

Diarrhea (IBS-D) and constipation (IBS-C) are the two dominant subtypes of IBS; a mixed subtype (IBS-M) occurs least frequently. The Rome foundation classifies IBS as an FBD with the subclassification letter C1[6] (see Table 1). The WHO grouped IBS in its ICD-10 revision in Chapter XI under 'Diseases of the Digestive System' and further into 'Other Diseases of Intestines' and K58 'Irritable Bowel Syndrome', which includes K58.0 'Irritable bowel syndrome with diarrhea' and K58.9 'Irritable bowel syndrome without diarrhea'.[3]

The slow onset of IBS over weeks and months shows a strong correlation with stress disorders such as depression and anxiety[31]

Table 1 Comparison between Rome II and Rome III criteria

Comparison of Rome III to Rome II criteria[6]	
Rome III criteria	Rome II criteria
Diagnostic criterion† Recurrent abdominal pain or discomfort‡ at least 3 days/month in last 3 months associated with two or more of the following: 1. Improvement with defecation. 2. Onset associated with a change in frequency of stool. 3. Onset associated with a change in form (appearance) of stool. In pathophysiology research and clinical trials, a pain/discomfort frequency of at least 2 days a week during the screening evaluation is recommended for subject eligibility.	At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two out of three features: 1. Relieved with defecation; and/or 2. Onset associated with a change in frequency of stool; and/or 3. Onset associated with a change in form (appearance) of stool. Symptoms that cumulatively support the diagnosis of IBS: – Abnormal stool frequency (for research purposes 'abnormal' may be defined as greater than 3 bowel movements per day and less than 3 bowel movements per week); – Abnormal stool form (lumpy/hard or loose/watery stool); – Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation); – Passage of mucus; – Bloating or feeling of abdominal distension.

†Criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.
‡'Discomfort' means an uncomfortable sensation not described as pain.
IBS, irritable bowel syndrome.

or can follow a GI infection,[32] in which case it is classified as post-infectious IBS (PI-IBS). In contrast to patients without a prior GI infection, PI-IBS patients can present with altered gut immune function represented by an increase in lymphocyte infiltrates and inducible nitric oxide synthase in the feces.[33,34] Following the Rome criteria, a patient can be diagnosed with IBS by considering the family and clinical history (colon cancer, onset of symptoms later than aged 50 years), symptom representation with a gradual onset and consistency, no specific warning signs indicative of a specific pathophysiology (including rectal bleeding, anemia, weight loss, fever) and normal laboratory results. Diagnosis with consideration of stress disorders and explanation to the patient about the relationship between altered central nervous system (CNS) signaling and IBS development may aid in establishing positive health-care provider–patient rapport with consistently better clinical outcomes.[35,36]

The limbic system in conjunction with paralimbic structures connects the gut with the CNS through the autonomic nervous system in a bidirectional way. This allows transmission of emotional states from the CNS to the gut and perception of GI changes (pain, contractions, bloating) to the CNS.[37,38] Independent of afferent connections from the CNS, the gut is able to release the neurotransmitters serotonin and acetylcholine as part of the enteric nervous system (ENS).[39] The main neurotransmitter that regulates GI motility is serotonin (5-HT), which is released from enterochromaffin cells in the GI mucosa to stimulate acetylcholine release that initiates GI motility.[40] The primary serotonin receptors involved in ENS transmissions are the 5-HT_3 and 5-HT_4 receptors, each with specific distribution patterns.[41–43] While 5-HT_3 receptors signal changes in intestinal motility to the ENS and serve as the main neurotransmitter for efferent nerves connecting to the CNS, 5-HT_4 receptors are exclusively presynaptic and therefore serve as interneurons to transmit a signal to effector acetylcholine neurons. Serotonin signaling is terminated by a specific serotonin reuptake transporter (SERT) located on enterocytes within the intestinal mucosa.[44] It has been shown that a decrease in SERT consistently leads to dysfunction of GI motility in animals and in humans through increased serotonin concentrations.[45] Elevated serotonin concentrations then constantly stimulate 5-HT_3 and 5-HT_4 receptors leading to dysregulated contractions and dilations of the intestinal tract. Attenuation of this signaling cascade is employed for treatment of IBS and various other GI disorders. Although the precise pathophysiology of IBS is still unknown, the above-mentioned factors contribute to development of this chronic disease complex.

Current treatment approaches

Irritable bowel syndrome treatment approaches depend on symptom representation and comorbid conditions such as lifestyle, diet and stress disorders. Because IBS classification is based on the predominant symptom of diarrhea, constipation or mixed IBS, treatment focuses on normalizing GI motility. Recently, the Task Force on Irritable Bowel Syndrome of the American College of Gastroenterology has published a detailed systematic review on the management of IBS.[26] An important consideration highlighted in IBS treatment guidelines of the British Society of Gastroenterology is the influence of placebo on the outcome.[25] The placebo effect during the first weeks of therapy is three times higher (46%) than the average placebo effect with drug therapy for other conditions (16%). It is also higher in patients who respond well to health-care provider–patient interactions and reassurance that their condition, although chronic in nature, is not a grave prognosis[25,36] and can be treated. The confounding variable of a psychological disorder presents with a lower placebo effect.

Lifestyle and dietary changes

Before pharmacological treatment is considered, lifestyle and diet should be evaluated as potential triggers for IBS symptoms. Lack of exercise, food deficiencies, lack or excess of dietary fiber intake, and lack of suitable times for defecation should be evaluated as determining factors that contribute to the development of IBS, specifically constipation-predominant IBS.[25] Thus, an increase in dietary fibers and regular exercise might benefit constipated IBS

patients.[46] Excessive caffeine consumption, indigestible carbohydrates and high lactose intake have been found to contribute to diarrhea-predominant IBS.[10,24] In general terms, a stepwise food exclusion approach should be tried if the symptoms are mild to moderate.[47] The evaluation of probiotics to treat IBS has been summarized in meta-analytic studies that showed modest improvements for bloating, abdominal pain and bowel movement difficulties. No specific probiotic strain was found to be superior to another, and often combinations of strains were used.[46,48]

Psychotherapy and psychopharmacological treatment

The impact of various forms of psychotherapy (e.g. cognitive behavioral therapy, dynamic psychotherapy, hypnotherapy, biofeedback and relaxation therapy) on IBS has been evaluated. According to guidelines of the British Society of Gastroenterology[25] and the American Gastroenterology Association,[27] psychotherapeutic interventions are usually reserved for severe forms of IBS that show high incidence of a comorbid psychological disorder[49] or if a known comorbidity with a depressive or anxiety disorder exists. The most effective psychotherapeutic interventions were hypnotherapy and stress management over the course of 6 weeks to 6 months in patients with IBS-D or IBS-M. Concomitant treatment of diagnosed depression or anxiety disorders through psychotherapy and pharmacological treatment often helps to alleviate specific IBS symptoms.[50,51]

A recent meta-analysis and systematic review showed that the heterogeneity of psychotherapeutic treatment results in a 25% chance that a patient will benefit from any type of psychotherapy,[49] while hypnotherapy and stress management had a higher rate of success with 52% and 67%, respectively.[52] In the same meta-analysis,[49] the use of both tricyclic (TCA) and selective serotonin reuptake inhibitor (SSRIs) antidepressants in the treatment of IBS were compared. Antidepressant treatment often requires patient counseling, particularly in the first 3–4 weeks of treatment, because side effects are pronounced, with a delayed onset of antidepressant action. While TCAs act both on norepinephrine and serotonin transmission with varying specificities, SSRIs specifically increase serotonin concentrations in the CNS. Both TCAs and SSRIs demonstrated a treatment benefit in IBS symptoms with a success rate in symptom reduction of 58% and 55%, respectively.[49] SSRIs, associated with fewer side effects than TCAs, may also prove beneficial in treating anxiety disorders although they do not alleviate abdominal bloating or reduction in visceral pain sensitivity.[53,54] While benzodiazepines are more frequently prescribed for anxiety disorders, their effectiveness in symptom alleviation for IBS is questionable.[27] Therefore, use of TCAs in doses below regular antidepressant effectiveness has become a mainstay of IBS because it alters GI motility (normalization of motility and secretion as well as reduction in visceral pain sensitivity)[52] which has recently been established through meta-analysis of clinical trials.[55]

Pharmacological treatment

After lifestyle and diet changes have failed to alleviate or resolve IBS symptoms, the most common treatment approach is pharmacotherapy. This follows the predominant symptom representation and is therefore symptomatic (not causative) treatment, because the exact mechanism for development of IBS is unknown. Pharmacological treatment of constipation-predominant IBS focuses on prokinetics that shorten transit time in the intestines and antispasmodics to alleviate cramping as a result of intestinal wall pressure. A high-fiber diet might improve symptoms in some patients, but mixed results have been shown in clinical studies.[25,27]

Prokinetics are used to enhance intestinal contractions and facilitate the movement of fecal matter by acting as dopamine antagonists, 5-HT_3 antagonists and/or 5-HT_4 agonists. Despite inconsistent benefits to IBS-C patients, they are widely used and increase GI motility with concomitant increase in secretory activity and effects as visceral analgesics.[56] Tegaserod is the only prokinetic drug approved by the US Food and Drug Administration for the treatment of IBS, but it was restricted in 2007 due to risk of cardiovascular ischemic events.[57] Other prokinetics commonly used in clinical practice without specific IBS indication are domperidone, metoclopramide, cisapride and renzapride.[56] Newly approved in 2008 for treatment of IBS-C in women is the laxative lubiprostone, which acts as a chloride channel activator that increases water secretion into the feces.[58,59]

A meta-analysis of clinical trials with antispasmodics revealed that the clinical benefit of cimetropium, pinaverium, hyoscine and otilonium was highest whereas studies with pirenzepine and propinox favored the placebo treatment over the actual drug.[60] As expected with the anticholinergic antispasmodics, the most common adverse effects were dry mouth, dizziness and blurred vision; effects about which patients must be clearly informed. In addition, the prescribed antispasmodic should be given on an as-needed basis with a maximum of three times per day for acute spastic episodes.[27] Antispasmodics will reduce GI motility and therefore need to be given in conjunction with a prokinetic or laxative in order to increase GI motility. Antispasmodics are mainly used in both IBS-C and IBS-D to reduce abdominal pain and cramping.

While the goal of IBS-C treatment is an increase in GI motility, the opposite is necessary for patients predominantly affected by IBS-D. Diarrhea-associated symptoms often include a social component, which might impact the patient's ability to maintain a normal daily routine or interact with other people because of constant worry of having loose stool. A more severe consequence of chronic diarrhea is malnutrition of vitamins and other nutrients. Commonly used pharmacological treatments for IBS-D are opioid agents, 5-HT_3 antagonists, and anticholinergic agents. Loperamide is an opioid agonist that acts on μ-receptors of the myenteric plexus in the large intestines without being absorbed or causing CNS effects after oral administration.[61] Loperamide, commonly used for short-term diarrhea due to bacterial GI infections, should only be given in low doses as needed to patients with IBS-D. Dose adjustment should occur if concomitant GI motility inhibitors such as anticholinergics are given. Codeine can also be given to slow GI motility but is associated with sedation and drug dependency because it reaches the CNS.[62]

Antagonism of 5-HT_3 receptors in the ENS has been shown to inhibit GI motility and benefit abdominal pain by reducing visceral sensitivity in patients with IBS-D predominance.[63] Ondansetron, granisetron, alosetron and cilansetron are all selective 5-HT_3 receptor antagonists frequently prescribed for IBS-D as well as for other conditions such as vomiting and nausea associated with chemotherapy.[64] Although ondansetron was the first 5-HT_3

antagonist to be discovered, the predominant treatment option for IBS-D is alosetron, due to its preferred side-effect profile and better reduction in visceral sensitivity.[65] The rare but severe effects of ischemic colitis and constipation led to restricted use of alosetron for the treatment of IBS-D in women who failed to respond to other treatments. The recommendation is to start with a reduced dose of 1 mg once daily and then increase if needed to 1 mg twice daily. Alosetron has an absolute contraindication for patients with constipation.[66]

The anticholinergic antispasmodics are frequently used to reduce abdominal pain, visceral sensitivity and GI motility. Whereas unspecific anticholinergics such as hyoscine or pinaverium are used to treat both IBS-C and IBS-D, specific muscarinic M_3 receptor antagonists such as darifenacin and zamifenacin might provide a more specific treatment approach.[67,68] Although commonly used for treatment of overactive bladder and urinary incontinence, these drugs are frequently used to reduce GI motility in IBS-D without currently being approved for this indication. Some drugs currently in clinical development target the treatment of visceral pain in IBS and include specific β_3-adrenoreceptor agonists, corticotropin-releasing factor (CRF)-receptor antagonists, κ-opioid receptor agonists and pregabalin. These new drugs showed promising results that may soon offer new options for treatment of abdominal pain in IBS.[69]

Complementary and alternative therapies

The American Gastroenterological Association technical review for IBS[27] mentions that complementary and alternative therapies have been used continually and reported benefit in persons with IBS although the effectiveness of the therapies has not been clinically well studied. A Cochrane review of herbal medicines for the treatment of IBS[70] identified several well-designed clinical studies that showed improvement of IBS symptoms. One study employing a variety of Chinese herbal medicines, given alone or in a fixed combination, showed significant improvement of various IBS symptoms over a placebo treatment that extended beyond the end of the study.[71]

Other herbal preparations included in the Cochrane review were a Tibetan herbal formula sold as Padma Lax (Padma, Schwerzenbach, Switzerland) and a combination of herbs under the trade name Iberogast (Steigerwald Arzneimittelwerk, Darmstadt, Germany). Treatment with these preparations were found to markedly improve IBS symptoms.[72,73] Padma Lax significantly reduced the severity of abdominal pain and increased transit time compared to placebo in patients with predominant IBS-C symptoms. Padma Lax capsules, containing 13 standardized herbal plant extracts, can be given orally. Iberogast, a liquid comprised of standardized extracts from nine herbal remedies, is given orally three times daily. The overall rating of IBS symptoms, such as abdominal pain, improved under Iberogast treatment compared to a placebo. It has been suggested that a combination of certain herbs may act synergistically on serotonin and acetylcholine receptors as with Iberogast in isolated human intestines.[74] Other alternative treatments frequently used by patients suffering from IBS are peppermint oil and acupuncture. The use of peppermint oil has been evaluated through two meta-analysis studies that compared clinical trials of peppermint oil preparations with a placebo.[60,75] These studies are based on the traditional use of preparations from peppermint leaves for the alleviation of stomach upset, which has been supported by other research findings of smooth muscle relaxation effect from use of both peppermint oil and the isolated compound menthol.[76,77] This is most likely attributable to the effect on calcium- and potassium-dependent ion channels on enterocytes. These clinical studies demonstrated that supplementation of peppermint oil, in addition to pharmacological standard treatments, was of benefit to both IBS-C and IBS-D patients.

Acupuncture, which has been used as a therapeutic treatment in Chinese traditional medicine for centuries, has gained significant attention over the past decades in Western medicine. A recent meta-analysis of a few small clinical trials involving the effect of acupuncture treatment in patients with IBS included only studies that used actual acupuncture versus sham acupuncture, any other active interventions, or no treatment (negative control) to alleviate IBS symptoms.[78] The meta-analysis revealed that the effects of acupuncture on IBS symptoms were variable and did not differ significantly from the sham acupuncture treatment or any other interventions.[78] This may be due to inconsistencies in study designs and possible inclusion of patients who were not thoroughly diagnosed with IBS prior to treatment. More research with consistency in study protocol, standardized outcome measures and tight sampling criteria are needed to determine whether acupuncture is a beneficial treatment for IBS symptoms.[79]

Implications and future outlook

The scientific evidence supports the importance of recognizing IBS as a clinically significant GI disorder that merits both diagnostic evaluation and an individual treatment approach based on symptom presentation (see Fig. 1).

Because symptoms are rather unspecific and often triggered by stress or other life events, it is crucial to assure the patient that her/his condition is benign and can be treated with appropriate treatment options. In choosing treatments, the patient should also be made aware of potential adverse effects associated with low-dose tricyclic antidepressants or careful dosing schemes for antidiarrheal and antispasmodic agents. A comfortable patient–provider relationship is a good basis for an open discussion about lifestyle changes and often allows the patient to be more forthcoming about otherwise socially restrictive topics such as bloating and diarrhea. In this context, the patient should understand that pharmacological treatment will help alleviate these symptoms and careful, temporary dose adjustment can be used for specific purposes in social interactions. In most primary care settings, psychotherapeutic intervention is not necessary unless severe underlying depressive or anxiety disorders are suspected that require referral to a specialist. The health-care provider should provide the patient with information and reassurance that her/his condition is taken seriously and can be appropriately treated.

Although the pathophysiology of IBS is still poorly understood, the future outlook for treatment of IBS is focused on modulation of innervating neurotransmitters in intestinal motility. Considerable investigation into a variety of new treatment approaches with both synthetic and traditional medicines is promising. Newer serotonin receptor modulators focus on either antagonizing specific subtype receptors of 5-HT_3 or serve as agonists on 5-HT_4 receptors while

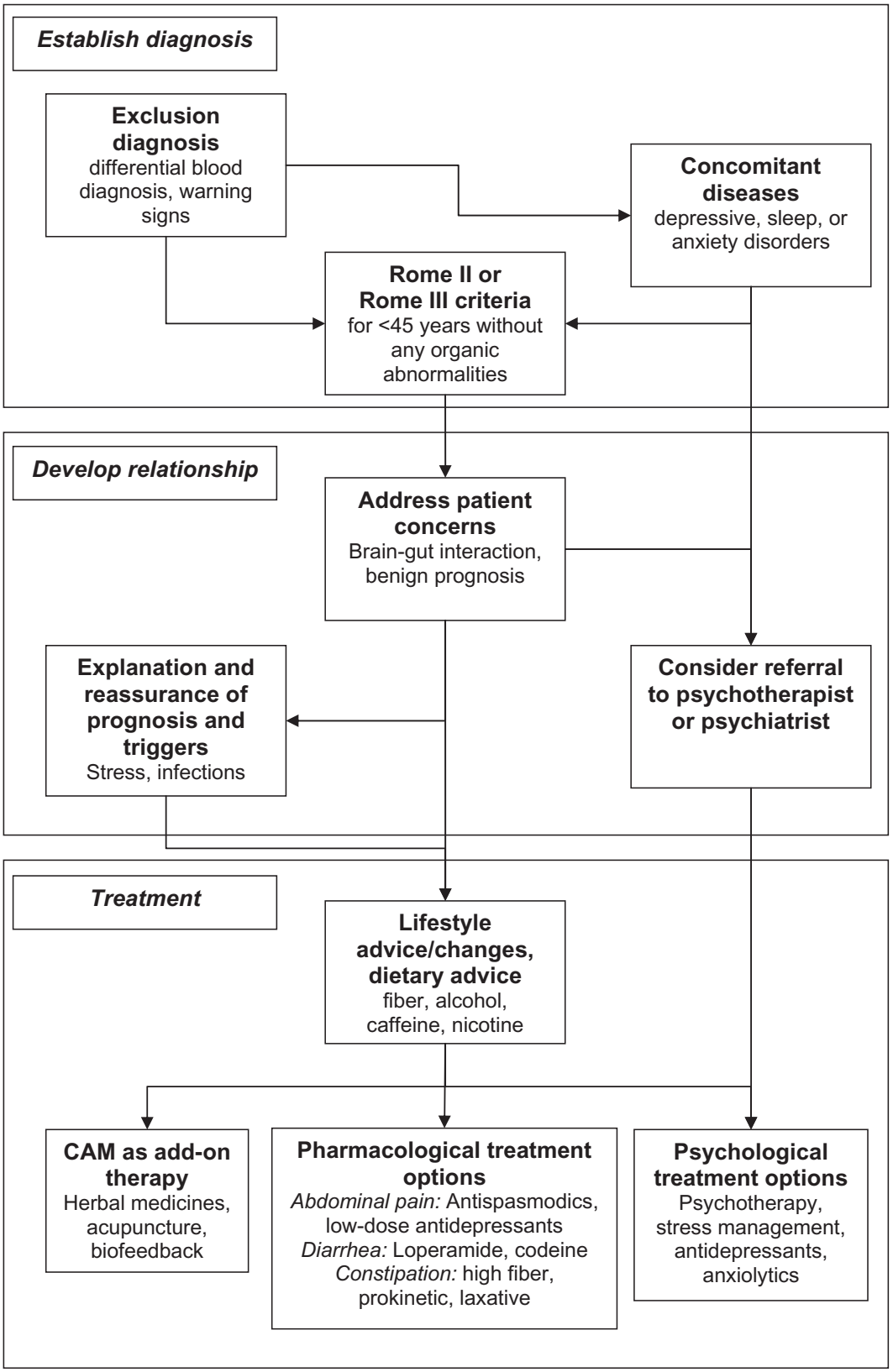

Figure 1 Flow chart for diagnosis, patient–health-care provider relationship, and treatment options in IBS (based on Jones *et al.* with modifications).[25] CAM, complementary and alternative medicine.

simultaneously reducing serious adverse effects such as ischemic colitis. The use of low-dose TCAs and SSRIs is targeted toward pain relief and normalization of GI motility by acting on both norepinephrine and/or serotonin neurotransmission. There is preclinical and clinical evidence to support the use of α_2 and β_3 adrenergic receptor agonists for disturbed GI motility and pain perception. Antagonists at neuropeptide (mainly neurokinin and corticotrophin-releasing hormone) receptors are currently evaluated for pain perception and reduction of nociception and visceral pain in patients with IBS.[79] Although some of the preclinical data for these agents were promising, clinical data are still lacking or inconsistent. Approaches that influence the flow of ions across the epithelial cell layer in the intestines have been translated in the new drug lubiprostone, which acts through chloride channels to increase water secretion into the lumen and therefore can be used as a laxative in IBS-C patients. Other drugs acting in a similar manner are currently being investigated and show some promising results in preliminary animal models and small clinical trials.

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