GASTROENTEROLOGY & HEPATOLOGY™
The Independent Peer-Reviewed Journal

October 2008 www.clinicaladvances.com Volume 4, Issue 10, Supplement 21

Faculty

Lin Chang, MD, AGAF
Center for Neurobiology of Stress
Division of Digestive Diseases
David Geffen School of Medicine at UCLA
Los Angeles, CA

Brian E. Lacy, PhD, MD, FACG (chairperson)
Director, GI Motility Laboratory
Dartmouth-Hitchcock Medical Center
Lebanon, NH

Eamonn M.M. Quigley, MD, FACG
Department of Medicine
Alimentary Pharmabiotic Centre
University College Cork
Cork, Ireland

Philip S. Schoenfeld, MD, MSEd, MSc (Epi), FACG
Training Program in GI Epidemiology
University of Michigan School of Medicine
Ann Arbor, MI

Emerging Diagnostic and Treatment Strategies for Irritable Bowel Syndrome

A CME activity approved for 2.0 *AMA PRA Category 1 Credit(s)™*

Release date: October 2008
Expiration date: October 31, 2009

This continuing medical education (CME) activity is jointly sponsored by the University of Wisconsin School of Medicine and Public Health and MDG Development Group.

Acknowledgment: The University of Wisconsin School of Medicine and Public Health and MDG Development Group gratefully acknowledge the independent educational grant provided by Prometheus Laboratories Inc.

Joint Sponsorship Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Wisconsin School of Medicine and Public Health and MDG Development Group. The University of Wisconsin School of Medicine and Public Health is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation

The University of Wisconsin School of Medicine and Public Health designates this educational activity for a maximum of 2 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Continuing Education Units

The University of Wisconsin-Madison, as a member of the University Continuing Education Association (UCEA), authorizes this program for 0.2 Continuing Education Units (CEUs) or 2 hours.

Statement of Need

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by abdominal pain in association with frequent diarrhea, constipation, abdominal discomfort, and a change in bowel habits. IBS has traditionally been diagnosed by exclusion based on history, physical examination, categorization of symptoms, and a battery of diagnostic studies. Given the wide range of causes of IBS, the best treatment results have been achieved with therapy tailored to the underlying etiology. The importance of proper diagnosis and treatment is highlighted by the fact that IBS is a significant economic burden to the individual patient and to society.

Intended Audience

This activity is designed to educate practicing physicians on the clinical challenges they may encounter in the diagnosis and treatment of IBS.

Special Prerequisites for Participants

There are no prerequisites to participating in this educational activity.

Learning Objectives

At the conclusion of this activity, participants should be able to:

1. Discuss the prevalence, symptomatology, and impact of IBS on patients, physicians, and society.
2. Describe the common types of IBS and their associated comorbidities.
3. Review the challenges in the differential diagnosis of IBS and the limitations of current criteria.
4. Compare and contrast the diagnostic tests currently used to differentiate IBS from inflammatory bowel disease and other conditions with similar symptoms.
5. Explain the current treatment options for IBS, as well as the rationale for emerging management strategies.

Faculty Disclosure Statement

As a sponsor accredited by the ACCME, it is the policy of the University of Wisconsin School of Medicine and Public Health to require the disclosure of the existence of any significant financial interest or any other relationship a faculty member or a sponsor has with either the commercial supporter of this activity or the manufacturer(s) of any commercial product(s) discussed in an educational presentation. The faculty reported the following:

Faculty:

Lin Chang, MD, AGAF: Dr. Chang has acted as a consultant for, and received honoraria from, GlaxoSmithKline PLC, Lexicon Pharmaceuticals, Inc., Salix Pharmaceuticals, Inc., and Takeda Pharmaceuticals North America, Inc. and has received research support from GlaxoSmithKline and Prometheus Laboratories Inc.

Brian E. Lacy, PhD, MD, FACG: Dr. Lacy has acted as a speaker for Takeda Pharmaceuticals North America, Inc. and has received research support from Novartis AG, Prometheus Laboratories Inc, and Takeda Pharmaceuticals North America, Inc.

Eamonn M.M. Quigley, MD, FACG: Dr. Quigley has acted as an advisor for AGI Therapeutics PLC, Boehringer Ingelheim GmbH, Procter & Gamble, and Salix Pharmaceuticals, Inc.

Philip S. Schoenfeld, MD, MSEd, MSc (Epi), FACG: Dr. Schoenfeld has acted as a speaker for Novartis AG, Shire Pharmaceuticals Group PLC, Takeda Pharmaceuticals North America, Inc., and Wyeth. He has acted as a consultant for AGI Therapeutics PLC, Epigenomics AG, Johnson & Johnson, MD-Evidence (partner), Novartis AG, Salix Pharmaceuticals, Inc., Shire Pharmaceuticals Group PLC, Takeda Pharmaceuticals North America, Inc., and Tioga Pharmaceuticals, Inc., as well as receiving dividends from Merck & Co, Inc, and Wyeth.

CME Reviewer:

John Bryant Wyman, MD: Professor of Medicine,
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin
Dr. Wyman has no relevant financial relationships to disclose.

Medical Director:

Bruce Greenberg, PhD: Executive Vice President, Medical Services,
MDG Development Group, Basking Ridge, New Jersey
Dr. Greenberg is a stockholder in Wyeth.

NOTICE: The University of Wisconsin School of Medicine and Public Health advises the participants that one or more presentations in this continuing medical education activity does contain reference(s) to unlabeled or unapproved uses of drugs or devices.

Course Format

The participant should first read the supplement, then complete and submit the post-test and evaluation form to the address on the post-test. This entire process should take the participant 2 hours to complete.

Included in EMBASE

Disclaimer

Funding for this symposium report has been provided through an educational grant from Prometheus Laboratories Inc. Support of this symposium report does not imply the supporter's agreement with the views expressed herein. Every effort has been made to ensure that drug usage and other information are presented accurately; however, the ultimate responsibility rests with the prescribing physician. Gastro-Hep Communications, Inc., the supporters, and the participants shall not be held responsible for errors or for any consequences arising from the use of information contained herein. Readers are strongly urged to consult any relevant primary literature. No claims or endorsements are made for any drug or compound at present under clinical investigation.

Introduction

Brian E. Lacy, PhD, MD, FACG

This supplement reports on the educational symposium, "Emerging Diagnostic and Treatment Strategies for Irritable Bowel Syndrome," which was held in association with Digestive Disease Week on May 17, 2008, in San Diego, California. The featured papers in this supplement review current clinical information on the diagnosis and management of patients with irritable bowel syndrome (IBS), and the impact of IBS on patients, physicians, and society.

In the first paper, Dr. Lin Chang highlights the fact that IBS is a worldwide phenomenon with a heterogeneous distribution. IBS affects approximately 10% of the US population and accounts for 12% of diagnoses made by generalists and 28% made by gastroenterologists. Dr. Chang also reviews the natural history of IBS, which, for most patients, is a chronic disease with recurrent symptoms.

IBS patients are more likely than the general population to suffer from a variety of comorbid disorders. It is not uncommon for patients to experience poor sleep, reduced libido, panic disorders, depression, and other psychiatric comorbidities. Compounding symptom expression are background risk factors such as childhood emotional traumas, stress, poor coping skills, and diminished social support systems. The complex interplay of physical, emotional, and social events that produces symptoms of IBS dictates that a comprehensive treatment approach is required that includes not only medical but also psychiatric and behavioral interventions.

In the next paper, Dr. Philip S. Schoenfeld discusses the diagnosis of IBS, and the clinical relevance of current diagnostic strategies. He notes that IBS is characterized by abdominal pain and/or discomfort accompanied by disturbed defecation. In a majority of cases, the routine use of multiple diagnostic tests is not necessary in patients without alarm symptoms. The most critical alarm symptom is onset of disease in patients older than 50 years of age. Screening for colon cancer with colonoscopy should be routine for all patients aged 50 years and older, regardless of their complaint. Testing for celiac disease may be considered for patients with diarrhea-predominant IBS, especially those with persistent symptoms who fail standard therapy.

In my paper, I review current treatment options for IBS. The evidence-based guidelines published by the American College of Gastroenterology rate agents for the treatment of IBS based on the quality of the supporting studies. Electronic searches and meta-analyses of hundreds of clinical trials revealed that the majority of studies were generally poorly designed and had important methodologic weaknesses. Newer agents, such as the 5-HT_3 receptor antagonists, alosetron and cilansetron, as well as the 5-HT_4 receptor agonist, tegaserod, are clinically effective but associated with serious adverse events in some patients. Lubiprostone, a recent US Food and Drug Administration-approved CIC-2 chloride channel activator, stimulates the movement of chloride into the bowel lumen, facilitating sodium and water flow.

Diet was also discussed during this portion of the symposium. Although an estimated 25% of patients with IBS are lactose intolerant, and up to 50% of patients with diarrhea are fructose intolerant, food allergies do not play an important pathogenetic role in IBS.

In the last paper, Dr. Eamonn M.M. Quigley reviews emerging strategies for managing IBS and highlights the fact that new therapies are urgently needed because the current standard therapies are not very effective. In addition, Dr. Quigley points out that many of the most commonly used IBS medications were never studied in clinical trials with rigorous guidelines. He discusses the inappropriate choice of study end points, the short duration of treatment, the vagueness of "significance," and the absence of adequate adverse events data. There is interest in newer agents such as linaclotide, an oral guanylate cyclase-C agonist, which appears to stimulate intestinal fluid secretion, accelerate stool transit, and reduce visceral hypersensitivity. Asimadoline, which binds to peripheral k-opioid receptors without entering the central nervous system, seems to improve symptoms in patients with mixed IBS but worsens symptoms in patients with diarrhea-predominant IBS.

Dr. Quigley also discusses probiotics, living microorganisms that compete with opportunistic pathogens in the intestinal flora, as well as controlled studies with nonpharmacologic therapies.

In summary, I hope that you enjoy the proceedings of this informative and interactive symposium. These papers illustrate that effective new therapies for the treatment of IBS are urgently needed to help manage the physical symptoms of IBS, and in addition, relieve coexisting psychological distresses.

Impact of Irritable Bowel Syndrome

Lin Chang, MD, AGAF

Address correspondence to:
Lin Chang, MD, AGAF
Professor of Medicine
Center for Neurobiology of Stress
Division of Digestive Diseases
David Geffen School of Medicine at UCLA
Los Angeles, CA 90073
Tel: 310-312-9276
Fax: 310-794-2864
E-mail: linchang@mednet.ucla.edu

Abstract: Irritable bowel syndrome (IBS), a chronic disease characterized by intermittent flares, is the most common functional bowel disorder worldwide. It is one of the most frequently diagnosed disorders in practice. The diagnosis of IBS is so stable that repeated investigation of recurrent or persistent symptoms is unwarranted. IBS afflicts more women than men, particularly a subgroup whose predominant bowel habit is constipation. The disease is associated with a significant health care and economic burden that greatly increases direct medical and indirect costs, and decreases work productivity. Patients with IBS generally tend to have a poorer health-related quality of life (HRQOL) than the general population and comparable or poorer HRQOL to patients with other chronic medical conditions, although symptoms may improve spontaneously or with treatment. IBS has a complex pathophysiology, with multiple factors influencing the illness experience. For example, psychosocial risk factors such as chronic stress, early-life adverse experiences, and psychological symptoms may interact with disease variables to amplify illness severity and HRQOL. Developing a greater understanding of the mechanisms underlying IBS and advances in pharmacologic and nonpharmacologic treatment may enable health care providers to assist patients in improving their HRQOL.

Keywords
Irritable bowel syndrome, health-related quality of life, diarrhea, constipation

Introduction

The prevalence of irritable bowel syndrome (IBS) in Western countries is believed to range from 3–12%. Prevalence estimates vary because of differences in diagnostic methodologies and definitions used, although the actual prevalence is likely closer to the upper limit of the range, since many IBS sufferers do not seek medical attention.[1-5] In the United States, IBS accounts for 12% of the diagnoses made by primary care physicians and 28% of diagnoses made by gastroenterologists. Approximately 20–40% of all visits to US gastroenterologists are for IBS symptoms.[1,6,7] Studies within the past decade have consistently shown a greater prevalence of IBS in women than in men in Western countries (but not in Asia).[1,8-10] Part of the reason for this gender difference is that women are more likely than men to seek medical care for IBS symptoms. This is supported by the higher female-to-male ratio in clinic populations compared with community populations. Another important gender difference is that women are more prone to constipation whereas men are more likely to have diarrhea or mixed symptoms.

Thompson and colleagues conducted the first population-based survey of functional gastrointestinal (GI) disorders based on the Rome II diagnostic symptom-based criteria. They found a significant difference in the prevalence of IBS between women and men (15.7% vs 8.7%).[10] When diarrhea was the predominant bowel disturbance (IBS-D), the difference between females and males was 6.5% versus 3.4% which was non-significant; however, when constipation was the predominant bowel habit (IBS-C), the difference between women and men was statistically significant (7.5% vs 3.2%; $P<.05$). Talley and coworkers analyzed the prevalence of IBS subgroups in 3,022 (536 with IBS) residents of Olmsted County, Minnesota.[11] After adjusting for age, female gender was found to be significantly associated with IBS-C (6.7%, 95% confidence interval [CI] 5.2–8.2 vs 3.5%, 95% CI 2.3–4.8 for men). There were no significant gender differences for other IBS subgroups.

The prevalence of IBS generally declines with age. In the United States, the prevalence pattern shows a rise throughout early adulthood, a peak at the age of 40 years, and a decrease thereafter.[1-4] The prevalence in the elderly is high enough to raise the question of whether physicians are reluctant to diagnose new cases of IBS in this population because they presume the symptoms are associated with organic disease.[11]

Results of 2 epidemiologic studies in the United States and United Kingdom suggest an inversely proportional relationship between socioeconomic status and the prevalence of IBS symptoms that meet the Rome II diagnostic criteria.[1,12] IBS prevalence is higher in individuals with a low socioeconomic status. A contrary result was documented in New Zealand, where a cohort study was conducted among 926 individuals born between 1972 and 1973 who were tracked with self-reported data until they reached the age of 26 years. Results indicated that childhood socioeconomic environment was significantly associated with adult IBS, although in an unexpected way. The diagnosis of IBS was present in 6.6% of individuals in the highest socioeconomic class category compared with 2.4% of those in the lowest socioeconomic class category.[13] The reasons for these differences are not well understood.

The Burden of IBS

Studies in the United States and United Kingdom have demonstrated that IBS has an impact on both direct and indirect costs.[14] Direct costs include hospitalization, emergency department visits, outpatient clinic visits, and medication. A large majority of patients take over-the-counter medications, and approximately half receive prescription drugs.[1]

A study by Levy and coworkers assessed the costs of medical care in a large health maintenance organization for patients diagnosed with IBS in comparison with age- and gender-matched controls and patients treated for other GI disturbances, such as inflammatory bowel disease (IBD) and gastroesophageal reflux disease (GERD).[15] The total costs of care in the index year were approximately 50% higher in patients with IBS than in the control group; the difference narrowed to approximately 20% in subsequent years. Relative to other diagnoses of GI disorders, the costs for IBS were similar to those for GERD but lower than those for IBD.

Factors That May Play a Role in the Pathogenesis of IBS

Since no etiology of IBS has been established, there is an ongoing search for factors that might increase susceptibility to IBS and exacerbate its symptoms. One of the most studied candidates is a link to prior infection. In a meta-analysis by Halvorson and associates, 8 studies reported an elevated risk of IBS following recovery from infectious gastroenteritis.[16] At follow-up, which ranged from 3–12 months, mean prevalence of IBS was 9.8% in those who had sustained bacterial gastroenteritis but only 1.2% in the control groups, a 7-fold increase in the risk of developing postinfectious IBS.

Natural History of IBS

An analysis of 14 observational longitudinal studies among 1,099 adult clinical patients with IBS indicated that only 2–5% were diagnosed with an alternative organic GI disorder after 6 months to 6 years of follow-up.[17] Clinic-based studies were specified because the primary objective was to examine the occurrence of organic GI disease in patients diagnosed with IBS. Symptoms present at baseline worsened in 2–18% of patients, were unchanged in 30–50%, and improved or resolved in the rest. Thus, symptom severity remained the same or worsened in up to two thirds of patients. The investigators concluded that repeated diagnostic evaluations of patients with recurrent or persistent symptoms similar to their baseline symptoms are not warranted. Their results seem to justify a prudent use of diagnostic testing, which could minimize the cost of health care and also spare patients the potential complications of unnecessary procedures. However, among the limitations of this analysis were dependence on studies that were not primarily designed to address the objectives of this analysis, an inability to ascertain the transition of IBS into other functional GI disorders (eg, chronic constipation and functional dyspepsia), and an absence of

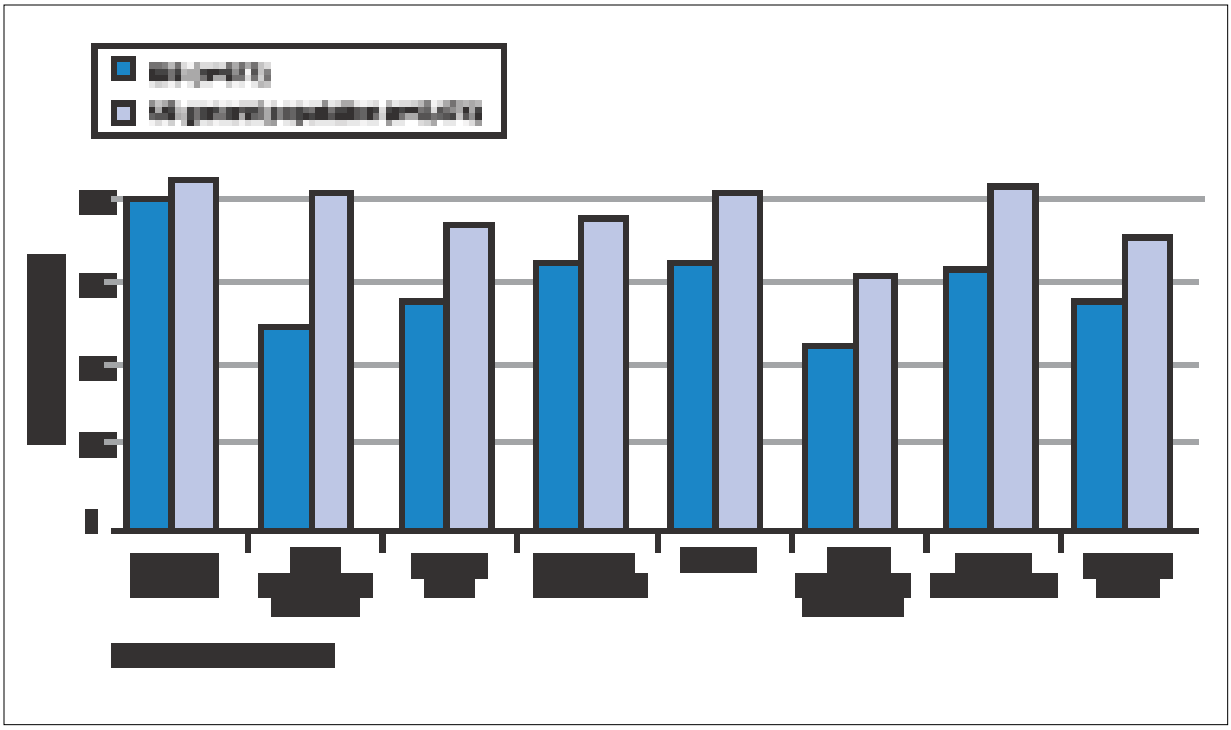

Figure 1. Reduced HRQOL in patients with IBS compared with the general US population. HRQOL was measured using a validated generic HRQOL instrument (SF-36).

HRQOL=health-related quality of life; IBS=irritable bowel syndrome; SF-36=short form-36.

Data (Adapted) from Gralnek IM et al.[18]

data on the frequency and duration of symptom flares. Further studies of defined cohorts of IBS patients are still needed.

HRQOL in Patients With IBS

Studies invariably find that IBS patients report decreased health-related quality of life (HRQOL). Figure 1 compares self-reported HRQOL using a generic instrument, (Short Form-36), in patients with IBS and healthy individual in the general US population[18] in the following domains: physical function, physical role limitations, bodily pain, emotional well-being, vitality, emotional role limitations, social functioning, and general health. All of the responses showed that patients with IBS scored lower in all 8 domains. This and another study showed that HRQOL in IBS patients was similar to or lower than in other chronic conditions.[19]

In a more recent study, Spiegel and colleagues tried to determine clinical predictors of HRQOL in patients with IBS.[20] Identification of such predictors can help health care providers make better assessments of HRQOL, which in turn can refine disease management. Pain and severe symptoms were the IBS-related symptoms that independently predicted the physical component of HRQOL (Figure 2). Interestingly, none of the other IBS symptoms significantly predicted the physical or mental components of HRQOL. Similarly, the main predictors of mental HRQOL were emotional thoughts or extra-intestinal symptoms. In descending order of impact, the key predictors were feelings of tension, feelings of nervousness, feelings of hopelessness, sleep difficulties, tiring easily, low sexual interest, and interference with sexual function.

The Longitudinal Outcomes Study of Gastro-Intestinal Symptoms in Canada (LOGIC) found that IBS impacts overall disease-specific HRQOL, particularly in the domains measuring health worries and food avoidance.[21] In addition, physicians reported nearly 87% of patients received IBS treatment during the 6 months prior to enrolling into the study and 72.5% had undergone a diagnostic procedure for their IBS symptoms. Although proponents of colonoscopy in the diagnosis of IBS claim that it provides reassur-

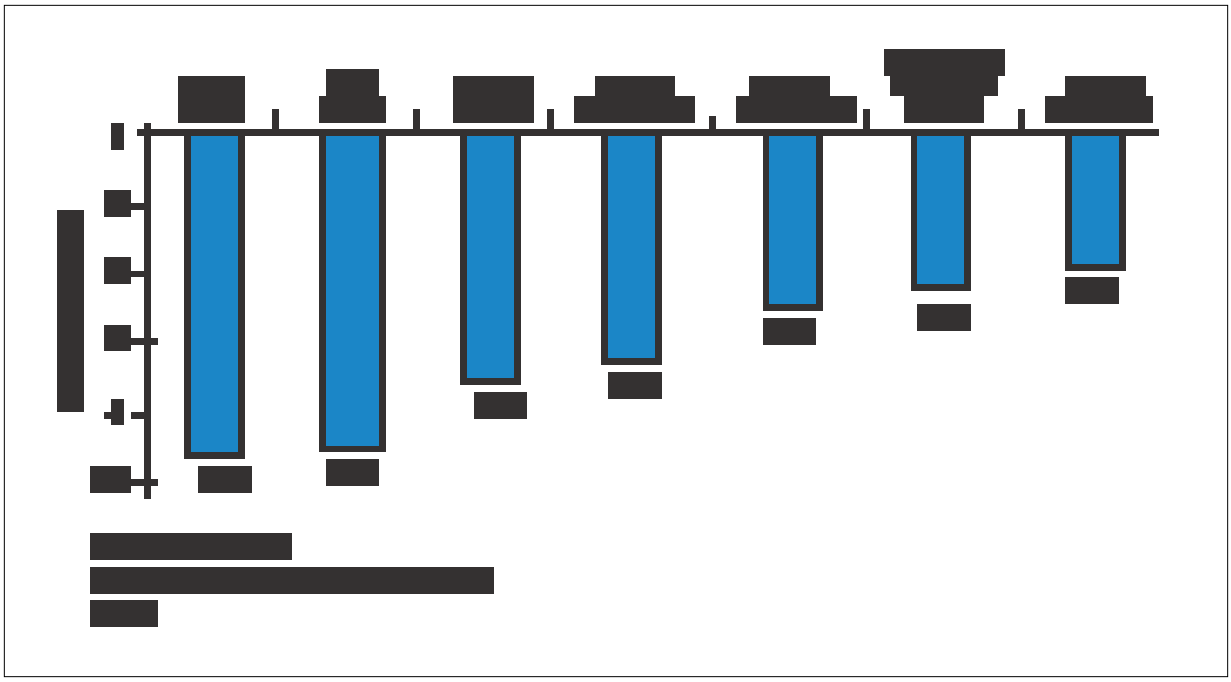

Figure 2. Clinical predictors of physical HRQOL (SF-36) in IBS.

HRQOL=health-related quality of life; IBS=irritable bowel syndrome; SF-36=short form-36.

Data (Adapted) from Spiegel BM et al.[20]

ance to patients, a retrospective evaluation of 458 IBS patients younger than 50 years of age, who completed questionnaires, indicated there was no independent association between a negative colonoscopy and reassurance or improved HRQOL.[22]

Spiegel and coworkers speculated that the disproportionate use of health care resources by patients with IBS may be due to high levels of comorbid somatization (ie, multiple unexplained somatic complaints and physical illnesses related to psychosocial distress).[23] Supporting the significant prevalence of non-GI symptoms in IBS particularly in those with greater illness severity, several studies have shown an increased number of medical visits and health care costs for non-GI related symptoms compared with healthy controls (Figure 3).[15, 23-26]

Improving HRQOL in Patients With IBS

Some pharmacologic and nonpharmacologic treatments have been found to improve HRQOL in patients with IBS. One study found that leuprolide, which was evaluated in the treatment of abdominal pain and nausea in premenopausal women with IBS, improved generic HRQOL in the health domain only.[27] Alosetron, a 5-HT_3

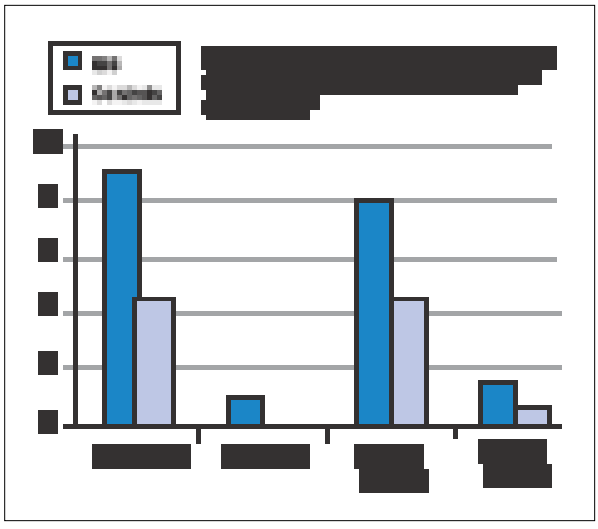

Figure 3. Greater number of annual outpatient visits for GI and non-GI symptoms in IBS.

GI=gastrointestinal; HRQOL=health-related quality of life; IBS-irritable bowel syndrome.

Data (Adapted) from Levy RL et al.[15]; Spiegel BM et al.[23]; Drossman DA et al.[24]; Levy RL at al.[25]; Sperber AD et al.[26]

antagonist approved for the treatment of severe IBS-D in women, has been shown to improve disease-specific HRQOL.[28] Desipramine, a tricyclic antidepressant, is used for the treatment of more moderate to severe IBS and was shown to have a trend in improving disease-specific HRQOL.[29] The use of standardized therapy in conjunction with multicomponent behavioral therapy has been shown to be superior to medical therapy alone and may improve HRQOL.[30] This management approach included IBS education, progressive muscle relaxation, and training patients in illness-related cognitive coping strategies. In another study, psychotherapy was shown to improve the physical component of HRQOL in patients with severe IBS.[31]

Summary

IBS has a significant worldwide prevalence and is associated with a major economic and health care burden that results in decreased HRQOL and work productivity. GI symptoms (particularly pain), as well as non-GI symptoms, are associated with increased health care visits and resource utilization, greater illness severity, and poorer HRQOL. Some treatments, most notably alosetron and behavioral therapy, have been found to improve HRQOL in patients with IBS.

Grant Support Information

Dr. Chang is supported by NIH grant # P50 DK64539 (NIDDK and ORWH) and #AR46122 (NIAMS). She has also received research grant support from GlaxoSmithKline and Prometheus Laboratories, Inc.

References

1. Andrews EB, Eaton SC, Hollis KA, et al. Prevalence and demographics of irritable bowel syndrome: results from a large web-based survey. *Aliment Pharmacol Ther.* 2005;22:935-942.
2. Hungin AP, Whorwell PJ, Tack J, Mearin F. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. *Aliment Pharmacol Ther.* 2003;17:643-650.
3. Hungin AP, Chang L, Locke GR, Dennis EH, Barghout V. Irritable bowel syndrome in the United States: prevalence, symptom patterns and impact. *Aliment Pharmacol Ther*. 2005;21:1365-1375.
4. Kumano H, Kaiya H, Yoshiuchi K, Yamanaka G, Sasaki T, Kuboki T. Comorbidity of irritable bowel syndrome, panic disorder, and agoraphobia in a Japanese representative sample. *Am J Gastroenterol.* 2004;99:370-376.
5. Lau EM, Chan FK, Ziea ET, Chan CS, Wu JC, Sung JJ. Epidemiology of irritable bowel syndrome in Chinese. *Dig Dis Sci*. 2002;47:2621-2624.
6. Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: a technical review for practice guideline development. *Gastroenterology.* 1997;112: 2120-2137.
7. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. *Gastroenterology.* 2002;123:2108-2131.
8. Gwee KA, Wee S, Wong ML, Png DJ. The prevalence, symptom characteristics, and impact of irritable bowel syndrome in an asian urban community. *Am J Gastroenterol.* 2004;99:924-931.
9. Sperber AD, Friger M, Shvartzman P, et al. Rates of functional bowel disorders among Israeli Bedouins in rural areas compared with those who moved to permanent towns. *Clin Gastroenterol Hepatol.* 2005;3:342-348.
10. Thompson WG, Irvine EJ, Pare P, Ferrazzi S, Rance L. Functional gastrointestinal disorders in Canada: first population-based survey using Rome II criteria with suggestions for improving the questionnaire. *Dig Dis Sci.* 2002;47:225-235.
11. Talley NJ, Zinsmeister AR, Melton LJ, III. Irritable bowel syndrome in a community: symptom subgroups, risk factors, and health care utilization. *Am J Epidemiol.* 1995;142:76-83.
12. Minocha A, Johnson WD, Abell TL, Wigington WC. Prevalence, sociodemography, and quality of life of older versus younger patients with irritable bowel syndrome: a population-based study. *Dig Dis Sci.* 2006;51:446-453.
13. Howell S, Talley NJ, Quine S, Poulton R. The irritable bowel syndrome has origins in the childhood socioeconomic environment. *Am J Gastroenterol.* 2004;99:1572-1578.
14. Maxion-Bergemann S, Thielecke F, Abel F, Bergemann R. Costs of irritable bowel syndrome in the UK and US. *Pharmacoeconomics*. 2006;24:21-37.
15. Levy RL, Whitehead WE, Von Korff MR, Feld AD. Intergenerational transmission of gastrointestinal illness behavior. *Am J Gastroenterol.* 2000;95:451-456.
16. Halvorson HA, Schlett CD, Riddle MS. Postinfectious irritable bowel syndrome–a meta-analysis. *Am J Gastroenterol*. 2006;101:1894-1899.
17. El Serag HB, Pilgrim P, Schoenfeld P. Systemic review: natural history of irritable bowel syndrome. *Aliment Pharmacol Ther.* 2004;19:861-870.
18. Gralnek IM, Hays RD, Kilbourne A, Naliboff B, Mayer EA. The impact of irritable bowel syndrome on health-related quality of life. *Gastroenterology.* 2000;119:654-660.
19. Frank L, Kleinman L, Rentza, Ciesla G, Kim JJ, Zacker C. Health-related quality of life associated with irritable bowel syndrome: comparison with other chronic diseases. *Clin Ther*. 2002;24:678-689.
20. Spiegel BM, Gralnek IM, Bolus R, et al. Clinical determinants of health-related quality of life in patients with irritable bowel syndrome. *Arch Intern Med.* 2004;164:1773-1780.
21. Pare P, Gray J, Lam S, et al. Health-related quality of life, work productivity, and health care resource utilization of subjects with irritable bowel syndrome: baseline results from LOGIC (Longitudinal Outcomes Study of Gastrointestinal Symptoms in Canada), a naturalistic study. *Clin Ther*. 2006;28:1726-1735.
22. Spiegel BM, Gralnek IM, Bolus R, et al. Is a negative colonoscopy associated with reassurance or improved health-related quality of life in irritable bowel syndrome? *Gastrointest Endosc.* 2005;62:892-899.
23. Spiegel BM, Kanwal F, Naliboff B, Mayer E. The impact of somatization on the use of gastrointestinal health-care resources in patients with irritable bowel syndrome. *Am J Gastroenterol.* 2005;100:2262-2273.
24. Drossman DA, Li Z, Andruzzi E, et al. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. *Dig Dis Sci*. 1993;38:1569-1580.
25. Levy RL, Von Korff M, Whitehead WE, et al. Costs of care for irritable bowel syndrome patients in a health maintenance organization. *Am J Gastroenterol.* 2001;96:3122-3129.
26. Sperber AD, Carmel S, Atzmon Y, et al. Use of the Functional Bowel Disorder Severity Index (FBDSI) in a study of patients with the irritable bowel syndrome and fibromyalgia. *Am J Gastroenterol*. 2000;95:995-998.
27. Mathias JR, Clench MH, Abell TL, et al. Effect of leuprolide acetate in treatment of abdominal pain and nausea in premenopausal women with functional bowel disease: a double-blind, placebo-controlled, randomized study. *Dig Dis Sci.* 1998;43:1347-1355.
28. Watson ME, Lacey L, Kong S, et al. Alosetron improves quality of life in women with diarrhea-predominant irritable bowel syndrome. *Am J Gastroenterol.* 2001;96:455-459.
29. 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.
30. Heymann-Monnikes I, Arnold R, Florin I, Herda C, Melfsen S, Monnikes H. The combination of medical treatment plus multicomponent behavioral therapy is superior to medical treatment alone in the therapy of irritable bowel syndrome. *Am J Gastroenterol.* 2000;95:981-994.
31. Creed F, Fernandes L, Guthrie E, et al. The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome. *Gastroenterology.* 2003;124:303-317.

Diagnosing Irritable Bowel Syndrome

Philip S. Schoenfeld, MD, MSEd, MSc (Epi), FACG

Address correspondence to:
Philip S. Schoenfeld, MD, MSEd, MSc (Epi), FACG
Associate Professor of Medicine
Director, Training Program in GI Epidemiology
University of Michigan School of Medicine
Ann Arbor, MI 48105
Tel: 734-845-5795
Fax: 734-845-3091
E-mail: pschoenf@med.umich.edu

Abstract: Irritable bowel syndrome (IBS) is a common diagnosis in gastroenterology practice. It is a functional gastrointestinal disorder characterized by abdominal pain and/or discomfort accompanied by disturbed defecation and is associated with significant disability and health care costs. The clinical presentation of IBS is familiar so that routine use of multiple diagnostic tests in patients without alarm symptoms is not recommended by the American College of Gastroenterology guidelines. Testing for celiac disease may be considered for patients with diarrhea-predominant IBS. Routine colon cancer screening with colonoscopy should be offered to all patients aged 50 years or older regardless of the presence or absence of symptoms suggestive of IBS.

Keywords
Irritable bowel syndrome, celiac disease, Rome criteria, gastrointestinal disorders

Introduction

The classification of irritable bowel syndrome (IBS) and other functional gastrointestinal disorders (FGIDs) has evolved over the years. Three decades ago, Manning and colleagues in the United Kingdom proposed a categorization referred to as the Manning criteria for IBS.[1] Of the many symptoms that were suggestive as being characteristic of IBS, only 4 (distension, relief of pain with defecation, and looser and more frequent bowel movements with the onset of pain) were found to be significantly more common in patients with IBS than organic disease. Subsequently, IBS was subsumed into the Rome criteria for FGIDs of unknown cause, which represents a monumental collaboration of international experts who studied the gastrointestinal tract.

Rome I was notable for approaching FGIDs as diagnoses of inclusion rather than diagnoses of exclusion. This was significant because it weaned clinicians from reliance on superfluous diagnostic procedures, such as routine colonoscopy in patients less than 50 years of age with chronic constipation. Rome II[2] focused on the frequency of symptoms, such as, how often they occurred over 12 weeks—not necessarily consecutive—within 12 months. Rome III (Table 1)[3] refines previous concepts and incorporates recent findings on the epidemiology, pathophysiology, diagnosis, and therapy of FGIDs. Rome III also changes the time frame for diagnosis to criteria fulfilled for the previous 3 months with symptom onset at least 6 months prior to diagnosis. Additionally, it discusses mental health implications for sufferers of IBS, and suggests "red flag" (alarm) signs

Table 1. Rome III Diagnostic Criteria for Irritable Bowel Syndrome

Recurrent abdominal pain or discomfort (uncomfortable sensation not described as pain)at least 3 days per month in the last 3 months associated with 2 or more of the following features:
• Improvement with defecation
• Onset associated with a change in frequency of stool
• Onset associated with a change in form (appearance) of stool
Symptoms that cumulatively support the diagnosis of irritable bowel syndrome
• Abnormal stool frequency (more than 3 bowel movements per day or fewer 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

and symptoms that may warrant further diagnostic testing. This review will discuss a practical approach to the diagnosis of IBS.

Procedures to Rule Out a Non-IBS Diagnosis

Comprehensive exclusionary diagnostic tests to rule out a non-IBS diagnosis are expensive, time-consuming, and usually unnecessary. In a prospective study, 196 patients who met the clinical criteria for IBS were subjected to hematologic, biologic, and metabolic testing, as well as structural evaluation of the colon.[4] Results of complete blood count, erythrocyte sedimentation rate (ESR), serum chemistries, thyroid profile, and urinalysis were normal or not clinically informative. Stool examinations showed no parasites.

Barium enema, x-ray, and colonoscopy or flexible sigmoidoscopy revealed 1 case of colon cancer in a patient aged greater than 50 years and 1 case of inflammatory bowel disease (IBD). Although other patients in this study were diagnosed with polyps (n=9), melanosis coli (n=2), diverticulosis (n=17), and hemorrhoids (n=11), none of these disorders accounted for the patients' abdominal discomfort with altered bowel habits. The end result was that 194 of the 196 patients (99%) had a negative workup and were given a final diagnosis of IBS. Combined data of 1,452 patients, who met the Rome criteria for at least 6 months, were analyzed in 2 multinational studies to assess the utility of additional investigations.[5] Lactose malabsorption was diagnosed in 23% (256/1,122) of patients, although lactose malabsorption is present in 20–25% of the general US population. It is unclear if lactose malabsorption accounted for IBS symptoms in these patients. Similarly, an abnormal thyroid stimulating hormone level was found in 6% (67/1,209) of patients. While 5–6% of the general US population also has an abnormal thyroid stimulating hormone level, it is unclear if thyroid dysfunction accounted for IBS symptoms in these patients.

Thus, the limited detection rates, added costs, and inconvenience of these tests suggest that their routine use in the diagnostic workup of established IBS patients is dubious. Similar data in a meta-analysis of observational longitudinal studies of clinic patients found only 2–5% of patients with IBS were diagnosed with an alternative organic gastrointestinal (GI) disorder after a follow-up period of 6 months to 6 years. It is unclear if these alternative organic GI disorders could have accounted for the earlier IBS diagnosis (eg, diagnosis of a gastric ulcer 2-3 years after an IBS diagnosis does not equate with a gastric ulcer causing the original IBS symptoms).[6]

A rectal biopsy to exclude melanosis coli and collagenous or microscopic colitis in patients with IBS is common, even though there are little data to support or refute this practice. The value of this invasive procedure was assessed in 89 patients with IBS and 59 control subjects who underwent flexible sigmoidoscopy.[7] Histologic analysis of the biopsy samples indicated all of the IBS patients and the controls had normal mucosa and were free from melanosis coli or collagenous or microscopic colitis. The findings clearly did not support a routine rectal biopsy in patients with IBS. However, the conclusions are not definitive since this is a small study and is the only study to address this issue.

In many cases, a patient with classic IBS symptoms (abdominal discomfort associated with altered bowel habits) may benefit from having a complete blood count, ESR, and a fecal occult blood test (FOBT). If the patient is anemic, with an elevated ESR, or has a positive FOBT, then the patient has an "alarm" sign or "red flag," and further diagnostic tests may be indicated. If no "alarm" signs or "red flags" are present, treatment for IBS should be initiated. If the patient does not have an adequate response to therapy, further diagnostic testing may be considered.

Red Flags to Consider

There are alarm symptoms, physical examination signs, and laboratory results that may be considered red flags, suggesting a higher likelihood of non-IBS organic dis-

Table 2. Common Red Flags*

History	Physical examination	Laboratory findings
• Onset in older patients (>50 years) • Family history of colon cancer or inflammatory bowel disease • Unintentional weight loss of ≥10 lbs • Hematochezia • Symptoms of underlying disorders such as hypothyroidism	• Abnormal findings on rectal examination • Abdominal mass	• ↓Hgb • ↑WBC count • Guaiac-positive stool • ↑ESR

*List not exhaustive.

ESR=erythrocyte sedimentation rate; Hgb=hemoglobin; WBC=white blood cell.

Data (Adapted) from Drossman DA et al.[8] Paterson WG et al.[9] Camilleri M, Choi MG.[10] Frissora CL, Harris LA.[11]

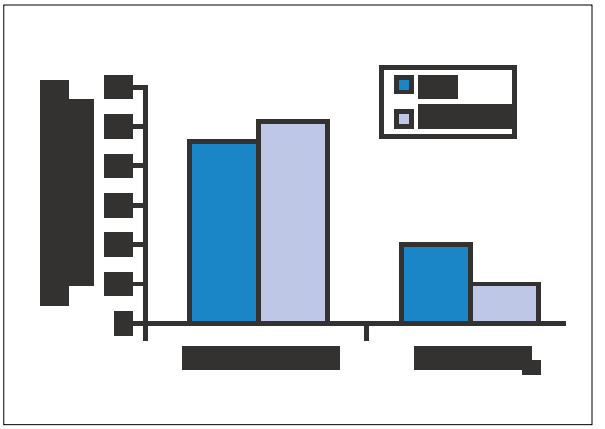

Figure 1. Prevalence of positive LBT in patients with IBS and healthy controls.

*Positive LHBT=Increase in breath H_2 >20 ppm.
Positive CH_4=Breath CH_4 detected at any concentration during test.
IBS=irritable bowel syndrome; LBT=lactulose breath test;
LHBT=lactulose hydrogen breath test; CH_4=methane.

Data (Adapted) from Bratten J et al.[14]

orders in these patients. The presence of these red flags suggests the need to perform more diagnostic testing. Table 2 lists the more common red flags and what the physician should be targeting.[8-11] New onset IBS-like symptoms in patients greater than 50 years of age is an important red flag that has been associated with a high likelihood of finding another organic disorder as a cause for the IBS-like symptoms when a diagnostic evaluation is performed.[12]

Are Patients With IBS-like Symptoms More Likely to Have Celiac Disease?

Whereas the pretest probability of finding IBD, colorectal cancer, or infectious gastroenteritis is low, celiac disease has a higher prevalence in patients meeting the Rome II criteria for IBS in the United Kingdom, where the prevalence of celiac disease is approximately 1%.

Previously, Sanders and colleagues had conducted a case control study of 300 new patients who fulfilled the Rome II criteria at a university hospital and compared them with 300 age- and sex-matched controls.[13] All patients were evaluated for celiac disease by analysis of serum immunoglobulin A (IgA) and IgG antigliadin and endomysial antibodies. Those with a positive serology were offered a confirmatory biopsy. Of 271 available patients who fulfilled the Rome II criteria, 5% (14/271) were confirmed to have celiac disease versus less than 1% in the control population. Thus, patients with IBS symptoms in the United Kingdom have about a 103 increase in the pre-test probability of celiac disease compared with a control population. Given this finding, it makes sense to routinely check for celiac disease among patients who present with IBS symptoms in the United Kingdom.

However, the prevalence of celiac disease in the United Kingdom is considerably higher than in the United States, both in the general population and in individuals with symptoms suggestive of IBS, so that the Sanders findings should not be extrapolated into US gastroenterology practice. Also, the prevalence of celiac disease is substantially higher in individuals who have close relatives with this disorder, and the onset of the symptoms of celiac disease can occur at any age. Therefore, a detailed family history should be taken of patients who present with GI symptoms suggestive of IBS, and if positive, patients should be investigated with serology and duodenal biopsy.

Breath Testing for Small Intestinal Bacterial Overgrowth

Small intestinal bacterial overgrowth (SIBO) may play a pathophysiologic role in some patients with IBS, and abnormalities in lactulose hydrogen breath testing (LHBT) may be used to diagnose SIBO. However, a recent study in 224 patients with IBS and 40 healthy subjects found that the majority of patients with IBS and controls met criteria for an abnormal LHBT. However, the test could not discriminate between IBS patients and healthy controls (Figure 1).[14] These results indicate that the appropriate use of LHBT amongst patients with IBS symptoms has not been adequately defined.

A Reason to Perform Diagnostic Tests

Even in patients without red flags, it may be appropriate to do some diagnostic testing in those with IBS symptoms to reassure them that they do not have more serious organic disorders like colorectal cancer. This may be especially important for patients with a high level of anxiety and/or depression. Although the likelihood of finding another organic disorder with colonoscopy or computed tomography scans is very low, offering the option of these diagnostic tests may help calm those patients who are apprehensive about the presence of other organic disorders.

Summary

IBS is a common presentation seen by gastroenterologists. The diagnosis is symptom-based, the symptoms are recurrent, and the likelihood of finding a different organic disorder causing the classic symptoms of abdominal discomfort and altered bowel habits is approximately 1–2%. The Rome III criteria and the American College of Gastroenterology guidelines make a strong case for a diagnosis of inclusion for IBS rather than one of laborious, costly, and unnecessary exclusion of potential underlying organic causes in the absence of alarm symptoms. A number of alarm symptoms (red flags) have been proposed, but the most critical is the onset of new symptoms in a patient older than 50 years. Procedures such as colonoscopy are unnecessary in patients aged less than 50 years with obvious IBS but may be offered as an option to patients with a high degree of concern and/or anxiety as a means of reassurance.

Grant Support Information

Dr. Schoenfeld has no conflicts of interest to report with respect to this manuscript.

References

1. Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. *BMJ.* 1978;2:653-654.
2. Thompson WG, Longstreth GF, Drossman DA, et al. Functional bowel disorders and functional abdominal pain. *Gut.* 1999;45(suppl 2):II43-II47.
3. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology.* 2006;130:1480-1491.
4. Tolliver BA, Herrera JL, DiPalma JA. Evaluation of patients who meet clinical criteria for irritable bowel syndrome. *Am J Gastroenterol.* 1994;89:176-178.
5. 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;94:1279-1282.
6. El-Serag HB, Pilgrim P, Schoenfeld P. Systematic review: natural history of irritable bowel syndrome. *Aliment Pharmacol Ther.* 2004;19:861-870.
7. MacIntosh DG, Thompson WG, Patel DG, et al. Is rectal biopsy necessary in irritable bowel syndrome? *Am J Gastroenterol.* 1992;87:1407-1409.
8. Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: a technical review for practice guideline development. *Gastroenterology.* 1997;112:2120-2137.
9. Paterson WG, Thompson WG, Vanner SJ, et al. Recommendations for the management of irritable bowel syndrome in family practice. *CMAJ.* 1999;161:154-160.
10. Camilleri M, Choi M-G. Review article: irritable bowel syndrome. *Aliment Pharmacol Ther.* 1997;11:3-15.
11. Frissora CL, Harris LA. Pathophysiology, clinical characteristics, and treatment of irritable bowel syndrome. *Emerg Med.* 2001;4:57-64.
12. Hammer J, Eslick GD Howell SC, et al. Diagnostic yield of alarm features in irritable bowel syndrome and functional dyspepsia. *Gut* 2004;53:666-672.
13. Sanders DS, Carter MJ, Hurlstone DP, Pearce A, 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;358:1504-1508.
14. Bratten JR, Spanier J, Jones MP. Lactulose breath testing does not discriminate patients with irritable bowel syndrome from healthy controls. *Am J Gastroenterol.* 2008;103:958-963.

Current Treatment Options for Irritable Bowel Syndrome

Brian E. Lacy, PhD, MD, FACG

Address correspondence to:
Brian E. Lacy, PhD, MD, FACG
Director, GI Motility Laboratory
Dartmouth–Hitchcock Medical Center
One Medical Center Drive
Lebanon, NH 03756
Tel: 603-650-5215
Fax: 603-650-5525
E-mail: brian.e.lacy@hitchcock.org

Abstract: Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disease characterized by abdominal pain and discomfort, bloating, and altered bowel function (constipation, diarrhea, or both). Since there is no known cause and no panacea for the multiple manifestations of IBS, therapy is targeted toward improving specific symptoms. The American College of Gastroenterology published an evidence-based position statement on the management of IBS. Treatments were graded from A (accurate based on evidence) to C (prone to multiple biases) based on the quality of the supporting studies. None of the traditional treatments (bulking agents, antispasmodics, tricyclic antidepressants, and behavioral therapy) received a grade A. The clinical trials for these agents were generally considered weak on methodologic grounds. Newer agents, such as 5-HT_3 antagonists and 5-HT_4 agonists, are effective but may cause serious complications in some patients. Lubiprostone is the newest agent approved by the US Food and Drug Administration for the treatment of women with IBS and constipation.

Keywords
Irritable bowel syndrome, constipation, diarrhea, lubiprostone, laxants, alosetron, tegaserod

Introduction

The treatment of patients with irritable bowel syndrome (IBS) focuses on alleviating individual symptoms, including abdominal pain and discomfort, bloating, and disordered bowel habits, while also attempting to relieve global symptoms that have a major impact on patients' quality of life.[1] A large number of agents are currently available for treating symptoms of IBS, including some that are available only on a restricted basis (Figure 1).[1,2] The level of evidence supporting the efficacy and safety of these agents is based in large part on how well the clinical trials met the standards set by the American College of Gastroenterology (ACG) Functional Gastrointestinal (GI) Disorders Task Force guidelines.[3] Levels of evidence range from high-quality randomized clinical trials (level I) to nonrandomized clinical trials or case series (level III to IV). Not surprisingly, results of IBS trials may be confounded by a placebo response, including increasing rates of global improvement with increasing dosing frequency.[4] This paper will focus on an evidence-based review of currently available treatment options for patients with IBS.

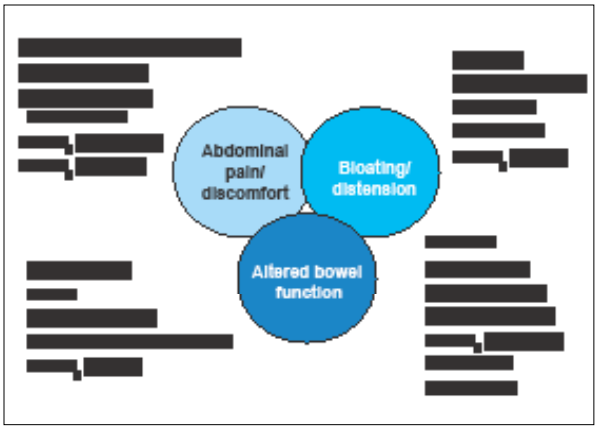

Figure 1. Current treatment options for IBS.

*Alosetron is only available to physicians who enroll in the Prometheus Prescribing Program for LOTRONEX.

**Tegaserod is only available for emergency situations that are immediately life-threatening or serious enough to quality for hospitalization.

TCAs = tricyclic antidepressants; SSRIs = selective serotonin reuptake inhibitors.

Adapted from Brandt LJ et al[1] and Drossman DA et al.[2]

Fiber Therapy for Constipation in IBS

Healthcare providers commonly recommend fiber (whether as a supplement or as part of the diet) as the first treatment for symptoms of IBS. The rationale for using fiber is that it adds bulk to the stool and accelerates orocecal transit. Fiber is safe, easy to use, and inexpensive. The evidence for using fiber comes from 13 randomized clinical trials that assessed the efficacy of bulking agents including psyllium, ispaghula husk, wheat bran, corn fiber, and calcium polycarbophil for the treatment of patients with constipation-predominant IBS (IBS-C).[1,5,6] These studies tended to have small sample sizes and were of low-to-intermediate quality. The effects did not reach statistical significance even after the low-quality studies were excluded. Polycarbophil improved symptoms and eased stool passage, and ispaghula improved constipation and stool frequency, but neither was found to relieve abdominal pain. These data show that fiber therapy is no more effective than placebo at improving global IBS symptoms and is associated with increases in intestinal gas, bloating, and distension in 25–40% of patients.

Smooth-Muscle Relaxants

Smooth-muscle relaxants (a subclass of antispasmodics) have been evaluated in a number of different trials for their ability to improve abdominal pain, the most frequent and disabling symptom of IBS. However, drugs in this class are unlikely to be approved by the US Food and Drug Administration (FDA) for the treatment of IBS because data on efficacy is limited, and because smooth-muscle relaxation may worsen constipation and produce typical anticholinergic side effects such as dry mouth and eyes, blurred vision, increased intraocular pressure, tachycardia, and urinary retention.[5-7]

Antidepressants

Non-gastrointestinal symptoms frequently occur in patients with IBS. Panic disorders, anxiety, and depression are far more common in patients with IBS who are referred for evaluation than in healthy controls. Physicians now routinely prescribe antidepressants for symptoms of depression and anxiety to many patients with IBS. Clinically, this may be advantageous since antidepressants also have neuromodulatory and analgesic properties that are independent of their psychotropic effects. Tricyclic antidepressants (TCAs) are 1 group of agents routinely used to relieve symptoms of IBS. Although TCAs may not relieve bloating, and high doses may worsen constipation, low doses of amitriptyline, desipramine, imipramine, and nortriptyline have been shown to lessen functional abdominal pain in some patients with IBS.[8–10] However, the anticholinergic side effects of TCAs tend to be bothersome for many patients.

Selective serotonin reuptake inhibitors (SSRIs) are used extensively in patients with IBS despite a lack of data from large, placebo-controlled clinical trials. These agents may improve symptoms of anxiety and this may translate into a global improvement in overall health. Four separate studies have evaluated the efficacy of fluoxetine, cilansetron, and paroxetine in the treatment of patients with IBS. However, these studies were all limited by small sample sizes and modest treatment periods (6 weeks on average). In addition, the impact on IBS-specific symptoms was limited. Overall, it is not yet clear what role antidepressants play in the treatment of IBS.

Antidiarrheal Agents

Although not approved by the US FDA for patients with IBS, antidiarrheal agents are commonly used to treat patients with IBS and diarrhea.[1] Loperamide was shown to improve diarrhea in 4 clinical trials. In 2 of the trials that were considered to be of high quality, significant improvement occurred with regard to stool consistency and stool frequency compared with placebo, although there was no improvement in abdominal pain or distension.[5] Loperamide was given a grade A recommendation (based on evidence) for the treatment of painless diarrhea but was considered to be no more effective than placebo in relieving global IBS symptoms.[1]

5-HT$_3$ Receptor Antagonists: Alosetron and Cilansetron

Disturbances in GI motility and visceral sensory perception may underlie IBS symptoms of abdominal pain/discomfort, bloating/distension, fecal urgency, constipation, and diarrhea. Serotonin (5-hydroxytryptamine; 5-HT) acts primarily on intestinal cells but also on the central nervous system and visceral neurons to facilitate communication between the enteric nervous system and its effectors. 5-HT modulates both pain perception and bowel motility. Receptor subtypes 5-HT$_3$ and 5-HT$_4$ play an important role in IBS and have become pharmacologic targets in patients with both non-constipated IBS (NC-IBS) and IBS with diarrhea (IBS-D). By selectively antagonizing the 5-HT$_3$ receptor, alosetron slows GI motility, decreases intestinal fluid secretion, and modulates visceral pain perception. Alosetron was previously given a grade A recommendation by the ACG.[1]

A meta-analysis of 6 studies containing 1,762 patients demonstrated that alosetron is clearly more effective than placebo at relieving global IBS symptoms (eg, diarrhea, pain, fecal urgency) in female patients (pooled odds ratio, 1.81; 95% confidence interval [CI] 1.57–2.10; *P*<.0001).[11] A recent systematic review and meta-analysis of 14 randomized clinical trials involving placebo (n=3,043) or mebeverine (n=304) as a comparator showed that alosetron (n=3,024) and the investigational agent cilansetron (n=1,116) significantly improve abdominal pain and discomfort and global IBS symptoms in men and women with NC-IBS or IBS-D.[12] Results of the meta-analyses of alosetron and cilansetron versus control are shown in Figure 2.[12] All 14 of the trials were considered to be of high quality and used comparable, standardized end points and similar study designs.

Constipation was the most common side effect of either drug (pooled relative risk, 4.28; 95% CI, 3.28–5.60; I^2, 65%). Patients with IBS-D experienced less constipation than did mixed study populations of patients with NC-IBS and IBS-D. Nine patients in the 5-HT$_3$ antagonist treatment group had possible ischemic colitis compared with none in the control group (*P*=.06). The events were all self-limited and did not require surgery. Due to increased risks of severe constipation and the association with ischemic colitis, alosetron was withdrawn from the US market in November 2000. It was, however, subsequently restored under a limited-use program for women with severe IBS-D who failed to improve on standard therapy. It is important to note that under this restricted-use program, no serious adverse events have occurred. Serious adverse events associated with cilansetron during drug development make it unlikely that this medication will be approved by the US FDA.

5-HT$_4$ Agonist: Tegaserod

Tegaserod, a selective partial 5-HT$_4$ agonist, whose mechanism of action is shown schematically in Figure 3,[13] activates GI motility, speeds orocecal transit, increases the frequency of defecation, improves the softness of stools, modulates visceral sensitivity, and reduces abdominal contractions.[14] Symptoms of constipation, abdominal pain, and bloating improved in many patients with IBS and constipation. Results from a large, randomized clinical trial involving 2,660 women with IBS-C showed tegaserod to be superior to placebo in each primary efficacy variable for both overall IBS symptoms and abdominal discomfort/pain.[15]

Based on 8 large, placebo-controlled, randomized clinical trials involving more than 18,000 patients who met Rome criteria for IBS, the ACG awarded tegaserod a grade A recommendation for the treatment of IBS-C and chronic constipation. Unfortunately, safety data from 29 clinical trials in patients with a variety of GI conditions, including IBS and chronic constipation, demonstrated that cardiovascular events occurred in 13 (0.1%) of 11,614 patients treated with tegaserod, compared with only 1 event (0.01%) in 7,031 patients treated with placebo. Although all of the affected patients had pre-existing cardiovascular disease and/or risk factors, tegaserod was removed from the US market in March 2007.[16]

CIC-2 Chloride Channel Activator: Lubiprostone

Lubiprostone, a bicyclic fatty acid metabolite of prostaglandin E$_1$ was approved by the US FDA for the treatment of chronic constipation in men and women in January 2006.[17,18] By activating the CIC-2 chloride channel (located on the luminal side of the epithelial cells), lubiprostone stimulates movement of chloride ions into the lumen and enhances sodium and water flow, thus easing intestinal transit and stool passage. The US FDA recently approved lubiprostone for the treatment of women with IBS-C, based on the results of 2 large, double-blind, placebo-controlled studies. The results of these studies are discussed in the accompanying paper in this supplement by Dr. Quigley.

The Role of Diet in IBS

Patients commonly assume that food allergies play an important role in IBS, but this is not borne out by the evidence. (Gluten, a known agonist in celiac disease, is a special case.) About 25% of patients with IBS are lactose intolerant; this prevalence is similar to that of the general population. In addition, it is estimated that up to 50% of patients with IBS-D are fructose intolerant.

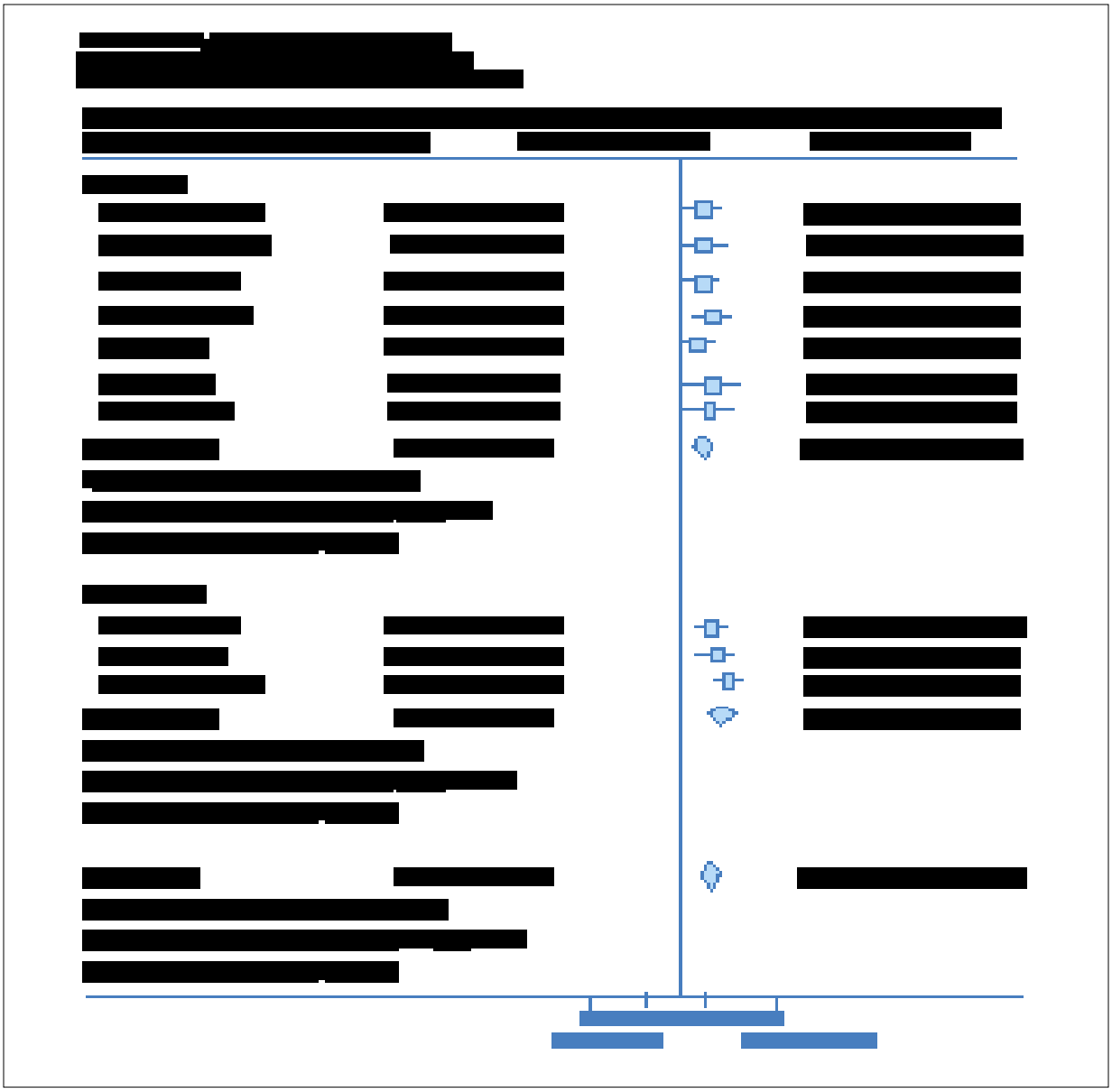

Figure 2. Patients responding to alosetron or cilansetron with relief of abdominal pain and discomfort.

A=Alosetron; APT=*Alimentary Pharmacology & Therapeutics*; AJG=*American Journal of Gastroenterology*; ArchIM=*Archives of Internal Medicine*; C=Cilansetron; GE=*Gastroenterology*; Lane=*Lancet*; M=Mebeverine.

Reprinted from Andresen V et al.[12]

Patients should be informed that sensitivity to food or beverages, a fairly common response to spices, sauces, fast foods, caffeine, and alcohol, is very different from a true food allergy, which is immunoglobulin E (IgE)- and mast cell–mediated, and which can trigger anaphylactic reactions to nuts, shellfish, and other foods in susceptible individuals.[19] The mechanisms underlying food sensitivities are not known.

It is possible, however, to have less serious immunoglobulin G (IgG)-mediated immune reactions to certain foods. This hypothesis was tested by Atkinson and coworkers in a 3-month controlled food-elimination trial in patients with IBS.[20] A total of 150 outpatients with IBS were randomized to a "true" diet devoid of all foods to which they mounted an IgG antibody response (detected with enzyme-linked immunosorbent assay [ELISA] at screening) or to a "sham" diet that included foods to which had they responded by producing IgG antibodies. After 12 weeks, the true diet resulted in a 10% lower symptom score than did the sham diet, as well as a higher global

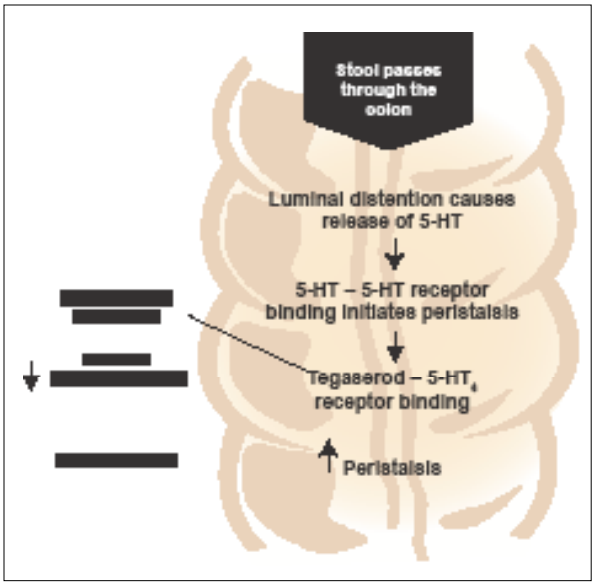

Figure 3. Tegaserod: Mechanism of action.

Reprinted from Cash BD et al.[13]

rating. These results suggest that food elimination based on IgG antibodies may be beneficial to patients with IBS and justify larger, well-controlled studies.

Summary

The treatment of patients with IBS is challenging and treatment options are limited. The dearth of treatment options particularly reflects the fact that we still do not completely understand the pathophysiology of IBS. In addition, not all individuals will respond to one medication. Even within specific IBS subtypes (ie, IBS-D), patients have a variety of symptoms and response variability to treatment.

A critical review of the literature shows that most early trials of IBS medications were generally deficient in their randomization, double-blinding, and recording of dropouts and withdrawals. Thus, these results must be viewed cautiously. The quality of randomized clinical trials has improved over the past decade, however, large, high-quality studies are still needed.

In general, studies have found that bulking agents are no more effective than placebo. TCAs are also no more effective than placebo in improving global symptoms of IBS but may improve abdominal pain. Smooth-muscle antispasmodics may improve symptoms in some patients with IBS, but side effects are limiting, and these agents are best used on an as-needed basis. The removal from the general market of tegaserod and alosetron is particularly discouraging.

Grant Support Information

During the last 24 months, Dr. Lacy has received investigator initiated, unrestricted educational grants for clinical research studies from Novartis Pharmaceuticals, Takeda Pharmaceuticals, AstraZeneca, and Medtronic. Dr. Lacy is supported in part by NIH grants DK 65713-03 and R44-DK063732.

References

1. Brandt LJ, Bjorkman D, Fennerty MB, et al. Systematic review on the management of irritable bowel syndrome in North America. *Am J Gastroenterol.* 2002;97(11 suppl):S7-S26.
2. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. *Gastroenterology.* 2002;123:2108-2131.
3. Brandt LJ, Prather CM, Quigley EMM, Schiller LR, Schoenfeld P, Talley NJ. Systematic review on the management of chronic constipation in North America. *Am J Gastroenterol.* 2005;100:S5-S22.
4. Pitz M, Cheang M, Bernstein CN. Defining the predictors of the placebo response in irritable bowel syndrome. *Clin Gastroenterol Hepatol.* 2005;3: 237-247.
5. Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. *Ann Intern Med.* 2000;133:136-147.
6. Lesbros-Pantoflickova D, Michetti P, Fried M, Beglinger C, Blum AL. Meta-analysis: the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther.* 2004;20:1253-1269.
7. Page JG, Dimberger GM. Treatment of irritable bowel syndrome with Bentyl (dicyclomine hydrochloride). *J Clin Gastroenterol.* 1981;3:153-156.
8. Drossman DA, Toner BB, Whitehead WE, et al. Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe bowel disorders. *Gastroenterology.* 2003;125:19-31.
9. Farthing MJ. Treatment options in irritable bowel syndrome. *Best Pract Res Clin Gastroenterol.* 2004;18:773-786.
10. Jackson JL, O'Malley PG, Tomkins G, Balden E, Santoro J, Kroenke K. Treatment of functional gastrointestinal disorders with antidepressant medications: a meta-analysis. *Am J Med.* 2000;108:65-72.
11. Cremonini F, Delgado-Aros S, Camilleri M. Efficacy of alosetron in irritable bowel syndrome: a meta-analysis of randomized controlled trials. *Neurogastroenterol Motil.* 2003;15:79-86.
12. Andresen V, Montori VM, Keller J, West CP, Layer P, Camilleri M. Effects of 5-hydroxytryptamine (serotonin) type 3 antagonists on symptom relief and constipation in nonconstipated irritable bowel syndrome: a systematic review and meta-analysis of randomized, controlled trials. *Clin Gastroenterol Hepatol.* 2008;6:545-555.
13. Cash BD, Lacy BE. Systemic Review: FDA-approved prescription medications for adults with constipation. *Gastroenterol Hepatol.* 2006;2:736-749.
14. Evans BW, Clark WK, Moore DJ, Whorwell PJ. Tegaserod for the treatment of irritable bowel syndrome and chronic constipation. *Cochrane Database of Systematic Reviews.* 2007;CD003960:1-45.
15. Tack J, Müller-Lissner S, Bytzer P, et al. A randomised controlled trial assessing the efficacy and safety of repeated tegaserod therapy in women with irritable bowel syndrome with constipation. *Gut.* 2005;54:1707-1713.
16. FDA public health advisory tegaserod maleate (marketed as Zelnorm). http://www.fda.gov/cder/drug/advisory/tegaserod.htm. Accessed July 21, 2008.
17. Lacy BE, Levy LC. Lubiprostone. A chloride channel activator. *J Clin Gastroenterol.* 2007;41:345-351.
18. Johanson JF, Drossman DA, Panas R, Wahle A, Ueno R. Clinical trial: phase 2 study of lubiprostone for irritable bowel syndrome with constipation. *Aliment Pharmacol Ther.* 2008;27:685-696.
19. MacDermott RP. Treatment of irritable bowel syndrome in outpatients with inflammatory bowel disease using a food and beverage intolerance, food and beverage avoidance diet. *Inflamm Bowel Dis.* 2007;13:91-96.
20. Atkinson W, Sheldon TA, Shaath N, Whorwell PJ. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomized controlled trial. *Gut.* 2004;53:1459-1464.

Emerging Strategies for Managing IBS: What Does the Future Hold?

Eamonn M.M. Quigley, MD, FACG

Address correspondence to:
Eamonn M.M. Quigley, MD, FACG
Professor of Medicine and
Human Physiology
Department of Medicine
Alimentary Pharmabiotic Centre
University College Cork
Cork, Ireland
Tel: 353-21-490-1228
Fax: 353-21-490-1289
E-mail: e.quigley@ucc.ie

Abstract: A review of any list of currently available therapies for irritable bowel syndrome (IBS) would remind gastroenterologists that the old "standard" agents are neither highly efficacious nor well studied. For example, a number of these therapies are not supported by evidence from robust clinical trials. The American College of Gastroenterology guideline recommends that IBS therapies should not be given a grade A recommendation if they have not been evaluated in randomized, placebo-controlled, clinical trials of adequate duration with well-defined end points. Patients enrolled in these trials should meet the Rome criteria for IBS and should, where appropriate, be categorized according to their predominant symptoms, with special consideration given to gender differences. New agents also need to consider new targets for drug action in IBS, such as the brain-gut axis, intestinal fluid secretion, the gut flora, and inflammation.

Keywords
Irritable bowel syndrome, alosetron, tegaserod, linaclotide, asimadoline, probiotics

Introduction

Older therapies for irritable bowel syndrome (IBS), including fiber and bulking agents, laxatives, antidiarrheal and antispasmodic agents, and antidepressants, are often not prescribed based on solid clinical evidence. The data to demonstrate the effectiveness of these therapies are not evidence-based, the trials from which these data derive were often underpowered and of insufficient duration, negative trials routinely went unreported, and diagnoses were not always based on standard definitions, such as those contained in the Rome criteria. As a reflection of the inefficacy of older treatments, more patients with IBS are now turning to nontraditional therapies for relief of their symptoms. It is time to usher in a new era with new targets and new therapies based on better-designed, standardized trials. This article will review emerging strategies in the management of IBS.

A New Era, New Targets

Although gastrointestinal (GI) motility has always been a target for IBS therapy, it is time to consider IBS in the context of the brain-gut axis. Although the fact that serotoninergic modulators have an effect in some patients suggests that these agents act exclusively through their modulation of enteric nervous system stimulation and inhibition of motility, it is also possible that such effects are central. Accordingly,

it is now widely accepted that the enteric nervous system is in bidirectional communication with the central nervous system (CNS). Cerebral blood flow measurements with positron emission tomography have demonstrated altered regional brain activation in response to visceral and somatic stimuli, particularly in women.[1–3] Disturbed sensation may be as important as altered motility. About 50% of patients with IBS, whether IBS-constipation (C), IBS-diarrhea (D), or IBS-mixed, have relatively lower tolerance of visceral pain than of external stimuli. Although visceral hypersensitivity is real and not subjective, it cannot serve as a diagnostic marker because it is not specific to any IBS subtype.

Increasing colonic water secretion, which enhances stool transit and frequency, would benefit patients with chronic constipation or IBS-C. Lubiprostone, a selective chloride channel activator, has already been approved by the US Food and Drug Administration, while linaclotide, a novel, poorly absorbed guanylate cyclase agonist, is currently being investigated for effectiveness in improving stool transit and frequency.

Another emerging strategy is the treatment of small intestinal bacterial overgrowth (SIBO) with antibiotics or replacement of offending flora by benign probiotics. Several pilot studies are investigating the role of low-grade inflammation in IBS.

New Rules for IBS Treatment Trials

Frustrated by the clinical trials used in the past to evaluate efficacy and safety, gastroenterologists are cognizant of the fact that investigators should follow internationally approved guidelines, including uniform definitions for IBS, such as those put forth in the Rome III criteria. Patients should be identified by gender as well as IBS subtype, because of differences in symptoms, as well as response to therapy. Homogeneity in study populations is difficult to achieve because of the inherent heterogeneity among patients with IBS but every effort should be made to produce as homogenous a patient population as possible for a clinical trial. The other key issues with respect to clinical trials include the selection of meaningful end points and the definition of significance, a term that has been used and misused in clinical trials. What constitutes a clinically significant therapeutic gain? Whether it is a 10%, 15%, or 20% gain compared with that afforded by placebo needs to be determined and agreed upon prior to the initiation of the study. The same can be said for the determination of primary and secondary study end points, as well as quality-of-life assessments. Lastly, the determination of safety and tolerability have to be clearly defined and assessed during the course of the study.

Serotoninergic Agents

Agents that operate at the level of the enteric nervous system may seem "right" in terms of their local mechanism of action, but serotonin (5-HT) receptors are so ubiquitous that agonism or antagonism may have unpredictable effects in various tissues. For example, the 5-HT_3 receptor subtype has 5 heterodimer subunits, 5-HT_{3A} through 5-HT_{3E}. Coexpression of heterodimers can modify the pharmacologic actions of 5-HT_3 antagonists such as alosetron and cilansetron.

A meta-analysis and systematic review of 14 controlled trials of alosetron (n=3,024) or cilansetron (n=1,116) compared with placebo (n=3,043) or the antispasmodic drug mebeverine (n=304) demonstrated the superiority of the two in global improvement of IBS symptoms (relative risk [RR], 1.60; 95% confidence interval [CI], 1.49–1.72) and relief of abdominal pain and discomfort (RR, 1.30; 95% CI, 1.22–1.30), although the study drugs were more likely to cause constipation (RR, 4.28; 95% CI, 3.28–5.60).[4] Moreover, 9 patients (0.2%) receiving the 5-HT_3 antagonists had possible ischemic colitis compared with no patients in the control groups.

The 5-HT_4 agonists, such as tegaserod, were introduced to avail the prokinetic effects of the 5-HT_4 receptor. This agent did show efficacy in IBS-C and was approved for this indication in the United States. Unfortunately, tegaserod has been associated with adverse cardiovascular events: 13 (0.11%) of 11,614 patients, compared with 1 (0.01%) of 7,031 patients treated with placebo. This led to its withdrawal in the United States and most countries where it had been approved. It was a jolt to gastroenterologists to see effective drugs like alosetron and tegaserod removed from the US market and a promising candidate like cilansetron not able to gain approval.

New Targets

IBS symptoms presumably reflect a derangement of the brain-gut axis, because anxiety, depression, and physical or psychological stress are known to alter GI function. Therefore, it may be feasible to relieve IBS symptoms by modulating the physiologic responses to stress. Elevated levels of adrenocorticotropic hormone (ACTH) have been observed in patients with IBS. As with other anterior pituitary hormones, the secretion of ACTH is triggered by a hypothalamic hormone, corticotropin-releasing hormone (CRH, formerly known as corticotropin-releasing factor). It has been postulated that CRH antagonism can block stress-induced alterations in GI motility and visceral hypersensitivity in patients with IBS. Sagami and associates administered α-helical CRH (αhCRH) peripherally to 20 patients (10 Rome II-diagnosed patients with

IBS and 10 healthy controls) and measured descending colon tone and sigmoid colon intraluminal pressure at baseline, during electrical stimulation, and at recovery after saline administration.[5] αhCRH improved GI motility, visceral perception, and negative mood in response to gut stimulation in patients with IBS without inhibiting the hypothalamic-pituitary-adrenal axis (ie, without suppressing ACTH or cortisol). Although these data suggest that CRH may play a role in the pathophysiology of IBS, the relevance of these findings to treatment requires further study.

Melatonin, secreted by the pineal body as well as by the GI tract, where it mediates gut motility and visceral sensation, has also been considered as adjunctive therapy for IBS. Song and coworkers studied 40 patients with IBS and concurrent sleep disturbance.[6] Twenty patients received melatonin 3 mg at bedtime for 2 weeks and 20 received placebo. Melatonin significantly attenuated abdominal pain and rectal pain sensitivity without improving sleep disturbance or psychological distress. The findings suggest that melatonin improves abdominal pain in patients with IBS who have disturbances independently of its effects on sleep or psychological state.

Because the pharmacologic treatment of IBS has been of limited value, attention has turned to strategies such as cognitive-behavioral therapy (CBT). In a randomized clinical trial in 10 general practices in London, United Kingdom, involving a total of 149 mebeverine-resistant patients with IBS, results of CBT delivered by trained primary care nurses in addition to mebeverine 270 mg 3 times daily (n=72) were compared with the results of mebeverine therapy alone (n=77).[7] The addition of CBT produced a significant benefit of 107.8 points on the Symptom Severity Scale for IBS at 3 months post treatment. However, the benefits began to wane at 6 months. Absence of a placebo arm and failure to blind the nurse therapists were methodologic weaknesses in the study. Additionally, the added cost of CBT and the availability of practitioners are practical considerations.

New Pharmacologic Agents

Linaclotide

Linaclotide is an oral agonist of guanylate cyclase-C, which, like lubiprostone, stimulates intestinal fluid secretion and transit, increases stool frequency while lessening its consistency, and reduces visceral hypersensitivity. A randomized, double-blind, placebo-controlled, dose-ranging trial in 36 women with IBS-C compared linaclotide 100 and 1,000 µg/day with placebo (Figure 1).[8] Only the 1,000–µg/day dose produced statistically significant changes from baseline in acceleration of ascending colonic transit (P=.015) and altered bowel function (P<.001).

Asimadoline

Recurrent abdominal pain and discomfort in some patients with IBS may be so severe that analgesia becomes necessary. Although standard opioids effectively relieve pain they often evoke constipation and CNS side effects and pose the danger of dependence; thus, they should be avoided in the management of IBS. Asimadoline promotes antinociception by binding to peripheral κ-opioid receptors, which mediate perceptions of visceral pain, without crossing the blood-brain barrier. Szarka and associates randomized 100 patients with IBS in a 3:2 ratio to receive asimadoline up to 1 mg 4 times daily or placebo for 4 weeks after a 2-week run-in period to establish baseline symptoms.[9] Reduction of abdominal pain severity and relief of anxiety did not differ significantly between the 2 groups. Asimadoline showed efficacy (P=.003) in patients with mixed bowel function, but symptoms worsened in patients with IBS-D.

Nonabsorbed Antibiotics

In some studies, significant numbers of patients with IBS have been reported to demonstrate abnormal lactulose breath tests, interpreted as suggestive of SIBO. To determine the impact of nonabsorbed antibiotics, a randomized, double-blind, controlled study was conducted in patients who met Rome I criteria for IBS at 2 tertiary care centers. The study compared a 10-day course of rifaximin 400 mg 3 times daily (n=43) with placebo (n=44).[10] Participants filled out a questionnaire before and 7 days after treatment and were instructed to keep a symptom follow-up diary for 10 weeks. Follow-up data were available for at least 34 participants per study arm at any time point. Rifaximin produced greater improvement in IBS symptoms (P=.020) and lower post-treatment bloating. A difference of 15–20% from placebo was sustained even after 10 weeks of follow-up. Breath hydrogen results were not reported and more recent studies suggest that bacterial overgrowth may be of minor importance in IBS and that antibiotic effects are more likely exerted on the colonic flora. In spite of the positive results, the study findings need to be confirmed in a larger population with long-term follow-up.

Probiotics

Ideally, the hundreds of species of microbial flora that ordinarily inhabit the GI tract coexist harmoniously with the host, although the equilibrium is complex and dynamic. If the balance is upset, as is increasingly thought to occur with IBS, pathophysiologic signs and symptoms may develop. An emerging strategy consists of the ingestion of probiotics, benign microorganisms that are active against opportunistic pathogens such as *Clostridium difficile.* Not only have *Lactobacillus* spp and *Bifidobacterium* spp—par-

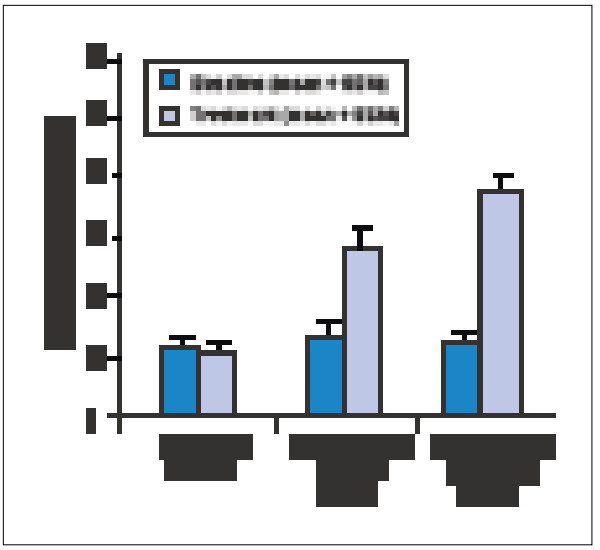

Figure 1. Effects of linaclotide on stool consistency in patients with IBS-C. Overall, *P*<.001; both pair-wise comparisons for 100- and 1,000-µg groups versus placebo, *P*<.05.

SEM=standard error of the mean.

Reprinted with permission from Andresen V et al.[8]

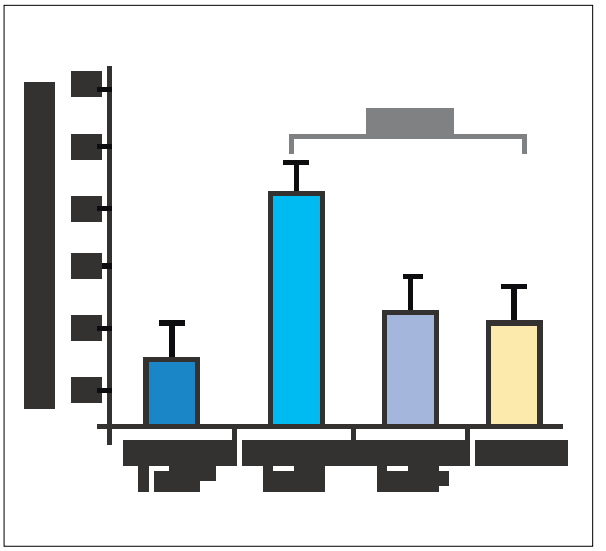

Figure 2. Comparison of effects of *Bifidobacterium infantis* and placebo on subjects' global assessment. Positive response rates recorded at week 4. Subjects responded "yes" or "no" to the following questions: "Please consider how you feel in the past week in regard to your irritable bowel syndrome (IBS), in particular your general well being, and symptoms of abdominal discomfort or pain, bloating or distension and altered bowel habit. Compared to the way you felt before beginning the medications, have you had adequate relief of your IBS symptoms?"

Reprinted with permission from Whorwell PJ et al.[14]

ticularly *Bifidobacterium infantis*—been shown to improve barrier function, inhibit pathogen binding, and modulate inflammatory responses, they may improve motility and reduce visceral hypersensitivity.[11] A recent meta-analysis of 8 randomized clinical trials yielded a significant RR of 1.22 (95% CI, 1.07–1.40; *P*=.0042).[12] In addition, a literature search identified 7 randomized clinical trials in which probiotics improved IBS symptoms relative to placebo.[13]

We performed a trial in which patients with IBS received 3 different doses of *B infantis* or placebo. Evaluation of global assessments of symptom relief at week 4 (Figure 2) showed that approximately 60% of patients answered "yes" about the effects of *B infantis* at 1×10^8 compared with 40% of patients who reported symptom relief from placebo (*P*=.0118).[14] Since each probiotic has unique features, and patients with IBS are a heterogeneous population, a "cocktail" containing multiple organisms, including *Bifidobacterium, Lactobacillus*, and *Enterococcus,* may be a future treatment option.[15] The 3 probiotics used in this Chinese study significantly decreased the fecal bacteroides (*P*<.05) and enterococci counts (*P*<.01) but did not significantly change the counts of *C difficile* or enterobacteriaceae. Ongoing studies of VSL#3, a composite probiotic, appear promising.

What Do We Still Need to Know?

We still need to gain more information on how the phenotypes for diarrhea and/or constipation are expressed. If the phenotypes vary widely, pharmacotherapy will have to be customized to the patient. Of equal interest are interactions with the genotype that is in line with the increasing prominence of pharmacogenomics in other diseases. We must know more about the role of microorganisms and whether we are putting too much emphasis on the small intestine while overlooking the colonic flora and to decide whether we are sufficiently informed about inflammatory processes in IBS, and what is happening at the mucosal level that is not being detected on routine biopsy.

Summary

New therapies for patients with IBS are urgently needed as the old ones are prescribed empirically and are seldom effective. There are many reasons for the slow progress

in finding effective treatments for IBS, starting with the diagnostic criteria used in older clinical trials. Moreover, the "old standard" therapies were approved without having undergone rigorous evidence-based clinical trials. Patient populations were small, trials were underpowered, placebo control was frequently absent, durations were too short to document improvement of sporadically recurring symptoms, gender differences were not fully taken into account, and end points were often arbitrary. Today there are new targets for therapy, such as the gut-brain axis, intestinal fluid secretion, gut flora, and inflammation, and new agents in development.

Grant Support Information

Dr. Quigley is supported by grants from Science Foundation Ireland.

References

1. Nakai A, Kumakura Y, Boivin M, et al. Sex differences of brain serotonin synthesis in patients with irritable bowel syndrome using alpha-[11C]methyl-L-tryptophan, positron emission tomography and statistical parametric mapping. *Can J Gastroenterol.* 2003;17:191-196.
2. Naliboff BD, Berman S, Chang L, et al. Sex-related differences in IBS patients: central processing of visceral stimuli. *Gastroenterology*. 2003;124:1738-1747.
3. Chang L. Brain responses to visceral and somatic stimuli in irritable bowel syndrome: a central nervous system disorder? *Gastroenterol Clin North Am.* 2005;34:271-279.
4. Andresen V, Montori VM, Keller J, et al. Effects of 5-hydroxytryptamine (serotonin) type 3 antagonists on symptom relief and constipation in nonconstipated irritable bowel syndrome: a systematic review and meta-analysis of randomized controlled trials. *Clin Gastroenterol Hepatol*. 2008;6:545-555.
5. Sagami Y, Shimada Y, Tayama J, et al. Effect of a corticotropin releasing hormone receptor antagonist on colonic sensory and motor function in patients with irritable bowel syndrome. *Gut.* 2004;53:958-964.
6. Song GH, Leg PH, Gwee KA, et al. Melatonin improves abdominal pain in irritable bowel syndrome patients who have sleep disturbances: a randomized, double blind, placebo controlled study. *Gut.* 2005;54:1402-1407.
7. Kennedy T, Jones R, Darnley S, et al. Cognitive behavior therapy in addition to antispasmodic treatment for irritable bowel syndrome in primary care: randomized controlled trial. *BMJ.* 2005;331:435-440.
8. Andresen V, Camilleri M, Busciglio IA, et al. Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. *Gastroenterology.* 2007;133:761-768.
9. Szarka LA, Camilleri M, Burton D, et al. Efficacy of on-demand asimadoline, a peripheral kappa-opioid agonist, in females with irritable bowel syndrome. *Clin Gastroenterol Hepatol.* 2007;5:1268-1275.
10. Pimentel M, Park S, Mirocha J, et al. The effect of a nonabsorbed oral antibiotic (rifaximin) on the symptoms of the irritable bowel syndrome. *Ann Intern Med.* 2006;145:557-563.
11. Camilleri M. Probiotics and irritable bowel syndrome: rationale, putative mechanisms, and evidence of clinical efficacy. *J Clin Gastroenterol.* 2006;40: 264-269.
12. Nikfar S, Rahimi R, Rahimi F, et al. Efficacy of probiotics in irritable bowel syndrome: a meta-analysis of randomized controlled trials. *Dis Colon Rectum.* 2008; May 9. Epub ahead of print.
13. Wihelm SM, Brubaker CM, Varcak EA, et al. Effectiveness of probiotics in the treatment of irritable bowel syndrome. *Pharmacotherapy.* 2008;28:496-505.
14. Whorwell PJ, Altringer L, Morel J, et al. Efficacy of an encapsulated probiotic Bifidobacterium infantis 35624 in women with irritable bowel syndrome. *Am J Gastroenterol.* 2006;101:1581-1590.
15. Fan YJ, Chen SJ, Yu YC, et al. A probiotic treatment containing Lactobacillus, Bifidobacterium and Enterococcus improves IBS symptoms in an open label trial. *J Zhejiang Univ Sci B.* 2006;7:987-991.

Emerging Diagnostic and Treatment Strategies for Irritable Bowel Syndrome

CME Post-Test: Circle the correct answer for each question on the answer form on the next page.

1. In the United States, irritable bowel syndrome (IBS) accounts for _____ of diagnoses made by primary care physicians.

   a. 3%
   b. 6%
   c. 12%
   d. 20%
   e. 28%

2. Clinical predictors of physical health-related quality of life in IBS include all of the following but _____.

   a. low sexual interest
   b. low in energy
   c. tire easily
   d. painful symptoms
   e. flares >24 hours

3. Common red flags found in the history of patients with IBS included all of the following except _____.

   a. family history of colon cancer or inflammatory bowel disease
   b. unintentional weight loss of more than 10 pounds
   c. guaiac-positive stool
   d. hematochezia
   e. onset in patients aged greater than 50 years

4. Symptoms that cumulatively support the diagnosis of IBS do not include _____.

   a. passage of mucus
   b. bloating
   c. abnormal stool form
   d. abnormal stool frequency
   e. aged greater than 50 years

5. The rationale for using fiber for constipation in IBS is that it _____.

   a. is effective, safe, and inexpensive
   b. improves symptoms of anxiety
   c. improves abdominal pain
   d. adds bulk to stools and accelerates orocecal transit
   e. stimulates the movement of chloride ions into the lumen

6. Which of the following facts about IBS and diet is not true?

   a. 25% of IBS patients are lactose intolerant
   b. Up to 50% of IBS patients with diarrhea are fructose intolerant
   c. Fiber is not the cure for all IBS symptoms and often worsens bloating
   d. Fad diets are rarely helpful and often cause patients to be food phobic
   e. None of the above

7. As a reflection of the inefficacy of older treatments for IBS, more patients are now turning to _____ for relief of their symptoms.

   a. nontraditional therapies
   b. probiotics
   c. nonabsorbed antibiotics
   d. diet
   e. none of the above

8. Probiotics are benign microorganisms that are active _____.

   a. against abdominal pain
   b. against abnormal lactulose breath tests
   c. against psychological stress
   d. against opportunistic pathogens
   e. none of the above

9. Which of the following is not considered a treatment option for IBS associated diarrhea?

   a. Probiotics
   b. Osmotic agents
   c. Antibiotics
   d. Loperamide
   e. Cholestyramine

10. Goals of IBS pharmacotherapy include all of the following but _____.

    a. relief of abdominal pain/discomfort
    b. altered bowel habits
    c. weight gain
    d. relief of bloating
    e. all of the above

Emerging Diagnostic and Treatment Strategies for Irritable Bowel Syndrome

Participant Evaluation

Did you find the information presented in the educational activity to be fair, balanced, and free of commercial bias? ❑ Yes ❑ No

If no, please explain:

_____

_____

Were the activity objectives met? ❑ Yes ❑ No

If no, please explain:

_____

_____

Is the information presented useful in your practice? ❑ Yes ❑ No

If no, please explain:

_____

_____

Please provide any further comments regarding this activity below:

_____

_____

Answer Form

On the answer form below, please circle the letter that represents your answer for each question. You must answer 70% or better of the questions correctly to receive credit.

1. a b c d e
2. a b c d e
3. a b c d e
4. a b c d e
5. a b c d e
6. a b c d e
7. a b c d e
8. a b c d e
9. a b c d e
10. a b c d e

Please mail or fax your answer and evaluation form to:
University of Wisconsin School of Medicine and Public Health
OCPD
2701 International Lane, #208
Madison, WI 53704
Fax: 608-240-2151

Please type or print clearly:

First Name _____ Last Name _____

Degree ❑ MD ❑ DO ❑ Other (please specify) _____

Address _____

City, State, ZIP _____

Country _____

Telephone _____ E-mail _____

I claim _____ *AMA PRA Category 1 Credits*™ (up to 2.0)

Signature _____ Date _____

Expiration Date: October 31, 2009