SUBJECT REVIEW

The Burden of Illness of Irritable Bowel Syndrome: Current Challenges and Hope for the Future

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ABSTRACT

OBJECTIVES: To review unmet medical needs associated with irritable bowel syndrome (IBS), to discuss factors that contribute to these unmet needs, and to provide an overview of advancements in IBS diagnosis and treatment options that may influence treatment strategies.

SUMMARY: IBS is characterized by a multiple symptom complex of abdominal pain or discomfort and altered bowel habits (i.e., constipation, diarrhea, or both in alternation) and is associated with a large unmet medical need. IBS symptoms are chronic and bothersome, and they have a profound negative impact on patients' quality of life (i.e., affecting sleep, personal relationships, travel, diet, and sexual functioning). IBS imposes a substantial economic burden in direct medical costs and in indirect social costs such as absenteeism from work and school and lost productivity, along with the less-measurable costs of a decreased quality of life. The annual cost of IBS treatment in the United States has been estimated to be between $1.7 billion and $10 billion in direct medical costs (excluding prescription and over-the-counter [OTC] drug costs) and $20 billion for indirect costs.

The goals of IBS therapy are to provide global relief of the multiple symptoms of IBS and to relieve single IBS symptoms. Although traditional IBS therapies (e.g., laxatives, antidepressants, antispasmodics, and bulking agents) are useful for some patients in relieving single IBS symptoms, patients generally are dissatisfied with their overall efficacy and tolerability. These agents have not been proven in randomized, controlled clinical trials to be more effective than placebo in providing global relief of the multiple symptoms of IBS. Over the past 2 decades, numerous advancements in the diagnosis and management of IBS have provided hope for the future, including research strides in our understanding of the underlying pathophysiology of IBS; new diagnostic and management recommendations based on a stepwise, symptom-based approach; and the development of novel pharmacologic agents.

CONCLUSION: IBS imposes a high socioeconomic burden on its sufferers and on society. Research strides in the underlying pathophysiology of this disorder have enhanced our understanding of IBS, but many questions remain to be answered. Development of evidence-based guidelines on the stepwise, symptom-based approach to IBS diagnosis and the continuing efforts to develop unique pharmacologic classes targeted at the multiple symptoms of this disorder are steps in the right direction. Though cost-effectiveness data on specific pharmacologic classes are not yet available, these ongoing efforts may help promote timely IBS diagnosis and patient satisfaction with care, optimally decreasing the use of health care resources.

KEYWORDS: Irritable bowel syndrome, Economic burden, Social impact, Diagnosis, Health care utilization, Symptoms, Treatment

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Irritable bowel syndrome (IBS), one of the most common functional gastrointestinal (GI) disorders (FGIDs),[1-3] is associated with a large unmet medical need. IBS symptoms are chronic and unsettling, have an intensely negative effect on patients' quality of life, and impose a substantial economic burden on patients and society. This article focuses on discussing factors that contribute to these unmet needs and providing a brief overview of advancements in IBS diagnosis and treatment that may influence treatment strategies. Ultimately, these advancements may lower the heavy socioeconomic burden caused by this disorder. The discussion of treatment options in this paper is brief, solely intended to provide the reader with background knowledge of traditional treatment approaches, recently approved agents, and treatments that are on the horizon.

IBS patients often experience comorbid GI and non-GI conditions with overlapping symptoms, such as celiac disease, functional dyspepsia, gastroesophageal reflux disease (GERD), fibromyalgia, chronic fatigue syndrome, and psychological disturbances (discussed in 2 sections that follow: Comorbid Conditions and Psychosocial Factors).[4-7] Presence of these comorbid conditions may account, at least in part, for the high health care utilization seen in this patient population. IBS patients use a significantly greater number of health care services and take a greater quantity of prescription drugs, both GI- and non–GI-related, per year than do persons without IBS.[8-10] The majority of the studies and surveys discussed throughout this paper questioned IBS patients specifically regarding the impact of IBS symptoms on their social and professional lives.

Prevalence and Definition

IBS affects up to 20% of the North American adult population.[11] Although IBS affects both sexes, 60% to 75% of sufferers are women.[4,12] Younger patients are more likely to be affected by IBS than are the elderly,[13] and patients with IBS symptoms typically

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TABLE 1 ROME II Diagnostic Criteria for Irritable Bowel Syndrome (IBS)[13,17]

Abdominal discomfort or pain for at least 12 weeks, which need not be consecutive, in the preceding 12 months that has 2 of the following 3 features:

- Abdominal discomfort or pain relieved with defecation
- Onset of abdominal discomfort or pain associated with a change in frequency of stool
- Onset of abdominal discomfort or pain associated with a change in form (appearance) of stool

Supportive symptoms suggestive of IBS:

- Fewer than 3 bowel movements/week*
- More than 3 bowel movements/day†
- Hard or lumpy stools*
- Loose or watery stools†
- Straining during a bowel movement*
- Urgency†
- Feeling of incomplete evacuation
- Passage of mucus
- Abdominal fullness/bloating

** Symptoms suggestive of IBS with constipation.*
† Symptoms suggestive of IBS with diarrhea.

present to a physician for the first time between the ages of 30 and 50 years.[3] The prevalence of IBS diminishes in patients older than 60 years.[14]

The ROME II criteria (Table 1) represent the current gold standard for the identification of characteristic and supportive symptoms of IBS and for the categorization of IBS patients into symptom-based subgroups (IBS with constipation [IBS-C], IBS with diarrhea [IBS-D], and IBS with alternating constipation and diarrhea [IBS-A]). While these criteria are primarily used for recruiting patients into clinical trials, they are also used for making therapeutic choices.[15-17] In clinical practice, IBS is broadly defined as a multiple symptom complex characterized by abdominal pain or discomfort that is associated with altered bowel function.[13,17]

Impact of Irritable Bowel Syndrome

Personal Impact

IBS symptoms are chronic and episodic,[2,3,18] causing many sufferers to endure symptoms for years.[2,14] In a survey of 1,597 patients with IBS,[2] 50% of respondents reported that they had suffered from IBS symptoms for more than 10 years.[2] Remarkably, 16% of survey respondents had suffered from IBS symptoms for 21 to 30 years.[2] Of patients who commented on symptom frequency (n = 1,454), 57% of respondents experienced IBS symptoms daily, 25% weekly, and 14% monthly.[2]

IBS symptoms are often bothersome. Results of a patient questionnaire administered to 443 consecutive IBS patients referred to a medical center for an FGID revealed that only 4% of patients considered their symptoms to be mild. Forty-nine percent and 12% of patients rated their symptoms as severe and very severe, respectively.[19] In a survey of 350 IBS sufferers conducted by the International Foundation for Functional Gastrointestinal Disorders (IFFGD) in 2002, more than one third (39%) of respondents rated their pain as extremely or very severe.[18] In the GI Sufferer Study—an in-depth telephone survey of 1,013 adults with GI disorders, including 411 respondents with IBS—88% of the women surveyed considered their IBS symptoms to be bothersome, and 60% regarded recurrences as extremely or very severe.[14]

Symptom severity waxes and wanes in IBS patients,[2,14,19] and symptom flares (characterized by severe symptoms over a period of a few days followed by a period of symptom-free days) are common.[3,13] Abdominal pain or discomfort are the most bothersome symptoms for many IBS patients[19,20] and seem to be the symptoms most likely to lead patients to seek medical care.[1]

IBS symptoms have a substantially negative impact on patients' quality of life.[21] A study comparing health-related quality of life (HRQoL) of individuals with IBS with that of U.S. population norms and patients with chronic conditions such as asthma, migraine, and GERD revealed that, overall, patients with IBS (particularly IBS-C) experience a poorer HRQoL than do those in the comparison groups.[22] The impairment in HRQoL for IBS patients has also been found to be worse in most domains than for patients with diabetes mellitus and in select domains (e.g., bodily pain, emotional well-being, energy/fatigue) than for patients with end-stage renal disease.[23]

IBS also has a negative impact on patients' activities of daily living, work, and leisure time.[24-28] It may affect sleep, diet, ability to travel, and sexual function,[14,27] as well as personal relationships with family and friends and work-related roles.[21,26,27,29]

More than two thirds of respondents (68%) to the IFFGD survey (n = 350) reported that they missed an average of more than 10 activities or social occasions in a 3-month period—equivalent to about 1 missed activity per week.[18] More than 50% of IBS sufferers in the Truth in IBS (T-IBS) Survey (n = 318) reported that IBS symptoms had a substantial impact on their social activities (e.g., going shopping, going out to eat), and 52% reported that IBS negatively affected their sex life or physical relationships.[28]

Direct Costs

Health Care Utilization

The annual cost of IBS treatment in the United States has been estimated to be between $1.7 billion and $10 billion in direct medical costs, excluding prescription and over-the-counter (OTC) drug costs (i.e., primary and specialist physician visits, outpatient care, and diagnostic testing),[30,31] and up to $20 billion in indirect costs (e.g., productivity loss).[32] In a study that evaluated total costs of care for IBS patients in a health maintenance organization, Levy and colleagues found that total costs of care were 49% higher for IBS patients than for population controls during the index year (starting with the visit at which IBS patients were diagnosed).[8]

IBS is the digestive disease most often diagnosed by gastroenterologists (GEs).[1,33] A survey of 704 GEs, all members of the American Gastroenterological Association, revealed that 28% of their patients have IBS.[34] Symptoms of IBS are also one of the top 10 reasons why patients consult a primary care physician, and IBS accounts for 12% of diagnoses made in primary care practices.[1,3] IBS may also be the reason for the largest percentage of referrals to GEs (30% to 50%).[35]

In 1998, 3.65 million physician visits were made because of IBS.[32] A study that reviewed resource utilization data for IBS in the United States between 1987 and 1997 found that prescription medications were prescribed for IBS symptoms at 89% of physician visits. The average number of prescribed medications ordered at each visit was 1.83.[36]

The estimated annual total (direct and indirect) cost of IBS (approximately $30 billion) is comparable with or greater than that of other common chronic conditions, including asthma, hypertension, and congestive heart failure. According to the Centers for Disease Control, the total cost of asthma in 2000 was approximately $14.5 billion,[37] and according to the 2003 Heart Disease and Stroke Statistical Update of the American Heart Association, the estimated costs of hypertension and congestive heart failure in 2003 were $50.3 billion and $24.3 billion, respectively.[38]

Patients with IBS incur higher prescription drug costs than population controls.[8,39] A cross-sectional case-control study conducted by Eisen and colleagues evaluated a random sample of patients enrolled in a managed care plan from 1998 to 1999; 94 of the 1,032 respondents (9%) had IBS. Study results demonstrated that, compared with non-IBS patients, IBS patients used more medications (5.9 versus 4.8) and had a greater mean number of outpatient visits (9.10 versus 6.85) in the preceding year.[40] In a survey of 2,613 patients enrolled in a managed care organization, IBS sufferers (n = 578) used a significantly greater number of health care resources (i.e., outpatient visits, prescription drugs, radiologic procedures, and laboratory services) than did patients without IBS.[41]

In a recent survey of 657 members of the Intestinal Disease Foundation (IDF), including 430 with IBS, 97% of IBS respondents had required 2 or more health care professional consults (visits and telephone calls), and approximately 75% had made 4 or more such visits/calls in the preceding 3 months.[20]

Out-of-Pocket Expenses for IBS Therapy

A recent survey of 429 IBS patients demonstrated that intensity of abdominal pain is a significant predictor of out-of-pocket expenses for OTC medication usage.[42] In this survey, 79%, 40%, and 28% of respondents reported that over a 3-month period, they had incurred out-of-pocket expenses for OTC medications, alternative therapies, and prescription medications, respectively. Linear regression analyses demonstrated that patients incurred significantly greater out-of-pocket expenses for OTC drugs as the abdominal pain increased (OTC medications, $P<0.001$; alternative therapies, $P = 0.09$; prescription medications, $P = 0.10$).[42] In the IDF survey, 89% of IBS patients (n = 430) reported that they had used at least 3 different therapies (prescription medications, OTC medications, and alternative therapies) to manage their IBS symptoms.[43] Only approximately one third of these patients rated their therapy as effective or reported satisfaction with their current therapy. In addition, patients reported incurring high out-of-pocket expenses related to IBS. In the 3 months preceding the survey, patients spent an average of $258 to treat their symptoms (nonprescription medications, $60; alternative therapies, $198).[43]

Indirect Costs

Lost Productivity

Surveys have found that IBS symptoms cause patients to lose time from work (absenteeism)[2,28,43] and to be less productive while at work (presenteeism).[43] Up to 26% of IBS sufferers who responded to the IFFGD survey (n = 350) reported that they had missed school or work because of their symptoms.[18] A survey of a random sample of 500 U.S. members of the IFFGD, conducted by Hahn and colleagues, found that 30% of U.S. respondents with IBS (n = 287) reported missing an average of 1.7 days and cutting back an average of 3 days of work over the previous month.[25] In the IDF survey (n = 430), of employed IBS respondents (n = 221), 39% reported missing work and decreased work productivity on an average of 6 days and 16 days, respectively, during the 3 months before the survey.[20] In a survey of 1,776 bank employees, respondents who met the ROME II criteria for IBS (n = 720) reported significantly higher absenteeism and presenteeism (19.8%) than were reported by employees without IBS (5.6%).[44]

In the T-IBS survey, IBS patients took twice as many days off from work per year because of illness (6.4 days) compared with healthy subjects (3 days).[45] More than 50% of respondents stated that IBS affected their work or job choice and ability to concentrate at work.[45] Similar results were found in the survey conducted by Silk.[2] Of 695 employed responders, 21% stated that they missed 5 to 10 days of work annually; 53% were embarrassed to use the bathroom at work; and 32% reported that they had passed up a job promotion that involved attending many presentations or meetings.[2] In the IDF survey, 39% of employed IBS patients (n = 221) reported that they had missed work, 34% had left work early, and 33% reported decreased productivity while at work during the 3 months before the survey.[43]

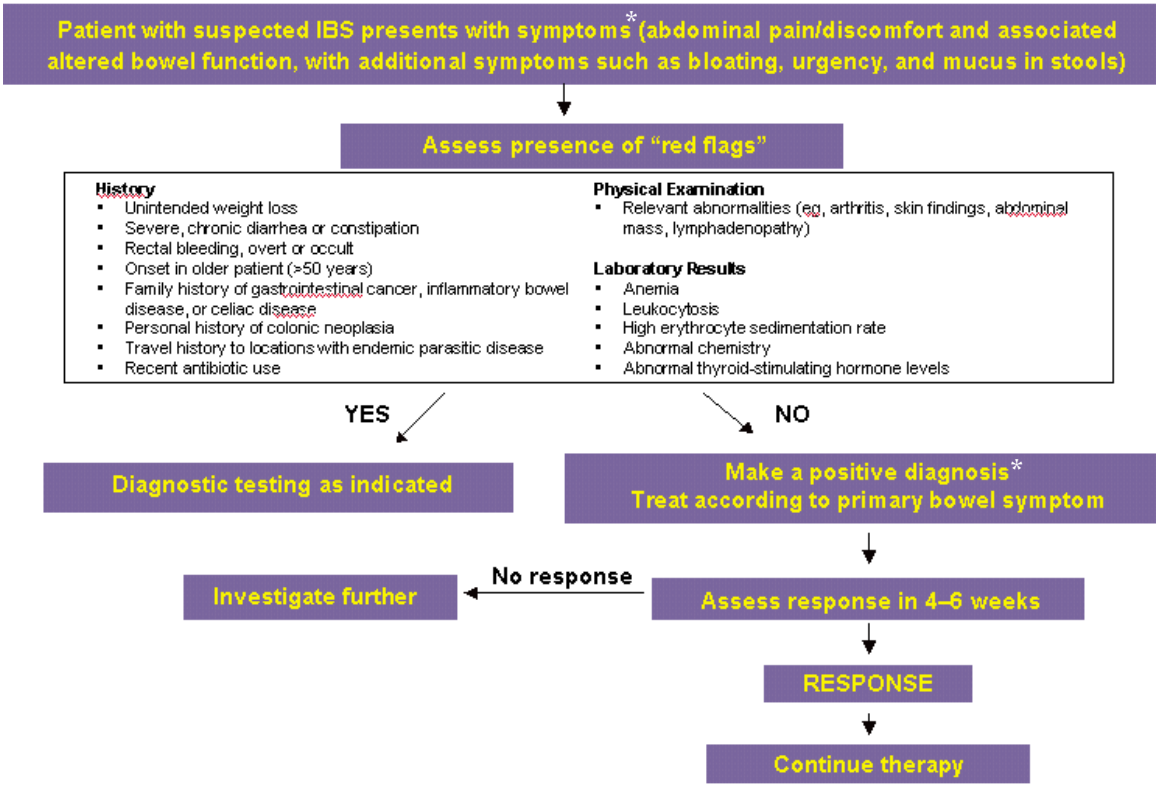
Factors Associated With Unmet Medical Needs

Diagnosis of IBS Is Often Delayed

Patient- and Physician-Related Factors

Up to 70% of IBS patients in the United States do not consult a health care provider regarding their symptoms.[3] Sufferers are

FIGURE 1 Stepwise, Symptom-Based Diagnostic Approach to Irritable Bowel Syndrome



* *Assess symptoms using ROME II criteria (Table 1).*[17]

This algorithm has been adapted from several sources and is representative of the current thinking on how to diagnose IBS.

Adapted from: Paterson WG, Thompson WG, Vanner SJ, et al. Recommendations for the management of irritable bowel syndrome in family practice. Can Med Assoc J. 1999;161:154-60, and Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. Gastroenterology. 2002;123(6):2108-31.

often reluctant to consult a physician because they assume their symptoms are not serious enough or are fearful that they will be diagnosed with a serious, life-threatening illness.[46]

Physicians oftentimes fail to recognize presenting symptoms as IBS, leading to a long lag time between symptom onset and diagnosis.[14,15] Forty-three percent of IBS patients who participated in the IFFGD survey (n = 350) experienced a lag time of at least 5 years from the time their symptoms began to the time they were formally diagnosed.[18] Because a positive diagnosis of IBS often is not made, sufferers may undergo extensive diagnostic testing, even though the usefulness of such testing is unwarranted in patients who meet the diagnostic criteria for IBS in the absence of "red flags" suggestive of organic disease (Figure 1).[11]

Comorbid Conditions

Patients with IBS often have comorbid GI and non-GI disorders with overlapping symptoms that can cloud the diagnostic picture.[4] For instance, the prevalence of IBS in patients with confirmed celiac disease is higher than in patients without celiac disease (20% versus 5%).[6] In one study, 87% of patients with IBS also met criteria for functional dyspepsia.[7] Another study showed that 46.5% of IBS patients also suffered from GERD.[4,5]

About 50% of IBS sufferers experience at least 1 comorbid non–GI-related symptom, such as headache, back pain, poor sleep, and fatigue. An estimated 48% of patients with fibromyalgia have IBS, and IBS symptoms have been reported in 50% of patients with chronic pelvic pain, 51% with chronic fatigue syndrome, and 64% with temporomandibular joint pain.[4]

High Rate of Abdominal Surgeries

The rates of abdominal surgery have been shown to be greater in IBS patients than in the general population.[47-50] This may result from misinterpretation of IBS symptoms as indicators of abdominal or gynecological conditions that can be remediated by surgery.[47] In population-based studies, the prevalence of cholecystectomy in IBS patients versus controls was reported as

TABLE 2 *Traditional Treatment Options for Irritable Bowel Syndrome*[3,11,13]

Predominant Symptom	Treatment	Efficacy	Adverse Effect Profile
Abdominal pain	Tricyclic antidepressants[3] Desipramine Amitriptyline Trimipramine Doxepin	No more effective than placebo in providing global relief of IBS symptoms May treat comorbid depression and anxiety[13]	Bothersome anticholinergic effects such as sedation, blurred vision, constipation, dry mouth, urinary retention, headache, dizziness, and hypotension Use with caution in patients with constipation[3,13,79]
Abdominal pain	SSRIs[3] Fluoxetine Paroxetine Sertraline Citalopram	No published clinical trials in manuscript form May treat comorbid depression and anxiety[13]	Insomnia, agitation, and diarrhea[3]
Abdominal pain/discomfort, bloating, and diarrhea	Antispasmodics[13] Dicyclomine Hyoscyamine Peppermint oil[80]	Insufficient data to enable a recommendation regarding effectiveness and use Poorly designed trials May improve abdominal pain[11,13]	Bothersome anticholinergic effects such as sedation, blurred vision, constipation, dry mouth, urinary retention, headache, and dizziness Use with caution in patients with constipation[13,63,79]
Constipation	Laxatives[81] Osmotic Stimulant Stool softeners	No published controlled clinical trials in patients with IBS No effect on abdominal pain[81]	Abdominal cramps Diarrhea[81]
Constipation	Bulking agents[13,81] Wheat bran Corn fiber Psyllium Calcium polycarbophil	May improve constipation No more effective than placebo in providing global relief of IBS symptoms No effect on abdominal pain[13,81]	Abdominal discomfort Bloating and gas[13]
Diarrhea	Antidiarrheal[13] Loperamide	May improve diarrhea and fecal urgency No more effective than placebo in providing global relief of IBS symptoms No effect on abdominal pain[13,81]	Avoid use in IBS patients with constipation Use with caution in patients with IBS-A[13]

SSRI = selective serotonin reuptake inhibitor. IBS = irritable bowel syndrome. IBS-A = IBS with alternating constipation and diarrhea.

4.6% versus 2.4%, respectively, and rates of hysterectomy were 18% versus 12%, respectively.[47] The rates of appendectomy (34.5% versus 7.9%) and hysterectomy or ovarian surgery (55.2% versus 18.5%) have been found to be substantially greater in patients with IBS than in those with ulcerative colitis.[48] It is of particular concern that Burns showed that most removed appendixes available for examination were normal.[48]

In the T-IBS survey (n = 318), a significantly greater number of patients with IBS underwent hysterectomy (11.2% versus 6.2%) and cholecystectomy (7.8% versus 4.0%) compared with patients without IBS (n = 4,301).[51] Significantly higher rates of abdominal surgery in IBS patients (appendectomy, cholecystectomy, hiatal hernia repair, ulcer surgery, intestinal resection, and hysterectomy) have been reported in several other studies.[50,52,53] These findings emphasize the need for an awareness of IBS as a diagnosis when patients who present with GI symptoms are assessed.

Psychosocial Factors

Psychosocial factors can exacerbate IBS symptoms. While a definitive link between psychological conditions and specific IBS symptoms has not been established, patients with IBS often experience comorbid psychological disturbances (such as depression and generalized anxiety disorder).[4,54] Overlap of these comorbid conditions is more common in tertiary medical center (referral) populations (54% to 94%)[4,55] than in the general community (18%).[56]

Dissatisfaction with Traditional Treatment Options

Many IBS patients initially attempt to treat their symptoms with lifestyle modifications (exercise, diet), alternative remedies (ginger, aloe, peppermint oil), and psychologic approaches (relaxation/stress management, cognitive/behavior therapy, hypnosis).[57-60] However, the efficacy of these therapies in IBS is

TABLE 3 FDA-Approved Serotonergic Agents

Multiple Symptoms	Agent	Clinical Trial Results*	Recommendation Based on Supportive Evidence and Quality of Clinical Trials	Limitations
Abdominal pain/discomfort, bloating, and constipation	Tegaserod (5-HT_4 receptor partial agonist)	In 2 12-week, multicenter, randomized, double-blind, placebo-controlled, pivotal clinical trials, for the primary efficacy variable (Subject's Global Assessment of Relief), absolute response rates at study end point (defined as completely or considerably relieved for at least 2 of the last 4 weeks or at least somewhat relieved for all of the last 4 weeks of the trial) were 46.3% versus 34.5% (NNT = 8.5, ARR = 11.8%)[82] and 43.5% versus 38.8% (NNT = 21, ARR = 4.7%),[83] for tegaserod 6 mg bid versus placebo, respectively.[82,83]	More effective than placebo in relieving global IBS symptoms in female IBS patients with constipation (Grade A rating)[13]	In pivotal clinical trials, the only adverse effects reported significantly more often with tegaserod than with placebo were headache (15% versus 12%, respectively) and diarrhea (9% versus 4%, respectively)[66,82,83] When diarrhea occurred, it was usually early; it was often a single episode, and it usually resolved with continued therapy[66,82,83]
Abdominal pain/discomfort, urgency, and diarrhea	Alosetron (5-HT_3 receptor antagonist)	In 2 12-week, prospective, randomized, double-blind, placebo-controlled, phase 3 clinical trials evaluating the efficacy of alosetron 1 mg bid in patients with severe IBS-D (the currently intended population), improvement in the primary end point (defined as relief of bowel urgency) was 69% versus 56% (NNT = 7.6, ARR = 13%)[67] and 73% versus 57% (NNT = 6.25, ARR = 16%)[84] for the alosetron-treated group compared with the placebo group, respectively. In one of these trials, global assessment of symptom improvement was a secondary end point[84]; after 12 weeks of treatment, 76% of alosetron-treated patients noted global improvement (defined as moderate or substantial improvement in IBS-D symptoms during the previous 4 weeks) compared with 44% of patients taking placebo.[84]	More effective than placebo in relieving global IBS symptoms in female IBS patients with diarrhea (Grade A rating)[13]	Constipation is the most common adverse effect associated with its use; in clinical trials, constipation occurred in up to 39% of patients receiving alosetron and in up to 14% of patients taking placebo1[3,84] Serious, sometimes fatal complications have been associated with alosetron (e.g., ischemic colitis)[13] Restrictive prescribing program for alosetron is now in place

** Intention-to-treat population.*
NNT = number needed to treat; ARR = absolute risk reduction; IBS = irritable bowel syndrome; IBS-D = IBS with diarrhea; bid = twice a day.

questionable,[58] and clinical studies largely fail to support their use. Psychotherapies offer the strongest supportive evidence.[58] According to the consensus recommendations published in 2002 by the American College of Gastroenterology (ACG) FGID Task Force, the goal of IBS therapy is to provide global improvement of the multiple symptoms of IBS (abdominal pain or discomfort associated with altered bowel habits).[11,15,61] Most studies comparing behavioral therapies with standard medical care, placebo, or other treatment approaches have demonstrated improvement in single IBS symptoms but not in global relief of the multiple

symptoms of IBS.[11] Also, behavioral and psychotherapeutic approaches may not be readily available to many patients. Such approaches also require well-trained professionals to implement and are often expensive.[62]

Historically, IBS treatments that target single symptoms (known as traditional treatment options [e.g., antispasmodics/anticholinergics and antidepressants for abdominal pain/discomfort and bloating, bulking agents and laxatives for constipation, antidiarrheals for diarrhea]) were the only available therapy. Commonly used traditional therapies for IBS are summarized in Table 2. Many IBS patients are dissatisfied with the efficacy and safety of traditional treatment options, leading to numerous physician consultations, multiple drug therapy, and switching.[14,51,63,64] In the GI Sufferer Study, about 75% of IBS patients (n = 411) had consulted more than 1 physician, and more than 25% had consulted 3 to 4 physicians regarding their IBS symptoms.[14]

Many patients try multiple traditional medications in an attempt to find symptom relief.[64] In the T-IBS survey, only 14% of IBS patients (n = 318) were completely satisfied with their IBS therapy.[51] In this study, 60%, 28%, 7%, and 20% of IBS sufferers used OTC medications, prescription drugs, alternative therapies, or no treatment, respectively, to manage their IBS symptoms.[51] Only 19%, 18%, 15%, and 10% of IBS patients reported that medical therapy was completely effective in relieving their symptoms of constipation, diarrhea, abdominal pain, and bloating, respectively.[51]

Lack of efficacy and associated adverse effects are common reasons for patient dissatisfaction with traditional agents. Many traditional prescription and OTC medications taken for IBS can aggravate single IBS symptoms.[63] In a survey of 504 IBS-C sufferers, 38% of respondents were not satisfied with their OTC laxative or fiber supplement therapy.[63] IBS-C sufferers experienced an average of 3.3 adverse effects, the most common of which were abdominal pain/discomfort, abdominal cramps, diarrhea, and bloating. Adverse effects often caused patients to miss work, school, or social activities. Of those patients who discontinued therapy, 70% did so because of adverse effects and 25% did so because of lack of efficacy.

Hope for the Future

Stepwise, Symptom-Based Recommendations for a Positive IBS Diagnosis

In the past, IBS has been considered a diagnosis of exclusion that requires numerous diagnostic tests before an official diagnosis can be made. However, recent, evidence-based consensus recommendations published by the ACG FGID Task Force advocate a stepwise, symptom-based approach to a positive IBS diagnosis (Figure 1).[13] According to this approach, after the primary symptoms have been identified, a thorough patient history and physical examination should be conducted to exclude the presence of "red flags" suggestive of other diagnoses. In the absence of red flags, diagnostic testing for IBS is generally considered unnecessary because the probability of alternative diagnoses is low and similar to that seen in the general population.[13,16] In the presence of red flags, directed diagnostic testing (e.g., colonoscopy, flexible sigmoidoscopy, barium enema, testing for blood in the stool) should be performed to rule out organic causes of the symptoms.[13]

Serotonergic Agents

Great strides in our understanding of the underlying pathophysiology of IBS have led to the development of novel pharmacologic agents. Altered GI tract motility, altered intestinal secretion, and visceral hypersensitivity have all been shown to play a role in the pathophysiology of this disorder. Serotonin (5-hydroxytriptamine [5-HT]) plays a key role in modulation of GI function.[65] In addition, an understanding of the role of the 5-HT_4 and 5-HT_3 receptors has led to the development of serotonergic agents for IBS. Tegaserod (Zelnorm), a partial 5-HT_4 receptor agonist, is FDA-approved for the treatment of women with IBS whose primary bowel symptom is constipation.[66] Too few men were enrolled in clinical studies to perform meaningful analyses of the efficacy of tegaserod in males. Alosetron (Lotronex) is a 5-HT_3 receptor antagonist indicated for the treatment of women with severe IBS-D for whom traditional treatment options have failed to provide adequate relief.[67] Both drugs have demonstrated efficacy in well-designed, large, randomized clinical trials in providing global relief of the multiple symptoms of IBS, as well as relief of single IBS symptoms[13] (Table 3). Although placebo response rates were relatively high in these studies, 35% to 39% in the tegaserod clinical trials and 56% to 57% in the alosetron clinital trials, robust placebo response rates are common in clinical trials of GI disorders characterized by symptoms that wax and wane, including IBS,[68] functional dyspepsia,[69] and GERD.[70]

One potential contributing factor to the high placebo response is the natural tendency of symptoms of chronic conditions (such as IBS) to lessen or fully resolve spontaneously over the course of a clinical trial.[71] For this reason, number-needed-to-treat (NNT) calculations may yield misleading results. Nevertheless, NNTs have been calculated for both tegaserod and alosetron. NNTs calculated using primary end point response rates from the clinical trials presented in Table 3 are 8.5[82] and 21[83] for the tegaserod trials, and 7.6[67] and 6.25[84] for the alosetron trials. In a meta-analysis of 4 randomized, placebo-controlled, phase 3 clinical trials evaluating the efficacy and safety of tegaserod in the treatment of patients with IBS-C, the NNT for tegaserod 6 mg twice daily was reported as 10 (7 to 20, 95% CI).[72] A meta-analysis of 6 alosetron clinical trials (randomized, placebo-controlled, or compared with mebeverine) reported an overall NNT of 7.15 (5.74 to 9.43, 95% CI), suggesting that, on average, 7 patients would need to be treated with alosetron in order for 1 patient to achieve improvement over placebo.[73]

TABLE 4 Emerging Pharmacologic Classes for Irritable Bowel Syndrome[79,80,85,86]

Drug Class	Proposed Mechanism	Examples
Alpha$_2$-adrenergic agonists	Decrease colonic tone and pain sensation Increase compliance	Clonidine, lidamidine
Kappa opioid agonists	Increase pain threshold induced by distension	Fedotozine, trimebutine
Neurokinin antagonists	Decrease visceral sensation	CJ-11974, MEN-11420, nepadutant
Somatostatin analogues	Decrease visceral sensation Decrease colonic response to distension	Octreotide
Anticholinergics (M3 receptor antagonists)	Decrease visceral sensation Decrease colonic transit	Zamifenacin
Calcium channel blockers	Decrease rectosigmoid response to distension	Verapamil, nicardipine
Oxytocin	Increases pain threshold induced by colonic distension	
Neutrophins	Improve constipation	Recombinant human neutrophin-3
Probiotics	Improve balance of intestinal flora	VSL#3, LP299V

Treatments on the Horizon

Additional serotonergic agents, including renzapride and cilansetron, are currently under investigation for the treatment of patients with IBS. Renzapride, a 5-HT$_3$ receptor antagonist and a 5-HT$_4$ receptor agonist, has demonstrated promising results in phase 2 trials of patients with IBS-C.[74,75] A 12-week, parallel-group, placebo-controlled, double-blind study compared the efficacy and safety of renzapride 1 mg, 2 mg, or 4 mg versus placebo in 510 patients with IBS-C. Results demonstrated up to an 8.2% increase over placebo in the primary end point (patients' weekly assessments of adequate relief of abdominal pain/discomfort) as well as increased bowel movement frequency (2 mg and 4 mg) and improved stool consistency (softness, 4 mg). Adverse effects across all treatment groups occurred at a similar rate (2.7%, 2.5%, and 3.1% per patient receiving renzapride 1 mg, 2 mg, and 4 mg, respectively, and 2.3% per patient for placebo).[75]

Cilansetron, a 5HT$_3$ receptor antagonist, has demonstrated positive findings in male and female patients with IBS-D.[76] A 6-month, double-blind, randomized, placebo-controlled global study evaluated the efficacy and safety of cilansetron 2 mg 3 times daily versus placebo in 358 male and 434 female patients with IBS-D. The primary efficacy variable in this trial was the proportion of patients reporting adequate IBS symptom relief in at least 50% of their weekly responses while on treatment. After 6 months of treatment, 60% of patients receiving cilansetron reported overall symptom relief compared with 45% of patients taking placebo. Constipation, the most common adverse effect in this trial, occurred in 12% of patients receiving cilansetron compared with 3% of patients receiving placebo. It was also the most frequent reason for study withdrawal in the active treatment group. Three cases of suspected ischemic colitis were reported in the cilansetron treatment group; all resolved without complications.[77] To date, the safety database consists of a total of 4,072 patients who received active drug in phase 1 and phase 2 cilansetron clinical trials. Of these, 8 suspected cases of ischemic colitis have been reported. All cases resolved successfully within 3 weeks. Solvay Pharmaceuticals plans to file a New Drug Application for IBS-D and is developing a risk management program.[78]

Numerous other pharmacologic classes are being evaluated for their potential benefits in the treatment of IBS, including neutrophins and tachychinin antagonists. Neutrophins are involved in modulating synaptic transmission at the neuromuscular junction in nerve cells and in promoting growth of select sensory neurons. Tachykinins (i.e., substance P) are present in the GI tract and are involved in functions such as GI motility, visceral sensation, and autonomic response to stress.[57] The potential benefits of these agents, as well as select other pharmacologic classes, in IBS patients are listed in Table 4. Data on these agents is currently limited.

Treatment Approach and Therapy-Related Costs

A step-by-step treatment flowchart for IBS is not currently available. In clinical practice, the approach taken is left to the discretion of the physician. Some physicians recommend lifestyle modifications or trials with OTC products as initial treatment strategies while others recommend the newer serotonergic agents as a first-line approach.

Based on the wholesale acquisition cost (WAC) of tegaserod ($2.30/pill), the cost of an initial 4- to 6-week treatment course (tegaserod 6 mg twice daily; $4.60 per day) ranges from approximately $129 to $193. Similarly, based on the WAC of alosetron, ($5.72 per pill), the cost of an initial 4-week treatment course (alosetron 1 mg once daily) is approximately $160. As per alosetron prescribing guidelines, if the patient tolerates treatment but symptoms persist, the dose can be increased to 1 mg twice daily for an additional 4 weeks. The cost of this additional 4-week treatment course (alosetron 1 mg twice daily; $11.44 per day) is approximately $320, or a total drug cost of $480 for 8 weeks of therapy.

Cost-efficacy analyses of the relative value of traditional

agents for IBS in comparison with novel approaches (i.e., serotonergic agents) are lacking. Such comparisons would be beneficial because very few alternatives for IBS treatment have demonstrated global symptom relief; however, it is difficult to compare the cost-benefit of single-symptom improvement therapies (e.g., laxatives, antidiarrheals, antispasmodics) with the cost-benefit of global symptom improvement therapies (e.g., alosetron, tegaserod). Furthermore, in the absence of controlled cost-efficacy trials with OTC products, it is challenging to track a typical treatment course from OTC purchases alone. This fact, along with the high likelihood of polypharmacy among IBS patients, partially explains the lack of cost-efficacy data in this area. Achievement of global symptom relief with the newer agents may potentially decrease the need for frequent visits to physicians and multiple medication trials, possibly translating into lower health care utilization and drug-related costs.

A study conducted by Creed and colleagues compared the cost-effectiveness of psychotherapy (8 sessions over 3 months) and paroxetine (20 mg per day for 3 months) with routine care by a primary care physician or gastroenterologist (treatment approaches not specified) in 257 patients with severe IBS in the United Kingdom.[87] Patients were assessed at study entry, after 3 months of treatment and 1 year after the end of treatment. Outcomes measures included IBS-related pain, HRQoL (physical and mental component scores of the Short-Form 36 survey) and associated costs (direct and indirect). Results showed that after 3 months of treatment and at 1-year follow-up, no significant differences were noted in the reduction of severity of abdominal pain between the 3 treatment groups, although at 3 months, the paroxetine group demonstrated a significant reduction in days with pain compared with the treatment-as-usual group. Psychotherapy and paroxetine were more effective than standard care in improving the physical but not the psychological aspects of HRQoL; this difference was significant at the 1-year follow-up period (ANCOVA $P<0.001$). During the follow-up year, health care costs were significantly reduced in the psychotherapy group ($P<0.05$) but not the paroxetine groups compared with the standard care group. The authors concluded that for patients with severe IBS, both psychotherapy and paroxetine improve HRQoL at no additional cost.

Conclusion

IBS imposes a high socioeconomic burden on its sufferers and on society. New diagnostic and management recommendations and unique pharmacologic options may help to improve patient satisfaction with care and decrease health care utilization, thereby potentially decreasing the heavy burden this disorder currently bears.

DISCLOSURES

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