Lucinda A. Harris, MD, MS, FACG
Margaret M. Heitkemper, PhD, RN, FAAN

CE

Practical Considerations for Recognizing and Managing Severe Irritable Bowel Syndrome

ABSTRACT

Irritable bowel syndrome (IBS) is a common disorder characterized by abdominal pain or discomfort and altered bowel habit (chronic or recurrent diarrhea, constipation, or both) that occurs more frequently in women than in men. Severe IBS may be underrecognized and inadequately managed in clinical practice. Although no consensus definition for "severe IBS" exists, patients may be categorized as having severe illness if they show an insufficient response to conventional treatments or if their functionality or quality of life is impaired as a result of their IBS symptoms. Nurses can be an important resource in optimizing the evaluation and treatment of these patients. Nursing assessments that delineate predominant symptoms and the history and nature of prior interventions (e.g., lifestyle changes, over-the-counter or prescription medication trials, psychotherapy, alternative treatments) and subsequent responses are important when advising patients and participating in the management of their IBS. Likewise, the nurse's assessment should include a history of symptom severity and impact on daily functioning, as these elements are important to choosing therapy. The nurse–patient dialogue should also include a description of available treatment options and the benefits and risks associated with each. By maintaining such a dialogue, nurses can hasten IBS recognition, improve management, limit the negative consequences of this common disorder, and improve overall treatment outcomes in this population.

Irritable bowel syndrome (IBS) is one of the most common conditions managed in gastroenterology and primary care practices today. It is characterized by symptoms including abdominal pain and alterations in bowel function that lead to diarrhea, constipation, or both (American College of Gastroenterology [ACG] Task Force on Irritable Bowel Syndrome, 2009). Developing in an estimated 5%–10% of the North American population, IBS is twice as common among women compared with men (ACG Task Force on Irritable Bowel Syndrome, 2009; Hungin, Chang, Locke, Dennis, & Barghout, 2005). The prevalence rates of the IBS subtypes are uncertain and contradictory, with separate studies suggesting that either IBS with diarrhea (IBS-D) or the alternating or mixed form of IBS (IBS-M) is most common (American Gastroenterological Association, 2002; Andrews et al., 2005; Hungin et al., 2005).

Overall, the severity of IBS symptoms ranges from mild and intermittent to severe and chronic (Lembo, Ameen, & Drossman, 2005). At one time, it was thought that the overwhelming majority of IBS patients experienced symptoms that were mild or moderate, with only a small proportion having severe symptoms (Drossman & Thompson, 1992). Data now suggest, however, that the number of patients with severe IBS is substantially higher than once thought, with prevalence rates as high as 69% depending on the population surveyed (e.g., primary care, gastrointestinal [GI] clinic) or

Received November 19, 2010; accepted May 1, 2011.

About the authors: *Lucinda A. Harris, MD, MS, FACG, is Associate Professor of Medicine, Division of Gastroenterology, Mayo Clinic School of Medicine, Scottsdale, Arizona.*

Margaret M. Heitkemper, PhD, RN, FAAN, is Elizabeth Sterling Soule Chair and Professor and Chairperson, Department of Biobehavioral Nursing & Health Systems, University of Washington, Seattle, Washington.

Writing support was provided with funding from Prometheus Laboratories, Inc., and Lucinda A. Harris has done consulting for Prometheus, Proctor & Gamble, Salix, Takeda, and Ironwood Pharmaceuticals. Otherwise, the authors declare no conflicts of interest.

Correspondence to: *Lucinda A. Harris, MS, MD, FACG, Mayo Clinic School of Medicine, Division of Gastroenterology, 13400 East Shea Boulevard, Scottsdale, AZ 85259 (e-mail: Harris.Lucinda@mayo.edu).*

DOI: 10.1097/SGA.0b013e31823ff0e8

diagnostic criteria used (range: 3%–69%) (Lembo et al., 2005).

Although no consensus definition exists for what constitutes "severe" IBS, it is increasingly apparent that assessing severity simply by focusing on GI symptoms (e.g., predominant bowel habit, level of pain and discomfort, fecal urgency) is inadequate. Optimally, assessing the level of IBS symptom severity includes evaluating patients' perceptions of their illness and considering its effect on quality of life (QoL) and functional abilities. Research has highlighted levels of impairments in health-related QoL and physical role limitations in IBS that are similar to, or greater than, those found in other chronic diseases, such as diabetes mellitus (Gralnek, Hays, Kilbourne, Naliboff, & Mayer, 2000) or major depressive disorder (Gralnek et al., 2000). The severity of IBS has been shown to relate not only to the number of days in pain or the number of days in bed, but also to deficits in the patient's QoL. Together, these factors often prompt patients to seek medical care (Hahn, Kirchdoerfer, Fullerton, & Mayer, 1997; Williams et al., 2006). Predictors of the impact of IBS on health-related QoL include the severity of symptoms, duration of symptom flares, abnormalities in mood or anxiety, and signs of poor vitality such as reduced energy level, sleep, and sexual drive (Spiegel et al., 2004).

Despite the high level of stress and dysfunction associated with IBS, its management is often suboptimal. Although conventional, over-the-counter medications such as antidiarrheals (e.g., loperamide) or laxatives may improve specific target symptoms, such as stool frequency or consistency respectively, these medications are no more effective than placebo at reducing abdominal pain or global symptoms of IBS (ACG Task Force on Irritable Bowel Syndrome, 2009). Likewise, antispasmodics (e.g., dicyclomine) are among the agents used most frequently to treat IBS, particularly in patients with abdominal pain and discomfort (Lacy, 2010), despite limited clinical trial experience demonstrating their efficacy for IBS and potential for high rates of adverse events compared with placebo (ACG Task Force on Irritable Bowel Syndrome, 2009; Lacy, 2010; Page & Dirnberger, 1981). Overall, a high proportion of patients report a lack of satisfaction with conventional treatments, particularly over-the-counter agents, and seek alternative treatments (Drossman et al., 2009; Harris & Roberts, 2008; International Foundation for Functional Gastrointestinal Disorders, 2007).

The purpose of this article is to discuss the positive effect nurses can have on the evaluation and management of patients with IBS. Suggested assessment and counseling points are outlined and various treatment options available are briefly reviewed. Finally, we discuss current recommendations from the U.S. Food and Drug Administration (FDA) regarding the conduct of future clinical investigations of new agents and the call for development of clinically validated patient-reported outcome tools to help establish effectiveness of potential new therapeutics.

Expanding Role of Nurses in Assessment and Management of IBS

Nurses in primary care and gastroenterology practices participate in the ongoing assessment and treatment of patients with IBS. The importance of the nurse in this capacity was illustrated in a 1999 survey that showed that although 56% of patients reported that physicians were their primary source of information about IBS, nearly 25% of female patients had recently consulted a nurse for health information or medical treatment (Heitkemper, Olden, Gordon, Carter, & Chang, 2001). In other surveys, IBS patients reported a lack of sufficient knowledge necessary to make informed treatment decisions regarding their own care (Harris & Roberts, 2008) and the perception that their physicians were not helpful in the management of IBS (Bertram, Kurland, Lydick, Locke, & Yawn, 2001). Given these findings, nurses are in a unique position to improve IBS outcomes by obtaining detailed information about current symptoms, allaying unfounded fears, assessing disease severity, evaluating outcomes from prior treatment trials including both efficacy and side effect burden, and assessing the risk of medication side effects the patient is willing to take in order to gain symptom relief. Useful questions in the diagnostic assessment of IBS are presented in Table 1.

Another important role that nurses can provide for patients diagnosed with IBS is the evaluation of symptom severity. Adequate assessment is important because of how symptom severity influences the treatment plan for the individual patient. Unfortunately, at present, there is a lack of consensus for a clear definition of *severe* IBS (Lacy, Weiser, & De Lee, 2009). Some clinicians have suggested that patients who do not respond adequately to conventional therapy (e.g., antidiarrheals for IBS-D) should be categorized as having severe illness (Lacy et al., 2009). Indeed, Spiegel et al. (2010) recently found that patients' answers to one simple question, "How much relief does your current treatment provide for your IBS symptoms?" provided a robust marker of illness severity. Patients who endorse lower levels of relief from their current treatment had higher severity scores and visceral anxiety resulting from IBS (Spiegel et al., 2010).

Likewise, assessment of a patient's QoL and functionality may aid in defining the severity of the syndrome. Indeed, restrictions in the performance of daily activities is a primary indicator of disease severity in IBS (Nicandro, Shin, & Chuang, 2010). Although patients may adjust to certain chronic

TABLE 1. Assessment Tool for IBS Diagnosis and Management

Symptoms
1. What are your symptoms?
2. What symptom or symptoms are most concerning to you?
3. How long have you been experiencing symptoms?
4. How frequently do your symptoms occur?
5. Rate the following symptoms on a 0- to 10-point scale (0 = *that symptom is not present*, 10 = *most severe*)
• Abdominal pain/discomfort
• Diarrhea
• Constipation
• Bloating
• Flatulence/gas/belching
• Fecal urgency
• Incontinence
6. With your current symptoms, have you experienced any of the following?
• Weight loss
• Anemia or low blood count
Previous testing
1. If known, what prior testing/evaluation have you had?
• Blood tests
• X-rays
• Procedures
• Stool studies
Family history
1. Has anyone in your family had:
• Colorectal cancer?
• Inflammatory bowel disease?
• Celiac disease?
• Ovarian cancer?

(*continues*)

TABLE 1. Assessment Tool for IBS Diagnosis and Management (*Continued*)

Current and past treatments
1. Prescription medications—current/past/side effects
2. Over-the-counter medications—current/past/side effects
3. Herbal medications—current/past/side effects
4. Psychological therapies—type/current/past/effectiveness
5. Alternative therapies—type/current/past/effectiveness
Patient comprehension of IBS
1. What is your understanding of IBS?
2. What symptoms are you most concerned about?
3. What are your hopes in coming for this visit?

Note. IBS = irritable bowel syndrome.

symptoms of IBS, it may indeed be the "adjustment" that leads to a poorer QoL; for example, patients who adjust to their symptoms by avoiding social events with family or friends because of the fear of intense abdominal pain or incontinence may report that this compromises QoL. If IBS symptoms have a negative effect on the patient's QoL and functionality, most would argue that the illness is severe and should affect treatment decisions. Table 2 provides a list of questions that may prove useful in the assessment of IBS symptom severity.

Nurses are well situated in the clinical setting to positively affect outcomes in patients seeking medical care for symptoms of IBS. In a study in IBS patients that compared observation (patients placed on a "waiting list"), sham acupuncture combined with a short practitioner interaction (<5 min), and sham acupuncture combined with a longer, more in-depth interaction (45 min), treatment outcomes were best in those patients who received the most time and attention, illustrating the importance of the patient–practitioner relationship (Kaptchuk et al., 2008). Given that physicians in busy office practices have time constraints that may preclude their ability to address the thoughts, feelings, and behaviors that complicate the pathophysiologic processes of IBS (Coon, 2005), nurses have a unique opportunity to step in and facilitate these communications and provide needed education regarding IBS.

In addition, the therapeutic interaction between nurses and patients can be used to convey and discuss realistic treatment goals and available treatment options and assess treatment response. In this manner, the nurse plays an integral role in helping to establish

TABLE 2. Questions to Assess IBS Symptom Severity

Overall severity of symptoms (none, minimal, moderate, severe, or very severe)
Rate individual IBS symptom severity (none, minimal, moderate, severe, or very severe)
• Abdominal pain/discomfort
• Diarrhea
• Constipation
• Bloating
• Flatulence/gas/belching
• Fecal urgency
• Incontinence
What is the effect of IBS on your life?
• Physically
• Socially (missed events, relationships with family, friends, significant other, spouse)
• Mentally (anxiety, depression, overall well-being)
• Occupationally (tardiness, missed work, effectiveness while at work)
What is most burdensome about your IBS symptoms?
How do you rate your overall ability to function? (0–10, 10 being the highest level)
How do you rate the effectiveness of your current treatments? (0–10, list each separately)

Note. IBS = irritable bowel syndrome.

TABLE 3. Questions to Assess Treatment Effectiveness

1. Are you taking treatment X as prescribed?
2. Has treatment X provided you with any benefit?
3. Has treatment X caused you any worrisome side effects?
4. Does treatment X help with some or all of your symptoms?
5. Rate the benefit of your treatment for each symptom (none, minimal, moderate, nearly complete, total relief).
6. Rate the quality of life taking treatment X compared to not taking it.
7. How would you rate your ability to function since starting treatment X on a 0- to 10-point scale? (0 = *not functioning*, 10 = *highly functioning*)
8. Are there still symptoms that cause you distress and what are they?
9. Do you have any reservations or concerns about taking treatment X?
10. Are you interested in trying any new therapies? Why or why not?

and nurture a productive therapeutic relationship, which, in its totality, may be the most important goal to realize with these patients. Table 3 contains inquiries for the ongoing assessment of treatment effectiveness.

In general, patients' perceptions of available IBS treatments are negative. One survey (International Foundation for Functional Gastrointestinal Disorders, 2007) found that less than one third of IBS patients reported being satisfied with their IBS treatment regimen. The effectiveness of over-the-counter medications was perceived as lower than that of prescription medications (International Foundation for Functional Gastrointestinal Disorders, 2007).

Treatment dissatisfaction is prevalent among patients with severe IBS symptoms. In an international Internet survey of more than 1600 patients with IBS, 35.2% of those with self-reported "severe" illness indicated that they would accept between a one in 10,000 and a one in two risks of death to achieve total symptom relief of their IBS symptoms with a new medication (Drossman et al., 2009). Nurse practitioners who manage the IBS spectrum of symptoms should possess a thorough understanding of the various potential treatment options, as well as benefits and risks of each, and should be able to clearly explain these options to their patients.

Later, we briefly review treatment options in IBS and the strength of evidence that the medical literature offers supporting the use of each. For evaluation purposes, each recommendation is either considered strong (Grade 1) or weak (Grade 2). The strength of the evidence is rated as strong (Level A), moderate (Level B), or weak (Level C) (ACG Task Force on Irritable Bowel Syndrome, 2009).

Psychotropic and Psychologic Treatment Approaches

Before discussing available psychotropic and psychologic therapies, it is important to appreciate that comorbid psychiatric disease may influence both IBS severity and treatment choices. Psychologic factors such as depression, anxiety, or a history of sexual and physical abuse may trigger or exacerbate IBS symptoms. An estimated 33%–50% of IBS patients report anxiety or depression, and up to 94% of patients meet the criteria for at least one primary psychiatric disorder at some time in their lives (Whitehead, Palsson, & Jones, 2002).

It is also important for the nurse practitioner to recognize that suicidal ideation can occur in patients with

IBS (Miller, Hopkins, & Whorwell, 2004). Miller et al. (2004) surveyed IBS patients in the United Kingdom for the presence of suicidal ideation and found a higher rate of patients contemplating suicide specifically because of their GI problem in the tertiary care setting (38%) than in the secondary (16%) or primary (4%) care settings. The utility of psychotropic agents and psychologic therapies in the management of IBS is briefly discussed later.

Antidepressants

Antidepressants, including the tricyclic antidepressants (TCAs) and the selective-serotonin reuptake inhibitors (SSRIs), have been used to treat IBS patients for more than three decades, particularly those with comorbid depression or severe abdominal pain (Lacy, 2010; Whitehead et al., 2004). Serotonin-norepinephrine reuptake inhibitors are just beginning to be studied; only one open-label trial exists to date for duloxetine (Brennan et al., 2009). Although the mechanism of action of these agents in IBS is not well understood, the hypothesis is that symptomatic relief of pain is achieved through central and/or peripheral mechanisms (ACG Task Force on Irritable Bowel Syndrome, 2009) with a reduction of afferent signals arising from the gut or by bowel symptom modulation (Drossman, 2009). Commonly used TCAs such as amitriptyline, imipramine, and desipramine have been shown to provide global improvement in IBS symptoms in a relatively small number of randomized controlled trials. Study limitations such as small sample size and the use of invalidated diagnostic criteria have many clinicians questioning their utility (ACG Task Force on Irritable Bowel Syndrome, 2009; Ford, Talley, Schoenfeld, Quigley, & Moayyedi, 2009).

Adverse event considerations with TCA use may prompt physicians and nurse practitioners to use one of the SSRIs instead, although the evidence for their effectiveness is more limited than for the TCAs. Despite the limited information available, both TCAs and SSRIs have shown greater efficacy than placebo in relieving global IBS symptoms and reducing abdominal pain (Grade 1B) by the ACG Task Force on Irritable Bowel Syndrome (2009). The choice of agent may be made on the basis of associated IBS symptoms; tricyclic and serotonin-norepinephrine reuptake inhibitor antidepressants can be beneficial when pain predominates, tricyclics are useful for diarrhea, and SSRIs are useful for constipation and bloating (Drossman, 2009).

Cognitive–Behavioral Therapy

Cognitive–behavioral therapy (CBT) is a nonpharmacologic approach to managing the symptoms of moderate-to-severe IBS in conjunction with other therapies. During 1-hour weekly sessions (up to 10 weeks), patients are trained to recognize thoughts, events, or behaviors that trigger or amplify their bowel as well as psychologic symptoms. Other areas of focus include stress education, muscle relaxation, and pain management (Lackner et al., 2008; Toner, 2005). Several clinical trials support the efficacy of CBT versus "usual management" in reducing the short-term symptoms of IBS. Appropriate patient selection for this treatment may include those patients with a considerable level of distress, openness to the potential that psychologic issues may have a role in current symptomatology, and motivation to participate (Hutton, 2005).

Cognitive–behavioral therapy has been combined with education, relaxation training, and diet management in what is termed a comprehensive self-management approach to IBS, with the intervention administered by trained psychiatric nurse practitioners (Heitkemper et al., 2004; Jarrett et al., 2009). In these two studies, an eight- or nine-session comprehensive self-management intervention brought about statistically significant improvements in individual IBS symptom scores that were sustained for up to 1 year. In addition, significant improvement in the Irritable Bowel Syndrome Quality of Life instrument total score also endured to 1 year (Jarrett et al., 2009). These findings demonstrate that CBT, used as part of a comprehensive self-management approach, can provide sustained improvement in symptoms for up to 1 year, longer than any acute pharmacotherapy trials have shown to date. Cognitive–behavioral therapy received a Grade 1C recommendation from the ACG Task Force on IBS for being more effective than usual care in relieving the global symptoms of IBS (ACG Task Force on Irritable Bowel Syndrome, 2009).

Hypnotherapy

Gut-directed hypnotherapy is a growing area of interest for the treatment of IBS patients with severe symptoms. Similar to CBT, hypnotherapy usually is divided into 10–12 1-hr sessions each week. After a hypnotic state is induced, patients are instructed to use imagery of symptom control and normalized GI function in an effort to control their IBS symptoms. For example, patients with IBS-D will commonly be asked to picture their bowel as a fast-flowing river, subsequently using imagery to slow down the flow to a controlled pace (Hayee & Forgacs, 2007).

Although the mechanisms by which hypnotherapy has been shown to be effective are not well validated, hypnosis is believed to reduce visceral pain sensitivity, relax intestinal smooth muscle, and reduce physiologic arousal (Palsson & Whitehead, 2002). A recent systematic review of 18 trials suggested that hypnotherapy is effective in IBS (Wilson, Maddison, Roberts, Greenfield,

& Singh, 2006), but stipulated that a high validity randomized controlled trial is needed to clearly assess its effectiveness in this population. Like CBT, hypnotherapy received a Grade 1C recommendation from the ACG IBS Task Force for being more effective in relieving global IBS symptoms compared with usual care (ACG Task Force on Irritable Bowel Syndrome, 2009).

Microbial-Related Treatment Approaches

Rifaximin

Rifaximin is a nonabsorbable antibiotic that is currently approved for the treatment of traveler's diarrhea and hepatic encephalopathy (Salix Pharmaceuticals, 2009). Interest in rifaximin for IBS arose from the hypothesis that small intestinal bowel overgrowth contributes to the IBS symptoms of gas, bloating, and altered bowel function through the fermentation of ingested lactulose by gut bacteria and the stimulation of a gut immune response (Lin, 2004). Although the prevalence of small intestinal bowel overgrowth in IBS has been reported to be as high as 84%, more often the prevalence is about 10% (Drossman, 2006; Pimentel, Chow, & Lin, 2003).

Results from two large, identically designed, multicenter trials of rifaximin in nonconstipated IBS were recently reported (Pimentel et al., 2011). In these studies, rifaximin 550 mg three times daily or placebo was administered for 2 weeks, and patients were observed for an additional 10 weeks. Compared with placebo, rifaximin was found to provide statistically significant relief of global IBS symptoms and of bloating for at least 2 of the first 4 weeks of the trial. Global symptom relief showed a durability of 3 months in one trial, but only 2 months in the other, bringing into question the potential need for multiple treatment courses of this agent for IBS. Thus far, QoL data from these two large studies have not been reported.

Overall, the acute safety profile of rifaximin appears similar to that of placebo; longer term safety data are awaited. The issue of potential antibiotic resistance with ongoing intermittent rifaximin use for IBS, which is chronic in nature, remains to be resolved. At present, rifaximin may be appropriate for patients with bloating as the key symptom; however, follow-up after 10 weeks should be encouraged. Rifaximin is under the FDA review for use in IBS but, at present, is not approved for this indication. The ACG IBS Task Force gave rifaximin a Grade 1B recommendation for being more effective than placebo in providing global improvement of IBS and for bloating (ACG Task Force on Irritable Bowel Syndrome, 2009).

Probiotics

Probiotics are live microbiologic organisms that, when administered in adequate amounts, can result in a positive health benefit (Lacy, 2010). The therapeutic mechanism of probiotics in IBS is not well understood, but one hypothesis asserts that these agents attach to the gut wall and exhibit antibiotic properties that alter gut microflora. Another hypothesis suggests that these agents possess a mechanism that stimulates an immune response and alters gut motility (Brenner, Moeller, Chey, & Schoenfeld, 2009). In one study, *Bifidobacterium infantis* 35624 provided a significant improvement in the composite score of abdominal pain/discomfort, bloating/distention, and/or bowel movement compared with placebo (O'Mahony et al., 2005), whereas in another study, *B. infantis* 35624 was superior to placebo on relief of abdominal pain ($p = .023$) as well as on the composite score ($p < .02$) (Whorwell et al., 2006). No other probiotic has shown significant improvements in appropriately designed studies. The ACG Consensus Statement gave probiotics only a Grade 2C recommendation for improving the global symptoms of IBS (ACG Task Force on Irritable Bowel Syndrome, 2009).

Targeted Serotonergic Treatment Approaches

Alosetron

Alosetron is a selective, serotonin receptor 3 ($5\text{-}HT_3$) antagonist. Serotonin influences GI motility, intestinal secretion, and pain perception or visceral hypersensitivity—three key pathophysiologic mechanisms in IBS—through its action on the brain—gut axis (Baker, 2005; Crowell, 2001; Gershon, 2003; Sikander, 2009). Unlike conventional agents, alosetron provides multisymptom relief by treating the underlying pathophysiologic mechanisms operant in IBS instead of focusing on a single symptom. Alosetron is approved only for women with severe IBS-D who have not shown an adequate response to conventional treatment. Severity is defined as having one or more of the following: frequent and severe abdominal pain/discomfort, frequent bowel urgency or fecal incontinence, disability, or restriction of daily activities due to IBS.

Several large, randomized, placebo-controlled studies have demonstrated the clinical efficacy of alosetron in women with IBS-D across multiple symptom domains, including providing significant improvements in global IBS symptoms, abdominal pain and discomfort, fecal urgency, stool consistency and frequency, and health-related QoL (ACG Task Force on Irritable Bowel Syndrome, 2009; Camilleri et al., 2000, 2001; Chey et al., 2004; Krause et al., 2007; Lembo et al., 2001, 2004; Watson et al., 2001).

In safety assessments, generally mild and transient constipation was the most common adverse event reported with alosetron (Lewis, 2010; Prometheus Laboratories, 2010a). The product label for alosetron

includes a black box warning regarding the risk of ischemic colitis and complications of constipation, which are rare but potentially serious (Prometheus Laboratories, 2010a). Alosetron is prescribed in accordance to the FDA-mandated Prescribing Program for Lotronex (PPL). The PPL is intended to help healthcare professionals and their patients gain an understanding of the benefits and risks of treatment with alosetron and to make fully informed treatment decisions (Prometheus Laboratories, 2010a). With a recent change to the PPL, nurse practitioners now have the option of prescribing alosetron to women with severe IBS who respond inadequately to conventional agents (Prometheus Laboratories, 2010b).

As healthcare professionals, nurses have a duty to inform patients of the risk and benefits of *any* treatment used in IBS. The PPL program for alosetron helps to simplify this task by providing the tools to enhance practitioner–patient communication. The ACG Task Force on IBS gives alosetron a Grade 1B recommendation for use in women who have not responded to conventional therapies, for whom the benefit-to-harm balance is favorable (ACG Task Force on Irritable Bowel Syndrome, 2009). In addition, a Grade 2A and a Grade 2B recommendation was given to alosetron in women and men, respectively, for the relief of global symptoms of IBS with diarrhea (ACG Task Force on Irritable Bowel Syndrome, 2009).

Tegaserod

Tegaserod is a 5-HT_4 receptor partial agonist approved in 2002 for use in the treatment of IBS with constipation in women. Clinical trials demonstrated that tegaserod induced significant improvements in global IBS symptoms compared with placebo and improved bowel habits in patients with chronic constipation (Novartis Pharmaceuticals, 2006). In 2007, tegaserod was withdrawn from the market because of an increased risk of cardiovascular events (U.S. FDA, 2007) and is now available from the FDA by means of an emergency investigational drug protocol (U.S. FDA, 2007, 2008). For the relief of global IBS symptoms, tegaserod received a Grade 1A evidence rating in female constipation-predominant IBS (IBS-C) and a Grade 1B rating in IBS-M patients from the ACG Task Force on IBS (ACG Task Force on Irritable Bowel Syndrome, 2009).

Other Agents for IBS

Lubiprostone

Lubiprostone is a C-2 chloride-channel activator approved for chronic idiopathic constipation in adults (24 µg twice daily) and for IBS-C in women (8 µg twice daily) more than 18 years of age (Takeda Pharmaceuticals, 2009). In two 12-week, double-blind, placebo-controlled clinical trials evaluating its use in IBS-C, significantly more patients receiving lubiprostone 8 µg twice daily than placebo were "overall responders." Improvements in individual bowel symptoms such as stool consistency, bloating, and straining (Chey, Drossman, Scott, Panas, & Ueno, 2008), and measures of QoL have also been shown to improve significantly with lubiprostone (Drossman, Chey, Scott, Panas, & Ueno, 2008). Lubiprostone received a Grade 1B evidence rating for relief of global IBS symptoms in women with IBS-C. A summary of treatment effects demonstrated in clinical trials for each agent or modality previously discussed is given in Table 4.

Future of Clinical Trial Investigation for IBS Treatments

Historically, IBS clinical trials used a binary patient-reported outcome with respect to overall improvement or change in condition as the primary end point (Trentacosti, He, Burke, Griebel, & Kennedy, 2010). For example, patients were asked whether they have received "adequate" or "satisfactory relief" of their IBS symptoms, to which patients would answer "yes" or "no" (Trentacosti et al., 2010). In recent guidelines for the conduct of clinical trials in IBS, the FDA recommended against such general ratings of overall change as primary end points, particularly because they do not capture which symptoms have improved. In addition, such rating systems do not reflect the patient's current state of symptoms, they rely on patient memory, and the questions are inconsistently interpreted by patients (U.S. FDA, 2010).

The FDA is advocating the development of a multi-item, patient-reported outcome instrument to capture signs and symptoms of IBS (U.S. FDA, 2010). In the interim, the organization recommends assessing abdominal pain intensity and stool frequency (for IBS-C) and abdominal pain intensity and stool consistency (for IBS-D) as primary end points in IBS clinical trials (U.S. FDA, 2010). This change and how it may affect the availability of new therapeutic options for IBS remain to be seen.

Conclusion

Irritable bowel syndrome, particularly severe IBS, is underrecognized and not adequately managed in the clinical setting, perhaps owing to the lack of a consensus definition of severe IBS and the use of conventional therapies that suboptimally manage the syndrome. Nurses involved in IBS patient care have the opportunity to reverse this trend by playing a more active role in the practitioner–patient relationship. By actively listening to IBS patients, nurses can impart important disease state education and allay irrational fears. By assessing the specific symptoms that are present, determining the severity of symptoms and the impact on the

TABLE 4. Summary of Therapies[a] for Severe IBS

Therapy/Medication	Treatment Effect	
	Indication	Level of Evidence[b]
TCAs	Abdominal pain, diarrhea	1B
SSRIs	Abdominal pain, bloat, constipation	1B
SNRIs	Abdominal pain	Not rated
Alosetron[c]	D-IBS (women only)	1B for women inadequately responsive to conventional agents; otherwise, 2A for women, 2B for men
Tegaserod[d]	C-IBS	1B
Lubiprostone[e]	C-IBS (women only)	1B
Probiotics (*Bifidobacterium infantis*)	Bloating, all types of IBS	2C
Rifaximin	Nonconstipated IBS	1B
Other modalities		
CBT	All IBS	1C
Hypnotherapy	All IBS	1C

Note. CBT = cognitive–behavioral therapy; C-IBS = constipation-type irritable bowel syndrome; D-IBS = diarrhea-type irritable bowel syndrome; IBS = irritable bowel syndrome; SNRIs = serotonin-norepinephrine reuptake inhibitors (duloxetine, venlafaxine); SSRIs = selective-serotonin reuptake inhibitors (fluoxetine, sertraline, paroxetine, citalopram, escitalopram); TCAs = tricyclic antidepressants (amitriptyline, imipramine, nortriptyline, desipramine).

[a]Includes only IBS therapies discussed in detail in this article. [b]ACG levels of evidence. Key: Grade 1 = strong recommendation; Grade 2 = weak recommendation. The strength of the evidence is rated as strong (Level A), moderate (Level B), or weak (Level C) (ACG Task Force on Irritable Bowel Syndrome, 2009). [c]FDA approved for female IBS patients only. [d]Withdrawn by FDA in March 2006. [e]FDA approved for female patients with IBS.

IBS patient's life, and being knowledgeable of available treatment options, the nurse involved in IBS care becomes an important conduit of information and a valuable facilitator of a positive practitioner–patient therapeutic relationship. In this way, nurses can help to limit the negative consequences of this common disorder and improve overall treatment outcomes in this population. ✪

ACKNOWLEDGMENTS

The authors thank John H. Simmons, MD, and Peloton Advantage for their assistance in the preparation of this manuscript. Writing support was provided with funding from Prometheus Laboratories, Inc.

REFERENCES

American College of Gastroenterology Task Force on Irritable Bowel Syndrome. (2009). An evidence-based position statement on the management of irritable bowel syndrome. *American Journal of Gastroenterology, 104*(Suppl. 1), S1-S35.

American Gastroenterological Association. (2002). American Gastroenterological Association medical position statement: irritable bowel syndrome. *Gastroenterology, 123*(6), 2105-2107.

Andrews, E. B., Eaton, S. C., Hollis, K. A., Hopkins, J. S., Ameen, V., Hamm, L. R., ... Mangel, A. W. (2005). Prevalence and demographics of irritable bowel syndrome: Results from a large Web-based survey. *Alimentary Pharmacology and Therapeutics, 22*(10), 935-942.

Baker, D. E. (2005). Rationale for using serotonergic agents to treat irritable bowel syndrome. *American Journal of Health-System Pharmacy, 62*(7), 700-711.

Bertram, S., Kurland, M., Lydick, E., Locke, G. R., III, & Yawn, B. P. (2001). The patient's perspective of irritable bowel syndrome. *Journal of Family Practice, 50*(6), 521-525.

Brennan, B. P., Fogarty, K. V., Roberts, J. L., Reynolds, K. A., Pope, H. G., Jr., & Hudson, J. I. (2009). Duloxetine in the treatment of irritable bowel syndrome: an open-label pilot study. *Human Psychopharmacology, 24*(5), 423-428.

Brenner, D. M., Moeller, M. J., Chey, W. D., & Schoenfeld, P. S. (2009). The utility of probiotics in the treatment of irritable bowel syndrome: a systematic review. *American Journal of Gastroenterology, 104*(4), 1033-1049.

Camilleri, M., Chey, W. Y., Mayer, E. A., Northcutt, A. R., Heath, A., Dukes, G. E., ... Mangel, A. M. (2001). A randomized controlled clinical trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant irritable bowel syndrome. *Archives of Internal Medicine, 161*(14), 1733-1740.

Camilleri, M., Northcutt, A. R., Kong, S., Dukes, G. E., McSorley, D., & Mangel, A. W. (2000). Efficacy and safety of alosetron in women with irritable bowel syndrome: A randomised, placebo-controlled trial. *Lancet, 355*(9209), 1035-1040.

Chey, W. D., Chey, W. Y., Heath, A. T., Dukes, G. E., Carter, E. G., Northcutt, A., & Ameen, V. Z. (2004). Long-term safety and efficacy of alosetron in women with severe diarrhea-predominant irritable bowel syndrome. *American Journal of Gastroenterology, 99*(11), 2195-2203.

Chey, W. D., Drossman, D. A., Scott, C., Panas, R., & Ueno, R. (2008). What symptoms drive global symptom improvement with lubiprostone in patients with irritable bowel syndrome and constipation: Data from two multicenter, randomized, placebo-controlled trials [abstract 157]. *Gastroenterology, 134*(4, Suppl. 1), A28.

Coon, K. A. (2005). Treatment of irritable bowel syndrome: Changing the paradigm. *Primary Care Companion to the Journal of Clinical Psychiatry, 7*(5), 242-243.

Crowell, M. D. (2001). The role of serotonin in the pathophysiology of irritable bowel syndrome. *American Journal of Managed Care, 7*(Suppl. 8), S252-S260.

Drossman, D. A. (2006). Treatment for bacterial overgrowth in the irritable bowel syndrome. *Annals of Internal Medicine, 145*(8), 626-628.

Drossman, D. A. (2009). Beyond tricyclics: New ideas for treating patients with painful and refractory functional gastrointestinal symptoms. *American Journal of Gastroenterology, 104*(12), 2897-2902.

Drossman, D. A., Chey, W. D., Scott, C., Panas, R., & Ueno, R. (2008). Health-related quality of life in adults with irritable bowel syndrome with constipation: Results of combined analysis of two Phase 3 studies with lubiprostone [abstract T1036]. *Gastroenterology, 134*(4, Suppl. 1), A469.

Drossman, D. A., Morris, C. B., Schneck, S., Hu, Y. J., Norton, N. J., Norton, W. F., ... Bangdiwala, S. I. (2009). International survey of patients with IBS: Symptom features and their severity, health status treatments, and risk taking to achieve clinical benefit. *Journal of Clinical Gastroenterology, 43*(6), 541-550.

Drossman, D. A., & Thompson, W. G. (1992). The irritable bowel syndrome: Review and a graduated multicomponent treatment approach. *Annals of Internal Medicine, 116*(12, Pt 1), 1009-1016.

Ford, A. C., Talley, N. J., Schoenfeld, P. S., Quigley, E. M., & Moayyedi, P. (2009). Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: Systematic review and meta-analysis. *Gut, 58*(3), 367-378.

Gershon, M. D. (2003). Serotonin and its implication for the management of irritable bowel syndrome. *Review of Gastroenterology Disorders, 3*(Suppl. 2), S25-S34.

Gralnek, I. M., Hays, R. D., Kilbourne, A., Naliboff, B., & Mayer, E. A. (2000). The impact of irritable bowel syndrome on health-related quality of life. *Gastroenterology, 119*(3), 654-660.

Hahn, B. A., Kirchdoerfer, L. J., Fullerton, S., & Mayer, E. (1997). Patient-perceived severity of irritable bowel syndrome in relation to symptoms, health resource utilization and quality of life. *Alimentary Pharmacology and Therapeutics, 11*(3), 553-559.

Harris, L. R., & Roberts, L. (2008). Treatments for irritable bowel syndrome: Patients' attitudes and acceptability. *BMC Complementary and Alternative Medicine, 8*(65), 1-11.

Hayee, B., & Forgacs, I. (2007). Psychological approach to managing irritable bowel syndrome. *British Medical Journal, 334*(7603), 1105-1109.

Heitkemper, M. M., Jarrett, M. E., Levy, R. L., Cain, K. C., Burr, R. L., Feld, A., … Weisman, P. (2004). Self-management for women with irritable bowel syndrome. *Clinical Gastroenterology & Hepatology, 2*(7), 585-596.

Heitkemper, M., Olden, K., Gordon, S., Carter, E., & Chang, L. (2001). Irritable bowel syndrome. A survey of nurses' knowledge. *Gastroenterology Nursing, 24*(6), 281-287.

Hungin, A. P., Chang, L., Locke, G. R., Dennis, E. H., & Barghout, V. (2005). Irritable bowel syndrome in the United States: Prevalence, symptom patterns and impact. *Alimentary Pharmacology and Therapeutics, 21*(11), 1365-1375.

Hutton, J. (2005). Cognitive behaviour therapy for irritable bowel syndrome. *European Journal of Gastroenterology & Hepatology, 17*(1), 11-14.

International Foundation for Functional Gastrointestinal Disorders. (2007). *IBS in the real world survey. Summary findings*. Retrieved September 1, 2009, from http://aboutconstipation.org/pdfs/IBSRealWorld.pdf

Jarrett, M. E., Cain, K. C., Burr, R. L., Hertig, V. L., Rosen, S. N., & Heitkemper, M. M. (2009). Comprehensive self-management for irritable bowel syndrome: Randomized trial of in-person vs. combined in-person and telephone sessions. *American Journal of Gastroenterology, 104*(12), 3004-3014.

Kaptchuk, T. J., Kelley, J. M., Conboy, L. A., Davis, R. B., Kerr, C. E., Jacobson, E. E., … Lembo, A. J. (2008). Components of placebo effect: Randomised controlled trial in patients with irritable bowel syndrome. *British Medical Journal, 336*(7651), 999-1003.

Krause, R., Ameen, V., Gordon, S. H., West, M., Heath, A. T., Perschy, T., & Carter, E. G. (2007). A randomized, double-blind, placebo-controlled study to assess efficacy and safety of 0.5 mg and 1 mg alosetron in women with severe diarrhea-predominant IBS. *American Journal of Gastroenterology, 102*(8), 1709-1719.

Lackner, J. M., Jaccard, J., Krasner, S. S., Katz, L. A., Gudleski, G. D., & Holroyd, K. (2008). Self-administered cognitive behavior therapy for moderate to severe irritable bowel syndrome: Clinical efficacy, tolerability, feasibility. *Clinical Gastroenterology & Hepatology, 6*(8), 899-906.

Lacy, B. E. (2010). Irritable bowel syndrome and disease severity: Are we undertreating our patients? *Expert Reviews in Gastroenterology & Hepatology, 4*(1), 1-3.

Lacy, B. E., Weiser, K., & De Lee, R. (2009). Review: The treatment of irritable bowel syndrome. *Therapeutic Advances in Gastroenterology, 2*(4), 221-238.

Lembo, A., Ameen, V. Z., & Drossman, D. A. (2005). Irritable bowel syndrome: Toward an understanding of severity. *Clinical Gastroenterology and Hepatology, 3*(8), 717-725.

Lembo, A. J., Olden, K. W., Ameen, V. Z., Gordon, S. L., Heath, A. T., & Carter, E. G. (2004). Effect of alosetron on bowel urgency and global symptoms in women with severe, diarrhea-predominant irritable bowel syndrome: Analysis of two controlled trials. *Clinical Gastroenterology & Hepatology, 2*(8), 675-682.

Lembo, T., Wright, R. A., Bagby, B., Decker, C., Gordon, S., Jhingran, P., & Carter, E. (2001). Alosetron controls bowel urgency and provides global symptom improvement in women with diarrhea-predominant irritable bowel syndrome. *American Journal of Gastroenterology, 96*(9), 2662-2670.

Lewis, J. H. (2010). Alosetron for severe diarrhea-predominant irritable bowel syndrome: Safety and efficacy in perspective. *Expert Reviews in Gastroenterology & Hepatology, 4*(1), 13-29.

Lin, H. C. (2004). Small intestinal bacterial overgrowth: A framework for understanding irritable bowel syndrome. *JAMA, 292*(7), 852-858.

Miller, V., Hopkins, L., & Whorwell, P. J. (2004). Suicidal ideation in patients with irritable bowel syndrome. *Clinical Gastroenterology and Hepatology, 2*(12), 1064-1068.

Nicandro, J. P. A., Shin, P., & Chuang, E. (2010). Disability or restriction of daily activities is the primary indicator of disease severity in female patients with severe IBD-D: An analysis of the alosetron patient survey [abstract P693]. Presentation at the 2010 American College of Gastroenterology Meeting, October 15–20, 2010, San Antonio, TX.

Novartis Pharmaceuticals. (2006). *Zelnorm* [package insert]. East Hanover, NJ: Novartis Pharmaceuticals.

O'Mahony, L., McCarthy, J., Kelly, P., Hurley, G., Luo, F., Chen, K., … Quigley, E. M. (2005). Lactobacillus and bifidobacterium in irritable bowel syndrome: Symptom responses and relationship to cytokine profiles. *Gastroenterology, 128*(3), 541-551.

Page, J. G., & Dirnberger, G. M. (1981). Treatment of the irritable bowel syndrome with Bentyl (dicyclomine hydrochloride). *Journal of Clinical Gastroenterology, 3*(2), 153-156.

Palsson, O. S., & Whitehead, W. E. (2002). The growing case for hypnosis as adjunctive therapy for functional gastrointestinal disorders. *Gastroenterology, 123*(6), 2132-2135.

Pimentel, M., Chow, E. J., & Lin, H. C. (2003). Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome. A double-blind, randomized, placebo-controlled study. *American Journal of Gastroenterology, 98*(2), 412-419.

Pimentel, M., Lembo, A., Chey, W. D., Zakko, S., Ringel, Y., Yu, J., … Forbes, W. P. (2011). Rifaximin therapy for patients with irritable bowel syndrome without constipation. *New England Journal of Medicine, 364*(1), 22-32.

Prometheus Laboratories, I. (2010a). *Lotronex (alosetron hydrochloride) tablets* [package insert]. San Diego, CA: Prometheus Laboratories, Inc.

Prometheus Laboratories, I. (2010b). *Prescribing program for Lotronex™ prescriber enrollment form*. Retrieved October 29, 2010, from http://www.lotronexppl.com/PDF/REMS_Prescriber%20Enrollment%20Form.pdf

Salix Pharmaceuticals, I. (2009). *Xifaxan* [package insert]. Morrisville, NC: Salix Pharmaceuticals, Inc.

Sikander, A., Rana, S. V., & Prasad, K. K. (2009). Role of serotonin in gastrointestinal motility and irritable bowel syndrome. *Clinica Chimica Acta, 403*(1/2), 47-55.

Spiegel, B. M., Bolus, R. E., Harris, L. A., Lucak, S. L., Esrailian, E., Chey, W. E., … Chang, L. (2010). Patient-reported symptom relief from current therapy is a robust marker of illness severity in IBS [abstract 865]. *Gastroenterology, 5*(Suppl. 1), S119.

Spiegel, B. M., Gralnek, I. M., Bolus, R., Chang, L., Dulai, G. S., Mayer, E. A., & Naliboff, B. (2004). Clinical determinants of health-related quality of life in patients with irritable bowel syndrome. *Archives of Internal Medicine, 164*(16), 1773-1780.

Takeda Pharmaceuticals. *Amitiza (lubiprostone) capsules* [package insert]. Deerfield, IL: Takeda Pharmaceuticals.

Toner, B. B. (2005). Cognitive–behavioral treatment of irritable bowel syndrome. *CNS Spectrums, 10*(11), 883-890.

Trentacosti, A. M., He, R., Burke, L. B., Griebel, D., & Kennedy, D. L. (2010). Evolution of clinical trials for irritable bowel syndrome: Issues in end points and study design. *American Journal of Gastroenterology, 105*(4), 731-735.

U.S. Food and Drug Administration. (2007). *Public Health Advisory: Tegaserod maleate (marketed as Zelnorm)*. Retrieved March 8, 2010, from http://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm078972.htm

U.S. Food and Drug Administration. (2008). *Zelnorm (tagaserod maleate) information*. Retrieved March 8, 2010, from http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103223.htm

U.S. Food and Drug Administration. (2010). *Guidance for industry. Irritable bowel syndrome: Clinical evaluation of products for treatment* [draft]. Retrieved April 19, 2010, from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM205269.pdf

Watson, M. E., Lacey, L., Kong, S., Northcutt, A. R., McSorley, D., Hahn, B., & Mangel, A. W. (2001). Alosetron improves quality of life in women with diarrhea-predominant irritable bowel syndrome. *American Journal of Gastroenterology, 96*(2), 455-459.

Whitehead, W. E., Levy, R. L., Von Korff, M., Feld, A. D., Palsson, O. S., Turner, M., & Drossman, D. A. (2004). The usual medical care for irritable bowel syndrome. *Alimentary Pharmacology and Therapeutics, 20*(11/12), 1305-1315.

Whitehead, W. E., Palsson, O., & Jones, K. R. (2002). Systematic review of the comorbidity of irritable bowel syndrome with other disorders: What are the causes and implications? *Gastroenterology, 122*(4), 1140-1156.

Whorwell, P. J., Altringer, L., Morel, J., Bond, Y., Charbonneau, D., O'Mahony, L.,… Quigley, E. M. (2006). Efficacy of an encapsulated probiotic *Bifidobacterium infantis* 35624 in women with irritable bowel syndrome. *American Journal of Gastroenterology, 101*(7), 1581-1590.

Williams, R. E., Black, C. L., Kim, H. Y., Andrews, E. B., Mangel, A. W., Buda, J. J., & Cook, S. F. (2006). Determinants of health-care-seeking behavior among subjects with irritable bowel syndrome. *Alimentary Pharmacology and Therapeutics, 23*(11), 1667-1675.

Wilson, S., Maddison, T., Roberts, L., Greenfield, S., & Singh, S. (2006). Systematic review: The effectiveness of hypnotherapy in the management of irritable bowel syndrome. *Alimentary Pharmacology and Therapeutics, 24*(5), 769-780.