

Research Update in Functional Gastrointestinal Disorders

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Digestive Disease Week 2006 featured noteworthy health-service and clinical-trial research presented by experts in functional gastrointestinal disorders. Two presentations were based on an Internet survey of both academic thought leaders in irritable bowel syndrome (IBS) and healthcare providers in community practice who deal with this malady continually. Using clinical vignettes, investigators captured data on caring for IBS patients and assessed respondents' knowledge, attitudes, and beliefs about this disorder. This survey showed that experts and community healthcare providers vary in their management of IBS, with experts generally not believing IBS to be a diagnosis of exclusion. Two other presentations investigated the efficacy and safety of lubiprostone for chronic constipation and constipation-predominant IBS. In one study, authors suggested that 24 and 48 weeks of lubiprostone therapy for chronic constipation were effective and safe. Short-term data linked lubiprostone with a dose-dependent improvement of constipation-predominant IBS. Nausea, diarrhea, and headache were the most frequent adverse events observed with use of the drug in all trials.

Functional gastrointestinal (GI) disorders include such prevalent conditions as irritable bowel syndrome (IBS) and chronic constipation, both of which lead to extensive healthcare resource use and decreased quality of life in the United States and abroad. Each year, the total cost of caring for an IBS patient may reach thousands of dollars and result in significant absenteeism.¹ Chronic constipation causes a similar consumption of resources and need to miss days of employment and education—and it also carries a long history of unsatisfactory attempts to design effective therapies.²

Important research presentations on functional GI disorders were presented at Digestive Disease Week 2006 in Los Angeles, California. As summarized in this report, two of the studies focused on IBS from a health-services/research perspective. Investigators from the Veterans Administration (VA) Greater Los Angeles Healthcare System and the David Geffen School of Medicine at the University of California, Los Angeles, conducted a provider survey to find out how academic thought leaders and community healthcare providers view the process of care for IBS. Two other studies, presented by John F. Johanson, MD, MS, of Rockford Gastroenterology Associates and colleagues from Sucampo Pharmaceuticals, Inc., provided long-term data on the effectiveness of lubiprostone in

treating chronic constipation and discussed the results of a dose-ranging, randomized controlled trial of lubiprostone in patients with constipation-predominant IBS.

Extreme Variations in Caring for IBS Patients

The framework of healthcare quality as described by Donabedian,³ a pioneer in health services, consists essentially of three components: structure, process, and outcomes of care (Figure 1).⁴ The process of care, which usually refers to the patient-provider interaction, is important to this conceptual model. Although minor variations in this process are expected in both the art and science of medicine, any extreme variation may suggest suboptimal care.⁵



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Methods

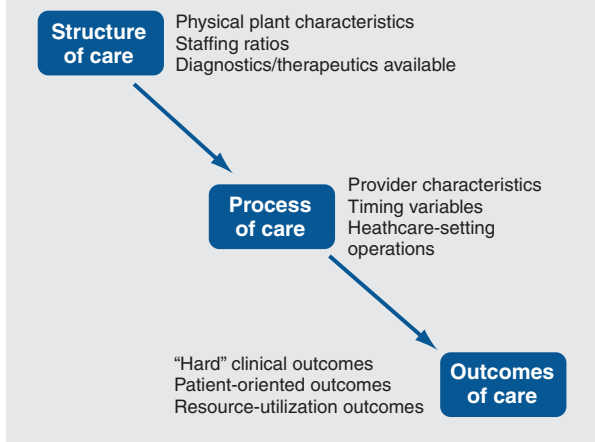
Spiegel et al⁶ conducted an online survey of academic thought leaders involved with IBS and a group of VA healthcare providers, including primary care providers and gastroenterologists, to assess for interindividual variation in the process of IBS care.

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Figure 1

Donabedian model of the structure, process, and outcome of healthcare. Adapted from UCLA/VA Center for Outcomes Research and Education (CORE).⁴



The investigators used clinical vignette methodology to capture ways in which professionals in the two groups order diagnostic tests and institute therapy. One group was made up of 45 recognized IBS experts, as identified by publications and their membership on practice guideline committees. The other, a community-practice group, included a random sample of 300 VA nurse practitioners, 300 VA primary care physicians, and 300 gastroenterologists from the American Gastroenterological Association's membership directory. Both groups of respondents were shown the same two clinical vignettes involving patients who were positive for Rome II diagnostic criteria; however, whereas the patient in one vignette suffered predominantly from diarrhea, the patient in the other suffered predominantly from constipation. Neither vignette offered any signs or symptoms to suggest alarm features.

After reading each vignette, the respondents rated the appropriateness of diagnostic tests or therapies described in the vignette using a nine-point Research and Development (RAND) Appropriateness Scale (RAS). A score of 1–3 meant that the respondent believed the intervention to be “generally inappropriate,” a score of 4–6 meant that it was considered “neither inappropriate nor appropriate,” and a score of 7–9 meant that it was considered “generally appropriate.”⁷ The investigators also took note of any “extreme variation” in expert opinion using the RAND “disagreement index” (DI), which is based on the distribution and symmetry of the scores across the nine-point

RAND scale. A DI greater than 1.0 indicates “extreme variation” in respondent scores.⁷

Results and Conclusions

The survey had a 33% response rate; in all, 27 IBS experts, 109 nurse practitioners, 89 primary care physicians, and 90 gastroenterologists responded.

Table 1 lists some of the diagnostic tests and interventions rated by respondents in both vignettes.⁸ In general, the community providers endorsed more tests and interventions than did the IBS experts. For example, in the diarrhea-predominant IBS vignette, the experts endorsed only performance of a complete blood count and celiac sprue serologies among all potential diagnostic tests. Faced with the same data, non-experts also endorsed ordering a chemistry panel, a stool sample for ova and parasites, and a stool sample for fecal leukocytes, but did *not* endorse the celiac sprue serology testing. Despite this notable difference between both respondent groups, and even within each group, an extreme variation in the process of care was noted, with a DI score > 1.0 found for numerous tests/interventions; this, too, is illustrated in Table 1.⁸

This presentation used clinical vignette methodology to capture the process of care and, therefore, was the target of criticism; however, the same approach was previously used and validated as a measure of the quality of clinical practice.⁹ Ultimately, the authors concluded that despite the dissemination of guidelines regarding diagnostic testing in IBS, both experts and non-experts demonstrated extreme variation in their processes of care. In addition, the authors emphasized the need for better distribution of IBS diagnostic guidelines to minimize the variation and potentially improve the cost-effectiveness of care.

Table 1

A Sample of Diagnostic Tests and Interventions Rated by Respondents for Appropriateness in the Diarrhea-Predominant IBS Vignette

Diagnostic test	IBS experts		IBS “non-experts”	
	Mean RAS	DI	Mean RAS	DI
Complete blood count	7.4	-1.4	7.5	-0.9
Celiac sprue serologies	6.8	-3.1	4.8	1.7
Erythrocyte sedimentation rate	5.4	4.1	5.4	1.8
Thyroid-stimulating hormone	4.8	1.8	6.2	-12.0
Colonoscopy	4.7	1.6	5.9	7.0
Breath test	2.3	0.5	4.1	1.0

IBS = irritable bowel syndrome; RAS = Research and Development (RAND) Appropriateness Scale; DI = disagreement index

The RAS ranges from 0 to 9, where a mean score > 6.5 means that the test or procedure was considered to be generally appropriate. A DI score > 1.0 denotes “extreme variation,” whereas a score < 1.0, including negative numbers, suggests a lack of consensus.

Adapted from Spiegel et al⁸

IBS Experts Do Not Believe in a Diagnosis of Exclusion

The accumulation of data and experience over time have led authorities to endorse IBS as a primary diagnosis in the medical literature, rather than as one of exclusion.^{10,11} This approach has been promoted, yet the extent to which it is followed in practice differs from what would be expected.

As part of the aforementioned online provider survey, Spiegel et al⁸ also presented data on provider knowledge, attitudes, and beliefs in IBS.

Methods

In addition to rating the appropriateness of various diagnostic tests and interventions, respondents in the study conducted by Spiegel et al⁸ were asked, “Based on your clinical experience, do you believe that IBS is primarily a diagnosis of exclusion (ie, one or more diagnostic tests should be performed before diagnosing IBS)?”

Results and Conclusions

A majority of nurse practitioners and primary care physicians (72% each), as well as 42% of the gastroenterologists and only 8% of the IBS experts who took part in the survey, answered that IBS was a diagnosis of exclusion (Figure 2). A statistically significant difference in these opinions existed between the four groups ($P < 0.0001$). By assigning costs to diagnostic tests based on published Medicare fee schedules, these investigators calculated a total incurred cost of the work-up and the total number of tests ordered for each vignette. A subset analysis presented during the conference showed that respondents who believed IBS to be a diagnosis of exclusion spent an average of \$364 more and ordered 1.6 more tests or procedures than did respondents who held that IBS was not a diagnosis of exclusion.

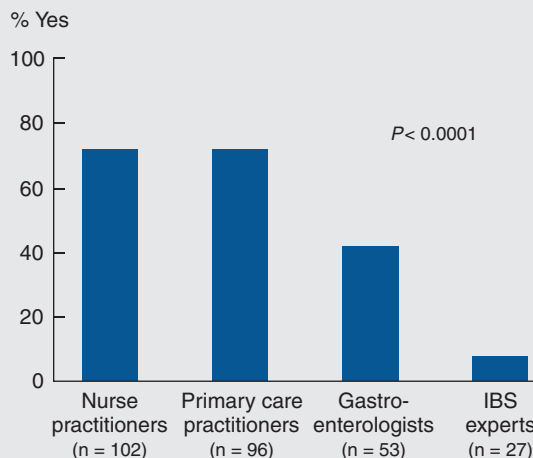
Based on these data, the researchers concluded that most community providers still believe IBS to be a diagnosis of exclusion, and this belief may predict increased use of diagnostic testing and consumption of healthcare resources. Furthermore, since few IBS experts believed the medical condition to be a diagnosis of exclusion, the investigators suggested that “experts comply more closely with guidelines and that these guidelines are either inadequately disseminated or not followed [by others in the health community].”⁸

Lubiprostone Sustains Long-Term Efficacy in Chronic Constipation

Chronic constipation is another functional GI disorder that may increase the use of healthcare resources

Figure 2

Responses of providers when asked, “Based on your clinical experience, do you believe that IBS is primarily a diagnosis of exclusion (ie, one or more diagnostic tests should be performed before diagnosing IBS)?” IBS = irritable bowel syndrome. Adapted from Spiegel et al.⁸



and negatively impact patients' lives over long periods.¹² The results of phase III studies have shown that tegaserod, a 5-hydroxytryptamine type 4 receptor agonist, is effective and well tolerated in patients who have chronic constipation.^{13,14}

In addition, lubiprostone, a drug with a notably different mechanism of action, was recently approved by the US Food and Drug Administration as a treatment for chronic idiopathic constipation. This orally administered fatty acid selectively activates type 2 chloride channels in the epithelium of the GI tract and leads to an increase in luminal fluid secretion.^{15,16} The resulting increase in intraluminal fluid content softens the stool, promoting an increase in spontaneous bowel movements and a reduction in abdominal discomfort and bloating.¹⁷

During Digestive Disease Week 2006, Johanson and colleagues¹⁸ provided long-term data on the use of lubiprostone in chronic constipation and summarized the results of three open-label trials.

Methods

The investigators defined chronic constipation as fewer than three spontaneous bowel movements per week, with a minimum 3-month history of hard stools, sensation of incomplete evacuation, or straining during at least 25% of these bowel movements. They also defined a spontaneous bowel movement as one that did not occur within 24 hours of taking a rescue laxative. Among exclusions for entry

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into the study were evidence of a documented mechanical obstruction, organic bowel disorders, secondary constipation following surgery, and significant comorbidities or laboratory abnormalities.

A majority of the subjects were Caucasian (86.9%) and female (86.1%). Some of the subjects were follow-up patients from the investigators' previous 4-week, short-term efficacy study.¹⁷ The study protocols were as follows:

- a 24-week, open-label trial with extension to a 4-week, double-blind trial (n = 308);
- a 48-week, open-label trial during which 87 patients were enrolled in a 7-week, randomized withdrawal study before beginning the open-label phase (n = 248); or
- a 48-week, open-label trial in treatment-naïve patients (n = 348).

Patients taking part in these trials received 24 µg of lubiprostone orally with food and water twice daily for a 24- to 48-week course, as needed. The investigators reported that subject need was "defined as perceived severity of constipation and need for relief," and investigators were allowed to adjust the dosing if necessary if adverse events occurred.¹⁸ Follow-up evaluations took place at regular intervals, and efficacy assessments were based on a five-point severity scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe).

Results and Conclusions

Johanson et al presented intention-to-treat efficacy data on 871 subjects taking part in the three trials.¹⁸ The investigators assessed efficacy by comparing the patients' therapeutic improvement according to the aforementioned severity scale with their scores at baseline.

Across all three trials and at each post-baseline follow-up time point, the investigators found statistically significant improvements in constipation severity, abdominal bloating, and abdominal discomfort with lubiprostone treatment ($P < 0.0001$). A total of 44 serious adverse events were reported in 31 subjects; no deaths occurred. One patient became pregnant during the course of the study, discontinued treatment, and subsequently delivered a child with bilateral clubfoot; this event was considered to be possibly related to treatment.

Table 2 lists the most common possible, probable, or definite adverse events observed among all patients taking at least one dose of lubiprostone (ie, the safety evaluable population).¹⁸ The most frequently reported adverse events were nausea (25.5%), diarrhea (12.3%), and headache (9.7%).

The authors of the report concluded that, given the consistent improvements in constipation severity, abdominal bloating, and abdominal discomfort observed among chronically constipated patients, treatment with 24 µg of

Table 2

Most Common Adverse Events of Long-Term Lubiprostone (24 µg Twice Daily) Therapy

Adverse event	Frequency, %
Nausea	25.5
Diarrhea	12.3
Headache	9.7
Abdominal distension	6.7
Flatulence	5.4
Abdominal pain	5.0

Adapted from Johanson et al¹⁸

lubiprostone twice daily apparently provides sustained, long-term relief and is well tolerated.

Lubiprostone Effective in Constipated Patients with IBS

Given the efficacy of lubiprostone in patients with chronic constipation and the need for better IBS therapy, Johanson and colleagues¹⁹ also conducted a randomized controlled trial of lubiprostone in patients with constipation-predominant IBS.

Methods

The dose-ranging study of lubiprostone was conducted in patients who met the Rome II diagnostic criteria for constipation-predominant IBS. This study had a 12-week, double-blind, multicenter design. Approximately 50 patients were randomized to receive one of the following regimens after a 4-week washout period:

- 8 µg of lubiprostone twice daily (16 µg/d);
- 16 µg of lubiprostone twice daily (32 µg/d);
- 24 µg of lubiprostone twice daily (48 µg/d); or
- placebo.

As in the previously described assessment of patients with chronic constipation, the investigators asked patients to rate symptom severity in electronic diaries during their follow-up period. Subjects used a five-point scale to rate abdominal symptoms (eg, bloating and discomfort/pain), bowel movements (eg, rating frequency, straining, and consistency), and the need for rescue laxative medication. The authors described using trend tests to detect dose-dependent efficacy relationships between the groups and assessing safety by examining the incidence of adverse events.¹⁹

Results and Conclusions

As in the chronic constipation trials, a majority of the subjects enrolled in this study (> 80%) were Caucasian women. When compared with patients taking placebo, those using lubiprostone at all three doses experienced sta-

tistically significant decreases in constipation at 1 month ($P < 0.05$). At months 2 and 3, a statistically significant improvement was observed only among patients using 32 or 48 μg of lubiprostone daily.

Investigators also observed statistically significant, dose-dependent trends in at least two of the three monthly time periods for abdominal discomfort/pain, abdominal bloating, spontaneous bowel movement frequency, and bowel straining. Severity-score improvements were typically highest among those taking 48 $\mu\text{g}/\text{d}$ of lubiprostone. Subjects receiving the two highest doses experienced treatment-related adverse reactions and discontinuation of therapy. As in the chronic constipation trial, nausea and diarrhea were the most frequent adverse reactions and were dependent upon dose. An analysis of efficacy and safety data revealed that a dose of 16 $\mu\text{g}/\text{d}$ (8 μg twice daily) offered the optimum balance of efficacy and safety for constipation-predominant IBS over a 3-month period.

Health-related quality of life (HRQOL) in patients with IBS may be related to extraintestinal symptoms rather than just GI symptoms.²⁰ Therefore, improving the bowel-specific symptoms in patients with IBS may not improve HRQOL to the extent seen in treated patients with chronic constipation. Although this study did not include a global symptom assessment as a primary outcome measure, the data suggested that bowel-specific symptoms improved in the short term and at a dose below that typically used for chronic constipation. This finding suggests that constipation in this group of IBS subjects was less severe than that of the subjects with chronic constipation who took part in the three open-label clinical trials previously discussed.

Conclusion

As shown by the results of the studies summarized in this report, experts generally agree that IBS is not a diagnosis of exclusion. However, extreme variations in the process of its care exist among both experts and community healthcare providers, suggesting a need for wider dissemination of practice guidelines and greater adherence to their principles.

Lubiprostone represents a promising new approach to the management of chronic constipation and, potentially, constipation-predominant IBS, with clinical trial data showing it to be both safe and effective in treating these functional GI disorders. Future trial results will help to clarify the place of this drug in this population.

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