The treatment of irritable bowel syndrome

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***Abstract*:** Irritable bowel syndrome (IBS) is a highly prevalent functional bowel disorder routinely encountered by healthcare providers. Although not life-threatening, this chronic disorder reduces patients' quality of life and imposes a significant economic burden to the healthcare system. IBS is no longer considered a diagnosis of exclusion that can only be made after performing a battery of expensive diagnostic tests. Rather, IBS should be confidently diagnosed in the clinic at the time of the first visit using the Rome III criteria and a careful history and physical examination. Treatment options for IBS have increased in number in the past decade and clinicians should not be limited to using only fiber supplements and smooth muscle relaxants. Although all patients with IBS have symptoms of abdominal pain and disordered defecation, treatment needs to be individualized and should focus on the predominant symptom. This paper will review therapeutic options for the treatment of IBS using a tailored approach based on the predominant symptom. Abdominal pain, bloating, constipation and diarrhea are the four main symptoms that can be addressed using a combination of dietary interventions and medications. Treatment options include probiotics, antibiotics, tricyclic antidepressants, selective serotonin reuptake inhibitors and agents that modulate chloride channels and serotonin. Each class of agent will be reviewed using the latest data from the literature.

***Keywords*:** abdominal pain, alosetron, bloating, constipation, diarrhea, irritable bowel syndrome, lubiprostone, probiotics, tegaserod, tricyclic antidepressants

Introduction

Irritable bowel syndrome (IBS) is a highly prevalent disorder that reduces patients' quality of life and which imposes a significant economic burden to the healthcare system [Lacy *et al.* 2006; Frank *et al.* 2002; Sandler *et al.* 2002; American Gastroenterological Association, 2001; Creed *et al.* 2001; Gralnek *et al.* 2000; Talley *et al.* 1995, 1991]. Many healthcare providers view IBS as a static disorder that is hard to define, difficult to diagnose and impossible to treat. These popular views are just several of the most common misconceptions related to the diagnosis and treatment of IBS. The truth, however, is that IBS is a dynamic field characterized by significant changes in diagnostic strategies and therapeutic options over the last decade. This paper will briefly review the current definition of IBS, and then focus on current therapeutic options using a symptom-based approach.

Defining and diagnosing IBS

The definition of IBS has evolved over the past decade in order to incorporate new information about this complex disorder. The Rome III committee defines IBS as a chronic disorder characterized by abdominal pain or discomfort associated with disordered defecation (either constipation [IBS-C], diarrhea [IBS-D], or mixed/alternating symptoms of constipation and diarrhea [IBS-M]) [Longstreth *et al.* 2006]. Symptom onset should be at least 6 months before the patient is first seen for formal evaluation. Abdominal pain or discomfort should be present at least 3 days per month for 3 months and should be associated with two or more of the following: improvement with defecation, onset associated with a change in stool frequency and onset associated with a change in stool form (see Box 1). The American College of Gastroenterology (ACG) guidelines emphasize a clinically oriented approach and define IBS as lower abdominal

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Box 1. Irritable bowel syndrome (IBS) defined.

Rome III criteria for the diagnosis of IBS (modified from Longstreth *et al.* 2006)

- Symptom onset at least 6 months prior to diagnosis
- Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with two or more of the following:
  - Improvement with defecation
  - Onset associated with a change in stool frequency
  - Onset association with a change in stool form (appearance)
- One or more of the following symptoms on at least a quarter of occasions for subgroup identification
  - Abnormal stool frequency (<3/week)
  - Abnormal stool form (lumpy/hard)
  - Abnormal stool passage (straining, incomplete evacuation)
  - Bloating or feeling of abdominal distension
  - Passage of mucous
  - Frequent, loose stools

The ACG (2002) defines IBS as (modified from Brandt *et al.* 2002):

- Abdominal discomfort associated with altered bowel habits
- Symptoms of constipation include infrequent stools, straining, feelings of incomplete evacuation, difficult evacuation, passage of rocky, hard stools

pain or discomfort with disordered defecation [Brandt *et al.* 2002].

The cost-effective diagnosis of IBS begins with taking a careful history to differentiate functional symptoms from organic disorders and to look for warning signs that signal the presence of a serious underlying disorder (see Box 2). Abdominal pain or discomfort is the cardinal symptom of IBS and should be temporally related to defecation in some way; pain related to urination, menstruation, or exertion suggests an alternative diagnosis. The absence of lower abdominal pain or discomfort is incompatible with the diagnosis of IBS. The presence of overlapping disorders commonly associated with IBS, both gastrointestinal and nongastrointestinal in nature, increases the pretest probability that IBS is the correct diagnosis (see Box 3). The Rome III criteria should be employed to categorize patients into one of the three major IBS subgroups (see Box 1). Bloating and abdominal distention are symptoms commonly found in IBS patients. These complaints generally reflect increased sensitivity to normal amounts of intestinal gas, although coexisting lactose or fructose intolerance and excess amounts of fiber may also play a role.

All patients with suspected IBS should undergo a careful physical examination. Other than mild tenderness over the sigmoid colon the physical examination of IBS patients should be normal. Abnormal findings on physical examination should alert the clinician to an alternative diagnosis. Although IBS was once considered a 'diagnosis of exclusion' mandatory laboratory and radiologic testing is not necessary in younger patients who meet criteria for IBS and who have a normal physical examination without any identifiable 'red flags' uncovered during the patient interview [Cash *et al.* 2008, 2002; Saito-Loftus *et al.* 2008]. In IBS patients, the goals of testing are to establish the diagnosis as early as possible, initiate treatment based on the predominant symptom, and avoid expensive and unnecessary tests.

Box 2. The diagnosis of irritable bowel syndrome: warning signs.

- Unintentional weight loss (>10% of ideal body weight)
- Evidence of gastrointestinal bleeding
- Anemia
- Recurrent nausea and vomiting
- Family history (first-degree relative) of gastrointestinal malignancy or inflammatory bowel disease

Box 3. Common disorders associated with irritable bowel syndrome.

(A) Overlapping gastrointestinal disorders

- Gastroesophageal reflux
- Functional dyspepsia
- Lactose intolerance (25% of adults)
- Fructose intolerance

(B) Associated nongastrointestinal disorders

- Fibromyalgia
- Chronic fatigue syndrome
- Migraine headaches
- TMJ syndrome
- Interstitial cystitis
- Dyspareunia

Table 1. Tricyclic antidepressant neurotransmitter activity.

Drug name	Trade name	ACh	Hist	5-HT	NE	Dop	Sedation	Comments
Amitriptyline	Elavil	+++	++	+++	++	–	+++	Commonly used for sleep disorder
Clomipramine	Anafranil	++	++	+++	+++	–	+++	Commonly used for OCD
Imipramine	Tofranil	++	++	+++	++	–	++	Used for nocturesis
Doxepin	Sinequan	+++	+++	++	+	–	+++	
Desipramine	Norpramin	+	+	–	+++	–	+	
Nortriptyline	Aventyl	++	+	++	++	–	++	Less hypotension than other TCAs

+, some effect; ++, moderate effect; +++, greatest effect; ACh, muscarinic antagonism; Hist, histamine antagonism; 5-HT, serotonin (5-hydroxytryptamine) antagonism; NE, norepinephrine antagonism; Dop, dopamine antagonism; OCD, obsessive–compulsive disorder.

Treatment

Clinicians should focus on four major goals when treating IBS patients: (1) improve the individual symptoms of IBS (i.e. abdominal pain and discomfort, bloating, constipation, and diarrhea); (2) ameliorate the global symptoms of IBS (3) prevent complications of IBS which include unnecessary surgery, risky diagnostic procedures, and adverse medication side effects from polypharmacy; and (4) reduce the impact of IBS on individual patients by improving quality of life, and minimize the global impact on society by reducing health care costs. These issues are discussed in the section below using appropriate evidence from the literature where data is available.

Abdominal pain and discomfort

Smooth muscle relaxants Therapy for abdominal pain over the past two decades has focused on the use of smooth muscle relaxants (commonly called antispasmodics). Although there are ample theoretical grounds for prescribing these medications, clinical experience has been disappointing. Most studies that have looked at these medications have been poorly designed, poorly controlled, and have not shown significant benefits above placebo [Poynard *et al.* 2001]. Nevertheless, some patients improve with antispasmodic drugs, particularly those whose symptoms are induced by meals and those who complain of tenesmus. When used for meal-induced symptoms, anticholinergics should be prescribed 30–60 minutes before meals so that peak serum levels of the drug coincide with peak symptoms.

A recent meta-analysis of 22 studies involving 1778 patients and 12 different antispasmodic agents demonstrated modest improvements in global IBS symptoms and abdominal pain [Ford *et al.* 2008a]. All IBS subtypes were included in the analysis. Unfortunately, few of the agents investigated are available in the US. A US study found that dicyclomine hydrochloride improved abdominal pain, tenderness, global functioning, and bowel habits in patients with IBS. However, up to 68% of patients suffered side effects when given the high dose required to improve abdominal pain [Page and Dirnberger, 1981].

Tricyclic antidepressants Tricyclic antidepressants (TCAs) have been used to treat functional bowel disorders for over three decades. Several TCAs (amitriptyline, nortriptyline, desipramine) have been studied in patients with IBS, although side effects (i.e. worsening constipation in patients with IBS and constipation) can limit their therapeutic potential. In fact, only seven studies have been conducted to date, and many of these were of limited duration and included only a small number of patients [Lesbros-Pantoflickova *et al.* 2004; Jackson *et al.* 2000]. In addition, side effects frequently develop as the dose is increased, and these side effects include dry mouth, dry eyes, sedation, urinary retention and visual changes. Concerns over potential cardiac arrhythmias and the risk of overdose, accidental or intentional, have also been raised.

TCAs likely modulate pain both centrally and peripherally. In the CNS, these drugs inhibit the reuptake of serotonin and norepinephrine. However, these agents also have effects on multiple other neurotransmitter pathways. In our experience the secondary amine TCAs such as nortriptyline and desipramine are better tolerated than their parent tertiary amine compounds,

such as amitriptyline, possibly due to a lower propensity for anticholinergic, antihistaminic, and alpha-adrenergic side effects (see Table 1).

The best data supporting the use of TCAs in the treatment of IBS is from a large placebo-controlled study evaluating desipramine for the treatment of functional bowel disorders in women. Although the intention-to-treat analysis did not show a statistically significant benefit compared with placebo (secondary to the drop-out rate due to side effects), the per-protocol analysis did show significant benefits compared with placebo [Drossman *et al*. 2003]. This highlights the fact that if a patient can tolerate some of the side effects of a TCA, then he or she is more likely to note an improvement in chronic abdominal pain compared with a patient treated with placebo.

Selective serotonin reuptake inhibitors (SSRIs) Data on the use of SSRIs in the treatment of IBS is even more limited. Only six studies have been conducted to date, two each involving fluoxetine, paroxetine and citalopram [Talley *et al*. 2008; Tack *et al*. 2006; Vahedi *et al*. 2005; Tabas *et al*. 2004; Kuiken *et al*. 2003; Masand *et al*. 2002]. Most patients noted an improvement in overall wellbeing, although none of the studies showed any benefit with regards to bowel habits, and abdominal pain was generally not improved. The paroxetine study provided some of the first evidence supporting the use of SSRIs in treating functional bowel disorders. One citalopram trial employed a controlled, crossover design and demonstrated a significant improvement in abdominal pain, bloating, and general well being independent of psychological improvement [Tack *et al*. 2006]. It is felt that SSRIs primarily mediate pain centrally, but they may also have effects on the enteric nervous system.

Table 2. Common dietary sources of lactose and fructose.

Lactose	Fructose
Milk and milk products: Yogurt Cheese Common, unexpected lactose sources: Pharmaceuticals Peanut butter Chocolate Instant mash potato Biscuits Sponge cake	Fresh fruits: Apples Pears Watermelons Fruit juices Dried fruits: including raisins High fructose corn syrup Sucrose Honey Sodas: diet and regular

Only one trial has provided a head-to-head comparison between a TCA (imipramine 50 mg) and an SSRI (citalopram 40 mg), although neither drug demonstrated significant improvements in global IBS symptoms over placebo [Talley *et al*. 2008]. In other studies, both TCAs and SSRIs have been shown to improve IBS symptoms independently of depression and anxiety measures [Ford *et al*. 2008b; Clouse, 2003]. TCAs in IBS patients are generally prescribed at dosages much lower than that for depression or anxiety. SSRIs are generally prescribed at dosages standard for treating mental health disorders. Further investigations are necessary to better define the roles of TCAs and SSRIs for the management of pain in the IBS population.

Selective serotonin and norepinephrine inhibitors (SSNRI/SNRI) such as venlafaxine and duloxetine may also have a role in the treatment of IBS pain, although these newer agents also require careful study. Of the SSNRIs, duloxetine (Cymbalta) has been uniquely studied and marketed for both psychiatric disease and neuropathic pain. Duloxetine received FDA approval in 2004 for the treatment of major depressive disorder and diabetic neuropathy. It received FDA approval for the treatment of fibromyalgia in 2008. Given its clinical effectiveness in treating these conditions, the medication has been applied off-label for visceral hypersensitivity syndromes, including IBS. Eli-Lilly is currently sponsoring an open-label trial of duloxetine for the treatment of irritable bowel syndrome in the absence of major depressive disorder [Brennan, 2003].

Anticonvulsants Anticonvulsant medications have been used for the treatment of chronic pain for over 40 years. Gabapentin (Neurontin) is the most frequently prescribed anticonvulsant for the treatment of chronic neuropathic pain. It first gained FDA approval in 1994 for epilepsy, and its labeling was expanded to include neuropathic pain in 2002. Off label, the drug has been prescribed for a number of other conditions including multiple sclerosis, bipolar disorder and methamphetamine withdrawal. Although the drug is biochemically similar to the inhibitory neurotransmitter GABA, its mechanism of action is still poorly understood. Gabapentin binds to the $\alpha 2\delta$ subunit of the voltage dependent calcium

channel in the central nervous system. It may thus decrease calcium influx into the nerve terminal and affect the subsequent release of multiple neurotransmitters, including substance P. Gabapentin is generally well tolerated, but dizziness, somnolence and peripheral edema are commonly reported. A study of 40 patients (mean age = 42, 50% female) with diarrhea-predominant IBS demonstrated increased threshold pressures for bloating, discomfort and pain with gabapentin compared with placebo [Lee *et al*. 2005]. A large meta-analysis investigating the utility of anticonvulsants such as gabapentin and carbamazepine have suggested less promising results for the treatment of both acute and chronic pain syndromes [Wiffen *et al*. 2000].

Pregabalin (Lyrica) was released and marketed as a successor to gabapentin. It was approved by the FDA for the treatment of epilepsy, diabetic neuropathy and postherpetic neuralgia in June 2005. It was approved for the treatment of fibromyalgia in 2007. Visceral hypersensitivity syndromes have also been targeted. Like gabapentin, it binds to the $\alpha 2\delta$ subunit of the voltage sensitive calcium channel. Animal and human trials have demonstrated blunted visceral pain perception [Ravnefjord *et al*. 2008; Houghton *et al*. 2007]. In one study of 26 IBS patients (aged 18–46 years, 7 males), pregabalin was found to increase sensory distension thresholds to normal levels in those with rectal hypersensitivity, decrease pain and improve rectal compliance [Houghton *et al*. 2007]. In summary, the anticonvulsant agents gabapentin and pregabalin make theoretical sense for the treatment of neuropathic pain and visceral hypersensitivity. However, clinicians need to be aware there is little data to support their use at this time in patients with IBS and all use is considered off-label.

Alternative and complementary medicine Peppermint, germanium, lavender oils and their derivatives have been used in the treatment of irritable bowel syndrome and other GI disorders. All of these agents may act to relax smooth muscle via a cAMP-dependent mechanism. A double-blind, placebo-controlled trial of 57 IBS patients randomized to receive either peppermint capsules or placebo demonstrated a significant benefit for the peppermint-treated group after 4 weeks. Seventy-five percent of the study group versus 38% of the placebo group reported a greater than 50% reduction in total IBS symptoms [Cappello *et al*. 2007]. A recent meta-analysis of four clinical trials involving 329 patients treated with peppermint oil suggested a significant benefit in overall IBS symptoms [Ford *et al*. 2008a]. Carmint is another herbal supplement that includes coriander, lemon and mint extracts. It has been used for its potential antispasmodic and sedative properties. A recent trial randomized 32 IBS patients to receive carmint or placebo. After 8 weeks, the carmint-treated group demonstrated significant improvements in the severity and frequency of abdominal pain and discomfort [Vejdani *et al*. 2007].

Several studies have evaluated the efficacy of acupuncture for the treatment of neuropathic, functional and IBS pain syndromes. The majority of these studies have been poorly designed and poorly controlled. A recent meta-analysis suggests that the benefit of acupuncture on IBS symptoms is no better than placebo [Lim *et al*. 2006]. Limited data on hypnotherapy suggests that it may be considered as an adjunct for treatment refractory patients [Spiller *et al*. 2007]. Cognitive behavioral therapy may be effective in improving patient coping strategies [Chiarioni and Whitehead 2008; Spiller *et al*. 2007].

Bloating

Dietary factors Abdominal distention and bloating are commonly reported symptoms in patients with IBS. Although many IBS patients believe they have more gas than other patients, research studies have demonstrated that the average volume of intestinal gas is not significantly different in IBS patients compared with healthy controls [Malegelada, 2002]. However, IBS patients have impaired gas transit which many contribute to symptoms of bloating and abdominal pain [Serra *et al*. 2001]. These studies suggest that visceral hypersensitivity contributes to pain perception in IBS patients. Further support for this comes from a small study that compared 12 patients with abdominal bloating to 12 healthy controls, while measuring the effects of colonic gas load on perception and abdominal girth. Patients with bloating (compared with controls) had significantly increased perception of abdominal pain [Tremolattera *et al*. 2006]. Interestingly, the patients with bloating symptoms also had a statistically significant increase in measured abdominal distention when compared with

controls, supporting impaired gas transit as a contributing factor for bloating symptoms.

Symptoms of abdominal distention and bloating have been described in the malabsorption of short-chain carbohydrates (fermentable oligo-, di-, and mono-saccharrides and polyols or FODMAPs), particularly lactose, fructose and sorbitol (see Table 2) [Barret and Gibson, 2007]. Lactose intolerance is common, affecting approximately 5% of Northern Europeans and up to 90% of persons of Asian and African descent. Given the high prevalence of both lactose intolerance and IBS, it is not surprising that there is significant overlap of these disorders. In fact, some patients with IBS suffer from symptoms attributable to undiagnosed lactose intolerance [Bohmer and Tuynman 2001]. In the study by Bohmer and colleagues, 24% of IBS patients had lactose malabsorption *versus* 5.7% of healthy controls ($p < 0.009$). However, a more recent study challenges the prevalence of lactose malabsorption in IBS patients [Farup *et al.* 2004]. In this case-control study of 82 IBS patients and 105 healthy volunteers, the prevalence of lactose malabsorption was only 4.1% in IBS patients and 3.8% in the healthy volunteer group. However, 40% of patients with IBS reported symptoms after lactose intake as opposed to 20% in healthy controls ($p = 0.01$).

Fructose consumption has rapidly increased over the last 30 years. The consumption of fructose has risen more than 1000-fold in the last 30 years and accounts for more than 40% of total caloric sweeteners added to food and beverages, particularly soft drinks [Bray *et al.* 2004]. Fructose intolerance presents similarly to lactose intolerance [Choi *et al.* 2003]. While the overall prevalence of fructose intolerance in unknown, a recent study did evaluate symptom response in IBS patients after eliminating dietary fructose. This prospective trial involved 26 patients with IBS and an abnormal fructose breath test, all of whom received instruction on a nonfructose diet [Choi *et al.* 2008]. Of the 14 IBS patients that were compliant with the diet, there was a statistically significant reduction in symptoms of belching, bloating, fullness and diarrhea. In the 12 noncompliant patients, there was no improvement in symptoms.

In 1977 the *Lancet* published a pivotal article by Manning *et al.* [1977] demonstrating the efficacy of fiber in the treatment of IBS. Since then, fiber has become a cornerstone of IBS treatment for many practitioners. While the efficacy of fiber supplementation remains unclear, given its safety profile, the potential for a positive placebo effect and its low cost, fiber remains an excellent first choice in the treatment of IBS IBS-C. However, in patients with IBS-D or symptoms of bloating, fiber may make symptoms worse [Cann *et al.* 1984]. In fact, reducing fiber intake may improve symptoms of bloating [Agrawal and Whorwell, 2008].

Probiotics The pathophysiology of IBS remains poorly understood. A variety of mechanisms, including altered gut flora and bacterial overgrowth, have been considered as possible etiologies, particularly with regard to gas/bloating. Probiotics are defined as organisms that, when administered in adequate amounts, exert a positive influence on the health of the host animal. While the precise therapeutic mechanism is unknown, it is theorized that probiotics may ameliorate IBS symptoms by stimulating an immune response, reducing inflammation or altering the composition of gut flora. A prospective trial of 77 IBS patients randomized them to receive *Bifidobacterium infantis* 35624, *Lactobacillus* or placebo in a malted drink [O'Mahony *et al.* 2005]. Quality of life assessment and measurement of interleukin (IL)-10 and IL-12 levels were performed at the beginning and at the end of the treatment phase (abnormal IL-10/IL-12 ratios have been demonstrated in some IBS patients, consistent with a proinflammatory state). The authors found that patients randomized to *B. infantis* had improvement in symptoms of abdominal pain/discomfort and bloating in the setting of a normalized IL-10/IL-12 ratio.

A recent study evaluated the efficacy of *B. infantis* in a large group ($n = 362$, all subtypes included) of IBS patients [Whorwell *et al.* 2006]. Women between the ages of 18 and 65 who met Rome II criteria were included. Subjects were randomized in a blinded fashion to placebo or one of three daily doses of *B. infantis* for the 4-week trial period: 1×10^6 colony forming units (cfu); 1×10^8 cfu; 1×10^{10} cfu. The primary efficacy endpoint was daily abdominal pain and discomfort; secondary endpoints included individual symptoms of bloating, straining, bowel dysfunction and incomplete evacuation. *B. infantis*, at a dose of 1×10^8 cfu, improved abdominal pain and discomfort significantly more than placebo ($p = 0.023$), although the other two doses were

not better than placebo. Analysis of secondary symptoms (bloating, passage of gas, straining, bowel satisfaction, and feelings of incomplete evacuation) demonstrated that *B. infantis* at 1×10^8 cfu daily was significantly better than placebo (p values all less than 0.05), although doses of 1×10^6 and 1×10^{10} were not better than placebo. Of note, no dose was associated with a significant change in stool frequency. Adverse events were few in number and no different between *B. infantis* and placebo. Post-hoc analysis found that the high dose capsules (1×10^{10}) coagulated, thus preventing adequate release of the bacterium.

In children with IBS-D, Kim *et al.* [2003] studied the probiotic formulation VSL#3 and its effect on gastrointestinal transit and symptoms. In this randomized, placebo-controlled trial of 25 patients, no changes were found in gastrointestinal transit, however abdominal bloating was reduced ($p = 0.05$). This led to a follow-up study in 48 adult patients who met Rome II criteria and reported significant bloating. In this double-blind, placebo-controlled trial, similar results were noted with improvement in flatulence and relief of bloating in the VSL#3 group when compared with placebo ($p = 0.014$) [Kim *et al.* 2005].

Most recently, Guandalini performed a prospective, multicenter, double-blind, placebo-controlled, crossover trial assessing the efficacy and safety of the probiotic, VSL#3, in children (aged 4–18 years) identified as having IBS (Rome II criteria, all subtypes) [Guandalini *et al.* 2008]. Patients were randomized to receive either VSL#3 (450 billion bacteria per capsule) or placebo for 6 weeks. Symptoms were measured every 2 weeks, and then after a 2-week washout period, patients were switched to the other group (either placebo or active drug). The authors reported that 59 children completed the study (mean age = 12.5 years; 41% were women). Compared with placebo, patients treated with VSL#3 had a significant improvement in the primary endpoint, which was the global relief of IBS symptoms ($p < 0.05$). Secondary endpoints of abdominal pain ($p = 0.05$) and bloating ($p < 0.001$) were also improved. Although interesting, results are limited by the study's small size and the crossover design. In summary, several studies suggest a possible role for probiotic therapy in the treatment of IBS and the common, difficult to treat, symptom of bloating. Limitations of probiotic studies performed to date include the small size and lack of long-term outcome data. Further studies are needed to better define the efficacy of probiotic therapy.

Antibiotics Over the past several years, many clinicians have begun to use antibiotics to treat IBS symptoms. There are several lines of evidence which support the use of antibiotics in this patient population. First, enteric flora may differ in IBS patients compared with healthy controls, resulting in increased hydrogen release during carbohydrate fermentation. In 2000, Di Stefano reported on the relationship between gaseous symptoms and colonic gas production in 21 healthy volunteers and 34 patients with functional GI disorders. Symptomatic patients were found to have higher H_2 production when compared with healthy volunteers (4.5 ± 2.1 ml H_2/g *versus* 3.0 ± 2.2 ml H_2/g, $p < 0.005$).

Later studies by the same group demonstrated that hydrogen production alone is not responsible for all bloating symptoms. In 2006, Di Stefano *et al.* [2006] demonstrated that in certain subgroups of patients (IBS and functional gas-bloating; $n = 60$) hypersensitivity to products of colonic fermentation may be responsible for generation of symptoms. Subjects underwent preliminary evaluation with a lactulose hydrogen breath test as well as rectal barostat testing to determine rectal sensitivity (in a fasting state). On a different day, subjects were given lactulose and, at the time there was a sustained increase in breath hydrogen excretion (indicating its arrival to the colon), repeat rectal barostat testing was performed. There was no significant difference in hydrogen breath excretion between age- and sex-matched healthy volunteers and patients, or in pretest rectal sensitivity. However, patients with IBS had greater post-lactulose rectal sensitivity testing with greater discomfort even at low/normal hydrogen production levels ($p < 0.0001$).

The second line of evidence to support the use of antibiotics in IBS is the relationship between IBS and bacterial overgrowth. Several controversial studies have suggested that bacterial overgrowth may be present in up to 84% of patients with IBS, including one published several years ago Pimentel *et al.* [2000] who reported that eradication of bacterial overgrowth eliminated IBS symptoms in 84% of subjects. However, this uncontrolled study was significantly flawed by the high dropout rate of patients, the retrospective

nature of diagnosing patients with IBS, the use of different antibiotics at unknown doses to treat small intestinal bacterial overgrowth (SIBO), and the short follow-up period (approximately 7–10 days). A second study, which was randomized, double-blinded and placebo-controlled, found that IBS patients were more likely than normal controls to have an abnormal lactulose breath test (84% *versus* 20%; $p < 0.001$), and that patients were more likely to note a global improvement in their symptoms if they achieved bacterial eradication ($p < 0.001$) [Pimentel *et al.* 2003]. It is important to note that other investigators have not been able to duplicate the impressive results noted above. Also, two large prospective studies have failed to identify any differences in the prevalence of SIBO between IBS patients and normal volunteers, and thus we consider it unlikely that small intestine bacterial overgrowth plays a significant role in symptom expression in most IBS patients [Bratten *et al.* 2008; Posserud *et al.* 2007].

If bacterial overgrowth does contribute to the development and expression of IBS symptoms then directed therapy for bacterial overgrowth should improve symptoms. Rifaximin, a gut-selective antibiotic that is not systemically absorbed, has broad-spectrum activity against gram-positive and gram-negative aerobes and anaerobes [Jiang and DuPont, 2005]. In a double-blind, randomized, placebo-controlled trial, 81 patients with IBS (Rome I criteria) were assigned to receive either rifaximin 400 mg three times daily or placebo for 10 days [Pimentel *et al.* 2006]. Patients filled out self-administered symptom questionnaires before and weekly for 10 weeks post-treatment. Patients who received rifaximin reported improvement in global IBS symptoms as well as in bloating symptoms, compared with those who received placebo ($p = 0.010$).

In a recent study, Sharara *et al.* [2006] attempted to objectively study the role of rifaximin on enteric flora. This group performed a randomized, placebo-controlled trial in which patients were evaluated during three separate 10-day periods: at baseline; during treatment with oral rifaximin (400 mg twice daily) or placebo; and after treatment. A lactulose hydrogen breath test was performed during each period. All 124 patients reported primary symptoms of gas and bloating and had a normal lactulose hydrogen breath test on study entry. At the end of the treatment period, the rifaximin group noted a statistically significant improvement in symptoms (41.3% *versus* 22.9%, $p = 0.03$). This improvement was maintained in 28.6% of patients at the end of the study (compared with 11.5% in the placebo group, $p = 0.02$). Patients that met criteria for IBS in addition to gas/bloating (37/63, 58.7%), reported an even greater improvement in symptoms with 40.5% having a favorable response to rifaximin compared with 18.2% in the placebo group.

The use of rifaximin in patients with IBS-D is an area of emerging interest. In 2008 Lembo and colleagues performed a phase II, multicenter trial comparing rifaximin to placebo [Lembo *et al.* 2008]. Patients that met Rome II criteria for IBS-D were randomized to receive either oral rifaximin (550 mg twice daily) or placebo for 14 days. The treatment group reported a statistically significant improvement in global IBS symptoms as well as IBS-associated bloating. This response was maintained at the 12-week follow-up visit. A secondary analysis from that same study demonstrated that rifaximin use was associated with improved quality of life scores in patients with IBS-D [Chey *et al.* 2008]. Similar symptom improvement in IBS-D patients was noted in a retrospective review of IBS patients who had received rifaximin 400 mg orally three times daily for 10 days alone or in combination with other treatments [Jolley, 2008].

Constipation

Lifestyle modifications Many clinicians initiate treatment for symptoms of IBS and constipation with lifestyle modifications, which may include changes in fluid intake, exercise and diet. Unfortunately, data to support these interventions is limited. Although the lay press has touted the benefits of drinking large amounts of water for years, there is no scientific data available to support the claim that drinking eight glasses of water each day will improve symptoms of constipation. Exercise has been shown to improve a number of health conditions; however, no data exists to support the notion that routine exercise can improve symptoms of IBS with constipation. The role of dietary fiber for the treatment of IBS-C is described below.

Bowel training and education Constipation develops in some IBS patients because they ignore the urge to have a bowel movement. In many patients this urge occurs upon awakening or shortly after eating. Many IBS-C patients

(especially those with overlapping pelvic floor dysfunction) note an improvement in symptoms of constipation if they can re-establish a set time to use the bathroom each day. A simple bowel regimen means getting up at approximately the same time each day, eating breakfast (to help initiate the gastrocolic reflex), and then using the bathroom at a routine, scheduled time each day, typically 30–45 minutes after the morning meal.

Over-the-counter medications Stool softeners are emollients which soften and lubricate the stool. In usual doses, docusate may increase the fluid content of stool by 3–5%. Although safe and inexpensive, stool softeners are rarely helpful in the treatment of IBS-C. No randomized, controlled trials have been performed in patients with IBS.

Typical agents include magnesium hydroxide (Phillips Milk of Magnesia), magnesium sulfate, or magnesium citrate. No studies have been performed in patients with IBS-C. We recommend that these agents be used only on an intermittent basis to treat mild symptoms of constipation. These agents generally do not cause abdominal bloating or distention, although they may cause abdominal cramps and spasms. They should be avoided in patients with renal dysfunction.

These agents include senna, cascara, aloe, castor oil and bisacodyl, and have two major mechanisms of action. One, they directly stimulate the colon and increase colonic contractions. Two, they increase fluid secretion in the intestinal tract, which increases intestinal transit. One study evaluated the efficacy of aloe vera in the treatment of 58 patients (18–65 years) with IBS-C [Davis *et al.* 2006]. Symptom improvement at the end of the 4-week trial and at 3-months was similar in both the placebo group and the aloe vera treatment group. Based on this small study, aloe vera cannot be recommended as a treatment for IBS-C. The other agents listed above have not been prospectively studied in IBS patients and should be used on an as needed basis only. Patients should be cautioned that excessive use may lead to chronic watery diarrhea and the development of electrolyte disturbances.

Despite their widespread use there is conflicting data about the efficacy of fiber. Twelve randomized controlled trials have been performed to date evaluating the efficacy of fiber in the treatment of IBS. Four of these studies noted an improvement in stool frequency (polycarbophil and ispaghula husk), while one noted an improvement in stool evacuation [Toskes *et al.* 1993; Jalihal and Kurian, 1990; Prior and Whorwell, 1987; Longstreth *et al.* 1981]. No study has demonstrated an improvement in abdominal pain with the use of any type of fiber product. In addition, 30–50% of patients treated with a fiber product will have a significant increase in gas, bloating, and abdominal distention [Lesbros-Pantoflickova *et al.* 2004; Jailwala *et al.* 2000]. In summary, fiber supplementation using a soluble fiber product such as ispaghula is a reasonable treatment option for symptoms of constipation in patients with IBS, *if* the patient is fiber deficient. However, patients need to be told that fiber products will not solve their abdominal pain and may worsen symptoms of gas and bloating [Ford *et al.* 2008c; Hebden *et al.* 2002; Cann *et al.* 1984].

Prescription medications Polyethylene glycol (PEG) is a high-molecular-weight osmotic agent that is neither absorbed nor metabolized as it passes through the GI tract. It is FDA-approved for the treatment of chronic constipation, but is not currently approved for the treatment of IBS-C [Cash and Lacy 2006]. One study evaluated the efficacy of PEG in 48 adolescents (ages 13–18; 60% women) diagnosed with IBS-C using the Rome II criteria [Khoshoo *et al.* 2006]. Patients were randomized to receive either 17 g of PEG each day or 17 g of PEG in addition to 6 mg of tegaserod twice daily during the 4-week study period. Stool frequency increased in both groups ($p < 0.05$) during the study period, although abdominal pain improved only in the PEG-tegaserod group ($p < 0.05$). No adverse events were reported in either group. These findings confirm the clinical experience of most healthcare providers that PEG solutions may improve symptoms of constipation in patients with IBS-C, but do not alleviate symptoms of abdominal pain or bloating.

Lactulose is a synthetic disaccharide composed of galactose and fructose. Lactulose cannot be metabolized by the small intestine, so it passes unchanged into the colon where it is broken down and fermented by colonic bacteria. Although several small studies have shown that lactulose improves symptoms in patients with chronic constipation [Cash and Lacy, 2006], it has never been formally evaluated for the

treatment of patients with IBS and constipation, and is not FDA approved for use in these patients. A major side effect of lactulose is that it significantly worsens symptoms of gassiness, bloating and distention. Similar to PEG, lactulose is unlikely to improve symptoms of abdominal pain in patients with IBS-C. In addition, lactulose commonly worsens symptoms of bloating.

Tegaserod, an aminoguanidine indole, acts as a specific 5-HT4 (serotonin-type-4) receptor agonist to stimulate gastrointestinal peristalsis, increase intestinal fluid secretion and reduce visceral sensation [Lacy and Yu 2002]. It was approved by the FDA for the treatment of women with IBS-C in July 2002 based on the results of two pivotal studies and the results of four large, randomized, double-blind placebo controlled studies showing improvement in both global and individual IBS symptoms compared with placebo [Evans *et al*. 2007; Nyhlin *et al*. 2004; Kellow *et al*. 2003; Novick *et al*. 2002; Muller-Lissner *et al*. 2001]. The therapeutic gain in these studies for improving global symptoms of IBS ranged from 5% to 19%. The relative risk of patients noting improvement in global IBS symptoms while on tegaserod was higher than when treated with placebo, although the results were not overwhelming (RR = 1.19; 95% CI = 1.09–1.129). Unfortunately, tegaserod was removed from the most markets worldwide in March 2007 due to concerns over possible adverse cardiovascular events (see www.fda.gov for further details). It is available now in the US only for emergency use.

Lubiprostone is a bicyclic fatty acid metabolite of prostaglandin E1. Lubiprostone selectively stimulates type 2 chloride channels in epithelial cells of the gastrointestinal tract thereby causing an efflux of chloride into the intestinal lumen [Cuppoletti *et al*. 2004]. Fluid secretion into the gastrointestinal lumen provides a bolus effect that softens stool, increases intestinal transit, and improves symptoms of constipation. Lubiprostone acts locally within the intestinal tract, is rapidly metabolized, and has very low systemic bioavailability. It was approved by the FDA for the treatment of adult men and women with chronic constipation in January 2006 [Lacy and Levy, 2008].

The safety and efficacy of lubiprostone in the treatment of IBS-C was first evaluated in a multicenter, double-blind, placebo-controlled dose-ranging study involving 195 patients [Johanson *et al*. 2006]. After a 4-week screening period, IBS-C patients (Rome II criteria) were randomized to 12-weeks of treatment with either placebo or one of three different doses of lubiprostone (8, 16, or 24 μg twice daily). The primary endpoint was the change in abdominal pain/discomfort during the first 4 weeks of therapy. Also evaluated were secondary endpoints of frequency of spontaneous bowel movements, stool consistency, straining at stool and abdominal bloating. Laboratory tests (CBC, electrolytes, BUN/Cr, glucose), EKGs, symptom diaries, and IBS-quality of life scores were monitored throughout the study. The majority of patients were women (92%) and Caucasian (83%). At both 1 and 2 months, patients treated with any dose of lubiprostone had a greater improvement in mean abdominal pain and discomfort scores compared with placebo ($p = 0.023$ and 0.039, respectively). Patients treated with 24 μg b.i.d. of lubiprostone had the greatest improvement in symptoms; however, they also had the greatest number of adverse events. Based on these findings, the authors concluded that the 8 μg twice-daily dose provided the best combination of efficacy and safety.

These initial promising results led to the initiation of two separate phase III studies to evaluate the safety and efficacy of lubiprostone in patients with IBS-C [Drossman *et al*. 2007]. These two studies randomized a total of 1171 adults diagnosed with IBS-C (Rome II criteria) to either 12 weeks of b.i.d. lubiprostone (8 μg) or placebo. Most patients were women (91.6%), and most were between the ages of 18 and 65 (91.7%). The primary efficacy variable was a global question rating overall IBS symptoms, while a seven-point balanced scale was used to rate changes in individual symptoms. Strict criteria were used to define a responder. Patients had to report at least moderate relief for 4 out of 4 weeks or significant relief for 2 out of 4 weeks in order to be considered a monthly responder. Patients had to be a monthly responder for at least 2 of the 3 months in order to qualify as an overall responder. The authors reported that patients who received lubiprostone were nearly twice as likely as those who received placebo to achieve overall symptom improvement (17.9% *versus* 10.1%; $p = 0.001$). Secondary endpoints, including abdominal pain, bloating, straining, stool consistency, and constipation were all significantly improved in the lubiprostone group compared with the

placebo group ($p < 0.05$ for all endpoints). Lubiprostone was generally well tolerated. The most common treatment related side effects were nausea (8% *versus* 4% in placebo) and diarrhea (6% *versus* 4% in placebo). The low placebo rate in this study, uncommon for IBS studies, is likely due to the very strict standards for determining whether a patient was classified as a responder.

Patients who demonstrated >70% study drug compliance during the 12-week blinded trial were invited to participate in a 36-week open-label extension study [Drossman *et al.* 2007]. The primary endpoint was the same as used in the phase III trials. A total of 476 patients received 8 μg twice daily lubiprostone during the extension trial. Patients initially treated with placebo noted an increase in response from 8% to 31%, while those treated with lubiprostone noted a further increase in response from 15% to 37%. No serious adverse events were recorded, while nausea (3.5%) and diarrhea (4.8%) were the most common reported adverse events. Further trials are planned to assess the long-term benefits of lubiprostone in patients with IBS and constipation.

Future therapies Linaclotide is a 14-amino-acid peptide that mimics the action of endogenous guanylin and uroguanylin, both of which activate the guanylate cyclase C (GC-C) receptor [Currie *et al.* 1992]. Activation of GC-C stimulates the production of cyclic GMP, which increases the flow of electrolytes and water into the lumen of the gastrointestinal tract. Preclinical studies demonstrated that linaclotide accelerated intestinal transit and improved visceral pain in animals, while a phase II study showed that it improved symptoms in patients with chronic constipation [Andresen *et al.* 2007]. In a recent multicenter, double-blind, placebo-controlled, dose-ranging study, 420 patients with IBS-C (modified Rome II criteria; <3 complete spontaneous bowel movements/week) were randomized to one of four different daily doses of linaclotide (75, 150, 300 or 600 μg) or placebo for 12-weeks [Lembo *et al.* 2008]. The primary endpoint was the change in complete spontaneous bowel movements (CSBM), while abdominal pain, other symptoms of constipation (e.g. straining) and bloating were secondary endpoints. Three-hundred-and-thirty-seven patients (80%) completed the entire study; 13 patients on the study medication, but none on placebo, discontinued the study due to significant diarrhea. Using a strict intention-to-treat analysis linaclotide at all study doses was shown to significantly improve stool frequency ($p < 0.023$ or better for all doses), in addition to symptoms of straining, bloating and abdominal pain (all with $p < 0.05$ except for bloating using the 150 μg dose which was not statistically better than placebo). In addition, patients treated with linaclotide (all doses) were more likely than those treated with placebo to report adequate relief of global IBS symptoms for at least 6 of the 12 weeks of the study period. Cessation of the study medication at the end of the trial did not appear to lead to a sudden worsening of IBS symptoms (i.e. no rebound effect was noted). These promising results resulted in the initiation of a large phase III clinical trial, which is currently ongoing.

Prucalopride is a highly selective 5-HT4 receptor agonist that improves colonic motility, colonic transit and symptoms of constipation in patients with chronic constipation [Camilleri *et al.* 2008; Emmanuel *et al.* 2002]. It has not been approved by the FDA for the treatment of chronic constipation. Studies are planned to evaluate the safety and efficacy of this novel agent for the treatment of IBS-C patients.

Diarrhea

Loperamide Loperamide is a synthetic phenylpiperidine derivative first approved by the FDA for the treatment of diarrhea in 1976. Although structurally similar to meperidine, it has minimal analgesic activity and does not produce euphoria at standard doses. By inhibiting intestinal secretion and peristalsis, loperamide slows intestinal transit and allows for increased fluid reabsorption, thus improving symptoms of diarrhea. It also increases external anal sphincter tone to a small degree and thus may decrease fecal incontinence and soiling in some patients [Ooms *et al.* 1984]. Four randomized controlled studies have evaluated the efficacy of loperamide for the treatment of patients with IBS and diarrhea [Efskind *et al.* 1996; Hovdenak, 1987; Lavo *et al.* 1987; Cann *et al.* 1984]. In general, stool frequency was reduced and stool consistency improved in patients treated with loperamide compared with placebo, although neither abdominal pain nor bloating improved.

Diphenoxylate-atropine This combination agent is frequently used to treat symptoms of acute and

chronic diarrhea from a variety of sources. No randomized, placebo-controlled trials have been performed in patients with IBS and diarrhea and thus a formal recommendation cannot be made.

Alosetron Alosetron is a 5-HT3 receptor antagonist that slows colonic transit, enhances small intestine fluid reabsorption, and improves visceral pain [Mayer *et al*. 2002; Houghton *et al*. 2000]. For women with diarrhea-predominant IBS, alosetron has been shown to be efficacious in several randomized, placebo-controlled studies [Camilleri *et al*. 2001; Lembo *et al*. 2001]. A recent systematic review and meta-analysis of eight randomized controlled trials involving 4842 patients determined that alosetron provided a significant reduction in the global symptoms of diarrhea, abdominal pain, and bloating in patients with IBS and diarrhea [Ford *et al*. 2008d]. Alosetron is currently the only medication approved by the FDA for the treatment of IBS and diarrhea (in women only), although it is not routinely used by many healthcare providers, likely due to its unusual marketing history. Alosetron was first approved by the FDA for the treatment of women with IBS and diarrhea in February 2000 and reached US markets in April 2000. Due to concerns over a possible association with severe constipation and ischemic colitis, alosetron was withdrawn from the US market in November 2000. In June 2002 the drug was reapproved by the FDA for women with severe IBS and diarrhea who had failed standard therapy. Alosetron was only available for women with IBS-D through physicians who had enrolled in a risk management plan. Of note, since the risk management plan was introduced, the number of adverse events has dropped significantly, and the rate of ischemic colitis was recently calculated at 1.1 per 1000 patient years while the rate of serious complications of constipation was found to be 0.66 per 1000 patient years [Chang *et al*. 2006]. Interestingly, since the initial reports of adverse events associated with alosetron were published, research has shown that all patients with IBS are at a two- to four-fold increased risk for ischemic colitis compared with the general population [Higgins *et al*. 2004]. It is quite possible that some of the initial adverse events attributed to alosetron were in fact due to the underlying disorder and not the medication.

Cilansetron Cilansetron, a 5-HT3 receptor antagonist, has been shown to improve symptoms of abdominal pain and diarrhea in both men and women with IBS in several double-blinded, randomized, placebo-controlled trials [Coremans *et al*. 2004]. Data from these studies was reviewed by the FDA in the spring of 2005; however the manufacturer did not receive a letter of approval. Due to concerns over adverse events, including ischemic colitis, no further trials are planned.

Cholestyramine Cholestyramine is a resin that binds bile acids. Although data is quite limited, it is frequently used by clinicians to treat patients with chronic diarrhea thought secondary to bile salt malabsorption [Niaz *et al*. 1997] or prior cholecystectomy. It has not been formally studied in patients with IBS-D.

Deodorized tincture of opium Patients with IBS and persistent symptoms of diarrhea that do not respond to loperamide, diphenoxylate-atropine or alosetron may benefit from routine use of deodorized tincture of opium (DTO). We generally recommend that patients start with one or two drops each morning in a small amount of water or juice and slowly increase the dose as necessary. Side effects are minimal at low dose, although some patients do note sedation at higher doses (more than ten drops per day). DTO is not approved by the FDA for use in IBS patients and has not been evaluated formally in any scientific study involving IBS patients.

Tricyclic antidepressants Low-dose tricyclic antidepressants (TCAs) have been used to treat symptoms of IBS for decades although well-designed clinical trials supporting their use in patients with IBS-D are limited [Rajagopalan *et al*. 1998; Greenbaum *et al*. 1987; Myren *et al*. 1984, 1982]. A recent double-blind, placebo-controlled prospective study evaluated the safety and efficacy of low-dose amitriptyline in 50 patients with IBS-D (Rome II criteria; mean age = 36; 42% women). At the end of the 2-month trial, patients treated with amitriptyline (10 mg q.d.) were more likely than those treated with placebo to note an overall improvement in IBS symptoms ($p = 0.01$), as well as symptoms of diarrhea and incomplete evacuation ($p < 0.05$). This low dose was well tolerated and adverse events were similar between the two groups [Vahedi *et al*. 2008]. The results of this study should encourage clinicians to use TCAs more frequently in the treatment of IBS-D patients, although a second agent, such as loperamide,

may be required to adequately control symptoms of diarrhea.

Future therapies Dextofisopam is an atypical benzodiazepine that binds to the 2,3 benzodiazepine receptor in the central nervous system, appears to reduce visceral pain and slow gastrointestinal transit in animal models. A recent pilot study evaluated the safety and efficacy of dextofisopam in the treatment of men and women with IBS-D and IBS-M ($n = 140$; 73% female) [Leventer *et al.* 2008]. Patients treated with dextofisopam (200 mg b.i.d.) noted adequate relief of global IBS symptoms at the end of month 1 ($p = 0.002$), but not at months 2 or 3, when compared with placebo. Stool frequency also improved during the first month of therapy in women, but not men, treated with this novel agent. Bloating was not improved in either men or women. Large prospective trials are needed to confirm these preliminary findings, and it is possible that this medication will find a role for the treatment of IBS-D symptoms, especially if used for short periods of time or on a p.r.n. basis.

The efficacy of the calcium channel blocker verapamil was prospectively studied in a group of 129 nonconstipated IBS patients meeting Rome II criteria [Quigley *et al.* 2007]. In this double-blind study, 12-week study, patients were randomized to receive either placebo or the r-enantiomer of verapamil. Doses were adjusted at 4-week intervals, increasing from 20 mg p.o. t.i.d. to 80 mg p.o. t.i.d. as tolerated. The authors reported that the medication was generally well tolerated, without any significant adverse events being reported. Intention-to-treat analysis showed a significant improvement for the r-verapamil group for both primary efficacy variables compared with control, including global symptom scores ($p = 0.0057$) and abdominal pain/discomfort ($p = 0.05$). Although not discussed in this preliminary report, verapamil may improve symptoms by modulating smooth muscle function in the gastrointestinal tract. Further studies are forthcoming from this active research group.

Conclusion

Irritable bowel syndrome greatly impacts the daily life of patients, generates substantial health-related fears and concerns, and remains poorly understood by patients. In the absence of warning signs, the diagnosis of IBS can usually be made at the first clinic visit and treatment initiated based on the predominant complaint. A key aspect of any treatment regimen involves educating the patient about his or her condition. Educating patients about IBS and correcting their inappropriate concerns about developing cancer may help decrease the number of patients seeking consultation. In fact, a study performed by Saito and colleagues found that an educational program for IBS patients reduced the number of office visits at 6 months of follow-up, although this did not reach statistical significance [Saito *et al.* 2004]. Patient-oriented educational programs for asthma, cardiovascular disease and diabetes have been shown to improve lifestyle behaviors and reduce health care utilization [Liu and Feekery, 2001; Vinicor *et al.* 1987; Morisky *et al.* 1980]. Collectively, these studies highlight the need for increasing time and effort spent educating our patients, as this may improve patients' overall health and well being and possibly translate into reduced healthcare costs.

Conflict of interest statement

None of the authors have any conflicts of interest to disclose with regards to the production of this manuscript.

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