Options for patients with irritable bowel syndrome: contrasting traditional and novel serotonergic therapies

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Abstract This article reviews the efficacy and tolerability of traditional therapies for irritable bowel syndrome (IBS) and concludes that they are limited by both poor efficacy and adverse effects. Serotonin, a neurotransmitter found mainly in the gut, appears to represent a link in IBS pathophysiological processes – altered gut motility, abnormal intestinal secretion and visceral hypersensitivity. Recently, available treatments for IBS have targeted serotonin receptors that are involved in motor, sensory and secretory functions of the gut. Serotonergic agents, such as alosetron (a 5-HT3 receptor antagonist) and tegaserod (a selective 5-HT4 receptor partial agonist), provide global relief of the multiple symptoms of IBS with diarrhoea and IBS with constipation, respectively, and represent important additions to the IBS treatment armamentarium.

Keywords alosetron, constipation, irritable bowel syndrome, serotonin, tegaserod, treatment.

OVERVIEW

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal (GI) disorders, with a prevalence of up to 20% in the United States.1 It is the most common diagnosis made by gastroenterologists (28% of total) and accounts for 12% of diagnoses made by primary care doctors.2,3 In North America, IBS affects twice as many women as men, and patients are generally between the ages of 30 and 50 years when they first consult a doctor.2

Irritable bowel syndrome is considered a functional bowel disorder characterized by abdominal discomfort or pain associated with altered bowel function (constipation [IBS-C], diarrhoea [IBS-D] or alternating constipation and diarrhoea [IBS-A]).4 Well-established diagnostic criteria are used to identify patients for clinical trials,4 but, in practice, a global definition of abdominal discomfort associated with altered bowel habits is more appropriate and clinically useful.1

The economic burden inflicted by IBS on both society and the health care system is tremendous, compared with that imposed by asthma, hypertension and stroke.5,6 The chronic and episodic nature of IBS symptoms accounts for up to 3.7 million doctor visits7 and more than two million prescriptions annually.8 Direct [e.g. doctor visits, outpatient care, diagnostic tests] and indirect [e.g. work absenteeism and decreased productivity] costs associated with IBS are estimated at $30 billion [adjusted for 1999 and 2000 dollars, respectively] per year.7,8

 Symptoms experienced by persons with IBS significantly impact quality-of-life.9 Studies using general or disease-specific quality-of-life instruments have consistently shown that the health status of those with IBS is poorer than that of the general population.10-12 Quality-of-life scores of IBS patients are directly correlated with their responses to therapy,12 and management of multiple IBS symptoms is important for overall improvement in patient well-being.

Until recently, treatment options for IBS have been limited by poor efficacy, poorly tolerated adverse effects or both. Research into the pathophysiology of IBS, which has uncovered the potential role of serotonin [5-HT], has led to the development of two serotonergic agents for the treatment of patients with IBS. This paper reviews the traditional single symptom-based treatment options for IBS and the novel serotonergic agents that target multiple IBS symptoms through pharmacological action in serotonin receptors.

TRADITIONAL IBS THERAPIES

Despite their limitations, many patients continue to rely on traditional pharmacological and non-pharmacological treatments that target individual IBS
Antispasmodics and antidepressants

Traditional medications evaluated in published clinical trials for the treatment of IBS-related abdominal pain or discomfort include antispasmodics and tricyclic antidepressants (TCAs). Some antispasmodics (e.g. cimetropium bromide) directly relax intestinal smooth muscle; others (e.g. dicyclomine) act indirectly via anticholinergic effects.\(^{19}\)

Smooth muscle relaxants have been evaluated in a number of double-blind, randomized, placebo-controlled clinical trials with IBS patients. Three systematic reviews – two meta-analyses of 26 and 23 randomized, controlled trials, respectively, and a systematic review of 16 randomized, controlled trials – examined the efficacy of these compounds for relieving the pain and discomfort associated with IBS.\(^{16-18}\) The two meta-analyses found that five\(^{16}\) and six\(^{17}\) smooth muscle relaxants have proven clinical efficacy in IBS without significant adverse reactions. In the systematic review, 13 studies, including seven high-quality trials, found these smooth muscle relaxants to be effective for abdominal pain;\(^ {18}\) significant improvement in constipation was reported in two of the high-quality trials. However, these agents are not available in the United States.

Although dicyclomine and hyoscyamine are available in the United States for the treatment of IBS patients, clinical trials examining these agents have had numerous methodological flaws. Moreover, they have demonstrated inconsistent efficacy, making evidence-based assessment of efficacy difficult.\(^{1,18}\) Of the three trials evaluating dicyclomine, only one (40 mg four times daily) demonstrated significant symptom improvement compared with placebo. At this high dose, however, close to 70% of patients experienced adverse effects.\(^{20}\) In their systematic review of all evidence available for these agents, the ACG FGID Task Force concluded that the data are insufficient to allow a meaningful evaluation of the effectiveness of these agents.\(^ {1}\)

Tricyclic antidepressants have been used in low doses (i.e. lower than those used for depression) to alleviate the abdominal pain or discomfort associated with IBS.\(^{19,21}\) The mechanistic evidence that they alter motor or sensory function is limited and their effects may reflect a central action. A meta-analysis of eight clinical trials in which five TCAs were used to treat IBS patients showed these agents to be effective in reducing pain-related symptoms. However, these trials were not adequately blinded, included small numbers of patients and were of relatively short duration (averaging only 46 patients and 6 weeks). In addition, many were crossover trials, which are suboptimal in that the effects of the drug may not be completely washed out before the patient is ‘crossed over’ to the control.\(^ {13}\)

A systematic review of the six published clinical trials with TCAs indicated that, in general, these trials were not sufficiently powered for statistically valid conclusions to be drawn, and they suffered from suboptimal methodologies (e.g. not using Rome criteria for enrolling patients, short durations of therapy and high dropout rates); thus, the validity of their results is in question. Overall, the data are inadequate to conclude whether TCAs are more effective than placebo in providing global relief of IBS symptoms.\(^ {1}\) A recent trial of desipramine did not show benefit over placebo in the intent-to-treat analysis.\(^ {22}\)
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Targeted symptom(s)</th>
<th>Study assessment(s)</th>
<th>Study assessment</th>
<th>Evidence-based classification*1</th>
<th>Evidence-based assessment of adverse effects¹</th>
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<tr>
<td><strong>Traditional</strong></td>
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<td><strong>Antispasmodics</strong></td>
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<tr>
<td>Dicyclomine</td>
<td>Abdominal pain/ discomfort</td>
<td>1. Individual IBS symptoms</td>
<td>1. Short duration (&lt;8 weeks)</td>
<td>Grade B recommendation: insufficient data for recommendation about effectiveness of antispasmodic agents available in the United States</td>
<td>May cause anticholinergic adverse effects at higher doses; Should be used cautiously in patients with constipation</td>
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<tr>
<td>Hyoscyamine</td>
<td></td>
<td>2. Symptom improvement</td>
<td>2. Small samples [29–96]</td>
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<td></td>
<td></td>
<td>4. symptoms</td>
<td>4. Inconsistent effectiveness</td>
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<td><strong>Tricyclic antidepressants</strong></td>
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<td>Desipramine</td>
<td>Abdominal pain/ discomfort</td>
<td>1. Individual IBS symptoms</td>
<td>1. Short duration (4–8 weeks)</td>
<td>Grade B recommendation: not more effective than placebo in providing global relief of IBS symptoms</td>
<td>Constipation and fatigue have been documented</td>
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<tr>
<td>Trimipramine</td>
<td></td>
<td>2. Symptom improvement</td>
<td>2. Small samples (most £ 31)</td>
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<td>Amitriptyline</td>
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<td>4. symptoms</td>
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<td><strong>Antidiarrhoeal</strong></td>
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<td>Loperamide</td>
<td>Urgency</td>
<td>1. Global IBS symptoms</td>
<td>1. Short duration (3–5 weeks)</td>
<td>Grade B recommendation: improves diarrhoea; not more effective than placebo in providing global relief of IBS symptoms</td>
<td>Limited adverse effects data, precluding evidence-based conclusions</td>
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<td></td>
<td>Diarrhoea</td>
<td>2. Abdominal pain/distension</td>
<td>2. Small samples (most £ 30)</td>
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<td>4. Urgency</td>
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<tr>
<td><strong>Bulking agents/fibre</strong></td>
<td>Constipation [stool frequency, stool consistency]</td>
<td>1. Global IBS symptoms</td>
<td>1. Short duration (3–12 weeks, most &lt;8 weeks)</td>
<td>Grade B recommendation: not more effective than placebo in providing global relief of IBS symptoms</td>
<td>Limited adverse effect data, precluding evidence-based conclusions</td>
</tr>
<tr>
<td>Psyllium Calcium polycarbophil</td>
<td></td>
<td>2. GI symptoms [e.g. abdominal pain, bowel movements]</td>
<td>2. Small samples (most &lt;30)</td>
<td></td>
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<tr>
<td>Wheat bran</td>
<td></td>
<td></td>
<td>3. Suboptimal study design (5–9)</td>
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<tr>
<td>Ispaghula/poloxamer</td>
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<td>Corn fibre</td>
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<td>Wheat fibre</td>
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<td>Ispaghula husk</td>
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<tr>
<td><strong>Serotonergic agonists/antagonists</strong></td>
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<tr>
<td>Tegaserod</td>
<td>Abdominal pain/ discomfort</td>
<td>1. Global IBS symptoms</td>
<td>1. Acceptable duration (12 weeks)</td>
<td>Grade A recommendation: more effective than placebo in providing global relief of IBS symptoms in female patients with IBS-C</td>
<td>May cause mild, transient diarrhoea</td>
</tr>
<tr>
<td></td>
<td>2. Constipation</td>
<td>2. Individual symptoms [e.g. abdominal pain/distcomfort, bloating, stool frequency, satisfaction with bowel habits]</td>
<td>2. Large samples [520–1519]</td>
<td></td>
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</tr>
</tbody>
</table>
The most common adverse effects among patients using low-dose TCAs for IBS-related abdominal pain include fatigue, dry mouth, sedation, weight gain, difficulty with urination and constipation. TCAs should, therefore, be used with caution in IBS-C patients and may be most beneficial for patients with IBS-D. Other limitations of these agents include a possible 6-week lag before therapeutic effects are seen and the requirement of continual use for maintenance of effect.

Antidiarrhoeals

The antidiarrhoeal agent most commonly used for IBS-D patients is loperamide, which works by binding to opiate receptors. Loperamide improves diarrhoea, urgency, and fecal soiling in IBS-D patients by slowing intestinal transit, enhancing absorption of intestinal water and ions, and strengthening the resting tone of the anal sphincter.

Fibre and laxatives

Patients with IBS-C are often advised to increase dietary fibre intake or to take commercially available fibre products such as psyllium or calcium polycarbophil. Fibre has been shown to decrease whole-gut transit time in persons with mild transit delays, thereby alleviating constipation. However, in most instances of moderate-to-severe constipation, fibre provides little therapeutic benefit.
Laxatives prescribed for IBS-C patients include osmotic laxatives [e.g. polyethylene glycol, lactulose and magnesium-containing products], stimulant laxatives [e.g. bisacodyl or cascara] and emollients [e.g. docusate]. With the exception of polyethylene glycol, the efficacy of laxatives has not been established in randomized, controlled trials in the United States, although their effectiveness in relieving constipation is generally well accepted. However, some medications in this class [e.g. lactulose] can worsen symptoms common to IBS, such as bloating and cramping, and excessive use can lead to diarrhea and dehydration. Long-term laxative use, especially of stimulant laxatives, generally is not recommended. Finally, laxatives do not treat IBS-associated abdominal pain or discomfort.

Table 2 Efficacy of traditional therapies for IBS

<table>
<thead>
<tr>
<th>Therapy</th>
<th>No. of trials</th>
<th>NNT*</th>
<th>Agents tested</th>
<th>Outcome measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antispasmodics</td>
<td>26 trials16</td>
<td>3.7</td>
<td>Cimetropium</td>
<td>Global improvement, individual symptom improvement (abdominal pain/discomfort, abdominal distension, constipation, transit)</td>
</tr>
<tr>
<td></td>
<td>23 trials17</td>
<td>5.6</td>
<td>Mebeverine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16 trials18</td>
<td>1.6–6.7</td>
<td>Dicyclomine, Trimebutine, Rociverine, Diltiazem, Pinaverium, Otilonium, Pirenzepine, Pirifinium</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>11 trials18</td>
<td>3.2 (95% CI, 2.1–6.5)</td>
<td>Amitriptyline, Clopigramine, Desipramine, Doxepin, Trimipramine, Mianserin</td>
<td>Global improvement, individual symptom improvement (abdominal pain/discomfort, diarrhoea/constipation, ability to work)</td>
</tr>
<tr>
<td>Antidiarrhoecal agents</td>
<td>One trial18</td>
<td>3.6</td>
<td>Loperamide</td>
<td>Global improvement (stool frequency, stool consistency, abdominal pain/discomfort), diarrhoea improvement</td>
</tr>
<tr>
<td>Bulking agents</td>
<td>Three trials18</td>
<td>2.2–3.5</td>
<td>Psyllium, Coarse bran, Concentrated fibre, Corn fibre, Polycarbophil, Ispaghula husk</td>
<td>Global improvement, individual symptom improvement (stool passage, satisfaction with bowel movements, constipation, stool frequency, abdominal pain, bloating)</td>
</tr>
<tr>
<td>Tegaserod</td>
<td>Four trials [phase III]15</td>
<td>10 (95% CI, 7.1–20)</td>
<td>6 mg b.i.d. tegaserod</td>
<td>Global IBS symptom improvement (abdominal pain/discomfort, bloating, constipation), individual symptom improvement (abdominal pain/discomfort, bloating, stool frequency)</td>
</tr>
<tr>
<td>Alosetron</td>
<td>Six trials14</td>
<td>7 (95% CI, 5.7–9.4)</td>
<td>Alosetron</td>
<td>Global IBS symptom improvement (abdominal pain, diarrhea, urgency), individual symptom improvement</td>
</tr>
</tbody>
</table>

*Global assessment.

Increasing evidence indicates that behavioural therapy may benefit IBS patients, particularly those with co-morbid psychiatric conditions [e.g. depression or severe anxiety] – estimated to be approximately 18% of IBS patients in the community. In one study, 23 patients with IBS were assessed before and after 12 weeks of hypnotherapy focused on the GI system; the results suggest that hypnotherapy improves abnormal sensory perception in IBS patients, while leaving normal sensation unchanged. The benefits of psychotherapy were evaluated by the FGID Task Force, whose members examined clinical trials that compared behavioural treatments (e.g. psychotherapy, hypnotherapy and relaxation) with placebo. Most clinical trials published to date suggest that behavioural therapy is more effective than placebo in alleviating...
individual IBS symptoms. However, numerous limitations in study design make difficult the determination of efficacy of behavioural therapy in the treatment of IBS patients. A recently reported, well-designed trial of cognitive behavioural therapy (CBT) vs education demonstrated that CBT was efficacious.

WHAT DO PATIENTS THINK OF TRADITIONAL IBS THERAPIES

It is not surprising that IBS patients are often dissatisfied with the efficacy and tolerability of traditional treatment options that address single symptoms. In a survey conducted by the International Foundation for Functional Gastrointestinal Disorders, 350 IBS patients (chosen randomly from a database of IBS patients in the United States) responded to questions regarding their IBS symptoms, the impact of these symptoms on their lifestyles and their satisfaction with treatment. Eighty-eight per cent of the respondents reported using prescription medications (antispasmodics and antidiarrhoeals being among the most common) at some point; 78 and 64% acknowledged using over-the-counter laxatives or antidiarrhoeals, respectively.

Less than half (45%) of patients surveyed believed their prescription IBS medications were effective, and 40% reported being dissatisfied with their current IBS medications or remedies. Dissatisfaction was related primarily to lack of effectiveness, although adverse effects, likely resulting from long-term use and the interaction of multiple medications, also contributed to patient dissatisfaction. Of those persons taking prescription medications, 62% reported adverse effects.

The results of a recent study reviewing utilization trends of GI medications by IBS patients support the hypothesis that patient dissatisfaction leads to the use of multiple medications, switching of medications, and repeated doctor visits. In this study, 5960 outpatient service claims records from 1995 to 1997 for the 12 months following an initial diagnosis of IBS were analysed. The results indicated that 53% of patients used prescription GI medications continuously throughout the year following IBS diagnosis – 36% used monotherapy and 64% used polytherapy. Among IBS patients using multiple IBS therapies, 22% switched from one drug to another, and 42% augmented the originally prescribed drug with another GI medication from a different drug class. In the year after the index diagnosis, expenditures related to outpatient services and pharmaceuticals were higher for polytherapy users who switched and augmented treatment than for monotherapy patients.

PATHOPHYSIOLOGICAL BASIS FOR SEROTONERGIC AGENTS IN IRRITABLE BOWEL SYNDROME

A number of discoveries over the past several years have shed new light on the pathophysiology of IBS and have focused attention on processes that regulate bowel sensorimotor responses and visceral pain perception. A unifying theory is that IBS involves dysregulation of the brain–gut axis. The enteric nervous system (ENS) operates semi-autonomously in controlling intrinsic bowel functions (both motility and secretion) and is modified centrally by the central nervous system (CNS), which supplies extrinsic sympathetic and parasympathetic innervation to the GI tract via the autonomic nervous system. Disruptions along the brain–gut communication path likely cause the various symptoms of IBS, such as altered gut motility, abnormal intestinal secretion and visceral hypersensitivity.

The neurotransmitter serotonin is a common link among these three processes – GI motility (peristaltic reflex), secretion and perception of visceral pain. Serotonin is an important signalling molecule in the ENS, and the GI tract is the largest source of serotonin in mammals; 95% is synthesized, stored and secreted in the gut. Serotonin acts on several receptors, including the 5-HT1p, 5-HT3, and 5-HT4 receptor subtypes localized in the gut, mediating numerous GI tract functions, such as stimulation of secretory and peristaltic reflexes (via intrinsic sensory neurones) and modulation of visceral sensation (via extrinsic sensory neurones and vagal spinal afferent neurones). Its diverse activity in modulating these processes is believed to be pivotal in the normalization of GI function, making 5-HT receptors and their associated neuronal pathways important targets for IBS-specific drugs.

GI motility and secretion

Irritable bowel syndrome patients have demonstrated increased intestinal motility in response to both intrinsic (e.g. food intake) and environmental factors (e.g. stress). In general, 5-HT3 receptors are associated with excitation in the GI tract, resulting in increased motility, secretion and sensation. 5-HT3 antagonists, therefore, slow colonic transit and increase fluid absorption, thus improving symptoms of IBS-D. 5-HT4 receptors mediate both excitatory or inhibitory effects on gut function. In vitro studies indicate that 5-HT4 receptors are essential mediators of the peristaltic reflex and synthetic 5-HT4 receptor agonists...
have been found to increase gut motility. Although the mechanism underlying the development of IBS is unknown, one hypothesis is that patients with different bowel symptoms differ in colonic 5-HT concentration and/or perhaps in 5-HT receptor composition.

Intestinal secretion, which is also mediated by 5-HT3 and 5-HT4 receptors, can be modulated by synthetic agonists or antagonists. Antagonism of 5-HT3 receptors leads to decreased fluid secretion and 5-HT4 receptor agonism results in increased intestinal fluid and electrolyte secretion.

Visceral hypersensitivity

Irritable bowel syndrome patients also appear to differ from controls in the way the CNS processes colorectal pain stimulation. It is interesting to note that this hypersensitivity to distension is not restricted to the distal bowel – IBS patients experience hypersensitivity to distension throughout the entire GI tract. Therefore, abnormal neurosensory function may occur in both the CNS and the peripheral nervous system in IBS patients. Alosetron, a 5HT3 antagonist, changes the pattern of blood flow during noxious rectal distension activating centres that downregulate pain sensation.

Serotonin appears to be involved in modulating visceral hypersensitivity in IBS patients. Results from animal studies suggest that 5-HT3 receptors mediate visceral noxious signals via spinal vagal afferent neurones. Painful colonic distension from visceral stimuli leads to increased CNS activation that is inhibited in a dose-dependent manner by 5-HT3 receptor antagonism.

Similarly, 5-HT4 receptors are believed to mediate visceral sensation and perception in experimental animals. The firing rate of rectal spinal afferents decreases in response to slow pressure distension when a 5-HT4 receptor agonist is applied. Moreover, 5-HT4 receptor agonism inhibits the visceral pain responses and afferent signalling induced by rectal distension. Data from human studies also suggest they alter reflex sensory responses.

SEROTONERGIC AGENTS: ALOSETRON AND TEGASEROD

The preclinical studies described previously led to the clinical development and approval of two medications for the treatment of IBS: alosetron, a 5-HT3 receptor antagonist, and tegaserod, a selective 5-HT4 receptor agonist.

Alosetron

Alosetron hydrochloride is currently indicated for use in women with severe diarrhoea-predominant IBS in whom traditional therapy has failed. Initial trials demonstrated that alosetron decreased gut transit in non-IBS and IBS subjects, increased fluid absorption by normal human intestine and reduced pain perception upon rectal distension in IBS patients. These pharmacodynamic effects are believed to be the reason for alosetron’s effective alleviation of multiple IBS symptoms, including abdominal pain and discomfort, diarrhoea, and urgency.

Two large, randomized, placebo-controlled, clinical trials comprising 1273 women assessed the efficacy of alosetron 1 mg twice daily for 12 weeks among patients with diarrhoea-predominant IBS. A comparator trial of 623 women with IBS assessed alosetron 1 mg twice daily vs the antispasmodic mebeverine. Significantly more subjects treated with alosetron reported adequate relief of abdominal pain and discomfort for all 3 months of treatment compared with those receiving placebo/comparator treatment. Alosetron also improved stool consistency and decreased stool frequency and bowel urgency compared with placebo. However, in the single study that examined the effects of alosetron on bloating, no statistically significant difference was observed between the two groups during the 12-week treatment course.

Constitution was the most common adverse effect reported in these trials and may be expected to occur in up to 25% of patients treated continually. Approximately 10% of patients taking alosetron withdrew prematurely because of constipation-related adverse events.

Alosetron 1 mg twice daily was also assessed in a placebo-controlled clinical trial of 801 women with severe diarrhoea-predominant IBS – enrolled patients experienced symptoms of urgency on at least 50% of days at study entry. Compared with placebo, subjects taking alosetron had a significantly greater proportion of days with satisfactory control of urgency, as well as greater global improvement in IBS symptoms. Alosetron-treated subjects also showed improvement in bowel symptoms compared with those receiving placebo.

The most common adverse effects, which were reported in at least 1% of IBS patients taking alosetron in clinical trials, included constipation, abdominal discomfort/pain and nausea. In patients receiving alosetron 1 mg twice daily, constipation was generally mildly to moderately severe and transient; typically occurring as a single episode during the first month of treatment; it resolved on its own or with an interruption in
treatment. However, serious complications such as constipation requiring hospitalization or ischaemic colitis have been reported in clinical studies and in postmarketing experience.  

These serious complications occurred in approximately one of 1000 patients. The cumulative incidence of ischaemic colitis in women taking alosetron was two of 1000 patients during 3 months and three of 1000 patients during 6 months. Long-term safety data have yet to be established.  

Alosetron was reintroduced in the United States in November 2002 after it had been voluntarily withdrawn from the marketplace in 2001 and is now indicated only for women with severe diarrhoea-predominant IBS for whom conventional IBS therapies have failed. A number of restrictions have been imposed on those prescribing alosetron, including mandatory doctor training and certification. Patients must also sign consent forms confirming the severity of their symptoms and their understanding of the potential risks associated with alosetron therapy. While undergoing treatment, patients should be monitored for the development of severe constipation or ischaemic colitis. In addition, alosetron should be used cautiously in patients with hepatic insufficiency because of its extensive metabolism by the liver.  

**Tegaserod**

The selective 5-HT4 receptor agonist tegaserod is indicated for women with IBS whose primary bowel symptom is constipation. Tegaserod is the first in a novel class of drugs (aminoguanidine indoles) designed to be similar in structure to serotonin and to act selectively at 5-HT4 receptors in the GI tract.

Tegaserod accelerates overall GI transit in healthy subjects and promotes gastric emptying, small bowel transit and colonic transit in IBS-C patients. Tegaserod was found to reduce the firing rate of spinal afferents in vivo, supporting its role in the modulation of visceral sensitivity. Tegaserod also increased fecal water and intestinal secretion in female subjects.

The efficacy of tegaserod has been evaluated in several large, multicentre, randomized, double-blind, placebo-controlled trials. In these trials, patients with IBS-C received placebo or tegaserod (2 or 6 mg twice daily) for 12 weeks. Two of the trials included 4-week follow-up without medication. When compared with placebo, tegaserod 6 mg twice daily produced statistically significant improvement in the Subject’s Global Assessment (a validated 5-point ordinal scale) of relief (overall symptom improvement), as well as in the single symptoms of abdominal pain/discomfort, number of bowel movements and stool consistency. Significant improvement in daily bloating scores was also observed in two of these trials and one study showed that tegaserod-treated patients experienced a significant reduction in the number of days with straining, compared with controls. More recently, the efficacy of tegaserod was evaluated in randomized controlled trials among Asian-Pacific and Nordic populations with IBS whose primary bowel habits were not diarrhoea. In both studies, patients received either tegaserod 6 mg b.i.d. or placebo for 12 weeks. The results showed that the mean proportion of patients with overall satisfactory relief was statistically significantly greater in the tegaserod group compared with placebo for the majority of the study period. Reductions in the number of days with at least moderate abdominal pain/discomfort, bloating, no bowel movements and hard/lumpy stools were also greater in the tegaserod group.

Tegaserod was well tolerated, with diarrhoea and headache being the most frequently reported adverse effects. In the 12-week trials, diarrhoea occurred in 9 and 4% of patients treated with tegaserod and placebo, respectively. The diarrhoea was typically mild and transient, causing less than 2% of subjects to withdraw prematurely. Headaches occurred more frequently among those taking tegaserod (15% vs 12%), but the incidence of migraine headaches was similar between the two treatment groups.

The long-term safety of tegaserod has been assessed in a multicentre, open-label, clinical trial of patients with IBS-C. The most common adverse effects related to tegaserod were mild and transient diarrhoea (10.1%), headache (8.3%), abdominal pain (7.4%) and flatulence (5.5%). The adverse effects profile, clinical laboratory evaluations, vital signs and electrocardiogram recordings revealed no evidence of any unexpected adverse effects and suggested that tegaserod treatment was safe over a 12-month period.

Because IBS patients may alternate between constipation and diarrhoea, the safety of tegaserod in patients with IBS-D was also examined. In a randomized, placebo-controlled, double-blind trial comparing patients with IBS-D receiving either placebo or 4 or 12 mg of tegaserod per day, no complications of diarrhoea or serious adverse effects were reported. When data from the two tegaserod groups were pooled, the overall frequency of diarrhoea was similar among patients receiving tegaserod (33%) and placebo (35%).

Tegaserod has also been shown to be devoid of untoward electrocardiographic effects. Recent studies have evaluated its cardiac safety profile. One analysed...
electrocardiographic data [11 535 electrocardiograms] from 2516 IBS patients participating in various clinical trials [receiving tegaserod 2 or 6 mg twice daily or placebo], the other analysed data from a study of 36 healthy male patients [receiving tegaserod 0.8–20 mg day\(^{-1}\) intravenously]. Clinical trial results revealed that tegaserod was no more likely than placebo to result in an electrocardiographic abnormality, and no serious dysrhythmias were reported. In healthy volunteers, no cardiac effects were noted, even when drug plasma concentrations reached 100 times those observed after a typical therapeutic dose [12 mg day\(^{-1}\)].

Tegaserod is classified as pregnancy category B.\(^{40}\) Although animal studies have indicated that tegaserod does not impair fertility or cause fetal harm at concentrations 15 to 51 times those expected at recommended doses, no adequate, well-controlled studies have been undertaken in pregnant women.\(^{40}\) Because experience drawn from clinical trials regarding tegaserod and pregnancy has been limited [15 unintended pregnancies on tegaserod and five on placebo], tegaserod is not recommended during pregnancy.\(^{69}\) Use in nursing mothers must be evaluated carefully as well; it is not known whether tegaserod is excreted in human milk, but it is excreted in the milk of lactating rats with high milk-to-plasma ratios.\(^{40}\)

**SUPPORT FOR THE USE OF SEROTONERGIC AGENTS IN THE TREATMENT OF PATIENTS WITH IBS**

In addition to evaluating traditional IBS therapies, the FGID Task Force used an evidence-based approach to evaluate the published tegaserod and alosetron clinical trials.\(^{1}\) Based on study methodologies and clinical trial evidence, tegaserod and alosetron were the only IBS therapies to receive grade A recommendations from the Task Force. This is not surprising given the fact that criteria for determining optimal study design were published relatively recently. Nevertheless, the Task Force concluded that, when compared with placebo, these agents provided significant global relief of symptoms of IBS-C and IBS-D, respectively.

Results of a recent meta-analysis of six alosetron-randomized, placebo-controlled clinical trials are analogous with the conclusions of the ACG FGID Task Force, providing further evidence to support the efficacy of alosetron in women with diarrhoea-predominant IBS.\(^{14}\) The meta-analysis used the Quality of Reports of Meta-analyses statement guidelines for ensuring quality of the analysis.\(^{70}\)

Adding alosetron and tegaserod to the armamentarium of treatments for patients with IBS offers patients the option of therapies that target IBS-specific pathophysiological pathways. Although this focus may help to provide global relief of the multiple symptoms of IBS for patients, it is a first step. These therapies do not address all the needs of all patients with IBS and more work in the area of IBS management needs to be done in order to provide all IBS patients with optimal treatment of their symptoms. It is important to note, however, that even in the clinical trials that show these medications to be superior to placebo or other comparators, the proportion of patients with global relief rarely reaches 70%. It is clear, therefore, that there is still room for improvement in IBS therapy.

**SUMMARY AND CONCLUSIONS**

Until recently, no drugs targeted IBS-specific pathophysiological pathways or the multiple symptoms of IBS. Patients are often dissatisfied with the efficacy and adverse effect profiles of traditional therapies. This leads to multiple doctor visits and frequent medication switching or augmentation – factors that often lead to increased medical costs. Alosetron and tegaserod represent a step in the right direction for the treatment of patients with IBS by providing these patients with options for treating the multiple and varied symptoms of IBS, resulting in global symptom improvement.

The future management of IBS appears promising in that agents now in clinical development will follow the lead of serotonergic modulators in targeting the multiple symptoms of IBS.

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