Tegaserod in the treatment of constipation-predominant functional gastrointestinal disorders

Anurag Agrawal & Peter Whorwell†

†Author for correspondence
ERC Building, First Floor, Wythenshawe Hospital, Southmoor Road, Manchester, M23 9LT, UK
Tel.: +44 161 291 5813
Fax: +44 161 291 4184

Irritable bowel syndrome is a common condition for which, until recently, treatment options have been limited. Tegaserod has selective serotonin subtype 4 receptor agonist activity and acts by increasing gastrointestinal motility, secretion and possibly reducing visceral sensitivity. It has been developed to treat patients with irritable bowel syndrome who suffer from abdominal pain, constipation and bloating. Studies so far suggest that it is an effective treatment for these symptoms with an excellent safety profile. Its role in other functional gastrointestinal disorders, such as functional dyspepsia, is still being assessed. This review describes the structure, pharmacokinetic and pharmacodynamic properties of tegaserod and its effect on gastrointestinal physiology, as well as its clinical utility.

Keywords: bloating, constipation, irritable bowel syndrome, serotonin, tegaserod

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Irritable bowel syndrome (IBS) is the most common condition dealt with by gastroenterologists, accounting for up to 30% of their practice and 10% of primary care case loads [1]. It is characterized by abdominal pain or discomfort often related to a change in bowel habit and frequently exacerbated by eating. Investigation reveals no structural abnormality, although a variety of gastrointestinal (GI) physiological changes have been described. Population-based studies have suggested that the prevalence is between 10 and 15%, with some variation according to the population group studied or the diagnostic criteria used [2].

IBS can be classified as diarrhea-predominant (d-IBS), constipation-predominant (c-IBS) or alternating bowel habit (a-IBS) subtypes according to the predominant bowel habit, with an approximately equal prevalence between the three groups. More recent studies have suggested that patients with alternating bowel habits tend to have a greater variation of their symptoms compared with the other subgroups, with this fluctuation tending to be greater between c-IBS and a-IBS rather than c-IBS and d-IBS or d-IBS and a-IBS. This has led to the suggestion that the term mixed IBS (m-IBS) should be used [3].

The diagnosis of IBS is based on a clinical history and the absence of certain red flag features such as rectal bleeding, weight loss, absence of family history of bowel cancer, inflammatory bowel disease or celiac disease. Investigations required to rule out other gastroenterological conditions should generally be kept to a minimum and treatment includes a range of approaches including dietary modification or drugs such as antidiarrheals, laxatives, antispasmodics and antidepressants. Behavioral therapy is sometimes tried in patients who do not respond to conventional treatment.

In addition to its costs to the patient, IBS also has a significant direct and indirect economic burden. The direct cost in terms of healthcare utilization has been estimated to be between US$1.7–10 billion/year in the USA alone. The indirect cost in terms of days off work and impairment whilst at work can amount to US$20 billion, with the common cold being the only condition that can match IBS in terms of its economic impact [4–6].

Functional constipation is a very common condition that affects the general population. It is defined as a group of functional disorders that present as persistent, difficult, infrequent or seemingly incomplete defecation in the absence of other features to suggest IBS (Rome II criteria). The estimates of the prevalence of constipation in North America range from 12 to 19% and up to 50% in patients above the age of 65 years, with a female-to-male ratio of 2.2:1 [7]. In one cohort, 89% of patients with constipation still reported constipation at 14.7 months follow-up. There is some evidence to suggest that quality of life (QoL) is impaired in constipation; however, this is not conclusive [7,8].

Treatment of IBS: unsatisfactory solution to a common problem

The ideal IBS treatment would provide rapid, sustained, global relief of the multiple symptoms of IBS with a single, effective, well-tolerated agent. Treatments that target only single IBS

symptoms are considered suboptimal forms of therapy by the Rome II Committee and the American College of Gastroenterology Functional Gastrointestinal Disorders Task Force (ACG FGID) [9–11].

Although in some patients traditional IBS treatment options are beneficial in relieving single symptoms (e.g., antispasmodics for abdominal pain, laxatives for constipation, and antidiarrheal agents for diarrhea), none of these drugs for IBS have been assessed in trials that fulfill the recently introduced, rather strict criteria set out by the European Committee for Medicinal Products for Human use (CHMP). The CHMP recommended in 2003 that drugs which are used for short-term relief of IBS should be assessed using a re-randomization design with two primary outcome variables. Furthermore, patient surveys demonstrate general dissatisfaction with most of the available agents and evidence-based support for their use is also lacking, with the ACG FGID Task Force claiming that the methodology in most clinical trials of these older agents was flawed. They also concluded that many studies only met the criteria for level 2 evidence (grade B recommendation), defined as randomized, controlled trials with $p > 0.05$, less than adequate sample sizes, poor methodology, or a combination of these flaws [12]. Although bulking agents, antidiarrheals and tricyclic antidepressants (TCAs) were found to relieve some of the single symptoms of IBS (constipation, diarrhea and abdominal pain, respectively), these agents were not considered more effective than placebo in providing global relief of the multiple symptoms of IBS. In addition, these agents often cause adverse reactions, some of which may mimic or exacerbate IBS symptoms (e.g., constipation from antidepressants and bloating from high doses of fiber).

Over the last few years there has been a surge of interest in a new class of drugs that modulate serotonin and its receptors, with the 5-HT_3 receptor antagonist alosetron and the 5-HT_4 receptor agonist tegaserod being the focus of much attention with respect to IBS therapy.

Role of serotonin and its receptors in IBS

Serotonin is distributed mainly in the enterochromaffin (EC) cells, which are located in the epithelium of the small intestine as well as the colon. There are many triggers for serotonin release from EC cells, including mechanical distension, nutrients, toxins, neurotransmitters and a change in pH, with mechanical stimulation being the greatest trigger. Serotonin has a number of effects in the GI tract that are mediated by a variety of receptor subtypes. Pancreatic and mucosal secretion as well as peristalsis are stimulated via the direct action of serotonin on enterocytes in addition to its stimulatory effects on intrinsic primary afferent neurons. In addition to this effect, serotonin also activates extrinsic sensory nerves such as the vagus and spinal nerves which innervate the GI tract and thus has a role in the perception of pain in the GI tract [13,14]. A recent study has suggested that IBS patients have reduced stores of serotonin in the gut mucosa, which is independent of the bowel habit subtype, although EC cells appear to be increased in the colonic mucosa of patients with post-infectious IBS [15,16]. There is evidence that circulating postprandial serotonin levels vary between c- and d-IBS, with the former tending to be lower in healthy controls and the latter higher [17]. These data, although somewhat conflicting, do suggest that disturbances in serotonergic function can lead to disturbance of GI motility, sensation and secretion.

One of the key components of normal serotonergic function is the rapid and effective clearance of serotonin following release. The serotonin reuptake transporter (SERT) is a specialized transporter protein that is responsible for the the transcellular transport and intracellular deactivation of serotonin. SERT is inhibited therapeutically by selective serotonin reuptake inhibitors (SSRIs) and TCAs. Recent reports have identified differences in the genetic coding of IBS patients with diarrhea and constipation subtypes [18].

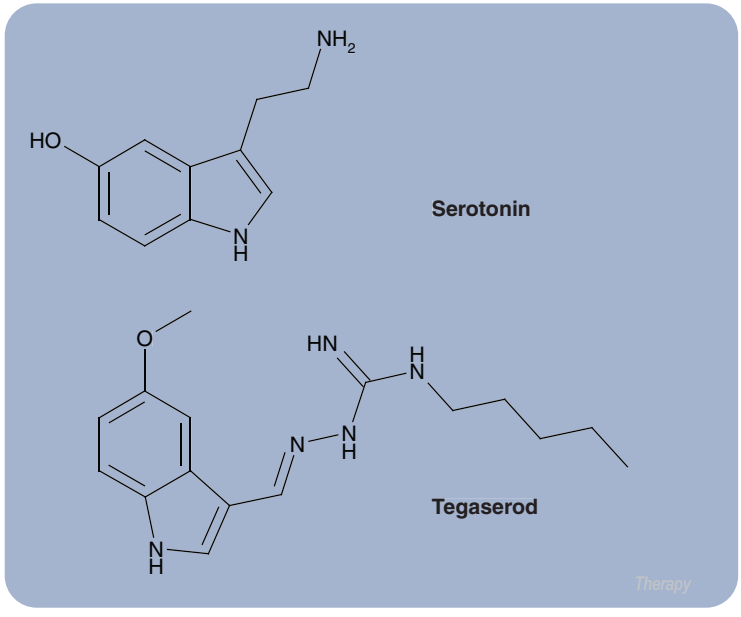
There are at least seven different subclasses of serotonin receptor, with at least 21 different subtypes. In the gut, serotonin receptors are present mainly on gut neurons, smooth muscle cells and EC cells. Of the different receptor subtypes the most important are the 5-HT_3 and 5-HT_4 subtypes.

There is a predominance of 5-HT_3 receptors on the enteric neurons of the gut, where they have a variety of effects including the potential to control motility, fluid secretion and visceral sensitivity. Studies have also indicated that 5-HT_4 receptors are located in the enteric neurons and the smooth muscle with their stimulation leading to a prokinetic effect and enhanced fluid secretion [13]. More recent work has indicated that 5-HT_4 receptors are present not only on submucous and myenteric plexus neurons but also on the interstitial cells of Cajal, which may have a role in regulating motility [19].

Serotonin receptor modulators: background

The serotonin receptors are among the most compelling targets for motility-modifying agents, given the central role that serotonin plays in the initiation of the peristaltic reflex and the excitatory action of serotonin on enteric neurons. Amongst the 5-HT_3 antagonists, alosetron was the first to be approved by the US FDA for the treatment of d-IBS. However, safety concerns led to the withdrawal of the drug from the market within a few months of its introduction, with between 1 in 700 and 1 in 1000 patients who took this drug suffering from ischemic colitis. The possible mechanisms include a reversal of blood flow from mucosa to serosa due to its constipating effect or preferential binding of serotonin to 5-HT_1 resulting in vasoconstriction. In addition, 1 in 10,000 patients on alosetron needed surgery for severe constipation, with eight deaths possibly attributed to the use of alosetron [20]. Following pressure from patient support groups, alosetron has now been reintroduced in the US market on a restricted basis and this incident indicates just how desperate sufferers are for a new form of treatment. Another 5-HT_3 antagonist, cilansetron, has recently undergone clinical trials ,with evidence of benefit in patients with d-IBS, and another member of this class of drug, ramosetron, is also in development.

Figure 1. Chemical structure of serotonin and tegaserod.



The most extensively studied 5-HT_4 agonists are cisapride, prucalopride and tegaserod. Unfortunately, cisapride has the potential to provoke ventricular arrhythmias and prolongation of the QT interval and this is linked to HERG potassium channel blockade rather than 5-HT_4 receptor agonism [101]. Similarly, despite being effective, prucalopride has produced problems in animals and it is unclear whether this drug will reach clinical practice. However, tegaserod, which is a partial agonist of the 5-HT_4 receptor, has proved to be very safe and is now in clinical use in many countries.

Chemistry

Tegaserod (Zelnorm®, Zelmac®, Novartis) is a derivative of indole carboxaldehyde and belongs to a class of drugs known as the aminoguanidine indoles (**Figure 1**) that display a natural affinity for the 5-HT_4 receptor. It has little or no binding affinity for any other receptors including other serotonergic, histaminergic, adrenergic or muscarinic receptors, whereas its binding to the 5-HT_4 receptor is approximately 3–8-times that of cisapride, which is a mixed 5-HT_4 agonist/5-HT_3 antagonist [21,22].

Pharmacokinetics

Tegaserod is rapidly, although incompletely, absorbed following oral administration and reaches peak plasma concentrations after approximately 1 h, with a bioavailability of 10% under fasting conditions. Food affects bioavailability as well as peak plasma concentration, with a reduction in bioavailability of 40–65% and peak plasma concentration of 20–40%. Tegaserod is approximately 98% bound to plasma proteins, primarily to α_1-acid glycoprotein, and has a volume of distribution at steady-state of 368 ± 223 l. It is metabolized via two pathways. The first is acid-catalyzed hydrolysis in the stomach followed by oxidation and conjugation with the 5-methoxyindole-3-carboxylic acid glucuronide (M 29.0) metabolite. The second is direct glucuronidation, which leads to generation of three isomeric *N*-glucuronides. All of these metabolites have negligible affinity for 5-HT_4 receptor and no promotile activity [23].

The plasma clearance of tegaserod is 77 ± 15 l/h, with an estimated terminal half-life of 11 ± 5 h following intravenous administration. Approximately two-thirds of the orally administered dose of tegaserod is excreted unchanged in feces, suggesting that some of its effects may be local. The pharmacokinetics of

tegaserod are proportional to its dose over the range 2–12 µg administered twice-daily for 5 days, with no relevant accumulation. The pharmacokinetics of tegaserod in patients with IBS are comparable to those in healthy individuals, and similar between men and women. In an open-label, parallel-group study, the pharmacokinetics of a single 12-µg oral dose of tegaserod in ten patients with severe renal insufficiency requiring haemodialysis was similar, with data obtained from ten healthy subjects matched for age, weight, height and gender [24]. However, the present license for tegaserod use extends to only mild-to-moderate renal disease and no dose adjustment is required in elderly patients or those with mild-to-moderate hepatic or renal impairment. *In vivo* drug interaction studies are covered under the safety profile of tegaserod.

Pharmacodynamic properties & mechanisms of actions

Effect on motility

In vitro studies have suggested that tegaserod enhances colonic motility, with increased velocity of propulsion of artificial pellets in the guinea pig colon [25]. These results have been reproduced in *in vivo* studies undertaken in animals with evidence suggesting that all segments of the GI tract are stimulated by tegaserod [26,27]. Tegaserod has also been shown to stimulate gastric emptying in animals under normal conditions as well as under stress. Furthermore, in dogs, both small as well as large intestinal motility was increased with activation of small intestinal rhythmic contractions and prolonged colonic contraction with this being associated with enhanced transit of a radioactive tracer [27].

Pharmacodynamic studies conducted on humans, both healthy and with c-IBS, suggest that tegaserod accelerates gastric emptying as well as small bowel and colonic transit. Degan and colleagues have demonstrated that tegaserod administered intravenously (0.6 µg) as well as orally (6 µg) led to accelerated motility of the whole GI tract [28], and that this effect is irrespective of gender [29].

Prather and colleagues performed similar studies on patients with c-IBS and came to the same conclusion, with the administration of tegaserod 2 µg twice-daily for 1 week resulting in significant acceleration of small bowel transit as assessed by a scintigraphic method. Large bowel transit compared with before treatment values accelerated, but failed to achieve statistical significance [30].

Effect on sensitivity

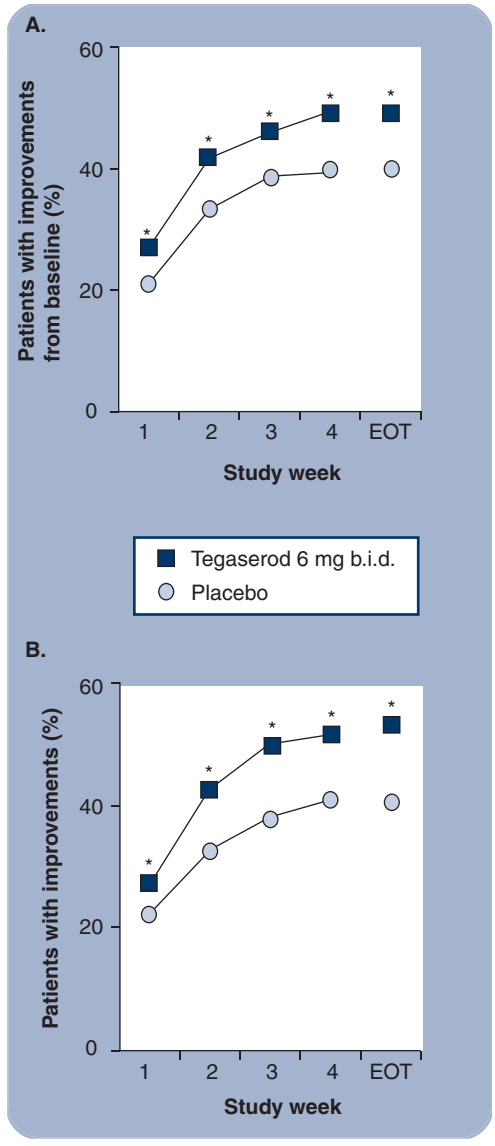
As already mentioned, serotonin plays an important role in the perception of pain in the GI tract. One animal study has reported the antinociceptive properties of tegaserod following the administration of intravenous tegaserod. A reduction in static discharge rates of afferents evoked by rectal distension in unanaesthetised cats was observed in a dose-dependent manner, with no change in tone or compliance [31]. Another randomized, double-blind, placebo-controlled study, performed in 20 healthy women, examined the effects of slow or rapid rectal distensions at baseline and on day 8 following treatment with either placebo or tegaserod (6 µg twice-daily). This showed that slow distensions performed up to the pain threshold induced gradual inhibitions of the RIII nociceptive reflex and on day 8, these inhibitory effects were significantly reduced in the tegaserod group, but not in the placebo. However, the effect of rapid distensions remained unchanged in both groups [32]. In addition, it has been shown that there is a dose-dependent reduction of the visceromotor reflex to colorectal distension in rats following the administration of tegaserod, and that this effect was reversed by a 5-HT_4 antagonist. [33]

Clinical efficacy

Tegaserod in c-IBS

There have been several randomized, controlled trials that have assessed the efficacy of tegaserod in this subgroup of patients and all have suggested similar results. One of the first studies examined 881 patients with IBS characterized by abdominal pain, bloating and constipation who received tegaserod or placebo for 12 weeks. The results showed that patients who took tegaserod experienced significant relief of overall IBS symptoms, measured by a weekly, self-administered questionnaire. At the end of 12 weeks, treatment difference from placebo was approximately 12% and this was independent of the dose. In IBS clinical trials, an advantage of the drug under investigation over placebo of 10% is usually considered a clinically useful effect [11]. The effect of tegaserod was noted as early as week 1 and sustained over the 12-week treatment period. Individual IBS symptoms assessed daily also showed a statistically significant improvement for abdominal discomfort/pain, number of bowel movements and stool consistency, with a favorable trend for reducing days with significant bloating [34].

Figure 2. Difference in satisfactory relief between patients on tegaserod and placebo.



A: First treatment; difference at EOT: 10.5%.
B: Repeated treatment; difference at EOT: 13.2%. For repeated treatment, both tegaserod and placebo groups had received tegaserod in first treatment.
b.i.d.: Twice-daily; EOT: End of treatment [36].

In a separate randomized, double-blind, multicenter study, 1519 women received either tegaserod, 6 µg twice-daily (n = 767), or placebo (n = 752) for 12 weeks, preceded by a 4-week baseline period without treatment and followed by a 4-week open withdrawal period. The primary efficacy evaluation was the patient's symptomatic response as measured by the Subject's Global Assessment of Relief, and other efficacy variables included abdominal pain/discomfort, bowel habits and bloating. The results were similar to the previous study, with tegaserod producing significant ($p < 0.05$) improvements in the Subjec''s Global Assessment of Relief and other efficacy variables. These improvements were seen within the first week, and were maintained throughout the treatment period. Adverse events were similar in both studies, with transient diarrhea being the only event observed more frequently with tegaserod than placebo [35].

A more recent study has evaluated the efficacy and safety of initial as well as retreatment with tegaserod in female c-IBS patients as recommended by the more stringent European regulators. This was a prospective, double-blind, randomized, multicenter study and included 2660 female subjects who were initially randomized to receive either tegaserod (n = 2125) 6 µg twice-daily or placebo (n = 525) for 4 weeks in the primary phase, followed by retreatment with tegaserod (n = 488) or placebo (n = 495) if symptoms recurred. Thus, if the participant received tegaserod in the first phase they may subsequently receive placebo or the drug. However, if the subject had received placebo initially, tegaserod was prescribed in the second phase. The results suggested that tegaserod was significantly superior to placebo, with a treatment difference rate in terms of overall IBS symptoms of 10.6% (95% confidence interval [CI]: 6.0, 15.1; $p < 0.001$; number needed to treat [NNT] = 9.4), with a similar benefit with respect to abdominal discomfort and pain. These benefits were maintained in the second phase of the study where the treatment difference for overall IBS symptoms was 17.0% (95% CI: 11.2, 22.7; $p < 0.001$; NNT: 5.9) with nearly 20% of the patients experiencing improvement in their abdominal pain/discomfort (**Figure 2**). Secondary outcomes such as QoL scores and work-productivity assessments also improved, with significantly more patients reporting overall treatment satisfaction and better work productivity as well as less absenteeism when compared with controls [36]. The majority of these trials have been undertaken on western populations; however more recently the efficacy of tegaserod in non-western populations has been confirmed in an Asia–Pacific study as well as one undertaken in Pakistan [37,38].

It would be of interest to know whether, in a patient already taking a laxative, the addition of tegaserod would lead to any additional benefit. This question has recently been answered in a

Table 1. Summary of randomized, controlled trials of tegaserod for constipation-predominant irritable bowel syndrome.

Study	Number of patients	Response on tegaserod (%)	Placebo response (%)	Treatment benefit (%)	Ref.
Muller-Lissner *et al.* (2001)	881	38	30	8	[31]
Novick *et al.* (2002)	1519	44	39	5	[32]
Kellow *et al.* (2003)	520	47	28	19	[37]
Nyhlin *et al.* (2004)	647	40	29	11	[60]
Tack *et al.** (2005)	2660	33	24	11	[36]

**1191 patients were retreated with a 16% response over placebo.*

study, which suggests that this approach not only leads to a further improvement in bowel habit but also a significant reduction in pain [39].

So far there have been two randomized, placebo-controlled, double-blind studies so far that have tested the effectiveness of tegaserod in 288 male patients. Neither of these studies have shown any differences in response rates between placebo and the tegaserod group. As a consequence, tegaserod usage is not approved in male patients in several countries [102]. A synopsis of studies in relation to c-IBS is listed in **Table 1**.

Tegaserod in constipation

There have been two large, multicenter studies published recently that have investigated the role of tegaserod in patients with chronic, idiopathic constipation, with more than 2500 individuals enrolled in total (**Table 2**) [40,41]. In one of these, following a 2-week baseline period, 1264 patients were randomized to 12 weeks of double-blind treatment with tegaserod or placebo. Responder rates for the primary efficacy variable (increase in bowel frequency over week 1–4) were 35.6 and 40.2% for tegaserod 2 and 6 µg twice-daily, respectively, compared with 26.7% for placebo. Moreover, tegaserod 6 µg twice-daily also reduced straining, abdominal bloating/distension, and abdominal pain/discomfort with significant improvements also seen in stool form and in global estimation of bowel habit and constipation [40]. The other tegaserod studies in chronic constipation have yielded comparable results.

Tegaserod in bloating

Bloating is one of the most troublesome symptoms associated with IBS and is more common in women than men. It seems to be somewhat more frequent in c-IBS and is particularly difficult to treat. It is therefore of interest to note that although not recorded as a primary, efficacy variable, all studies have noted that tegaserod appears to have a positive effect on bloating and in an analysis combining the data from three studies, this reached statistical significance [42].

Other potential indications

Dyspepsia is a multifactorial disorder in which a variety of underlying pathophysiological mechanisms have been described. These include delayed gastric emptying, impaired gastric accommodation to a meal and hypersensitivity to gastric distension, in approximately 30–40% of patients respectively [43–45]. There is evidence to suggest that tegaserod accelerates gastric emptying as well as having an effect on gastric compliance [29,46]. Theoretically, this makes it a suitable agent for patients with functional dyspepsia, particularly those with delayed gastric emptying.

Indirect treatment benefits: health economics of tegaserod

When compared with placebo in 1675 c-IBS patients, tegaserod was associated with a 2.6% decrease in absenteeism ($p = 0.004$); a 5.4% reduction in impaired work performance ($p < 0.0001$); a 6.3% reduction in loss of productivity ($p < 0.0001$); and a 5.8% reduction in impairment of daily activity ($p < 0.0001$). The authors concluded that work productivity was better in the tegaserod group than those receiving placebo [47]. Another study has reported a reduction in both community practitioner as well as hospital visits, with a reduction in endoscopic and nonendoscopic procedures [48].

Table 2. Summary of randomized controlled trials of tegaserod for functional constipation.

Study	Number of patients	Dose of tegaserod (µg b.i.d.)	Tegaserod response (%)	Placebo response (%)	Treatment benefit (%)	Ref.
Kamm *et al.* (2002)	1264	2 6	35.6 40.2	26.7	8.9 13.5	[40]
Johanson *et al.* (2004)	1348	2 6	41.4 43.2	25.1	16.3 18.1	[41]

b.i.d: Twice-daily dose.

Safety & tolerability

The adverse effects of tegaserod have been similar in most randomized, controlled trials, with diarrhea and headache being the two most commonly reported problems. In these trials, the incidence of diarrhea ranged from approximately 5 to 10% (2–3% more than placebo); however the duration was short-lasting (usually less than 3 days) and either resolved spontaneously or following the prescription of an antidiarrheal or the cessation of treatment. Secondary and serious complications, such as electrolyte imbalance, dehydration or hospitalization, have been infrequent. The mean NNT value of 9 (**Table 1**) is less than the mean number needed to harm (NNH), which was between 50–60, indicating that there is a positive risk–benefit relationship.

Other symptoms, such as flu-like complaints, abdominal pain, dizziness, dyspepsia, urinary tract infection, nausea, nasopharyngitis and back pain, have all been reported, although pooled data suggests that none of these have occurred any more frequently than with placebo. Furthermore, it is a well recognized fact that many of these symptoms are commonly reported by IBS patients irrespective of the medication they are receiving.

In view of the adverse effect on the QT interval observed with the prokinetic drug cisapride, it is important to establish whether tegaserod could be associated with similar problems, even though it is chemically unrelated to cisapride. A range of echocardiographic studies have been undertaken and no such changes have been recorded, even following the administration of high doses 100-times the therapeutic levels [49]. In fact, there is now consensus that the main mechanism by which cisapride induces cardiotoxicity is by blocking potassium currents which leads to a prolonged repolarization phase, and not by activation of 5-HT_4.

There have been some concerns over the possibility that the incidence of abdominal and pelvic surgery might be increased in patients receiving tegaserod. A review of this situation in 6197 patients taking the drug compared with 3660 on placebo has revealed similar prevalences of pelvic surgery (0.16 vs 0.19%; $p = 0.80$) and abdominal surgery (0.15 vs 0.19%; $p = 0.61$). However, cholecystectomy did appear to be more common in patients receiving tegaserod (0.13 vs 0.03%), although after further analysis this value dropped to 0.06% [50]. It is not clear as to why patients on tegaserod have a slight, nonsignificant increase in the incidence of gall bladder surgery, but a subsequent study that assessed gall bladder emptying and common bile duct diameter in IBS patients receiving tegaserod or placebo ($n = 30$) did not report any significant differences [51]. It therefore appears that gallstone disease is probably not associated with the administration of tegaserod.

As a proportion of IBS patients will be taking SSRIs and TCAs, it is important to assess the safety profile of tegaserod in such individuals. In a study that compared data from four pooled studies including 105 c-IBS patients on either tegaserod, placebo and a TCA and 252 patients on tegaserod, placebo and an SSRI, the frequencies of adverse events, including serious adverse events, were similar in both groups [52].

Up to March 2004, 21 cases of ischemic colitis have been reported worldwide in patients who were taking tegaserod therapy [53,54], which equates to an incidence of seven cases per 100,000 patient-years. However, the incidence of ischemic colitis in IBS patients not taking tegaserod has been reported as varying between 6.1 and 179/100,000, suggesting that this problem is more common in IBS patients irrespective of which medications they are taking [55–58]. Although ischemic colitis is associated with the consumption of some 5-HT_3 antagonists, it appears unlikely that tegaserod is associated with this particular adverse effect. This conclusion is supported by animal studies that have assessed

Highlights

- Irritable bowel syndrome (IBS) is a common condition with a significant health and economic impact.
- Until recently, treatment options have been limited.
- Serotonin and its receptors have an important role in regulating gastrointestinal (GI) physiology.
- Tegaserod is a selective serotonin (5-HT)$_4$ receptor agonist and acts by increasing small and large intestinal motility and secretion with a possible reduction in rectal sensitivity.
- It is effective treatment in patients with IBS who suffer from constipation, abdominal pain and bloating as well as patients with functional constipation.
- Its role in other functional GI diseases, such as functional dyspepsia, is still under investigation.
- Tegaserod has been shown to be remarkably safe.

the effects of serotonin modulators on mesenteric blood flow in rats and found that whilst alosetron and cilansetron (5HT$_3$ antagonists) caused a reduction in mean blood flow by 15 and 20%, respectively, tegaserod did not result in such an effect [59]. Furthermore, it has been shown that tegaserod does not produce vasoconstriction in isolated human mesenteric artery preparations [102].

Thus, the consumption of tegaserod does not appear to place the patient at risk for ischemic colitis, although the occurrence of severe abdominal pain along with bloody diarrhea should alert one to the possibility whether or not the patient is taking this drug.

Expert commentary

The development of drugs modifying the serotonin receptor is an advance in the treatment of IBS. However, these drugs have to be used in a specific subgroup of patients depending on their bowel habit, although this may not be of such concern with the 5-HT$_4$ agonists. The 5-HT$_4$ agonist tegaserod is clinically effective in women with nondiarrheal forms of IBS, has an excellent safety profile so far and it remains to be seen if it has utility in other functional disorders such as functional dyspepsia.

Outlook

It is now being recognized that IBS can, in some instances, be very severe and as a consequence adversely affect many aspects of the lives of sufferers. Its economic impact is also considerable both in terms of healthcare costs and loss of productivity resulting from absenteeism or inefficiency at work.

Therefore, there is a strong need for new pharmacological agents to help manage this condition and tegaserod represents a significant step forward. Hopefully further developments will be forthcoming as other potential therapeutic targets such as cortisol-releasing factor receptor are identified. However, the regulatory authorities appear to be setting especially high standards for pharmaceutical companies to surmount and this could be a problem.

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Affiliations

Anurag Agrawal, MRCP,
Clinical Research Fellow,
Wythenshawe Hospital,
Neurogastroenterology Unit, Southmoor Road,
Manchester, M23 9LT, UK
Tel.: +44 161 291 4191
Fax: +44 161 291 4184

Peter Whorwell, MD, FRCP,
Professor of Gastroenterology and Medicine,
ERC Building, First Floor, Wythenshawe Hospital,
Southmoor Road, Manchester, M23 9LT, UK
Tel.: +44 161 291 5813
Fax: +44 161 291 184