Drug Treatment of Irritable Bowel Syndrome with Serotonin (5-HT) Modulators

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Irritable bowel syndrome (IBS) is a common disorder affecting up to 20% (1) of the population and is associated with significant burden of illness (2). Having IBS is associated with decreased productivity, increased absenteeism and significantly greater rate of health care utilization (3). Despite the enormous economical, psychological, and social burdens imposed by IBS, its treatment remains unsatisfactory for many patients at the present time. Current treatment approach is at best, symptom based as there is no single available agent effective for treatment of the entire symptom complex (i.e., pain/discomfort and abnormal bowel habits) compared to placebo (4). Efforts in drug development in IBS are plagued by the incomplete understanding of the physiological alterations involved in its pathogenesis and the lack of consistent and reliable biological markers. These challenges are further compounded by the inexplicably high placebo effect found in IBS treatment studies. Despite these obstacles, recent advances in pharmacological modulation of gut related serotonin receptors appear to constitute a major promising therapeutic modality. This article is intended to provide information on the clinical significance of serotonin receptor modulation in the treatment of IBS.

BACKGROUND ON CURRENT IBS TREATMENT

IBS is defined as “a functional bowel disorder in which abdominal pain and/or discomfort is associated with defecation or a change in bowel habit, with features of disordered defecation and distention” (5). It is one of the most common disorders diagnosed by gastroenterologists and accounts for up to 12% of total visits to primary care providers (3). Although only a quarter of all persons with IBS seek medical care (6), there are between 2.4 and 3.5 million annual physician visits for IBS in the United States, during which 2.2 million prescriptions are written (7). The cost to society in terms of direct medical expenses and indirect costs associated with loss of productivity and work absenteeism is considerable (8). A recent study reported that the prevalence of IBS was 15 million and the annual direct and indirect costs in United States were 1.4 billion and 205 million.
dollars, respectively, with a total annual cost of almost 1.7 billion dollars (2).

Current therapy for IBS has been suboptimal, in part because the pathophysiologic mechanisms underlying this disorder have not been well understood and the placebo response is so pervasive (Talley Lancet 2001). A recent systematic review of randomized, placebo-controlled IBS treatment trials concluded that there are few agents with proven efficacy for selective symptoms associated with this disorder (4). Treatment approach is therefore, at best, symptom based as there is no single agent available for treatment of the multiple symptoms of IBS (i.e., pain/discomfort, abnormal bowel habits, bloating, etc.). Despite the enormous economic, medical and psychosocial burdens imposed by IBS, its treatment remains unsatisfactory. With recent advances in the understanding of the altered physiologic responses involving the brain-gut axis in IBS, drugs targeted at the modulation of serotonin (e.g. 5-HT₃ and 5-HT₄) receptor subtypes have emerged as promising therapeutic agents.

**SEROTONIN AND THE GUT**

There are now many known modulators of gut motility and/or sensation such as acetylcholine, norepinephrine, substance P, and vasoactive intestinal peptide, but serotonin which modulates both motility and sensation has recently gained the most attention as playing an important role in functional bowel disorders. The characterization of serotonin, as an enteric nervous system neurotransmitter was first described by Gershon, et al in 1965 (9) and has since become the subject of further investigation. Serotonin is found in both the brain and the gut, but it is now widely reported that 95% of the serotonin distributed in the body resides in the gut (10). Serotonin, also known as 5-hydroxytryptamine (5-HT), is synthesized from the amino acid tryptophan. Upon its release, it exerts its actions on 5-HT receptors before it is either quickly metabolized by the enzyme monoamine oxidase or undergoes reuptake by the presynaptic nerve terminal. Serotonin interacts with an array of receptors, some of which are presynaptic and others postsynaptic. Approximately 14 types of serotonin receptors have been identified in humans. The 5-HT₂C receptors are suspected in control of food intake as mice lacking this gene become obese from increased food intake and are also subject to fatal seizures. The 5-HT₃ and 5-HT₄ receptors are present in the gastrointestinal tract where they have functional roles in secretion, peristalsis, and sensation (11).

Clinically relevant gut-related 5-HT receptors (i.e., 5-HT₃ and 5-HT₄) are found on intrinsic (i.e., interneuronal and primary enteric) and extrinsic (i.e., vagal and spinal) afferent neurons, intestinal smooth muscle cells, and enterochromaffin cells (12–15). Mucosal stimulation in form of a meal stimulates the enterochromaffin cells to release serotonin. Subsequent receptor stimulation results in cephalad contraction and caudad relaxation of the smooth muscle, a process commonly referred to as the “peristaltic reflex.” (Figure 1) (11,16,17). 5-HT₃ receptors are also found in the brain particularly in limbic regions. There

![Tegaserod Mechanism of Action](image)

**Figure 1.** Proposed mechanism of action of tegaserod in modulating the “peristaltic reflex.” Relaxation of circular muscle is mediated by the inhibitory neurotransmitters: vasoactive intestinal peptide (VIP), pituitary adenylate cyclase–activating peptide (PACAP), and nitric oxide (NO). Contraction of circular muscle is mediated by the excitatory neurotransmitters: acetylcholine (Ach) and substance P (SP). (CGRP= calcitonin gene related product). Adapted from Grider JR, et al. (1).
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is a class of compounds collectively known as selective 5-HT₃ antagonists which includes Granisetron (Kytril®), Ondansetron (Zofran®) and Dolasetron (Anzemet®). These selective 5-HT₃ antagonists are currently approved by the Food and Drug Administration (FDA) for prevention and treatment of post operative nausea and vomiting as well as prevention and treatment of chemotherapy or radiation induced nausea and vomiting. Alosetron has been recently reapproved by the FDA under restricted use for the treatment of diarrhea-predominant IBS in females (see below).

SEROTONIN AND IBS

The putative role of serotonin in IBS has been supported by higher postprandial serum levels of serotonin in patients with the diarrhea predominant IBS compared to healthy controls(18). There is also evidence of an increased number of enterochromaffin cells which contain serotonin in the gut mucosa of patients with post-infectious IBS (19) and of a decreased number in patients with constipation (20). Further studies are needed to fully understand the pathophysiologic role of serotonin in IBS.

CLINICAL UTILITY OF GUT RELATED 5-HT RECEPTOR AGONISM

The 5-HT receptors in the lower gut are mainly comprised of 5-HT₃ and 5-HT₄ subtypes. When serotonin is released from enterochromaffin cells in the gut, it stimulates these receptors on primary intrinsic afferent nerves, which in turn stimulate both proximal excitation and distal inhibition of motor neurons, resulting in peristaltic contraction in the gastrointestinal tract. 5-HT₄ receptor agonists which stimulate the peristaltic reflex and accelerate gastrointestinal transit have been developed for the treatment of functional bowel disorders such as IBS with constipation.

Tegaserod

A partial 5-HT₄ agonist, tegaserod appears to be a promising agent for treatment of constipation-predominant IBS (21). It is categorized as a partial agonist since its affinity for the 5-HT₄ receptor is approximately 21% of that of naturally occurring serotonin (22). In the blood stream, tegaserod is predominantly protein-bound and due to its polarization, it does not cross the blood brain barrier to any significant extent. Approximately two-thirds of tegaserod and its metabolites are eliminated in the stool while the remaining one third undergoes renal excretion. Dose adjustments do not appear to be necessary in patients taking H₂-blockers or proton pump inhibitors (22). Dose adjustments also do not need to be made in patients with mild to moderate liver and renal impairment (23).

The potential promotility effect of tegaserod was first described in animal studies and later confirmed in human subjects. In these studies, tegaserod was shown to induce the peristaltic reflex in rat small bowel, guinea pig colon and human jejunum (16). In a rat model of postoperative ileus, tegaserod was able to increase both gastric and colonic motility (24). Its prokinetic effect on the human gastrointestinal tract was investigated in 24 constipation predominant IBS patients who underwent scintigraphic gastric emptying

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as well as small bowel and colonic transit studies in a prospective placebo controlled design. Tegaserod was associated with an acceleration of orocecal transit time in IBS patients (25). In addition to its prokinetic properties, tegaserod has been shown to have antinociceptive properties in several different animal studies (26,27). Tegaserod administration was associated with decreased visceromotor response during colorectal balloon distention in rats, without an effect on compliance (28). These data support the notion that tegaserod decreases visceral pain sensation.

Unlike other currently available medications for IBS with constipation, tegaserod appears to be effective in treating the multiple symptoms of IBS. Subject’s global assessment of relief of IBS symptoms, change in number of bowel movements, abdominal pain and bloating are all reportedly improved in female patients with constipation-predominant IBS taking tegaserod as compared to placebo (see Figures 2-4) (29). Tegaserod is currently under review for approval by the Food and Drug Administration.

Tegaserod has several unique safety advantages over other previously used serotonin modulators used to treat dysmotility of the gastrointestinal tract. For instance, cisapride (Propulsid), initially approved by FDA to treat GERD, was widely used to treat other disorders including esophageal dysmotility, gastroparesis, and chronic constipation. Because of its effect on QT interval prolongation and potential development of fatal cardiac arrhythmia, cisapride was removed from the U.S. market in July 2000. Unlike cisapride, tegaserod, does not appear to affect the QT interval based on evaluation of over 11,000 EKG tracings. Cisapride has a different molecular structure than tegaserod, and possesses both serotonergic stimulatory and inhibitory properties, while tegaserod is a specific 5HT₄ agonist and does not possess any antagonistic capability (22).

**Prucalopride**

As a full 5-HT₄ agonist, prucalopride has recently demonstrated efficacy in accelerating colonic transit time in functional constipation (30). Although this group is theoretically distinct from constipation-predominant IBS, there appears to be substantial overlap between these two constipation subgroups (31). The effect of this agent on abdominal pain has not been adequately investigated and will remain unknown until the temporary hold on clinical trials involving prucalopride, intended to investigate its potential intestinal carcinogenicity, is removed.

**CLINICAL UTILITY OF GUT RELATED 5HT₃ RECEPTOR ANTAGONISM**

5-HT₃ antagonists have been shown to increase colonic compliance (32), reduce postprandial rectal sensitivity and motility (33), enhance jejunal water and sodium absorption (34), and prolong left colon transit time (35).

**Alosetron**

As a selective 5-HT₃ antagonist, alosetron (Lotronex®), was the first U.S. FDA approved gut related serotonin modulator for the treatment of diarrhea-predominant IBS. It was shown to be effective in relieving pain, nor-
malizing bowel frequency, and reducing urgency in female patients with diarrhea-predominant IBS (36).

The reasons for a gender difference in the response to this agent are not completely understood. Interestingly, similar gender specific results have been observed in functional dyspepsia (37). The serum concentration of alosetron is 30%–50% higher in females but this seems unlikely to explain the observed gender specific variance (17). While there may be central and/or peripheral mechanisms to explain these gender differences, current efforts are aimed at exploring potential gender related differences in brain activation patterns {Naliboff abstract in Gastro 2002 from DDW}. Recent brain imaging studies have demonstrated that brain activation in response to rectal distension differs in patients with IBS compared to healthy individuals (38,39,40). In addition, brain activation in response to colorectal distension has been shown to be different in non-constipated IBS patients taking alosetron compared to those taking placebo (41).

Alosetron was previously withdrawn from use for IBS before its recent re-approval under restricted use. This was mainly due to its adverse effects profile which included ischemic colitis and constipation. Acute ischemic colitis was observed in 0.1%–1% of patients receiving the medication which ultimately led to its voluntary withdrawal from the market in November of 2000. There had been 84 reported cases of ischemic colitis and 113 cases of serious complications from constipation. Of those with ischemic colitis, 54 were hospitalized, 11 needed surgery and 2 died (42). The causal nature of this poorly understood association is debatable and has been challenged by recent data showing a 3-1/2 fold increase in the baseline incidence of colonic ischemia in the 5HT₃ antagonist naive IBS population as compared to age and sex adjusted rates for the general population (43). Of the constipation cases, 83 were hospitalized, 34 had surgery and 2 died (42). The complications due to severe constipation may in part be due to inappropriate use of alosetron in a subgroup of IBS patients (i.e. non-diarrhea-predominant IBS). On June 7th, 2002, the FDA announced approval of a supplemental New Drug Application (sNDA) that allows restricted marketing of Lotronex (alosetron hydrochloride), to treat only women with severe diarrhea-predominant irritable bowel syndrome (IBS). The approved sNDA for Lotronex includes a risk management program to ensure patients and physicians are fully informed of risks and possible benefits of alosetron. Specifically, the Lotronex Risk Management Program includes the following components(42):

- Requirement for physicians to provide information on the risks and benefits of alosetron treatment, and to provide patients with a copy of the FDA-approved Medication Guide.
- Requirement for patients to read and sign a Patient-Physician Agreement before receiving their initial prescription for alosetron.
- Restricted prescription privileges to those physicians who self attest to their qualifications with diagnosing and treating IBS and its potential complications. In addition, enrolled physicians will have agreed to report serious adverse events to GSK at 1-888-825-5249 or to FDA at 1-800-FDA-1088
- Requirement for pharmacists to fill only prescriptions that display a prescribing program sticker affixed by an enrolled physician, and to give patients

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a copy of the FDA-approved Medication Guide every time they dispense the drug.

These features have been instituted to secure patient safety while at the same time ensuring access to those in need of its therapeutic benefit. For an in depth review of the current FDA recommendations, please log on to: www.fda.gov/cder/drug/infopage/lotronex

References
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42. FDA Lotronex information. *FDA* Website. 6-7-2002. 6-25-2002. Electronic Citation.


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