



## Review Article

# 5HT<sub>3</sub> Antagonists a Newer Concept in Treatment of IBS-D in Females: A Review Article

**Rasmirekha Behera\***

Professor Pharmacology, I.M.S &amp; SUM Hospital, Bhubaneswar, India

\*Corresponding author: Rasmirekha Behera, Professor Pharmacology, I.M.S &amp; SUM Hospital, Bhubaneswar, India

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## Abstract

Irritable Bowel Syndrome (IBS) is a functional bowel disorder in which recurrent abdominal pain and/or discomfort is associated with a change in bowel habit. IBS is subtyped based on predominant bowel habit: IBS with constipation (IBS-C), diarrhea (IBS-D) and mixed pattern (IBS-M). Supportive symptoms of IBS include change in frequency of stool, abnormal stool form, straining with defecation, urgency, feeling of incomplete defecation, passage of mucus and bloating. Females diagnosed with IBS seek more health care service compared to men. Symptoms of IBS greatly impact the Health Related Quality Of Life (HRQOL) of the affected individuals and is associated with a significant healthcare and economic burden. Several studies have reported that women have a higher prevalence of pain. 5-HT also known as serotonin is an immunoregulatory factor and neurotransmitter. 5-HT has certain specificity and is of great significance in the physiological and pathological processes of the human body, such as thermoregulation, the regulation of blood pressure, the production of algnesia, as well as nausea and vomiting. 5-HT is also an important signal in maintaining intestinal balance i.e. it regulates the intestinal motility, sensation and secretion of intestinal glands. The sex and gender related differences in disease prevalence, symptom presentation, pathophysiology treatment response of different drugs varies. Hence this article will review the concept of 5-HT<sub>3</sub> antagonists in treatment of females diagnosed with IBS-D.

**Keywords:** Irritable bowel syndrome; Abdominal pain; Rome criteria; IBS-D; 5HT<sub>3</sub> Antagonists; Alosetron; Ondansetron; Cilansetron

## Introduction

Irritable Bowel Syndrome (IBS) is a functional disorder of the gastrointestinal (GI) tract, affecting between 5 and 20% of the general population [1-3]. The condition is characterized by abdominal pain and disturbed bowel habit [4]. IBS sufferers report lower thresholds of pain during colonic, rectal, and foregut stimulation [5,6]. 5-Hydroxytryptamine (5-HT) plays an important role in GI motility and sensation, and abnormal levels have been shown in individuals with IBS [7]. Patients with IBS are subdivided on the basis of their bowel symptoms into 4 subgroups: IBS with constipation, IBS with diarrhea (IBS-D), alternating or mixed IBS, and un-subtyped IBS, with up to 40% suffering from the IBS-D form [8]. The diagnosis of IBS is based on the symptom

based classification system known as the Rome criteria [9]. The diagnostic criteria the changes have included the Rome I criteria, which were revised to the Rome II guidelines and Rome III allow for ease of diagnosis. The Rome III diagnostic criteria simply state that a patient must have recurrent abdominal pain or discomfort at least 3d/month in the last 3 months and there is improvement with defecation, associated with a change in stool frequency or onset associated with a change in stool consistency [10,11]. Rome IV defined Irritable Bowel Syndrome (IBS) as a functional bowel disorder in which recurrent abdominal pain is associated with defecation or a change in bowel habits. Disordered bowel habits are typically present (i.e., constipation, diarrhea or a mix of constipation and diarrhea), as are symptoms of abdominal bloating /distension. Symptom onset should occur at least 6 months prior to diagnosis and symptoms should be present during the last 3 months. The Rome IV criteria differ from Rome III criteria in several distinct ways. The term discomfort was removed from

the current definition and diagnostic criteria. Additionally, based on a study of IBS patients who reported wide variations in their understanding of these terms, it is unclear whether the distinction between pain and discomfort is qualitative and quantitative [12]. Drugs acting on 5-HT receptors have the potential to ameliorate the smooth muscle spasm, abdominal pain and change in bowel habit that IBS patients experience [13,14].

This article will review the current concept of 5HT<sub>3</sub> antagonists in treatment of female patients diagnosed with irritable bowel syndrome with diarrhea.

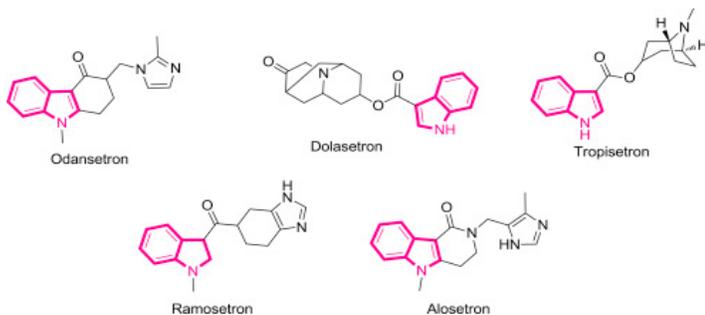
### 5-HT Receptors and 5-HT<sub>3</sub> Receptor Antagonists

5-Hydroxytryptamine (5-HT) receptors are classified into seven subtypes and 5-HT<sub>3</sub> receptors are known to be localized on intestinal plexuses, sensory nerves, sympathetic and parasympathetic nerves, to stimulate the release of neurotransmitters. 5-HT acts on the 5-HT<sub>3</sub> receptors on the parasympathetic ganglia to cause smooth muscle contraction and increased intestinal secretion by stimulating nerve terminal acetylcholine release [15]. The serotonin 3 receptor (5-HT<sub>3</sub>R) is an ion channel receptor found in the central and peripheral nervous systems [16]. 5-HT<sub>3</sub>R is of great significance for the transmission of the information of digestive tract activity, regulation of intestinal peristalsis and secretion of intestinal glands [17]. There are different clinical manifestations when 5-HT combines with different receptors. 5-HT mainly combines with 5-HT<sub>3</sub>R in patients with D-IBS, which leads to some intestinal dysfunctions, such as visceral hypersensitivity and abdominal discomfort [18]. Most of 5-HT in the gastrointestinal tract is synthesized and stored by the chromaffin cells of the intestinal mucosa [19]. When the intestinal tract is stimulated, it causes an increase of 5-HT in the chromaffin cells, and the combination of 5-HT and 5-HT<sub>3</sub>R which is in the nerve endings of exogenous primary afferent neurons, so that the visceral afferent nerve and the intestinal nervous system are in a hypersensitive state which result in symptoms, such as diarrhea, abdominal pain and discomfort [20]. 5-HT<sub>3</sub> receptor antagonists inhibit the activation of 5-HT<sub>3</sub> receptors on the mucosal processes of the intrinsic and extrinsic primary afferent neurons and attenuate motor and secretory reflex activity while decreasing the depolarization of extrinsic sensory neurons that transmit signals to the brain, thereby inhibiting the sensory signals leading to abdominal pain and discomfort and are likely directly or indirectly related to pathophysiology of IBS [20].

### 5-HT<sub>3</sub> Receptor Antagonists and IBS-D

Serotonin (5-HT) is a key neurotransmitter and a signaling

molecule that plays an important role in sensation, secretion and absorption [21]. Several large clinical trials have demonstrated that serotonin receptor 5-HT<sub>3</sub>R antagonists, like alosetron, cilansetron and ramosetron are among the most effective therapeutic options to date for both male and female IBS-D patients [22]. The other compounds granisetron and ondasetron are indicated for the treatment of nausea and vomiting and are not as potent in the lower GI tract as alosetron. The 5-HT<sub>3</sub>R antagonists alleviate specific IBS symptoms, such as frequent bowel movements, feeling of urgency, and chronic abdominal pain and discomfort, acting through central and peripheral mechanisms. Symptom improvement associated with an interaction with dopamine, cholecystokinin, glutamate, acetylcholine and GABA [23]. Inhibition of the spinal cord c-fos expression by 5-HT<sub>3</sub>R antagonists in response to noxious CRD suggests that 5-HT<sub>3</sub>R plays a role in the transmission of noxious information within the spinal cord [24]. The expression levels of 5-HT and 5-HT<sub>3</sub> receptors in the intestinal mucosal tissues are significantly higher in female patients diagnosed with IBS-D than the male patients, Female with IBS-D, ≤40yrs, history of gastrointestinal infection are also express higher levels of 5-HT and 5-HT<sub>3</sub> receptors than that of male patients [25]. The more potent effect of the 5-HT<sub>3</sub> receptor is to activate extrinsic sensory nerves in the gut. The release of 5-HT from EC cells can stimulate 5-HT<sub>3</sub> receptors on vagal afferents, which may result in nausea and possibly nonpain-full GI sensations such as bloating and fullness. The 5-HT<sub>3</sub> antagonists thereby can reduce these sensory symptoms. The effect on visceral hypersensitivity may be due to both its peripheral effects on mechano-elastic properties [26]. Chemically, alosetron is designated as 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyridol[4,3-b]indol-1-one monohydrochloride. Alosetron is achiral and has the empirical formula: C<sub>17</sub>H<sub>18</sub>N<sub>4</sub>O.HCl, representing a molecular weight of 330.8. Alosetron hydrochloride (HCl) is a potent selective 5HT<sub>3</sub> receptor antagonist [27]. Chemically cilansetron has been represented as 10-R(-)-5,6,9,10-tetrahydro-10-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-pyrido[3,2,1-jk}carbazol-11(8H)-1 monohydrochloride monohydrate. Cilansetron has a high affinity for the 5-HT<sub>3</sub> receptor and has been shown to be more potent than ondasetron both *in vitro* and *in vivo* [28,29]. Competitive antagonism achieved by Cilansetron at the 5-HT<sub>3</sub> receptors *in vitro* is ten times greater than that of ondansetron [28]. Ondansetron's potency in blocking the 5-HT<sub>3</sub> receptor is 3-10 times lower than alosetron [30]. Ramosetron is another 5-HT<sub>3</sub> receptor antagonist proven effective in IBS-D [31] (Figure 1).



**Figure 1:** Chemical Structures of 5-HT<sub>3</sub> Antagonists.

### Clinical Efficacy of 5-HT<sub>3</sub> Antagonists in IBS-D Females

5-HT<sub>3</sub> Antagonist Alosetron is indicated for women with severe diarrhea-predominant irritable bowel syndrome (IBS-D) who have: chronic IBS symptoms (generally lasting 6 months or longer), not responding adequately to conventional therapy. Severe IBS-D includes: diarrhea associated with frequent and severe abdominal pain/discomfort or frequent bowel urgency or fecal incontinence and disability or restriction of daily activities due to IBS. Alosetron given as 0.5 and 1mg tablet for oral administration. The drug is rapidly absorbed after oral administration and the absorption is decreased about 25% with food. The half-life of alosetron is 6-10 hrs. Plasma concentrations are 30-50% lower and less variable in men compared with women given the same oral dose. The drug clearance is 28% lower in women resulting approximately 30-50% higher concentration in women compared with men for a given dose [32,33]. In February 2000, Alosetron was approved by the FDA for the treatment of IBS-D in women. Later that year in November 2000, alosetron was removed from the market owing to concerns about ischemic colitis and serious complications of constipation [34]. In June 2002, the FDA announced the approval of a supplemental New Drug Application (sNDA) that allowed alosetron hydrochloride to treat only women with severe diarrhea-predominant Irritable Bowel Syndrome (IBS) [35]. Since alosetron's withdrawal in 2000 and reintroduction in 2002, several clinical trials have demonstrated the efficacy of alosetron in severe IBS-D. The efficacy of alosetron for treatment of IBS at a 1 mg dose BD was investigated in women with severe IBS-D in 12 week randomized placebo controlled studies by Lembo, et al. [36,37]. All of the ischemic colitis cases are associated with alosetron were reversible without long term sequelae. Alosetron is available for treatment of severe IBS-D in women who failed conventional therapy [38]. Cilansetron 8 mg orally given thrice daily had clear effects on colonic motility and perception of visceral Distension. Cilansetron also had a consistent moderate dose dependent inhibitory effect on total colonic transit [39,40].

### Future Targets in Treatment of IBS

The pathophysiological mechanism of IBS may be explained by multiple factors like psychological, genetic factors, chronic stress, altered brain-gut axis mediated by both central and peripheral mechanism with evidence of inflammation and infection [41]. In addition significant molecular alterations in the gut with relation to SERT expression and 5-HT signaling affecting 5-HT availability may also be playing a role in the development of the symptom complex of IBS [42]. Particularly important for gut function and regulation are the 5-HT<sub>1B</sub>, 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors. Agents targeting the serotonergic receptors in combination (5-HT<sub>4</sub> agonist, 5-HT<sub>3</sub> antagonist agents), opioid receptor agonists and antagonists, neurokinin receptor agents, chloride channel activators and neurohormonal modulators [43]. The 5-HT<sub>7</sub> and 5-HT<sub>2B</sub> receptors are yet another potential serotonergic potential serotonergic target for future IBS treatment [44]. The 5-HT<sub>7</sub> receptors play an important role in regulating smooth muscle relaxation in the GI and nociceptive pathways [45]. One of the newly targeted classes of drugs for the treatment of visceral pain are benzodiazepine (BZD) receptor modulators. BZD receptors are located in subcortical and hypo-thalamic regions and appear important in controlling autonomic function, such as motor and sensory activity of the gut [46]. NK1R antagonist reduced activation of both the interoceptive afferent and emotional arousal network in response to noxious and non-noxious visceral stimulus in female IBS patients, causing a large decrease in pain induced negative effect and decreased anxiety and pain rating. This positive correlation suggests a potential for use of NK1R antagonists in IBS patients to decrease pain related distress [47]. Toll like Receptors (TLRs) have been localized on mucosal surfaces including the colonic epithelial cells and their expression is increased in the colonic mucosa of rat models of visceral hypersensitivity and mucosal biopsies from IBS patients [48]. TLRs are activated by various by various bacterial and viral cell components [49].

### Conclusion

The irritable bowel syndrome with diarrhea predominance are being treated with different types of drugs. Treatment options are considered depending upon symptom relief combined with acceptable adverse event profile. Recent progress has been made drugs targeting specific serotonergic subtypes. These agents typically provide relief from multiple symptoms of either IBS with constipation predominance (IBS-C) or IBS-D [50,51]. Alosetron, a selective 5-HT<sub>3</sub> antagonist that impedes intestinal transit and prolongs colonic transit time was the first drug to demonstrate global symptom efficacy in nonconstipated IBS patients. Alosetron provided adequate relief of abdominal pain and discomfort and Improved bowel symptoms when compared with

placebo; however, these beneficial effects were seen exclusively among women [52]. Cilansetron is a novel 5-HT<sub>3</sub> antagonist that has been shown to improve multiple IBS-D symptoms, including abdominal pain, stool frequency and urgency, as well as health related quality of life. Among alosetron and cilansetron only cilansetron is effective in relieving symptoms in both men and women with IBS-D [53]. Hence 5-HT<sub>3</sub> antagonist based therapies require the implementation of a risk management plan, as ischemic colitis and complications of constipation may occur [54].

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