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EDITORIAL

Systematic review of modulators of benzodiazepine receptors in irritable bowel syndrome: Is there hope?

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Abstract

Several drugs are used in the treatment of irritable bowel syndrome (IBS) but all have side effects and variable efficacy. Considering the role of the gut-brain axis, immune, neural, and endocrine pathways in the pathogenesis of IBS and possible beneficial effects of benzodiazepines (BZD) in this axis, the present systematic review focuses on the efficacy of BZD receptor modulators in human IBS. For the years 1966 to February 2011, all literature was searched for any articles on the use of BZD receptor modulators and IBS. After thorough evaluation and omission of duplicate data, 10 out of 69 articles were included. BZD receptor modulators can be helpful, especially in the diarrhea-dominant form of IBS, by affecting the inflammatory, neural, and psychologic pathways, however, controversies still exist. Recently, a new BZD receptor modulator, dextofisopam was synthesized and studied in human subjects, but the studies are limited to phase Ⅱb clinical trials. None of the existing trials considered the neuroimmunomodulatory effect of BZDs in IBS, but bearing in mind the concentration-dependent effect of BZDs on cytokines and cell proliferation, future studies using pharmacodynamic and pharmacokinetic approaches are highly recommended.

Key words: Benzodiazepines; Benzodiazepine receptor modulators; Dextofisopam; Irritable bowel syndrome; Systematic review

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PRESENT KNOWLEDGE ON IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is well-defined as a functional abdominal disorder categorized by intestinal pain or distress, and changes in bowel habits without recognizable malefactor[1]. The symptoms are either constant or intermittent and vary from diarrhea or constipation, hypersecretion of colonic mucus, flatulence, to the sensation of weakness or depression[2]. The pathophysiology of IBS is in some ways multifaceted, yet no consistent biomarker, anatomic, or biochemical alteration has been found[3]. Several pathophysiologic paths have been deliberated for elucidation leading symptoms such as motor and sensory dysfunction, neuroimmune mechanisms, dysregulation of mucus secretion, emotions, colonic motility, enteric nervous system, changes in intraluminal situation and visceral feeling[4]. Gut motility turbulence creates

different bowel behaviors and IBS subtypes, according to these outlines they are presented as IBS-D (diarrhea-predominant), IBS-C (constipation-predominant) and IBS-M (mixed)[5].

Earlier, the role of parasympathetic and hormonal provocations in motor activity of some portions of the gut was demonstrated[2]. The most important observation is well-thought-out visceral hypersensitivity as a substantial element in combination with fluctuations in gastrointestinal (GI) motility and secretory activity[6]. Recent epidemiological findings further underline the central and peripheral disease activators or exacerbations as psychosomatic contributions[7-9] and gastroenteric infections[10]. In addition, the brain-gut axis endorses the strong relationship between the brain and the gut *via* neural, immune and endocrine paths which is affected by neuroimmunological or neuroendocrinological stressors[11,12]. A summary of the pathophysiological mechanisms involved in IBS are presented in Table 1.

Contemporary treatment approaches depend on patients' signs and symptoms as well as comorbid conditions. Other than lifestyle and dietary changes, psychotherapy and psychopharmacological treatment, prokinetics (dopamine antagonists, 5-HT3 antagonists and/or 5-HT4 agonists), antispasmodics, sedatives and tranquilizers, antibiotics[13], probiotics[14], fecal bulking agents and complementary and alternative therapies are now considered as symptomatic treatment[2,15]. Prokinetics and antispasmodics[16] are usually used in IBS-C type, while patients with IBS-D benefit from opioid agonists, anticholinergics, and 5-HT3 antagonists. Treatment options are summarized in Table 2.

Despite the wide range of medications and the high prevalence of the disease, to date no completely effective remedy is available. Therefore, investigations in this area should be continued. Pain relief is one of the challenges in the management of IBS as existing visceral analgesics have significant adverse effects and there is a balance to be struck between their usage and side effect profiles. Although various classes of drugs are used for visceral analgesia or other symptoms of IBS such as 5-HT3 antagonists[17], tricyclic antidepressants (TCAs)[18], selective serotonin reuptake inhibitors (SSRIs)[19,20], gabapentinoids, corticotrophin-releasing factor receptor-1 antagonists[21], β3 adrenoceptor agonists[21], somatostatin, and N-methyl d-aspartate receptor antagonists, melatonin[22], and sildenafil[23], there are hopes for new drug investigations. In accordance with this idea, the efficacy of benzodiazepines (BZD) receptor modulators is being determined in ongoing phase Ⅲ clinical trials[24].

Bearing in mind the new advances in drug classes, and the special attention paid to new BZDs, we intend to study the promising advantageous effects of BZDs from diverse themes including neuroimmunology, anxiolytic, and visceral pain.

In the present review, the most relevant articles on the subject were searched using PubMed, Scopus, Web of Science, and Google Scholar databases up to February 2011. MeSH terms including irritable bowel syndrome, benzodiazepines, benzodiazepine receptor modulators, and gabamimetics were used as search terms. The search was limited to English articles only. All non-clinical and clinical studies were included. The search resulted in 69 papers on the role of benzodiazepines in IBS; of these, after thorough evaluation and the omission of duplicate or non-relevant articles, 10 papers were included and evaluated in detail.

Table 1 A summary of the pathophysiological mechanisms of irritable bowel syndrome

Mechanism	Description
Visceral hypersensitivity	↓ Threshold of visceral perception, hyperalgesia; ↑ Viscerosomatic referral areas
Modulation of CNS	Altered activation in reaction to rectosigmoid stimuli; fail to inhibit pain perception; activation of pain facilitatory pathways
Stress	Changes in visceral perception and neuro-endocrine responses to stressor
Infection	↑ Incidence after bacterial, viral, parasitic infections
Inflammation	Increased inflammatory cytokines; decreased anti-inflammatory cytokines
Serotonin	Influencing gut motility, sensation and secretion; altered serotonin signaling in IBS
Genetic factors	Familial clustering

CNS: Central nervous system; IBS: Irritable bowel syndrome.

FINDINGS

Visceral pain

Visceral sensitivity and abdominal pain are dual warning signs of IBS but are not present in all patients[25,26]. These patients show diminished visceral perceptual edges, augmented viscerosomatic referral area and larger sensory scores[26]. The regulation of sensory neurotransmission in the gut is indicative of a satisfactory goal in the treatment of IBS. Incidentally, sensory afferents from the intestine have been examined in preclinical and clinical models.

New approaches in brain imaging provided new understandings of the likeness between IBS symptoms and different non-gastrointestinal disorders which pointed to the reformed sense of visceral drive in the central nervous system (CNS) in IBS[27-29]. There is the possibility that the CNS fails to excite pain inhibitory pathways or activates pain facilitatory trails in patients with IBS[30]. As a consequence of the convenient connection between the brain and gut *via* neural, immune, and endocrine pathways (Figure 1), the involvement of the CNS in the pathophysiology of IBS is prominent[8,11,31-36]. Several parts of the CNS including cerebral regions, dorsal vagal nuclei, as well as the enteric nervous system contain γ-amino butyric acid (GABA) receptors[37,38]. Vagal fibers influence migrating motor complex activity *via* the enteric nervous system[38]. With the intention of reducing visceral hypersensitivity and the consequential pain, different pathological and pharmacological tactics have been used, for instance motility modulators (SSRIs), and special receptors or ion channels on visceral afferent pathways.

Table 2 Common therapeutic modalities

Therapeutic approach	Mechanism	Example of drugs	Therapeutic issues
Cholinergic system	Muscarinic receptor antagonists	Hyoscine, cimetropium, zamifenacin, solifenacin	Limited value, limited side effects, no interaction
Serotonin system	5-HT receptor antagonists	Alosetron, tegaserod, renzapride	Safe on cardiovascular system, anxiolytic, psychological side effects, adverse effects
Antidepressants (SSRIs, TCAs, SNRIs)	Neurotransmitter reuptake inhibitor	Paroxetine, desipramine, venlafaxine	Limited use, serious side effects, limited efficacy
Adrenergic agents	α, β3 adrenergic agents	Clonidine, solabegron	Limited use, side effects, limited efficacy
Corticoid system	CRF antagonists	A-Helical CRH9-41	Limited use, under investigation
Cholecystokinin		Loxiglumide, dexloxiglumide	Limited use, under investigation
Neurotrophins	Enhance neuron survival and development	NT3	Expensive, under investigation, limited use
Sleeping process	Sleep regulator	Melatonin	Limited use
BZD receptor modulators		Gabapentin, dextofisopam, pregabalin	Side effects, limited use, under investigation
Guanylate cyclase-c agonists	Activates guanylate cyclase-c receptor in enterocytes	Linaclotide	Limited use, well toleration, minimal side effects, under investigation
Opioid system	Modulating visceral nociception	Asimadoline, naloxone, naltrexone	Limited central side effects, good efficacy
Neurokinin antagonists	Affect colonic motility	Ezlopitant, nepadutant	Under investigation

SSRIs: Selective serotonin reuptake inhibitors; TCAs: Tricyclic antidepressants; SNRIs: Serotonin norepinephrine reuptake inhibitors; NT3: Neurotrophine-3; BZD: Benzodiazepine; 5-HT: 5-hydroxytryptamine; CRF: Corticotrophin-releasing factor.

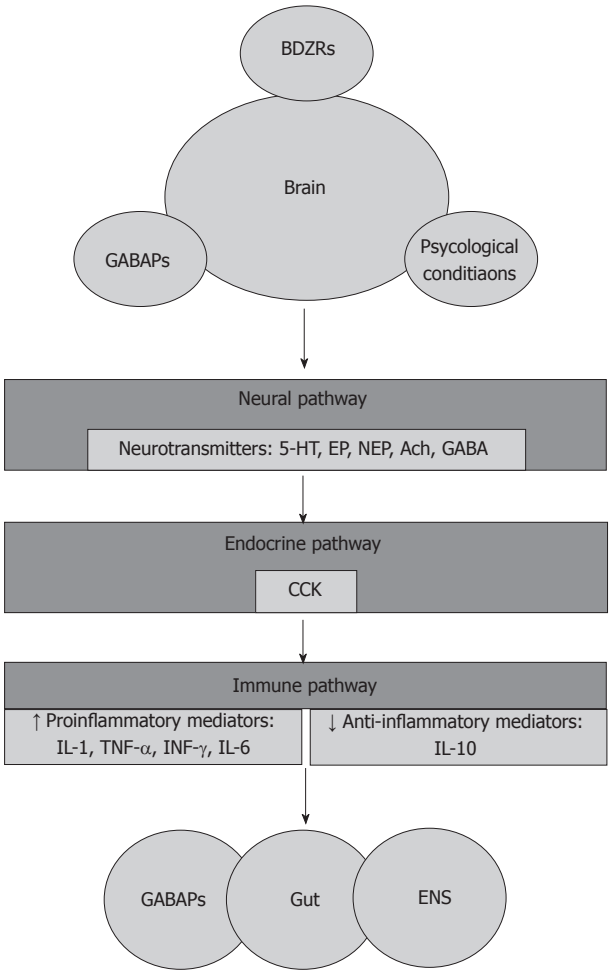

Figure 1 The brain-gut axis. BDZRs: Benzodiazepine receptors; GABARs: γ-aminobutyric acid receptors; 5-HT: 5-hydroxytryptamine; EP: Epinephrine; NEP: Norepinephrine; GABA: γ-aminobutyric acid; Ach: Acetylcholine; CCK: Cholecystokinin; IL-1: Interleukin-1; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; IFN-γ: Interferon-γ; IL-10: Interleukin-10; ENS: Enteric nervous system.

One of the newly targeted classes of drugs for the treatment of visceral pain, BZD receptor modulators, reduce sensitivity and ache perception. Consistent with the promising effects of these modulators, dextofisopam the R enantiomer of tofizopam was developed for the management of IBS-D[39].

BZDs interact with GABA receptors which exist in the CNS and influence the autonomic nervous system, dorsal vagal nuclei, and the enteric nervous system. Vagal fibers affect migrating motor complex movement by the enteric nervous system[40].

BZD receptors were identified in subcortical and hypothalamic regions and appear important in controlling autonomic function[41], such as motor and sensory activity of the gut[42]; nevertheless they do not exist in the gut[43]. Animal studies on the R-enantiomer of tofisopam (the non-sedating anxiolytic), dextofisopam, showed encouraging results in reducing colonic motility and visceral sensitivity with little effect beneath basal conditions[44]. Leventer *et al*[45] in a phase Ⅱb study of dextofisopam for 12 wk in 140 patients with IBS observed overall symptom relief (primary end point) in 57% of patients as compared with placebo (43% of patients). Although dextofisopam improved stool consistency in men and women, the recurrence rate was only decreased in females. This occurred within one week. The most common side effects were headache and abdominal pain (in 12% of patients in comparison with 4% in the placebo group) which was comparable to placebo. No benefit on bloating, partial defecation, or hospital anxiety and depression scale scores was observed[45]. Interestingly, dextofisopam showed a slight influence on basal GI movement in animals, while after induction of hypermotility, it showed more efficacy[46].

There are a few studies on other BZDs in IBS patients. Castedal *et al*[40] showed a small effect of midazol-

am on small bowel motility using manometry, however, phase Ⅲ related retroperistalsis did not work.

Other than the anxiolytic effect of BZDs, their effect on GABA may be constructive. Two antiepileptic drugs, gabapentin and pregabalin are effective in neuropathic pain. They equally affect GABA receptors in the CNS and increase their binding affinity for endogenous GABA ligand and elevate chloride ion efflux. In this regard, numerous studies assessed the beneficial influence of pregabalin and gabapentin on visceral pain.

Gabapentin, an amplifier of GABA transmission, prevents central neurotransmitter release by impeding α_2-δ subunits of voltage-dependent calcium channels[47,48]. Gabapentin has favorable effects on neuropathic pain and hyperalgesia[49,50]. Lee *et al*[51] demonstrated the effect of gabapentin in reducing human experimental hyperalgesia. They randomized 40 IBS-D patients to receive gabapentin 300 mg/d and then 600 mg/d for 5 d. Gabapentin reduced rectal sensory thresholds by decreasing rectal sensitivity to expansion and improving rectal compliance.

Although the structure of pregabalin is related to GABA, it is inactive at GABA and BZD receptors. It strongly attaches to the α_2-δ subunit of voltage-dependent calcium channels and reduces calcium arrival at nerve endings[52] and results in the release of excitatory neurotransmitters (noradrenaline, glutamate, substance P, and calcitonin gene-related peptide) decreasing their involvement in pain pathogenesis[53]. Accordingly, pregabalin reduces normal colonic pain responses and colonic hyperalgesia in a dose-dependent manner in animal studies[54,55]. In animal studies, pregabalin reduced viscerosomatic and autonomic responses caused by colorectal distension resulting in visceral pain relief[56]. In addition, the effect of $GABA_B$ receptors in visceral pain was confirmed[57]. In another preclinical study, pregabalin reduced both visceral allodynia and hyperalgesia with no change in basal sensitivity. Houghton *et al*[58] randomized 26 hypersensitive IBS patients to increasing doses of pregabalin for 3 wk or placebo. They reported significant increases in sensory thresholds from baseline for first defecation and pain, and rectal compliance. In IBS patients, pregabalin restored sensory thresholds to normal levels[58].

Neuroimmunology

Recent approaches to the pathophysiology of IBS have changed from spastic colitis to mucosal immune activation[59,60] and inflammation[61] which is supported by animal studies[62,63]. Generally, in 7%-30% of patients, there is a history of recent bacterial gastroenteritis[64]. Failure to reduce the inflammatory reaction to infection may increase cytokines or special inflammatory cells[65]. There is a discrepancy between pro-inflammatory and anti-inflammatory cytokines in IBS. The influence of the neuroimmune system in the pathogenesis can be elucidated by an augmented number of activated mast cells in the vicinity of colonic nerves, decreased interleukin-10/interleukin-12 (IL10/IL12) ratio and changes in local defense mechanisms in the sigmoid and colonic mucosa in IBS[65-67]. In fact, a number of investigators have proposed low-grade inflammation in IBS which is defined as infiltration of T lymphocytes, mast cells, and enteroendocrine cells into colonic mucosa with mast cells priority[68]. Excessive production of tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ), a trend toward excessive production of interleukin-6 (IL-6), and a defect in the production of interleukin-10 (IL-10) were reported in IBS[15,69]. In accordance with cellular infiltrations, increased levels of interleukin-1β (IL-1β), IL-6, INF-γ and TNF-α, and an abnormal ratio of IL-10/IL-12 in IBS patients were observed[68].

There is a counteraction between the endocrine, central and autonomic nervous and immune systems which is mediated by signal transduction, cytokines and mediators[70]. BZD receptors in both central and peripheral forms and their ligands create a regulatory network between anxiety and the immune system[71]. Central BZD receptors located in the CNS and their activation affects GABA binding to $GABA_A$ receptors which regulates chloride flux[72]. The peripheral receptors are located in peripheral tissues and are involved in cell proliferation, heme biosynthesis, cholesterol transport and immunomodulation[73]. Peripheral BZD receptors have been identified on immune cells such as macrophages, neutrophils, leukocytes, and lymphocytes and may have a crucial role in the relationship between the CNS, behavior and immunity[74-78]. Activation of cell growth and DNA synthesis requires nanomolar concentrations of BZDs, thus inhibition of cell proliferation is subject to micromolar concentrations of these compounds[79]. Of BZDs, diazepam and tofizopam bind to both types of receptors[80,81]. Kalashnikov *et al*[70] in an *in vitro* study confirmed the inhibitory effect of diazepam on cell proliferation at high doses, while tofizopam enhanced cell proliferation at low and moderate doses. In addition, they found dose-dependent suppression of TNF-α production with both diazepam and tofizopam and a wide range of effects of tofizopam on IL-2 production (enhancement to suppression), while diazepam suppressed IL-2 production[70].

Psychotherapy

A history of psychiatric complaints or mental instabilities in patients is a key factor in IBS and some studies have indicated extensive occurrence of psychiatric disorders in IBS[82,83]. Similarly, the mental state of the patient affects bowel symptoms and may relieve symptoms[84]. The most dominant psychological features of IBS patients are hypochondriasis, depression, anxiety, obsession, and neuroticism[84]. Whitehead *et al*[85] demonstrated higher scores of psychopathology in IBS patients. High comorbidity exists between functional bowel and stress-related psychiatric disorders[86,87]. Stress precipitates or exacerbates IBS[88].

Since the possibility of comorbidity with mood disturbances such as depression and anxiety is high in IBS, almost all patients with IBS may benefit from TCAs or BZDs. These agents may also decrease pain perception.

Guidelines of the Britain Society of Gastroenterol-

ogy and the American Gastroenterology Association endorse psychotherapeutic interventions for severe forms of IBS[89,90] to relieve psychological, visceral, and somatic symptoms. Overall benefit was found in IBS patients following psychological treatments in a meta-analysis[91]. In these conditions, combining psychotherapy with psychopharmacological treatment is effective[92]. Studies show that the two most common antidepressant and anxiolytic classes of drugs, TCAs and SSRIs, are effective in symptom relief[93]. Compared to TCAs, SSRIs have fewer side effects but do not improve bloating or visceral pain[93,94]. BZDs are used routinely in anxiety disorders but their efficacy in symptom relief of IBS is under debate[90].

Clouse *et al*[95] studied the effect of antidepressants in a retrospective study in 138 IBS patients. They evaluated patients' response to a wide range of antidepressants such as TCA (amitriptyline, doxepin, *etc*.), trazodone, amoxapine, alprazolam and thioridazine at lower doses than used for affective disorders. They reported significant responses regardless of the presence or absence of psychiatric illness .

CONCLUSION

In the present work, all possible beneficial effects of BZD receptor modulators in IBS from the view points of visceral pain, psychopharmacologic effects, and neuroimmunologic properties were reviewed. It seems that these BZDs influence IBS symptoms *via* different mechanisms, and these mechanisms are under investigation. There are a small number of studies examining the effects of dextofisopam on patient's symptoms, however, we are still waiting for the results of phase Ⅲ trials. In addition, none of these trials have considered the neuroimmunomodulatory effect of BZDs in IBS. Moreover, bearing in mind the concentration-dependent effect of BZDs on cytokines and cell proliferation, future studies using pharmacodynamic and pharmacokinetic approaches are highly recommended.

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