REVIEW

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Neuromodulators in the Brain-Gut Axis: their Role in the Therapy of the Irritable Bowel Syndrome

Mihaela Fadgyas Stanculete[1], Dan Lucian Dumitrascu[2], Douglas A Drossman[3]

1) Department of Neurosciences, Discipline of Psychiatry and Pediatric Psychiatry, Iuliu Hatieganu University of Medicine and Pharmacy, Romania;
2) 2nd Department of Internal Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania;
3) Center for Education and Practice of Biopsychosocial Care, Drossman Gastroenterology, University of North Carolina, Chapel Hill, NC, USA; The Rome Foundation, Raleigh, NC, USA

Address for correspondence:
Dan Lucian Dumitrascu
2nd Department of Internal Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
ddumitrascu@umfcluj.ro

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ABSTRACT

Irritable bowel syndrome (IBS) is a clinically well-defined chronic condition that is now understood as a disorder of gut-brain regulation, as established in the work of the Rome IV committees coordinated by Drossman, 2016. People with IBS often report high disability levels and poor health-related quality of life. Drug therapy focuses on reducing main symptoms and disability and improving health-related quality of life. Central neuromodulators reduce IBS symptoms by targeting dysregulated pain and motility related to gut-brain dysregulation. It can also treat associated mental health symptoms. Based on their multiple effects on central and peripheral mechanisms, neuromodulators have been used to treat IBS patients. This review presents the rationale supporting medication treatments for specific IBS symptoms, discusses evidence-based management of IBS with central neuromodulators, and reviews the progress in the research for new neuromodulators.

Key words: antidepressants – antipsychotics – central neuromodulators – irritable bowel syndrome IBS – psychotropic medication – 5-hydroxytryptamine-3 – serotonin.

Abbreviations: 5HT3: 5-hydroxytryptamine-3; AA: atypical antipsychotics; IBS: irritable bowel syndrome; IBS-C: constipation predominant IBS; IBS-D: diarrhea-predominant IBS; NaSSa: noradrenaline and specific serotonergic agent; RCT: randomized controlled trial; SNRI: serotonin-norepinephrine reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants.

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic polysymptomatic condition that generates high direct and indirect healthcare costs. It has a significant effect on the lives of affected patients and their families and poses a significant burden on healthcare systems [1]. It is more common in females, the female: male ratio being 1.8 [2]. According to a recent study prevalence rates of IBS among internet survey countries ranged from 1.3% to 7.6% in adults [3], but it also occurs in children [3, 4]. In line with the consensus criteria, IBS's core clinical features are abdominal pain or discomfort, gas, bloating, and altered bowel transit.

Furthermore, IBS patients are characterized by extraintestinal and psychological symptoms (anxiety, depression, insomnia, fatigue, somatization), and these associations are not explained by health-care-seeking behavior alone. Moreover, these types of symptoms affect the outcome and clinical management decisions [4-9]. Therefore, IBS symptoms usually require a multidisciplinary approach using both pharmacological and non-pharmacological interventions [10].

Currently, IBS is redefined as a disorder of gut-brain interaction [11, 12]. Newly suggested top-down and bottom-up models help integrate reported physio-pathological mechanisms and provide an opportunity to understand better and treat the disease process. The pathophysiology of IBS includes, but is not limited to, an interaction between intestinal microbiota, the mucosal barrier, immune activation, nerve plasticity, visceral hypersensitivity, enteroendocrine factors, and amplification contributors by psychological factors [11, 13-19].

Patients with IBS can be challenging to treat and have a significant annual impact on healthcare systems and society [20]. Physicians and patients may feel frustrated about medically unexplained pain and are unfamiliar with obtaining

effective treatment since conventional medical therapy sometimes seems to be of no significant effect on IBS. Some physicians even think that IBS patients' symptoms are less severe than reported when the symptoms could not be well explained by organic pathology, leading to trust crises between physicians and patients. This results in communication difficulties that erode the patient-provider relationship and health care practice for these patients in general [21]. As with any chronic pain state, comorbid depression, anxiety, and sleep disturbances are common [22-25].

Drugs that were developed to target specific receptors in the gut via the enteric nervous system and the brain via the central nervous system and its spinal and autonomic connections alter the levels and activity of neurotransmitters and are called neuromodulators. In IBS, peripheral neuromodulators acting in the gut enteric system include chloride channel agents and 5-hydroxytryptamine-3 (5HT3) receptor antagonists as examples. Medical treatments targeting disordered brain–gut axis activity (central neuromodulators) can also lead to improved symptoms and a better quality of life (see Table I).

Table I. Common central neuromodulators used in irritable bowel syndrome

Pharmacological class	Examples
Tricyclic antidepressants (TCAs)	Amitriptyline (tertiary TCA) Imipramine (tertiary TCA) Desipramine (secondary TCA) Nortriptyline (secondary TCA)
Selective serotonin reuptake inhibitors (SSRI)	Fluoxetine Sertraline Escitalopram Citalopram
Serotonin-norepinephrine reuptake inhibitors (SNRI)	Duloxetine Venlafaxine Milnacipran
Noradrenaline and specific serotonergic agent (NaSSa)	Mirtazapine
Antipsychotics	Quetiapine Olanzapine Aripirazole
Anticonvulsants	Gabapentin Pregabalin

The treatment with central neuromodulators for IBS consists of different psychotropic medications (antidepressants, anxiolytics, antipsychotics, and hypnotics/sedatives), that have a general effect on pain and bloating symptoms and secondarily on bowel habits. Some of these medications may be considered base on IBS subtypes. Thus, knowledge and confidence in prescribing the most used neuromodulators aid the management of the symptoms associated with IBS, and the management of psychiatric symptoms triggered by IBS symptoms.

Based on the previous consideration when selecting a specific medication, clinicians should check the clinical characteristics of IBS, such as pain or abdominal discomfort, the presence of diarrhea or constipation, psychiatric comorbidities. In addition, it is necessary to select the appropriate drug according to the patients' current clinical condition. The evidence for the benefit of neuromodulators in IBS treatment is based on randomized controlled trials (RCTs) and nonrandomized trials with controls. However, a recent systematic review reported very few well conducted trials using central neuromodulators for IBS and much of the information is derived from treating other chronic painful medical disorders [12]. Also, these treatments are considered "off label" because they do not have an official FDA indication for IBS treatment.

The interest in the therapy with neuromodulators in IBS is reflected by the emergence of a new subspeciality called psychogastroenterology [26, 27]. It is also reflected in the prescription practice of gastroenterologists [28]. Therefore, the aim of this review is to present an update on the use of neuromodulators in IBS.

NEUROMODULATORS IN THE BRAIN-GUT AXIS

Tricyclic Antidepressants (TCAs)

Tricyclic antidepressants (TCAs) represented the first-line pharmacological treatment of major depression for decades. They are classified in tertiary amines, such as amitriptyline, doxepin, imipramine, clomipramine, and secondary amines: nortriptyline, desipramine, and protriptyline. In general, the secondary amines have less frequent or severe anticholinergic or antihistaminic side effects. The effectiveness of TCAs depends on both dosage and duration of therapy [29].

In IBS treatment, TCAs are prescribed in low doses and are usually safe, although their use may be limited by safety and tolerability concerns. Appropriate use of TCAs requires a good understanding of their mechanism of action and pharmacological characteristics, slow adjustment of the dosage given, and careful assessment of the somatic comorbidities.

Tricyclic antidepressants modulate central pain via modulation of ascending visceral sensory afferents and central transmission, have a peripheral analgesic effect via alternations of histaminergic and/or cholinergic transmission within the gastrointestinal tract, improve the quality of sleep, and influence gastrointestinal motility. They also have a dose related effect of reducing afferent signaling from the gut [30].

Another mechanism of action is activating interneurons that will release inhibitory substances as gamma-aminobutyric acid (GABA) or endogenous opioids [31]. In addition, mechanisms such as inhibitions of the N-methyl-D-aspartate receptor (a subtype of glutamate receptors) and inhibition of voltage-gated Ca^{2+} probably also play a role in their pain-relieving effect [32].

Tricyclic antidepressants have been the subject of many RCTs and are most suitable for patients with diarrhea-predominant IBS (IBS-D); adherence should be monitored because side effects often determine therapy discontinuation. The anticholinergic effects of the TCAs are a less likely mechanism which could improve symptoms, as anticholinergic agents give less benefit [33, 34]. Their ability to prolong intestinal transit times is why these drugs are preferred over the selective serotonin-reuptake inhibitors (SSRIs) in IBS-D. The choice of antidepressants and dosing should be based on potential side effects (Table II).

Table II. Tricyclic antidepressants used for irritable bowel syndrome (IBS) treatment

Medication	Start dosage	Maximal dosage	Precautions	Adverse events	Comments
Amitriptyline	25 mg	75 mg	Glaucoma History of urinary retention History of seizure disorder Cardiac problems Benign prostatic hyperplasia	Sedation Orthostatic hypotension Drowsiness Urinary retention Blurred vision Dry mouth Palpitations Weight gain Sexual dysfunction Arrhythmia Dizziness	Treatment of refractory diarrhea-predominant IBS Anti-pain effect Gut-slowing effect Once daily at bedtime Off label use
Imipramine	25 mg	50 mg			
Doxepin	25 mg	75 mg			
Desipramine	50 mg	150 mg			
Nortriptyline	25 mg	100 mg			

Despite the side effects, several meta-analyses have suggested that TCAs are safe for IBS treatment [35, 36]. Symptom improvement appears to be independent of changes in anxiety or depression scores.

In general, before starting a therapy with TCAs, the cardiac status should be checked (baseline electrocardiogram considered particularly for the elderly or patients with a cardiac history, resting blood pressure, and pulse rate). The contraindications for TCAs are presented in Table III.

Table III. Contraindication of tricyclic antidepressants use

Family history of QTc interval prolongation or sudden cardiac death
Severe liver disease
Hypersensitivity reactions to a tricyclic antidepressant drug
Concomitant use of monoamine oxidase inhibitor agents, clonidine, anticholinergic drugs

Patients with hypokalemia should have periodical monitoring to reduce the risk of arrhythmias. The elderly population is particularly susceptible to side effects when given TCAs. More frequent monitoring may be required if clinically appropriate when the dose is increased, or additional QT-prolonging drugs are added to the regimen.

It is recommended to start the therapy with a low dose; titrating it up to the desired therapeutic dose may decrease patients‘ side effects, hence promoting treatment adherence. Tricyclic antidepressants seem to be the preferred antidepressant class in patients with IBS-D, with pain refractory to antispasmodics as the main symptom [37].

The response to treatment should be measured in quality-of-life improvement, daily functioning, number, and intensity of IBS symptoms, particularly pain.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Serotonin is an important neurotransmitter in the brain and gastrointestinal tract, where it plays an important role in regulating sensory and motor functions. Selective serotonin reuptake inhibitors (SSRIs) inhibit serotonin transporter, thereby increasing levels of serotonin.

Among the many antidepressants, SSRIs are the most prescribed because they are safer and have a more favorable side-effect profile than the previous generations of antidepressants [38]. Reported experience with the selective SSRIs is much less robust than in TCAs, but improvement in global well-being was found even among non-depressed IBS patients. However, SSRIs are typically used in full psychiatric dosages, the onset of effect on IBS symptoms is slow, and the benefits may be related more to a decrease in associated anxiety or depressive symptoms and an indirect effect on IBS symptom reporting (see Table IV).

The SSRIs are less effective for gastrointestinal pain due to the lack of action on synaptic levels of norepinephrine. Some benefit in small studies has been shown for esophageal pain [12]. Studies suggest that it is appropriate to initiate the treatment with an SSRI when the patient presents a high level of anxiety contributing directly to symptom increase [39]. Also, they may not improve bloating [40, 41]. Selective serotonin reuptake inhibitors could be used combined with other drugs such as a serotonin-norepinephrine reuptake inhibitor (SNRI) or a TCA [42]. Based on studies of the side effects of antidepressants, SSRIs could be used safely for the most part in constipation predominant IBS (IBS-C), as they demonstrate a prokinetic effect and have a side effect of diarrhea [12, 43]. There are some differences between different SSRIs, citalopram has effects on colonic tone and sensitivity, and paroxetine has an anticholinergic effect useful when patients have diarrhea [44, 45]. Selective serotonin reuptake inhibitors with a medium

Table IV. Selective serotonin inhibitors used for irritable bowel syndrome treatment

Medication	Start dosage	Maximal dosage	Precautions	Adverse events	Comments
Fluoxetine	20 mg	40 mg	History of mania Epilepsy Glaucoma Hepatic/renal impairment	Nervousness, agitation, or restlessness Diminish sexual interest, desire, performance, satisfaction Insomnia Dry mouth Nausea, vomiting Diarrhea	Administration with food may reduce the risk of nausea Risk of bleeding: consider prescribing a gastroprotective drug in older people who are taking nonsteroidal anti-inflammatory drugs or aspirin Off label use in constipation predominant IBS
Citalopram	20 mg	40 mg			
Escitalopram	10mg	20 mg			
Paroxetine	10 mg	40 mg			
Sertraline	50 mg	150 mg			

half-life, such as escitalopram, are more appropriate than longer half-life drugs such as fluoxetine [46, 47].

Careful consideration of limitations of RCTs on SSRIs in IBS is warranted to formulate a safe and beneficial treatment regimen for patients with IBS.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Specific SNRIs are a more recent class of antidepressants. The double-action of serotonin and norepinephrine reuptake inhibition determines a profile of effectiveness comparable to TCAs [48]. The prominent representatives of this class are duloxetine, venlafaxine, and milnacipran (Table V). In healthy participants, SNRIs are associated with increased colonic compliance and reduced sensations to distension [49, 50]. Due to pharmacological characteristics, SNRIs are more potent analgesics than SSRIs subsequent to their noradrenergic effects [51]. They do not determine the same degree of sedation or anticholinergic side effects such as TCAs [52, 53]. Their main side effect is nausea which can be partially relieved by taking the medication with food [54]. In healthy participants, venlafaxine alters colonic compliance and tone and reduces sensation during colonic distention [55].

Duloxetine has appeared helpful for IBS in several open-label IBS trials, but still, there is little data regarding the efficacy of duloxetine in IBS treatment [56-58]. Open-label studies have shown benefit of duloxetine in patients with IBS and comorbid depression [59] and anxiety [57]. Duloxetine was moderately well tolerated. Nevertheless, based on empiric evidence the Rome committees recommend its use in chronic gastrointestinal painful symptoms based on a relatively low side effect profile compared to TCAs and established benefit in other somatic chronic pain disorders [12].

Milnacipran was active in models of IBS and abdominal visceral pain in rodents suggesting the possible use in IBS patients [60]. It shows clear benefit for fibromyalgia, and widespread body pain and by association may be considered for IBS [61]. However, its role in addressing IBS symptoms in humans has yet to be investigated.

Venlafaxine has shown benefit for patients with functional chest pain [62] but its efficacy in IBS while not yet established, may be considered as a SNRI. However, when using this medication the noradrenergic effect does not occur until higher dosages (over 175 mg/day) [12, 63].

The use of SNRIs in IBS focuses on reducing key symptoms and improving the quality of life. Some patients with IBS might experience substantial symptom relief without clinically relevant adverse events with duloxetine or milnacipran. Because SNRIs are less constipating than TCAs, they should be considered in a patient with IBS-C, particularly for those who also have anxiety or depressive symptoms [64, 65].

Clinicians should be aware of adverse phenomena that occur when the antidepressants are stopped too suddenly. The emergence of physical and neuropsychiatric symptoms within days to weeks after discontinuation of an SSRI or SNRI that results in significant distress and are not accounted for by other causes is defined as serotonin reuptake inhibitor discontinuation syndrome [66-68]. The symptoms are presented in a concise format in Table VI. They usually occur within three days after stopping the antidepressant. To avoid the discontinuation syndrome, SSRIs and SNRIs should be slowly decreased over several weeks under the physician's guidance [69-71].

Table VI. Clinical symptoms of antidepressants discontinuation syndrome

Common symptoms	Occasional symptoms
Flu-like symptoms	Perspiration
"Electric shock"-like sensations	Impaired temperature regulation
Dizziness	Ataxia
Sleep disturbances (insomnia, vivid dreams)	Attention and memory impairments
Irritability	
Crying spells	
Nausea, vomiting, diarrhea	

Noradrenaline and Specific Serotonergic Agent (NaSSa)

The rationale for using mirtazapine, a noradrenaline and specific serotonergic agent (NaSSa) as a treatment for refractory IBS emerges from a large body of evidence that pointed out the efficacy of 5HT3 receptor antagonists in IBS-D and non-constipated IBS patients.

Mirtazapine blocks alpha two adrenergic presynaptic receptors on serotonin neurons, thereby increasing serotonin neurotransmission and blocks 5HT2A, 5HT2C, and 5HT3 serotonin receptors [72]. 5-HT3 receptor antagonists are known to reduce stool frequency, urgency, consistency, and abdominal pain in patients with diarrhea by decreasing reflex activity in the gut, motor, and secretory and diminishing the extrinsic activation of sensory neurons, which transmit signals to the brain.

Also, it has been pointed out that the 5HT3 receptor takes a valuable role in gut functioning by mediating the gut central nervous signaling. Mirtazapine is a 5HT3 receptor antagonist, which in addition to treating depression and anxiety, may be beneficial for managing patients with IBS [73, 74]. The action of mirtazapine as a potent H1 antagonist has been linked to its ability to decrease visceral sensitivity, also it has been noted that mirtazapine, like TCAs, has a marked antinociceptive effect, but the exact mechanism of action it is still unknown [75]. A case report on the benefit of the mirtazapine in a female patient with major depression and IBS underlined the major improvement of cramping and bloating after two-weeks of treatment [76].

Table V. Serotonin-norepinephrine reuptake inhibitors used for irritable bowel syndrome treatment

Medication	Start dosage	Maximal dosage	Precautions	Adverse events	Comments
Venlafaxine	37.5 mg/bid	225 mg	History of mania	Nausea	Useful for abdominal pain
Duloxetine	30 mg	90 mg	Epilepsy Glaucoma	Agitation Dizziness Sleep disturbance	Off-label use
Milnacipran	50 mg/bid	100 mg/bid	Hepatic/renal impairment Hypertension Diabetic gastroparesis	(both insomnia and somnolence) Fatigue, Liver dysfunction	

A recent randomized, double-blind, and placebo-controlled study from 2021, which evaluated the effects of mirtazapine on IBS-D patients, showed a reduction of severity of IBS symptoms. The positive effects were given by increasing stool consistency and decreasing stool frequency, urgency, and abdominal pain scores, which all led to a larger number of days without diarrhea, bowel urgency, and pain [77].

Other case reports and small studies sustained the efficacy of mirtazapine in IBS patients with diarrhea or mixed symptoms. Doses of 15 to 30 mg were used with beneficial effects on both gastrointestinal and psychological symptoms, but important side effects such as weight gain, sedation, dry mouth, and hypotension were noted. Nevertheless, mirtazapine (as presented in Table VII) appears to be beneficial and well-tolerated, and safe, and some of its side effects may be beneficial, such as weight gain in patients with a low body mass index, and sedation may become more tolerable in time [78-81].

Antipsychotics

The rationale of using atypical antipsychotics (AA) in IBS is based on a bidirectional relationship between IBS and psychiatric comorbidities, on a high prevalence of IBS in psychiatric patients, and on the fact that IBS is frequently comorbid with depression, anxiety disorders, and other psychiatric disorders.

Antidepressants are used in severe and refractory IBS patients with limited efficacy. It has been suggested that AAs, such as quetiapine, olanzapine, and aripiprazole, which are approved for major depressive disorders, could be used as augmentation therapy in IBS [82].

Potential mechanisms of action of atypical antipsychotics (AA) in IBS are represented by their antihistaminergic mechanism, reduction of proinflammatory cytokine levels, analgesic effect, anticholinergic effect, and prokinetic effect through D2 receptor antagonism. The contribution of these mechanisms of action in IBS is complex and not fully understood, but they resemble the mechanisms of action of antidepressants used in IBS treatment [83].

The use of quetiapine in IBS patients has been reported as an augmentation of antidepressant treatment [84]. In addition, the clinical benefit of small doses of quetiapine ranging from 25 mg 100 mg daily has been described in small clinical trials and some case reports in patients with severe refractory IBS [85]. The potential use of olanzapine in augmentation for abdominal pain reduction and improved sleep resides, possibly in its inhibitory action at serotonin receptors [86]. Also, animal models demonstrated the effect of olanzapine on inhibition of colonic motility associated with 5HT-receptors and myosin-light chain kinase [87]. Animal studies revealed analgesic properties of aripiprazole via D2 and 5HT receptors antagonism [88, 89]. The recommended doses of AA in IBS and its side effects are presented in Table VIII.

Anticonvulsants

Anticonvulsants such as gabapentin and pregabalin are voltage-sensitive calcium channel blockers used in epilepsy but also neuropathic pain, chronic pain, and anxiety disorders. These agents are classified as peripheral neuromodulators and could have a potential benefit for IBS patients [90]. A potential mechanism of action increases the sensory threshold for distension in patients with IBS with visceral hypersensitivity [91]. Pre-clinical studies evidenced that the alpha (2) delta ligands reduce both visceral allodynia and hyperalgesia [92].

A RCT that compared pregabalin to placebo in IBS patients evidenced that pregabalin might be beneficial for IBS abdominal pain, bloating, and diarrhea, but not for constipation. Doses of 450 mg pregabalin were used for 12 weeks [93]. Another pilot study that assessed pregabalin‘s effects, at a dose of 200 mg, on colonic compliance, sensory and motor functions in patients with IBS-C found that pregabalin does not reduce distension-related colonic pain in this type of patient [94].

The effects of 300-600 mg/day of gabapentin on the rectum‘s motor and sensory function in patients with diarrhea-predominant IBS were evaluated in a small clinical trial and showed that gabapentin reduces rectal sensory thresholds by attenuating rectal sensitivity to distension and by enhancing rectal compliance [95]. Gabapentin has also been shown to inhibit spontaneous pain and behavioral anxiety in IBS animal models induced by zymosan administration [96].

Dosing tips, recommendations, and side effects of anticonvulsants used in IBS are presented in Table IX.

Augmentation Treatment

Experienced clinicians can treat more refractory symptoms using augmentation methods [12] which involves combining two or more neuromodulators, or other treatments. Examples include using an antidepressant with a gut-acting medication, with an antipsychotic agent or with behavioral treatment such as cognitive behavioural therapy. It is useful when monotherapy is unsuccessful, partially successful, or produces side effects. It is helpful in IBS with multiple somatic and psychological symptoms [12].

The duration of treatment with neuromodulators varies from patient to patient. The antidepressant treatment may show benefit in 4-8 weeks but should be continued for 6-12 months to prevent relapse after discontinuation [12]. Meanwhile, others, especially those with a long history of IBS, may need to take them for a more extended period. However, future studies are needed that follow subjects over more extended periods to elucidate how

Table VII. Noradrenaline and specific serotonergic agent (NaSSA) used for irritable bowel syndrome treatment

Medication	Start dosage	Maximal dosage	Precautions	Adverse events	Comments
Mirtazapine	15 mg	45 mg	Renal/hepatic/cardiac impairment may require a lower dose May induce mania	Weight gain Dry mouth Sedation Dizziness Confusion Hypotension	Initial dose 15 mg in the evening Sedation may decrease as dose increases 7.5 mg may increase sedation

Table VIII. Antipsychotics used in irritable bowel syndrome (IBS) treatment

Medication	Start dosage	Maximal dosage	Precautions	Adverse events	Comments
Quetiapine Olanzapine	25 mg 2.5	100 mg 10 mg	Cardiac problems Obesity Diabetes mellitus	Dizziness Sedation Orthostatic Hypotension Tachycardia Weight gain	Refractory IBS Augmenting treatment with antidepressants Off label use
Aripiprazole	2.5	7.5 mg	Cardiac problems Obesity Diabetes Mellitus	Headache Nervousness Restlessness Dizziness Akathisia	Refractory IBS Augmenting treatment with antidepressants Off label use

Table IX. Anticonvulsants used in the irritable bowel syndrome (IBS) treatment

Medication	Start dosage	Maximal dosage	Precautions	Adverse events	Comments
Gabapentin	300 mg	600 mg	Renal impairment	Sedation Dizziness Ataxia Tremor	IBS-D Off label use Antacids may reduce bioavailability
Pregabalin	150 mg	450 mg	Renal impairment	Sedation Ataxia Fatigue Tremor	IBS-D Off label use

long would be enough for patients with IBS to get well, remain stable, and prevent relapse. It is very important to explain to the patient the rationale of using neuromodulators. If the patient has not been given an adequate explanation for prescribing a neuromodulator, they may feel that their illness is not being taken as genuine and lose trust in the doctor. When describing the illness experience, the patients with IBS underline three significant themes: loss of control (which derives from poorly understood pathophysiology, inability to anticipate, prevent, or control the symptoms of IBS), social isolation generated by the avoidance behaviors, concerns about stigmatization and concerns regarding interference with dating, intimacy, and sexuality, dissatisfaction with the medical system [97]. A patient-centered approach with a priority on effective communication is required when evaluating and treating patients with IBS [98].

CONCLUSIONS

This article offers an overview of the neuromodulators used to alleviate the symptoms of IBS. The IBS treatment will be more effective when it is tailored to the patient's needs, the success relying on a good physician-patient relationship. The neuromodulators do not represent the first line of treatment, but they are essential drugs if the proper indications are endorsed, particularly when the patient has more severe painful symptoms.

Part of the gastroenterologist's role is to promote an integrated treatment approach and help the IBS patient establish a connection with other specialists (mental health clinicians, nutritionists) if indicated. In the IBS case, gastrointestinal symptoms and emotional functioning need to be viewed as influencing each other, but the physicians and patients should be realistic about the potential benefits of neuromodulators in IBS treatment. Thus, integration of care is necessary for this patient group.

Conflicts of interest: None to declare.

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