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Review article

Disorders of Gut-Brain Interaction (Functional Gastrointestinal Disorders): Neuromodulators in Clinical Practice (Part I)

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Abstract

Introduction: This review article develops the basic principles for the use and action mechanisms of neuromodulators applied in clinical practice and their role in treating different disorders of gutbrain interaction (DGBI), particularly, esophageal disorders in part I. **Materials and methods:** The working group reviewed the most frequent pathologies and medications used according to the most recent literature and presented those with the best clinical evidence in each case. **Results:** Due to the diversity of disorders, types of studies, and therapeutic options, we decided to present the evidence with the best results for each case. We determined the doses used, their results, and the side effects of each one. **Conclusions:** The basic principles of the use and mechanisms of action of the main neuromodulators were reviewed, including their use in this section in the main esophageal gastrointestinal functional disorders. Given that the available evidence is not definitive, more controlled clinical trials are needed for each condition to confirm the effectiveness and safety of neuromodulators.

Keywords

Antidepressants, antipsychotics, central neuromodulators, disorders of gut brain interaction, functional gastrointestinal disorder.

INTRODUCTION

Functional gastrointestinal diseases result from a neurohumoral imbalance of the brain-gut axis caused by various factors: alterations in the microbiome, changes in intestinal permeability, activation of the mucosal immune response, visceral hypersensitivity, and altered central sensory processing, among others [(1)]. These alterations are amplified bidirectionally by emotions, stress, and the patient's psychosocial environment[(2)]. This is the basis of the biopsychosocial model proposed by The Rome Foundation for addressing these disorders. This group also suggests that the traditionally termed *functional gastrointestinal disorders* (FGID) be redefined as disorders of brain-gut interaction (DGBI) to highlight the neurobiological nature of these diseases[(2)]. Consequently, understanding the medications that modulate the brain-gut axis is essential for physicians to treat patients with FGIDs more rationally and effectively. This article aims to review the pharmacological aspects and clinical utility of antidepressant or neuromodulatory medications in FGIDs.

BASIC PRINCIPLES OF USING NEUROMODULATORS IN THE BRAIN-GUT AXIS

The enteric nervous system (ENS) and the central nervous system (CNS) share a common embryonic origin and, consequently, the same neurotransmitters and neuronal receptors. As a result, emotional disorders directly affect gastrointestinal physiology, and gastrointestinal disturbances reciprocally cause dysfunction in the CNS. This bidirectional influence also applies to neuromodulatory medications, which exert pharmacological effects on both the CNS and ENS[1-3].

Antidepressants or neuromodulators act at the postsynaptic level by downregulating and desensitizing the receptors for one or more of the three main monoamines: serotonin (5-HT), norepinephrine (NA), and dopamine (DA)[4]. This mechanism is responsible for pain modulation and also accounts for undesirable side effects such as diarrhea, increased heart rate, and sexual dysfunction[4,5]. These medications influence brain circuits related to pain and emotion processing, producing a direct analgesic effect and altering the patient's experience of symptoms[6,7]. They also act on the posterior horns of the spinal cord, regulating visceral nociceptive sensitivity mediated by opioid, serotonergic, and noradrenergic receptors[8]. Additionally, they provide a direct peripheral visceral analgesic effect that is independent of their antidepressant or anxiolytic actions[8]. Furthermore, there is evidence that neuromodulators induce neuroplasticity changes in the hippocampus and anterior cingulate cortex, regenerating neurons lost due to chronic pain or psychological trauma[9]. Given the stigma and rejection that patients often associate with antidepressants, we recommend that physicians use the term *neuromodulators* instead of *antidepressants* when prescribing these medications. It is important to clearly explain that these medications can alleviate both gastrointestinal and associated psychological symptoms.

BASIC MECHANISM OF ACTION AND CLINICAL USE OF DIFFERENT NEUROMODULATORS

Tricyclic antidepressants (TCAs), such as amitriptyline and imipramine, are noted for their ability to bind to multiple neuronal receptors, including 5-hydroxytryptamine (5-HT), norepinephrine (NA), muscarinic type 1, α1-adrenergic, H1-histaminergic receptors, and sodium channels[4]. Due to this broad receptor affinity, TCAs tend to produce more side effects compared to other classes of neuromodulators. These side effects include xerostomia, constipation, and, at high doses, cardiac arrhythmias. TCAs are particularly valuable for patients with irritable bowel syndrome with diarrhea and for cases of functional dyspepsia, such as epigastric pain syndrome[5]. However, they are not recommended for patients with constipation, as their anticholinergic action can worsen this condition. Using low doses reduces the incidence of undesirable effects, but these agents should still be avoided in patients with left bundle branch block, prolonged QT interval, and elderly patients[4,5].

Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, escitalopram, and sertraline, selectively block the presynaptic serotonin transporter (SERT), increasing the availability of this neurotransmitter at the postsynaptic receptors. Although they lack analgesic properties, SSRIs are very useful for addressing symptoms of depression, anxiety, and hypervigilance, which are common in patients with FGIDs[4]. Common side effects include diarrhea, insomnia, night sweats, agitation, headache, weight loss, and sexual dysfunction[5]. SSRIs can also be useful in cases of constipation as they increase gastrointestinal transit.

Serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine and duloxetine, share analgesic properties with TCAs but have a lower incidence of side effects due to their reduced affinity for muscarinic and α-adrenergic receptors[4]. SNRIs are useful in treating visceral hypersensitivity associated with various FGIDs and somatic pain syndromes such as fibromyalgia[6]. Side effects, including nausea and sleep disturbances, are infrequent and tend to improve with prolonged use[6].

Tetracyclic antidepressants, such as mirtazapine and trazodone, enhance the neurotransmission of 5-HT and NA by blocking α2-adrenergic autoreceptors[4]. Mirtazapine, as an H1 and 5-HT2C antagonist, is particularly suitable for patients with postprandial distress-type dyspepsia, as it has demonstrated improvements in gastric accommodation and reductions in dysmotility symptoms. These medications are beneficial for FGID patients experiencing appetite loss and weight loss[5].

Other less frequently used antidepressants include azapirones, atypical antipsychotics, and delta ligand agents. Azapirones, such as buspirone and tandospirone, act both centrally and peripherally, affecting areas related to fear and gastrointestinal function, especially in mechanisms of gastric accommodation[4,5]. Atypical antipsychotics, including olanzapine and quetiapine, exhibit diverse pharmacological actions, including anticholinergic properties. They reduce gastric sensitivity in patients with functional dyspepsia, alleviating visceral pain and nausea, and have a lower risk of extrapyramidal side effects compared to typical antipsychotics like haloperidol. Common adverse effects include weight gain, dizziness, and sedation. These medications are useful as adjunctive analgesic therapy, although the formal evidence supporting their application in FGIDs is limited[4,5]. Lastly, delta ligand agents, such as gabapentin and

pregabalin, block the α2δ subunit of presynaptic calcium channels and are effective in managing neuropathic pain and somatic syndromes with central sensitization, such as fibromyalgia. Their primary application in FGIDs is as adjuvant therapy for pain management[7].

UTILITY OF NEUROMODULATORS IN SPECIFIC FUNCTIONAL GASTROINTESTINAL DISORDERS

Functional Heartburn

Patients with functional heartburn are characterized by chronic heartburn with negative diagnostic studies for gastroesophageal reflux disease (GERD) and a lack of response to proton pump inhibitors (PPIs). The most appropriate approach for managing functional heartburn (FH) involves a multi-component strategy that includes lifestyle changes, neuromodulator pharmacotherapy, alternative medicine, and psychotherapy[8]. PPIs are only indicated in cases of functional heartburn that coexist with GERD confirmed by endoscopy or esophageal pH monitoring studies. If GERD is fully ruled out during the diagnostic process and PPIs have not been beneficial in the past, they should be discontinued.

Neuromodulators are the cornerstone of pharmacological treatment in FH as they modify the neurotransmission of different monoamines and reduce esophageal pain, primarily at the central level and, to a lesser extent, at the peripheral level[3,8,9]. Fluoxetine was studied in a group of patients with heartburn refractory to PPIs and normal endoscopy[9]. Sixty patients with abnormal pH monitoring and 84 patients with normal pH monitoring were randomized. Those who received fluoxetine experienced a greater benefit in the percentage of days without heartburn (median: 35.7; interquartile range [IQR]: 21.4-57.1) compared to those who received omeprazole (median: 7.14; IQR: 0-50; $p < 0.001$) or placebo (median: 7.14; IQR: 0-33.6; $p < 0.001$). In the normal pH subgroup, fluoxetine was superior to omeprazole and placebo in terms of the percentage of days without heartburn (median improvement: 57.1; IQR: 35.7-57.1 vs. 13.9; IQR: 0-45.6 and 7.14 vs. 0-23.8; $p < 0.001$), but no significant differences were observed between the medications in the abnormal pH subgroup.

Fluoxetine was only useful in patients with normal pH monitoring. In another controlled clinical trial, imipramine 25 mg daily was compared with placebo in 83 patients with functional heartburn and hypersensitive esophagus over eight weeks[10]. No significant differences were found in heartburn improvement between imipramine and placebo, but there was an improvement in quality of life in the per-protocol analysis ($p = 0.045$). As observed, the evidence supporting the use of neuromodulators in functional heartburn is scarce and limited; however, it is considered the first line of pharmacological treatment due to its regulatory properties of central and peripheral visceral sensitivity. The doses used in the published studies are imipramine 25 mg/day, amitriptyline 25 mg/day, fluoxetine 20 mg/day, tegaserod 6 mg every 12 hours, ranitidine 150 mg/day, and melatonin 6 mg every 12 hours. When using TCAs, they should be administered at bedtime due to their sedative effect, initial doses should be as low as possible, and the increase should be slow and progressive to reduce the occurrence of adverse side effects[3].

Reflux Hypersensitivity

Unlike FH, patients with reflux hypersensitivity (RH) exhibit a relationship between reflux events and symptom generation, even with normal esophageal acid exposure time[11-13]. Consequently, conventional antireflux therapies are generally effective. In a prospective study involving patients with GERD symptoms and normal endoscopy, omeprazole (40 mg/day) improved symptoms in 61% of patients with normal acid exposure and a positive symptom index[14]. Therefore, it is advisable to maximize acid suppression using double doses of PPIs or vonoprazan in patients with confirmed RH[15,16]. Conversely, antisecretory agents should be discontinued in patients with non-acid reflux hypersensitivity identified through pH-impedance monitoring without PPIs[17].

Antireflux surgery has also proven effective in highly selected groups of patients with RH. A controlled study compared Nissen fundoplication with two other intervention groups: PPIs plus desipramine and PPIs plus placebo plus baclofen and desipramine in patients with refractory heartburn and a positive symptom association probability (SAP) during pH-impedance monitoring with PPIs. Nissen fundoplication yielded better outcomes (67%) than the other groups at a one-year follow-up, and the surgical result was not influenced by acid exposure time[18]. In a prospective study, imipramine was compared to placebo in 83 patients with RH and FH[19]. Those who received imipramine did not achieve a higher rate of symptom relief than those who received placebo (37.2% vs. 37.5%, respectively; odds ratio (OR), 0.99; 95% confidence interval (CI), 0.41-2.41). However, treatment with imipramine provided a significant improvement in quality of life in the per-protocol analysis (72 ± 17 vs. 61 ± 19; $p = 0.048$), although the intention-to-treat (ITT) analysis revealed no significant difference (68 ± 19 vs. 61 ± 19; $p = 0.26$). Thus, imipramine may improve the quality of life for RH patients but does not alleviate heartburn. A study conducted in Greece found that citalopram 20 mg was superior to placebo in 75 well-selected patients with a hypersensitive esophagus[20].

At the end of the follow-up period, 38.5% of the citalopram group and 66.7% of the placebo group continued to experience reflux symptoms ($p = 0.021$). Finally, another study mentioned in the previous section found that fluoxetine was superior to omeprazole and placebo in patients with FH or RH[9].

Pharyngeal Globus

Pharyngeal globus (PG) is a somatoform disorder characterized by a sensation of a lump, foreign body, or globus in the upper cervical or pharyngeal region without any structural or functional abnormalities to explain it. After ruling out structural disorders, GERD, and esophageal motor disorders, the initial treatment consists of reassuring the patient, applying non-pharmacological measures, and using neuromodulators. Approximately 50% of patients report symptom improvement when they receive clear information about the benign nature of the condition[21-23]. Non-pharmacological interventions, such as relaxation techniques and hypnotherapy, can also improve symptoms[23]. Physical therapy aimed at improving pharyngolaryngeal tension, administered by speech therapists, has shown satisfactory results in uncontrolled studies[24]. In a randomized controlled trial comparing pantoprazole 40 mg with 25 mg of amitriptyline once a day in patients with PG, the response to amitriptyline was significantly superior to pantoprazole (75% vs. 36%)[25]. Another similar study found that paroxetine provided greater symptomatic relief for PG compared to amitriptyline (44.1% vs. 15.9%; $p = 0.01$) and lansoprazole (64.7% vs. 15.9%; $p = 0.001$)[26]. **Table 1** presents the neuromodulators commonly used in clinical practice for functional esophageal disorders, their dosages, and their main clinical effects.

Non-Cardiogenic Chest Pain

Non-cardiogenic chest pain (NCCP) is a syndrome characterized by chronic retrosternal pain similar to angina but without any underlying heart disease. The causes associated with this syndrome include GERD, esophageal motility disorder (EMD), esophageal hypersensitivity, and psychiatric comorbidities[27,28]. Neuromodulators are considered the cornerstone of treatment for NCCP not related to GERD, regardless of whether EMD is present. When combined with psychological therapy, these medications

Table 1. Recommendations for the Use of Neuromodulators in Functional Esophageal Disorders

Clinical Condition	Neuromodulator	Dosage	Evidence (Reference)	Clinical Effect
Functional heartburn	Fluoxetine	20 mg/day	DBRCT[9]	Improvement in heartburn compared to placebo and omeprazole
	Imipramine	25 mg/night	RCT[10]	Improvement in quality of life compared to placebo
Reflux hypersensitivity	Citalopram or escitalopram	Citalopram 20 mg Escitalopram 10 mg	CCT[19]	Improvement in reflux symptoms compared to placebo
	Imipramine	25 mg/night	CCT[20]	Improvement in quality of life compared to placebo
	Fluoxetine	20 mg/day	CCT[9]	Improvement in reflux symptom quality compared to placebo and omeprazole
Pharyngeal Globus	Amitriptyline	25 mg/night	CCT[24]	Improvement in globus sensation compared to pantoprazole
	Paroxetine	20 mg/day	CCT[25]	Improvement in globus sensation compared to amitriptyline and placebo
NCCP	Imipramine	50 mg/day	DBRCT[29]	Improvement in NCCP frequency by 50% compared to placebo and clonidine
	Paroxetine	10-50 mg/day, mean: 30 mg/day	DBRCT[30]	Improvement in clinical perception
	Trazadone	100-150 mg/day	RCT[28]	Overall symptom improvement compared to placebo

TCAs: tricyclic antidepressants; CM: centrally mediated; NCCP: non-cardiogenic chest pain; CCT: controlled clinical trial; RCT: randomized controlled trial; DBRCT: double-blind randomized controlled trial; SSRIs: selective serotonin reuptake inhibitors; SNRIs: serotonin-norepinephrine reuptake inhibitors; SRMA: systematic review and meta-analysis; IBS: irritable bowel syndrome; CBT: cognitive-behavioral therapy. Adapted from references[9,10,19,20,24,25,29,30].

increase the likelihood of a good short-term response[29]. Imipramine at 50 mg/day for 12 weeks showed a significant reduction in chest pain frequency (50%) compared to clonidine and placebo, although it did not improve quality of life due to the side effects of imipramine compared to placebo[30]. Paroxetine at 5-50 mg/day for 8 weeks and sertraline at 50-200 mg/day for 8 weeks, either alone or in combination with psychotherapy, demonstrated improvement in chest pain scores compared to placebo and also significantly alleviated anxiety symptoms[30]. Trazodone at 100-150 mg/day for 6 weeks was evaluated in a randomized controlled trial and proved effective in treating both functional chest pain and pain related to EMD. Cognitive-behavioral therapy (CBT) and other techniques such as hypnotherapy, biofeedback through breathing exercises, and Joheri window have shown favorable results in reducing pain scales compared to placebo [28,30].

CONCLUSIONS

After reviewing the literature on each DICI, we have selected clinical studies (systematic reviews, controlled clinical trials [CCTs], or the best available evidence in each case) that propose various therapeutic options for pain modulation, as well as obtaining therapeutic benefits from these medications for our patients.

In general, starting with low doses is beneficial, as is the potential to gradually increase the dose and combine certain subgroups of medications or use them simultaneously with psychotherapy targeting gastrointestinal symptoms. However, we emphasize the importance of considering the side effects and interactions of these medications.

There is also a clear need for more CCTs in the future to obtain higher-quality evidence to support the recommendation of these medications in each case.

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Trastornos de la interacción cerebro-intestino (trastornos funcionales digestivos): neuromoduladores en la práctica clínica (parte I)

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