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Review article

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

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Abstract

Introduction: This article continues the review of neuromodulators used in clinical practice and their role in treating various disorders of brain-gut interaction (DGBI), particularly gastric, intestinal, and anal disorders. **Materials and Methods:** The working group reviewed the most common pathologies and medications according to the latest literature and the best clinical evidence in each case. **Results:** Due to the diversity of disorders, study types, and therapeutic options, the decision was made to present the evidence with the best outcomes for each case, including the doses used, their results, and side effects. **Conclusions:** The best available evidence of medications used for each DGBI is presented. At the end, a table highlights the most commonly used drugs, their doses, and gastrointestinal effects for each clinical condition, along with another table listing the most important side effects. Since the available evidence is not definitive, more controlled clinical trials are needed for each condition to confirm the effectiveness and safety of these treatments.

Keywords

Digestive system disorders, neurotransmitters, antidepressants.

INTRODUCTION

This article continues the review of neuromodulators used in clinical practice and their role in the treatment of various disorders of brain-gut interaction (DBGI), particularly those affecting the stomach, intestines, and anus.

FUNCTIONAL DYSPEPSIA

Upon confirmation of a functional dyspepsia diagnosis[1-3], treatment should be initiated with acid secretion inhibitors (proton pump inhibitors [PPIs]), H_2 receptor antagonists, potassium-competitive acid blockers (PCABs), and pro-

kinetic agents (acetylcholinesterase inhibitors, dopamine receptor antagonists, and serotonin receptor agonists)[1,2]. If there is no improvement, the use of neuromodulators should be considered as a second-line treatment[2]. These are recommended for patients who do not respond to acid suppression and *Helicobacter pylori* eradication, in accordance with British and American guidelines, due to their pain-modulating properties at various levels of the gut-brain axis[4,5]. Their effectiveness may be linked to the high correlation between functional dyspepsia and psychiatric conditions such as anxiety and depression, which impact the brain-gut axis.

The efficacy of tricyclic antidepressants (TCAs) has been studied, showing effectiveness as a second-line treatment, particularly for abdominal pain management. However, in cases of anxiety or depression, they may be considered as first-line treatment.

Both TCAs and selective serotonin reuptake inhibitors (SSRIs) modulate serotonin levels, influencing motility and visceral nociception. Neither SSRIs nor serotonin-norepinephrine reuptake inhibitors (SNRIs) have demonstrated benefit in patients with functional dyspepsia[6]. These medications should be started at low doses, preferably at night, and gradually titrated based on tolerance to avoid side effects that may lead patients to discontinue treatment. The estimated treatment duration is between 6 and 12 months; in some cases, based on clinical progression, they may be continued longer, particularly when there are psychiatric comorbidities. Discontinuing these medications in such cases could result in relapses of these concomitant conditions[4].

Tricyclic Antidepressants

Among the TCAs, imipramine, at a dose of 25 mg for two weeks and then 50 mg for up to 12 weeks, has shown satisfactory overall relief of global dyspepsia symptoms compared to placebo (63% vs. 36%), with a number needed to treat (NNT) of four. It also reduces the overall score of epigastric pain, abdominal distension, postprandial fullness, satiety, and vomiting, along with improvement in mood and anxiety[6]. TCAs should be used with caution due to their side effects, starting with low doses (10 mg/day) and slowly titrating up to a maximum of 30-50 mg/day[4,5]. The side effects are described in **Table 1**[6]. Amitriptyline at a dose of 50 mg, compared to escitalopram at 10 mg and placebo for 10 weeks, showed better symptom improvement in its group, with a global improvement of symptoms. However, both amitriptyline and escitalopram improved quality of life without significant adverse effects (**Table 2**)[6].

Selective Serotonin Reuptake Inhibitors (SSRIs)

One of these medications is sertraline. In a double-blind, randomized, placebo-controlled study, a dose of 50 mg of sertraline was administered for eight weeks. The results

Table 1. Side Effects of Neuromodulators

Group	Medication	Side Effects
TCA	Amitriptyline, imipramine, desipramine, nortriptyline	Sedation, constipation, hypotension, dry mouth, nausea, arrhythmias, weight gain, sexual dysfunction, QT prolongation[6-9]
SSRI	Citalopram, escitalopram, fluoxetine, paroxetine, sertraline	Agitation, diarrhea, insomnia, night sweats, headache, weight loss, sexual dysfunction, drowsiness, dry mouth, headache[8,9]
SNRI	Duloxetine	Nausea, agitation, dizziness, sleep disturbances, fatigue, liver dysfunction[8,9]
Atypical Antipsychotics	Quetiapine	Sedation, drowsiness, dry mouth, metabolic syndrome, cardiac arrhythmias, liver dysfunction, weight gain, diabetes[8,9]
Delta Ligands	Gabapentin, pregabalin	Sedation, headache, dizziness, vertigo, fatigue, weight gain, peripheral edema[8,10,11]
Tetracyclic Antidepressant	Mirtazapine	Weight gain, increased appetite, dry mouth, nausea, constipation, vomiting[6-8]
Antipsychotics	Levosulpiride	Mild drowsiness[6,7]
Anxiolytics	Buspirone	Sedation, headache, diziness[6,7]

Adapted from: Bosman L, and colleagues. 2023[6]; Wauters L, and colleagues. 2020[7]; Drossman DA, and colleagues. 2018[8]; Younger J, and colleagues. 2014[9]; Rao SSC, and colleagues. 2016[10]; Carrington EV, and colleagues. 2020[11].

Table 2. Summary of Neuromodulator Use for Each Clinical Condition

Clinical Condition	Medication	Dose	Study Type	Effects
Functional Dyspepsia	**Tricyclic Antidepressants**			
	Imipramine	25 mg for 2 weeks 50 mg for 12 weeks	RCT[6,7]	Overall relief of dyspepsia, improvement in anxiety
		50 mg/day for four weeks compared to placebo	Cross-over RCT[6,7]	Reduction in IG symptoms in four weeks
	Amitriptyline	Amitriptyline 50 mg Escitalopram 10 mg	RCT[6,7]	Relief of 40% with placebo, 53% with amitriptyline, 38% with escitalopram
	SNRI			
	Venlafaxine	75 mg for two weeks, 150 mg for four weeks	Cross-over double-blind RCT with placebo[6,7]	No significant difference in symptoms compared to placebo
	SSRI			
	Sertraline	50 mg/day for eight weeks	Double-blind placebo-controlled trial[6,7]	Improvement in dyspepsia index, no changes in overall symptoms
	Tetracyclic Antidepressant			
	Mirtazapine	15 mg for eight weeks	Double-blind placebo-controlled trial[6,7,12]	Weight gain, better tolerance to nutrients
	Antipsychotics			
	Levosulpiride	25 mg/day	CCT vs. placebo[6,7]	Overall symptom relief, improved gastric emptying time
	Anxiolytic Agents			
	Buspirone	20-30 mg/day for four weeks	RCT with placebo[6,7,12]	Relief of dyspepsia, postprandial fullness, and distension
IBS	TCA	25-100 (150) mg	Network meta-analysis[19]	Most effective for pain relief between weeks 4 and 12 (RR 0.53; 95% CI: 0.34-0.83)
	Amitriptyline, imipramine, desipramine, nortriptyline		Systematic review and meta-analysis, 12 TCA-specific studies[19]	RR for symptom improvement: 0.65 (CI: 0.55-0.77); NNT: 4.5
	SSRI			
	Citalopram, escitalopram, fluoxetine, paroxetine, sertraline	Psychiatric dose range: citalopram 10-20 mg, escitalopram 20 mg/day, fluoxetine 20 mg/day, paroxetine 20 mg/day, sertraline 50 mg for eight weeks	Systematic review and meta-analysis, 7 SSRI-specific studies[19]	RR for symptom improvement: 0.68 (CI: 0.51-0.91); NNT: 5
	SNRI	Duloxetine 30-90 mg Venlafaxine 225 mg	Case series[19]	40% achieved pain score reduction
	Atypical Antipsychotics	Quetiapine 25-100 mg	Case reports[19]	Improvement in pain and insomnia
		Olanzapine 2.5-10 mg	Case reports[19]	Improvement if diarrhea is present
Centrally Mediated Abdominal Pain	**TCA**	Amitriptyline, imipramine, desipramine, nortriptyline: 25-100 mg	Systematic review and meta-analysis[13,14]	RR for symptom improvement: 1.36 (CI: 1.07-1.71); NNT: 4.5
	Duloxetine	30-60 mg	Cohort studies[15]	Pain reduction
	Pregabalin	75-225 mg	CCT[10]	Improvement in pain scale and quality of life
Functional Anorectal Pain	**TCA**		Case series[10,11]	Pain reduction
	Gabapentin		Case series[10,11]	Pain reduction

TCA: tricyclic antidepressants; CM: centrally mediated; RCT: randomized controlled trial; DB: double-blind; SSRI: selective serotonin reuptake inhibitors; SNRI: serotonin-norepinephrine reuptake inhibitors; NNT: number needed to treat; RR: relative risk; SR & M: systematic review and meta-analysis; IBS: irritable bowel syndrome; CBT: cognitive-behavioral therapy. Adapted from: Bosman L, and colleagues. 2023[6]; Wauters L, and colleagues. 2020[7]; Rao SSC, and colleagues. 2016[10]; Carrington EV, and colleagues. 2020[11]; Engsbro AL, and colleagues. 2021[12]; Ford AC, and colleagues. 2019[13]; Kilgallon E, and colleagues. 2019[14]; Yang H, and colleagues. 2021[15]; Black CJ, and colleagues. 2020[19].

showed a statistically significant improvement in the mean dyspepsia index, but there was no difference in quality of life, subjective global symptom resolution, depression, or anxiety. The reported side effects included constipation and agitation (**Table 1**)[6,16].

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Venlafaxine is one such drug. In a double-blind, randomized, placebo-controlled study, venlafaxine was administered at a dose of 75 mg/day for two weeks, followed by 150 mg/day for four weeks, and then 75 mg/day for the final two weeks. The study results showed no improvement compared to placebo, neither in symptom severity nor in the number of symptoms, anxiety, depression, or overall health quality[6,16].

Tetracyclic Antidepressant

Mirtazapine has shown effects in relaxing the gastric fundus, reducing early satiety, improving food tolerance, enhancing quality of life, promoting weight gain, and alleviating depressive symptoms and somatization[6,7]. In a randomized placebo-controlled study, mirtazapine at a dose of 15 mg for eight weeks reduced the severity of dyspepsia symptoms and improved early satiety, but there was no difference in key symptoms of functional dyspepsia such as fullness, weight gain, or tolerance to nutrient volumes, nor did it affect gastric emptying. It did improve quality of life and gastrointestinal anxiety, but it did not significantly impact anxiety or depression[6]. Side effects included weight gain, increased appetite, nausea, vomiting, dry mouth, and constipation[16].

Antipsychotics

Levosulpiride at a dose of 25 mg once daily, compared to placebo, showed significant improvement and greater efficacy in relieving dyspeptic symptoms and motility issues, as well as a reduction in gastric emptying time, though mild drowsiness was reported. The effect of levosulpiride on gastric emptying has been evaluated against placebo, showing a reduction in upper abdominal pain, distension, early satiety, nausea, and vomiting, with no reported side effects. British guidelines for functional dyspepsia recommend providing careful explanations about its use and its side effect profile[4].

Anxiolytic Agents

Buspirone, a serotonin 1-A receptor antagonist, relaxes the gastric body and improves gastric accommodation, significantly reducing overall symptoms of functional dyspepsia and postprandial distress syndrome[6,7]. In a randomized, double-blind, placebo-controlled crossover study, a reduction in the severity of dyspepsia symptoms was observed, along with a significant decrease in postprandial fullness and distension[7].

IRRITABLE BOWEL SYNDROME (IBS)

Treatment for irritable bowel syndrome (IBS) begins with educating patients about the condition, emphasizing its benign nature, and explaining the usefulness and safety of diagnostic tests and treatment options. Treatment should be tailored to the specific symptoms and their severity[12,17-20]. Management focuses on controlling pain as the predominant symptom and addressing other symptoms, whether constipation, diarrhea, or alternating between the two, as well as additional symptoms like bloating, which is common in all types of IBS. Thus, treatment options include prokinetics, secretagogues, laxatives, antispasmodic analgesics, among others[8,18]. Pain management often requires a synergistic approach, combining medications that provide peripheral neuromodulation, such as antispasmodics, secretagogues, opioid agonists/antagonists, serotonin receptor antagonists, and centrally acting agents, including the better-known *neuromodulators*, which are discussed in more detail later[19].

First-Line Treatment

For moderate to severe pain, tricyclic antidepressants (TCAs) present the strongest evidence. A recent network meta-analysis ranked TCAs as the most effective for pain relief between weeks 4 and 12 (RR 0.53; 95% confidence interval [CI]: 0.34-0.83)[19]. Due to their complex mechanism of action, their therapeutic properties can derive from both the intended effects and side effects. For example, sedation can help treat insomnia, or increased intestinal transit can help manage diarrhea[8,9]. Regarding the medications in this group:

- Amitriptyline and imipramine (tertiary amines) more commonly cause side effects due to their stronger antimuscarinic and antihistaminic effects.
- Desipramine and nortriptyline (secondary amines) have fewer antihistaminic and antimuscarinic effects than amitriptyline.
- Doses range from 10/25 to 150 mg/day, but the final dose is determined by the balance between side effects and therapeutic benefits (therapeutic index)[8,9].

Serotonin-norepinephrine reuptake inhibitors (SNRIs) also have evidence of efficacy for conditions that often coexist with IBS, such as back pain, headaches, and fibromyal-

gia. They have fewer side effects than TCAs and can be used when TCA side effects are poorly tolerated. This is due to their serotonergic effect and lack of antimuscarinic effects, making this group useful for managing IBS when constipation and depression are part of the clinical picture[8,9].

Selective serotonin reuptake inhibitors (SSRIs) are also part of the first-line treatment, especially when anxiety, depression, obsessive, or phobic characteristics are central alongside IBS symptoms. It is important to note that SSRIs do not help with pain management but rather with overall symptom control, and are used in psychiatric dose ranges[8].

Second-Line Treatment

Drugs like olanzapine and quetiapine are considered atypical antipsychotics, producing fewer extrapyramidal side effects and used as co-treatment in managing abdominal pain in IBS. Quetiapine has multiple effects on different receptors: D_2, 5-HT_2A, H1 receptor antagonist, partial 5-HT_1A receptor agonist, affinity for α_1 and α_2 receptors, and inhibition of norepinephrine reuptake through one of its metabolites (N-desalkylquetiapine). It has shown effects on pain associated with fibromyalgia and is used at low doses (25-200 mg/day for gut-brain axis disorders). Olanzapine has been studied more extensively in managing chronic pain associated with fibromyalgia and headaches, with doses ranging from 2.5-10 mg/day. The adverse effects are described in **Table 1**[8].

Delta ligands are another group of peripheral neuromodulators that block the $\alpha_2\delta$ subunit of voltage-gated calcium channels in neurons. These include gabapentin and pregabalin, both of which have demonstrated a reduction in visceral hypersensitivity in IBS. The coexistence of IBS with fibromyalgia and parietal abdominal pain could be a scenario where this treatment option is viable[8,9].

Lastly, low-dose naltrexone (4.5 mg/day) offers an alternative for chronic pain management, which can be extrapolated to IBS. Its analgesic effect seems to stem not only from opioid antagonism but also from its anti-inflammatory and neuroprotective effects via microglial cells[9].

CENTRALLY MEDIATED ABDOMINAL PAIN SYNDROME

Managing centrally mediated abdominal pain syndrome (CAPS) requires establishing an effective physician-patient relationship, setting treatment goals, and tailoring treatment based on symptom severity, offering a combination of treatment options, including pharmacological and psychological therapies[21-23]. Medical treatment is most effective in the context of a strong physician-patient relationship and a comprehensive biopsychosocial treatment plan[24]. There is limited evidence from studies specifically designed for CAPS treatment, which is why many concepts are general and similar to other pain disorders in brain-gut interaction disorders (DBGI), such as IBS. Therefore, the following insights are mainly based on IBS studies, particularly those addressing severe cases[21].

Tricyclic Antidepressants (TCAs)

Twelve randomized clinical trials (RCTs) evaluated the efficacy and safety of TCAs in treating IBS patients. Of those receiving active therapy, 63.8% improved. The number needed to treat (NNT) with TCAs was 4.5 (95% CI: 3.5-7). The latest systematic reviews and meta-analyses assessed the effect of antidepressant therapy on abdominal pain[13,19]. Antidepressants were more likely to improve abdominal pain symptoms compared to placebo; however, the beneficial effects were due to TCAs, not SSRIs. TCAs also improved global symptoms in IBS patients relative to placebo (relative risk [RR]: 1.36; 95% CI: 1.07-1.71). The number needed to treat (NNT) with TCAs was 4.5 (95% CI: 3.5-7)[14]. A recent clinical guideline for managing IBS strongly recommends using TCAs for treating global IBS symptoms, with moderate-quality evidence supporting this recommendation[25].

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

In two cohort studies[14,26], specifically targeting patients with CAPS, a favorable response was observed with duloxetine at an initial dose of 30 mg/day for pain improvement, compared to various interventions (TCAs, opioids, gabapentin) ($p = 0.003$)[14,26].

Pregabalin

A CCT with 107 CAPS patients compared quality of life scores (PHQ-15) and pain scale scores (GAD-7). It found that patients tolerated pregabalin at a dose of 75 mg three times a day, or a combined regimen of pregabalin and pinaverium, with a greater reduction in pain compared to pinaverium bromide alone ($p = 0.0002$ vs. $p = 0.0033$)[27].

Other Agents

A prospective randomized controlled trial (RCT) was conducted to explore the short-term efficacy of the local analgesic (lidocaine) and the opioid analgesic (sufentanil) in 130 CAPS patients. Both treatments showed negative efficacy during short-term observation, with no worsening of symptoms from the opioid receptor blocker (sufentanil)[15]. Regarding the doses and side effects of the mentioned medications, see **Table 3**.

Table 3. Side Effects of Neuromodulatory Medications

Group	Medication	Side Effects
TCA	- Amitriptyline - Imipramine - Desipramine - Nortriptyline	Sedation, constipation, hypotension, dry mouth, nausea, arrhythmias, weight gain, sexual dysfunction, QT prolongation[6,8,14,15]
SSRI	- Citalopram - Escitalopram - Fluoxetine - Paroxetine - Sertraline	Agitation, diarrhea, insomnia, night sweats, headache, weight loss, sexual dysfunction, drowsiness, dry mouth, headache[14,15]
SNRI	- Duloxetine	Nausea, agitation, dizziness, sleep disturbances, fatigue, liver dysfunction[14,15]
Atypical Antipsychotics	- Quetiapine	Sedation, drowsiness, dry mouth, metabolic syndrome, cardiac arrhythmias, liver dysfunction, weight gain, diabetes[14,15]
Delta ligands	- Gabapentin - Pregabalin	Sedation, headache, dizziness, vertigo, fatigue, weight gain, peripheral edema[11,14,27]
Tetracyclic Antidepressant	- Mirtazapine	Weight gain, increased appetite, dry mouth, nausea, constipation, vomiting[6,8,14]
Antipsychotics	- Levosulpiride	Mild drowsiness[6,8]
Anxiolytics	- Buspirone	Sedation, headache, diziness[6,8]

TCAs: tricyclic antidepressants; SSRIs: selective serotonin reuptake inhibitors; SNRIs: serotonin-norepinephrine reuptake inhibitors. Adapted from: Bosman L, and colleagues. 2023[6]; Drossman DA, and colleagues. 2018[8]; Carrington EV, and colleagues. 2020[11]; Kilgallon E, and colleagues. 2019[14]; Yang H, and colleagues. 2021[15]; Xu R, and colleagues. 2023[27].

FUNCTIONAL ANORECTAL PAIN

Functional anorectal pain is classified into three types of disorders: levator ani syndrome, nonspecific functional pain, and proctalgia fugax. Their clinical differentiation is based on the duration of pain and the presence or absence of anorectal tenderness[10].

Treatment

Treatment for levator ani syndrome (LAS) typically includes electrical stimulation, biofeedback therapy (which has been shown to be more than 90% effective in improving defecation effort in the short term), and muscle relaxants such as methocarbamol, diazepam, and cyclobenzaprine. Additionally, therapies like levator ani muscle massage and sitz baths have also proven useful[10].

Therapeutic approaches in neuromodulation for levator ani syndrome and nonspecific functional anorectal pain include measures such as low-dose tricyclic antidepressants (TCAs), gabapentin, and cyclobenzaprine. However, there are no controlled clinical studies on these treatments, but TCAs are suggested for patients who also have coexisting anxiety[11].

CONCLUSIONS

After reviewing the literature for each disorder of brain-gut interaction (DBGI), clinical studies were selected (systematic reviews, CCTs, or the best available evidence in each case) to propose various therapeutic options for pain modulation and to obtain some therapeutic benefits from these types of medications in patients.

In general, it is notable that these medications are initially used in low doses, with the option to gradually increase the dose and to combine certain subgroups of medications or use them simultaneously with psychotherapy targeting gastrointestinal symptoms. However, special attention should be given to the potential side effects and drug interactions.

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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