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GUIDELINES AND CONSENSUS STATEMENTS

Clinical practice recommendations on the use of neuromodulators in gastroenterology: AMG (Asociación Mexicana de Gastroenterología) - AMNM (Asociación Mexicana de Neurogastroenterología y Motilidad) expert joint review

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KEYWORDS
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Irritable bowel syndrome

Abstract: Disorders of gut-brain interaction (DGBI) are characterized by alterations in both central and peripheral gut-brain axis (GBA)-related stimuli, and include esophageal, gastroduodenal, intestinal and anorectal disorders. Despite the fact that several pathophysiologic mechanisms are involved, the mainstay of treatment is neuromodulators, a heterogeneous group of drugs that act on pathways related to central and peripheral pain processing. This expert review by both the AMG (Asociación Mexicana de Gastroenterología) and AMNM (Asociación Mexicana de Neurogastroenterología y Motilidad) summarizes a series of updated clinical recommendations based on an exhaustive review of the literature, regarding the use of neuromodulators for DGBI, and is grouped into six sections: pharmacologic principles, definition, classification, mechanism of action, indications and use in each DGBI subtype, up/downscaling strategies, combination therapy, adverse events, joint use along with psychiatry in the case of comorbidities, and non-pharmacologic neuromodulation. Furthermore, drug selection process tips and dose personalization according to individual groups and sensitivities are provided, and special cases with DGBI-psychiatric comorbidity, as well as overlap with another DGBI, are considered.

PALABRAS CLAVE
Trastornos cerebro-intestino;
Neuromoduladores;
Eje cerebro-intestino;
Dispepsia funcional;
Gastroparesia;
Síndrome de intestino irritable

Recomendaciones de buena práctica clínica para el uso de neuromoduladores en gastroenterología: revisión conjunta de expertos de la Asociación Mexicana de Gastroenterología (AMG) y Asociación Mexicana de Neurogastroenterología y Motilidad (AMNM)

Resumen Los trastornos de la interacción cerebro-intestino (TICI) se caracterizan por alteraciones en el procesamiento central y periférico de estímulos en el eje cerebro-intestino (ECI), e incluyen padecimientos esofágicos, gastroduodenales, intestinales y anorrectales. Aunque los mecanismos fisiopatológicos son múltiples, la base del tratamiento son los neuromoduladores, un grupo heterogéneo de medicamentos que actúan sobre las vías y procesamiento central y periférico del dolor. Esta revisión de expertos de la Asociación Mexicana de Gastroenterología (AMG), y la Asociación Mexicana de Neurogastroenterología y Motilidad (AMNM) resume una serie de recomendaciones clínicas actualizadas basadas en una revisión exhaustiva de la literatura para el uso de neuromoduladores en TICI, organizada en seis secciones: principios farmacológicos, definición, clasificación, mecanismos de acción, pautas de uso en cada subtipo de TICI, estrategias para inicio, escalamiento, combinación, retiro, efectos adversos, manejo conjunto con psiquiatría en caso de comorbilidades, y neuromodulación no farmacológica. Además, se detalla el proceso de selección de fármacos y la personalización de dosis, adaptadas según la sensibilidad y las necesidades individuales de cada paciente, considerando factores como comorbilidades psiquiátricas y la posible sobreposición de síntomas y TICI.

Introduction

In recent years, the better understanding of the conditions previously known as functional gastrointestinal disorders has enabled their reclassification, according to the Rome IV criteria, as disorders of gut-brain interaction (DGBI).[1] The complex mechanisms within the gut-brain axis (GBA) can manifest in the digestive tract with symptoms at different levels, with both disorder and pathophysiologic mechanism overlap, but with the common denominator of altered peripheral and central processing of sensations and stimuli. Treatment of DGBI is based on neuromodulators, a heterogeneous group of medications that acts either on pain transmission pathways or pain processing at the level of the central nervous system (CNS) and peripheral nervous system (PNS). The Rome Foundation Working Group has recently proposed a guideline with recommendations for their use in gastroenterology,[2] but at present, there are no guides, guidelines, or recommendations, regarding the drugs available in Mexico, joint management with psychiatry, or nonpharmacologic neuromodulation options. Given the frequent association with psychologic disorders, the approach to these patients should be multidisciplinary, and both the gastroenterologist and psychiatrist should be familiarized with the associations between the two entities, as well as the different indications for the use of these medications, as well as their dose and interactions.

Methodology

This expert review was commissioned by the 2024 Board of Directors and the Scientific Committee of the *Asociación Mexicana de Gastroenterología* (*AMG*), with the aim of establishing updated good clinical practice recommendations for neuromodulator use in DGBI and publishing them in a document for their diffusion in the medical community. The present document is neither a clinical practice guideline nor a consensus because of the strict methodology those types of papers require, and so quality of evidence grades based on the GRADE system[3] were not issued. Instead, the document is made up of expert recommendations based on an exhaustive review of the current literature. The recommendations are divided into sections according to the organ of origin of each group of DGBI and structured through clinically relevant statements in accordance with the available evidence on each subgroup of neuromodulators. The statements were discussed at an in-person session of the participants, similar to the way the recently published good practice recommendations for other digestive diseases were discussed.[4,5]

The main clinical practice recommendations discussed were divided into six sections that include:

1) Basic pharmacologic concepts of neuromodulation and the definition, classification, and mechanisms of action of the neuromodulators.
2) Recommendations on neuromodulator use, according to region and indication by DGBI subtype (esophageal, gastroduodenal, intestinal, and anorectal).
3) Recommendations for starting, scaling, increasing, combining, and discontinuing neuromodulators.
4) Adverse effects.
5) Joint use with psychiatry.
6) Nonpharmacologic neuromodulation.

Members of the *AMG* and the *Asociación Mexicana de Neurogastroenterología y Motilidad* (*AMNM*) were jointly summoned to make up an expert panel. The participants were divided into working groups by the general coordinators (OGE/JMRT/ECA/KRGZ). Two psychiatrists were invited to participate in the joint management with psychiatry section, as well as in the discussion on the starting, combination, and discontinuation of neuromodulators. Each group was in charge of carrying out an exhaustive collection of the available evidence, through a cross-over search of the PubMed and IMBIOMED websites (for articles published up to September 2024), critically reviewing the information collected, and issuing their good clinical practice recommendations on the assigned themes, in the form of statements accompanied by a discussion explaining the rationale for each recommendation. After an initial review, the coordinators sent the statements to all the experts for a second review, for making corrections, comments, or suggestions. The statements that were confusing were either eliminated or jointly rewritten, as deemed necessary. The first draft (V1.0) was created and discussed by the expert panel at an in-person meeting on September 19, in Ensenada, Baja California, prior to the *AMG* Northern Regional Postgraduate Course. After the contributions and corrections were made at the face-to-face session, the final document (V2.0) was prepared and signed by all the participants, with the inclusion of a conflict-of-interest declaration, and then sent for peer review, according to the standard journal procedures of the *Revista de Gastroenterología de México*.

Basic pharmacologic concepts of neuromodulation, definition, classification, and mechanisms of action of neuromodulators

Definition

- *Neuromodulators are endogenous or exogenous molecules that act modulating the synthesis and/or release of one or more neurotransmitters, the activity of ion channels and neural potentials, and the activation or blockade of presynaptic and postsynaptic receptors in the CNS or PNS.*
- *We recommend adopting the term ''neuromodulators'' proposed by the Rome Foundation for describing the medications that act on the gut-brain axis.*

Motor, sensory, and gastrointestinal (GI) secretory activity is connected to and regulated by cortical brain activity through a system of afferent and efferent neuronal pathways called the gut-brain axis (GBA). This axis consists of a complex bidirectional network, formed by reflex loops that control the homeostasis of GI function, and is impacted by the enteric microbiota/microbiome.[6,7] The GBA is divided into a brain connectome that includes the CNS, with different involuntary interconnected areas involved in different mental processes, such as discrimination and localiza-

tion (primary sensorimotor cortex), processing of emotions (brain stem), behavior (medial thalamus, cingulate cortex, and insula regions), the blood-brain barrier, afferent and efferent branches, the spinal dorsal horn, the autonomous nervous system (ANS), the enteric nervous system (ENS), and a gut connectome made up of the microbiota, microbiome, epithelial barrier, neuroreceptors, inflammatory cells, and immune mediators.[6,7] Dysfunction in one or several of those mechanisms can result in motor, secretory, autonomic tone, hypothalamic-pituitary-adrenal axis, and central and peripheral sensory alterations that clinically translate into one or more DGBI, which can affect one or more segments of the GI tract.[1,8,9] Among the multiple pathophysiologic mechanisms of the DGBI, the most common are alterations in the central processing of stimuli arising from the target organ, neuroimmune dysfunction, and visceral hypersensitivity, and even though there are drugs directed at other mechanisms, such as dysmotility or altered intestinal secretion, treatment is based on neuromodulators.[1,8,10] Neuromodulators are considered to be any endogenous or exogenous molecule, that without being accumulated and released by nerve endings, acts presynaptically, modulating the synthesis and/or release of one or more neurotransmitters, and secondarily regulates ion channel activity and membrane potentials in neural cells through the activation or blockade of different presynaptic and postsynaptic receptors in the CNS or PNS. Some exogenous devices with similar properties can also be classified as neuromodulators.[8,11,12] Due to the heterogeneity of pharmacologic groups considered neuromodulators and to the fact that they are a fundamental part of treatment of DGBI, the Rome Foundation has proposed re-labeling and redefining the terminology of medications acting within that system, coining the name neuromodulators, instead of referring to them as antidepressants, antipsychotics, anticonvulsants, or neurolytic agents, given that the doses prescribed for inducing neuromodulation are different from their other indications.[13] There is a marked heterogeneity regarding the knowledge, attitude, and level of practice among primary care physicians and some gastroenterologists, as was recently described at a university hospital in Korea, where less than 30% of physicians prescribed neuromodulators due to little familiarity with the pharmacologic group.[14]

Main pharmacologic neuromodulation pathways

- *Neuromodulation is the physiologic process by which a stimulus regulates the neuronal population, activity, and functions through the action of one or more neurotransmitters that can activate or block receptors, to induce a modulating effect.*
- *Neuromodulators have the capacity to modulate pain perception and induce neuroplasticity due to the effect on one or more neurotransmitters and postsynaptic receptors at the central or peripheral level.*

Neuromodulators affect ascending neural transmission (they interfere with the brain circuits related to pain, emotional and cognitive, and interfere with the transmission of pain in the spinal dorsal horn), as well as descending neural transmission (control of projections arising from diverse brain structures, mediated by serotonergic, noradrenergic, and opioidergic receptors). At the synaptic level, they induce a rapid increase in the action of one or more monoamines, according to each subgroup, causing their accumulation in the synaptic space. A second mechanism is delayed downregulation or desensitization of the postsynaptic receptors of the respective receptor. Neuromodulators have been described to induce neuroplasticity that involves anti-neurodegenerative properties, particularly in syndromes associated with chronic pain. One of the mechanisms appears to be cortical neuron loss and neurogenesis induction, through an increase in brain-derived neurotropic factor (BDNF) levels, given that over time, chronic pain, depression, anxiety, and other forms of emotional stress lead to loss of cortical neuron density, a process that neuromodulators can reverse.[1,8,15]

The mechanism of action in the GI tract varies, according to each neuromodulator subgroup, and can include partial or total stimulation and/or inhibition of one or more presynaptic and postsynaptic serotonergic, muscarinic, cholinergic, or noradrenergic transporters or receptors, with therapeutic effects (increase or decrease in motility and gastrointestinal tone, gastric accommodation, antinociceptive effect), as well as adverse effects (somnolence, dry mouth, constipation, diarrhea, urinary retention, weight gain) that vary, depending on the stimulated or inhibited receptor.[1]

Concept of agonism/antagonism/reuptake

- *Therapeutic (and adverse) effects of neuromodulators depend on their agonism or antagonism on one or more receptors, which can induce an increase or decrease in the reuptake of different neurotransmitters.*

Pharmacodynamics refers to the mechanisms and effects of medications on biologic functions in the organism, i.e., what they do in the body and how they do it. In order to have an effect, neuromodulators have to reach the target cells and bind to one or more receptors that are specialized proteins located inside the cell or on its membrane. After binding to a signaling molecule, called a ''ligand'', they can alter its form or activity, according to the effect the ligand has on the receptor, and there are two large pharmacologic categories: agonists and antagonists.[16]

Agonist. Any substance that mimics the action of the signaling ligand by binding to a receptor and activating it.

Antagonist. Any substance that binds to a receptor without activating it, impeding its activation by other signals, i.e., decreasing the capacity of the receptor to be activated by another agonist, or blocking it. Receptor antagonists can be classified into reversible and irreversible. Reversible antagonists are easily separated from their receptor; irreversible antagonists form a stable, permanent, or almost permanent, bond with their receptor.

Reuptake. This process consists of the reabsorption of neurotransmitters or other substances, after been released in the synapse. Reuptake is a form of neurotransmitter inactivation, which is crucial for the termination of synaptic signaling and for regulating the concentration of neurotransmitters available in the synaptic space, which in turn, has direct implications on modulating both central and periph-

eral nervous system function. In the CNS, reuptake processes are especially relevant for neurotransmitters, such as serotonin, noradrenaline, and dopamine.

Classification

- *Neuromodulators are classified according to their chemical structure, pharmacologic group, and site of action (central or peripheral).*
- *Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), azapirones, atypical antipsychotics, and anticonvulsants are central neuromodulators. Delta-ligands are peripheral neuromodulators.*
- *The concept of the neuromodulator and its indication should be explained to the patient, avoiding the use of terms, such as antidepressant, anxiolytic, antipsychotic, and neurolytic, to prevent confusion with other indications for the same drug.*

Neuromodulators are classified according to their chemical structure, pharmacologic group, and site of action (central or peripheral) (Table 1).[2,11,17] Due to the heterogeneity of groups considered neuromodulators, most of those drugs have more than one therapeutic indication, and include treatment of psychiatric disorders, such as depression, anxiety, obsessive-compulsive disorder (OCD), schizophrenia, neuropathy, and convulsive crises, among others. Therefore, the physician must take the time to explain to the patient, not only the pathophysiologic mechanisms behind pain, but also the neuromodulation mechanisms of each of those pharmacologic groups and their desired clinical effect, specifying the fact that the primary indication for their use in gastroenterology is to modulate pain perception, in an effort to avoid confusion and stigma on the part of patients.[8,18]

Mechanism of action by subgroup

- *The antinociceptive effect of each group of neuromodulators may differ, depending on the activation or inhibition of different receptors and neurotransmitters. Some can have an effect on gastrointestinal motility.*

In general, neuromodulators modify the synaptic action of one or more of the three main monoamines: dopamine, serotonin, and noradrenaline (Table 1). The mechanism of action of each group of neuromodulators may vary due to their pharmacologic structure. Each subgroup can partially or totally stimulate and/or inhibit one or more presynaptic and postsynaptic serotonergic (5-HT), histaminergic, muscarinic, or noradrenergic receptors, with pharmacologic effects on motility, secretion, and visceral analgesia. In many cases, the adverse effects on GI motility and secretion may help control secondary symptoms such as constipation, diarrhea, or weight loss.[2,11]

Tricyclic antidepressants (TCAs). They induce antagonism and inhibition of multiple presynaptic (α2) and postsynaptic (5-HT_2, 5-HT_3, H1, muscarinic-1, α1) receptors, which translates into a decrease in GI motility (cholinergic, noradrenergic effect) and a central antinociceptive effect. Imipramine, amitriptyline, nortriptyline, desipramine, doxepin, and trimipramine belong to this group.[11]

Selective serotonin reuptake inhibitors (SSRIs): They selectively block the presynaptic 5-HT transporter, resulting in an increase in GI motility with no significant effect on sensitivity (they have little analgesic effect). The SSRIs are citalopram, escitalopram, sertraline, fluoxetine, fluvoxamine, and paroxetine.[19] Some, such as fluoxetine (5-HT_{2C} antagonism) or paroxetine (anticholinergic effect), possess a second mechanism of action.[2]

Serotonin and norepinephrine reuptake inhibitors (SNRIs). They block the presynaptic 5-HT and presynaptic noradrenaline transporters. Venlafaxine, desvenlafaxine, duloxetine, milnacipran, and levomilnacipran belong to this group. Venlafaxine induces 5-HT blockade at low doses and noradrenergic reuptake inhibition at high doses (>225 mg) and duloxetine has the same affinity for the 5-HT and noradrenergic transporters, whereas milnacipran has a greater noradrenaline reuptake inhibitory effect. The antinociceptive effects of the SNRIs appear to be superior to those of the SSRIs.[2,20]

Tetracyclic agents. They increase noradrenergic activity, with a specific increase in serotonergic activity through the presynaptic neuronal antagonism of the noradrenaline and 5HT auto and heteroreceptors. The antidepressant effects are a result of 5-HT_{2A} and 5-HT_{2C} antagonism, whereas the GI effects are a result of 5-HT_3 antagonism. Mirtazapine, mianserin, amoxapine, and trazodone belong to this group.[2] At low doses, mirtazapine exhibits H1 antagonism, which can cause sedation, whereas 5-HT_{2C} antagonism stimulates appetite and weight gain.[21]

Azapirones. They are partial presynaptic and postsynaptic $5HT_1$ receptor agonists and have a certain affinity for the $5HT_2$ receptor, as well as a moderate affinity for the dopamine D2 receptors.[22] They are considered nonbenzodiazepine anxiolytics. Buspirone and tandospirone belong to this group and have a similar mechanism of action.[2]

Atypical antipsychotics. They are a heterogeneous medication class, also known as second-generation antipsychotics. Sulpiride, amisulpride, levosulpiride, quetiapine, olanzapine, risperidone, aripiprazole, brexpiprazole, and clozapine belong to this group. Their mechanism of action is through dopamine D2 receptor antagonism, as well as partial D2 agonism (sulpiride, amisulpride, levosulpiride), partial 5-HT_{1A} agonism (quetiapine), and 5-HT_{2A} antagonism (olanzapine, quetiapine).[2] All of these additional mechanisms of action reduce the risk of adverse effects, particularly extrapyramidal ones. Some first-generation antipsychotics, also called neuroleptics, such as chlorpromazine or trifluoperazine, have been utilized for the treatment of nausea but they tend to be more frequently associated with extrapyramidal side effects.[23]

Anticonvulsants. They are a heterogenous group divided into 8 drug subgroups, according to their mechanism of action. Some have more than one mechanism, such as the repeatedly-activated sodium channel blockers (phenytoin, carbamazepine, oxcarbazepine), gamma-aminobutyric acid (GABA) analogues and potentiators (phenobarbital, benzodiazepines, baclofen), glutamate modulators (topiramate, lamotrigine, felbamate), *T* calcium channel blockers (ethosuximide, valproic acid), *N* and *L*-type

Table 1 Neuromodulators: Gastrointestinal effects and adverse events.

Class	Neuromodulator	Effects on the gastrointestinal tract	Adverse events
Tricyclic antidepressants (TCAs)	Imipramine	Reduces gastrointestinal motility, modulates visceral pain.	Prolonged QT interval, dry mouth, dizziness, constipation.
	Amitriptyline	Reduces gastrointestinal motility, has a visceral analgesic effect.	Somnolence, dizziness.
	Nortriptyline	Reduces visceral pain perception.	Adjust dose in the elderly; precaution in cases of heart disease.
Selective serotonin reuptake inhibitors (SSRIs)	Sertraline	Modulate visceral pain perception and improves gastric emptying.	Nausea, agitation, dry mouth, diarrhea.
	Citalopram	Modulating effect on gastrointestinal motility.	Risk of prolonged QT interval; avoid high doses.
	Escitalopram	Improves gastric emptying, modulates pain perception.	Insomnia and weight loss; risk of serotonergic syndrome when combined with other neuromodulators.
	Fluoxetine	Improves gastric emptying, modulates pain perception.	Insomnia and weight loss; risk of serotonergic syndrome when combined with other neuromodulators.
	Paroxetine	Improves the visceral pain threshold, modulates pain perception.	Headache, dry mouth, risk of serotonergic syndrome; do not use in patients with uncontrolled high blood pressure.
Serotonin and norepinephrine reuptake inhibitors (SNRIs)	Venlafaxine	Improves the visceral pain threshold, modulates pain perception.	Headache, dry mouth, risk of serotonergic syndrome; do not use in patients with uncontrolled high blood pressure.
	Duloxetine	Improves the visceral pain threshold.	Avoid in patients with liver diseases; risk of serotonergic syndrome.
Tetracyclic antidepressants	Mirtazapine	Increases gastric emptying, modulates pain perception.	Sedative effects; avoid in patients with a history of obesity.
	Trazodone	Modulates visceral pain.	Orthostatic hypotension, diurnal somnolence, and rare cases of priapism; precaution in patients with cardiovascular diseases.

Table 1 (*Continued*)

Class	Neuromodulator	Effects on the gastrointestinal tract	Adverse events
5-HT_{1A} receptor partial agonist	Buspirone	Improves gastric motility and reduces bloating.	Do not use in combination with SSRIs or monoamine oxidase inhibitors (MAOIs).
	Tandospirone	Improves gastric motility and reduces bloating.	Fatigue at high doses; precaution when combined with other serotonergic agonists.
Atypical antidepressants	Levosulpiride	Increases gastric emptying, improves gastrointestinal motility.	Hyperprolactinemia, somnolence, and galactorrhea; avoid in patients with a history of epilepsy.
	Olanzapine	Can improve the control of vomiting in certain cases of functional disorders.	Weight gain, somnolence, risk of metabolic syndrome.
	Quetiapine	Anxiolytic and sedative effect and can help modulate visceral pain.	Significant sedation; adjust in patients with kidney failure.
Delta-ligands	Pregabalin	Reduces neural excitability and visceral pain.	Potential for abuse; monitor for signs of fluid retention.
	Gabapentin	Modulates visceral neuropathic pain.	Can cause significant sedation; adjust in patients with kidney failure.
Anticonvulsants	Baclofen	Improves gastric motility and reduces bloating.	Somnolence, muscle weakness; precaution when combined with other central nervous system (CNS) depressants.
	Topiramate	Modulates neural excitability, is useful in the management of cyclic vomiting.	Weight loss, paresthesia, mood fluctuations, concentration difficulty.
	Levetiracetam	Can aid in stabilizing the nervous system by reducing vomiting episodes.	Somnolence, fatigue, dizziness, irritability, depression, risk of suicidal ideation and other mood fluctuations.

calcium channel blockers (lamotrigine, topiramate, zonisamide, valproic acid), *H*-current modulators (gabapentin, lamotrigine), carbonic anhydrase inhibitors (topiramate, zonisamide), and specific binding site blockers (gabapentin, levetiracetam).[8,24]

Delta-ligands or α2-delta ligands. Delta-ligands block the α2-delta subunit of the presynaptic voltage-dependent calcium channels in the medullary dorsal horn, and so they are considered peripheral neuromodulators. They have no effect on GI motility. Pregabalin and gabapentin belong to this group. As previously stated, gabapentin is also an *H*-current modulator, and therefore, is classified as an anticonvulsant, and may have a partial central neuromodulating effect.[25,26]

Therapeutic effect on the motility/sensitivity group (Table 1)

- *TCAs (imipramine, amitriptyline, nortriptyline, desipramine, doxepin, trimipramine) have a visceral analgesic effect and decrease GI motility and secretion. Their main indication is for pain as the predominant symptom or diarrhea-associated DGBI.*

TCAs have several mechanisms of action: they possess antagonism and inhibition of multiple presynaptic (α2) and postsynaptic (5-HT_2, 5-HT_3, H1, muscarinic-1, α1) receptors that result in a decrease in GI motility (cholinergic,

noradrenergic, serotonergic effect) and a central antinociceptive effect.[22] Their analgesic properties are due to a combination of 5-HT and noradrenaline reuptake inhibition properties. Because of their dual action, TCAs theoretically have a more potent analgesic effect, compared with other neuromodulators, such as SSRIs.[27] In addition, they act as muscarinic-1 receptor antagonists, associating them with slow orocecal transit (amitriptyline, imipramine, desipramine).[2,28]

- *SSRIs (citalopram, escitalopram, sertraline, fluoxetine, paroxetine, fluvoxamine) increase GI motility but have no effect on visceral sensitivity/analgesia. They are useful for treating anxiety, phobias, and DGBI-associated obsessive-compulsive disorder (OCD).*

The mechanism of action SSRIs have in common is through selective blockade of the presynaptic 5-HT transporter, resulting in increased GI motility but with no significant effect on sensitivity.[19] Acute serotonin transporter inhibition in humans increases colonic phasic contractility and the frequency of high-amplitude propagated contractions, also increasing colonic compliance and suppressing the colonic tonic response to foods, whereby SSRIs increase gastric and intestinal propulsive motility.[29] They may be used for reducing the anxiety or hypervigilance associated with different DGBI.

- *SNRIs (duloxetine, venlafaxine, desvenlafaxine, milnacipran, levomilnacipran) inhibit gastro-colonic tone to a lesser degree than TCAs and have a visceral analgesic effect. They are useful for disorders with a predominance of pain, including associated conditions (fibromyalgia, headache) or when TCAs are not tolerated.*

SNRIs act as 5-HT_3 receptor antagonists, delaying gastric emptying and decreasing colonic transit time.[2] Their safety profile is more favorable than that of the TCAs, so they are an alternative for treatment of disorders associated with chronic pain, when TCAs are not tolerated. The antinociceptive effects of SNRIs appear to be superior to those of SSRIs.[30]

- *Tetracyclic agents (mirtazapine, mianserin, amoxapine, trazodone) have a relaxing effect on the gastric fundus, and their potential use is in disorders associated with satiety, nausea, and weight loss.*

The GI effects of the tetracyclic agents are due to their specific mode of action on noradrenergic and serotonergic receptors, particularly, increased noradrenergic activity and 5-HT_1 and 5-HT_3 antagonism, which can explain their effects on reducing nausea, pain, and diarrhea. However, because histamine plays an important role in satiety and appetite regulation, its inhibition is associated with weight gain. There is evidence on their inhibition of gastric and colonic tone, but more studies are needed to evaluate their effect on GI motility.[31]

- *Azapirones (buspirone, tandospirone) increase esophageal contractility and have a predominant effect on gastric accommodation, with less evidence of an antinociceptive effect. Their potential use is in early satiety, postprandial fullness, nausea, and associated anxiety.*

Azapirones are nonselective postsynaptic 5-HT_{1A} receptor agonists, presynaptic D_2, D_3, and D_4 receptor antagonists, and partial α1-adrenergic agonists. They have effects on gastric accommodation and relaxation, no effects on esophageal or colonic motility, and there is less evidence of an antinociceptive effect. Studies on dyspepsia have shown their usefulness for improving symptoms in patients with early satiety, postprandial fullness, and nausea. Because they are non-benzodiazepine anxiolytics, they are useful when there is associated anxiety.[32,33]

- *Atypical antipsychotics (sulpiride, levosulpiride, olanzapine, quetiapine, aripiprazole, brexpiprazole, risperidone, clozapine, flupentixol) and some typical antipsychotics (chlorpromazine, trifluoperazine) have different therapeutic and adverse effects according to subtype, and their main use in DGBI is control of nausea and vomiting. Levosulpiride improves gastric relaxation and has a mixed prokinetic and anxiolytic effect.*

There is no evidence on the effect of atypical antipsychotics on GI motility in healthy subjects. Nevertheless, due to their dopamine and serotonergic antagonist effect, and in some cases their muscarinic effect, they have been used to treat nausea and vomiting associated with different conditions.[23] Sulpiride and levosulpiride are occasionally used to treat functional dyspepsia (FD) and gastroparesis (GP) because of their effects on gastric emptying.[34,35] There is evidence of improvement in nausea and vomiting with olanzapine in different disorders, including postoperative states and after the administration of chemotherapy.[36]

- *There is limited evidence on the effects of anticonvulsants (carbamazepine, oxcarbazepine, baclofen, lamotrigine, valproic acid, topiramate) on GI sensitivity and motility. Topiramate is useful for preventing different forms of headache and cyclic vomiting syndrome.*

Anticonvulsants have a potential analgesic effect but evidence on their effectiveness in acute and chronic pain is limited,[37] and there is insufficient evidence on their effects on GI motility. Topiramate has been used as a prophylactic agent in different forms of headache, and more recently, in cyclic vomiting.[38,39] Gabapentin is a dual-action drug, given that it is considered an anticonvulsant that blocks a specific binding site, but its main mechanism of action is as a peripheral neurolytic agent. Its principal role is pain control in neuropathy, albeit little is known about its central antinociceptive effect.[37]

- *Delta-ligands (pregabalin, gabapentin) are useful in DGBI-related neuropathic pain and associated diseases, such as fibromyalgia.*

Pregabalin and gabapentin have a similar mechanism of action, acting by binding to calcium channels and modulating the flow of calcium, in addition to influencing GABAergic receptor-associated neurotransmission. Pregabalin has an

Table 2 Recommended neuromodulator doses.

Neuromodulator	Initial dose	Maximum dose
Imipramine	25 mg/d	150 mg/d
Amitriptyline	10 mg/d	150 mg/d
Nortriptyline	25 mg/d	150 mg/d 50 mg/d in the elderly
Sertraline	50 mg/d	200 mg/d
Citalopram	20 mg/d	40 mg/d 20 mg/d in patients > 60 years of age
Escitalopram	10 mg/d	20 mg/d 10 mg/d in the elderly
Fluoxetine	20 mg/d	80 mg/d
Paroxetine	20 mg/d	60 mg/d 40 mg/d in the elderly
Venlafaxine	75 mg/d	225 mg/d
Duloxetine	30 mg/d	90 mg/d
Mirtazapine	7.5 mg/d	45 mg/d
Trazodone	75 mg/d	150 mg/d
Buspirone	15 mg/bid	45 mg/bid
Tandospirone	10 mg/d	30 mg/d
Levosulpiride	25 mg/tid	50 mg/tid
Olanzapine	10 mg/d	20 mg/d
Quetiapine	25 mg/d	800 mg/d
Pregabalin	150 mg /d	150 mg /d
Gabapentin	300 mg/d	1200 mg/d
Baclofen	5 mg/bid	20 mg/tid
Topiramate	12.5-25 mg/d	50-100 mg/d
Levetiracetam	500 mg/d	3000 mg/d

analgesic and anxiolytic effect, and gabapentin has an analgesic, anxiolytic, as well as an anticonvulsant effect.[40] The effect of delta-ligands on GI sensitivity and motility has yet to be elucidated, but due to their known mechanism of action at the level of the CNS, they appear to have an effect on neuromodulation.[25]

- *Some neuromodulators may be useful for controlling psychiatric comorbidities in DGBI, including anxiety, hypervigilance, OCD, and depression, among others.*

In addition to their antinociceptive effect, neuromodulators may be used in DGBI to treat associated comorbidities, including extragastrointestinal manifestations, such as fibromyalgia, migraine, and interstitial cystitis, or in patients with psychiatric comorbidities. These drugs may reduce anxiety, hypervigilance, selective attention, and catastrophizing associated with GI symptoms and are indicated for the treatment of other conditions, such as OCD and depression. They can also reverse cortical neuron loss and induce neurogenesis, because over time, chronic pain, depression, anxiety, and other forms of emotional distress are conducive to cortical neuron density loss. As previously stated, central neuromodulators can reverse that process by increasing BDNF levels, leading to an increase in neurogenesis.[11,12]

Table 2 shows the recommended doses of each of the different types of neuromodulators utilized in DGBI.

Recommendations on neuromodulator use according to region and indication by DGBI subgroup

Esophageal disorders

Functional heartburn (FH)

- *We recommend the use of SSRIs and TCAs for the treatment of FH*

FH is defined as a retrosternal burning sensation that is refractory to optimum antisecretory therapy, in the absence of gastroesophageal reflux disease (GERD), histologic abnormalities, major motor disorders, or structural abnormalities.[41] The 1.0 and 2.0 Porto and Lyon consensuses have better defined this patient group, which has normal esophageal acid exposure and negative symptom association, differentiating it from the reflux hypersensitivity group,[42,43] albeit there may be overlap between groups.[44,45] For a long time, treatment was empiric, but a better understanding of the pathophysiology in recent years has provided evidence in favor of neuromodulator use for treating FH.[46,47]Current evidence suggests that some SSRIs, such as fluoxetine, or TCAs, such as imipramine or amitriptyline, can be effective in treating the condition.[47] At present, only two trials have directly evaluated the use of neuromodulators in FH. A study that evaluated patients

with heartburn and normal endoscopy, who underwent pH monitoring, compared the use of fluoxetine, omeprazole, or placebo for 6 weeks. The treatment with fluoxetine was associated with a higher number of heartburn-free days and there was no improvement in the group with abnormal pH monitoring.[48] In a study that evaluated patients with FH that did not respond adequately to proton pump inhibitor (PPI) treatment, imipramine showed no significant difference in symptom relief compared with placebo, but was associated with improved quality of life, according to the SF-36 score.[49] In patients with GERD and symptom persistence, overlap with FH has been reported. In that subgroup of patients, as well as in patients with coexisting anxiety, amitriptyline, in combination with an antisecretory agent, is useful for symptom control.[50] A meta-analysis that evaluated the use of neuromodulators in esophageal DGBI found inconsistent results in FH, but most of the studies included the evaluation of patients with FH and reflux hypersensitivity as one group.[51] Finally, a network meta-analysis that assessed the effect of different groups of antidepressants on GERD suggested that SSRIs could aid in symptom control but the study did not specify whether there was GERD/FH overlap.[52]

Functional chest pain (FCP)

- *We recommend the use of TCAs, SSRIs, venlafaxine, and trazodone for the treatment of FCP. Gabapentin and pregabalin may also be considered.*

FCP is defined as inexplicable, recurrent chest pain that is not associated with other esophageal symptoms, such as heartburn or dysphagia, nor caused by GERD, major motor disorders, or mucosal alterations, such as infection or eosinophilic esophagitis. FCP belongs to the clinical spectrum of noncardiac chest pain (NCCP).[41,53] FCP is currently considered a DGBI, given that, in addition to esophageal hypersensitivity and esophageal comorbidity, there is an abnormal process of central esophageal stimuli,[54] with both central and peripheral hypersensitivity.[53] As a result, the treatment of FCP is based on neuromodulators.[55] Current evidence suggests that TCAs, SSRIs, venlafaxine, trazodone, and peripheral neuromodulators (gabapentin and pregabalin) are associated with variable improvement rates. Imipramine increased the pain threshold to balloon distension in healthy volunteers,[56] and at a dose of 50 mg/day, was associated with a significant decrease in chest pain in 52% of patients, compared with clonidine or placebo in patients with normal coronary angiograms regardless of psychiatric and esophageal tests, suggesting a visceral analgesic effect.[57] The combination of low dose (10 mg/day) of amitriptyline with a standard dose PPI (rabeprazole) was more efficacious than the PPI at a double dose, in patients with FCP.[58] A study comparing amitriptyline with citalopram after 3 months of treatment reported improvement in 56.3% of the patients with the TCA and in 47% with citalopram versus 11% with placebo.[59] In another study, Prakash et al. reported a therapeutic effect of up to 3 years in patients with persistent NCCP and an incomplete response to antireflux surgery, who continued using different TCAs.[60]

At least three SSRIs have been evaluated in NCCP (sertraline, paroxetine, citalopram). Sertraline was assessed in two studies. The first was a double-blind randomized clinical trial (RCT) that reported that a dose of 50-200 mg significantly reduced pain perception scores, with improvement in up to 57% of patients at 8 weeks.[61] The second study compared sertraline with placebo and coping skills training (CST), assessing daily pain diaries (completed using the visual analogue scale) at weeks 10 and 34, and reported that both, the drug and CST, either alone or in combination, were superior to placebo.[62] Paroxetine was evaluated in two studies. In the first, it was superior to placebo on a symptom scale measured by the physician and not on self-perception scales,[63] but in the second, it was not superior to either placebo or cognitive therapy at 12 weeks of treatment.[64] A single intravenous dose of 20 mg of citalopram reduced chemical and mechanical esophageal hypersensitivity without altering motility.[65] However, a systematic review including all those studies reported that SSRIs as a group were not superior to placebo in improving the symptoms of NCCP and that the quality of evidence was moderate.[66]

Venlafaxine has been the only SNRI evaluated in FCP. It was evaluated in a RCT and shown to be superior to placebo, at a dose of 75 mg/day for 4 weeks, with symptom improvement in 52% of patients, compared with 4% in the placebo group, as assessed by an intention-to-treat analysis that defined primary efficacy as the number of patients with symptom improvement greater than 50%.[67] A systematic review found venlafaxine to be the most effective antidepressant for reducing esophageal pain and for overall improvement.[68] It is considered a good option for managing FCP in patients that do not tolerate TCAs.[69]

Trazodone has been evaluated in two studies. In the first, a dose of 100-150 mg, 4 times a day for 6 weeks, significantly improved pain scores in NCCP and motor disorders, without inducing a change in esophageal motility, with a response rate of 41%.[70] In the second study, there was a modest benefit in patients with NCCP associated with diffuse esophageal spasm, compared with clomipramine.[71]

Evidence regarding peripheral neuromodulators has recently been published. Pregabalin has been shown to reduce sensitivity to esophageal distension in healthy persons. However, there are no clinical trials on NCCP.[72] Gabapentin, at a dose of 300 mg/day administered along with a PPI, improved the sensation of globus in patients with chest pain and there is preliminary evidence of a central neuromodulation effect.[73]

In the 2012 systematic review by Nguyen and Eslick[68] that included 6 controlled studies, there was significant overall improvement with imipramine, sertraline, paroxetine, venlafaxine, and trazodone. Venlafaxine, sertraline, and imipramine showed greater efficacy, with reduced percentages of 50%, compared with placebo, vs 10% for venlafaxine, 63% vs 15% for sertraline, and 52% vs 1% for imipramine. Furthermore, in the most recent meta-analysis, neuromodulators as a group were associated with a 52-71% reduction in retrosternal pain.[51]

Reflux hypersensitivity (RH)

- *We recommend the use of SSRIs for the treatment of RH, with or without adjunct acid-suppressive therapy, or TCAs as a first alternative. In cases of psychiatric comorbidity, other neuromodulators may be considered.*

RH was introduced by the Rome IV group as a new esophageal DGBI and is defined as the presence of typical heartburn symptoms in a patient with normal endoscopy and biopsies, normal esophageal acid exposure, but with a positive correlation between symptoms and changes in pH measured by pH monitoring, replacing the previous term of hypersensitive esophagus.[41,74] The treatment of RH is based on neuromodulators and there is published evidence on citalopram (SSRI) and imipramine (TCA). In a study that evaluated healthy subjects with esophageal hypersensitivity that underwent a balloon distension test, intravenous citalopram increased the threshold to the first sensation of heartburn and discomfort during the test.[65] In a RCT that included 75 patients with PPI-refractory symptoms, normal esophageal acid exposure, and a positive symptom index, the administration of 20 mg/day of citalopram significantly eliminated symptoms, compared with placebo (61.5% vs 33.3%).[75]

TCAs are considered efficacious for treating some esophageal symptoms. Imipramine has been described to reduce pain perception in healthy volunteers, following balloon distension,[56] but its usefulness in RH has not been confirmed. As stated above, treatment with imipramine in patients with persistent reflux symptoms after PPI use was associated with improved quality of life, measured by the SF-36 score, but has not been associated with symptom reduction, compared with placebo, as reported in the study by Limsrivilai et al.[49] that included patients with FH and RH. In addition, a study that evaluated the effect of nortriptyline on the brain response to esophageal acid infusion showed that the drug significantly reduced pain response in the prefrontal cortex, although the clinical significance of such a finding is not known.[76]

At present there are no studies that evaluate the role of other neuromodulators (SNRIs, trazodone, GABA analogues) in the treatment of RH. In selected patients, central acting neuromodulators can be beneficial for symptoms, depending on comorbidities, the coexistence of FCP, treatment response, adverse effects, previous exposures, and availability.[2]

Globus

- *TCAs may be considered for globus that is not associated with reflux or motor disorders, and in cases of psychiatric comorbidity, other neuromodulators may be considered.*

Globus is defined as an intermittent or persistent nonpainful sensation of a foreign body or lump in the throat, more commonly between the thyroid cartilage and the sternal notch, and is frequently associated with dysphagia or odynophagia and improves upon swallowing.[41] It can be associated with GERD, RH, mucosal inlet patch in the upper esophagus, esophageal motor disorders, alterations in the perception or peripheral or central processing of sensations, as well as psychologic/psychiatric abnormalities, including anxiety and somatization.[77] If the patient has an associated psychiatric disorder, it should be treated with the indicated neuromodulator at the appropriate dose. A study comparing the effectiveness of SNRIs with selective potassium blockers concluded that response to the neuromodulator increased if the patient had somatization.[78] In patients with negative tests, treatment is based on neuromodulators, despite scant evidence. A study compared the use of amitriptyline at a low dose (25 mg/day) with pantoprazole, at 4 weeks. The amitriptyline group had significant improvement in both the Glasgow Edinburgh Throat Scale (GETS) score and the SF-36 questionnaire, as well as in quality of sleep.[79] A descriptive review that evaluated the use of escitalopram in different DGBI reported improvement in 64% of patients in a case series of 14 subjects with globus.[80] The meta-analysis conducted by Yeh et al.[51] evaluated neuromodulators in esophageal DGBI and the response rate with neuromodulators in globus varied between 46% and 75%, with an odds ratio (OR) of 6.30 (95% CI 4.17-9.50), but it only included 3 studies.

Fig. 1 shows the recommended neuromodulators, according to the different groups of esophageal DGBI.

Gastroduodenal disorders

Functional dyspepsia (FD)

- *We recommend the use of TCAs for symptomatic control of epigastric pain syndrome (EPS). TCAs may also be considered for postprandial distress syndrome (PDS).*

As a group, neuromodulators have been shown to be useful for treating FD, with a number-needed-to-treat (NNT) of 6.[81] Early studies and systematic reviews classified them as antidepressants or anxiolytics, or grouped them into a single category,[82] but the better understanding of DGBI has shown there are important differences between groups. Several studies have described the usefulness of TCAs in FD, with that particular subgroup showing a better level of evidence. Among the TCAs, amitriptyline has been the most widely studied, and five trials have provided evidence on its usefulness. The first was a case series, in which all of the 7 patients with FD reported symptom improvement after 4 weeks of treatment with 50 mg/day of amitriptyline.[83] The second reported reduced nausea intensity and postprandial symptoms after a 2-week dose of 25-50 mg/day, compared with placebo.[84] In the third study, a dose of 12.5-50 mg/day reduced nausea and total symptom scores in 38 patients with FD, with no differences in bloating, satiety, upper abdominal pain, or tolerance of liquids in a nutrient drink test. The adverse event rate was significantly higher for amitriptyline (72% vs 35%, $p = 0.03$), particularly somnolence.[85] A recent study compared the effect of TCAs with SSRIs in FD and found that amitriptyline was superior to escitalopram and placebo for symptom relief (53% vs 38% and 40% vs 28%, respectively) in the subgroup of patients with PDS-FD, with an OR of 3 (95% CI 1.1-9.0).[86] The most recent study compared the effect of pantoprazole with a low dose of amitriptyline (25 mg at bedtime) in EPS. At 4 weeks, symptom severity was lower in the amitriptyline group, but there was no improvement in psychologic stress or anxiety scores.[87] Evidence with imipramine comes from a recent study that evaluated 107 patients with FD refractory to esomeprazole and domperidone, in which an increasing dose every 2 weeks versus placebo was compared. Overall dyspepsia symptom scores showed significant improvement in the treatment group in an intention-to-treat analysis (63.6% vs 36.5%) with a NNT of 4. In that study, 18% of the patients in the imipramine

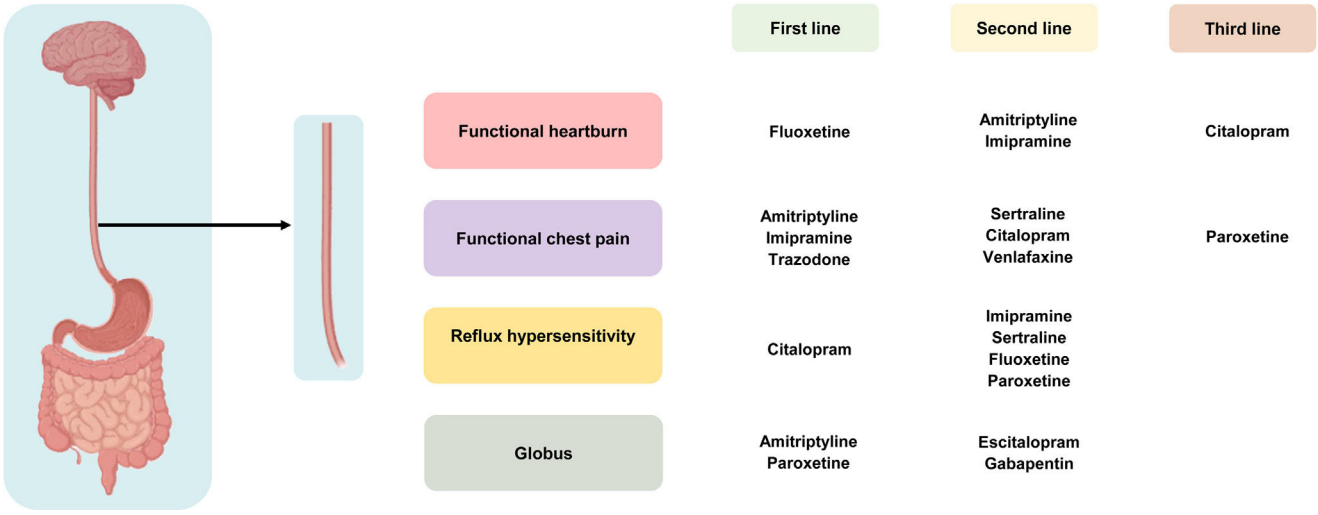

Figure 1 Esophageal disorders.
Classification and therapeutic options for functional esophageal disorders, treatment lines based on efficacy and available clinical evidence.

group withdrew from the study due to adverse effects versus 8% in the placebo group, and the most common adverse effects were dry mouth, constipation, and somnolence.[88] Five studies have evaluated the usefulness of nortriptyline in FD. In the first, it was not superior to placebo in symptom improvement or quality of life.[89] The second study showed similar effectiveness to that of mosapride at 4 weeks,[90] and in the third study, nortriptyline was inferior to mirtazapine in PDS.[91] In the fourth study, nortriptyline was not superior to metacognitive therapy,[92] but in the fifth study, it was superior to duloxetine in symptom improvement, despite the fact that duloxetine was more effective for reducing anxiety.[93] In a systematic review with a network meta-analysis that evaluated treatments for FD, TCAs were ranked in second place for effectiveness (relative risk [RR] 0.71, 95% CI 0.58-0.87), just behind antipsychotics, and in first place when only studies with a low risk of bias were included.[94] Another systematic review concluded that the most effective neuromodulators in FD were those that not only had an antinociceptive effect, but also an effect on reducing anxiety. In that review, TCAs (amitriptyline) and the antipsychotic levosulpiride were significantly superior to placebo for symptom control.[95] A meta-analysis on efficacy (measured through the overall FD symptom score) and acceptability reported an OR superior to placebo for imipramine (2.21, 95% CI 1.02-4.79) and amitriptyline (1.71, 95% CI 1.06-3.09). The only neuromodulator from another group superior to placebo in that study was tandospirone.[96] Furthermore, in the 2017 meta-analysis by Ford et al.,[81] the risk of symptom persistence in FD with TCAs was less than one (RR 0.74, 95% CI 0.61.-0.91), with a NNT of 6 (4-18) and a number-needed-to-harm (NNH) of 7 (3-40). After grouping them along with psychotropics, the NNT was 2 (1.5-10).

- *The use of SSRIs and SNRIs may be considered in FD patients with psychiatric comorbidities, particularly OCD, anxiety, or depression, or when there is intolerance to TCAs.*

In comparative studies of the efficacy between different groups of antidepressants, SSRIs have not been shown to be superior to either TCAs or tetracyclic agents for symptom control. A small study conducted in Hong Kong reported improvement in the symptom rate after administration of 50 mg/day of sertraline versus placebo for 8 weeks.[97] Another study comparing amitriptyline, escitalopram, and placebo reported similar symptomatic control rates between the SSRI and placebo, but inferior to the TCA.[86] Paroxetine was inferior to mirtazapine in patients with FD and weight loss.[98] A comparative analysis between antidepressants reported escitalopram and sertraline were the less tolerated drugs due to adverse events.[99] In the meta-analysis of psychotropic drugs by Ford et al.,[81] SSRIs were not superior to placebo (RR 1.01, 95% CI 0.89-1.15) and the NNH was 16. The Rome Foundation guidelines on neuromodulator use suggest they can be useful when there is psychiatric comorbidity, particularly OCD, catastrophizing, anxiety, or depression.[1,2]

There is little evidence of the use of SNRIs in FD. The most relevant study showed no global or individual symptom improvement after comparing venlafaxine with placebo at 4 and 8 weeks of treatment, with a follow-up of 20 weeks.[100] In the study comparing nortriptyline with duloxetine, the SNRI was not superior to the TCA in symptom improvement but was more effective for anxiety control.[93] Like SSRIs, SNRIs were not superior to placebo in the meta-analysis on psychotropics (RR 1.02, 95% CI 0.80-1.30) and the NNH was

6.[81] Several guidelines and reviews consider this group as second-choice drugs for pain control, when TCAs are not tolerated.[2]

- *We recommend the use of mirtazapine for PDS, particularly when associated with weight loss. Mirtazapine may also be considered in patients with PDS/EPS overlap.*

Several mirtazapine studies have shown symptom improvement in PDS. In two controlled studies, mirtazapine, at a dose of 15-30 mg/day, was significantly associated with symptom improvement, particularly early satiety, as well as in quality of life, anxiety scale scores, and weight gain from week 2 to week 8, compared with placebo.[98,101] In one of the two studies, mirtazapine decreased depressive symptoms, when administered along with paroxetine, and the reported adverse event rate was 10-15%, with dizziness, lethargy, and fatigue as the most common symptoms.[98] Mirtazapine's therapeutic effect appears to be related to an up-regulatory effect on the ghrelin, neuropeptide Y, motilin, and gastrin receptors and a decrease in leptin, 5-hydroxytryptamine, and cholecystokinin.[98] Another trial compared the effect of mirtazapine with nortriptyline in FD, and mirtazapine significantly reduced epigastric pain, belching, and bloating, with no significant differences on the anxiety scale.[91] Despite the results of those three studies, the meta-analysis on psychotropic agents reported a risk of symptom persistence above one (RR 0.73, 95% CI 0.50-1.08).[81]

- *We recommend the use of azapirones in patients with PDS (buspirone) and EPS (tandospirone).*

The azapirones, buspirone and tandospirone, have been evaluated in two separate studies on FD. In a RCT published by the Tack group, buspirone, at a dose of 10 mg three times a day for 4 weeks, significantly reduced the severity of overall symptoms of dyspepsia, as well as individual symptoms, such as early satiety, postprandial fullness, and upper abdominal bloating, compared with placebo.[32] The second study compared a lower dose of buspirone (20 mg/day) with a low dose (15 mg/day) of clebopride or amitriptyline at 3 months, and found that buspirone reduced early satiety, which correlated with an increase in mean gastric emptying time.[102] Tandospirone was evaluated in 144 patients with FD, at dose of 10 mg three times a day for 4 weeks, and significantly reduced pain and upper abdominal discomfort scores, with a significant number of responders at weeks three and four.[103] In that and another study, tandospirone also reduced anxiety scores associated with epigastric pain.[104] Neither of those azapirones is currently available in Mexico.

- *We recommend the use of levosulpiride in patients with PDS. Olanzapine and quetiapine may be considered for controlling nausea and vomiting in FD.*

Atypical or second-generation antipsychotics are a heterogeneous group of medications that are not related to each other, and the most widely studied is levosulpiride. It is a dual-acting drug that has both a prokinetic effect due to its dopamine antagonism, as well as anxiolytic and neuromodulating effects. Several studies conducted during the 1990s reported overall FD symptom improvement associated with delayed gastric emptying.[105] A later study compared levosulpiride, at dose of 25 mg three times a day, with cisapride, in what was then called dysmotility-type dyspepsia (now renamed PDS), and reported a similar efficacy between groups for symptom control and quality of life, with a higher adverse event rate in the levosulpiride group.[106] In a network meta-analysis of treatments for FD, both sulpiride and levosulpiride showed greater efficacy (RR 0.49; 95% CI 0.36-0.69), but study quality was low and only 86 patients were included.[94] Only one study has evaluated quetiapine in FD. It was a case series of 21 patients, of whom 10 discontinued therapy due to side effects, particularly somnolence. Of the remaining 11, 6 reported improved overall symptoms.[107] Olanzapine has been evaluated for controlling nausea and vomiting in other illnesses, including cyclic vomiting syndrome, and in chemotherapy, but has never been evaluated in FD.[108,109] In the systematic review by Hojo et al.,[95] levosulpiride and amitriptyline, in combination, were superior to placebo due to their dual neuromodulating and anxiolytic effect. In the 2017 meta-analysis by Ford et al.,[81] the antipsychotic drug group was associated with a risk of symptom persistence below one (RR 0.50, 95% CI 0.37-0.67), with a NNT of 3 (4-12) and a NNH of 21 (10-74).

- *We recommend the use of peripheral neuromodulators (pregabalin and gabapentin) as adjunct therapy in EPS.*

Delta-ligands are peripheral neuromodulators that also have anxiolytic activity. Evidence of improvement in FD has been reported in three studies, one with pregabalin and two with gabapentin. Pregabalin was evaluated in a RCT that included 72 patients who were non-responders to PPIs, and the authors reported significantly higher overall self-perceived improvement rates with the drug at 4 (70.6% vs 42.1%) and 8 (70.6% vs 44.7%) weeks, in addition to reduced overall symptoms and improved quality of life.[110] Gabapentin was evaluated as adjunct therapy in a study that included 126 patients with FD that was resistant to conventional treatment, and the combination of gabapentin with omeprazole was significantly superior for overall symptomatic control, compared with omeprazole alone.[111] A retrospective open study that also evaluated gabapentin, yielded similar therapeutic results. However, the withdrawal rate due to adverse effects was superior to placebo.[112]

Gastroparesis (GP)

- *TCAs may be considered as symptomatic adjunct therapy in GP.*

GP is defined by the presence of symptoms of gastric retention, with objective evidence of delayed gastric emptying, in the absence of gastric outflow mechanical obstruction.[113] The most common symptoms in GP are nausea and/or vomiting, early satiety, bloating, and abdominal pain. The latter is a common symptom in GP, reported in up to 90% in some case series and in 72% as the main symptom, often affecting patient quality of life.[114] Different mechanisms involved in the genesis of pain in GP have been described, including gastric overdistension, autonomic dys-

function, neuronal damage, neuroimmune dysfunction, and altered central processing of pain, and GP has even been proposed to be a severe form of FD.[115] Between 37% and 42% of patients with an initial diagnosis of either GP or FD were reported to later be reclassified with the other diagnosis (GP as FD, and FD as GP).[116] Neuromodulators may reduce pain perception at different levels of the GBA through a number of mechanisms, and their efficacy has been proven in FD. Some of them may induce changes in compliance and gastric emptying, improving the main symptoms in GP.[117,118] TCAs have been shown to be effective in FD but there is less evidence in GP. Amitriptyline at 50 mg/day or nortriptyline at 25-50 mg/day reduced the frequency of nausea and vomiting in a group of patients with FD and intermittent vomiting, as well as in diabetics with nausea and vomiting, but with no objective diagnostic criteria for GP.[119,120] In a study that added nortriptyline to on-demand prokinetics or anti-emetics in refractory GP (NORIG trial), there was no improvement in the primary outcomes (global symptoms measured by the Gastrointestinal Cardinal Symptom Index [GCSI] or the subscores of satiety, fullness, or bloating) at 15 weeks.[121] Due to their central antinociceptive effect, TCAs have been proposed for GP-associated pain control, but the evidence is scarce.[122]

- *The use of SSRIs and SNRIs may be considered in GP with associated anxiety symptoms.*

SSRIs may improve associated anxiety and depression in patients with refractory GP but there is less evidence for control of symptoms related to visceral pain. In one study, the SNRI, duloxetine, improved pain associated with peripheral neuropathy in diabetics, at a dose of 60-120 mg for 12 weeks, compared with placebo, but there was a higher rate of nausea and constipation.[123]

- *Mirtazapine may be considered for controlling nausea, vomiting, and weight loss in GP.*

Tetracyclic agents have indirect effects on serotonin and noradrenaline activity through neuronal and muscarinic antagonism and an effect on 5-HT_2 and 5-HT_3 receptors.[2,124] In FD/PDS, mirtazapine has been shown to be superior over placebo for symptom improvement and weight restoration.[101] Several case reports have been published in recent years describing improvement with mirtazapine in prokinetic-refractory GP,[125,126] as well as symptom resolution in confirmed post-infectious GP.[127] In an open label trial, mirtazapine improved nausea and vomiting sub-scores in the GCSI and Clinical Patient Grading Assessment Scale (CPGAS) questionnaires at 2 and 4 weeks in patients with GP that was refractory to conventional treatment. Among the predictors of response, the group with idiopathic GP had a trend toward improvement in vomiting, and advanced-age patients had less loss of appetite. In that study, 46% of patients presented with adverse events, with 57% having more than one.[128] Mirtazapine has also been described as a possible option for reversing the effects of longstanding use of opioids for pain syndromes, including nausea and vomiting.[129]

- *Levosulpiride may be considered for the treatment of nausea and vomiting in GP.*

Levosulpiride is an atypical antipsychotic drug that accelerates gastric emptying due to its antidopaminergic and 5-HT_4 agonist effect. Two studies have reported symptom improvement in both diabetic and idiopathic GP, with a prokinetic effect similar to that of cisapride, but with no significant increase in gastric emptying.[34,130] However, another study reported that levosulpiride accelerated gastric emptying in patients with FD.[131]

- *Azapirones may be considered for controlling early satiety and bloating associated with GP.*

Buspirone and tandospirone have been shown to be beneficial in FD. Buspirone improved postprandial symptoms, such as early satiety and fundic relaxation in FD studies, but there is no similar evidence in GP. A recent RCT (the BESST trial) compared buspirone with placebo in GP, finding no differences between groups after 4 weeks of treatment. However, there was a statistical trend toward improvement in bloating with buspirone.[132,133]

- *Delta-ligands may be considered for patients with GP and peripheral neuropathy.*

The two peripheral neuromodulators, pregabalin and gabapentin, have shown efficacy in treating neuropathic pain associated with a number of medical conditions, including diabetic peripheral neuropathy, post-herpetic, post-traumatic, oncologic, and mixed conditions, and central neuritis, with a wide range of doses (pregabalin 75-600 mg/day, gabapentin 300-1200 mg/day).[134,135] A recent Cochrane review has confirmed those findings.[136] However, their usefulness in GP-associated pain control has not been evaluated in clinical studies. The fact that a chronic parallelism between the development of peripheral and autonomic neuropathy has been reported in diabetes mellitus, and that GP shares several pathophysiologic mechanisms, such as neuro-immune dysfunction, abnormal peripheral signaling, and central pain processing, suggests that from a theoretical perspective, peripheral neuromodulators could be useful in some GP subtypes with signs of peripheral neuropathy, although at present there is no evidence from clinical trials.[137]

Cyclic vomiting syndrome (CVS)

- *We recommend the use of TCAs as the first-line prophylactic approach in patients with CVS.*

CVS is a disorder characterized by recurrent and disabling self-limited episodes of nausea, vomiting, and abdominal pain that can last several days, with intervening periods of absent or minimal symptoms or even symptom-free periods between episodes,[108,138,139] and has been incorporated into the Rome IV gastroduodenal DGBI criteria.[140] Its pathophysiology is multifactorial and includes alterations in mitochondrial polymorphisms, the endocannabinoid signaling system, nervous system dysregulation, and allostasis.[141] Because it is a condition that only recently has been rec-

ognized in adults, the majority of evidence justifying the recommendation of TCA use in the 2019 American Neurogastroenterology and Motility Society (ANMS) guidelines came from earlier studies in pediatric populations with CVS, and later from studies with mixed, adult, and pediatric populations.[142–145] Two clinical practice guidelines have been published in recent years: a joint guideline by the ANMS-Cyclic Vomiting Syndrome Association and another by the American Gastroenterological Association (AGA), in addition to four reviews.[108,138–141,146,147] In general, those guidelines and reviews recommend the inclusion of triptans, ondansetron, antihistamines, phenothiazines, and benzodiazepines as abortive medications during the acute treatment phase. Neuromodulators can be used between episodes to prevent recurrences, particularly in severe forms of the disease (>4 episodes per year, episode duration >2 days, long recovery time between episodes, and need for emergency room visits or hospitalization during the attack). Current guidelines recommend TCAs, particularly amitriptyline, as prophylaxis. Evidence on TCA effectiveness in adults with CVS is based on retrospective open studies and two RCTs in children. From a total of 14 studies that included 600 adult and pediatric patients, 413 (70%) achieved complete or partial improvement, with a decrease in frequency, duration, or severity of the symptoms of CVS, after being treated with a TCA, more commonly amitriptyline. There is less evidence with nortriptyline and doxepin, but both drugs have shown a decrease in episode frequency and duration.[141,143,145,148–150] In the open study by Hejazi et al.,[143] TCAs reduced the frequency of episodes from 17 to 3, duration from 6 to 2 days, and number of emergency room visits from 15 to 3. Another study reported similar efficacy between amitriptyline and cyproheptadine in children.[145] According to guidelines, the average effective TCA dose is 75 to 100 mg/day and can be titrated to weekly or bi-weekly increases of 10-25 mg, in order to improve tolerability and avoid withdrawal due to adverse events, reported in 9-25% of patients.[138] Different comorbidities associated with acute attacks of CVS have been reported, such as episodes of extreme stress, anxiety, depression, panic disorders, migraine, chronic headache, autonomic dysfunction, sleep disorders, and illicit drug use, which are important factors to identify, given that they can be prevented. Migraine and a family history of migraine are more frequently associated with CVS, with a prevalence of 13-70%. An additional benefit of TCAs is their usefulness in the treatment (anxiety/depression) or prophylaxis (migraine, chronic headache) of some of the triggering factors associated with CVS crises.[151]

- *We recommend topiramate as prophylaxis in CVS when there is intolerance to TCAs. Levetiracetam and zonisamide are alternatives. Mirtazapine, olanzapine, or quetiapine may be considered as symptomatic adjunct therapy in CVS.*

Other second-line medications recommended for prophylaxis in CVS, particularly when there is no response to or intolerable adverse events from TCAs, are: neurokinin antagonists (aprepitant), certain anticonvulsants (topiramate, levetiracetam, zonisamide, valproic acid, phenobarbital), and riboflavin and coenzyme Q10 nutritional supplements; they have similar therapeutic outcomes to those of TCAs, but a higher rate of adverse effects.[24,152,153] Evidence for levetiracetam and zonisamide comes from a retrospective case series,[24] whereas evidence on other neuromodulator groups is scarce. There are no studies with SSRIs, SNRIs, or delta-ligands. Among the tetracyclic agents, anecdotal improvement with mirtazapine has been reported. A small case series that included children and youths with associated anxiety disorders reported a decrease in the frequency of vomiting episodes with mirtazapine.[154] In patients with a suboptimal response, different types of anti-emetic agents have been proposed, including ondansetron, olanzapine, and quetiapine, based on the response reported in studies involving conditions associated with severe emetogenic events, such as chemotherapy use. For instance, a Cochrane meta-analysis showed that olanzapine significantly reduced the probability of having nausea or vomiting during treatment, compared with placebo, in 25-50% of patients, with a RR of 5.48 (1.35-22.20),[155] but there are no studies on CVS.

Chronic nausea and vomiting syndrome (CNVS)

- *TCAs and neuromodulators with 5-HT$_3$ antagonist action (mirtazapine, levosulpiride, olanzapine, quetiapine), as well as gabapentin, may be considered as symptomatic adjunct therapy in CNVS.*

According to the Rome IV criteria, CNVS is classified as a gastroduodenal disorder, in the section of disorders associated with nausea and vomiting.[140] The main criterion is the presence of nausea and/or vomiting that occurs at least once a week in the absence of eating disorders, rumination, or metabolic or structural disorders that explain the symptoms.[140] Given the very complex pathophysiology of nausea, involving the activation of multiple peripheral and central receptors (histamine, acetyl choline, dopamine, serotonin, neurokinin), as well as different neural transmission pathways (vestibular system, area postrema, and abdominal vagal afferent routes),[23] different drug groups with very different mechanisms have been empirically used for the symptomatic treatment of nausea and vomiting.[23,156] With CNVS now being considered a specific group of the gastroduodenal DGBI, its pathophysiology involves a complex relation between psychologic alterations, gastric accommodation, neuromuscular dysfunction, dysautonomia, abnormal parasympathetic responses, and the activation of different receptors,[157,158] all of which are associated with a decline in quality of life and reduced work productivity.[159] Some patients may benefit from the effect those drugs have on fundic relaxation, their antiemetic effect, their effect on central neuromodulation, or the effect associated with a decrease in anxiety, but most of the evidence is indirect and comes from studies of PDS, GP, and CVS. There is evidence supporting the use of central neuromodulators (TCAs, mirtazapine, levosulpiride, olanzapine, quetiapine) and peripheral neuromodulators (gabapentin), for the management of chronic nausea and vomiting, mainly from case series with oncologic, surgical, and neurologic patients, in addition to the evidence on other gastroduodenal DGBI.[36,154,160–164] The mechanism of action is primarily central and includes effects on sleep, anxiety, and depression.[154] There is little direct benefi-

cial evidence of neuromodulator use in CNVS. Two studies have evaluated TCAs in functional nausea and vomiting syndrome; the first was a retrospective study conducted before the development of the Rome criteria and the second used Rome III criteria. The first trial reviewed the clinical charts of 37 patients that used TCAs, and 57% had persistent symptoms. There was an 84% response rate, with complete remission in 51% of patients, with an average dose of 50 mg of amitriptyline, desipramine, nortriptyline, doxepin, or imipramine.[119] The largest study evaluating the response to neuromodulators in functional nausea and vomiting (according to the Rome III criteria), reported symptomatic improvement rates in 72% and resolution in 22% of 94 patients followed for 8.5 months. That study included all neuromodulator groups, but the majority of patients used TCAs (n = 65), with a symptomatic response of 72%, followed by SNRIs (n = 10), with a response of 70%, and SSRIs (n = 5), with a response of 100%. Other neuromodulators used by fewer patients but with similar responses were mirtazapine, buspirone, and the anticonvulsant, zonisamide. The authors concluded that a symptom response could be obtained in at least two-thirds of the patients, regardless of the neuromodulator used.[165] Two case series of patients with chronic nausea and vomiting evaluated the usefulness of mirtazapine. The first reported symptom remission in 51%, and 84% had significant improvement, and the second reported reduced vomiting episode duration in patients with chronic CVS and nausea and vomiting, particularly when associated with anxiety and other psychiatric disorders.[154,160] A systematic review and meta-analysis evaluated the effect of mirtazapine on postoperative nausea and vomiting in 7 studies. The drug was superior to placebo and reduced anxiety but increased the risk of sedation.[161] For some time, antipsychotics have been used as treatment for refractory nausea and vomiting associated with different conditions, including first-generation drugs, such as chlorpromazine or trifluoperazine, or second-generation drugs, such as olanzapine or quetiapine.[23] Olanzapine is one of the atypical antipsychotics tested for different conditions associated with chronic nausea and vomiting. A systematic review reported its anti-emetic usefulness in patients hospitalized with different illnesses, particularly oncologic disease, and at least two of the studies reported them to be of benefit in refractory nausea and vomiting not associated with chemotherapy or radiotherapy.[36] Quetiapine has been reported as useful for controlling nausea and vomiting in Parkinson's disease.[163] Lastly, the peripheral delta-ligand, gabapentin, has been utilized for managing nausea and vomiting associated with different medical problems, including postoperative causes, chemotherapy, hyperemesis gravidarum, CVS, and chronic headache; some reviews suggest it can be useful in other causes of chronic nausea and vomiting, including functional nausea and vomiting.[2,166]

Belching syndromes

- *Neuromodulators may be considered in combination with speech therapy and diaphragmatic breathing for the treatment of gastric belching (GB) and supragastric belching (SGB) associated with GERD (baclofen) and psychiatric comorbidity associated with DGBI (mirtazapine and buspirone).*

The treatment of disorders associated with gastric belching (GB), as well as supragastric belching (SGB), is based on their association with other disorders (GERD, dyspepsia) or the pathophysiologic mechanism involved (learned behavior, psychologic factors, or transitory lower esophageal sphincter [LES] relaxation), or both. In SGB, the clinician should explain the pathophysiologic mechanisms leading to belching, in order to establish an understanding and create awareness of the maneuvers of the passage of air into the esophagus (psychoeducation), diaphragmatic breathing exercises, cognitive therapies, and speech therapies. In the majority of cases, those measures are sufficient for the control or symptom improvement of SGB.[167–170] The usefulness of neuromodulators has not been shown in isolated GB or SGB, even though central neuromodulators could be useful when the conditions are associated with psychiatric disorders, such as anxiety or OCD linked to symptom onset or persistence, or even to anxiety related to associated bloating. Baclofen may be useful when SGB is associated with GERD due to its inhibitory effect on transitory LES relaxations.[167,171,172] In GB associated with PDS-FD, the use of gastric fundus relaxants, such as mirtazapine or buspirone, might be useful.[32]

Rumination

- *Neuromodulators may be considered in combination with behavioral therapy focusing on diaphragmatic breathing for patients with rumination (TCAs), rumination associated with GERD (baclofen), or psychiatric comorbidities (SSRIs).*

Rumination is a disorder characterized by recurrent effortless regurgitation of recently ingested food, that is subsequently re-chewed and re-swallowed, not preceded by retching, and subsides when the regurgitated material becomes acidic.[140,173] The mechanism of onset is a sudden increase in intragastric pressure that triggers LES relaxation, which induces retrograde movement of the gastric contents into the esophagus.[174] A primary maintenance pathway and several potential secondary pathophysiologic mechanisms have been described, and they may include premonitory urge, learned associations, response to specific stimuli, or an additional condition, such as SGB (supragastric rumination) or GERD (secondary rumination).[175] Treatment of rumination is based on behavioral therapy that focuses on diaphragmatic breathing, because using the diaphragm to breathe during the postprandial period competes with the desire to regurgitate. The therapy can be combined with electromyography-controlled biofeedback, in order to decrease intercostal and anterior abdominal activity.[173,176] Only one study has evaluated the usefulness of TCAs in rumination. Forty-four patients with rumination, according to Rome IV, received a TCA plus instructions and support for carrying out diaphragmatic breathing, and were followed for 3 months. After a mean follow-up period of 8.8 months, 90.9% of patients reported symptom improvement and 45% of them reported more than 80% improvement. In

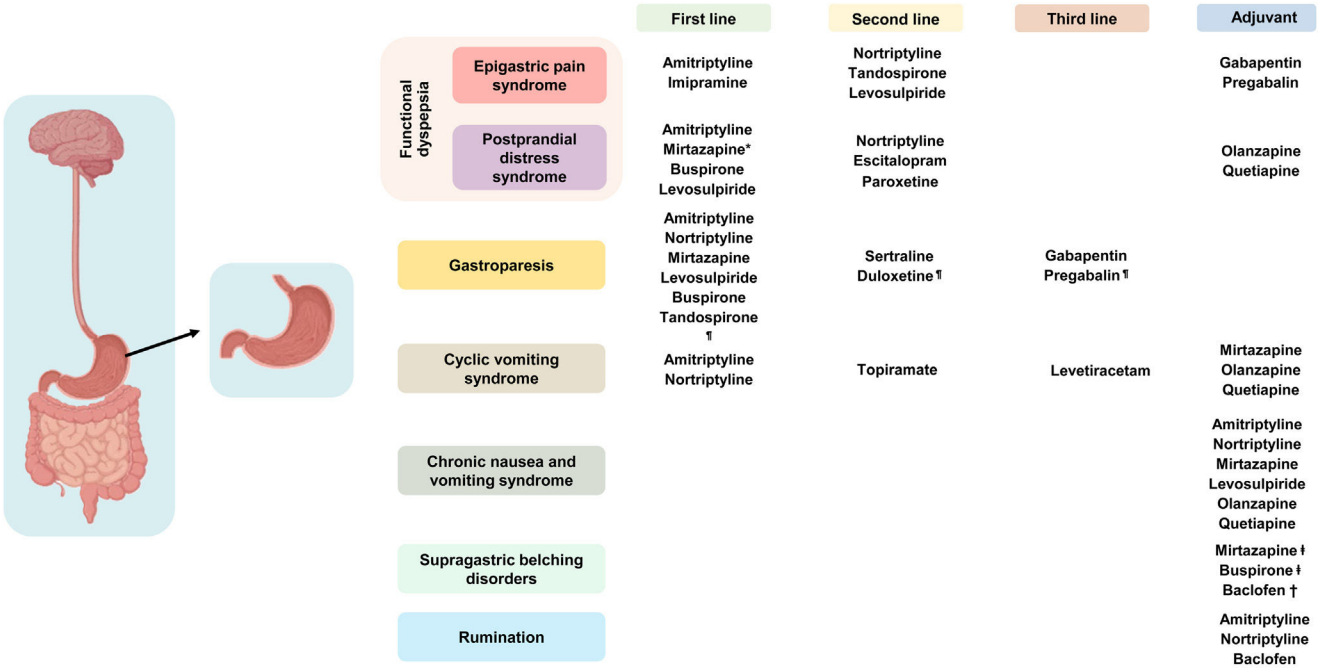

Figure 2 Gastroduodenal disorders.
ł: EPS/PDS overlap or weight loss ¶: Adjuvant symptomatic therapy, ł: Associated with PDS, †: Associated with GERD.
Classification and therapeutic approaches for functional gastroduodenal disorders, including treatment lines based on efficacy and the adjunctive role in therapy.

addition, weight was stabilized in 80.6% of the patients. Because previously published response rates with diaphragmatic breathing alone are high, the net effect of adding a neuromodulator to the behavioral therapy is not known.[177] With the exception of that single study, current evidence does not support the effectiveness of neuromodulators for reducing rumination episodes, and therefore, they are not recommended as monotherapy. Some guidelines suggest their use only for treating psychiatric comorbidities, following the indications for the associated DGBI.[175]

Fig. 2 summarizes the principal neuromodulators recommended for managing gastroduodenal DGBI.

Intestinal disorders

Centrally mediated abdominal pain (CMAP)

- *The use of TCAs, SNRIs, and delta-ligands is recommended for managing patients with CMAP. Additive or combined therapy can be considered in patients with suboptimal response.*

Because of the neuromodulators' analgesic effect (see previous sections), this group of medications is recommended for the management of CMAP. Nevertheless, it is important to point out that specific evidence of their use in CMAP is limited, and the majority of studies extrapolate their results of abdominal pain onto other functional intestinal disorders, especially irritable bowel syndrome (IBS). For example, amitriptyline, nortriptyline, and duloxetine have been shown to improve abdominal pain in IBS.[178–180] There is only one study specifically on CMAP that evaluated pregabalin efficacy. In that RCT, patients were assigned to either pregabalin (75 mg) or pinaverium bromide, or a combination of both, three times a day for 4 weeks.[181] The primary results measured the severity and frequency of abdominal pain at weeks 2 and 4 and the secondary results evaluated the decrease in abdominal pain scores and changes in the self-reported Somatic Symptom Scale (SSS), the Patient Health Questionnaire 15 (PHQ-15), and the Generalized Anxiety Disorder scale 7 (GAD-7). A total of 102 patients participated in the study and the results showed that those that received pregabalin, whether alone or together with pinaverium bromide, had a greater decrease in the severity and frequency of abdominal pain, compared with the patients that received pinaverium bromide alone. Upon comparing the SSS, PHQ-15, and GAD-7 scores, the patients on pregabalin or the combined regimen had a greater reduction than those that received pinaverium bromide alone ($p = 0.0002$, $p = 0.0002$, and $p = 0.0033$). In addition, the patients in the pregabalin groups also reported significant improvement in somatic and anxiety symptoms, compared with the pinaverium bromide group. In conclusion, that study suggested that pregabalin could be beneficial in pain management in CMAP, as well as for the associated somatic symptoms and symptoms of anxiety.

''Additive'' therapy, i.e., the combination of two or more neuromodulators with different action pathways, has not been explored in CMAP or other DGBI. Its use is based on expert recommendation and on extrapolating evidence from the individual use of each drug. Strict follow-up is required,

with close monitoring of the patients with said treatment due to potential drug interactions and adverse effects.

- *The use of nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, and opioid analgesics is not recommended for the management of CMAP.*

Given that within the very complex pathophysiology of CMAP, tissue inflammation has not been described as a cause of symptoms, the use of NSAIDs, steroids, and opioids have no role in treatment. Moreover, extrapolating their toxicity data (predominantly gastrointestinal and renal), their use for a chronic condition like CMAP can be more harmful than beneficial. An entity called narcotic bowel syndrome/opioid-induced gastrointestinal hyperalgesia has been described that is associated with continuous use and increasing doses of those types of analgesics for pain control. Many patients with CMAP have a DGBI and are started on narcotics, making the rapid detection of narcotic bowel syndrome/opioid-induced gastrointestinal hyperalgesia crucial for discontinuing their use as soon as possible, and the intervention of pain specialists for reducing the established use of those medications is also important for managing the problem.[182]

Irritable bowel syndrome (IBS)

- *We recommend TCAs for managing abdominal pain in IBS without constipation.*

TCAs are the group of neuromodulators with greater evidence in the management of IBS.[10,178–181,183,184] Among them, amitriptyline has been shown to be effective for abdominal pain relief and overall symptom improvement. Due to its anticholinergic effect, it often induces constipation and may improve stool consistency and reduce stool frequency, making it particularly useful in diarrhea-predominant IBS (IBS-D) and mixed IBS (IBS-M). The evidence supporting the use of TCAs comes from several meta-analyses. In the meta-analysis by Ford et al.[185] that included 12 RCTs and 787 patients, out of the 436 patients that received active therapy, 186 (42.7%) had no symptom improvement after treatment, compared with 224 (63.8%) of the 351 that received placebo. The NNT with TCAs was 4.5 (95% CI 3.5-7). The recently published ATLANTIS study can be considered the evidence that was lacking for supporting the use of amitriptyline in IBS.[186] In that RCT, amitriptyline was evaluated as second-line therapy for patients with IBS in any of its clinical subtypes, starting at a dose of 10 mg with weekly increases up to 30 mg, according to patient tolerance. Treatment was maintained for 6 months, after which there was a mean decrease of 27 points on the IBS-SSS scale (95% CI 7-46.9) ($p = 0.0079$) in the group treated with amitriptyline, compared with the control group. In addition, adequate symptom improvement was significantly superior in the amitriptyline group, with a RR of 1.56 (95% CI 1.20-2.30) ($p = 0.008$). The greater effect was seen in abdominal pain reduction, with no significant impact on bloating. Usual amitriptyline doses start at 6.25 mg (1/4 of a 25 mg tablet, which is the lowest presentation available in Mexico) every 24 hours, with the possibility of increasing the dose up to 50 mg, if needed. Afterwards, maintenance treatment for 6 to 12 months is recommended to prevent relapses. Importantly, if during treatment there are relapses with the dose reached, it can be adjusted as necessary.

- *In patients with IBS, SSRIs may be considered for managing anxiety and hypervigilance, and SNRIs for pain.*

Some studies have shown the efficacy of SSRIs in IBS. For example, a RCT reported that citalopram, compared with placebo, reduced abdominal pain and bloating scores, independent from anxiety or depression.[29] In another study, paroxetine was associated with global symptom improvement in individuals with IBS,[187] and fluoxetine decreased abdominal discomfort in IBS-C.[188] However, the most recent meta-analyses reported that SSRIs are not effective for pain management in IBS. In a trial conducted by Ladabaum et al.,[189] in which citalopram was compared with placebo, patients receiving citalopram did not have a higher response rate than that of the placebo group, with an OR for weekly clinical response of 0.80 (95% CI 0.61-1.04). In a meta-analysis by Xie et al.,[190] SSRI use did not show a statistically significant difference in overall symptom improvement in patients with IBS, compared with controls (RR = 1.38, 95% CI 0.83-2.28). Likewise, the sub-analysis showed that SSRIs did not improve pain or quality of life in the affected patients. Based on a meta-analysis with 7 RCTs and 356 participants, the use of SSRIs in IBS may be considered when anxiety is the predominant symptom and neither pain nor diarrhea are a relevant problem. The RR in favor of SSRIs was 0.74; (95% CI 0.58-0.95) and the NNT was 6.8.[191]

SNRIs have been used in chronic pain management, with greater evidence in patients with fibromyalgia. However, there is growing evidence supporting their use in IBS. In a pilot study conducted by Brennan et al.,[192] duloxetine, at a dose of 60 mg for 12 weeks, had a positive impact on quality of life, abdominal pain, and other symptoms related to visceral hypersensitivity, such as bowel urgency and subjective bloating. Nevertheless, as with TCAs, in that study the most frequent GI adverse effect was an exacerbation of constipation. In another trial carried out by Kaplan et al.,[193] in patients with IBS and anxiety, duloxetine was effective for treating anxiety, symptom severity, and quality of life in patients with IBS, according to the IBS-SSS and IBS-QOL scores.

- *Delta-ligands (pregabalin and gabapentin) may be considered for managing pain and abdominal distension in IBS, particularly in patients with comorbidities, such as fibromyalgia or pain originating from the abdominal wall.*

The effect of pregabalin on visceral sensitivity has been evaluated in patients with IBS. The first study included 26 patients diagnosed according to the Rome II criteria, and those with rectal hypersensitivity (pain threshold $\leq$ 28 mmHg) receiving pregabalin for 3 weeks (ascending dose: 50 mg tid on days 1 to 3, 100 mg tid on days 4 to 7, 150 mg tid on days 8 to 11, and 200 mg tid on days 12 to 21 $\pm$ 4) had significant improvement in visceral sensitivity, compared with placebo ($p = 0.045$).[194] Pregabalin also increased thresholds of bowel urgency ($p = 0.008$) and pain, and had an effect on allodynia ($p = 0.048$) and greater rectal compliance ($p < 0.0001$), suggesting a positive effect on both sensory

and motor responses in those patients. However, a second study with 18 IBS-C patients who received a single dose of 200 mg of pregabalin versus placebo found no significant reduction in pain during measurements of compliance or other motility parameters of the colon.[195] In a recent RCT by Saito et al.,[196] the efficacy of pregabalin was evaluated in 85 patients (86% women) with IBS diagnosed with the Rome III criteria. A pregabalin dose of 225 mg twice a day for 12 weeks was administered, and there was a significant decrease in pain scores at weeks 9 to 12, compared with the placebo group ($p = 0.008$), as well as improvement in the severity of intestinal symptoms, diarrhea ($p = 0.049$), and bloating ($p = 0.016$), with no significant differences in constipation between groups.

Functional abdominal distension (FAD)

- *Neuromodulators may be considered in selected patients with FAD, especially when it coexists with other DGBI or with psychiatric comorbidities.*

FAD (objective/subjective) significantly affects patient quality of life.[197] This condition tends to be the result of dysfunction of multiple mechanisms along the GBA, including visceral hypersensitivity due to a central dysregulation of incoming visceral signals. Those symptoms can be amplified, especially when disorders, such as anxiety, depression, or somatization, coexist. Treatment is multifactorial and includes dietary changes, probiotics, antibiotics, prokinetic agents, and neuromodulators, which have been shown to be effective in managing FAD. Central neuromodulators, such as TCAs and SSRIs, have been particularly effective in reducing visceral sensations.[198] FAD often coexists with other DGBI, such as IBS and FD, and TCAs, such as amitriptyline, are useful because of their capacity to decrease intestinal motility and improve the visceral pain threshold, resulting in a significant decrease in bloating in patients with IBS-D. On the other hand, a study conducted on patients with FAD showed that both amitriptyline (50 mg daily) and escitalopram (10 mg daily) significantly improved postprandial bloating, compared with placebo ($p = 0.03$ and $p = 0.02$, respectively).[199] In another study, buspirone significantly improved upper abdominal bloating in patients with FD,[32] an effect apparently related to fundic compliance and relaxation. The tested dose in the treatment of bloating associated with FD ranged from 15 to 45 mg twice a day.

Functional anorectal pain

- *Neuromodulators may be considered in patients who do not respond adequately to conservative treatments for managing functional anorectal pain.*

According to the Rome IV criteria, the painful anorectal syndromes include levator ani syndrome (LAS), nonspecific functional anorectal pain (FARP), and proctalgia fugax. LAS and nonspecific FARP are characterized by the presence of chronic or recurrent rectal pain or sensation of discomfort that lasts at least 30 minutes, with no evidence of a structural or systemic explanation for the symptoms, and is distinguished by the presence (LAS) or absence (nonspecific FARP) of pain upon palpating the levator ani muscle.[200] Proctalgia fugax is characterized by acute recurrent anorectal pain, in the absence of organic pelvic or proctologic disease. It is separate from bowel movements and lasts fewer than 30 minutes, with complete remission between episodes. Neuromodulators may be considered a therapeutic option for the management of functional anorectal disorders, in patients who do not adequately respond to conservative treatments, such as pelvic floor physical therapy or stress management. Neuromodulators, such as TCAs or SSRIs, as well as gabapentin, may be used due to their analgesic properties and may be combined with muscle relaxants, such as cyclobenzaprine. No RCTs have been conducted that confirm the efficacy of medical therapies in that particular group of patients, and their side effects could limit their usefulness. However, different groups of experts (e.g., C. Knowles at Cleveland Clinic London) use low doses of clomipramine in patients with coexisting anxiety disorders.[201]

Fig. 3 summarizes the main neuromodulators recommended for managing intestinal and anorectal DGBI.

Recommendations for the starting, scaling, addition, and discontinuation of neuromodulators

- *We recommend selecting neuromodulators based on their pharmacologic properties, adverse effects, and predominant symptom.*

The mechanism of action of each group of neuromodulators on the stimulation or inhibition of central or peripheral receptors and transporters, results in an increase or decrease in the levels and/or availability of monoamines in the presynaptic space (serotonin, noradrenaline, and dopamine), with a subsequent effect on sensitivity, secretion, and GI motility.[2] Neuromodulator selection should be guided by pharmacologic properties, potential adverse effects, and the predominant symptom, as well as the coexistence of more than one DGBI or psychiatric comorbidities.[10] When prescribing a neuromodulator, the physician should explain the reasons for its use to the patient, describe the adverse effects, and resolve all doubts and concerns, given that the terms ''antidepressants'' or ''antipsychotics'' contribute to the stigma regarding psychopharmaceuticals and can develop false perceptions about mental health and the effects on behavior.[18] When the main symptom is abdominal pain, the first-line neuromodulators are TCAs and SNRIs because SSRIs have shown little overall effect on visceral pain, due to the lack of interaction with the norepinephrine receptors, except in patients with FCP.[2,18,202] SNRIs can be useful in patients that do not tolerate TCAs. The baseline bowel habit can also guide the selection of a particular group of neuromodulators. Patients with constipation benefit more from SNRIs and quaternary TCAs (desipramine and nortriptyline), avoiding tertiary TCAs (amitriptyline and imipramine) because of their anticholinergic effect. However, amitriptyline and imipramine, together with duloxetine, are useful in patients that present with diarrhea or a mixed pattern. In those with anxiety, hypervigilance, obsessive behaviors, social phobia, or agoraphobia as the main symptom, SSRIs are the drugs of

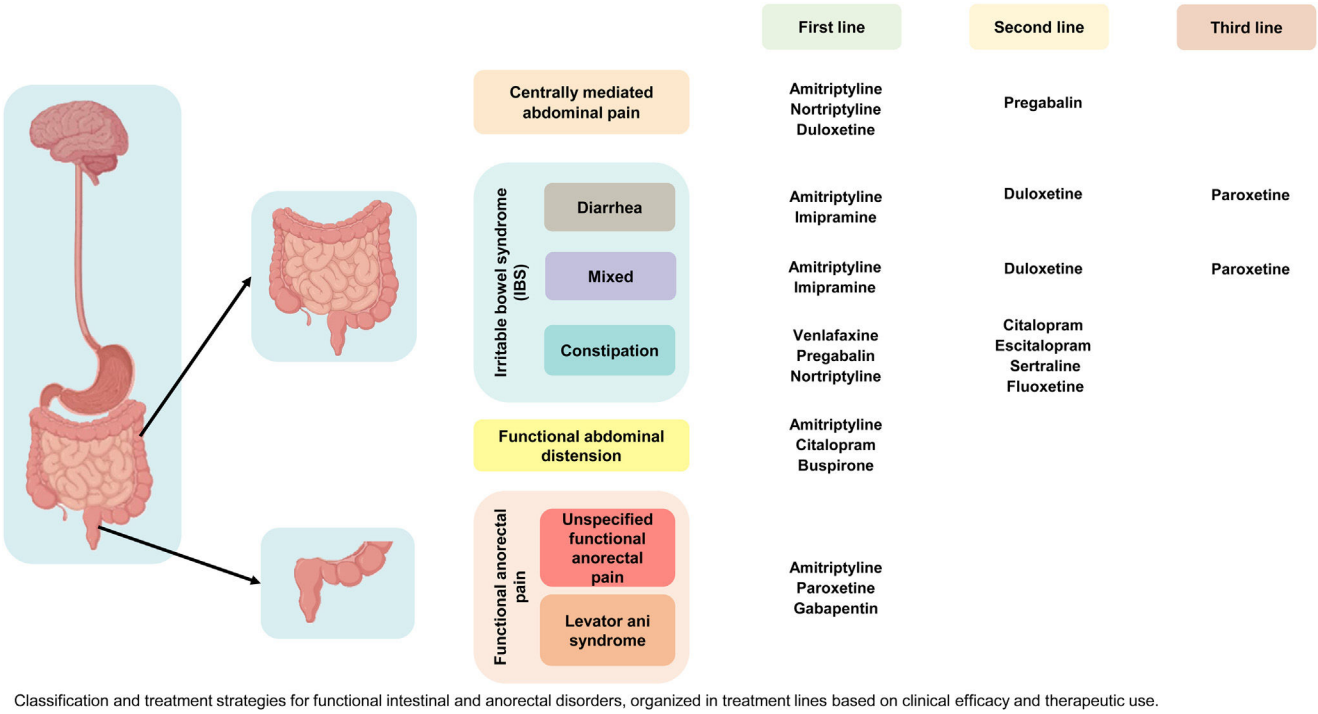

Figure 3 Intestinal and anorectal disorders.
Classification and treatment strategies for functional intestinal and anorectal disorders, organized in treatment lines based on clinical efficacy and therapeutic use.

choice. Nevertheless, it should be underlined that paroxetine is the only SSRI that has an anticholinergic effect and therefore can cause constipation.[2,10]

- *We recommend starting treatment with neuromodulators at low doses and progressively increasing them every 2-4 weeks, as tolerated, until reaching clinical response or maximum dose.*

The clinical effect of neuromodulators tends to be reached between 4 and 6 weeks, in contrast to the adverse effects that can be experienced within the first 2 weeks and are the main reason for treatment withdrawal. However, side-effects gradually subside, and the patient should be encouraged to continue with treatment until surpassing that threshold. The best strategy for starting a neuromodulator is with one-fourth or one-half of the dose for 1 to 2 weeks, to evaluate tolerance and adverse effects, and then increase the dose at biweekly intervals, until achieving the clinical response or reaching maximum dose.[2] The ATLANTIS study conducted on 463 patients with IBS from 55 primary care centers in England perfectly exemplifies the sequence of adverse events followed by the therapeutic effect, by comparing amitriptyline, at low doses (10 mg with increases of 10 mg every 3 weeks until reaching 30 mg a day) versus placebo for 6 months, reporting a significant difference in favor of the amitriptyline group. In that study, 20% of the patients discontinued amitriptyline (13% due to adverse effects), whereas 26% discontinued placebo (9% due to adverse effects).[186] Upon completing the follow-up, 61% of the patients in the amitriptyline group reported considerable symptom relief or complete resolution, compared with 45% in the placebo group (OR 1.78, 95% CI 1.19-2.66; p = 0.005), underlining the importance of the placebo effect in DGBI.[203]

- *We recommend maintaining neuromodulators at a stable dose for 6 to 12 months after reaching clinical response, before considering their discontinuation.*

Long-term neuromodulator use has been associated with an increase in neurogenesis related to increased BDNF levels (see neuromodulation pathways), with an eventual effect on neuroplasticity.[15] Treatment with neuromodulators requires a long period of time, and even though some patients respond in 4 to 8 weeks, a higher remission rate and lower relapse rate after continuing treatment for at least 6 to 12 months following symptom control have been estimated.[10] In a meta-analysis of 31 randomized studies in patients with depression, the relapse rate went down in 70% of the patients that continued with antidepressants for more than 6 months.[204]

- *We recommend switching or combining neuromodulators (additive therapy) in patients with suboptimal or partial response, in those with poor tolerance of adverse effects after dose increase, and in patients with multiple somatic symptoms or who are receiving psychiatric treatment.*

The combination of neuromodulators, also called augmentation or additive therapy, is effective because it enables the potentiating of different pharmacologic mechanisms of action, thus achieving better symptom control. However, precaution with and adequate knowledge of drug

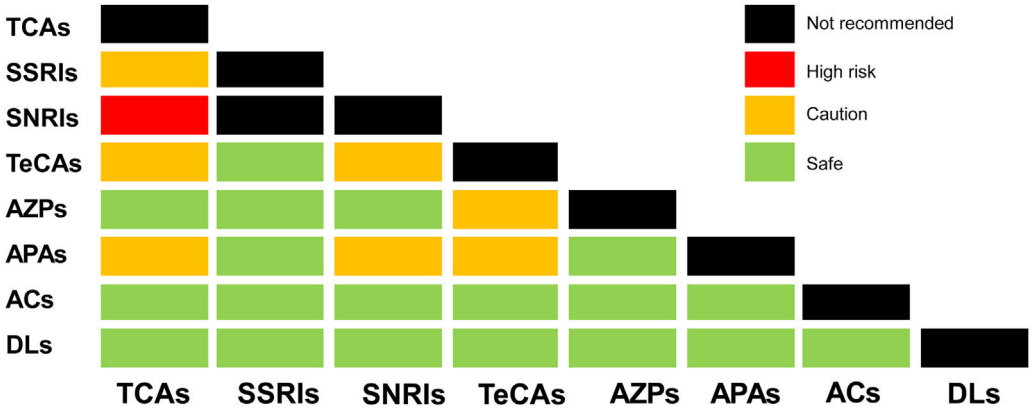

Figure 4 Potential combinations of neuromodulators.
It is not recommended to combine two or more neuromodulators of the same class. There is a high risk of serotonin syndrome, risk of falls, and/or lowering of the seizure threshold with the combination of SSRIs with SNRIs.
TCAs: Tricyclic antidepressants, **SSRIs:** Selective serotonin reuptake inhibitors, **SNRIs:** Serotonin and norepinephrine reuptake inhibitors, **TeCAs:** Tetracyclic antidepressants, **AZPs:** Azapirones, **APAs:** Atypical antipsychotics, **ACs:** Anticonvulsants, **DLs:** Delta-ligands.

interactions between neuromodulators and other drugs are recommended because they can result in severe adverse effects or the suspension of both medications. Fig. 4 illustrates the potential combinations of neuromodulators, according to their safety and risks. If a patient is considered a candidate for the combination of neuromodulators but there is insufficient experience, assessment with other areas of mental health (e.g., neurogastroenterology and/or psychiatry) to provide optimal indications for the patient and his/her follow-up is recommended, to avoid delaying the therapeutic intervention. It is also very important to explain to the patient the need for neuromodulator combination, as well as the expected therapeutic goals, given that patients can sometimes have concerns and consequently lose confidence in the physician.[202]

There are two basic strategies for combining neuromodulators:

1) Adding a peripheral neuromodulator to a central-acting one (e.g., gabapentin and sertraline).
2) Adding a central neuromodulator to another central-acting one (e.g., amitriptyline and escitalopram).

The combination of neuromodulators should be personalized, regarding unresolved symptoms (e.g., symptoms of anxiety in a patient with FD controlled with amitriptyline) or comorbidities (e.g., fibromyalgia and IBS-C controlled with sertraline). The same general recommendations are used for the starting and scaling of doses (start low and slowly increase), with greater monitoring of patient tolerance, given that adverse effects (e.g., somnolence or change in bowel habit) can be potentiated in the same way therapeutic effects are. Combining drugs of the same class (e.g., two TCAs) or with similar mechanisms of action (e.g., an SSRI with a SNRI) is not recommended because it can condition potentially fatal adverse effects (e.g., serotonergic syndrome).

- *We recommend performing a 12-lead electrocardiogram to measure the QT interval before starting TCAs or SSRIs.*

A prolonged QT interval may be observed with TCA use due to their weak affinity for sodium channels. Patients with bundle branch block or prolonged QT interval, as well as patients with concomitant use of antiarrhythmic agents (amiodarone, sotalol, quinidine, procainamide, verapamil, diltiazem) and other non-cardiovascular drugs (ondansetron, macrolides, fluoroquinolones, antibiotics, and antipsychotics, such as haloperidol, thioridazine, and sertindole) should not be given SSRIs. Mortality from antidepressant-induced arrhythmia increased with high doses of TCAs (OR 2.11, 95% CI 1.10-4.22) and with high doses of SSRIs (OR 2.78, 95% CI 1.24-6.24).[205] The risk of a prolonged QT interval should be evaluated in all patients through a 12-lead electrocardiogram with QTc (corrected QT) interval measurement before starting those classes of neuromodulators, and if QT interval prolongation is documented during treatment, the drug should be immediately discontinued and the patient should be referred for a cardiology evaluation.[10]

- *Neuromodulator gradual tapering and discontinuation, reducing the dose by* 25% *every 2-4 weeks according to patient tolerance, is recommended.*

During the continuous administration of neuromodulators, a new neurobiologic adaptation is established that leads to homeostatic balance. In this new state, the system accommodates itself to the alterations produced by the drug. Following drug dose reduction, or if it is discontinued, the new point of homeostatic balance is altered, resulting in the appearance of withdrawal and suppression symptoms. This is very common after longstanding high doses of neuromodulators, such as amitriptyline, imipramine, venlafaxine, desvenlafaxine, duloxetine, paroxetine, and fluvoxamine, that produce frequent and severe withdrawal symptoms. Symptom severity and duration depends on the time it takes

the brain to readapt itself to low levels of the drug or its absence, and the most common symptoms are anxiety, agitation, irritability, insomnia, nausea, vertigo, dysesthesias, or hallucinations.[206,207] The incidence of withdrawal symptoms is 53.9% and the development of four or more symptoms is known as discontinuation syndrome. The risk factors for discontinuation or abstinence syndrome are female sex, use of neuromodulators with a short half-life, high doses, and prolonged use (more than one year).[208]

Adverse effects

- *We recommend knowing the main adverse events and serious reactions of neuromodulators before prescribing them.*

Neuromodulators are generally safe and those used in psychiatry are indicated at low doses. However, adverse events that merit dose adjustment or discontinuation should be known and identified. The main side effects of neuromodulators are associated with the agonism or inhibition of the receptors over which they act, and some are class dependent. They usually occur before the therapeutic effect and can be reduced by starting with a low dose with periodic increases. The nocebo effect is defined as negative perceptions of the administration of a treatment (real or simulated) in a therapeutic context and tends to be triggered by symbolisms, rituals, and experiences that accompany patients during clinical activity.[209] The nocebo effect is mainly seen in patients with anticipatory anxiety due to previous treatments and not to the actual effects of the medication. It manifests as rare adverse effects or even after the first dose (before reaching therapeutic concentrations in the blood). Thus, the importance of continuing the treatment and the gradual dose increase should be emphasized to the patient, before considering the change or suspension of the drug.[8]

TCAs. The main adverse effects, as a class, are dry mouth, constipation, sexual dysfunction, urinary retention, arrhythmias, and weight gain, among others. Amitriptyline, doxepin, imipramine, and trimipramine are more commonly associated with drowsiness, but they can also cause weight gain. TCAs are more prone to cause sedation and orthostatic hypotension, and so their nighttime administration is recommended. Very early non-anticholinergic adverse events tend to be more correlated with the patient's level of anxiety, rather than the serum concentrations of the drug or the number of doses received (nocebo effect).[2,11,12,210]

SSRIs. The most common side effects of SSRIs are nausea, diarrhea, agitation, insomnia, nocturnal diaphoresis, headache, dizziness, weight loss, and sexual dysfunction. SSRI use can be accompanied by agitation and exacerbate anxiety, complicating treatment and limiting functionality. In such cases, the use of benzodiazepines (clonazepam 0.25-0.5 mg twice a day) has been proposed for symptom relief and as ''bridging'' therapy for 2 to 4 weeks, with a reduction in 4 weeks once the SSRI is better tolerated.[11] Likewise, an increase in the risk of GI bleeding has been reported, particularly when SSRIs are combined with an NSAID (OR 1.75, 95% CI 1.32-2.33).[211] Therefore, it is recommended to avoid such a combination, discontinue or avoid NSAID co-administration and monitor for signs of bleeding, or discontinue the SSRI and monitor for discontinuation syndrome, or even switch it to mirtazapine or bupropion, if necessary.[2,11,12,210]

SNRIs. Among the potential side effects related to SNRIs are nausea, agitation, dizziness, dry mouth, headache, pruritus, hypertension, sleep disorders, fatigue, and liver dysfunction. SNRI use can be accompanied by nausea, and that adverse effect decreases if the drug is taken with food. Some patients with depression can present with occult bipolar disorder, and upon starting a SNRI, or after high doses of an SNRI or SSRI, they can ''cycle'' into a hypomanic or manic episode (excessive energy and talking, accelerated thinking, euphoria, impulsiveness, insomnia, and hypersexuality), within the first 2 weeks of treatment, and should be referred for psychiatric evaluation.[11] In an English cohort study that included 21,012 electronic case records of adults with depression, the risk of mania/hypomania after starting antidepressants increased with SSRI use (HR 1.34, 95% CI 1.18-1.52) and with venlafaxine (HR 1.35, 95% CI 1.07-1.70).[2,12,212,213]

Tetracyclic agents. They can be associated with sedation, headache, dry mouth, and weight gain.[2,12,21]

Azapirones. They can cause agitation, dizziness, sedation, headache, confusion, vertigo, palpitations, and extrapyramidal manifestations.[2,12]

Atypical antipsychotics. Depending on the subgroup, they can induce sedation, dizziness, hyperprolactinemia, weight gain, diabetes mellitus, hyperlipidemia, and intestinal dysbiosis. Upon comparing them with typical or first-generation antipsychotics, they have a lower risk for causing extrapyramidal effects, such as muscle rigidity or tremors.[2,12]

Anticonvulsants. Because they are a heterogenous group, they may be associated with a variety of side effects, such as drowsiness, dizziness, weight gain, enzyme induction and interaction with other drugs, visual alterations, skin rash, hepatotoxicity, nephrotoxicity, systemic lupus erythematosus induction, movement disorders, and pruritus.[12,214]

Delta-ligands. The most common effects are sedation, dizziness, headache, vertigo, weight gain, and peripheral edema.[2,12,26]

One of the most severe complications of neuromodulator use is serotonergic syndrome. This toxidrome was first described in 1955 in a patient with tuberculosis that received treatment with iproniazid (an irreversible monoamine oxidase inhibitor) and meperidine,[215] characterized by the triad of neuromuscular anomalies, autonomic hyperactivity, and altered mental state. It occurs due to the excess of central and peripheral activation of the serotonin postsynaptic receptor and is manifested by the triad of neuromuscular anomalies (clonus, myoclonus, tremor, hyperreflexia, hypertonicity), autonomic hyperactivity (hyperthermia, tachycardia, hypertension, diarrhea), and altered mental state (agitation, confusion, anxiety, coma).[216] Serotonergic syndrome is not exclusive to antidepressants and can occur with a single drug at a therapeutic dose or in overdose, but it is more frequent with the combination of various serotonergic agents. The five most commonly associated drugs are citalopram, fluoxetine, sertraline, bupropion, and tramadol. Serotonergic syndrome should be suspected in patients with a recent history of exposure to a serotonergic drug and at least one of the fol-

Table 3 Communication strategy.

Recommended (what to do)	Not recommended (what not to do)
• Recognize symptoms and their severity • Understand the patient and the effect symptoms have on him/her • Show the patient that you believe he/she has symptoms. They are real and physically experienced • Be honest when a patient has unusual or inconsistent symptoms • Think of ways to empower the patient • Explain the connections between physical and psychologic stress with clear and positive language • Negotiate an explanation that takes culture into account • Normalize: all symptoms are biopsychosocial	• Tell the patient that there is nothing bad • Tell the patient that the symptoms are normal • Repeatedly calm the patient (unending cycle) • Tell the patient there is nothing that can help him/her • Give normal test results and calm the patient, thinking this will help him/her • Suggest to the patient that the ''real'' cause of symptoms is psychologic • Offer simplified and dichotomous explanations that are purely psychologic or somatic

lowing Hunter criteria: spontaneous clonus, inducible clonus with agitation or diaphoresis, ocular clonus with agitation or diaphoresis, tremor and hyperreflexia, or hypertonia or temperature > 38°C with ocular or inducible clonus.[217] Patients with a history of stable dose or adequate tolerance are not likely to develop the syndrome, but the risk increases with the combination of neuromodulators, even with low doses, or with drug interactions that inhibit the metabolism of the serotonergic agent. At the follow-up visits, the recommendation is to ask the patient about somatic or psychiatric symptoms related to neuromodulator use because patients often normalize them or omit them during the consultation, which can result in the delayed identification and treatment of a serious disease.

Joint use with psychiatry

- *Joint management with psychiatry is recommended in patients with DGBI and psychiatric comorbidity, or when combination therapy with neuromodulators and psychotherapy is required.*

Stress and psychologic factors have been established as contributors, and in many cases, as triggering factors of symptoms in patients with DGBI, particularly hypervigilance, anxiety, somatization, and catastrophizing. Those same factors can often perpetuate the symptomatology. Not all gastroenterologists are familiar or comfortable with the search for and discussion of those factors. Therefore, a multidisciplinary approach that involves mental health personnel (psychologist and psychiatrist) is recommended.[218]

Communication skills and adherence strategies (Table 3)

- *We recommend teaching communication skills, such as active listening and emotion validation, to guarantee comprehensive and empathetic care, improving patient satisfaction, perception of physician approachability, and treatment adherence.*
- *We recommend establishing two-way communication between physicians and patients, to improve understanding and involve the patients in their own treatment and adherence. We recommend explaining the pathophysiologic mechanisms of DGBI, the concept of neuromodulation, and the rationale for treatment.*

An approach that includes the evaluation of anxiety specifically related to each DGBI, effect on quality of life, and behavior toward the disease is recommended. Examples of specific anxiety include fear of having a cardiac comorbidity in FCP, fear of food triggers in FD, fear of bowel movements in IBS, or fear of accidental stool leakage when outside of the home in fecal incontinence (FI). This requires communication skills, as well as a good doctor-patient relationship that enables validating, empathizing, providing trust, conceptualizing behavior, educating, and discussing management options.[218] In Germany, a cross-sectional study examined the doctor-patient relationship through conversations and validated questionnaires on difficult doctor-patient relationships. A total of 520 physicians and 5,354 patients participated, and among the hypotheses on the development of DGBI, the physicians mainly suspected burdens related to stress as the cause in the majority of cases (65.4%), whereas patients more often felt that the main reasons for their symptoms were food (55.4%) or other somatic causes (43.6%). Functional and/or somatoform symptoms led to difficult interactions more often than ''somatic'' symptoms, and to the perception of patients as time-consuming. Even though the physicians reported taking enough time to speak to their patients with DGBI, only one-third completely agreed they had enough time, and only 5% felt sufficiently compensated by those conversations with patients.[219] Good communication in medical care correlates with better adherence by the patient (OR 1.62), compared with poor communication.[220] Interpersonal interventions improve communication in the doctor-patient relationship. This was demonstrated by a systematic review of RCTs and controlled observational studies that evaluated interpersonal doctor-patient interventions in 73 studies, reporting that up to 67% of interventions were directed

toward the physician. The impact on patient experience was measured and there were improvements in patient satisfaction, a patient-centered experience, and a decrease in unmet needs, which often corresponded to a positive impact on other patient health outcomes, such as quality of life, depression, and adherence. Improved interpersonal interactions positively impacted physician wellbeing, burnout, stress, and confidence in communicating with difficult patients.[221]

In their analysis on communication skills, the Rome group concluded that evidence supports the fact that interventions targeting patient-physician interaction improve population health and the patient-physician experience, and training in communication skills was the most common intervention, leading to better communication, satisfaction, and perception of physician approachability. They recommend a series of 5 practical points: 1) preparation with intent before seeing the patient, 2) listening intently and entirely, 3) formulating an agreed agenda with the patient as to what matters most, 4) connecting with the patient's story, and 5) exploring emotional cues by naming and validating the patient's feelings.[13] Taking the time to explain the pathophysiologic mechanisms behind DGBI, the concept of neuromodulation, the mechanisms of action of the medication, the rationale for its use, and the expected response is recommended. This will improve the understanding of its pharmacologic value, reducing the stigma attached to neuromodulator use, and most likely increase treatment adherence.[2]

Primary affective disorder

- *Screening for depression and anxiety in all patients with DGBI, using self-rated scales (HADS, PHQ-9, or GAD-7), is recommended.*

An important association between DGBI and primary affective disorders has been described.[218] Given that symptoms may overlap between entities, cognitive and affective symptoms are key in the differential diagnosis. Our group of experts found no validation studies using the hospital anxiety and depression scale (HADS) in IBS or other DGBI populations. However, it has been validated in Mexico in other GI entities with a high prevalence of depression and anxiety, such as inflammatory bowel disease (IBD).[222] On the HADS, 20 to 23 points represents moderate symptoms and a score above 24 points signifies severe symptoms. The PHQ-9 patient health questionnaire has been validated in a Mexican population for major depressive disorder screening, and a score of 10 or more indicates a moderate-to-severe depressive episode that requires starting treatment with an antidepressant.[223] The GAD-7, developed by the World Health Organization (WHO), established a cutoff point above 10 for moderate-to-severe anxiety that requires anxiolytic neuromodulators. These same cutoff points have been validated in international populations with IBS.[224]

- *Consultation with mental health professionals (psychiatry/psychology) is recommended for patients with DGBI and moderate-to-severe depression or anxiety, patients using central acting agents at the neuromodulation dose, and patients with eating disorders.*
- *When there is a moderate-to-severe depressive episode, without treatment for DGBI, gradual titration of the neuromodulator is recommended until reaching the minimum effective dose. If atypical antipsychotics, delta-ligands, or azapirones are used, or there is intolerance to TCAs or mirtazapine, combination with a SSRI at an antidepressive dose is suggested.*

Depressive symptoms, as well as major depressive disorder and anxiety disorders are frequent comorbidities in DGBI. The average overall prevalence of major depressive disorder and anxiety disorder as comorbidities associated with IBS is 15.2% and 20.7% respectively, but up to one-third of the patients with DGBI may develop symptoms of anxiety and/or depression. Evidence supports a higher risk of presenting with anxiety and depression before and after the diagnosis of a DGBI, particularly within the first year of diagnosis, as well as greater GI symptom severity associated with the comorbidity. The relationship between DGBI with depression and anxiety appears to be bidirectional. The mechanisms behind that relationship include low-grade inflammation, altered vagal signaling, and alterations in central and peripheral neural signaling.[225,226] It is important to know the minimum effective dose of central neuromodulators for treating depression in gastroenterology.[227]

Special considerations (somatic symptom disorders)

- *We recommend a multidisciplinary approach to and management of DGBI associated with affective and somatic disorders. Training physicians to have knowledge of these associations, with the support of mental health professionals, is suggested.*
- *Health professionals should adopt a more comprehensive and patient-centered approach, considering both physical symptoms and psychologic and behavioral aspects, and severity predictors, such as alexithymia, persistent somatization, and demoralization, should be detected.*
- *The use of validated and accessible evaluation instruments (PHQ-15 and SCL-90) is recommended.*

Somatization is the tendency to experience and communicate somatic discomfort in response to psychosocial stress and consequently seek medical help.[228] In the diagnostic and statistical manual of mental disorders (DSM-5), the category of somatoform disorders of the DSM-4-TR was replaced by somatic symptom disorders and related disorders.[229] The change is the identification of a physical symptom associated with significant discomfort and decline. Somatic symptom disorder underlines the importance of basing the diagnosis on the presence of positive signs and symptoms, such as the response to distressing somatic symptoms with abnormal thoughts, feelings, and behaviors, eliminating the criterion of absence of a medical explanation for the somatic symptoms.[230] There are studies that identify mental health as a strong predictor of perceived difficulty in the doctor-patient relationship, particularly in patients with multi-somatoform disorders, with an OR of 12.3 of being perceived as difficult.[219] The

application of a structured interview with revised diagnostic criteria for psychosomatic research (DCPR-R) showed that IBS symptoms were more intense when associated with psychologic comorbidities, such as alexithymia (46.8%), persistent somatization (34%), and demoralization (19.7%), with a 3-times higher prevalence of somatic symptom disorder (PHQ-12) and hypochondriasis (Whiteley index). In addition, both alexithymia and persistent somatization were predictors of severe somatic symptoms.[231] A systematic review identified 40 scales for evaluating somatic symptoms, concluding that the PHQ-15 and the symptom checklist (SCL-90) were the best options for use in large-scale population studies because of their psychometric characteristics and low burden to participants.[232] Diagnostic evaluation in patients with DGBI and those comorbidities are suggested, along with professional conduct recommendations.[233]

Nonpharmacologic neuromodulation options

Psychologic therapies

- *We recommend nonpharmacologic interventions as part of the comprehensive care for DGBI.*
- *We recommend the promotion of self-management programs to identify specific triggers, as well as the implementation of self-control strategies for managing stress.*
- *We recommend different forms of psychotherapy (cognitive behavioral therapy, gut-directed hypnotherapy, mindfulness, and psychodynamic interpersonal therapy), according to patient characteristics and goals.*
- *We recommend working on effective physician communication skills, essential for a solid and trusting relationship, to aid the patient in accepting recommendations and feeling comfortable with the referral to a mental health specialist.*

Behavior-based therapies are short, personalized, nonpharmacologic interventions focused on GI symptoms and based on skills that improve said symptoms and the psychologic comorbidity.[2,234] They may be combined with other neuromodulation and behavioral therapies, offering comprehensive and targeted therapy for DGBI.[18,235]

The Rome Foundation recommends different nonpharmacologic interventions for the treatment of DGBI:[236]

1 *Self-management programs*. They promote self-care and trust in the ability to control health and may lead to GI and psychologic symptom improvement, as well as better quality of life. They emphasize the identification of triggering factors, such as diet, exercise, and stress, as well as stress management through self-management training, available in pamphlets or manuals.
2 *Cognitive behavioral therapy (CBT)*. A technique that focuses on modifying behaviors and dysfunctional thought patterns, CBT helps patients unlearn maladaptive coping skills developed in response to GI symptoms or stress. Several RCTs have described the efficacy of CBT in DGBI, and even though an inclusion criterion in most of them was at least 4 sessions, a program of a minimum of 10 sessions (range 12-16) is recommended. Traditionally, sessions are taken in a setting of person-to-person direct contact, but currently they can be group-based, with minimal contact, or internet-delivered via an online application (app).[234,237–239] In a meta-analysis of psychologic therapies for IBS, CBT proved to be effective, whether self-administered, with minimal contact, or face-to-face, carried out by telephone, or through an online app (RR 0.61, 95% CI 0.45-0.83).[240]
3 *Gut-directed hypnotherapy*. A technique developed by Whorwell et al.[241] in 1984, it is a form of medical hypnosis where the patient is placed into a heightened state of openness to specific suggestions, usually during a series of 7-12 weekly sessions for at least 3 months, with frequency depending on the severity of each case. It can be delivered on an individual basis or via groups or video calls, at the office, or at home. Most of the evidence on its usefulness in DGBI comes from a number of studies on IBS.[242,243] The current protocol for at-home hypnosis was developed by Palsson and Whitehead in 1994.[244] During each session, a trained physician induces a heightened state of focus and awareness to increase openness to personalized post-hypnotic suggestions, focused on gut-brain dysregulation, directed at reducing the attention to and perception of abdominal pain and the impact of stress on symptoms, and increasing the sensation of control over symptoms. There is solid evidence of its efficacy in IBS, with more than 15 RCTs and a meta-analysis reporting it to be superior to education and routine therapy (symptom persistence RR 0.67, 95% CI 0.49-0.91),[234,240] and evidence on other DGBI has recently started to emerge.[245]
4 *Mindfulness*. This practice can be described as the desire to be grounded in the moment, accepting pain or painful sensations or emotions as inevitable,[234] which can help to reduce suffering and stress and improve the regulation of emotions. Patients are instructed to observe and identify details of their symptoms, without passing judgement or reacting to triggers, and the primary aim is not symptom reduction, but rather their identification and acceptance. Due to their stress-sensitive nature, symptoms can be lessened when learning to remain steady and calm in the face of stressful situations. Mindfulness therapy has been shown to be effective in a wide range of conditions by reducing stress, improving the regulation of emotions, and reducing visceral hypersensitivity. Clinical studies have reported that mindfulness may improve specific GI symptoms, such as constipation, diarrhea, bloating, and anxiety. A meta-analysis described the usefulness of mindfulness therapies in different DGBI.[246] For examples of mindfulness therapy exercises, see the Appendix B link, to access the audio supplementary material.
5 *Psychodynamic-interpersonal therapy*. Offered by a trained psychotherapist, this therapy is based on a solid and trusting relationship for repairing negative emotions associated with DBGI. There is evidence of its benefits in functional somatic syndromes, IBS, and dyspepsia.[247]

Several meta-analyses have evaluated the benefit of the different psychotherapy or psychologic therapy options, including psychoeducation, self-help, cognitive therapy, psychodynamic psychotherapy, hypnotherapy, mindfulness therapy, and relaxation therapy in IBS, reporting NNTs of 2[248] and 4.[185] In the two most recent studies that included

41 RCTs and more than 4,072 patients, the most effective psychologic interventions that also had the largest number of trials and patients were self-administered or minimal contact CBT, in-person CBT, and gut-directed hypnotherapy. However, none of them showed superiority over the other. The most effective long-term interventions were those based on CBT and gut-directed hynotherapy.[240,249]

External and digital devices

- *The use of nonpharmacologic neuromodulation devices, such as transcutaneous auricular vagus nerve stimulation (taVNS) may be considered in FD, GP, and IBS.*
- *Continuous sacral nerve stimulation (CSNS), percutaneous/transcutaneous tibial nerve stimulation (PTNS/TTNS), and translumbar and transsacral magnetic neurostimulation (TLTSMNS) may be considered in FI.*
- *CBT administered* via *digital apps or virtual reality (VR)/extended medical reality (EMR) may be considered in FD and IBS.*
- *Music therapy (MT) may be considered for associated anxiety disorders.*

Various external devices have recently been developed that function as nonpharmacologic neuromodulators. Transcranial alternating current stimulation (tACS) is a form of non-invasive brain stimulation capable of modulating phasic neural activity and central descending pathway transmission, which can induce neuromodulation and neuroplasticity, restoring neuro-intestinal signaling homeostasis.[250–252] Several external tACS devices have been evaluated for different DGBI, including transcranial vagus nerve stimulation (tVNS), transcranial cervical vagus nerve stimulation (tcVNS), transcranial auricular vagus nerve stimulation (taVNS), transcutaneous electrical acustimulation (TEA), transabdominal electrical stimulation (TES), sacral nerve stimulation (SNS), percutaneous tibial nerve stimulation (PTNS), translumbar and transsacral magnetic neurostimulation (TLSMNS). In recent years there has been evidence of preliminary improvement with taVNS in FD, CVS, and FCP.[253–255] Most of the evidence of benefits of taVNS in DGBI comes from two studies on FD. The first showed that two taVNS sessions were superior to sham therapy at 2 weeks, for reducing symptom scores and anxiety and depression scales, improving gastric accommodation, and increasing efferent vagus nerve activity and the percentage of gastric slow waves.[256] A more recent study included 300 patients with FD (Rome IV) assigned to two different taVNS groups (10 Hertz, 25 Hertz, or placebo) for 4 weeks. Response rates, defined as a decrease of more than 5 points in the daily symptom score (81.2% vs 75.9% vs 47%, respectively, $p < 0.001$), and adequate improvement (85.1% vs 80.8% vs 67%, $p < 0.05$) were significantly superior in the two treatment groups, compared with placebo.[257] TEA reduced symptom intensity in FD in 55% of patients at 2 weeks,[258] whereas in another study, it improved quality of life scores, gastric accommodation, and gastric emptying.[259] Both taVNS and tVNS have been evaluated in GP, and decreased nausea severity and improved symptoms of nausea and vomiting, satiety, fullness, bloating, and abdominal pain were reported with taVNS.[259,260] TEA has also been evaluated in IBS-C, and showed an increase in the number of complete spontaneous bowel movements, being the first study to report that finding. It also showed an improvement in abdominal pain scores.[261] Another study reported similar findings with taVNS, which improved quality of life scores and had a beneficial effect on bowel movements and pain.[262] At least three forms of neurostimulation have recently been evaluated, showing success in FI: SNS, PTNS, and TLSMNS. In general, they reduced the weekly number of FI episodes, episodes of fecal leakage, and improved quality of life.[263–268]

Digital technology has transformed the way in which we communicate and access information on any topic. Therapeutic interventions based on technology have evolved in recent years, helping in the prevention, management, and treatment of different medical problems. Symptom questionnaires and self-applicable scales, as well as recreational and relaxation programs that include varied forms of psychotherapy, are now accessible through different digital apps.[269] CBT and hypnotherapy administered online or via digital apps, with visual aids, videos, and at-home exercises, have been shown to have similar results to in-person CBT, with a reduction in symptom severity, as well as nausea, abdominal pain, and bloating scores in subjects with FD or IBS, albeit with no control groups or blinding.[269,270] The development of those apps, with the support of artificial intelligence, appears to optimize response time and reduce the number of sessions.[271]

A technology called virtual reality (VR) has recently emerged. VR is a computer-generated depiction of a three-dimensional (3D) environment that makes the users feel as if they are part of a virtual environment, with motion sensors integrated into the device that adjust the image when the person moves and limit the capacity to process and be aware of the harmful stimuli and sensations outside of the virtual world. In medicine, VR has been evaluated, showing success for the treatment of experimentally induced pain and somatic pain. In the United States, the Food and Drug Administration has renamed it ''extended medical reality'' (EMR). VR/EMR has recently been incorporated into relaxation techniques and psychotherapy modalities, such as CBT, for the treatment of DGBI, particularly FD and IBS.[272–274] In the first study evaluating VR in FD (Rome IV), patients were assigned to VR and a control group with videos of nature in 2D, every day for 2 weeks. In addition to being safe, VR was associated with improved symptom and quality of life scores.[273] In IBS, an initial validation study reported that a standardized 8-week CBT program administered through VR might help patients manage their symptoms.[274] This emerging technology is growing, and most certainly in the coming years there will be more evidence on the use of VR in other DGBI.

Musical therapy, or music therapy (MT), is reported to be associated with pleasure, which can alter brain biochemistry, inducing the release of different neurotransmitters and hormones, such as dopamine, serotonin, and oxytocin,[275] with a beneficial effect on motivation, stress reduction, and social affiliation, in addition to effects of reduced anxiety and improved quality of sleep.[276,277] Functional neuroimaging studies have shown that music induces analgesia through several mechanisms, such as the modulation of descending pathways, and has effects on the circuits associated with emotion, such as the amygdala and the cingulate cortex.[278]

A recent study reported that two MT strategies, an active improvised one, and a receptive one, for 50 minutes twice a week for 3 months, was associated with reduced depression scores.[279] Another study compared the effect of MT versus no therapy on the use of sedatives during endoscopic examinations, and the authors found that the group in MT had lower anxiety scores, greater tolerance, and less propofol use during their procedures.[280] Lastly, a meta-analysis of 14 controlled studies published in 2017 reported that MT was associated with reduced pain in conditions associated with chronic pain, with no fixed exposure or duration strategy in the majority of the studies.[281]

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Declaration of competing interest

O. Gómez-Escudero has been a speaker for Carnot, Chinoin, Adium Pharma, Alfa-Sigma, and Faes Farma.

J.M. Remes-Troche is an advisor and member of the advisory board for Adium Pharma, Carnot, Pro.Med.CS. Praha a.s., and Pisa. He is a speaker for Adium Pharma, Abbot, Carnot, Chinoin, Ferrer, Johnson and Johnson, Medix, and Medtronic.

E. Coss-Adame has been a speaker for Adium Pharma, Alfa-Sigma, Megalabs, Astra-Zeneca, Carnot, Medtronic, Abbott, Chinoin, and Grunenthal.

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Appendix A. Supplementary data

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