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SPECIAL REPORT

# Neuromodulators for Functional Gastrointestinal Disorders (Disorders of Gut–Brain Interaction): A Rome Foundation Working Team Report

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**BACKGROUND & AIMS:** Central neuromodulators (antidepressants, antipsychotics, and other central nervous system–targeted medications) are increasingly used for treatment of functional gastrointestinal disorders (FGIDs), now recognized as disorders of gut–brain interaction. However, the available evidence and guidance for the use of central neuromodulators in these conditions is scanty and incomplete. In this Rome Foundation Working Team report, a multidisciplinary team summarized available research evidence and clinical experience to provide guidance and treatment recommendations. **METHODS:** The working team summarized the literature on the pharmacology of central neuromodulators and their effects on gastrointestinal sensorimotor function and conducted an evidence-based review on their use for treating FGID syndromes. Because of the paucity of data for FGIDs, we included data for non-gastrointestinal painful disorders and specific symptoms of pain, nausea, and vomiting. This information was combined into a final document comprising a synthesis of available evidence and recommendations for clinical use guided by the research and clinical experience of the experts on the committee. **RESULTS:** The evidence-based review on neuromodulators in FGID, restricted by the limited available controlled trials, was integrated with open-label studies and case series, along with the experience of experts to create recommendations using a consensus (Delphi) approach. Due to the diversity of conditions and complexity of treatment options, specific recommendations were generated for different FGIDs. However, some general recommendations include: (1) low to modest dosages of tricyclic antidepressants provide the most convincing evidence of benefit for treating chronic gastrointestinal pain and painful FGIDs and serotonin noradrenergic reuptake inhibitors can also be recommended, though further studies are needed; (2) augmentation, that is, adding a second treatment (adding quetiapine, aripiprazole, buspirone $\alpha 2\delta$ ligand agents) is recommended when a single medication is unsuccessful or produces side effects at higher dosages; (3) treatment should be continued for 6–12 months to potentially prevent relapse; and (4) implementation of successful treatment requires effective communication skills to improve patient acceptance and adherence, and to optimize the patient–provider relationship. **CONCLUSIONS:** Based on systematic and selectively focused review and the consensus of a multidisciplinary panel, we have provided summary information and guidelines for the use of central neuromodulators in the treatment of chronic gastrointestinal symptoms and FGIDs. Further studies are needed to confirm and refine these recommendations.

*Keywords:* Functional Gastrointestinal Disorders; Central Neuromodulators; Antidepressants; Antipsychotics; Disorders of Gut Brain Interaction; Chronic Abdominal Pain.

This Rome Foundation Working Team Report provides guidance in central nervous system (CNS)–targeted pharmacotherapy for functional gastrointestinal symptoms and disorders (FGIDs). We recognize that the value and utility of antidepressants and other neuromodulators in treating patients with these disorders are not well understood by many gastroenterologists and other clinicians. This may occur because their application is not well taught in training programs or because these agents may have stigmatizing features that result from mind–body dualistic thinking.[1,2]

New evidence is changing the thinking about these disorders and their treatments. With the 2016 publication of Rome IV, the FGIDs have been redefined as disorders of gut–brain interaction,[2] characterized by any combination of motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and

***Abbreviations used in this paper:*** **CBT, cognitive behavioral therapy; CNS, central nervous system; CVS, cyclic vomiting syndrome; $D_2$, dopamine 2; DA, dopamine; EPS, epigastric pain syndrome; FD, functional dyspepsia; FGID, functional gastrointestinal disorder; GI, gastrointestinal; H1, histamine-1; 5-HT, 5-hydroxytryptamine; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; NA, noradrenalin; NBS, narcotic bowel syndrome; PDS, postprandial distress syndrome; SNRI, serotonin noradrenalin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.**

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altered CNS processing. Dysfunction in this brain–gut axis (the bidirectional neurohumoral communication between the gastrointestinal [GI] tract and CNS) is the biologic basis for these disorders and symptoms. The brain–gut axis derives from a common embryologic basis: in the developing fetus, the neural crest differentiates into the brain and spinal cord, and sends down ganglia to populate the developing endoderm, which ultimately becomes the enteric nervous system. Thus, the nervous systems of the brain and gut are "hardwired"; they share the same neurotransmitters and receptors. These neurotransmitters have actions that depend on their location, so increased serotonin in the CNS can treat depression and in the gut can cause diarrhea. The brain–gut axis with its noradrenergic, serotonergic, and dopaminergic neurotransmitter systems is particularly relevant with regard to gut motor functioning and visceral pain. Thus, antidepressants will have effects not only on psychiatric disorders, but also on chronic GI symptoms.

With this evolving understanding of gut–brain interactions, it is necessary to redefine and relabel the terminology for medications acting within this system because patients may be reluctant to use "antidepressants" for GI symptoms. Similarly, clinicians not well trained in their use may prescribe them solely to treat comorbid psychiatric disease or to reduce stress. In the light of modern research, this terminology can limit their potential clinical value. **Consistent with the Rome Foundation's new definitional guidelines, we relabel agents working both in the brain and gut as *gut–brain neuromodulators*. This term includes the primarily central neuromodulators (eg, antidepressants and antipsychotic or other centrally acting agents, such as buspirone) and the primarily peripheral neuromodulators, including serotonergic, chloride channel, $\alpha 2\delta$ (delta) ligand agents, and others. We believe this new terminology will improve understanding of their pharmacologic value, reduce stigma, and likely improve treatment adherence.**

## Methodological Approach

The Rome Foundation creates multidisciplinary working teams to evaluate areas where there is scientific uncertainty or a lack of evidence to answer clinical questions or make treatment recommendations. When the knowledge acquired is unclear or controversial, discussions ensue to achieve consensus (ie, Delphi approach).[3,4] For this working team, committee members were selected representing gastroenterology, GI motility, psychiatry, pain management, evidence-based data acquisition, and psychopharmacology. An outline was created to cover basic pharmacology of the central neuromodulators (Table 1, Figures 1–5), effects on GI physiology (Table 2), available clinical studies relating to chronic pain, non-GI painful disorders and FGIDs, and treatment approaches. A systematic evidence-based review was conducted to include the major classes of central modulators used for treating specific FGID syndromes (functional heartburn and functional chest pain, functional dyspepsia, irritable bowel syndrome [IBS], and cyclic vomiting syndrome [CVS]) (Table 3). However, we were aware

**Table 1.** Action of Neuromodulators on Transporters and Receptors

| Transporter or receptor | Stimulate or inhibit | Action | Clinical | Adverse effects | Drug class |
|---|---|---|---|---|---|
| SERT (t) | Inhibit serotonin reuptake | Increase serotonin | AD and anti-anxiety | Nausea, diarrhea | SSRI, SNRI, TCA |
| NET (t) | Inhibit norepinephrine reuptake | Increase norepinephrine | AD and analgesic | Dry mouth, sweats, constipation | SNRI, TCA |
| DAT (t) | Inhibit dopamine reuptake | Increase dopamine | Increase activation | Nausea | Buproprion, sertraline |
| $D_2$ | Receptor antagonist | Decrease dopamine | Antipsychotic and antiemetic | EPS galactorrhea | All antipsychotics |
| 5-$HT_1$ | Receptor agonist | Stimulate 5-$HT_1$ | AD and improves gastric compliance | Nausea, headache, nervousness | Buspirone |
| 5-$HT_{2A}$ | Receptor antagonist | Increase dopamine in striatum and pituitary | Antipsychotic without EPS or galactorrhea | Akathisia agitation | Atypical antipsychotics |
| 5-$HT_3$ | Receptor antagonist | Inhibit 5-$HT_3$ | Less nausea, diarrhea, pain | Constipation | Mirtazapine, olanzapine |

NOTE. Reprinted with permission from Sobin et al.[27]
AD, antidepressant; DAT, dopamine transporter; SERT, serotonin transporter.