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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 queetiapine, aripiprazole, buspirone α2δ 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...
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 (e.g., 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 (i.e., Delphi approach).\(^2\) 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...
that there would be a lack of studies adequately addressing their use in some FGIDs, so our analysis also included painful non-GI disorders (eg, fibromyalgia, low back pain, and chronic headache), given the understanding that centrally targeted agents would have similar mechanisms of action on pain. We also looked at specific symptoms, such as pain, nausea, and vomiting. The committee then proceeded to evaluate smaller studies and case reports on painful FGIDs. This information, combined with clinical experience and expert opinion, was used to generate recommendations for use of central neuromodulators (Table 4, Figure 5), including strategies for relapse prevention and avoidance of opioids and the use of communication skills to improve patient acceptance and adherence. The committee interacted through conference calls, finalizing the document during a 15-month period between April 2016 and July 2017.

The final document is a synthesis of available evidence guided by the research and clinical experience of the experts on the committee. It highlights a newer understanding of the value of central neuromodulators for FGIDs that we believe will ultimately help clinicians in the care of their patients with these GI disorders.

**Mechanisms of Action of Central Neuromodulators and Impact on Brain and Gut Physiology**

**Mechanisms of Action**

The most accepted mechanism of action of the available antidepressants remains based on the “monoamine hypothesis,” in which depression is believed to result from a deficiency in 1 or more of the 3 highly interacting monoamines: serotonin (5-hydroxytryptamine [5-HT]), noradrenalin (NA), and, to a lesser extent, dopamine (DA), in various brain circuits (whether or not accompanied by compensatory up-regulation of their post-synaptic receptors). According to this hypothesis, antidepressants work by rapidly boosting the synaptic actions of 1 or more of these monoamines, followed by a slower adaptive down-regulation and/or desensitization of post-synaptic...
monoamine receptors (Figure 1). The same mechanisms of action are believed to underlie the well-documented anxiolytic effects of antidepressants. Most classes of antidepressants boost monoamine activity by blocking the presynaptic transporters for 1 or more monoamines, which terminate their synaptic action by reuptake into the presynaptic neuron. Information on the synaptic actions of the 3 main monoamine neurotransmitter systems is provided in Figure 2.

The overall boost of monoaminergic neurotransmission, resulting in acute stimulation of pre- and post-synaptic receptors in the CNS, may also induce some of the centrally/autonomically mediated side effects of antidepressants. Boosting 5-HT neurotransmission, for example, may induce agitation, anxiety, insomnia, and sexual dysfunction (due to stimulation of 5-HT2A and 5-HT2C receptors at various sites in the CNS), as well as nausea and vomiting (due to stimulation of 5-HT3 receptors in the brainstem). Tolerance to most of these side effects usually develops relatively rapidly, although sexual dysfunction is more likely to persist. Boosting NA receptors may induce cardiovascular side effects, including alterations in heart rate and blood pressure, as well as motor activation/agitation. Nevertheless, the fact that antidepressants are typically used in somewhat lower dosages in the treatment of FGIDs compared with treatment of anxiety or mood disorders (especially with tricyclic antidepressants [TCAs]), may limit the risk of side effects.

The same pharmacologic properties that explain the antidepressant action of these drugs may also account for their analgesic effects via the brain–gut axis, which constitutes the biologic basis of visceral pain perception. First, through their monoaminergic actions, antidepressants may interfere with the function of pain-related brain circuits, especially as emotional and cognitive circuits targeted by antidepressants are highly intertwined with pain-processing regions. This may also account for the profound psychological modulation of pain experience, particularly relevant for the large group of FGID patients with comorbid mood or anxiety disorders. Second, antidepressants interfere with the complex mechanisms of pain transmission at the level of the dorsal horn of the spinal cord (ie, the first synapse in the afferent pain transmission cascade). There are important descending projections from brainstem nuclei, including the peri-aqueductal gray, raphe nuclei, locus ceruleus, and rostroventral medulla, to the dorsal horn of the spinal cord, modulating ongoing afferent pain transmission at the level of the first synapse (Figure 3). These descending pathways are controlled in a top–down fashion by brain regions, including the amygdala and perigenual anterior cingulate cortex. Importantly, these projections are primarily opioidergic, noradrenergic, and serotonergic in nature and, as a result, antidepressants can profoundly interfere with these modulatory processes.

Over the last decade, there has been increasing evidence for another mechanism of action for antidepressants relevant to treating painful FGIDs. Neuroplasticity, the loss of cortical neurons with chronic pain, traumatic life events, and psychiatric disease, and neurogenesis (or regrowth) of neurons with clinical treatment, are improving our understanding of how antidepressants can help reduce GI symptoms. The age-old concept that neural cells are...
established at birth or soon after and die, mostly in relation to major events like an ischemic stroke or brain hypoxemia, is now being revisited by evidence that CNS neurons are plastic and capable of new growth. Brain cells in regions such as the hippocampus can die after severe psychological trauma, and this is associated with developing post-traumatic stress disorder or chronic pain. Reduced cortical density after trauma is seen in other brain regions involved in emotional and pain regulation, and relevant here to pain control regions such as the cingulate cortex, in chronic and painful GI conditions including IBS and even chronic pancreatitis.

Adding to this is the evidence that antidepressant, and possibly psychological, treatments, appear to increase precur sor neuronal growth in these regions. Brain-derived neurotrophic factor levels increase with antidepressant treatment, and this correlates with longer periods of treatment and with the degree of recovery from depression. Furthermore, the longer patients are treated with antidepressants, the lower the frequency of relapse or recurrence of the depression. This may help explain why these treatments have more than immediate effects of symptom reduction; over time they may help “rewire” the brain to approach a premorbid state of functioning.

Figure 3. Simplified overview of ascending (A) and descending (B) neural pathways involved in visceral perception and pain regulation. The descending modulatory fibers from brain stem centers can alter the sensitivity of the dorsal horn neuron signaling and can serve as a central control of pain perception during visceral stimulation. Reprinted with permission from Rome Foundation.
Antidepressants

Tricyclic antidepressants. The hallmark feature of TCAs, believed to be primarily responsible for their antidepressant (and analgesic) properties, is a variable combination of 5-HT and NA reuptake inhibition properties. Due to this dual action, TCAs theoretically have a stronger potential for antidepressant effects compared with other antidepressant classes targeting only 1 monoamine system, such as selective serotonin reuptake inhibitors (SSRIs) (see Figure 4). However, this can also make these drugs more prone to the potential side effects induced by boosting 5-HT and NA neurotransmission, as outlined. Most of the TCAs have additional receptor affinities, some of which (5-HT2A and 5-HT2C receptor antagonism, for example) can contribute to their antidepressant and/or analgesic properties, while others may be primarily responsible for their side effect profile. Examples of the latter include muscarinic-1 receptor antagonism (may cause classic anticholinergic side effects, including dry mouth, constipation, drowsiness, and blurred vision), α1 adrenergic receptor antagonism (may lead to dizziness, drowsiness, and orthostatic hypotension), and histamine 1 (H1) receptor antagonism (may lead to weight gain, especially in combination with 5-HT2C antagonism, as well as drowsiness). Finally, most TCAs have weak sodium channel blocking properties, which leads to a risk of arrhythmias, and coma or seizures upon overdosing. Thus, TCAs should be avoided in patients with bundle branch block or prolonged QT intervals. In the context of FGID treatment, some of the side effects may actually be beneficial, such as slowing of GI transit due to anticholinergic properties in patients with IBS with diarrhea, and increased appetite and weight gain in patients with functional dyspepsia (FD) with early satiation and weight loss.

The general pharmacologic properties of TCAs are shown in Figure 4A, but vary slightly between different drugs within this class.

Selective serotonin reuptake inhibitors. SSRIs are characterized by selective blockade of the presynaptic 5-HT transporter (Figure 4B), thereby boosting 5-HT neurotransmission. Their primary serotonergic effect, without noradrenergic effect, leads to greater expected benefit in treating anxiety, obsessive–compulsive disorder, and phobic-related behaviors, rather than for chronic painful symptoms or disorders. This class includes the drugs fluoxetine, fluvoxamine, paroxetine, sertraline, and (es)citalopram. Besides the common feature of 5-HT reuptake inhibition, each of them can have various secondary pharmacologic properties, including 5-HT2C antagonism for fluoxetine and mild anticholinergic action for paroxetine. It remains unclear, however, how clinically relevant these secondary properties are, particularly at the rather low dosages commonly used to treat FGIDs. By boosting 5-HT neurotransmission in general, SSRIs can induce centrally mediated side effects, as explained in the section on “Mechanism of Action” as well as impact on gut physiology, as explained in the following section.

Serotonin noradrenaline reuptake inhibitors. Like the TCAs, serotonin noradrenaline reuptake inhibitors (SNRIs) primarily block both 5-HT and NA reuptake (Figure 4C), thereby boosting 5-HT and NA neurotransmission. Again similar to the TCAs, the degree of serotonergic, relative to noradrenergic reuptake inhibition activity differs somewhat between individual drugs in this class. Venlafaxine only exerts significant NA reuptake inhibition effects at doses of 225 mg or more. Duloxetine has a strong,
<table>
<thead>
<tr>
<th>Drug class, drug</th>
<th>Mode of action</th>
<th>Actions on GI sensorimotor function</th>
<th>Relevance to symptom control</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TCAs</strong></td>
<td><strong>Amitriptyline, imipramine, desipramine, nortriptyline</strong></td>
<td>Presynaptic SRI and NRI. Antagonism/inhibition of multiple post-synaptic (5-HT₂, 5-HT₃, H₁, muscarinic-1, α₁) and presynaptic (α₂) receptors.</td>
<td>Motility: slow GI transit, largely related to their anticholinergic and noradrenergic properties&lt;br&gt; Sensitivity: limited and inconsistent evidence that TCAs decrease visceral sensitivity</td>
<td>Pain reduction. Best documented for IBS, but also FD (EPS). Potential usefulness in all FGIDs where pain is a prominent feature. Side effect profile can be useful in order to reduce diarrhea and improve sleep. Drowsiness, dry mouth, constipation, sexual dysfunction, arrhythmias, and weight gain</td>
</tr>
<tr>
<td><strong>SSRIs</strong></td>
<td><strong>Citalopram, escitalopram, fluoxetine, paroxetine, sertraline</strong></td>
<td>Presynaptic SRI.</td>
<td>Motility: enhancement of gastric and small bowel propulsive motility&lt;br&gt;Sensitivity: no major impact on visceral sensitivity in healthy subjects or patients with FGIDs</td>
<td>Treatment of associated anxiety, phobic features, and OCD in FGIDs. Agitation, diarrhea, insomnia, night sweats, headache, weight loss, and sexual dysfunction.</td>
</tr>
<tr>
<td><strong>SNRIs</strong></td>
<td><strong>Duloxetine, milnacipran, venlafaxine</strong></td>
<td>Pre-synaptic SRI and NRI. Equally strong for duloxetine. NRI for venlafaxine in higher doses. Milnacipran stronger NRI than SRI effects.</td>
<td>Motility: inhibitory effect on gastric and colonic tone, but not to the degree of TCAs; more studies are needed</td>
<td>Treatment of associated pain (based on efficacy in fibromyalgia, back pain, and headache) in FGIDs. Potential use for painful FGIDs; however, formal evidence in treatment of specific FGID-related pain is lacking. Nausea, agitation, dizziness, sleep disturbance, fatigue, and liver dysfunction</td>
</tr>
<tr>
<td><strong>NA and specific serotonergic antidepressants</strong></td>
<td><strong>Mirtazapine, mianserin, trazodone</strong></td>
<td>Indirect effects resulting in increased NA and serotonergic activity through α₂ antagonism on NA and 5-HT neurons. Also 5-HT₂, 5-HT₃, H₁, muscarinic-1 antagonism</td>
<td>Motility: lack of detailed studies&lt;br&gt;Sensitivity: lack of detailed studies</td>
<td>Potential use for treatment of early satiation, weight loss, and chronic nausea/vomiting. Side effect profile can be useful to improve sleep. Sedation, headache, dry mouth, and weight gain</td>
</tr>
<tr>
<td><strong>Azapirones</strong></td>
<td><strong>Buspirone, tandospirone</strong></td>
<td>Partial pre- and post-synaptic 5-HT₁ agonists</td>
<td>Motility: enhanced esophageal contractions and increased gastric accommodation in health and FD&lt;br&gt;Sensitivity: limited data suggest no effect</td>
<td>Treatment of associated anxiety. Potential use for treatment of early satiety, fullness, and nausea, but consistent evidence in FGIDs is lacking. Sedation, headache, and vertigo</td>
</tr>
</tbody>
</table>
and roughly equal, affinity for the 5-HT and NA transporter, thereby acting as a true SNRI even at lower doses. Finally, milnacipran has stronger NA reuptake inhibition compared with 5-HT reuptake inhibition properties. These drugs are largely devoid of additional receptor affinities, as can be seen in Figure 4C. Therefore, they have a more favorable side effect profile compared with the TCAs, while still maintaining their potential analgesic benefits. However, the side effects related to boosting 5-HT and NA neurotransmission per se (see in the section on “Mechanism of action”) can obviously occur, with hypertension under venlafaxine and nausea under duloxetine being common. This makes them good candidates for treating conditions characterized by chronic painful physical symptoms (not limited to the context of depression), including neuropathic pain and functional somatic syndromes, such as fibromyalgia, which are often comorbid with FGIDs.

Noradrenergic and specific serotonergic (tetra-cyclic) antidepressants. Mirtazapine (and the older related agent mianserin) is the prototypical antidepressant in this class. It boosts both 5-HT and NA neurotransmission, not by blocking their reuptake pumps, but by blocking presynaptic α2 noradrenergic auto- and heteroreceptors on NA and 5-HT neurons, respectively, which act as brakes on both NA and 5-HT release from these respective neurons. In addition, like some of the TCAs, it has 5-HT2A and 5-HT2C receptor antagonist properties, which may account for some additional antidepressant properties, as well as a more favorable side effect profile by blocking some of the unwanted receptor actions of boosting 5-HT transmission (see section on “Mechanism of action”). The same applies to its 5-HT3 antagonist properties, which may explain its more favorable GI side effect profile, which would include reduction in nausea, pain, and diarrhea. However, through its H1 and 5-HT2C antagonist properties, mirtazapine may cause increased appetite and weight gain (a possible advantage in some FGID populations), as well as sedation. Its receptor affinity profile is shown in Figure 4D.

5-Hydroxytryptamine 1A Receptor (Partial) Agonists (Azapirones)

These agents, including buspirone and tandospirone, have been developed as non-benzodiazepine anxiolytics, which can dampen activity in fear circuitry in the brain, centered around the amygdala, through their partial agonist action at pre- and post-synaptic 5-HT1A receptors. Through the same receptor affinity at the peripheral level, this class of drugs can also directly affect GI physiology (see section on “Actions on Gastrointestinal Motility and Sensitivity”). Which of these effects (central and/or peripheral) primarily accounts for the putative effect of these agents on functional GI symptoms remains unclear.

**Atypical Antipsychotics**

Dopamine 2 (D2) receptor antagonist activity is the hallmark of antipsychotics as a class of drugs, which is responsible for both the desired antipsychotic effect and

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**Table 2.** Continued

<table>
<thead>
<tr>
<th>Drug class, drug</th>
<th>Mode of action</th>
<th>Actions on GI sensorimotor function</th>
<th>Mechanism of action</th>
<th>Side effects</th>
<th>Relevance to symptom control</th>
<th>Potential use in augmentation for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical antipsychotics</td>
<td>D2 receptor antagonist as main mechanism. Partial D2 agonism for the suprises. Various profiles of 5-HT2A antagonism (quetiapine), 5-HT1A agonism (quetiapine), H1, d1, d2 receptor antagonism.</td>
<td>Motility: lack of data Sensitivity: decreased gastric sensitivity in functional dyspepsia Motility: no data Sensitivity: increased sensitivity to rectal distention in IBS</td>
<td>5-HT1A receptor agonism (quetiapine), 5-HT3 receptor antagonism.</td>
<td>Sedation, dizziness, weight gain, hyperlipidemia, and diabetes</td>
<td>Diabetes</td>
<td>Treatment of associated general anxiety disorder or fibromyalgia</td>
</tr>
</tbody>
</table>
Table 3. Summary of Evidence for Different Classes of Central Neuromodulators as Treatments for Painful Non-Gastrointestinal Disorders and Functional Gastrointestinal Disorders

<table>
<thead>
<tr>
<th>Drug</th>
<th>Condition</th>
<th>Highest level of evidence</th>
<th>No. of participants</th>
<th>End point studied</th>
<th>Effect</th>
<th>GRADE quality of evidence</th>
<th>Adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCA</td>
<td>FD</td>
<td>Meta-analysis of 3 RCTs</td>
<td>339</td>
<td>Persistence of global symptoms Pain scores</td>
<td>RR favored TCAs (RR = 0.74; 95% CI, 0.61 to 0.91), NNT = 6</td>
<td>Moderate</td>
<td>More common with TCAs, NNH = 7</td>
<td>Only amitriptyline and imipramine studied</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Persistence of abdominal pain</td>
<td>No effect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBS</td>
<td>Meta-analysis of 11 RCTs</td>
<td>744</td>
<td>Persistence of global symptoms Persistence of abdominal pain</td>
<td>RR favored TCAs (0.69), NNT = 4</td>
<td>Moderate</td>
<td>More common with TCAs, NNH = 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noncardiac</td>
<td>Meta-analysis of 2 RCTs of imipramine</td>
<td>58</td>
<td>Percentage reduction in episodes of chest pain Mean number of episodes of chest pain</td>
<td>Reduced with TCAs</td>
<td>Very low</td>
<td>More common with TCAs</td>
<td>No evidence for other TCAs</td>
<td></td>
</tr>
<tr>
<td>chest pain</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Functional heartburn</td>
<td>1 RCT of imipramine</td>
<td>83</td>
<td>≥50% improvement in GERD scores Chest pain scores</td>
<td>No effect</td>
<td>Low</td>
<td>Constipation commoner with imipramine</td>
<td>Only 1 RCT, no evidence for other TCAs</td>
<td></td>
</tr>
<tr>
<td>Functional anorectal pain</td>
<td>1 case series</td>
<td>26</td>
<td>Pain status at discharge</td>
<td>38.5% improved</td>
<td>Very low</td>
<td>Not reported</td>
<td>No RCTs, specific TCAs not reported</td>
<td></td>
</tr>
<tr>
<td>Functional nausea and vomiting</td>
<td>1 case series</td>
<td>37</td>
<td>Complete remission of symptoms Response to therapy</td>
<td>51.4% achieved remission 83.8% achieved response</td>
<td>Very low</td>
<td>Agitation, drowsiness, and anticholinergic side effects</td>
<td>No RCTs</td>
<td></td>
</tr>
<tr>
<td>CVS</td>
<td>Pooled analysis of 4 case series</td>
<td>237</td>
<td>Response to therapy</td>
<td>75.5% achieved response</td>
<td>Very low</td>
<td>Not reported</td>
<td>No RCTs</td>
<td></td>
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<tr>
<td>Fibromyalgia</td>
<td>Meta-analysis of 4 RCTs of amitriptyline</td>
<td>275</td>
<td>Pain relief ≥50%</td>
<td>RR favored amitriptyline (RR, 2.9; 95% CI, 1.7 to 4.9), NNT = 4</td>
<td>Very low</td>
<td>More common with TCAs, NNH = 3</td>
<td>No evidence for other TCAs</td>
<td></td>
</tr>
<tr>
<td>Low back pain</td>
<td>Meta-analysis of 3 RCTs</td>
<td>148</td>
<td>Pain scores Number of days per month with headache ≥50% improvement in headaches</td>
<td>No effect</td>
<td>SMD in number of days favored TCAs RR favored TCAs (RR, 1.41; 95% CI, 1.02 to 1.89)</td>
<td>Very low</td>
<td>Not reported</td>
<td>More common with TCAS</td>
</tr>
<tr>
<td>Chronic headache</td>
<td>Meta-analysis of 8 RCTs</td>
<td>608</td>
<td></td>
<td></td>
<td>Very low</td>
<td>Not reported</td>
<td>More common with TCAS</td>
<td></td>
</tr>
</tbody>
</table>

Notes:
- RCT: Randomized Controlled Trial
- CVS: Cardiovascular System
<table>
<thead>
<tr>
<th>Drug</th>
<th>Condition</th>
<th>Highest level of evidence</th>
<th>No. of participants</th>
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<tr>
<td>SSRI</td>
<td>FD</td>
<td>Meta-analysis of 2 RCTs</td>
<td>388</td>
<td>Persistence of global symptoms</td>
<td>No effect</td>
<td>Moderate</td>
<td>No more common with SSRIs</td>
<td>Only sertraline and escitalopram studied</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pain scores</td>
<td>No effect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBS</td>
<td>Meta-analysis of 7 RCTs</td>
<td>356</td>
<td>Persistence of global symptoms</td>
<td>RR favored SSRIs (RR = 0.74; 95% CI, 0.58 to 0.95), NNT = 6</td>
<td>Moderate</td>
<td>No more common with SSRIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noncardiac chest pain</td>
<td>Meta-analysis of 4 RCTs</td>
<td>184</td>
<td>Chest pain scores</td>
<td>No effect</td>
<td>Moderate</td>
<td>No more common with SSRIs</td>
<td>Only sertraline and paroxetine studied</td>
<td></td>
</tr>
<tr>
<td>Functional heartburn</td>
<td>1 RCT of citalopram</td>
<td>75</td>
<td>Relief of predominant symptom at baseline</td>
<td>Favored citalopram, NNT = 4</td>
<td>Low</td>
<td>No more common with citalopram</td>
<td>Only 1 RCT, no evidence for other SSRIs</td>
<td></td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>Meta-analysis of 7 RCTs</td>
<td>383</td>
<td>Global symptoms Reduction in pain by ≥30%</td>
<td>RD favored SSRIs (RD, 0.14; 95% CI, 0.06 to 0.23), NNT = 7</td>
<td>Very low</td>
<td>No more common with SSRIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low back pain</td>
<td>Meta-analysis of 3 RCTs</td>
<td>199</td>
<td>Pain scores</td>
<td>No effect</td>
<td>Very low</td>
<td>Not reported</td>
<td>Only paroxetine and fluoxetine studied</td>
<td></td>
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<tr>
<td>Chronic headache</td>
<td>Meta-analysis of 2 RCTs</td>
<td>108</td>
<td>Analgesic requirement Number of days per month with headache</td>
<td>Mean difference favored SSRIs (mean difference, -1.87; 95% CI, -2.09 to -1.65)</td>
<td>Very low</td>
<td>Not reported</td>
<td>Only citalopram and sertraline studied</td>
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<tr>
<td>SNRI</td>
<td>FD</td>
<td>1 RCT of venlafaxine</td>
<td>160</td>
<td>Absence of global symptoms</td>
<td>No effect</td>
<td>Low</td>
<td>Not reported</td>
<td>Only 1 RCT, no evidence for other SNRIs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pain scores</td>
<td>No effect</td>
<td></td>
<td></td>
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<tr>
<td>IBS</td>
<td>Case series of duloxetine</td>
<td>15</td>
<td>Global symptom improvement</td>
<td>40% achieved response</td>
<td>Very low</td>
<td>Nausea, insomnia, constipation, and drowsiness</td>
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<tr>
<td>Noncardiac chest pain</td>
<td>1 crossover RCT of venlafaxine</td>
<td>50</td>
<td>&gt;50% improvement in chest pain scores</td>
<td>OR favored venlafaxine (26.0)</td>
<td>Very low</td>
<td>More common with venlafaxine</td>
<td>Only 1 RCT, no evidence for other SNRIs</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Condition</td>
<td>Highest level of evidence</td>
<td>No. of participants</td>
<td>Effect</td>
<td>GRADE quality of evidence</td>
<td>Adverse events</td>
<td>Comments</td>
<td></td>
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<tr>
<td>Biliary pain and sphincter of Oddi dysfunction</td>
<td>1 case series of duloxetine</td>
<td>18</td>
<td>Global symptom improvement Pain scores</td>
<td>50% achieved response Pain scores reduced</td>
<td>Very low</td>
<td>Fatigue, nausea, headaches, constipation, and insomnia</td>
<td>No RCTs, no evidence for other SNRIs</td>
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<tr>
<td>Fibromyalgia</td>
<td>Meta-analysis of 6 RCTs of duloxetine Meta-analysis of 3 RCTs of milnacipran</td>
<td>2249 1925</td>
<td>Pain relief ≥50% Pain relief ≥30%</td>
<td>RR favored duloxetine (1.57), NNT = 8 RR favored milnacipran (1.4), NNT = 9</td>
<td>Low High</td>
<td>More common with duloxetine More common with milnacipran, NNH = 11 to 15</td>
<td>Only duloxetine and milnacipran studied</td>
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<tr>
<td>Low back pain</td>
<td>3 RCTs of duloxetine</td>
<td>1263</td>
<td>&gt;30% reduction in pain scores Pain scores</td>
<td>Favored duloxetine in 1 RCT Reduced with duloxetine in 2 RCTs</td>
<td>Low</td>
<td>More common with duloxetine</td>
<td>No evidence for other SNRIs</td>
<td></td>
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<tr>
<td>Chronic headache</td>
<td>1 RCT of venlafaxine</td>
<td>60</td>
<td>Number of days per month with headache</td>
<td>Favored venlafaxine</td>
<td>Very low</td>
<td>More common with venlafaxine</td>
<td>Only 1 RCT, no evidence for other SNRIs</td>
<td></td>
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<tr>
<td>TCA</td>
<td>FD</td>
<td>1 RCT of mirtazapine</td>
<td>34</td>
<td>Global symptom scores Epigastric pain scores</td>
<td>Favored mirtazapine No effect</td>
<td>Very low</td>
<td>Not reported</td>
<td>Only 1 RCT, no evidence for other tetracyclic antidepressants</td>
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<tr>
<td>IBS</td>
<td>1 case series of trazodone and amoxapine</td>
<td>47</td>
<td>Global symptom improvement Global symptom remission</td>
<td>41.7%–87.5% achieved response 25.0%–33.3% achieved remission</td>
<td>Very low</td>
<td>Not reported</td>
<td>No RCTs, no evidence for other tetracyclic antidepressants</td>
<td></td>
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<tr>
<td>Noncardiac chest pain</td>
<td>1 RCT of trazodone</td>
<td>29</td>
<td>Global symptom improvement Chest pain scores</td>
<td>Favored trazodone No effect</td>
<td>Very low</td>
<td>Dizziness, drowsiness, and fatigue</td>
<td>Only 1 RCT, no evidence for other TCAs</td>
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<td>Functional nausea and vomiting</td>
<td>1 case report</td>
<td>1</td>
<td>Response to therapy</td>
<td>Patient had complete response</td>
<td>Very low</td>
<td>Not reported</td>
<td>No RCTs or case series</td>
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<tr>
<td>Fibromyalgia</td>
<td>1 RCT of mirtazapine</td>
<td>40</td>
<td>&gt;30% reduction in pain scores Pain scores</td>
<td>No effect Reduced with mirtazapine</td>
<td>Very low</td>
<td>Increased appetite, weight gain, and constipation</td>
<td>Only 1 RCT, no evidence for other tetracyclic antidepressants</td>
<td></td>
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<tr>
<td>Low back pain</td>
<td>2 RCTs of maprotiline and trazodone</td>
<td>111</td>
<td>Pain scores</td>
<td>Favored maprotiline No effect with trazodone</td>
<td>Very low</td>
<td>Constipation, dizziness, drowsiness, dry mouth, and confusion</td>
<td>Only 2 RCTs, no evidence for other tetracyclic antidepressants</td>
<td></td>
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<tr>
<td>Chronic headache</td>
<td>1 RCT of mianserin and 1 crossover RCT of mirtazapine</td>
<td>102</td>
<td>Pain scores Headache frequency, duration, and intensity</td>
<td>Favored mianserin Reduced with mirtazapine</td>
<td>Very low</td>
<td>Drowsiness, dizziness, and weight gain</td>
<td>Only 2 RCTs, no evidence for other TCAs</td>
<td></td>
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<tr>
<td>Drug</td>
<td>Condition</td>
<td>Highest level of evidence</td>
<td>No. of participants</td>
<td>End point studied</td>
<td>Effect</td>
<td>GRADE quality of evidence</td>
<td>Adverse events</td>
<td>Comments</td>
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<tr>
<td>Azapirones</td>
<td>FD</td>
<td>Meta-analysis of 3 RCTs</td>
<td>220</td>
<td>Persistence of global symptoms</td>
<td>No effect</td>
<td>Moderate</td>
<td>No more common with azapirones</td>
<td>Tandospirone beneficial for global symptoms and pain in the largest RCT</td>
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<tr>
<td></td>
<td>IBS</td>
<td>1 RCT of tandospirone</td>
<td>200</td>
<td>Global symptom improvement Abdominal pain improvement</td>
<td>Favorited tandospirone</td>
<td>Low</td>
<td>No more common with tandospirone</td>
<td>Only 1 RCT, no evidence for other azapirones, all patients also received pinaverium</td>
</tr>
<tr>
<td>Chronic headache</td>
<td>One case series of buspirone</td>
<td>26</td>
<td>&gt;50% reduction in number of days per month with headache Reduction in pain by ≥50% Reduction in pain by ≥30%</td>
<td>54.5% achieved response</td>
<td>Very low</td>
<td>Dizziness, drowsiness, and nausea</td>
<td>No RCTs, no evidence for other azapirones</td>
<td></td>
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<tr>
<td>Fibromyalgia²</td>
<td>Meta-analysis of 2 RCTs of quetiapine</td>
<td>155</td>
<td></td>
<td>No effect</td>
<td>Very low</td>
<td>Weight gain commoner with quetiapine, NNH = 12</td>
<td>Only 2 RCTs, no evidence for other atypical antipsychotic drugs</td>
<td></td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>FD</td>
<td>Meta-analysis of 3 RCTs</td>
<td>172</td>
<td>Persistence of global symptoms</td>
<td>RR favored atypical antipsychotics (RR, 0.50; 95% CI, 0.37 to 0.67), NNT = 3</td>
<td>Very low</td>
<td>No more common with atypical antipsychotics</td>
<td>Only sulpiride and levosulpiride studied</td>
</tr>
<tr>
<td>IBS</td>
<td>1 case report</td>
<td>1</td>
<td>Remission of symptoms</td>
<td>No effect Patient had complete remission</td>
<td>Very low</td>
<td>Not reported</td>
<td>No RCTs or case series</td>
<td></td>
</tr>
<tr>
<td>Chronic headache</td>
<td>1 case series of olanzapine</td>
<td>50</td>
<td>Number of days per month with headache Headache severity Improvement in headaches</td>
<td>Reduced with olanzapine Reduced with olanzapine 74.0% achieved response</td>
<td>Very low</td>
<td>Weight gain and drowsiness</td>
<td>No RCTs, no evidence for other atypical antipsychotic drugs</td>
<td></td>
</tr>
<tr>
<td>Delta ligand agents</td>
<td>FD</td>
<td>1 case series of gabapentin and pregabalin</td>
<td>41</td>
<td>Global symptom scores Pain scores</td>
<td>Reduced Reduced</td>
<td>Very low</td>
<td>Not reported</td>
<td>No RCTs</td>
</tr>
<tr>
<td>IBS</td>
<td>1 RCT of pregabalin</td>
<td>85</td>
<td>Adequate relief of global symptoms Pain scores</td>
<td>No effect Reduced with pregabalin</td>
<td>Very low</td>
<td>Not reported</td>
<td>Only 1 RCT, no evidence for other delta ligand agents</td>
<td></td>
</tr>
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</table>
Table 3. Continued

<table>
<thead>
<tr>
<th>Drug</th>
<th>Condition</th>
<th>Highest level of evidence</th>
<th>No. of participants</th>
<th>End point studied</th>
<th>Effect</th>
<th>GRADE quality of evidence</th>
<th>Adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibromyalgia</td>
<td></td>
<td>1 RCT of gabapentin</td>
<td>150, 2027</td>
<td>Reduction in pain by ≥30% Pain scores Reduction in pain by &gt;30%</td>
<td>Favored gabapentin Reduced with gabapentin RR favored pregabalin (depending on the dosage range, RR, 1.53; 95% CI, 1.18 to 1.98 for 300 mg/d to RR, 1.92; 95% CI, 1.49 to 2.48 for 450 mg/d), NNT = 7 to 11</td>
<td>Very low</td>
<td>Low</td>
<td>Dizziness, drowsiness, and light-headedness more common with gabapentin Dizziness, drowsiness, dry mouth, weight gain, and peripheral edema commoner with pregabalin</td>
</tr>
<tr>
<td>Low back pain</td>
<td></td>
<td>1 RCT of gabapentin</td>
<td>108, 44</td>
<td>Pain scores</td>
<td>No effect Reduced with pregabalin</td>
<td>Very low</td>
<td>Very low</td>
<td>Fatigue, dry mouth, difficulty concentrating, and dizziness commoner with gabapentin No more common with pregabalin</td>
</tr>
<tr>
<td>Chronic headache</td>
<td></td>
<td>1 crossover RCT of gabapentin</td>
<td>133</td>
<td>Mean difference in headache-free rates &gt;50% reduction in headache frequency</td>
<td>Favored gabapentin Favored gabapentin, NNT = 4</td>
<td>Very low</td>
<td>Very low</td>
<td>Dizziness, drowsiness, and ataxia</td>
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</tbody>
</table>

NOTE. The table summarizes the level of evidence, number of subjects and end points studied, the effect and effect size where available, quality of evidence grading, and adverse events occurrence. GRADE, grading of recommendations assessment, development and evaluation; GERD, gastroesophageal reflux disease; NNT, number need to treat; RCT, randomized controlled trial; RD, risk difference; RR, relative risk; SMD, standardized mean difference.

aBecause the more robust studies have been done in painful non-GI conditions, they are included in this table. More detailed information is included in the Supplementary Material.
Table 4. Summary of Recommended Use of Gut–Brain Neuromodulators by Condition, Based on Existing Literature and Clinical Expertise in Treating Chronic Painful and Non-Gastrointestinal Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Chronic GI pain, general considerations | 1. Low to modest dose regimens of TCAs have the most convincing evidence of benefit for treating chronic GI pain  
2. SNRIs may have at least equal benefit as TCAs based on data in other chronic, painful disorders like fibromyalgia, migraine headaches, widespread body pain, and peripheral neuropathy, though they have not been adequately tested for chronic GI pain  
3. In the patient with anxiety or multiple somatic symptoms (somatization) or where there are incomplete benefits from TCAs or SNRIs, adding an augmenting agent is the recommended next option for treating chronic GI pain  
4. Delta ligand agents treat neuropathic pain, or pain associated with fibromyalgia, a condition commonly associated with FGIDs, particularly IBS and may be of help with chronic GI pain, though studies have not adequately addressed their benefits in this condition. |
| IBS | 1. Generally, when the pain is mild to moderate and intermittent, peripherally acting agents may be sufficient, but when pain is more severe or persistent, central agents may be added or substituted  
2. The TCA class of drugs is the first-line central neuromodulator for treating IBS, especially for IBS-D. In particular, the tertiary amine TCAs (amitriptyline and imipramine) can reduce diarrhea, and also improve poor sleep quality. A secondary amine TCA (desipramine and nortriptyline) may be selected if less anticholinergic or antihistaminic effect is desired (eg, for treating pain with IBS-M or IBS-C)  
3. The SNRI class of medications (duloxetine, venlafaxine, or milnacipran) has potential to improve the pain component of IBS based on data from treating other pain disorders, and has fewer side effects than TCAs, but these agents have not been adequately studied in IBS  
4. SSRIs can be considered in IBS if anxiety states are present, and the abdominal pain and diarrhea are not the dominant clinical features |
| Functional heartburn and functional chest pain | 1. In patients with troublesome heartburn or chest pain where gastroesophageal reflux disease has been excluded, a treatment trial with a centrally acting pharmacologic agent may be considered  
2. There is insufficient evidence to recommend a particular class of central agent, though SSRIs have shown some benefit for esophageal pain along with TCAs and SNRIs. |
| FD | 1. When treating functional dyspepsia, it is best to consider the Rome IV symptom-specific subgroups: PDS and EPS  
2. Buspirone, an anxiolytic azapirone may be used for PDS where early satiety, fullness, and nausea predominate  
3. Mirtazapine is a good treatment option for PDS when there is chronic nausea and vomiting, or weight loss, and it may also help coexisting abdominal pain  
4. When the dyspeptic symptoms are consistent with EPS, studies mainly support the use of TCAs, either initially or after an unsuccessful response to a proton pump inhibitor  
5. As with other painful FGIDs, the SNRI group of medications can also be considered for patients with EPS who do not tolerate TCA treatment though confirmatory studies are lacking |
| CVS | 1. First, for treating acute episodes, the effort is to reduce the symptom severity and duration of the attacks with anti-emetic agents like ondansetron or promethazine, minimizing the use of opioids for the abdominal pain, and intravenous hydration. Benzodiazepines can be used to treat acute anxiety and distress and have independent effects on nausea reduction.  
2. Second, to prevent future episodes, cannabinoids must be eliminated and prophylactic treatment using central neuromodulators (TCAs, SNRIs, tetracyclics, atypical antipsychotics and perhaps anticonvulsants) should be instituted to reduce the severity and frequency of acute attacks. |

IBS-M, irritable bowel syndrome with diarrhea and constipation.
the undesired side effects, such as extrapyramidal symptoms/tardive dyskinesia, prolactin elevation, and affective (apathy, anhedonia) and cognitive symptoms.\(^5\) Unlike the older conventional or typical antipsychotics, in addition to \(D_2\) antagonist properties, the newer class of atypical antipsychotics is characterized by \(5-HT_{2A}\) receptor antagonist properties (olanzapine, quetiapine), rapid dissociation from the \(D_2\) receptor (most atypical antipsychotics), \(D_2\) partial agonism (amisulpiride, (levo)sulpiride, and/or \(5-HT_{1A}\) partial agonism (quetiapine).\(^2\) As \(5-HT_{1A}\) and \(5-HT_{2A}\) receptors act as brakes and accelerators, respectively, on dopaminergic neurons, all of these additional mechanisms of action reduce the impact of DA blockade in some of the pathways mentioned in the section on “Mechanism of action” and, hence, the side effects mentioned there. This includes a reduction in risk of extrapyramidal side effects, such as dystonic reactions or Parkinsonism, when compared with older typical antipsychotics like haloperidol. However, even the atypical antipsychotics are not devoid of side effects. Moreover, as with some of the typical antipsychotics, due to additional \(H_1\), \(5-HT_{2C}\), \(\alpha_1\)- and/or \(\alpha_2\)-noradrenalin receptor antagonist, anticholinergic properties (particularly olanzapine and, to a lesser extent, quetiapine), as well as some unknown properties, additional side effects, such as increased appetite; weight gain; cardiometabolic illness (dyslipidemia/diabetes); and sedation may occur. Therefore, like the typical antipsychotics, these agents should be used with sufficient care and monitoring of side effects, especially when used chronically.\(^2\) However, in the context of FGID treatment, far lower doses than the antipsychotic doses are often used, which may limit the risk of side effects.

Whether and how these central pharmacologic properties underlie the potential effect of these agents on FGID symptoms in general, and nausea and abdominal pain in particular (either as monotherapy or augmentation therapy, see section on “Actions on Gastrointestinal Motility and Sensitivity”), remains, at present, unclear. However, interference with the complex neurotransmission of ascending and descending pain pathways at the level of the dorsal horn through various receptor affinities is a theoretical possibility. In addition, atypical antipsychotics may have a profound effect on gut physiology through the receptor affinities described in the section on “Actions on Gastrointestinal Motility and Sensitivity,” which may also account for their putative effects.

Olanzapine and quetiapine have combined \(D_2/5-HT_{2A}\) antagonist properties characteristic of most atypical antipsychotics, with in addition \(H_1\), \(5-HT_{2C}\), and \(\alpha_1\)-antagonist, as well as anticholinergic properties. Quetiapine (or its active metabolite norquetiapine) has additional \(5-HT_{1A}\) partial agonist properties, as well as noradrenalin reuptake inhibitory effects, which may provide a rationale for its use in FGIDs through mechanisms explained in the section on “Actions on Gastrointestinal Motility and Sensitivity.” Amisulpiride and the older related compound, sulphuride, on the contrary, can be considered atypical antipsychotics through their partial \(D_2\) agonist rather than DA antagonist properties, particularly at the lower doses typically used in the treatment of FGIDs.\(^5\) These agents do not have significant affinities for other receptor systems, making them less prone to side effects.

### Delta Ligand Agents

These agents, with gabapentin and pregabalin being the prototypical examples, exert their effect by blocking the \(\alpha_2\) subunit of (mostly presynaptic) voltage-sensitive calcium channels, which can, in turn, result in reduction of the excessive release of excitatory neurotransmitters such as glutamate. This mechanism of action accounts for their anticonvulsant properties but can also underlie their anxiolytic properties.\(^5\) Probably most importantly in this context, however, as signal transduction in nociceptive pathways critically depends on voltage-sensitive calcium channels, these agents may dampen activity in overly active pain circuitry (from the dorsal horn to the brain).\(^5\) This mechanism likely underlies their well-established efficacy in neuropathic pain as well as, although to a lesser extent, functional somatic syndromes putatively characterized by central sensitization, such as fibromyalgia,\(^21,24\) which then can lead to benefit in IBS and other FGIDs.\(^25\) These agents are classified as peripheral neuromodulators. However, pregabalin has also been shown to alter brain connectivity, leading to a central analgesic response in experimental pain.\(^26\) By virtue of these properties, these agents are promising treatment options for pain-predominant FGIDs.

Table 1 illustrates the action of the transporters and receptors as discussed, their clinical and adverse effects, and the drug class most closely linked to the transporter or receptor.\(^27\)

### Actions on Gastrointestinal Motility and Sensitivity

This section provides an overview of the physiological actions of central neuromodulators specifically on GI motility and sensitivity related to their use in the treatment of FGIDs (summarized in Table 2).

#### Tricyclic Antidepressants (Amitriptyline, Imipramine, Desipramine, Nortriptyline, and Doxepin)

**Motility.** As noted, TCAs have 5-HT and NA reuptake inhibition properties, but also have variable antimuscarinic effects that affect motility. Several studies have addressed the actions of TCAs on GI motility, but the extent to which observed effects are attributable to serotonin transporter inhibition or to other aspects of their pharmacology is unclear.\(^28\)

Amitriptyline 25 mg for 2 weeks slowed solid gastric emptying in healthy volunteers,\(^29\) but a dosage of 12.5 mg 3 times daily did not alter liquid gastric emptying rate\(^30\) and nortriptyline up to 50 mg daily for 14 days did not alter solid gastric emptying.\(^31\) Treatment with desipramine 50 mg for 4 days slowed both orocecal and whole-gut transit
times in healthy volunteers.32 Similarly, imipramine and amitriptyline 12.5 mg 3 times daily were shown to slow orocecal transit time in healthy subjects, as measured with the lactulose breath test.30,33 Acute administration of amitriptyline 80 mg to healthy volunteers did not alter rectal compliance but reduced pressures in the anal canal.34 Taken together, TCAs slow GI transit, largely related to their anticholinergic and noradrenergic properties.

**Sensitivity.** TCAs are often advocated for the treatment of visceral hypersensitivity. Using 3 different TCAs, a rat study showed a dose-related attenuation of visceral afferent pelvic nerve signaling to noxious colonic distension.35 However, the evidence that they are effective in reducing visceral sensitivity in humans is limited. Amitriptyline 80 mg acutely administered did not alter rectal sensitivity in healthy controls.34 In healthy volunteers, amitriptyline 50 mg had no effect on sensitivity to esophageal or rectal balloon distention.36 Imipramine in ascending doses up to 75 mg did not alter the level of distention needed to induce first sensation, but increased the volume, although not the pressure, needed to induce pain during esophageal balloon distention.37 It is unclear whether anticholinergic effects underlie the lower volume sensitivity. Amitriptyline 25 mg for 2 weeks did not alter nutrient volume tolerance.38

In a controlled study in patients with noncardiac chest pain, 3 weeks treatment with imipramine 50 mg improved symptoms and decreased sensitivity to esophageal balloon distention compared with placebo.39 In a small cross-over study in FD, amitriptyline improved symptoms, but this was not accompanied by a change in visceral hypersensitivity, as assessed by gastric balloon distention.40 In a cross-over study in 19 IBS patients, amitriptyline did not alter perception ratings during rectal balloon distention, but reduced the effect of stress on rectal distention-induced activation of brain areas involved in visceral perception.40 In an open-label study, amitriptyline up to 50 mg given for 3 months to IBS patients decreased the stress-induced increase in rectal sensitivity to electrical stimulation.41 Taken together, there is limited and inconsistent evidence that TCAs decrease visceral sensitivity in healthy humans and in some patients with FGIDs.

**Selective Serotonin Reuptake Inhibitors**  
*Paroxetine, Fluoxetine, Sertraline, Citalopram, and Escitalopram*  

**Motility.** Acute administration of SSRIs prolongs the availability of physiologically released serotonin, thereby potentially enhancing effects of serotonin released from the GI tract, but also from the CNS.28 Acute administration of citalopram did not alter esophageal motor function in healthy volunteers.31 Five days of pretreatment with paroxetine enhanced gastric accommodation in healthy volunteers.32 Paradoxically, acute intravenous administration of citalopram enhanced fasting gastric volumes, inhibited accommodation, and significantly enhanced solid gastric emptying rate.44 In the inter-digestive state, citalopram stimulated occurrence of small intestinal phase 3 propulsive activity, while suppressing gastric phase 3 propulsive activity.44 Two days of pretreatment with paroxetine 20 mg inhibited gall-bladder emptying in healthy volunteers.35 Four days of paroxetine 30 mg reduced orocecal transit time, but did not significantly affect whole-gut transit time in healthy controls;32 and 11 days of treatment with paroxetine 20 mg enhanced small bowel transit in healthy volunteers.46 Acute serotonin transporter inhibition in humans increased colonic phasic contractility and the occurrence of high-amplitude propagated contractions, increased colonic compliance, and suppressed the colonic tonic response to a meal.47 Taken together, these data show SSRIs enhances gastric and small bowel propulsive motility.

**Sensitivity.** Administration of citalopram to healthy controls does not alter sensitivity to multimodal esophageal stimulation.48 In contrast, in hypersensitive healthy volunteers, acutely administered citalopram decreased sensitivity to acid perfusion and to balloon distention.42 Intravenously administered citalopram did not alter sensitivity to gastric distention, but decreased meal-induced satiation scores and increased the amount of nutrient ingested until satiation.44 The latter may relate more to motor than to sensory effects. Citalopram intravenously did not alter sensitivity of the rectum and the colon to distention.47,49 In IBS, citalopram also did not alter rectal or colonic sensitivity, and fluoxetine did not alter rectal sensitivity.47,49,50 Taken together, SSRIs have no major impact on visceral sensitivity in healthy subjects or patients with FGIDs.

**Serotonin Noradrenalin Reuptake Inhibitors**  
*Duloxetine, Venlafaxine, and Milnacipran*  

**Motility.** The actions of SNRIs on esophageal motility have not been studied to date. Venlafaxine 75 mg did not affect gastric emptying rate in healthy volunteers,71 although venlafaxine overdose has been associated with gastric bezoar formation.52 Venlafaxine increased the meal-induced change in gastric volumes in healthy volunteers, suggesting an effect on gastric accommodation.51 Venlafaxine 75 mg increased colonic compliance and decreased fasting colonic tone and the tonic response to a meal, but did not affect colonic transit in healthy controls.51 Taken together, there are some indications of an inhibitory effect of SNRIs on gastric and colonic tone, but not to the degree of TCAs; more studies are needed.

**Sensitivity.** SNRIs are known to have somatic analgesic properties and are generally accepted to exert visceral analgesic properties as well.53 However, few studies have addressed the effects of SNRIs on visceral sensitivity in health or disease. In a colonic barostat study in healthy controls, venlafaxine 75 mg increased colonic compliance, decreased tone, reduced postprandial colonic contractions, and reduced pain intensity ratings during graded distensions.51

**Noradrenergic and Specific Serotonergic**  
*Tetracyclic Antidepressants* (Trazodone, Mirtazapine, and Mianserin)  

**Motility.** Tetracyclic antidepressant drugs are used for some functional disorders; trazodone mainly for esophageal disorders and mianserin/mirtazapine mainly for FD. In
healthy volunteers, mianserin 10 mg did not alter gastric emptying rate, but inhibited gastric accommodation to a meal. Mirtazapine did not alter gastric emptying rate and gastric accommodation in healthy volunteers. The effect of tetracyclic antidepressants on motility has not been studied in much detail.

**Sensitivity.** The effects of trazodone on visceral sensitivity in healthy have not been tested. Neither mianserin 20 mg, nor mirtazapine 15 mg, altered sensitivity to gastric distention in healthy volunteers. In FD patients, mirtazapine increased nutrient volume tolerance, while gastric emptying rate was not significantly altered. No conclusions can be drawn on the effects of tetracyclic antidepressants on visceral sensitivity due to limited studies.

**Azapirones (Buspirone and Tandospirone)**

**Motility.** Only a handful of studies have evaluated the actions of this class of agents on GI function. Buspirone enhances contractile amplitude in the esophagus. Also, probably through 5-HT1A receptor–mediated inhibition of acetylcholine release from cholinergic nerve endings in the enteric nervous system, buspirone relaxed the proximal stomach and slowed gastric emptying rate in healthy controls in a dose-dependent manner. In a cross-over pilot study of FD, buspirone improved symptoms, and this was associated with enhanced gastric accommodation. There are limited data to suggest that azapirones enhance esophageal contractions and increase gastric accommodation in health and in FD.

**Sensitivity.** Buspirone did not alter sensitivity to esophageal multimodal stimulation, sensitivity to gastric distention, or rectal distention. Buspirone did not significantly alter colonic compliance, tone or sensitivity in healthy controls. Limited data suggest that azapirones do not alter GI sensitivity.

**Atypical Antipsychotics (Sulpiride, Levosulpiride, Quetiapine Aripiprazole, and Olanzapine)**

**Motility.** Sulpiride and levosulpiride are occasionally used for the treatment of FD and gastroparesis, based on their beneficial effects on gastric emptying rate in these patients. No data for atypical antipsychotics or other antipsychotics have been published on motility effects in healthy volunteers.

**Sensitivity.** Levosulpiride was shown to decrease sensitivity to gastric distention in FD patients. Studies are available on the effects of atypical antipsychotics on GI sensitivity in healthy volunteers and very limited information suggests that it reduces gastric sensitivity in patients.

**Delta Ligand Agents (Pregabalin and Gabapentin)**

**Motility.** The effect of delta ligands on GI motility has not been studied.

**Sensitivity.** The effect of delta ligands on sensitivity in the upper GI tract has not been studied. Both pregabalin and gabapentin increased distension sensory thresholds in IBS patients with rectal hypersensitivity.
as the Hospital Anxiety Depression scale) may need to be a primary consideration when selecting a neuromodulator. Neuromodulators can also be selected based on their specific peripheral effects, such as to treat a co-occurring disturbed bowel habit or chronic nausea. Also there are no scientific data to support the common use of opioids in chronic visceral pain and their use carries a substantial risk of unwanted side effects, including opioid-induced constipation and opioid-induced central hyperalgesia, also known as narcotic bowel syndrome (NBS).

In the sections that follow, treatment advice is based on the predominant GI symptom, FGID diagnosis, concurrent non-GI symptom profiles, and underlying assumptions of pathophysiological mechanisms of relevance, as illustrated in Table 2. The key recommendations are boldfaced in the text and summarized in Table 4.

Selection of Treatment Options Based on Clinical Profiles

Chronic gastrointestinal pain. Abdominal pain is a key symptom in many FGIDs and, depending on its bodily location and time course, is a central part of the diagnostic criteria in several disorders. Examples of painful FGIDs include functional heartburn, epigastric pain syndrome (EPS) (eg, FD), IBS, centrally mediated abdominal pain syndrome, biliary pain, and anorectal pain or levator ani syndrome. In those patients with an FGID where pain is dominant and of frequent occurrence, a central neuromodulator would be a logical part of the treatment profile.

Tricyclic antidepressants. Low to modest dosage regimens of TCAs have the most convincing evidence of benefit for treating chronic GI pain. TCA dosages in the range of 25–75 mg/d have been used in most studies, apart from 1 study where a wider dosage regimen was allowed with desipramine up to 150 mg/d. Evidence for analgesic effects from doses <25 mg is lacking. Only 1 study for IBS, which is referred to frequently (Vahedi et al) used a 10-mg dose. The authors reported a significant improvement from baseline to end of treatment on the primary outcome in the intention-to-treat analysis, but this was also observed with placebo. Of note, there was no significant difference between treatment and placebo in the between group comparison. We believe these data are not sufficient to justify using what is likely a nonpharmacologic dose. However, a low starting dose of 10 mg can help patients overcome early side effects, which can then lead to increasing to a more desirable dose thereafter. This strategy can also help address symptoms reported as side effects that are present before treatment, or which relate to anxiety about TCA treatment. One can adjust the TCA dose within the first 4–6 weeks of treatment within the range of 25–75 mg at night, and then further increase to 100–150 mg if no disturbing side effects develop. Most often the occurrence of anticholinergic and anti-histaminic side effects sets a natural upper limit, although it should be recognized that the tertiary amine TCAs (eg, amitriptyline and imipramine) are more likely to produce these side effects compared with the secondary amine agents (eg, desipramine, nortriptyline).

The antihistaminic and anticholinergic actions that might cause drowsiness, dry mouth, palpitations, or constipation are sometimes clinically useful for employing the tertiary amine agents when the abdominal pain is associated with sleep problems or diarrhea.

Serotonin noradrenaline reuptake inhibitor. SNRIs may have at least equal benefit as TCAs for treating chronic GI pain based on data for treating other chronic painful disorders like fibromyalgia, migraine headaches, widespread body pain, and peripheral neuropathy, though they have not been adequately tested for chronic GI pain. Although studies are lacking in the FGIDs, SNRIs have empiric value based on the previously discussed mechanisms. The advantage of SNRIs compared with TCAs is that they do not have antihistaminic or anticholinergic side effects, which can preclude adequate dosing with TCAs. However, nausea is a common side effect. The risk for significant side effects can be reduced by starting treatment in the low-dose range, and supporting patients through the first week of treatment before increasing to full doses. Other side effects include palpitations, sweating, sleep disorders, dizziness, and visual impairment. Some patients can experience anticholinergic side effects mediated through a modulation of sympathetic tone by norepinephrine. Comparing the different SNRIs, venlafaxine is probably more prone to side effects when treating pain, including increased diastolic blood pressure, which requires monitoring, at least in the higher dosage range of treatment. The serotonergic effects dominate in the lower dosage range for venlafaxine, and the dosage needs to be escalated to 225 mg/d in order to reach norepinephrine effects sufficient for pain modulation. Thus, duloxetine may be easier to use in FGIDs, as it has clinically meaningful noradrenergic even in the low dose range at start of treatment. Milnacipran is an SNRI that is marketed for fibromyalgia and widespread body pain and is not used for depression in the United States, but is in European countries. Although there are no studies to support its use in FGIDs, we recommend considering this agent if there are difficulties in using the other SNRIs due to side effects.

Augmentation by combining central neuromodulators. In the patient with anxiety or multiple somatic symptoms (somatization) or where there are incomplete benefits from TCAs or SNRIs, adding an augmenting agent is the recommended next option for treating chronic GI pain. For further details see the section: “Augmentation with Central or Peripherally Acting Treatments.”

Delta ligand agents. Delta ligand agents treat neuropathic pain, or pain associated with fibromyalgia, a condition commonly associated with FGIDs, particularly IBS and may be of help with chronic GI pain, though studies have not adequately addressed their benefits in this condition. Pregabalin or gabapentin may reduce visceral hypersensitivity. Theoretically, in clinical practice these agents might also be helpful for abdominal wall pain, although no studies to assess this effect are available. There are data showing some benefit for postoperative patients taking gabapentin. Aside from its
Peripheral effects, pregabalin has been shown to have central effects in patients with chronic fibromyalgia by improving brain connectivity, which was associated with a reduction in pain. Studies in FGIDs are largely lacking, but its clinical use in certain situations, like when a general anxiety disorder or fibromyalgia/abdominal wall pain coexist, is reasonable in a dosage between 150 and 600 mg/d with effects expected within a month.

**Other Potential Agents**

The following classes are of potential value in treatment of these disorders, but data are not sufficient to make stronger recommendation.

**Aminoketones.** There is no formal evidence for using bupropion in the treatment of abdominal pain, but it may be considered from extrapolation of SNRI effects on descending inhibitory nerve fibers, which can lead to an antihyperalgesic effect. It is also associated with lower frequencies of sexual dysfunction compared with other antidepressants. A theoretical advantage could be to use bupropion if there is a problem with fatigue and sleepiness because the treatment effects of bupropion from this respect are better when compared with the SSRIs. It has also been used as an augmenting agent in treating depression, when other antidepressants are not successful. Dosage is the same as for the psychiatric indications, that is, 150–300 mg/d.

**N-methyl-D-aspartate receptor antagonists.** Memantine, ketamine, and dextromethorphan are N-methyl-D-aspartate—receptor antagonists that can help reduce pain of presumed neuropathic origin. Memantine in particular has shown analgesic effects in the clinical setting of fibromyalgia and migraine headache, which are commonly associated with the FGIDs, as well as for peripheral neuropathic pain. The tolerability was good, with a number needed to treat of 6 in a double-blind, placebo-controlled, randomized trial in fibromyalgia with a dosage titrated to 20 mg/d within the first month of treatment. With the limited evidence at hand, this should be considered as a third-line treatment in patients with FGID-associated abdominal pain, where other more common treatment options have failed.

**Irritable Bowel Syndrome**

IBS can have both peripheral (ie, visceral hypersensitivity) and central contributions to the pain. Generally, when the pain is mild to moderate and intermittent, peripherally acting agents may be sufficient, but when pain is more severe or persistent, central agents may be added or substituted. For IBS, there are first-line treatment options that act peripherally on gut function for use in patients without psychiatric comorbidity and moderate to severe symptom intensity. These agents are briefly mentioned for completeness as putative peripheral neuromodulators, and their indications and pathophysiology can be reviewed elsewhere. When diarrhea dominates (IBS-D), alonsetron, a highly selective 5-HT3 antagonist has been shown to increase the thresholds for visceral sensation and slow-down intestinal transit, by inhibiting the extrinsic visceral pain pathway. This class of drug, while effective for IBS-D, is available under restricted license in the United States. A recent alternative, eluxadoline, is approved by the FDA and the European Medicines Agency as a new class of drug interacting with peripheral opioid receptors and reducing symptoms in IBS-D with more convincing effects on bowel habit compared with the reduction in abdominal pain. In patients where constipation is the predominant bowel disturbance (IBS-C), linaclotide has shown to be safe and with convincing effects on the combined endpoint that includes significant reductions in both abdominal pain and relief of constipation. This is mediated by a prosecretory effect from binding to the guanylate cyclase C receptor on intestinal epithelial cells, which activates intracellular formation of cyclic guanosine monophosphate that both stimulates chloride secretion through interaction at the CFTR channel, as well as increases the threshold for colonic sensation through effects on the primary afferent gut neuron. Yet another secretagogue, lubiprostone, is indicated for treatment of IBS-C, but with a mode of action that involves activation of type-2 chloride channels.

The TCA class of drugs is the first-line central neuromodulator for treating IBS, especially IBS-D. In particular, the tertiary amine TCAs (amitriptyline and imipramine) can reduce diarrhea, and also improve poor sleep quality. In selected cases of IBS-D, the combined central and peripheral effects of a TCA can suffice as a single therapy option. A secondary amine TCA (desipramine and nortriptyline) may be selected if less anticholinergic or antihistaminic effect is desired (eg, for treating pain with IBS with diarrhea and constipation or IBS-C).

The SNRI class of medications ( duloxetine, venlafaxine, or milnacipran) has potential to improve the pain component of IBS, based on data from treating other pain disorders, and has fewer side effects than TCAs, but these agents have not been adequately studied in IBS. Bowel habits may be influenced by both the serotonergic effect and the change in noradrenergic tone that might have an indirect anticholinergic effect, but in general these effects are fewer than with TCAs and may be favored for treating IBS-C. These agents are desired particularly where abdominal pain is the major or primary problem of significance to the patient.

SSRIs can be considered in IBS if anxiety states, including hypervigilance, somatic symptom disorder, visceral anxiety, and maladaptive cognitions, are present, and the abdominal pain and diarrhea are not the dominant clinical features. It can also be helpful when constipation is present. Citalopram has been shown to increase colonic contractility and reduce colonic tone during fasting conditions and reduce the colonic tone increase after meal ingestion. In IBS, the same drug decreased scores for abdominal pain, as well as bloating, independent of anxiety, depression, and colonic sensorimotor function in a small
crossover study involving 23 patients at a tertiary referral center.\textsuperscript{47} Also, improvements in overall well-being, regardless of coexisting depression, with paroxetine treatment in IBS patients\textsuperscript{98} and decreased abdominal discomfort in IBS-C patients treated with fluoxetine\textsuperscript{99} lends support that subgroups of patients benefit from mechanisms other than the antidepressive and anxiolytic ones.

**Functional heartburn and functional chest pain.** In patients with troublesome heartburn or chest pain where gastroesophageal reflux disease has been excluded, a treatment trial with a centrally acting pharmacologic agent may be considered. There is insufficient evidence to recommend a particular class of central agent, though SSRIs have shown some benefit for esophageal pain along with TCAs and SNRIs.

TCAs involving low-dose imipramine\textsuperscript{38} or amitriptyline\textsuperscript{100} can be considered. Both studies are small, and the latter study that showed superior effects compared with double-dose proton pump inhibitor was open label.

The SSRIs have been shown to benefit some patients with functional chest pain\textsuperscript{101} or in situations where esophageal hypersensitivity is suspected as a pathophysiological mechanism of importance.\textsuperscript{44} Like the considerations in previous diagnostic groups, coexisting anxiety, depression, and phobic features strengthens a decision for a therapeutic trial with a SSRI.

Regarding SNRIs,\textsuperscript{102} a small dose (75 mg) of venlafaxine in an extended-release formulation at night was superior to placebo in a study involving a young patient group only (20–29 years) with functional chest pain, which indicates a putative positive effect with a good tolerance at this low-dose regimen.

**Functional dyspepsia.** When treating FD, it is best to consider the Rome IV symptom-specific subgroups: postprandial distress syndrome (PDS) and EPS. With PDS, meal-induced symptoms like fullness and early satiation dominate, and in EPS, epigastric pain and a burning sensation that may or may not be associated with meal intake is prominent. Where basic measures, like lifestyle adaptations and eradication of *Helicobacter pylori*, if present, do not result in sufficient symptom control, 1 or more of the treatments outlined here can be used.

**Postprandial distress syndrome.** Buspirone, an anxiolytic azapirone may be used for PDS where early satiety, fullness, and nausea predominate. It has relatively few side effects and no potential for physical dependence. The mode of action involves 5-HT\textsubscript{1A} agonism, which may improve receptive relaxation of the gastric fundus. In a 4-week study of buspirone in FD patients, dyspeptic symptoms significantly decreased over placebo with regard to nonpainful discomfort, such as early satiety, fullness, bloating, and nausea. Interestingly, this was associated with greater increases in postprandial gastric volumes, suggesting that gastric accommodation may be the physiological basis for this positive effect.\textsuperscript{57} The same symptom response has been seen after a nutrient satiety drink test as well.\textsuperscript{106} The buspirone dosage should be the same as in the treatment of anxiety, that is, 30 mg divided 2 or 3 occasions daily, but can be increased to 60 mg/d.

Mirtazapine is a good treatment option for PDS when there is chronic nausea and vomiting, or weight loss, and it may also help coexisting abdominal pain. The antihistaminic action may reduce sleep latency as shown when treating depression.\textsuperscript{103} Among FD patients with weight loss, without coexisting anxiety or depression, 15 mg of mirtazapine in the evening for 8 weeks was superior to placebo in improving overall symptom scores, early satiation, and nutrient tolerance, and resulted in weight recovery.\textsuperscript{56} The regular dosage range is from 15 to 45 mg/d given in the evening, to reduce daytime sedation. In those patients having too much sedation from mirtazapine or with an incomplete response, olanzapine is an alternative treatment option, as shown in anesthesiology and oncology.\textsuperscript{104} Using a dosage range of 2.5 to 10 mg/d, the risk for its potential to cause neurologic side effects, akathisia and dystonic reactions included, is low.

**Epigastric pain syndrome.** When the dyspeptic symptoms are consistent with EPS, studies mainly support the use of TCAs, either initially or after an unsuccessful response to a proton pump inhibitor. A small study including 38 patients showed benefit for amitriptyline over placebo in improving total symptom score and nausea, as well as upper abdominal pain.\textsuperscript{105} A more recent multicenter study also indicated a positive effect of treatment with amitriptyline in FD patients with epigastric pain.\textsuperscript{106} Patients labeled as ulcer-like dyspepsia (Rome II definition for EPS) had the most favorable response, with a more than 3-fold higher likelihood of adequate relief compared with placebo or escitalopram, which did not show symptomatic benefit in any FD subgroup. This effect was not seen in the subgroup dysmotility-like dyspepsia (Rome II definition for PDS). The American College of Gastroenterology guideline also advocates the use of amitriptyline in FD patients when proton pump inhibitors have failed to provide relief.\textsuperscript{107}

As with other painful FGIDs, the SNRI group of medications can also be considered for patients with EPS who do not tolerate TCA treatment, although confirmatory studies are lacking. The side effect of nausea may limit the usefulness in this group of patients, particularly in the group having clinical features that overlap with PDS.

**Cyclic vomiting syndrome.** CVS is characterized by sudden, stereotypical episodes of intense nausea and vomiting lasting up to days at a time with symptom-free intervals.\textsuperscript{108} The condition varies in severity from a few, self-limiting episodes per year to a debilitating situation with need for frequent hospital admissions. There are 2 treatment components for CVS. First, for treating acute episodes, the effort is to reduce the symptom severity and duration of the attacks with anti-emetic agents like ondansetron or promethazine, minimize the use of opioids for the abdominal pain, and intravenous hydration. Benzodiazepines can be used to treat acute anxiety and distress and have independent effects on nausea reduction. Second, to prevent future episodes, cannabinoids must be eliminated, and prophylactic treatment using central neuromodulators (TCAs, SNRIs, tetracyclines, atypical antipsychotics, and anticonvulsants as discussed in the next paragraph) should be
Instituted to reduce the severity and frequency of acute attacks to every 4 months or less.

Acute episodes of CVS are often triggered by physiological or emotional stress, so it is important to identify comorbid psychiatric problems and treat them accordingly. This is in line with the general approach to FGID management. In patients with frequent attacks of intense vomiting, the first factor to consider is whether the patient may have the cannabinoid hyperemesis syndrome, which can mimic CVS. In that situation, treatment involves eliminating this substance. Following this, TCAs can be considered as first-line treatment for prophylaxis. Among them, amitriptyline has some weak evidence in support of it.6

Combining central agents is accepted in treating chronic pain. Alternative management, that is, adding a second agent to the above regimen, has been recommended empirically for functional GI pain.6

Augmentation treatment, that is, adding an atypical antipsychotic agent to an antidepressant), is recommended when monotherapy is not successful. Another option is to add an atypical antipsychotic. These agents, unlike the previous classes of antipsychotics, have less risk for extrapyramidal side effects. There is some experience from the use of quetiapine in the treatment of chronic pain. Most data are found in the treatment of fibromyalgia, where a controlled study reported effects superior to placebo on the pain domains, but with effects inferior to amitriptyline in yet another study.115 Quetiapine has also been shown to improve pain when used to augment the effects of a TCA or SNRIs.66 The complex actions at the receptor level can have added clinical effects, like anxiety reduction and establishment of a normal sleep pattern.65,117 Its main metabolite also has effects as a norepinephrine transporter inhibitor, which is of theoretical advantage for analgesic effects.118 Higher dosage ranges of 1200–400 mg/d as seen in psychiatry can lead to poor tolerability, with a high proportion of patients experiencing excess sedation and dizziness, in addition to metabolic side effects like weight gain, hyperlipidemia, and diabetes (metabolic syndrome). In balance, because most studies in psychiatry report adverse events with the higher doses, the recommended range of 25–200 mg for GI symptoms might be considerably safer.

When combining medications, it is important to have a familiarity with each agent’s side effect profile, and be aware of potential hazardous side effects, such as serotonin syndrome, which is characterized by fever, hyper-reflexia; spontaneous clonus; muscle rigidity; and, if not treated immediately, increased risk of death. A simplified algorithm of augmentation strategies for chronic abdominal pain is summarized in Figure 5.

Psychological/behavioral augmentation. Psychological or behavioral treatment adds to the benefit to pharmacologic agents working on deeper brain areas by their action on more frontal “executive” areas of the brain.119 Cognitive behavioral therapy (CBT) helps to reduce catastrophic thinking, increases one’s sense of control, and reframes the sense of threat. These brain changes are associated with reduced intensity of pain experiences and improves psychological well-being and function. Many randomized controlled trials support the efficacy of behavioral interventions as an adjunct to pharmalogic strategies in managing FGID symptoms. CBT, gut-directed hypnotherapy, and mindfulness meditation have been studied most in patients with FGIDs and show empirical support. The most significant improvements (moderate effect size) occurred for abdominal pain intensity, IBS...
symptom severity, quality of life, anxiety, depression, and daily functioning. Although CBT is associated with convincing short-term improvement, gut-focused hypnotherapy has the more consistent support in longer-term efficacy, although in a primary care study longer-term hypnotic effects were not maintained. Comprehensive self-management interventions combining CBT with relaxation and dietary strategies have also shown promise both short-term and long-term (12 months) in patients with IBS.

Virtual therapies delivered via the internet or on mobile electronic platforms may be an effective option for patients with FGIDs. Nurse-led hypnotherapy to improve IBS care is showing promise. Although these behavioral approaches are often used to supplement pharmacologic strategies, few studies compare behavioral interventions alone to their combination with specific psychotropic agents. Instead, this comparison has to be extrapolated from studies where those in the treatment as usual arm were receiving medications and little psychosocial care.

Relapse prevention. Relapse prevention relates to the concept that continued treatment with a neuromodulator beyond the period of achieving clinical benefit will reduce the likelihood of relapse or recurrence. This is supported by evidence that continued antidepressant treatment may be associated with reversal of the clinical disorder through neurogenesis. It has also been demonstrated from clinical experience of the authors when treating FGIDs. It offers guidance for the FGIDs because many of the same agents are utilized. For major depression, it is recommended that antidepressants be continued for at least 4 to 9 months after an initial positive response. To reduce the likelihood of relapse when treating FGIDs, we empirically recommend that treatment be continued 6–12 months after treatment response. In a meta-analysis of 31 randomized trials involving more than 4000 patients with depression, continuing treatment with antidepressants reduced the odds of relapse by 70%. Relapse is higher in patients where treatment is stopped, compared with those where it is continued. Continuing or starting behavioral interventions (CBT and hypnosis) also reduced relapse risk. Where factors such as ongoing psychosocial stress, positive family history, history of multiple prior episodes, or current psychiatric comorbidities exist, longer-term treatment can be empirically considered.

Risks of Using Opioids for Management of Chronic Abdominal Pain and Availability of Non-Opioid Alternatives

Opioids. The number of opioids prescribed around the world for chronic pain, particularly in the United States and Canada (see Supplementary Figure 1), is growing dramatically. This rate parallels increased heroin use,
incidence of HIV and hepatitis C, and numbers of overdose deaths involving prescription narcotics and heroin.\textsuperscript{150–153} In the United States, more than 12 million people reported misusing opioids, with at least 2 million endorsing addiction in 2015\textsuperscript{154} (www.samhsa.gov/data). Despite the growing use of opioids to treat chronic non-malignant pain, there is no evidence that such treatment leads to lasting clinical response for FGIDs, and prolonged use is associated with greater clinical harm, including opioid-induced constipation and NBS.\textsuperscript{70,71,155} Furthermore, nonmedical prescription opioid misuse disorders have increased in the past decade, and prevalence was highest in whites and Native Americans, those with lower socioeconomic status, and in patients with mood disorders, post-traumatic stress disorder, and personality disorders.\textsuperscript{156} Risk factors for death from prescription opioids include male sex, sedative hypnotic use, total number of prescriptions, and receiving a daily average of >40 mg morphine equivalents.\textsuperscript{157} Unfortunately, there has been little change in the medical management of prescription-opioid consumers, even after substance abuse is diagnosed.\textsuperscript{158} The Surgeon General of the United States strongly discourages the prescription of opioids as first-line treatment for chronic non-cancer pain in adults.\textsuperscript{159}

Approximately 20% of patients with FGIDs use opioids chronically for management of their GI symptoms,\textsuperscript{160,161} yet there are no randomized controlled trials documenting the efficacy of opioids for chronic abdominal pain. Furthermore, the known GI side effects of chronic opioid use can be particularly problematic, and include constipation, nausea, abdominal pain, gaseousness, ileus, and acid reflux.\textsuperscript{162} Opioid-induced constipation is associated with high medical utilization.\textsuperscript{163} There is also an increasing recognition of NBS, consisting of increased abdominal pain with chronic opioids, which is thought to be a centrally mediated hyperalgesia.\textsuperscript{164} This is due to inflammatory processes in the spinal cord and changes in the functioning of the opioid mu receptor within the dorsal root ganglion.\textsuperscript{165} Chronic opioid use is also associated with increased risk for addiction and other psychopathology, particularly mood and anxiety disorders.\textsuperscript{166,167}

**Non-opioid alternatives.** For patients with FGIDs who are on chronic opioids, a careful tapering is recommended when there is insufficient relief of pain, evidence of opioid misuse, and/or side effects, or other negative sequelae covered in the section above.\textsuperscript{71,160,169} Patients with NBS showed a reduction in pain intensity 3 months after detoxification, although there was a high rate of opioid recidivism at 6 months.\textsuperscript{168} Here it is important to offer patients nonopioid alternatives, such as central neuromodulators and behavioral interventions longer-term, to adequately manage chronic abdominal pain. Clonidine has been used to prevent withdrawal effects, although several studies show that buprenorphine may be even more effective during and immediately after detoxification.\textsuperscript{170,171} The most supported nonopioid alternatives for chronic abdominal pain include TCAs and SNRIs, which can also treat comorbid mood and anxiety symptoms. Mood stabilizers, such as gabapentin, carbamazepine, and topiramate, have shown efficacy in neuropathic chronic pain syndromes, but their utility in FGIDs has not been studied specifically.

CBT, gut-directed hypnotherapy, and mindfulness techniques have a growing evidence base for treating GI symptoms of IBS and other FGIDs, and multidisciplinary treatment of pain involving behavioral experts who are integrated into the medical care can help with longer-term management of chronic pain.\textsuperscript{172}

**Implementation: Use of Communication Skills to Improve Patient Engagement, Acceptance, Adherence, and the Patient—Provider Relationship**

The decision to prescribe a neuromodulator for GI symptoms is based on reasons that are not necessarily (and often not) consistent with the patient’s understanding for their use. This lack of concordance often relates to a dualistic perspective that the medications being recommended to the patient are “psychiatric”\textsuperscript{1} rather than related to treating disorders of gut–brain interaction.\textsuperscript{2} Thus, the clinician must educate the patient on the value of these treatments, and this is best implemented through an effective patient–provider relationship. To merely recommend treatment and not engage with the patient on this understanding may lead to refusal to take the medication, nonadherence, or reporting side effects not related to the medication but due to anxiety relating to taking it.\textsuperscript{74}

**Establish the Therapeutic Relationship**

An effective therapeutic relationship is essential when caring for patients with disorders of gut–brain interaction, and when prescribing neuromodulator treatment. Certain recommendations should be considered, the first being to understand patient expectations. Some patients may adhere to a more acute model of care: their symptoms are presented, they expect the doctor to conduct tests, make a diagnosis, and institute treatment that resolves the problem. However, with chronic and painful illnesses, the primary focus is adaptation to chronic or recurring symptoms with little chance of cure. This must be addressed on the first visit by asking: “What brought you to see me at this time?”; “What worries or concerns do you have?”; and “What do you expect from treatment?” More detailed guidelines for establishing a therapeutic relationship can be found elsewhere.\textsuperscript{173} General guidelines to establish a therapeutic relationship include: (1) listening actively to determine the patient’s understanding of the illness and his or her concerns, (2) providing a thorough explanation of the disorder, (3) identifying and responding to the patient’s concerns and expectations, (4) setting realistic and consistent limits, (5) involving the patient in the choice of treatment, and (6) establishing a long-term commitment to the care.\textsuperscript{173,174} This type of approach is associated with reductions in health care visits\textsuperscript{175} and nonadherence, and improvements in patient satisfaction, symptom reduction, and other health outcomes.\textsuperscript{173} Guidelines are provided in a video link: http://www.youtube.com/watch?v=BeHPpvuB_mc.
Educate to Legitimize the Disorder

Education is an iterative process in which the physician assesses the patient’s level of knowledge about the possible treatment(s) and provides information to enhance understanding. Usually, patients want to understand the basis for their symptoms and often seek validation that their symptoms are “real.” They want to know that a particular treatment will target the reasons for their symptoms. For example, patients may say: “I don’t want a cover up just to treat my symptoms; I want you to find and take care of my problem.” Here it is valuable to help the patient understand gut–brain disorders and the rationale for their treatment, first by asking about the patient’s understanding of their disorder: “What do you think is causing this?” Using IBS as an example, if the patient says “My doctor says I have IBS, but I want to be sure there isn’t something being missed,” you can reassure by indicating that nothing structural has been found from the diagnostic studies, and the patient fulfills positive (Rome) criteria for IBS. Then add, “So, it might be best now to focus on treating your disorder, rather than doing unnecessary testing,” and finish with “However, we will stay vigilant to evaluate further if new problems were to arise.” Sometimes the patient’s belief can be used to help explain the physiological basis for the symptoms. If the patient says: “I believe my symptoms are caused by an intestinal infection,” you can say: “The studies for infection are negative, however, your IBS may have started with an infection (vis-à-vis post-infection IBS), and that led to some injury to the nerves to make them more sensitive, so the symptoms make you feel like you still have an infection. This is similar to ‘phantom limb,’ where a hand or leg may be removed but the person still has sensations as if the limb were still there. In your case there is no infection to treat and we can focus on reducing the sensitivity of those nerves that have been injured.” You can add: “If in several weeks you are feeling maybe 25% better, would you be satisfied with this plan?”

Provide a physiological rationale for treatment: “Your chronic abdominal pain occurs because the gut–brain axis is out of balance. Usually pain from the gut goes to the brain and the brain sends down nerve signals to block the pain, much like if you were running in a race and sprained your ankle; you may not feel it as much during the race because with attention to the race, the brain can block those pain signals. With your symptoms, you have increased nerve signals coming from your GI tract (visceral hypersensitivity) or spinal cord (central hypersensitivity), and possibly also a problem in the way the brain controls those nerve signals (dissociation). Over time the pain you feel may be a combination of increased nerve firing in the GI tract and reduced ability of the brain to block the pain signals. Furthermore, chronic and painful bowel symptoms may trigger symptoms of anxiety or depression, which in turn, lowers pain thresholds and makes your symptoms worse. We need to understand and treat both your physical symptoms and the associated emotional distress related to it.”

Address Patient Perceptions and Expectations About Neuromodulators

Some patients may refuse to take a neuromodulator or may be nonadherent because they perceive: (1) they are being treated for a psychiatric problem, (2) the medication may be addictive or “mind altering,” or (3) they do not think the doctor accepts the symptoms as “real.” Patient reluctance to take neuromodulators must be addressed and clarified by giving the patient the opportunity to voice their concerns. If the patient states they do not want a “psychiatric” drug, you can note that all medications can have multiple purposes. For example, aspirin can be used as an analgesic, or to prevent a heart attack. In this manner, antidepressants, although originally developed for depression, are also used as central analgesics for a variety of painful conditions, including peripheral neuropathy, migraine headaches, and visceral pain. Also, medications designed to have central actions also generate GI effects, especially as the brain and the bowel use the same neurotransmitter signals and receptors. Then, with this new understanding you can explain why the medicine is being used. “This medication reduces nerve impulses arising from the gut and going to the brain or by facilitating inhibitory pathways from the brain that block the incoming pain signals [It may help to show a diagram of the brain–gut axis and how pain regulation is facilitated, eg, Figure 3]. The medication usually works sooner for pain, and often in lower dosages than when treating psychiatric disorders like major depression, and also works when there is no evidence for depression and anxiety. However, they can also treat the understandable emotional distress people get from the illness even when they don’t have a psychiatric diagnosis. Also, these medications, unlike opioids, are not habit forming and don’t alter your thinking.” During the medical history, the clinician should also ask which antidepressants or neuromodulators the patient has taken in the past and what benefits and side effects they had, positive or negative. This information will help later, when making treatment recommendations, either by using the same medication that worked before or a different medication, or a reduced dosage of one that had side effects.

Select a Medication and Negotiate a Treatment Plan

Selecting the proper medication is based on: (1) the target symptoms to be treated, such as pain, or nausea and vomiting, for example; (2) the medication’s side effect profile; (3) cost; (4) availability; and (5) the patient’s previous experiences and preferences. The patient should be involved in making an educated choice of a particular medication through discussion of treatment expectations, including the benefits and risks or side effects. Patients not fully informed of treatment expectations, and who do not feel they have made a choice, may stop the medication after a few days, claiming that it did not work or because of possible side effects. Thus, the patient needs to know from the outset that any benefit may
take 3 to 4 weeks (although may occur sooner), and that side effects, if they occur, tend to diminish in 1 to 2 weeks. Importantly, the patient must notify the clinician or assistant if side effects occur, so a dialogue can take place leading either to reassurance or continue or a modification of the original plan. Regarding dosage, with TCAs one can start with lower dosages and work up to full therapeutic dosages over several weeks. With SNRIs, one may work up to full dosages similar to those used for psychiatric disorders.

Importantly, treatment is continued for 6–12 months before tapering, and dosage adjustments are usually mutually determined based on degree of benefit or side effects. The patient can be informed that continued treatment may influence central neurogenesis126 leading to “rewiring” with improved brain–gut functioning and restoration of a better clinical state over time. As shown with depression treatment, relapse prevention can occur; of 31 randomized trials at 1 year, 41% relapsed on placebo and only 18% if they were maintained on antidepressant.20 In effect, the longer a patient is on the medication the lower the likelihood of relapse.

Continue Phone Contact With the Patient to Assess Compliance and Side Effects

Once the patient agrees to treatment, and the risks and benefits are discussed, the patient should be informed that for the first several weeks, ongoing contact by phone or e-mail is needed to get on course. This is because clinical benefit will not occur for several weeks and side effects might occur immediately, so it helps to have an initial phone contact during the first week of treatment (and possibly repeat the phone call or visit 2–3 weeks later). At these times, decisions are made about possible dose or medication changes and when needed to help motivate the patient to continue the medication. The response to the treatment is based not only on symptom reduction, but also by improvement in daily function, quality of life, and emotional state. If after a few weeks symptoms persist, but the patient is gaining weight and getting out of the house more, this is a treatment gain. If side effects occur, it is best to hold the same dosage or reduce it, and switch to another medication (preferably within the same class) only if required.

If Treatment Response Is Suboptimal

When symptoms do not improve after 4–6 weeks consider: (1) increasing the dose, (2) augmenting with a second agent in low dose, or (3) switching to a different medication. Increasing the dose is reasonable if there are no side effects and the optimal dose of the medication has not yet been reached. For example, if the patient has been on 30 mg of duloxetine or 50 mg of desipramine, increasing up to double the dose is reasonable. However, if the dose is maximized, or if there are mild side effects, the medication can be maintained or adjusted down and a second treatment added (augmentation). Examples would be adding a peripheral agent, such as gabapentin/pregabalin, especially if there is an abdominal wall component; adding an atypical antipsychotic, such as quetiapine at bedtime, especially if there is associated anxiety and sleep disturbance; or adding a psychological treatment, such as CBT or hypnosis.

If Side Effects Develop

Side effects occur usually within the first few days, and it is important to take a careful history. Did these symptoms occur in the past, even when the patient was not on the medication? How severe are the symptoms, is it mild and tolerable or a more severe adverse event? Are the symptoms diminishing or worsening? Do the symptoms interfere with activities? With this information, one can decide whether to maintain the dose longer, reduce the dose, or discontinue and switch to another medication. Switching medications merely in response to the patient reporting side effects should be avoided. The patient needs to be informed that side effects usually occur before treatment benefit, and they usually diminish over time. Thus, the effort is to stay on the drug a bit longer to see whether the side effects diminish and are replaced with clinical improvement. Also, the patient may report symptoms not even related to the medication. In a clinical trial using desipramine, patients filled out a list of 16 common symptoms before starting treatment and again 2 weeks later when on the medication, and the symptoms were compared with the pretreatment symptoms. To help determine the reasons for the symptoms, patients took a test measuring anxiety and psychological distress (Symptom Checklist-90), and also pill counts, and a blood level of desipramine was obtained at 2 weeks. Only a few patients had mild and expected anticholinergic side effects from the TCA, such as dry mouth. However, many of the patients reported side effects at 2 weeks that were the same symptoms that were present before taking the desipramine—patients were now attributing these symptoms to medication effect. Furthermore, the severity of the side effects reported did not correlate with either the desipramine pill count or blood level, but correlated significantly with anxiety scores on the psychological test.74 The conclusion was that side effects were more often related to psychological distress than a desipramine drug effect. For this reason, the clinician might be more cautious in indiscriminately discontinuing medication when patients report side effects, to avoid a cycle of repeatedly switching treatments. A better course of action is to reassure the patient and commence a dialogue about staying on the drug longer, or reducing the dose slightly, and reevaluating in a few weeks.

A New Approach to Improve Clinical Response and Reduce Side Effects

Pharmacogenomics. Rome IV introduced pharmacogenomics as a potential new tool for diagnosis and management of patients with disorders of gut–brain interaction,176 and this builds on growing evidence promoting its value in clinical practice.177 Pharmacogenomics is the study of the variability of the expression of individual genes relevant to disease susceptibility, as well as drug response, at cellular, tissue, individual, or population
levels. Genetic polymorphisms, one area of pharmacogenomics, may predispose to the development of IBS, FD, and other such disorders and, relevant to this article, polymorphic genetic variations can also influence the response to medications vis-à-vis their effect on drug metabolism.

In the last several years pharmacogenomic profiling of patients using a buccal brush assay are being done by commercial laboratories, and reports are generated that are reliable and relatively inexpensive, costing approximately $300. The reports summarize the metabolism profiles of hundreds of medications and the results are life-long. To date, assays on GI medications are somewhat limited (usually confined to proton pump inhibitors). Pharmacogenomic measurement of almost all central neuromodulators currently exist, and their use is growing, particularly in the management of chronic pain. Thus, pharmacogenomic testing may be of value for selecting an optimal neuromodulator, as a means to optimize benefit and reduce toxicity, or when augmenting treatment by using several medications, where interaction effects are to be avoided.

While the pharmacogenomics field is relatively new for GI, there are some studies to support their clinical value in psychiatry. To date, no studies have studied pharmacogenomic profiling testing in patients with GI disorders.

Recommendations for Future Research

While good understanding exists in the pharmacology and application of use of central neuromodulators for treatment of psychiatric disorders and chronic somatic pain, considerable gaps still exist in our understanding of their use in the disorders of gut–brain interaction. To date there is reasonable evidence for the value of low-dose TCAs and psychological treatments, particularly for IBS and FD. However, newer agents may provide additional, and possibly optimal, benefit. Accordingly, the committee recommends that future research should consider the following studies for disorders of gut–brain interaction:

1. Randomized trials of SNRIs
2. Randomized trials of delta ligand agents
3. Confirmatory multicenter treatment studies for FGIDs of available single-site studies
4. Trials of neuromodulators for poorly studied disorders, including biliary pain/sphincter of Oddi dysfunction, anorectal pain, CVS, and functional nausea and vomiting
5. Factorial trials (2 × 2) to assess the degree to which augmentation treatment offers added benefit to monotherapy
   a. Central neuromodulator with psychological treatment (CBT, hypnosis)
   b. Two central neuromodulators (SNRI or TCA with atypical antipsychotic)
   c. Central and peripheral neuromodulators (eg, SNRI or TCA with delta ligand agent)
   d. Empirically supported adjunctive behavioral therapies
6. Randomized studies to assess the value of teaching communication skills and modern knowledge of diagnosis and treatment of FGIDs on patient satisfaction with care, adherence to treatment, clinical outcomes, and costs

Conclusions

Based on systematic and selectively focused reviews of the literature, and the consensus of a multidisciplinary panel of clinicians and investigators, we have provided guidelines for the use of central neuromodulators in the treatment of GI symptoms and disorders of gut–brain interaction. A clear consensus of this group is that the clinical application of these agents is driven more by empiric evidence than well-designed investigations targeted to these particular disorders, and such studies are much needed in the future. Nevertheless, the existing knowledge is compelling in the need to apply such treatments either solely, or in combination with other peripheral neuromodulators in patients with disorders of gut–brain interaction. Low to modest doses of TCAs have the most convincing evidence of benefit for treating chronic GI pain. SNRIs are also expected to be effective based on data in other chronic painful disorders, although they have not been adequately tested for chronic GI pain. SSRIs can be considered if anxiety is present and if abdominal pain is not the dominant clinical feature. Buspirone and mirtazapine can be applied in FD/PDS. Delta ligand agents and atypical antipsychotics can be of help with chronic GI pain, although studies addressing their benefits in these conditions are needed. Augmentation treatment (ie, adding a central with a peripheral or combining 2 centrally acting agents or adding a psychological therapy) is recommended when monotherapy is not successful, and relapse prevention is encouraged through continuation of treatment for at least 6–12 months.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Gastroenterology at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2017.11.279.

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Supplementary Figure 1. Evolution of opioid consumption from 1994 to 2014 in different countries around the world. There are rising trends of per capita opioid consumption from around the world, the United States and Canada have the highest growing rates.