CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on Management of Chronic Gastrointestinal Pain in Disorders of Gut–Brain Interaction: Expert Review

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DESCRIPTION: This expert review summarizes approaches to management of pain in disorders of gut–brain interaction. This review focuses specifically on approaches to pain that persist if first-line therapies aimed at addressing visceral causes of pain are unsuccessful. The roles of a therapeutic patient–provider relationship, nonpharmacologic and pharmacologic therapies, and avoidance of opioids are discussed.

METHODS: This was not a formal systematic review but was based on a review of the literature to provide best practice advice statements. No formal rating of the quality of evidence or strength of recommendation was performed. BEST PRACTICE ADVICE 1: Effective management of persistent pain in disorders of gut–brain interaction requires a collaborative, empathic, culturally sensitive, patient–provider relationship. BEST PRACTICE ADVICE 2: Providers should master patient-friendly language about the pathogenesis of pain, leveraging advances in neuroscience and behavioral science. Providers also must understand the psychological contexts in which pain is perpetuated. BEST PRACTICE ADVICE 3: Opioids should not be prescribed for chronic gastrointestinal pain because of a disorder of gut–brain interaction. If patients are referred on opioids, these medications should be prescribed responsibly, via multidisciplinary collaboration, until they can be discontinued. BEST PRACTICE ADVICE 4: Nonpharmacologic therapies should be considered routinely as part of comprehensive pain management, and ideally brought up early on in care. BEST PRACTICE ADVICE 5: Providers should optimize medical therapies that are known to modulate pain and be able to differentiate when gastrointestinal pain is triggered by visceral factors vs centrally mediated factors. BEST PRACTICE ADVICE 6: Providers should familiarize themselves with a few effective neuromodulators, knowing the dosing, side effects, and targets of each and be able to explain to the patient why these drugs are used for the management of persistent pain.

Keywords: Irritable Bowel Syndrome; Functional Dyspepsia; Disorders of Gut–Brain Interaction.

Disorders of gut–brain interaction (DGBI), including irritable bowel syndrome (IBS), functional dyspepsia (FD), and centrally mediated abdominal pain syndrome (CAPS), are present in more than 40 % of the population globally.[1] Most patients with DGBI are treated initially with therapies directed at visceral stimuli, such as food and bowel movements. For example, patients with esophageal or gastroduodenal DGBI, such as functional heartburn or FD, often are treated with proton pump inhibitors (PPIs), which can be efficacious.[2,3] First-line dietary treatments, antidiarrheals, and laxatives are used frequently in IBS but have limited evidence for efficacy for abdominal pain.[4]

Unfortunately, a subset of patients with DGBI continue to experience pain, which impacts negatively on health-related quality of life and leads to health care utilization.[5,6] Management of patients with pain that does not respond to first-line therapies directed at visceral stimuli is complex and influenced by a range of cognitive, affective, and behavioral factors, including learning

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and expectations around pain, and other psychosocial modifiers such as overlapping mood and anxiety disorders.[7,8] Effective pain management requires establishment of a collaborative patient–provider relationship and avoidance of medications with the potential for misuse, such as opioids (Figure 1). Management options include both nonpharmacologic and pharmacologic therapies. This Clinical Practice Update focuses on management of patients with DGBI whose pain has not improved with therapies directed at visceral stimuli. This review does not discuss the use of complementary or alternative therapies such as marijuana, and does not apply to treatment of abdominal wall or pelvic pain syndromes.

This expert review was commissioned and approved by the AGA Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer-review by the Clinical Practice Updates Committee and external peer-review through standard procedures of *Clinical Gastroenterology and Hepatology*.

Best Practice Advice 1

Effective management of persistent pain in disorders of gut–brain interaction requires a collaborative, empathic, culturally sensitive, patient–provider relationship.

Development of a collaborative, empathic, patient–provider relationship is required to address management of persistent pain in DGBI.[9–11] Patients may have seen multiple providers without clear benefit or improvement and may be dissatisfied with their medical care. A sensitive nonjudgmental approach to the patient will integrate medical care with psychosocial information to achieve the desired outcomes. Because of cultural differences in the understanding and interpretation of pain, as well as preferred management strategies, addressing

pain in a culturally sensitive manner also is necessary for effective reporting by patients and treatment.[12,13]

The medical history initially should be obtained using a nondirective interview with open-ended questions.[9] Closed-ended questions can be used later for clarification. In addition, addressing the impact of symptoms on patients' health-related quality of life and daily functioning explicitly, using open-ended questions, helps to build rapport and allows the provider to target interventions more specifically at improving function. Examples include "how do your symptoms interfere with your ability to do what you want in your daily life?" or "how are these symptoms impacting your life the most?" Such questions also can help providers identify patients who might benefit most from behavioral health interventions.

Asking about symptom-specific anxiety also can help gastroenterology providers understand and address patient concerns. For example, understanding that symptoms do not necessarily indicate the presence of undiagnosed cancer, or indicate that surgery is required, may relieve significant anxiety and allow treatment aimed at improving quality of life. Gastroenterology providers should show their willingness to address both medical and psychosocial aspects of the patient's illness. Many patients are relieved to hear that a diagnosis of IBS or FD does not shorten life expectancy.[14] Providers can gain an understanding of the patient's perspective on their symptoms using questions such as "what do you think is causing your symptoms," "why are you coming to see me now," and "what are you most concerned about with your symptoms?" The patient and provider should come to a shared set of expectations and goals around pain relief and management and continue to revisit and modify these as needed as the therapeutic relationship develops. Overall, understanding the patient's experience of their pain and its impact on their functioning allows providers to develop care plans to
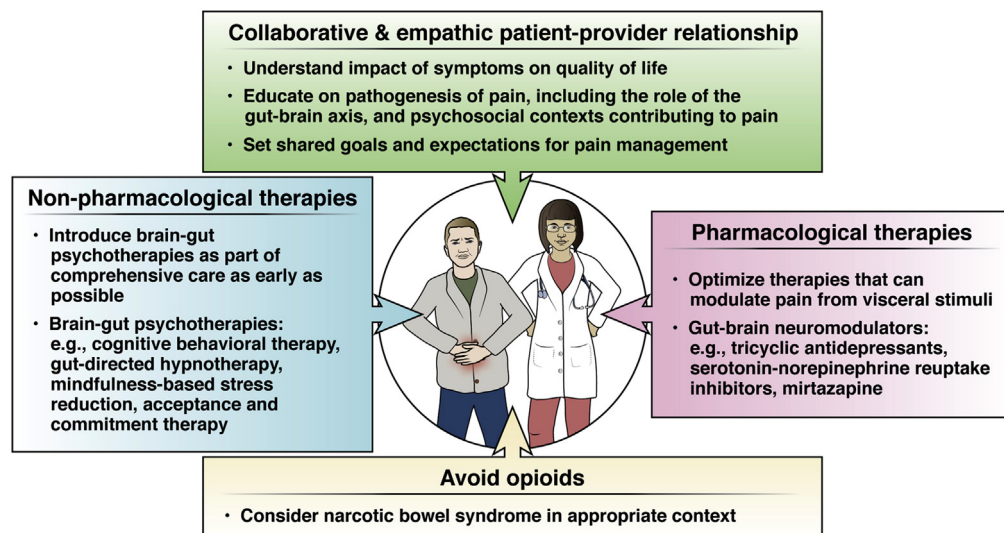

Collaborative & empathic patient-provider relationship
- Understand impact of symptoms on quality of life
- Educate on pathogenesis of pain, including the role of the gut-brain axis, and psychosocial contexts contributing to pain
- Set shared goals and expectations for pain management

Non-pharmacological therapies
- Introduce brain-gut psychotherapies as part of comprehensive care as early as possible
- Brain-gut psychotherapies: e.g., cognitive behavioral therapy, gut-directed hypnotherapy, mindfulness-based stress reduction, acceptance and commitment therapy

Pharmacological therapies
- Optimize therapies that can modulate pain from visceral stimuli
- Gut-brain neuromodulators: e.g., tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, mirtazapine

Avoid opioids
- Consider narcotic bowel syndrome in appropriate context

Figure 1. Management of persistent pain in disorders of gut-brain interaction.

address concerns more directly and improve quality of life.

Best Practice Advice 2

Providers should master patient-friendly language about the pathogenesis of pain, leveraging advances in neuroscience and behavioral science. Providers also must understand the psychological contexts in which pain is perpetuated.

It is critical that patients hear the following from their gastroenterology provider: (1) chronic DGBI pain is real, (2) pain is perceived from sensory signals that are processed and modulated in the brain, (3) peripheral factors can drive increased pain, and (4) pain is modifiable. Unlike acute pain, which can be thought of as informative or as an alarm (eg, a perforated appendix), chronic gastrointestinal pain is perpetuated by a complex interaction of nerve impulses, which can be unrelated (eg, CAPS) or out of proportion to actual sensory input (eg, postprandial fullness).[15] These impulses, which originate from the enteric nervous system or digestive viscera, activate a wide range of perceptual and behavioral brain networks that amplify the painful experience. Beyond the sensory-discriminative component of pain (location, intensity), higher-order brain processes can be cognitive-evaluative (based on prior experiences/expectations) and affective-motivational (unpleasantness/fear/desire to take action).[16]

We can tell patients that these sensory inputs may result from increased attention to innocuous (or normal) abdominal sensations as the brain continues to scan for potential threats coming from the gut, based on its prior experience with infection, injury, or inflammation (eg, postinfection IBS or FD) and instead of turning off (down-regulating) and being confident in one's safety, the brain mistakenly engages higher-order (and unhelpful) processes. This framework, drawn from the Fear-Avoidance model of pain,[17] helps providers explain why some people have more pain than others, despite a similar diagnosis, and instills hope that a change in one's approach to pain could improve function.

The context in which patients experience pain also is important. It is helpful to explain that factors that initiate one's problems (eg, an infection, a surgery, a stressful life event) are not always the same as those that perpetuate the problem. Psychological inflexibility, or overfocusing on a cause or solution, is common in chronic pain syndromes and interferes with pain acceptance and response to treatment.[18] Pain solicitation from members of the patient's support system (routinely asking about pain) or the presence of psychological comorbidity such as depression, anxiety, post-traumatic stress, or somatization also interferes with pain processing.[19] People with chronic pain also tend to show behaviors of pain hypervigilance,[20] such as checking to see if pain occurs after a meal or bowel movement. They may avoid

activities that are important to them out of fear that symptoms will occur, furthering the impact of chronic pain on daily function.[21] Finally, pain catastrophizing, the process of overestimating the seriousness of the pain coupled with feelings of helplessness, is associated with higher health care utilization and opioid misuse.[22] Providers should avoid engaging in pain catastrophizing by avoiding language that the patient "shouldn't be in so much pain" or continuing to order tests to find the "cause" of pain.

Best Practice Advice 3

Opioids should not be prescribed for chronic gastrointestinal pain because of a disorder of gut–brain interaction. If patients are referred on opioids, these medications should be prescribed responsibly, via multidisciplinary collaboration, until they can be discontinued.

Use of opioid medications for management of non–cancer-related pain is under heavy scrutiny owing to risks of opioid use disorders and overdose-related deaths. Gastroenterology providers frequently are asked to see patients who have been treated with opioids long term for associated gastrointestinal symptoms. In patients with chronic gastrointestinal conditions, including DGBI, use of opioid medications is not infrequent,[23] but is ineffective and potentially harmful.[24] Patients with overlapping inflammatory bowel disease and DGBI are more likely to be using opioids than those without a DGBI,[25] as are patients with DGBI compared with those with structural diagnoses.[26]

Patients who use opioids long term are at risk for development of narcotic bowel syndrome, which often is under-recognized and occurs in approximately 6 % of this population.[27] Narcotic bowel syndrome is characterized by chronic or frequently recurring paradoxic increases in abdominal pain, despite continued or escalating dosages of opioids. It is associated with significant impairment in quality of life.[28] However, narcotic bowel syndrome can be difficult to diagnose because its symptoms overlap with IBS and CAPS. In fact, it may coexist with, and complicate, the management of patients with painful DGBI.

A high index of suspicion for a diagnosis of narcotic bowel syndrome is needed because continued treatment with opioids can lead to clinical worsening and repeated medical evaluations. Using techniques to develop an open and collaborative patient–provider relationship and patient-friendly language to explain the pathogenesis of narcotic bowel syndrome can help gain the patient's acceptance of this disorder and collaboration in its management. It also is important to recognize that tramadol is considered an opioid and has the potential for addiction and other opioid-associated adverse events. The primary treatment is cessation of opioids, if possible, but behavioral and psychiatric approaches are

needed for long-term management and reduced recidivism.[28]

Patients may be referred to a gastroenterologist having already received opioid medications. In this situation, providers should prescribe opioids responsibly in a multidisciplinary setting, with monitoring for efficacy, side effects, and potential for abuse until other forms of pain management can be implemented.[29] The Centers for Disease Control and Prevention guideline for prescribing opioids for chronic pain is a useful resource in this regard.[30]

Best Practice Advice 4

Nonpharmacological therapies should be considered routinely as part of comprehensive pain management, and ideally brought up early on in care.

Brain–gut psychotherapies are brief evidence-based interventions that have been adapted to address the unique pathophysiology associated with gut–brain dysregulation. Brain–gut psychotherapies can be highly customized, based on an individual patient's needs, symptoms, and context, and therefore can be used across the spectrum of painful DGBI, including IBS, FD, and CAPS. It is important that the gastroenterology provider include at the outset of care the role of brain–gut psychotherapies in the treatment of chronic gastrointestinal pain. Although many patients will not require this level of care, patients are more likely to adopt these recommendations when they do not feel like it is a last-ditch effort, after every other intervention has failed or as a "punishment" for not improving with traditional approaches. Furthermore, these therapies typically are well-tolerated with minimal side effects. There are a few classes of brain–gut psychotherapy that have been shown to improve painful symptoms specifically, and it is helpful for the gastroenterology provider to familiarize themselves with the approach, structure, and targets of each intervention to increase clinical use.[31] It also is important that the gastroenterology provider identify a few mental health providers in their community with whom they can collaborate if such services are not already integrated.[31]

Cognitive behavior therapy is a brief (4–12 sessions) brain–gut psychotherapy that focuses on remediation of skills deficits, such as pain catastrophizing, pain hypervigilance, and visceral anxiety through techniques such as cognitive reframing, exposure, relaxation training, and flexible problem solving.[32] There are more than 30 randomized controlled trials (RCTs) supporting the use of cognitive behavior therapy for IBS in multiple forms of delivery (self-administered, web-based, group, or individual) (Appendix Table 1).[33]

Gut-directed hypnotherapy is another well-tested brain–gut psychotherapy that focuses on somatic awareness and the down-regulation of pain sensations through guided imagery and posthypnotic suggestions.[34]

It also can be delivered in groups[35] or online,[36] and by non–mental health professionals. There is evidence from systematic reviews and meta-analyses for pain relief in IBS and evidence from RCTs in CAPS and FD.[33]

Mindfulness-based stress reduction also has been shown to be effective in IBS and musculoskeletal pain syndromes. In IBS, mindfulness has been shown to improve specific symptoms such as constipation, diarrhea, bloating, and gastrointestinal-specific anxiety, especially in women.[37] Furthermore, it can decrease visceral hypersensitivity, improve cognitive appraisal of symptoms, and improve quality of life.[33] This approach also can be delivered by non–mental health professionals.

Acceptance and commitment therapy is a promising approach to chronic gastrointestinal pain that pairs acceptance and mindfulness strategies with behavior change techniques to reduce suffering. It is believed to work through improving psychological flexibility via the use of metaphor, paradox, and experiential exercises designed to help the patient build a meaningful life despite chronic pain. In the pain literature more broadly, acceptance and commitment therapy is a highly effective therapy[38] and research in painful DGBI specifically is ongoing.[39]

Again, it is important that the gastroenterology provider familiarize themselves with the brain–gut psychotherapies that are available but defer decisions as to the choice of treatment to the mental health provider.

Best Practice Advice 5

Providers should optimize medical therapies that are known to modulate pain and be able to differentiate when gastrointestinal pain is triggered by visceral factors vs centrally mediated factors.

Abdominal pain in DGBI often is intermittent and arises as a result of peripheral stimulation, as seen in visceral hypersensitivity, which is a common phenomenon in both IBS and FD.[40] However, because of the establishment of central sensitization,[41] pain in DGBI can become persistent, even in the absence of ongoing peripheral stimulation, and worsen with minimal nonpainful stimulation, termed *allodynia*. This central sensitization may be accompanied by central nervous system changes, which are visible on imaging.[42] Factors that predispose to the development of central sensitization in patients with DGBI include, but are not limited to, a history of abuse, anxiety, catastrophizing, and hypervigilance.[42,43]

Pain has been studied as an end point in multiple trials of peripherally acting drugs in DGBI, and a detailed discussion of all drugs studied in all painful DGBI is beyond the scope of this article. Peripherally acting drugs used in painful DGBI include antispasmodics, peppermint oil, secretagogues, 5-hydroxytryptamine (5-HT) receptor drugs, such as alosetron and tegaserod, nonabsorbable

antibiotics (eg, rifaximin), and the mixed opioid receptor drug eluxadoline. These drugs have been studied extensively in IBS, and their relative efficacy has been the subject of several network meta-analyses.[44–46] Data for other painful DGBI are limited, although tegaserod and rifaximin have been shown to be efficacious in RCTs in FD.[47,48]

In a network meta-analysis examining the efficacy of antispasmodics and other therapies for patients with IBS irrespective of predominant bowel habit,[46] tricyclic antidepressants (see later), antispasmodic drugs as a class, and peppermint oil were ranked first, second, and third, respectively, for relief of abdominal pain, although they performed similarly (Table 1). The relative efficacy of the secretagogues linaclotide, lubiprostone, plecanatide, and tenapanor for treatment of abdominal pain also has been examined in patients with IBS with constipation.[45] Overall, although all treatments were more efficacious than placebo, in terms of reducing the likelihood of abdominal pain persisting, linaclotide 290 mcg once daily ranked first and tenapanor 50 mg twice daily ranked second (Table 1).[45] Finally, the relative efficacy of the 5-HT$_3$–receptor antagonists alosetron, ramosetron, eluxadoline, and rifaximin have been compared in patients with IBS with diarrhea.[44] Rifaximin was not superior to placebo in terms of likelihood of abdominal pain persisting, but ramosetron, alosetron, and eluxadoline were efficacious. Ramosetron 2.5 mcg daily ranked first, ramosetron 5 mcg daily ranked second, and alosetron 1 mg twice daily ranked third (Table 1). Eluxadoline is contraindicated in patients with prior sphincter of Oddi problems or cholecystectomy, alcohol dependence, pancreatitis, or severe liver impairment, and ramosetron is available only in Asia.

Best Practice Advice 6

Providers should familiarize themselves with a few effective neuromodulators, knowing the dosing, side effects, and targets of each, and be able to explain to the patient why these drugs are used for the management of persistent pain.

The enteric nervous system shares its embryologic development with the brain and spinal cord, and therefore its neurotransmitters and receptors. This gut–brain axis, with its norepinephric, serotonergic, and dopaminergic neurotransmitters, is relevant to gut motor function and visceral sensation. Thus, drugs acting on these pathways also have effects on gastrointestinal symptoms. Low-dose antidepressants, now termed gut–brain neuromodulators, are used in painful DGBI because they have pain-modifying properties, in addition to their known effects on mood.[49] Such drugs include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and others, such as mirtazapine. Of these, SSRIs, which act solely on 5-HT receptors, have the least analgesic effect, and the 2014 AGA guideline suggested against using them for patients with IBS, while the 2021 American College of Gastroenterology guideline did not make a strong recommendation for their use.[50,51] In contrast, drugs such as TCAs, SNRIs, and mirtazapine, which have norepinephric effects, have greater effects on pain. These drugs should be started at a low dose, and titrated according to symptom response and tolerability, with patients made aware of potential side effects (Table 2). As discussed earlier, opioid drugs should be avoided in painful DGBI, but naltrexone at a low dose may have analgesic effects without gastrointestinal side effects.

The efficacy of TCAs and SSRIs has been studied in several painful DGBI (Appendix Table 1), including functional heartburn, FD, and IBS.[46,52–54] A trial of the TCA imipramine in functional heartburn showed no benefit of active treatment,[52] whereas an RCT of citalopram showed superiority over placebo for hypersensitive esophagus.[53] There are more data for TCAs and SSRIs in both FD and IBS. In a network meta-analysis of RCTs, TCAs ranked second for the treatment of FD

Table 1. Relative Efficacy of Drugs for Pain in Irritable Bowel Syndrome According to Predominant Stool Pattern in Network Meta-Analyses[44–46]

	First-ranked drug (relative risk of persistent pain with 95 % CI)	Second-ranked drug (relative risk of persistent pain with 95 % CI)	Third-ranked drug (relative risk of persistent pain with 95 % CI)
Trials recruiting patients with IBS irrespective of predominant bowel habit	Tricyclic antidepressants (0.53; 0.34–0.83)	Antispasmodics (0.64; 0.49–0.84)	Peppermint oil (0.64; 0.44–0.93)
Trials recruiting only patients with IBS with constipation	Linaclotide 290 mcg once daily (0.79; 0.73–0.85)	Tenapanor 50 mg twice daily (0.82; 0.75–0.90)	Linaclotide 500 mcg once daily[a] (0.83; 0.77–0.91)
Trials recruiting only patients with IBS with diarrhea	Ramosetron 2.5 mcg once daily (0.75; 0.65–0.85)	Ramosetron 5 mcg once daily (0.82; 0.75–0.89)	Alosetron 1 mg twice daily (0.83; 0.78–0.88)

IBS, irritable bowel syndrome.
[a]The maximum approved dose for linaclotide in the United States is 290 mcg once daily.

Table 2. Starting Dose, Dose Titration, and Common Side Effects of Gut–Brain Neuromodulators

Drug class	Starting dose	Dose titration	Common side effects
Tricyclic antidepressants[a] (eg, amitriptyline or nortriptyline)	10 mg at night	By 10 mg/wk or 10 mg/fortnight according to response to treatment and tolerability to a maximum of 30–50 mg at night	Sedation, dry eyes, dry mouth, constipation
Serotonin- norepinephrine reuptake inhibitors (eg, duloxetine)	30 mg once daily	According to response to treatment and tolerability to a maximum of 60 mg once daily	Sedation, dry mouth, constipation or diarrhea, anxiety, reduced appetite, nausea, headache, fatigue
Mirtazapine	15 mg once daily	According to response to treatment and tolerability to a maximum of 45 mg once daily	Sleep disorders, constipation or diarrhea, anxiety, increased appetite and weight gain, nausea, headache, fatigue

[a]Secondary amines include desipramine and nortriptyline; tertiary amines include amitriptyline and imipramine. Secondary amines may have fewer anticholinergic side effects than tertiary amines.

(Table 1), and ahead of PPIs, even though all 3 trials of TCAs recruited patients with symptoms refractory to PPIs.[54] SSRIs were no more efficacious than placebo in this analysis. In another network meta-analysis of the efficacy of antispasmodics and other therapies for patients with IBS, irrespective of predominant bowel habit,[46] TCAs ranked first for efficacy for pain (Table 1). SNRIs have been less well studied, although there has been 1 trial of venlafaxine in FD,[55] which did not show any benefit. Evidence in IBS is limited to case series of patients taking duloxetine.[56] Interestingly, there is high-quality evidence that duloxetine is efficacious in other chronic painful disorders, such as fibromyalgia and low back pain.[57,58] Mirtazapine was used in 1 small trial in FD, but seemed to have greater effects on early satiety than epigastric pain.[59] A recent trial in patients with IBS with diarrhea showed significant improvements in abdominal pain with mirtazapine.[60] An open-label trial of low-dose naltrexone in IBS showed a significant improvement in pain-free days.[61]

Conclusions

Management of persistent pain in DBGI is challenging and complex. Patients frequently present with co-existing psychiatric comorbidities and a limited range of coping skills. This clinical practice update presents best practice advisories to assist in management of these patients through improved patient–provider communication and a variety of pharmacologic and non-pharmacologic approaches. Development of a collaborative and empathic patient–provider relationship can improve patient anxiety, functional status, and quality of life, while helping patients understand the pathogenesis of their condition and allowing the introduction of appropriate pharmacologic and non-pharmacologic therapies. Avoiding opioid medications is critical to prevent development of opioid use disorders

and narcotic bowel syndrome. In patients who do not respond to the measures outlined here, involvement of a pain management specialist may be required. Overall, management of patients with DGBI with persistent pain requires a multipronged approach to optimize patient outcomes (Figure 1).

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2021.07.006.

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Appendix Table 1. Evidence for Efficacy of Gut–Brain Neuromodulators and Nonpharmacologic Therapies in Painful Disorders of Gut–Brain Interaction[49]

Drug	Functional dyspepsia	Irritable bowel syndrome	Noncardiac chest pain	Functional heartburn	Functional biliary pain	Functional anorectal pain
Tricyclic antidepressants	Efficacious in a meta-analysis of 3 RCTs	Efficacious in a meta-analysis of 11 RCTs	Efficacious in a meta-analysis of 2 RCTs	Not efficacious in 1 RCT	No data	Efficacious in 1 case series
Selective serotonin reuptake inhibitors[a]	Not efficacious in a meta-analysis of 2 RCTs	Efficacious in a meta-analysis of 7 RCTs	Not efficacious in a meta-analysis of 4 RCTs	Efficacious in 1 RCT	No data	No data
Serotonin- norepinephrine reuptake inhibitors	Not efficacious in 1 RCT	Efficacious in 2 case series	Efficacious in 1 RCT	No data	Efficacious in 1 case series	No data
Mirtazapine	Efficacious in 1 RCT	Efficacious in 1 RCT	No data	No data	No data	No data
Cognitive behavior therapy	Efficacious in 3 RCTs	Efficacious in a meta-analysis of 21 RCTs	Efficacious in RCTs	No data	No data	No data
Gut-directed hypnotherapy	Efficacious in 4 RCTs	Efficacious in a meta-analysis of 5 RCTs	Efficacious in 2 RCTs	Efficacious in 1 case series	No data	No data
Mindfulness-based stress reduction	No data	Efficacious in a meta-analysis of 3 RCTs	No data	No data	No data	No data

RCT, randomized controlled trial.

[a]The 2014 AGA guideline on pharmacologic therapy for IBS suggested against using selective serotonin reuptake inhibitors for patients with IBS. The 2021 American College of Gastroenterology guideline on treatment of IBS did not make a strong recommendation for their use.[50,51]