REVIEW

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Approach to Disorders of Gut-Brain Interaction

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Abstract

Disorders of gut-brain interaction, previously known as functional gastrointestinal disorders (eg, functional dyspepsia and irritable bowel syndrome), are commonly encountered in both the primary care and gastroenterology clinics. These disorders are often associated with high morbidity and poor patient quality of life and often lead to increased health care use. The management of these disorders can be challenging, as patients often present after having undergone an extensive workup without a definite etiology. In this review, we provide a practical five-step approach to the clinical assessment and management of disorders of gut-brain interaction. The five-step approach includes (1) excluding organic etiologies of the patient's symptoms and using Rome IV criteria for diagnosis, (2) empathizing with the patient to develop trust and a therapeutic relationship, (3) educating the patient about the pathophysiology of these gastrointestinal disorders, (4) expectation setting with a focus on improving function and quality of life, and (5) establishing a treatment plan with central and peripherally acting medications and nonpharmacological modalities. We discuss the pathophysiology of disorders of gut-brain interaction (eg, visceral hypersensitivity), initial assessment and risk stratification, as well as treatment for a variety of diseases with a focus on irritable bowel syndrome and functional dyspepsia.

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Disorders of gut-brain interaction (DGBIs), previously known as functional gastrointestinal disorders (eg, functional dyspepsia and irritable bowel syndrome [IBS]), are commonly encountered in both primary care and gastroenterology clinics as well as the acute care setting. Chronic functional gastrointestinal symptoms can be associated with increased health care use, and patients with such symptoms can have significant morbidity and decreased quality of life compared with the general population.[1,2] Disorders of gut-brain interaction are prevalent worldwide with rates up to 40% reported in a large-scale multinational study.[3] The approach to workup of chronic digestive symptoms can be particularly challenging for clinicians given the broad initial differential diagnoses and the vast array of diagnostic tests that may be pursued. Given the high prevalence of DGBI, it is imperative that clinicians have a framework for the presentation, diagnostic criteria, as well as treatment options for these conditions. In this review, we provide a practical approach to the management of DGBI (Figure 1). This approach can be easily remembered using the five "Es," namely, excluding organic etiologies and using Rome IV criteria for diagnosis, empathizing with and educating patients, expectation setting, and establishing a treatment plan.

STEP 1: EXCLUDE ORGANIC ETIOLOGIES AND USE ROME IV CRITERIA FOR DIAGNOSIS

A detailed history and comprehensive physical examination are key components of the initial evaluation of a patient presenting with suspected DGBI. It is important to clarify the onset of symptoms (sudden vs gradual), duration (acute vs chronic), characteristics of pain (location, quality, and continuous vs episodic), associated symptoms (abdominal pain, nausea, bloating, and change in bowel habits), and psychosocial stressors (life events in relation to

symptoms). Some patients with DGBI may report that food is a trigger for their symptoms. A thorough review of the patient's comorbid medical conditions, medication list, family history, and alcohol and substance use history should be performed. A psychiatric history is also important as some patients with DGBI may have a history of sexual or physical abuse.[4] Assessment of alarm symptoms including fever, unintentional weight loss, melena, hematemesis, hematochezia, jaundice, sudden change in bowel habits, and family history of gastrointestinal cancers is essential, as these may be suggestive of an organic or structural cause for the patient's condition. Family history of inflammatory bowel disease, celiac disease, lactose intolerance, and IBS should also be obtained.

The physical examination should generally be guided by the patient history and presentation. In general, patient vital signs should always be noted, and a detailed abdominal examination should also be performed. A rectal examination should be considered in patients presenting with constipation, hematochezia, and rectal pain. It is important to evaluate the pelvic floor muscles in patients with suspected pelvic floor dysfunction. The Carnett sign should be elicited in patients with suspected abdominal wall pain. This sign is based on an examination technique where the clinician first palpates the area of maximal pain on the patient's abdomen. The patient is then asked to tense their abdominal wall muscles and the Carnett sign is considered positive when palpation of the abdomen in the tense position elicits the same or greater pain compared with the rest position.[5,6] Patients with abdominal wall pain classically present with pain that is localized to a focal part of the abdomen and worsens with positional activities that tense the abdominal wall muscles (eg, coughing and sitting). Surgical history is important as patients with prior abdominal surgeries may have abdominal wall pain localized near a scar. Clinicians should also evaluate for red flags on physical examination (eg, jaundice, abdominal mass, lymphadenopathy, and blood in the rectum) as these would warrant further assessment.

The initial laboratory evaluation, imaging studies, and procedures are guided primarily by the patient history and physical examination. In general, it may be reasonable to obtain basic laboratory studies such as a complete blood count, electrolytes, creatinine, liver biochemistries, C-reactive protein, fecal calprotectin, and tissue transglutaminase antibody for assessment of anemia, electrolyte derangements, liver disease, inflammatory conditions, and celiac disease, respectively. For patients without alarm symptoms and normal physical examination and laboratory tests, the initiation of appropriate therapy without additional evaluation may be considered. In other cases, a focused workup with imaging of the abdomen or esophagogastroduodenoscopy and/or colonoscopy may be necessary for further

ARTICLE HIGHLIGHTS

- Disorders of gut-brain interaction, previously known as functional gastrointestinal disorders, are commonly encountered in both primary care and gastroenterology clinics, and can be associated with significant morbidity, decreased quality of life, and increased health care use.
- A practical approach to management of disorders of gut-brain interaction can be remembered using the five "Es": excluding organic etiologies and using Rome IV criteria for diagnosis, empathizing with and educating patients, expectation setting, and establishing a treatment plan.
- A detailed history and comprehensive physical exam are key components of the initial evaluation of a patient with suspected disorder of gut-brain interaction. In particular, alarm symptoms and red-flag signs should be elicited, as these may be suggestive of an underlying organic or structural cause.
- Treatment options for disorders of gut-brain interaction include pharmacotherapy and nonpharmacological interventions and are based on the patient's predominant symptom and response to prior treatments. The general approach to pharmacotherapy is based on various targets, ranging from those that target the gastrointestinal tract lumen or wall, to others that impact the enteric and central nervous system.

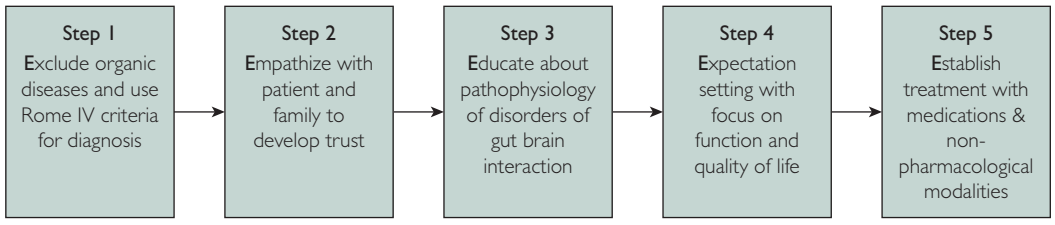


FIGURE 1. Five-step approach to disorders of gut-brain interaction.

investigation based on the suspected differential diagnoses. DGBI are diagnoses of exclusion after other organic etiologies have been systematically ruled out.

DGBI encompass a broad spectrum of conditions such as IBS, functional dyspepsia, and functional abdominal pain syndrome, that share a diagnostic framework as defined by the Rome IV criteria.[7] Certain conditions such as functional dyspepsia can be further categorized into subtypes including postprandial distress syndrome and epigastric pain syndrome.[8,9] For these disorders, the symptoms must be present for at least 3 months in duration, with onset 6 months or greater before diagnosis, and occur in the absence of organic disease. Each specific DGBI is further characterized by additional specific diagnostic criteria that are beyond the scope of this review article.

STEP 2: EMPATHIZE

The patient-provider relationship is the cornerstone in the management of DGBI. When encountering such patients, clinicians should strive to validate the patient's experiences, listen actively and attentively, and show compassion to develop trust and rapport with the patient and family.[4] A patient is more likely to share private physical or mental life stressors that may have precipitated their symptoms when clinicians display empathy towards them. Communication skills should be adapted to optimize the patient-provider relationship. The use of open-ended questions may be useful when inquiring about a patient's symptom-specific anxiety, early life adversity, and functional impairment in relation to digestive symptoms. In a survey of 1242 patients with IBS, a substantial number of patients believed that their disorder could develop into a serious medical condition such as colitis (43%) or cancer (21%).[10] Addressing such misconceptions is an important aspect of care after developing trust and rapport with the patient.

Figure 2 shows the escalation of functional gastrointestinal symptoms for patients following an initial "hit" or a triggering event that may further be exacerbated by additional stressors and life events, along with numerous medical visits and tests that fail to reveal a clear diagnosis. "Medicalization," the process of labeling and treating conditions or behaviors as medical issues, and fragmented care may occur as patients seek opinions from different specialists. "Disintegration," the process where patients stop doing their normal activities such as exercising, meeting with friends and family, and working may also occur. In addition to showing empathy, clinicians should aim to understand the patient's existing comprehension of their illness as well as prior barriers to medical treatment.

STEP 3: EDUCATE

After building a therapeutic relationship with the patient, the next essential step is to explain the diagnosis to the patient in a clear, easy to follow, and concise manner. The pathophysiology of DGBI is thought to be multifactorial rather than one specific etiology. There are several proposed mechanisms based on alterations in the function

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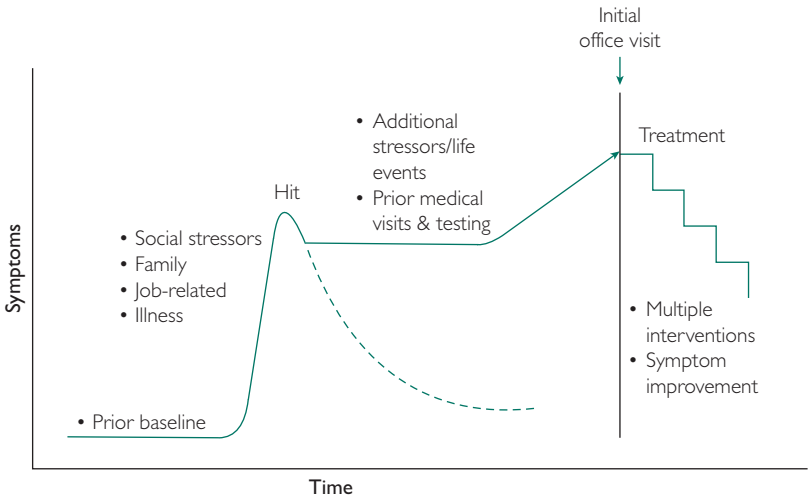


FIGURE 2. Gastrointestinal symptoms precipitated by various stressors.

of the microbiome-gut-brain axis (Figure 3). Patients may have a lower threshold for pain despite having normal gastric motility and accommodation, a phenomenon referred to as visceral hypersensitivity.[11] This consequently results in the enhanced sensation of pain in the internal organs in response to a normal stimulus that may have not previously elicited pain for the patient or may not reach the threshold for triggering pain for others. In addition to the augmentation of peripheral nerve signals, there may also be a component of central sensitization when the brain is hyper-responsive to signals and standard stimuli from the peripheral nerves in the gastrointestinal tract.[12] Central sensitization may also be characterized by allodynia, which refers to a sensation of pain in response to a stimulus that would typically not be expected to provoke discomfort or irritation. These interactions of the bidirectional brain-gut pathway should be described in patient-friendly language while avoiding the use of medical jargon.

In addition to explaining why DGBIs occur, it is equally important to review prior normal laboratory testing, procedures, and imaging tests with the patient as well, as this can serve to inform patients that their prior medical care has been carefully reviewed by the provider. This can help avoid the need to duplicate much of the same testing which is unlikely to be fruitful, allay patient concerns that prior testing was incomplete or incorrect, and can validate the patient's experience leading to improved patient satisfaction and outcomes. An important component of patient education is also addressing behavioral factors (eg, coping mechanisms) that can exacerbate and perpetuate gastrointestinal symptoms. Patients with DGBI may have comorbid psychiatric conditions[13] and addressing potential overlap regarding how these disorders may aggravate digestive symptoms is a key component of patient education. Providing education serves as the foundation for minimizing unnecessary health care use and procedures, as well as providing patients with insight into their disease and appropriate management strategies. The use of techniques such as "teach-back" can help health care providers assess whether a patient has accurately understood this information. Moreover, adequately explaining the brain-gut axis will set the stage for the pharmacotherapeutic options available to treat DGBI.

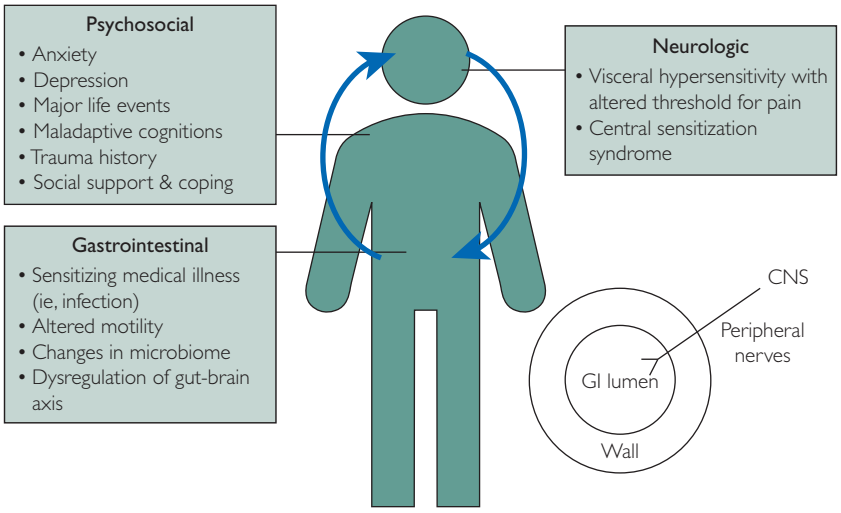


FIGURE 3. Pathophysiology of disorders of gut-brain interaction. CNS, central nervous system; GI, gastrointestinal.

STEP 4: EXPECTATION SETTING

The mainstay of treatment for DGBI consists of reassurance and lifestyle modifications for those with mild symptoms and pharmacological therapy when symptoms are moderate to severe. Clinicians should communicate to patients that the goal of treatment is to gradually decrease the severity of symptoms over the coming months using a variety of different interventions. It is important to highlight that, similar to other chronic health conditions, such as hypertension and depression, DGBIs do not improve immediately nor rapidly but require longitudinal care to maximize the possibility of steady and continued improvement. Establishing routine outpatient follow-up visits to frequently reassess symptoms and setting realistic targets with patients are critical to ensuring long-term success. The use of a singular intervention alone is unlikely to resolve symptoms and patients typically require a multidisciplinary approach, particularly in those with comorbid psychiatric illness such as depression, anxiety, or post-traumatic stress disorder.

As previously discussed, the patient-physician relationship is the cornerstone of developing a successful treatment plan and therapeutic partnership. A strong emphasis should be placed on reiterating that the goal of management is to improve the patient's ability to function and regain their quality of life, rather than achieving a cure or total resolution of symptoms.[14] Establishing realistic expectations can help with patient adherence to the treatment plan. It is also useful to share expectations with family members that may be present at the office visit or are actively involved in the patient's care to further reinforce the plan and provide support to the patient. Disease-specific quality of life questionnaires, although not commonly used in clinical practice, may be beneficial for quantifying the patient's current symptoms and can serve as clinical aids for comparing disease activity over time at subsequent visits.[15] Examples of validated questionnaires include the Gastrointestinal Symptom Rating Scale—Irritable Bowel Syndrome which is a 13-item measure of IBS symptom severity and the Irritable Bowel Syndrome—Quality of Life instrument which assesses 8 domains of quality of life.[16,17]

STEP 5: MANAGEMENT

Pharmacological Therapy

The general approach to pharmacotherapy for DGBI is based on various targets for

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TABLE 1. Treatment of Disorders of Gut-brain Interaction[a]

Targets for intervention		
GI lumen	Wall	PNS/CNS
Diet/lifestyle modification with small, frequent meals, or low FODMAP or gluten-free diet	Antispasmodics (eg, hyoscyamine, dicyclomine)	Tricyclic antidepressants (eg, amitriptyline)
Histamine H2 receptor antagonists or proton pump inhibitors	Anticholinergics	Selective serotonin/ norepinephrine re-uptake inhibitors (eg, sertraline, duloxetine)
Trial of anti-diarrheal agents (e.g., loperamide), mu-opioid receptor agonist eluxadoline, 5-HT_3 antagonist alosetron, or bile acid sequestrants (eg, cholestyramine) for diarrhea; fiber, or osmotic laxatives, or secretagogues (eg, linaclotide) for constipation	Stimulant laxatives (eg, bisacodyl) for constipation	Neuromodulators (eg, pregabalin, gabapentin)
	Prokinetic agents (eg, metoclopramide)	Cognitive behavioral therapy
	Trigger point injections or topical creams (eg, lidocaine) for abdominal wall pain	Lifestyle interventions for stress reduction (eg, adequate rest, psychosocial support networks, exercise, acupuncture) and mindfulness-based activities (eg, yoga, tai chi, meditation)

[a]5-HT3, 5-hydroxytryptamine 3 receptor antagonist; CNS, central nervous system; FODMAP, low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; GI, gastrointestinal; PNS, peripheral nervous system.

treatment, ranging from those that target the gastrointestinal tract lumen or wall, to others that impact the enteric and central nervous system as shown in Table 1. A variety of central and peripheral agents may be used alone or in combination for the treatment of DGBI, based on the patient's predominant symptoms and prior adverse effects to medications.

Pharmacological therapy for functional dyspepsia includes a trial of histamine H2-receptor antagonists (eg, famotidine) or proton pump inhibitor (PPI) therapy (eg, omeprazole).[18] Hyoscyamine and dicyclomine are antispasmodic medications indicated primarily for patients with symptoms of abdominal cramping.[19,20] Peppermint oil and its active ingredient, l-menthol, is another antispasmodic that may be used for DGBI.[21,22.] Similarly, caraway oil is also used as an antispasmodic and available in various commercial formulations that are accessible over the counter. A systematic review and meta-analysis of nine randomized placebo-controlled trials has shown that peppermint oil was significantly superior to placebo with a relative risk of 2.23 (95% CI, 1.78 to 2.81) and a number needed to treat (NNT) of 3 to induce global improvement of symptoms.[23]

For those with diarrhea-predominant IBS, medications such as antidiarrheals (eg, loperamide) or bile acid binders (eg, cholestyramine) may be considered.[24] Other medications such as fiber, osmotic laxatives (eg, polyethylene glycol), stimulant laxatives, and the chloride channel activator lubiprostone or the guanylate cyclase C receptor agonist linaclotide may be used in patients with constipation predominant IBS.[25,26] Lubiprostone is typically well tolerated, although nausea is one of the most common side effects. In two phase 3 trials, linaclotide compared with placebo showed improvement in symptoms of abdominal pain, discomfort, bloating, fullness, and cramping ($P<.01$) as well as improved quality of life scores ($P<.01$).[27] The NNT ranged from 3.0 to 3.7 with linaclotide. The improvement in symptoms such as abdominal pain may be in part attributed to the relief of constipation. Diarrhea was the most common side effect observed with this medication. In patients presenting with constipation, it is also important to consider the diagnosis of pelvic floor dysfunction as the mainstay of treatment for this is pelvic floor biofeedback physical therapy in addition to pharmacotherapy. The digital rectal examination can provide clues as to whether a patient may have this condition, which can then be confirmed using anorectal manometry.

For localized abdominal wall pain, topical creams may be used (eg, diclofenac

or lidocaine) in addition to trigger point injections.[6] A randomized control trial (RCT) in adults with chronic abdominal wall pain who received a trigger point injection vs a transversus abdominis plane injection reported significantly lower pain at 3-month follow-up with a difference in pain scores of 1.7 (95% CI, 0.3 to 3.0).[28]

For patients with functional nausea and vomiting, a variety of antiemetic agents may be considered including 5-hydroxytryptamine 3 receptor (5-HT_3) antagonists (eg, ondansetron, granisetron), phenothiazines (eg, promethazine, prochlorperazine), butyrophenones (eg, haloperidol and droperidol), and anticholinergic and antihistamine medications (eg, meclizine and diphenhydramine).[29,30] Selection of antiemetic should be tailored to the patient with consideration of potential side effects such as QT prolongation with 5-HT_3 antagonists. Anticholinergic medications in older patients should be used with caution due to the risk of precipitating delirium, urinary retention, and other adverse effects. In addition to the use of 5-HT_3 antagonists for functional nausea and vomiting, these medications may also be useful in patients with IBS and diarrhea or urgency.[31] A network meta-analysis including a total of 21 RCTs has shown that 5-HT_3 antagonists lead to improved symptoms of IBS compared with placebo or control drugs.[32]

Other pharmacotherapy options include the use of prokinetic agents (eg, metoclopramide) for certain DGBIs (eg, functional dyspepsia) that are refractory to other medications.[33] These agents should be used at the lowest effective dose and for a limited duration due to the risk of extrapyramidal side effects with long-term use (eg, parkinsonism, akathisia, and tardive dyskinesia). Some patients may require a repeat course of therapy if symptoms recur after cessation. There are limited studies comparing the efficacy of prokinetic agents for DGBI. Several trials comparing PPI vs prokinetic therapy in functional dyspepsia showed that PPI therapy is more effective in reducing gastrointestinal symptoms.[34] Specific treatments for the subtypes of functional dyspepsia, epigastric pain syndrome, and postprandial distress syndrome are beyond the scope of this review.

A variety of antidepressants such as tricyclic antidepressants (TCAs) (eg, amitriptyline and desipramine), selective serotonin or norepinephrine reuptake inhibitors (eg, sertraline and duloxetine), and mirtazapine may also be used for treating DGBI.[35] TCAs are best suited for patients with diarrhea and selective serotonin reuptake inhibitors (SSRIs) for patients with constipation, respectively, as TCAs can result in constipation and SSRIs in diarrhea. In a systematic review and meta-analysis of 53 RCTs evaluating the treatment for IBS, the relative risk of symptoms not improving with antidepressants vs placebo was 0.66 (95% CI, 0.57 to 0.76), with similar outcomes observed between TCAs and SSRIs. The NNT with antidepressants was 4.5 (95% CI, 3.5 to 6).[36] A randomized, double-blind, placebo-controlled study of the atypical antidepressant mirtazapine showed that it significantly improved patients' quality of life (P=.04) and significantly decreased the severity of symptoms (P=.002).[37]

Neuromodulators may also be considered (eg, pregabalin and gabapentin) for DGBI.[38,39] It is postulated that these agents impact the central processing of pain and also decrease the visceral hypersensitivity associated with DGBI. An RCT of patients with functional dyspepsia evaluating the use of pregabalin vs placebo showed that 70.6% and 42.1% of patients at week 8 (P=.03) had reduction of symptoms, respectively, and that pregabalin improved overall quality of life (P=.03).[40] In general, the use of opioid medications should be avoided to treat pain in patients with DGBI. Opioids may lead to impaired gastric motility and can worsen symptoms such as nausea. Additionally, these agents carry a risk of long-term dependence.

Additional Treatments

Nonpharmacological interventions include dietary modification consisting of small, frequent meals as well as avoidance of certain patient-specific triggers such as

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caffeine, alcohol, or lactose. Patients may benefit from a trial of a gluten-free diet or low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet.[41,42] A systematic review and meta-analysis showed that patients following a low FODMAP diet had significantly reduced severity of abdominal pain (odds ratio [OR], 1.81; 95% CI, 1.13 to 2.88), bloating (OR, 1.75; 95% CI, 1.07 to 2.87), and overall symptoms (OR, 1.81; 95% CI, 1.11 to 2.95).[43] To maximize the chances of a success with dietary modifications, consultation with an experienced gastrointestinal dietician can be extremely helpful. After the initial restriction of FODMAPs, it is important for clinicians to properly instruct patients on the second and third stages of the plan that include the gradual reintroduction of foods while assessing symptoms, followed by the personalization of the diet to avoid foods that are triggers.

Nonpharmacological treatment may also include physical therapy to increase the strength, flexibility, and mobility of abdominal muscles in those with abdominal wall pain. Physical therapy may additionally help those with overlapping pelvic floor dysfunction and DGBI. Lastly, in patients with comorbid anxiety or depression, interventions such as cognitive behavioral therapy may help decrease the intensity of pain and gastrointestinal symptoms.[44] In an RCT of 436 patients with IBS, a primarily home-based version of cognitive behavioral therapy produced significant and sustained improvement in gastrointestinal symptoms compared with standard patient education ($P<.05$).[45] Additionally, there is increasing support for gut-direct hypnotherapy, particularly in the pediatric population, for DGBI.[46,47] Hypnotherapy, with a trained therapist, can create a focused state of somatic awareness and help downregulate pain sensations.

Various complementary and alternative medicine treatments have been reported for DGBI including herbal supplements (eg, ginger, vitamin B6, and turmeric), acupuncture, and biofeedback therapy.[48] However, studies have shown inconsistent results and there is limited evidence for these therapies currently. In addition, studies investigating the use of probiotics for conditions such as IBS are composed of small studies involving multiple different types and strains of probiotics, with varying benefits.[49]

CONCLUSION

DGBI are commonly encountered in primary care and gastroenterology and their management can often be challenging. Using a practical five-step approach can help build a therapeutic relationship with patients and lead to better patient-centered outcomes. A comprehensive history and physical examination form the framework for the diagnosis of DGBI and guide further testing. Management is focused on validating the patient's experience, explaining the diagnosis and role of visceral hypersensitivity, and using a multidisciplinary treatment approach with both pharmacological and nonpharmacological interventions.

POTENTIAL COMPETING INTERESTS

The authors report no potential competing interests.

Abbreviations and Acronyms: **DBGI,** disorders of gut-brain interaction; **FODMAP,** low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; **IBS,** irritable bowel syndrome; **NNT,** number needed to treat; **PPI,** proton pump inhibitor; **RCT,** randomized control trial; **SSRI,** selective serotonin reuptake inhibitor; **TCA,** tricyclic antidepressant

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