SYMPOSIUM ON PAIN MEDICINE

Common Functional Gastroenterological Disorders Associated With Abdominal Pain

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Abstract

Although abdominal pain is a symptom of several structural gastrointestinal disorders (eg, peptic ulcer disease), this comprehensive review will focus on the 4 most common nonstructural, or functional, disorders associated with abdominal pain: functional dyspepsia, constipation-predominant and diarrhea-predominant irritable bowel syndrome, and functional abdominal pain syndrome. Together, these conditions affect approximately 1 in 4 people in the United States. They are associated with comorbid conditions (eg, fibromyalgia and depression), impaired quality of life, and increased health care utilization. Symptoms are explained by disordered gastrointestinal motility and sensation, which are implicated in various peripheral (eg, postinfectious inflammation and luminal irritants) and/or central (eg, stress and anxiety) factors. These disorders are defined and can generally be diagnosed by symptoms alone. Often prompted by alarm features, selected testing is useful to exclude structural disease. Identifying the specific diagnosis (eg, differentiating between functional abdominal pain and irritable bowel syndrome) and establishing an effective patient-physician relationship are the cornerstones of therapy. Many patients with mild symptoms can be effectively managed with limited tests, sensible dietary modifications, and over-the-counter medications tailored to symptoms. If these measures are not sufficient, pharmacotherapy should be considered for bowel symptoms (constipation or diarrhea) and/or abdominal pain; opioids should not be used. Behavioral and
psychological approaches (eg, cognitive behavioral therapy) can be helpful, particularly in patients with chronic abdominal pain who require a multidisciplinary pain management program without opioids.

This review will focus on nonstructural, or functional, rather than structural (eg, peptic ulcer disease and ulcerative colitis) gastrointestinal (GI) disorders associated with abdominal pain. Symptoms provide the basis for classifying the functional disorders, which affect the entire GI tract (Figure 1). Many physicians refer to these conditions with the umbrella term irritable bowel syndrome (IBS). It is critical to recognize that although these conditions share several features, they can and should be distinguished from each other primarily on the basis of the nature of symptoms (Figure 2). These specific diagnoses are not only more precise but also facilitate management, which is tailored to the specific symptoms. This review will focus on the 4 most common functional disorders associated with abdominal pain: functional dyspepsia, constipation-predominant and diarrhea-predominant IBS, and functional abdominal pain syndrome.

METHODS
We searched MEDLINE on the PubMed and Ovid platforms, as well as the Cochrane Database of Systematic Reviews, using the keywords abdominal pain, chronic abdominal pain, abdominal wall pain, visceral pain, narcotic bowel, and functional abdominal pain for English-language articles with no date restrictions. Search terms were cross-referenced with review articles, and additional articles were identified by manually searching reference lists.

Epidemiology and Natural Course
In North America, approximately 20% of adults have symptoms of dyspepsia and 10% to 15% have symptoms of IBS. Among the latter, approximately 5% each have diarrhea- and constipation-predominant IBS, which are more common in men and women, respectively. By comparison, the prevalence of functional abdominal pain is much lower (0.5%-1.7%). Even this figure is probably an overestimate, because the definition of functional abdominal pain in these studies did not incorporate all the criteria for functional abdominal pain syndrome, such as the loss of daily function associated with the pain. Most cases of IBS are diagnosed by primary care specialists.

It is not uncommon for patients to simultaneously have symptoms of 2 or more disorders (eg, dyspepsia and constipation). The severity and nature of symptoms vary with time. Over the long term, symptoms were unchanged in 50%, worse in approximately 20%, and improved in 30% of patients with IBS seen in clinics. In the general population, approximately 20% of patients with IBS had the same symptoms, 40% had no symptoms, and 40% had different symptoms at follow-up 12 years later. The nature of symptoms may change over time, most frequently from constipation- or diarrhea-predominant IBS to mixed type or vice versa. In postinfectious IBS, the prognosis is better; symptoms resolve in approximately 50% of patients after 6 to 8 years.

Relevant Anatomy, Physiology, and Pathophysiology
Clinically Oriented Introduction to GI Motor and Sensory Functions
Motility is regulated by coordinated neurohormonal mechanisms that affect smooth muscle contractility. Gut motor activity is primarily controlled by the intrinsic or enteric nervous system. The central nervous system modulates gut motor activity via the extrinsic sympathetic and parasympathetic pathways, whereas descending pathways in the spinal cord modulate transmission of sensory input from the dorsal horn to supraspinal centers. Visceral sensation is conveyed via afferents that travel to the spinal cord and ultimately to the cerebral cortex, as well as through the vagus to the brainstem. There is a 10:1 ratio of afferent to efferent fibers in the vagus at the level of the diaphragm. The vagus primarily conveys subnoxious messages, whereas the spinal afferents...
convey nonnoxious and noxious input to the dorsal horn of the spinal cord. Thereafter, information is conveyed via the spinothalamic tract to the medial and posterior thalamus and subsequently to the primary somatosensory cortex, which localizes and discriminates somatic and visceral sensations. The spinoreticular and spinomesencephalic tracts project to the brainstem reticular formation and medulla from which information is conveyed to the medial thalamus and the anterior cingulate cortex and insula. These areas process the affective-motivational aspects of pain. Descending inhibitory fibers from the anterior cingulate cortex to the dorsal horn of the spinal cord use endogenous opioids, serotonin, and noradrenaline to modulate or gate visceral sensation, including pain, such that only some messages from the viscera are conveyed to higher centers (Figure 3).

**Pathogenesis of Symptoms**

Current concepts suggest that the functional GI disorders result from the combined effect of biological, psychological, and social factors (ie, the biopsychosocial model). Exemplifying this model, postinfectious IBS, which occurs after the infection resolves in 4% to 40% of patients with infectious gastroenteritis, is more likely to occur after severe or prolonged gastroenteritis in women older than 60 years, smokers, and patients with anxiety, depression, hypochondriasis, or an adverse life event in the preceding 3 months. The following factors have been implicated in the pathogenesis of functional GI disorders.

**Luminal Irritants.** Luminal irritants primarily include bile acids, nonabsorbed complex carbohydrates, and the products of their bacterial metabolism (ie, short chain fatty acids). Bile acids and short chain fatty acids activate secretion of enteroendocrine cell products (eg, 5-hydroxytryptamine [5-HT]) and stimulate colonic motility and defecation. Enteric microbiota, including both commensal and pathogenic organisms, also communicates with the host.

**Increased Visceral Sensitivity.** Increased visceral sensitivity is documented with increased perception of GI (eg, rectal) balloon distention. Healthy people have little awareness of GI physiological processes except for the sensation of postprandial fullness after a satiating meal or the desire to defecate. Increased sensitivity refers to an exaggerated awareness of normal events and differs from hyperalgesia, in which painful stimuli evoke more pain than usual, or allodynia, which refers to perception of nonnoxious stimuli as being painful. Increased sensitivity may be due to sensitization of peripheral afferent receptors or spinal dorsal horn neurons, alterations in descending modulation, or central amplification. Sensitization of peripheral receptors may be secondary to low-grade inflammation, which activates silent nociceptors and increases the sensitivity and field of peripheral receptors. Peripheral sensitization may increase afferent input to the dorsal horn, causing central sensitization. Exemplifying this phenomenon, acid infusion in the distal esophagus causes hyperalgesia not only in the acid-exposed distal esophagus but also in the unexposed proximal esophagus. Repeated distention of the sigmoid colon causes rectal hyperalgesia. Central amplification or sensitization is the hallmark of fibromyalgia.
mechanisms (eg, reduced descending modulation or central amplification) (Figure 3) that may explain increased visceral sensitivity have been evaluated in fibromyalgia and IBS.13,17

Normal and Disordered GI Motility. Disordered GI motility may contribute to symptoms. Normally, the stomach relaxes or accommodates after a meal, providing room for food to be digested into smaller particles. Impaired gastric accommodation may explain postprandial symptoms (eg, early fullness or satiety) in functional dyspepsia.11 The colonic response to feeding, or gastrocolonic response, refers to reflex contraction of the distal small intestine and colon in response to nutrients in the stomach and small intestine. This reflex, which is mediated by afferent vagal pathways and efferent sacral parasympathetic pathways, explains why healthy people experience the desire to defecate after eating. An exaggerated response may explain postprandial discomfort and diarrhea in patients with diarrhea-predominant IBS. The contractile response to colonic distention may also evoke abdominal discomfort. Indeed, the perception of distention may be due to the contractile response to distention rather than distention per se.

Decreased motility may affect the stomach, small intestine, and/or colon; delay GI transit; and explain symptoms.18 For example, opioids markedly delay colonic transit and may predispose to colonic retention of stool, colonic distention, and abdominal distention. Pelvic floor dysfunction (ie, a disturbance in the normal rectoanal coordination during defecation) may impair rectal evacuation of stool, which also predisposes to rectal and colonic distention with stool and similar symptoms.

Hormonal and Other Chemical Mediators. Serotonin, which is released from enterochromaffin cells, initiates the peristaltic reflex and activation of extrinsic vagal and spinal afferents that activate extrinsic reflexes and sensation.11 This reflex involves excitatory (eg, acetylcholine and tachykinins) and inhibitory (primarily vasoactive intestinal peptide and nitric oxide) neurotransmitters. Irritable bowel syndrome is associated with serotonergic disturbances.19 Ingestion of calories stimulates the release of hormones such as cholecystokinin and glucagon-like peptide-1, which stimulate vagal afferents and mediate postprandial symptoms such as nausea and satiety.11

Abdominal Wall Accommodation. Normally, meal ingestion is accompanied by relaxation of the diaphragm (ie, diaphragmatic ascent),

FIGURE 2. Diagnostic criteria and algorithm for common functional gastrointestinal disorders associated with abdominal pain. This algorithm applies the Rome criteria, which are widely used in research studies. Irritable bowel syndrome (IBS) is defined by abdominal pain accompanied by 2 of these 3 criteria: relief with defecation, altered stool consistency (loose or hard stools), or altered frequency (less or more frequent). The other syndromes are defined by the listed criteria. The criteria also specify the duration and frequency of symptoms: in general, a duration of 6 months and a frequency of 2 days every week or more often.
which provides extra space in the upper abdominal cavity, and compensatory contraction of the upper anterior abdominal wall, which prevents abdominal distention in the upright position. In contrast, patients with dyspepsia have aberrant abdominal accommodation characterized by paradoxical contraction of the diaphragm (ie, diaphragmatic descent) and relaxation of the upper anterior abdominal wall, which increases abdominal girth. Similar disturbances (ie, diaphragmatic contraction and relaxation of the lower rectus and internal oblique) have been observed during intestinal gas infusion in IBS and functional bloating.

**Psychosocial Factors.** Early life experiences (eg, verbal, sexual, or physical abuse), adult stressors (eg, divorce or bereavement), lack of social support, and other social learning experiences can affect an individual's physiological and psychological responses. The changes in these responses can lead to maladaptive earned-illness behaviors and predispose to functional GI and psychiatric disorders. Women with IBS are more likely to have experienced abuse. These experiences may affect the brain-gut axis and lead to increased visceral sensitivity. Earlier studies suggested that psychosocial factors affect illness behavior (ie, the decision to seek...
care and excessive expressions of suffering) rather than symptoms per se. More recent studies suggest that psychological disturbances are common even among people with IBS in the community, many of whom have not sought medical attention. Whether psychological and somatic symptoms (eg, chronic fatigue and fibromyalgia) reflect the shared expression of a common substrate or whether they cause each other is unknown. Somatization, hypervigilance, and catastrophizing amplify GI and non-GI symptoms in patients with IBS.

**CLINICAL FEATURES**

**Characteristics of Pain, Physical Examination, and Associated Conditions**

The location of pain may suggest its origin; for example, postprandial epigastric pain likely originates from the stomach. The pattern of pain, particularly its relationship to meals, and associated symptoms are also useful. Patients with *dyspepsia*, which is derived from the Greek word for indigestion, have pain that occurs shortly (eg, within 60 minutes) after meals, often associated with upper GI symptoms such as nausea, bloating, early satiety, or heartburn (Figure 2). However, *dyspepsia* is not associated with disordered bowel habits. In contrast, patients with IBS have intermittent abdominal pain, often related to meals. Moreover, the abdominal pain is associated with 2 of these 3 features: improvement with defecation, harder and/or less frequent stools in constipation-predominant IBS, and the opposite in diarrhea-predominant IBS. Some patients with functional constipation and diarrhea also have abdominal pain; however, the pain is not temporally associated with bowel symptoms.

On physical examination, patients may have tenderness to abdominal palpation, but not guarding or rigidity. The absence of features of autonomic arousal (eg, tachycardia) when patients report severe pain suggests a functional rather than a structural disorder. When the abdomen is palpated, patients with functional pain might wince with their eyes closed (closed eyes sign) whereas patients with an acute abdominal pain episode usually keep their eyes open in anxious anticipation. When the abdomen is palpated with a stethoscope, the behavioral response to pain decreases in functional but increases in acute causes of abdominal pain (stethoscope sign). In patients with constipation, stool may be palpable in the colon. Somatic symptoms (eg, chronic fatigue, fibromyalgia, and cardiopulmonary symptoms) that are not due to an organic disorder and psychiatric disorders (major depression, anxiety, and somatization) are also common in patients with IBS. In patients with chronic abdominal pain, the prevalence of depression and impaired overall functioning is comparable with that in patients with chronic back pain. Hence, all patients with moderate or severe symptoms should be screened for psychiatric symptoms and illness-related disability either during the interview or, perhaps more efficiently, with a screening questionnaire (eg, Generalized Anxiety Disorder-7 or Patient Health Questionnaire-9, Health Anxiety Inventory, and Sheehan Disability Scale). Physicians should also inquire about the relationship of stressors to symptoms; a history of sexual and/or physical abuse, which often is not volunteered by patients; and the presence of social support networks, which are often limited, resulting in maladaptive strategies (eg, catastrophizing thoughts and frustration) to cope with symptoms. The physical and mental quality of life in patients with severe IBS is comparable to or worse than that in patients with severe chronic obstructive lung disease or congestive heart failure. The mental distress is less severe than in patients with severe depression but worse than in patients with cancer.

**Other Conditions**

**Musculoskeletal Abdominal Pain.** In contrast to visceral abdominal pain, musculoskeletal abdominal pain is sharp, localized to an area of the abdominal wall usually smaller than 2 cm, and associated with Carnett sign. Patients with abdominal wall pain are likely to be women, are often obese, and have painful comorbid conditions (eg, IBS and functional dyspepsia). Carnett sign is elicited by palpating the abdomen before and during contraction of the abdominal muscles (eg, by raising the head from the bed without using the arms); abdominal wall pain and visceral abdominal pain are characterized by more and less pain, respectively, during than before contraction. A
positive Carnett sign has a diagnostic accuracy of 97% for abdominal wall pain.37 Conversely, less than 10% of patients with visceral pain had a positive Carnett sign.38

Opioid Bowel Dysfunction, Opioid-Induced Constipation, and Narcotic Bowel Syndrome. These conditions can occur with opioid use for any intra-abdominal or extra-abdominal disease.39 Opioid bowel dysfunction (OBD) comprises the full spectrum of peripheral, μ-opioid receptor–mediated GI adverse effects, including anorexia, nausea, vomiting, gastroparesis, biliary pain, gastroesophageal reflux, constipation (ie, opioid-induced constipation [OIC]), ileus, pseudo-obstruction, abdominal bloating, and straining. In contrast, narcotic bowel syndrome (NBS) is characterized by incompletely controlled abdominal pain that cannot be explained by another known or previous diagnosis in patients receiving steady or increasing doses of opioids. In contrast to OBD, NBS is mediated by centrally mediated visceral hyperalgesia rather than GI dysmotility. Approximately 50% to 60% of patients on opioid therapy have OBD, 40% have OIC, and 5% have NBS. Narcotic bowel syndrome may coexist with OBD and OIC.

Structural Diseases. Functional and structural diseases may coexist. For example, persistent abdominal pain in patients with quiescent inflammatory bowel disease likely reflects a coexistent functional GI disorder. Alarm features (ie, symptom onset after age 50 years; severe or progressive symptoms; unexplained weight loss; nocturnal pain or diarrhea; family history of organic GI diseases, including colon cancer, celiac disease, or inflammatory bowel disease; rectal bleeding or anemia; and unexplained iron deficiency anemia) should increase the index of suspicion for structural diseases. However, many patients with structural disease do not have alarm symptoms.

DIAGNOSTIC TESTING
Diagnostic testing should be limited and tailored to the clinical features, alarm symptoms, symptom severity, and response to previous therapy (Figure 4). Absent alarm features, symptoms generally suffice to diagnose functional GI disorders.28 Although alarm features may prompt additional testing, most patients with alarm features will have negative test results. After a negative evaluation for structural lesions, the risk is less than 5% that a patient with diagnosed IBS will have a structural disease diagnosed in the future.7 A complete blood cell count should be checked in all patients. Some guidelines recommend consideration of a blood test (eg, tissue transglutaminase antibodies) or duodenal mucosal biopsies to diagnose celiac disease, given the potential long-term consequences of missing this diagnosis.28 Contradicting this recommendation, the prevalence of celiac disease was lower in patients with IBS than in patients without IBS in a US population.40 Abdominal pain and diarrhea occur in inflammatory bowel disease as well as in IBS, but rectal bleeding and systemic symptoms are much more common in inflammatory bowel disease. In a prospective study,41 inflammatory bowel disease was later diagnosed in less than 1% of patients with IBS symptoms and in no controls. Noninvasive biomarker testing is a cost-effective approach to screen for inflammatory bowel disease. When the C-reactive protein level is less than 5 mg/L or the fecal calprotectin level is less than 40 μg/g, the risk of inflammatory bowel disease is less than 1% in patients with typical IBS symptoms.28 A minority of patients with diarrhea-predominant IBS have microscopic colitis, especially patients older than 50 years or those who have nocturnal stools, weight loss, shorter duration of diarrhea, recent introduction of new drugs, or comorbid autoimmune diseases.42

In patients with constipation, colorectal cancer and, more importantly, pelvic floor dysfunction (ie, defecatory disorders [DDs]) should be considered. Absent concerning features, less than 1% of patients with typical constipated IBS have colorectal cancer, which is not greater than in asymptomatic controls. Hence, only age-appropriate colorectal cancer screening is required.33,44 Defecatory disorders, which are attributed to the dyscoordination among the abdominal wall, anal sphincter, and pelvic floor muscles during defecation, are a common but underrecognized cause of constipation and abdominal symptoms such as pain, discomfort, and bloating.45,46 Although selected symptoms (eg, the need for digital
mechanic maneuvers to facilitate defecation) and a meticulous rectal examination may suggest DDs, anorectal testing is necessary to diagnose DDs, which are appropriately managed with pelvic floor retraining through biofeedback therapy rather than with laxatives. Hence, patients with constipation unresponsive to laxatives should be referred for evaluation of rectoanal dysfunction with a digital rectal examination, anorectal manometry, balloon expulsion testing, or anorectal imaging.45,46

Mechanical small bowel obstruction generally presents with acute or recurrent acute symptoms rather than constant abdominal pain. Although adhesions and chronic abdominal pain may occur concurrently after surgery, whether adhesions cause pain is debatable.47

Rare causes of intermittent or chronic abdominal pain include hereditary angioedema, acute intermittent porphyria, and endometriosis.48,49 Endometriosis is identified in up to 80% of women presenting with chronic pelvic pain (defined as noncyclic lower abdominal pain lasting for at least 6 months). It typically presents with perimenstrual lower abdominal pain and dyspareunia, dysuria, urgency, and hematuria are other symptoms. The diagnosis is confirmed by laparoscopy-guided biopsy.50

MANAGEMENT

Establishing an Effective Patient-Physician Relationship

Many patients with functional GI disorders feel abandoned and undertreated and seek care from multiple doctors with limited success. Physicians caring for these patients may feel frustrated because of the lack of specific diagnostic
Helping the Patient Take Responsibility.

Engaging patients in their treatment increases the likelihood of success and improves patient and physician satisfaction. A 2-week symptom diary may identify precipitating and alleviating factors and point to appropriate behavioral treatment strategies. This task should be done with the explicit understanding that it is intended for implementing change and not for uncovering some, as yet, undiscovered pathway of disease.

Designing a Treatment Strategy on the Basis of Severity of Symptoms

The approaches include dietary modification, pharmacotherapy, and behavioral or psychological therapy. These should be tailored to the symptoms and individual patient preferences and integrated whenever necessary.

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For instance, lifestyle changes (eg, dietary advice) and psychological therapy may suffice for patients with mild symptoms related to emotional problems rather than a physical illness. Education provided by a trained nurse in an individual or group setting is as effective as longer education programs or those involving specialists. Interactive patient education was superior to self-education obtained from an IBS guidebook.

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**TABLE 1. Suggested Approaches When Caring for Patients With Chronic Abdominal Pain and Other Functional Gastrointestinal Disorders**

<table>
<thead>
<tr>
<th>Goal</th>
<th>Prefer</th>
<th>Avoid</th>
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<tr>
<td>Express empathy</td>
<td>Acknowledge patient suffering (eg, “I am sorry you feel this way… I can see that the pain has really affected your life. I will do my best to help you.”)</td>
<td>Dismissing symptoms (eg, “There is nothing wrong with you.”)</td>
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<tr>
<td>Assess the patient’s insight into the functional nature of the pain</td>
<td>Ask open-ended questions (eg, “Can you tell me what you think is causing your symptoms?” or “Tell me about what concerns you the most about your symptoms.”)</td>
<td>Closed-ended questions (eg, “Do you think your pain is caused by eating?”)</td>
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<tr>
<td>Understand the patient’s expectation from the physician</td>
<td>Ask open-ended questions (eg, “Tell me a little about what you were expecting from this consultation” or “I see that you have been suffering from pain for many years. Could you tell me a little bit about what made you come to see me today?”)</td>
<td>Judgmental statements (eg, “I am not sure I can help you. You have been to so many doctors already.”)</td>
</tr>
<tr>
<td>Understand the patient’s expectations from treatment(s)</td>
<td>Ask probing, open-ended questions (eg, “If I asked you what would be a reasonably tolerable pain level that we can try to achieve, what would you say?”)</td>
<td>Imposing a treatment plan (eg, “My plan is to refer you to the psychiatrist and the pain specialist.”)</td>
</tr>
<tr>
<td>Assess the patient’s understanding of education provided by the physician</td>
<td>“I provided you with quite a bit of information today and want to make sure you understood what I said. Can you tell me what you have understood so far?”</td>
<td>Unilateral flow of information (eg, “I hope you understood all the things we discussed today and implement the suggestions I gave you.”)</td>
</tr>
<tr>
<td>Help the patient take responsibility for the illness</td>
<td>Suggest that the patient keep a diary of symptoms for 3-4 wk.</td>
<td>Prescribing treatments in which the patient is a passive recipient</td>
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dietary triggers or other stressors. Patients with severe, disabling symptoms will also typically require prescription medications and behavioral and/or psychological therapy (Figure 4).

**Dietary Measures**

Food triggers symptoms in most patients with IBS, underscoring the importance of dietary modification. Although reducing fat intake seems sensible, fat has not been selectively eliminated in controlled clinical trials. Other food intolerances have been implicated, for example, to sugar alcohols (eg, mannitol, sorbitol, maltitol, and erythritol), caffeine, and nonceliac gluten sensitivity. Low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diets contain reduced content of these, and other ingredients may improve symptoms and have adverse effects. A recent controlled trial observed that a low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet was as effective as a sensible, frequently recommended diet for IBS; the latter is characterized by regular meals, avoidance of large meals, and reduced intake of fat, insoluble fiber, caffeine, and gas-producing foods, such as beans, cabbage, and onions.

Dietary fiber supplementation with a soluble (eg, psyllium) but not an insoluble (eg, bran) fiber preparation is effective, and often the initial approach, for managing constipation (Table 2). The dose should be increased gradually, and patients should be reminded that the effect may not be evident for up to 12 weeks. Probiotics (eg, VSL#3 and *Bifidobacterium infantis*) improve bloating and flatulence in IBS. *B infantis* also improved abdominal pain and the ease of defecation, but not stool frequency or consistency.

**Pharmacotherapy for Symptoms**

**Visceral Pain.** Except for select indications (eg, managing intractable diarrhea when all other options have failed), opioids should not be used to manage functional GI symptoms because of the likelihood of abuse, dependency, and addiction and the adverse effects of opioids, particularly NBS.

The pharmacotherapy of pain is often guided by associated symptoms (Table 2). Antidepressants enhance the sense of general well-being; may remedy the psychological comorbidity (eg, anxiety), which can amplify the pain experience; and facilitate central pain modulation, perhaps by increasing descending inhibition. In addition, tricyclic antidepressants (TCAs) prolong and many selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) accelerate intestinal transit, which may be beneficial. A Cochrane meta-analysis observed that 59% of patients treated with antidepressants improved as compared with 39% of patients receiving placebo; the number needed to treat was 5. Tricyclic antidepressants are the first choice for patients with chronic abdominal pain. The initial dose is 10 to 50 mg/d, titrated to effectiveness and adverse effects up to a range of 25 to 150 mg/d. The dose should be increased only if necessary and as tolerated. In the largest controlled trial, desipramine (150 mg/d) was not significantly different (P=.16) from placebo for patients with moderate or severe functional bowel disorders. However, after the 25% of patients who had dropped out were excluded, desipramine was superior to placebo. Patients should be reassured that as in other painful medical conditions (eg, migraine and diabetic neuropathy), antidepressants are not being used for a psychiatric condition, but as central analgesic agents. Although adverse effects occur early, beneficial effects may take 4 to 6 weeks to appear. In addition, many symptoms attributed to adverse effects of desipramine often predated treatment, which suggests that they were not related to drug per se.

Selective serotonin reuptake inhibitors can reduce anxiety and depression and improve the sense of overall well-being. However, there are limited data to suggest that these drugs reduce abdominal pain, perhaps because, in contrast to TCAs and SNRIs, they do not have much noradrenergic effect. Adverse effects (eg, diarrhea, sexual dysfunction, and nightmares) are less common with SSRIs than with TCAs, which can be beneficial for patients who have a low threshold for adverse effects.

Serotonin and norepinephrine reuptake inhibitors block norepinephrine and serotonin reuptake, which should reduce pain sensation. They also have other beneficial effects; for example, venlafaxine reduced the colonic...
contractile response to a meal and also colonic perception of balloon distention. Duloxetine is effective for treating peripheral diabetic neuropathic pain and fibromyalgia. Despite a lack of evidence, SNRIs may be considered for patients with severe refractory abdominal pain. Because they lack anticholinergic and antihistamine adverse effects, SNRIs are mostly better tolerated than TCAs. When a single antidepressant is not helpful, augmentation therapy, such as multiple antidepressants, or combining an antidepressant with psychological treatment may be tried. Excess sedation can be reduced by lowering the dose of the tricyclic agent and/or by supplementing with an SSRI. A benzodiazepine agent or a low-dose TCA at bedtime can reduce “jitteriness” from an SSRI. For patients with dyspepsia and anxiety, the 5-HT3 agonist buspirone, an anxiolytic agent that improved gastric accommodation and reduced postprandial fullness and bloating, should be considered. Pregabalin may be considered in patients with a general anxiety disorder or fibromyalgia and abdominal wall pain.

**Constipation.** In patients who do not have a DD, a stepwise approach beginning with dietary fiber supplementation and escalating as necessary to simple osmotic laxatives (eg, polyethylene glycol and milk of magnesia) and stimulant laxatives (eg, bisacodyl and senna) and then to a secretory agent (liclotide or lubiprostone) is recommended (Table 2). In each class, the alternative agent should be considered if one fails. Both lubiprostone and linaclotide increase intestinal secretion of fluids and electrolytes; linaclotide may also have antihyperalgesic effects. Among patients with constipation with severe abdominal symptoms (eg, bloating, fullness, discomfort, and pain), approximately 60% treated with linaclotide vs 30% treated with placebo reported adequate relief of IBS symptoms at week 12 of therapy.

**Diarrhea.** The initial options are loperamide, taken regularly or on demand (eg, 2 to 4 mg 30 minutes before meals, up to a maximum of 8 tablets daily), and anticholinergic agents.
such as diphenoxylate and amitriptyline; amitriptyline may also reduce rectal urgency.\textsuperscript{75} Up to 30% of patients with idiopathic diarrhea have idiopathic bile salt malabsorption, suggesting a role for bile acid–binding resins.\textsuperscript{75,76} However, these drugs have not been evaluated in controlled clinical trials. Cholestyramine is inexpensive but often associated with bloating, which is not a common adverse effect with colesevelam. Eluxadoline, rifaximin, and alosetron are approved by the US Food and Drug Administration for treating diarrhea-predominant IBS.\textsuperscript{77} Alosetron is available under a restricted-use program.\textsuperscript{77} Clonidine, an $\alpha_2$-adrenergic agonist, improves fluid and electrolyte absorption and improved symptoms in a phase II study in diarrhea-predominant IBS;\textsuperscript{63} clonidine also reduces the perception of colonic distention.\textsuperscript{78} At a dose of 0.1 mg tablet twice daily, it is well tolerated, and adverse effects (eg, dry mouth, sedation, and hypotension) are uncommon.

Abdominal Wall Pain. Injection of a local anesthetic (eg, lidocaine and bupivacaine) with or without a corticosteroid (eg, methylprednisolone acetate) at the site of maximal tenderness is both diagnostic and therapeutic.\textsuperscript{79} Other options, supported by limited evidence, include lidocaine patches,\textsuperscript{80} local application of heat, low-dose TCAs, and gabapentin.\textsuperscript{36} In a series,\textsuperscript{36} various approaches eased the pain in 47% of patients.

Narcotic Bowel Syndrome. Treatment requires withdrawal of narcotics, often in combination with medications to control withdrawal symptoms (eg, clonidine and lorazepam), and use of antidepressants (eg, paroxetine, desipramine, duloxetine, and cyclobenzaprine) to control visceral pain and decrease anxiety.\textsuperscript{81,82}

Nausea and Vomiting. Phenothiazines (eg, prochlorperazine) and antihistamine agents (including promethazine), which can be administered as a suspension or suppositories, should be tried initially,\textsuperscript{14} followed, when necessary, by serotonin 5-HT\textsubscript{3} receptor antagonists (eg, ondansetron), which are more expensive. The neurokinin 1 receptor antagonist aprepitant is approved for treating emesis due to chemotherapy.\textsuperscript{81,82}

Psychological and Behavioral Interventions

These interventions are tailored to the symptoms, functional impairment, psychological distress, and symptom expression. Patients should be reassured that the goals are to manage pain, improve daily function, and relieve psychological distress.

Cognitive behavioral therapy, which is the most effective psychological therapy for functional abdominal pain, is generally imparted by therapists, but can be self-administered by patients with similar efficacy.\textsuperscript{83} Cognitive behavioral therapy helps patients identify maladaptive thoughts, perceptions, and behaviors. Thereafter, they are taught to develop new approaches to increase control over their reactions and functioning, including an emphasis on stress management, decreasing illness behaviors, increasing social support, and more effective problem solving. Any intervention that enhances the ability to relax will give the patient a sense of control over symptoms and induce more parasympathetic activity. A recent meta-analysis\textsuperscript{84} of 41 trials involving 2290 patients observed that psychological therapy is moderately effective for improving IBS symptoms for up to 1 year after therapy. Cognitive behavioral therapy was effective whether it was administered in person or online, individually or in a group. The number, duration, and frequency of sessions did not affect its efficacy.

Behavioral interventions targeted to specific symptoms can be useful. By activating the diaphragm, diaphragmatic breathing is a form of habit reversal training that serves as a competing response and thereby prevents belching, regurgitation, and vomiting.\textsuperscript{85,86} Patients should begin diaphragmatic breathing at the onset of cues of belching and continue to engage the technique until the cues subside. Measures to prevent aerophagia (eg, cease drinking through a straw) should be emphasized in patients with belching.

Multidisciplinary Pain Treatment Centers

Comprehensive pain rehabilitation involves physical therapy, occupational therapy, and cognitive behavioral therapy in an intensive interdisciplinary outpatient setting. Most pain rehabilitation centers offer daily treatment for 2 to 4 weeks. The emphasis is on physical
reconditioning and elimination of medications for pain and other symptoms (eg, benzodiazepines), along with activity management and behavior therapy. Patients who benefit from this approach do so because of a change in their behavior, beliefs, and physical status. These programs are successful. In a study of 356 patients with chronic pain (abdominal pain in 8%), 132 of 135 patients receiving opioids discontinued them after a pain rehabilitation program.

CONCLUSION
Identifying the precise phenotype, which is predominantly based on clinical features, is essential for appropriate and cost-effective diagnosis and treatment of nonstructural, or functional, GI disorders associated with abdominal pain. The need for and choice of diagnostic tests are guided by the clinical features and alarm symptoms. Testing should evaluate for conditions that are not widely recognized and are amenable to therapy (eg, pelvic floor dysfunction). Multidisciplinary treatment approaches that integrate dietary modification, pharmacotherapy, and behavioral or psychological therapy and are tailored to the symptoms should be considered. The focus is on improving symptoms and restoring quality of life.

Abbreviations and Acronyms: DD = defecatory disorder; GI = gastrointestinal; 5-HT = 5-hydroxytryptamine; IBS = irritable bowel syndrome; NBS = narcotic bowel syndrome; OBD = opioid bowel dysfunction; OIC = opioid-induced constipation; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant

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The Symposium on Pain Medicine will continue in an upcoming issue.

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