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Cleveland Clinic Center for Continuing Education

Irritable Bowel Syndrome

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Irritable bowel syndrome (IBS) is common in the general population and has a significant medical and socioeconomic impact. Its pathophysiology is still not entirely clear, and the diagnosis and management can be challenging. It is desirable to make a positive diagnosis rather than to rely on a diagnosis of exclusion. A step-by-step approach for management and a realistic goal of therapy is advocated. An effective treatment strategy should address the dominant symptoms, their severity, and psychosocial factors.

Definition

IBS is defined on the basis of the recently modified Rome III criteria as recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months that started at least 6 months before diagnosis, cannot be explained by a structural or biochemical abnormality, and is associated with at least two of the following: improvement with defecation, onset associated with a change in frequency of stool, and onset associated with a change in form (appearance) of stool.[1] Other symptoms that support the diagnosis but are not part of the criteria include abnormal stool frequency (≤3 bowel movements per week or >3 bowel movements per day), abnormal stool form (lumpy/hard or loose/watery), defecation straining, urgency, or feeling of incomplete bowel movement, passing mucus, and bloating. Four possible IBS subtypes include IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed IBS (IBS-M) and un-subtyped IBS depending on the predominant stool pattern.[2]

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Prevalence

IBS is one of the most commonly diagnosed gastrointestinal (GI) conditions and also one of the most common functional GI disorders seen in clinical practice.[3] Estimates of prevalence vary, largely because of the differences among epidemiologic studies (e.g., the use of different diagnostic criteria, population selection, and data sources). Approximately 10% to 20% of the general adult population has reported symptoms compatible with IBS.[4,5] However, only 15% of those affected actually seek medical attention.[5,6] IBS accounts for 12% of primary care patients and 28% of gastroenterology practice patients (41% of all functional GI disorders).[6] Patients often experience the onset of symptoms as young adults, but the prevalence is similar in older adults. IBS is diagnosed in women more than twice as often as men; however, studies have found the prevalence of pain-related symptoms of IBS to be equal among men and women and the prevalence of symptoms not related to pain, such as constipation, bloating and extra-intestinal manifestations, to be greater among women.[7]

The financial burden of IBS is high, both in direct and indirect costs.[8] IBS has a major impact on the quality of life of those afflicted, affecting social interactions and professional opportunities.[9]

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Pathophysiology

To date, no physiologic mechanism unique to IBS has been identified. Rather, it is currently viewed as a biopsychosocial disorder resulting from an interaction among a number of factors: visceral hyperalgesia, genetic and environmental factors, infection, inflammation, gut motility, and psychological factors[10] Dietary factors, GI dysmotility dysfunction, and the role of gut flora are evolving mechanisms.

Visceral Hypersensitivity

Many studies have shown that in patients with IBS, both awareness and pain caused by balloon distention in the large and small bowel are experienced at significantly lower balloon volumes than those reported by healthy subjects.[11-13] It is not known at which level of pain-signal transmission (starting at the receptor in the gut wall, through the spinal cord to the brain) this increased sensitivity is expressed, but it is selective to visceral stimuli, because patients with IBS have normal or even decreased sensitivity to somatic stimuli.[14,15]

Abnormal Gut Motility

The changes in gut motility observed in IBS are qualitative, with no distinct pattern that can distinguish patients from healthy subjects. Two major changes are observed: Changes in gut transit and increased motility. Enhanced gut transit is seen in some patients with diarrhea-predominant IBS, and decreased gut transit is seen in some patients with constipation-predominant IBS. Increased motility compared with healthy subjects is seen in response to various stimuli, such as psychological stress, meals, and balloon inflation in the gut.[10]

Psychosocial Factors

IBS has long been dismissed as a psychosomatic condition because it has no clear cause or pathophysiology. Psychological stress and emotional events, such as physical or sexual abuse, can result in GI symptoms in healthy subjects, but they affect patients with IBS to a greater degree. The common psychological symptoms associated with IBS are depression, somatization, anxiety, hostility, phobia, and paranoia. Up to 50% of patients with IBS meet criteria for a psychiatric diagnosis as compared with an average of 20% with organic GI disorders and 15% of control subjects.[10] Although there are no psychological or psychiatric disorders specific to IBS, identification of such disorders can help in planning psychological or psychopharmacologic treatment.

Brain-Gut Interaction

The central nervous system (CNS) modulates various functions such as secretion, motility, and blood flow.[16] Signals from the gut, in turn, are involved in regulating reflexes. Perception of events in the gut involves activation of afferent pathways, with information being modulated at different levels, peripheral as well as central.[17] A major advance in our understanding of brain-gut interaction and its alteration in IBS occurred with the introduction of functional magnetic resonance imaging (MRI). This technique allowed assessment of the difference in cortical function in response to gut stimulation between healthy subjects and IBS patients,[18] opening the door for potential pharmacologic and behavioral interventions.

Latent or Potential Celiac Disease

The concept of latent or potential celiac disease has recently been introduced into the pathogenesis of IBS. Abdominal symptoms in the absence of mucosal abnormalities are features of IBS and latent or potential celiac disease.[19] In a study of genetic, serologic, and histologic markers of celiac disease in 102 patients with diarrhea-predominant IBS, 35% of the patients had positive findings for human leukocyte antigen (HLA)-DQ2, 23% had increased intraepithelial lymphocyte counts, and 30% had increased celiac disease–associated antibodies in the

duodenal aspirates, including antibodies against gliadin, tissue transglutaminase, β-lactoglobulin, and ovalbumin.[19] Stool frequency and the intestinal immunoglobulin A (IgA) level decreased significantly under a gluten-free diet in a subgroup of IBS patients with positive HLA-DQ2 and positive intestinal celiac disease–associated antibodies when compared with IBS patients without these markers.[19] Celiac disease–associated IgG and HLA-DQ2 expression can identify likely responders to gluten-free diet in patients with IBS-D (diarrhea predominant IBS).[20]

Infection and Inflammation

Clinical, epidemiologic, and physiologic studies have shown that acute, transient GI infection is associated with a syndrome that often meets diagnostic criteria for the diagnosis of IBS. This was observed after documented outbreaks of enteric infections with organisms such as *Campylobacter jejuni* or *Salmonella*.[21,22] IBS and small intestine bacterial overgrowth might share similar symptoms. In a study of 202 patients with IBS, 157 (78%) had small bowel bacterial overgrowth. Intraepithelial lymphocytes, lamina propria CD3 and CD25 cells, neutrophils, and mast cells are increased in patients with IBS.[23]

The exact mechanisms whereby the inflammatory changes cause the symptoms are not clear. The inflammatory response may be associated with activating enterochromaffin cells to produce 5-hydroxytryptamine (5-HT) and CD3 cells to produce cytokines, which in turn leads to enhanced motility, increased intestinal permeability, and lowered visceral sensation thresholds.[24] In one prospective study of postinfectious IBS, it was found that patients whose symptoms remained 3 months after an enteric infection not only had increased mucosal cellularity but also had increased psychosocial distress at the time of the infection. Lowered visceral sensation thresholds and increased motility were present after the infection, regardless of whether or not the symptoms remained.[25] Therefore, in patients with IBS refractory to a gluten-free diet, small bowel bacterial overgrowth may be suspected, and prompt hydrogen breath testing may be warranted.

Fructose and Lactose Intolerance

Common symptoms of dietary fructose and lactose intolerance include bloating, flatulence, pain, and diarrhea which have also been found in patients with unexplained dyspepsia or functional bowel disorders such as IBS. It has been shown that approximately one third of patients with suspected IBS might also have fructose intolerance as identified by a positive fructose breath test. Although there are no data documenting the efficacy of a fructose-restricted diet, a study of 80 suspected IBS patients showed significant relief of symptoms in those who were compliant with a fructose-restricted diet.[26] Patients with IBS have subjectively reported higher incidence of lactose intolerance, but it is hard to tell whether reported symptoms are secondary to lactose intolerance or IBS in the absence of documented lactose malabsorption. A period of avoiding dairy products or requesting a test for lactose malabsorption (or both) may be beneficial in this area.

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Signs and Symptoms

Patients with IBS can present with a wide variety of GI and extraintestinal symptoms. However, the symptom complex of chronic abdominal pain and altered bowel habits that cannot be explained by identifiable structural or biochemical abnormalities is the main clinical pattern of IBS.

Chronic abdominal pain in IBS is usually described as a crampy sensation, with varying intensity and periodic exacerbation. The pain is generally located in the lower abdomen, although the location and character of the pain can also vary. Emotional stress and eating can exacerbate the pain, whereas defecation often provides some relief. Progressive pain that awakens the patient from sleep or prevents sleep should prompt a search for causes other than IBS.

Because the range of normal bowel habits is broad, a careful history should include the volume, frequency, and consistency of the patient's stool. Assuming no use of laxatives or antidiarrheals, subtyping of IBS by predominant stool pattern has been divided into the following: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed IBS (IBS-M) and unsubtyped IBS. The frequency of bowel movements in normal persons is variable, and it can range from three times a day to three times a week. Patients with IBS complain of diarrhea, constipation, alternating diarrhea and constipation, or normal bowel habits alternating with diarrhea or constipation reflecting intestinal transit time.[2]

Irritable Bowel Syndrome with Diarrhea

Diarrhea is generally characterized as a condition of at least 25% frequent loose stools of small and moderate volume without abdominal comfort in at least 75% of stools[2] or Bristol Stool Form Scale 6-7 (fluffy pieces with ragged edges, a mushy stool or watery, no solid pieces, entirely liquid). In addition, hard and lumpy stool typically occurs in less than 25% of bowel movements. Bowel movement generally occurs during waking hours, most often in the morning or after meals. Most bowel movements are preceded by urgency and may be followed by a feeling of incomplete evacuation. Pseudodiarrhea—frequency defecation and urgency without solid stools—is not considered diarrhea.[27] Nocturnal diarrhea, bloody stools, dehydration, or weight loss are not features of IBS.

Irritable Bowel Syndrome with Constipation

Constipation can last from days to months, with interludes of diarrhea or normal bowel function. Stools are often hard and may be described as pellet shaped in at least 25% of bowel movements, or Bristol Stool Form Scale 1-2 (separate hard lumps like nuts that are difficult to pass, or sausage shaped but lumpy). In addition, loose (mushy) or watery stools account for less than 25% of bowel movements. Patients might also experience a sense of incomplete evacuation, even when the rectum is empty. This can lead to straining with defecation, prolonged time on the toilet, and inappropriate use of enemas or laxatives.

Mixed Irritable Bowel Syndrome

Mixed IBS is defined as hard or lumpy stool at least 25% of bowel movements and loose or mushy stools at least 25% of bowel movements using Bristol scale 1-2 for constipation and scale 6-7 for diarrhea.

Unsubtyped Irritable Bowel Syndrome

Unsubtyped IBS is defined as insufficient abnormality of stool consistency to meet criteria for IBS-D, IBS-C or IBS-M.

Other Gastrointestinal Symptoms

Upper GI symptoms are not uncommon in patients with IBS. These include symptoms of heartburn, dysphagia, nonulcer dyspepsia, nausea, and noncardiac chest pain.[28] Patients with IBS often complain of abdominal bloating and increased gas production in the form of flatulence or belching.

Extraintestinal Symptoms

Patients with IBS have a high frequency of non-GI symptoms, including rheumatologic symptoms, headache, genitourinary symptoms such as urinary frequency and urgency, dyspareunia, sexual dysfunction, and sleep-related disturbances.[29]

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Active Diagnosis

A diagnosis is based on identifying positive symptoms consistent with IBS and excluding other conditions with similar clinical presentations in a cost-effective manner. In the absence of biologic markers, attempts have been made to standardize the diagnosis of IBS using symptom-based criteria. These include criteria proposed by Manning and colleagues in 1978[30] and the international workshop criteria, Rome I and II, with the updated current Rome III criteria.[1] In the criteria of Manning and associates,[1] the symptoms associated with IBS included relief of pain with bowel movements, looser and more frequent stools with onset of pain, passage of mucus, and a sense of incomplete evacuation. The current Rome III criteria, described earlier, are a simplification of the Rome II criteria—for example, by using stool form as a criterion. A key feature of the Rome III definition is the presence of abdominal discomfort or pain.

The diagnostic evaluation of patients with IBS can be challenging. It is generally agreed that the initial diagnosis of IBS can be fulfilled by the following: symptom-based diagnostic criteria are met, such as Rome III; negative results are obtained on physical examination; and a cost-effective, conservative set of screening studies has been performed. It is important to exclude organic causes of symptoms compatible with IBS. However, to avoid unnecessary and costly testing, the diagnosis of IBS should not be made simply by excluding organic disorders. Emphasis should be placed on identifying a symptom complex compatible with IBS and then using prudent, although not exhaustive, testing to make a positive diagnosis. The Rome and Manning criteria provide guidelines to identify patients with suspected IBS.

In 2002, the American Gastroenterological Association (AGA) published an extensive review and position statement[6] regarding pathophysiology, role of psychosocial factors, diagnosis, and treatment of IBS, and in April 2006, the Rome III criteria were again modified to include the IBS bowel habit subgroups that emphasized the use of the stool consistency as outlined in April 2006 *Gastroenterology*. It has been acknowledged that evidence exists for a diagnostic and treatment approach based on the predominant symptom, its severity, and associated psychosocial features, although more studies are needed to understand the mechanism underlying these symptoms and to develop effective treatments (Box 1).

Box 1: Stepwise Approach to Irritable Bowel Syndrome

Step 1: Assessment of Symptoms

- Use nonjudgmental, open-ended questions that include dietary history and medications.
- Identify abdominal pain as the dominant symptom, with altered bowel function.
- Consider psychological factors by gently questioning the patient about physical and sexual abuse once the physician–patient relationship has been established.
- Identify red flag symptoms such as weight loss, fever, persistent diarrhea, rectal bleeding, anemia, nocturnal symptoms of pain and abnormal bowel habit, new onset of symptoms in patients >50 yr old, and the family history of gastrointestinal (GI) malignancy, inflammatory bowel disease, and celiac disease.

Step 2: Physical Examination

- The physical examination findings are generally normal in IBS. The patient may have nonspecific abdominal tenderness.
- Identify red flag signs such as anemia, jaundice, organomegaly, and abdominal mass.

Step 3: Laboratory Tests

- Complete blood count, chemistry panel, and thyroid function studies help exclude organic diseases.
- Stool analysis for ova, parasites, and fecal leukocytes should be done if diarrhea is the predominant symptom.
- Because of overlap of clinical presentations of celiac disease and IBS, antigliadin and antiendomysial IgA antibody serologies may be reasonably effective screening tests, given that the sensitivities and positive predictive values range from 90% to 100%. However, in populations in which the prevalence of celiac disease is low, many positive serologic tests will be false-positives.
- These tests are indicated for most patients for exclusion and inclusion of diagnosis.

Step 4: Invasive Tests

Invasive tests include flexible sigmoidoscopy and colonoscopy.

- Invasive tests are indicated for select patients, in particular:
    1. Age >50 years with chronic, stable symptoms
    2. Age >50 years and recent onset
    3. Persistent diarrhea, rectal bleeding
- Routine flexible sigmoidoscopy with biopsy has a low diagnostic yield and is not cost effective, particularly in young patients. It might help reassure an anxious patient or may be performed in an older patient with chronic, stable symptoms.
- Colonoscopy is recommended for patients older than 50 years (because of a higher pretest probability of colon cancer), but in younger patients, performing a colonoscopy or sigmoidoscopy is determined by clinical features suggestive of structural disease (e.g., hematochezia, diarrhea, weight loss) and might not be indicated.
- In patients with persistent diarrhea, if inflammatory bowel disease or microscopic colitis is suspected, a mucosal biopsy should be taken.

Step 5: Initiate a symptom-oriented treatment program

- The treatment goal should be relief of symptoms and addressing the patient's concerns.

Step 6: Follow-up

- Assess clinical response in 3 to 6 weeks.

The predominant symptom subtype is helpful for clinicians to determine the type of evaluation. For example, for the constipation-predominant subtype, a therapeutic trial of fiber may be sufficient. If symptoms persist, confirmation of a slow colonic transit test with a whole-gut transit test or evaluation for obstructed defecation (pelvic floor dysfunction) may be indicated. For the diarrhea-predominant subtype, clinical judgment determines the choice of studies. Particularly for loose or watery stools, a lactose-dextrose hydrogen breath test, celiac serology, or small bowel or colon biopsy may be indicated. If results of these tests are negative, a therapeutic trial of loperamide may be ordered. For patients with predominant symptoms of abdominal pain, a plain abdominal x-ray during an acute episode to exclude bowel obstruction and other abdominal pathology is recommended. If the x-ray is negative, a therapeutic trial of an antispasmodic agent may be tried.[6]

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Treatment

IBS is a chronic disorder with no specific cause, and there is no cure. The patient's confidence in the physician's diagnosis, explanation, and reassurance are vital therapeutic tools.

General Principles

The treatment strategy is based on the nature and severity of the symptoms, the character and degree of functional impairment, and the presence of psychosocial difficulties affecting the course of the illness. Patients with mild symptoms usually respond to education, reassurance, and simple treatments not requiring prescription medication. Some patients with moderate symptoms have more disability and require pharmacologic therapy directed at altered gut physiology or psychological treatments. A small group of patients with severe and refractory symptoms seen more often at referral centers may benefit from antidepressant therapy and psychological treatment.[6]

The treatment goal should be set on relief of symptoms and addressing the patient's concerns.[31] An important question is why the patient is seeking help at this time. Possible reasons may include recent exacerbating factors (e.g., concurrent medical disorders, new medications, dietary changes), concern about serious illness (e.g., recent family death), environmental stressors (e.g., major loss, abuse history), psychiatric comorbidity (e.g., depression, anxiety), impairment of daily function (e.g., recent inability to work), or a hidden agenda (e.g., disability claims, narcotic requests, laxative abuse, secondary gain). In a subgroup of patients with clear concurrent psychosocial disturbance, specific treatments for the triggering factors are reasonable. An effective treatment strategy should address the dominant symptoms, their severity, and psychosocial factors.

Therapeutic Relationship and Patient Education

As proposed by Drossman,[31] the most important component of treatment is to establish a therapeutic physician-patient relationship coupled with patient education, with the following steps:

1. Obtain the history through a nonjudgmental and patient-centered interview.
2. Conduct a careful examination and cost-efficient investigation.
3. Determine the patient's understanding of the illness and his or her concerns (“What do you think is causing your symptoms?”).
4. Provide information regarding proposed mechanisms of IBS, which helps validate the patient's disease experience and sets the basis for therapeutic interventions.
5. Explain to patients that their symptoms of IBS are real and not life-threatening, the disease course is likely to be chronic, the diagnosis, if well established, is not likely to be changed, and that he or she should have a normal life span.
6. Establish realistic expectations with consistent limits (“I appreciate how bad the pain is, but narcotic medication is not indicated”), and involve the patient in treatment decisions (“Let me suggest some treatments for you to consider”). IBS is a condition that can be managed but not cured.

Modification of Diet

A diet history might reveal patterns of symptoms related to dairy or gas-producing foods. Exclusion of foods that increase flatulence (e.g., beans, onions, celery, carrots, raisins, apricots, prunes, Brussels sprouts, wheat germ, pretzels, bagels) should be considered in patients with symptoms of bloating or gas. Underlying visceral hyperalgesia in IBS may explain the exaggerated discomfort experienced with the consumption of gas-producing foods.

An increase in the intake of fiber is generally recommended, through diet or the use of commercial bulking supplements. Although the efficacy of fiber supplements has not been proved, some improvement has been demonstrated in patients with IBS whose primary complaints are abdominal pain and constipation.[32,33]

Many types of fiber supplements are available; some are synthetic, such as polycarbophil or methylcellulose, and others are from natural sources, such as bran or psyllium compounds. All types of fiber can cause increased bloating and gaseousness because of the colonic metabolism of nondigestible fiber.

Because of its safety, a trial of fiber supplementation is advised for patients with IBS, especially those with constipation-predominant symptoms. The amount should be titrated to symptoms.

Psychosocial Treatment

Psychological therapy is initiated when symptoms are severe enough to impair the health-related quality of the patient's life. Mental health referral may also be made for the treatment of associated psychiatric disorders, such as major depression or history of physical and sexual abuse that interferes with adjustment to illness.

Behavioral treatment may be considered for motivated patients who associate symptoms with stressors. Cognitive-behavioral treatment, interpersonal (psychodynamic) therapy, hypnosis, biofeedback, stress management and relaxation training, and family or group therapy can be tried. They help reduce anxiety levels, encourage health-promoting behavior, increase patient responsibility and involvement in the treatment, and improve pain tolerance. Factors that favor a good response to psychotherapy include[34]:

- The patient is motivated.
- The patient has predominant diarrhea or pain.
- IBS is associated with overt psychiatric symptoms.
- Intermittent pain is exacerbated by stress.

Patients with constant abdominal pain do poorly with psychotherapy or hypnotherapy.

Medications

Pharmacologic agents are only adjuvants to the treatment of IBS. The drug chosen depends on the patient's major symptoms; diarrhea-predominant IBS is treated differently from constipation-predominant disease. Common strategies include using dietary fiber for constipation, loperamide or diphenoxylate for diarrhea, and anticholinergic, antispasmodics, tricyclic antidepressants, or selective serotonin reuptake inhibitors (SSRIs) for pain (Table 1).

Table 1: Select Drug Therapies for Irritable Bowel Syndrome

Pharmacologic Agent	Usual Adult Dosage
Diarrhea-Predominant IBS	
Opioid μ-Receptor Agonists	
Loperamide (Imodium)	2-4 mg, up to qid prn
Diphenoxylate (Lomotil)	5 mg qid prn
Smooth-Muscle Relaxants	
Dicyclomine (Bentyl)	20 mg qid initially, then up to 40 mg qid
Hyoscyamine (Levsin, NuLev, Levbid)	0.125 mg sublingually tid prn or 0.375 mg bid PO
Tricyclic Antidepressants	
Amitriptyline (Elavil, Endep)	10-25 mg bid or 25-50 mg qhs

Desipramine (Norpramin)	50 mg tid
Selective 5-HT$_3$ Receptor Antagonist	
Alosetron (Lotronex)	1 mg qd × 4 wk, may increase to 1 mg bid × 4 wk*
Constipation-Predominant IBS	
Bulking Agents	
Psyllium (Metamucil)	20 g/day, divided, with >250 mL water
Polycarbophil (Konsyl Fiber)	1-6 g/day, divided, with >250 mL water
Methylcellulose (Citrucel)	3-6 g/day, divided, with >250 mL water
Osmotic Laxatives	
Polyethylene glycol (MiraLax)	1 dose (17 g in glass of water) qd or bid
Lactulose (Kristalose, Cephulac, Chronulac, Constulose, Duphalac, Enulose, R O Lactulose)	15-60 mL/day, divided
Sorbitol (Ora-Sweet)	120 mL of 25% solution
Pain	
Smooth-muscle relaxants	
Dicyclomine (Bentyl)	20 mg qid initially, then up to 40 mg qid
Hyoscamine (Levsin, NuLev, Levbid)	0.125 mg sublingually tid prn or 0.375 mg bid PO
Tricyclic Antidepressants	
Amitriptyline (Elavil, Paregoric)	10-25 mg bid or 25-50 mg qhs
Desipramine (Norpramin)	50 mg tid

* Prescribing physicians need to enroll in a special Lotronex Risk Management Program.

Chronic use of drugs should be minimized or avoided because of the lifelong nature of the disorder and the lack of convincing therapeutic benefit. The difficulty in demonstrating efficacy may in part be a result of the heterogeneous population with IBS, the lack of disease markers, and high placebo-response rates.[35]

Smooth-Muscle Relaxant Agents

Smooth-muscle relaxants include those directly affecting intestinal smooth muscle relaxation (e.g., mebeverine, pinaverium) and those that act in a similar fashion via anticholinergic pathways (e.g., dicyclomine, hyoscyamine). The rationale for using smooth-muscle relaxants to treat patients with IBS is based on the hypothesis that intestinal dysmotility results in abdominal pain, bloating, and disturbed defecation. Overall, the

published trials with smooth-muscle relaxants were generally of short duration and included small numbers of patients. These agents may be beneficial in patients with postprandial abdominal pain, gas, bloating, and fecal urgency.

In a meta-analysis of randomized, controlled trials, 13 of 16 studies of smooth-muscle relaxants have shown these agents to be efficacious in global or symptomatic improvement.[36] The meta-analysis of the effects of smooth-muscle relaxants found them to be helpful, with 4.1 patients needing to be treated for each therapeutic success, although the effects on patient symptoms were relatively modest.[37] In a separate meta-analysis, four smooth-muscle relaxants that directly affect intestinal smooth muscle relaxation—cimetropium, pinaverium, otilonium, and trimebutine—have been consistently shown to be efficacious.[38] However, these smooth-muscle relaxants are currently not approved in the United States.

Common side effects of anticholinergic agents are dry mouth, dizziness, blurred vision, drowsiness, and tachycardia. Because of these side effects and the intermittent nature of pain in IBS, we advise using such agents on an as-needed basis or in anticipation of stressors with known exacerbating effects. Hyoscyamine (Anaspaz, Cystospaz, Levsin, Neoquess) can be given for pain at a dose of 0.125 mg to 0.25 mg sublingually or orally, three or four times daily, or sustained-release tablets, 0.375 mg to 0.75 mg orally every 12 hours. The typical dose of dicyclomine is 20 mg orally three or four times daily or three or four times daily as needed.

Antidepressants

Antidepressants are purported to be beneficial and are often used in patients with chronic refractory symptoms. These drugs are particularly helpful for patients with comorbid depressive and anxiety disorders. The odds ratio for improvement with antidepressant therapy from the pooled data of seven randomized trials was 4.2 (95% confidence interval [CI], 2.3-7.9), with substantial improvement in severity of pain.[39] A randomized, controlled study has shown that desipramine improves pain in women with IBS who can tolerate the drug.[40] Tricyclic antidepressants and possibly selective serotonin reuptake inhibitors (SSRIs) modulate visceral afferent activity from the GI tract and might improve abdominal pain.[41] Tricyclic antidepressants are helpful in patients with diarrhea-predominant IBS,[42] possibly because of the constipating effect of this class of drugs. Conversely, if SSRIs are to be used, they should be avoided in patients with diarrhea-predominant IBS because diarrhea is a side effect of some of these agents, such as sertraline.

Improvement in neuropathic pain with tricyclic antidepressants occurs at lower doses than those required for treating depression. Thus, low doses should be tried initially and titrated to pain control or tolerance. Because of the delayed onset of action, 3 to 4 weeks of therapy should be attempted before considering treatment insufficient and increasing the dose. The medications often used include amitriptyline (Elavil, Endep) 10 to 25 mg orally every hour at bedtime, and imipramine (Tofranil) 25 to 50 mg orally every hour at bedtime. The initial dose should be adjusted based on tolerance and response.

Although SSRIs are increasingly preferred over tricyclic agents because of their low adverse-effect profile, data on the use of SSRIs in IBS are limited.[36,39] As with tricyclic antidepressants, treatment should start with a once-daily low dose of paroxetine (Paxil) 20 mg orally, fluoxetine (Prozac, Sarafem) 20 mg orally, or sertraline (Zoloft) 100 mg orally.

Antidiarrheal Agents

Loperamide (Imodium, Pepto Diarrhea Control) has been shown to be beneficial in diarrhea-predominant IBS by slowing whole-gut transit and enhancing intestinal water and electrolyte absorption.[43] It does not require a prescription and is the antidiarrheal drug of choice. Diphenoxylate (Logen, Lomanate, Lomotil, Lonox) can be tried next if loperamide is not effective.

Serotonin Receptor Agonists and Antagonists

5-HT serves both as a neurotransmitter and as a paracrine signaling molecule in the bowel.[37] 5-HT is distributed throughout the gut, predominantly within enterochromaffin cells in the mucosal crypts and, to a lesser extent, within the nerve fibers of the myenteric and submucosal plexuses. The concentration of 5-HT in the bowel is substantially greater than that in the brain. It is estimated that 95% of the body's 5-HT is synthesized and stored in the enterochromaffin cells of the gut. Thus, 5-HT has become a primary focus of recent research.

The postprandial plasma level of 5-HT in patients with diarrhea-predominant IBS is significantly higher than that in healthy controls.[44] 5-HT_3 antagonists were shown to increase colonic compliance, delay colonic transit, improve stool consistency, and increase thresholds for sensation and discomfort during distention of the rectum.[45] Alosetron produced statistically significant improvements in abdominal pain, stool consistency, frequency, and urgency in women with IBS, although symptoms rapidly returned after cessation of therapy.[46] The U.S. Food and Drug Administration (FDA) first approved alosetron (Lotrinex), a 5-HT_3 antagonist, for treating women who have diarrhea-predominant IBS in February 2000. After its introduction, serious and life-threatening cases of ischemic colitis and complications of constipation, including deaths, were reported. The cumulative incidence of ischemic colitis in women receiving alosetron was 0.3% in 6 months. The drug was withdrawn from the market in November 2000 and reintroduced in 2002 with limited approval through the enrollment in the Lotronex Risk Management Program.

Tegaserod (Zelnorm) is an aminoguanidine indole with selective and partial 5-HT_4 receptor agonist activity. 5-HT_4 agonists possess GI stimulatory effects, partially by facilitating enteric cholinergic transmission. In a randomized, double-blind, placebo-controlled study of patients with constipation-predominant IBS, tegaserod significantly improved abdominal pain and bowel function.[47] The medication was approved by the FDA for treating female patients who have constipation-predominant IBS. However, it was removed from the market because of cardiovascular adverse effects.

Lubiprostone (Amitiza, a locally acting type II sodium channel blocker) was the subject of a 4-week double-blind, placebo-controlled multicenter trial in patients with chronic diarrhea. The study showed that stool consistency, straining, consiptation severity, and patient-reported treatment effectiveness were significantly improved with lubiprostone compared with placebo at all weeks of the trial. The most commonly reported adverse event was mild to moderate nausea, which resulted in treatment discontinuation in 5% of treated patients. [48] This agent has been approved since 2006 by the FDA for IBS-C in women and has been shown to have similar efficacy in elderly patients (>65 years).

The cornerstone of IBS therapy is a strong patient-physician relationship that is based on empathy, education, and reassurance. Active dialogue about treatment risk and benefits has been shown to lead to compliance and treatment efficacy as shown by the risk-management program following the reintroduction of Lotronex to the U.S. market for women with severe IBS-D. Patients ultimately engaged in active dialogue about their symptoms with their physicians, leading to better compliance and treatment outcome.[49]

Probiotics and Antibiotics

Probiotics are live microbial organisms provided as food supplements. Preliminary studies in patients with IBS have demonstrated that *Bifidobacterium infantis* reduces inflammatory mediators.[50] Various commercial preparations are available, and studies have shown a potential benefit for such agents in the treatment of IBS.[51] In addition, multispecies probiotics such as *Lactobacillus rhamnosus* GG, *L. rhamnosus* LC705, *Bifidobacterium breve,* and *Propionibacterium freudenreichii* have shown promising results, with decreased symptom severity and decreased serum inflammatory markers when used for greater periods of time (5-6 months).[52] In a double-blind, randomized study of IBS patients, treatment with the antibiotic rifaximin resulted in a greater improvement in symptoms as compared with placebo.[53] Prebiotics, short-chain carbohydrates that allow for changes in the gut composition and activity of gut microflora, and symbiotics (combination of prebiotics and

probiotics) will likely be in the future of IBS-C. These studies suggest that manipulation of gut flora may be a promising new modality of treatment for IBS.[52]

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Outcomes

IBS is a chronic disease with an extremely variable clinical course in the general population. IBS is a safe diagnosis; patients with a diagnosis of IBS seldom turn out to suffer from serious organic disease, and the time-honored clinical strategy of reassuring the patient that the diagnosis is benign, without significant risk of missing an organic disease, is well justified.[54,55]

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Summary

- Irritable bowel syndrome (IBS) is common in the general population and has significant medical and socioeconomic impact.
- IBS is defined on the basis of the modified Rome III criteria as recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months that started at least 6 months before diagnosis, cannot be explained by a structural or biochemical abnormality, and is associated with improvement with defecation, onset associated with a change in frequency of stool, and onset associated with a change in form (appearance) of stool.
- IBS pathophysiology is still unclear, and the diagnosis and management are often challenging. Research is inconclusive, but evidence supports a role for visceral hypersensitivity, abnormal gut motility, psychosocial factors, neurotransmitter imbalance, latent or potential celiac disease, infection, and inflammation.
- A diagnosis is based on identifying positive symptoms consistent with IBS and excluding other conditions with similar clinical presentations in a cost-effective manner.
- IBS is a chronic disorder with no specific cause, and there is no cure. The patient's confidence in the physician's diagnosis, explanation, and reassurance are vital therapeutic tools. The treatment goal should be focused on relieving symptoms and addressing the patient's concerns.
- IBS is a safe diagnosis; patients with a diagnosis of IBS seldom turn out to suffer from serious organic disease, and the time-honored clinical strategy of reassuring the patient that the diagnosis is benign, without significant risk of missing an organic disease, is well justified.
- IBS as a multifactorial disease will continue to evolve as pathophysiologic mechanisms become clearer.

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