Chapter 4
Irritable Bowel Syndrome with Constipation

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Chapter Objectives

At the conclusion of reading this chapter, the reader will be able to:

1. Describe the epidemiology and pathophysiology of IBS with constipation
2. Evaluate the patient with suspected IBS-C
3. Manage patients with IBS-C to improve quality of life and ameliorate symptoms

Key Points

This chapter covers the topic of irritable bowel syndrome with constipation. The high prevalence of this problem makes understanding the pathophysiology, evaluation, and management of patients with IBS-C all that more important. Gastroenterologists will not be the only healthcare providers seeing the IBS patient in the office. These patients will be evaluated by internists, family practitioners, gynecologists, physician assistants, nurse practitioners, and others. A few key points:

1. IBS is NOT a diagnosis of exclusion; you may be able to make a definitive diagnosis after careful history and physical examination.
2. Patients without any alarm signs and/or symptoms may be treated without further evaluation and testing in many cases.
3. Some patients will have a history of a recent infectious illness prior to the development of IBS.

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4. It is not uncommon for patients with IBS to switch subtypes (constipation, diarrhea, mixed).
5. Therapy should be targeted to the patient's main complaint.
6. There are promising therapies for the future based on novel mechanisms.
7. Education, good communication, and careful listening are the hallmarks of effective patient–physician or healthcare provider relationship.

Epidemiology

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder that most clinicians have undoubtedly encountered—if not repeatedly—during the course of patient care. Worldwide, estimates propose that anywhere from 4 to 35% of the adult population is affected by IBS; in the United States, the prevalence demonstrates a narrower range, from 10 to 15% [1–3]. IBS appears to be slightly more prevalent in women than in men [1–3], although no cause has satisfactorily explained this gender discrepancy. Patients with symptoms that alternate between constipation and diarrhea are the largest cohort of the IBS patient population, followed closely by those who experience predominantly diarrhea (IBS-D), and then those who suffer most from constipation (IBS-C). Women are more likely than men to have symptoms of IBS-C. The incidence of IBS in the United States is estimated to be 200–400 cases per 100,000 people [4, 5]; typically, symptoms develop insidiously during the late teenaged years or early 20s, although there is usually a prolonged interval between symptom onset and diagnosis. The peak prevalence of IBS occurs in the third and fourth decades of life; thus, although IBS can be diagnosed at any age, a new diagnosis of IBS should be made cautiously in patients older than age 60, since other diseases (e.g., colon cancer or diverticulitis) may present with similar symptoms. Importantly, for most patients, IBS is a chronic disorder—nearly 75% of patients will still carry the diagnosis of IBS 5 years after its initial presentation [4, 6]. Fortunately, IBS does not predispose patients to more serious disorders (e.g., colon cancer), nor does it shorten life expectancy.

Pathophysiology

Our understanding of the pathophysiology underlying IBS is continually evolving. Fifty years ago, IBS was considered a somatic manifestation of neuroses or psychoses, nominally identified as "nervous colitis." Decades of technological and intellectual innovation have dramatically increased our appreciation for the complexity of the enteric nervous system (ENS) and its normal and diseased function. For instance, Almy and Mullin [7] demonstrated that emotion influences the gastrointestinal tract, experimentally observing changes in colonic motility in patients who had been given stressful information.

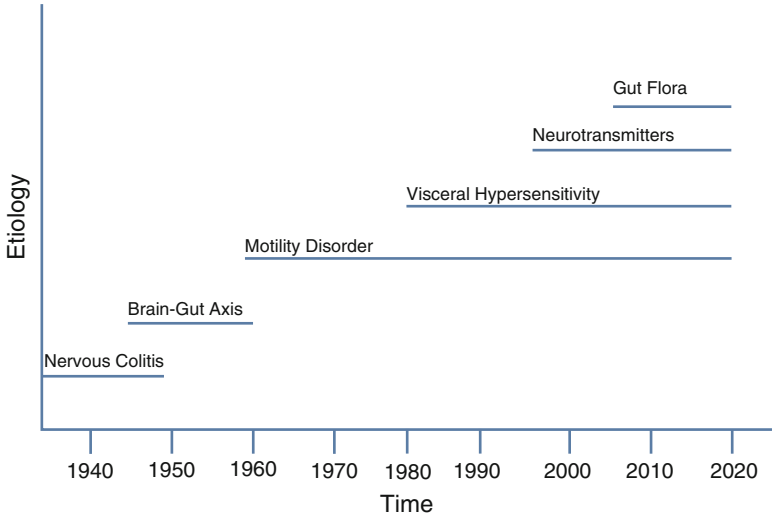

Fig. 4.1 Mechanistic evolution in the understanding of IBS pathophysiology

Subsequent research further elucidated the bidirectional information highway that connects the central nervous system (CNS) and ENS, labeling it the "brain-gut axis." In the 1970s, numerous research groups demonstrated that a subset of IBS patients experience alterations in GI motility; later research identified the importance of a panoply of neurotransmitters in both normal and abnormal GI physiology. Investigation then turned to the interface between the CNS and the ENS, revealing that IBS patients process sensory information from the GI tract differently than do healthy volunteers; today, this phenomenon is called "visceral hypersensitivity." Most recently, investigators have focused on the gut microbiome and its ability to mediate GI motility and sensation (Fig. 4.1).

Once thought to be the somatic manifestation of a nervous disorder, a synthesis of research in both the basic sciences and clinical wards has identified IBS as a complex disorder of multiple, overlapping pathophysiological processes that can include changes in CNS and ENS function. However, the precise etiology of IBS remains elusive. It is likely that IBS develops as a consequence of multiple etiological factors, especially given the complexity of its pathophysiology and the variety of its clinical course.

Currently, a widely accepted [8] theory suggests that some patients are genetically predisposed to develop IBS. In these susceptible individuals, an insult or injury to the GI tract disrupts normal GI homeostasis (Fig. 4.2), followed by the development of generally mild IBS symptoms. Such insults can involve anything from infection, inflammation, and medications to abdominal trauma or surgery. Resultant changes to the GI tract may include abnormalities in intestinal motility, alterations in visceral sensory function or CNS processing of sensory information, inflammation, alteration in the gut microbiome, or the development of food sensitivities. In some patients, mild IBS symptoms are intensified and exacerbated by poor coping

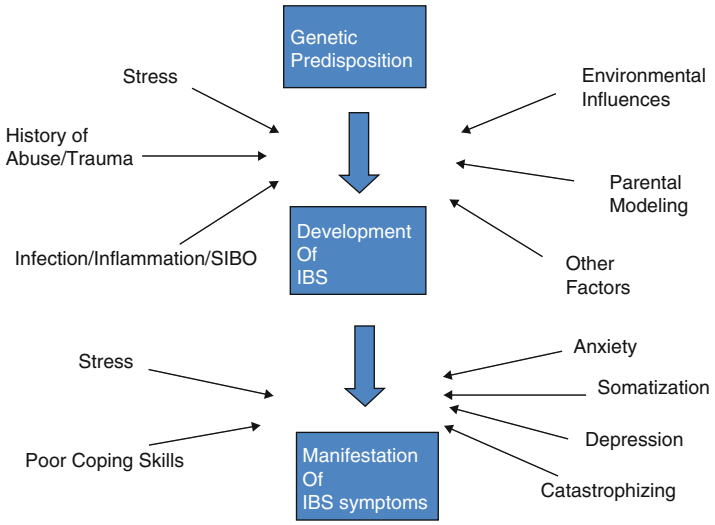

Fig. 4.2 Putative etiology of IBS

skills in the setting of concurrent and/or persistent stress, depression, anxiety, somatization, and catastrophizing behavior. These complex pathophysiological processes are described in further detail below.

IBS as a Motility Disorder

IBS is strongly associated with disorders of defecation (e.g., constipation or diarrhea); naturally, this relationship appears to identify abnormal GI motility as the underlying etiology of the disorder. Specialized gastric and small bowel motility studies (e.g., antroduodenal manometry) directly measure motor function in the upper GI tract. Although a number of different patterns of abnormal GI motility have been described in patients with IBS, no single pattern is pathognomonic for the disorder.

For example, discrete clustered contractions (DCCs) are bursts of rhythmic motility in the small intestine that are associated with episodes of abdominal pain in some IBS patients [9]. In others, the colon or small intestine experience prolonged and/or very high amplitude, propagating contractions, especially in the postprandial period; these also may be associated with episodes of abdominal pain [10]. Furthermore, alterations in the migratory motor complex (MMC), cyclical patterned waves of activity during interdigestive periods, may either delay (constipation) or accelerate (diarrhea) intestinal transit time [11]. In general, the underlying alterations in GI motility seen in some IBS patients appear to be concordant with the signs and symptoms of the disorder and may reflect an exaggeration of the normal patterns of GI motility rather than a unique process specific to IBS patients.

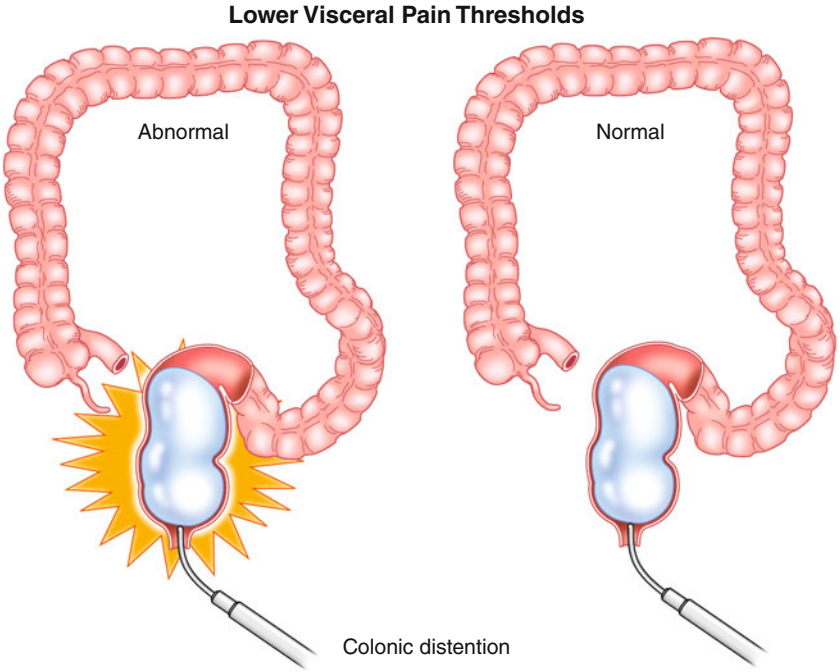

Fig. 4.3 Lower visceral pain thresholds are found in IBS patients. *Source*: Whitehead WE et al. *Gastroenterology*. 1990; 98:1187–1192

IBS as a Disorder of Visceral Hypersensitivity

Abdominal pain is intrinsic to the definition of IBS; its absence precludes diagnosis of the disorder. Historically, clinicians searched in vain for an organic cause of their patients' chronic abdominal pain. However, Thompson et al. [12, 13] seminally demonstrated that patients with IBS are more sensitive to pain within the GI tract. Many subsequent protocols used to assess visceral hypersensitivity in IBS patients involved balloon distention of the GI tract [14], with a balloon placed in the rectum, sigmoid colon, and/or the ileum which is gradually inflated. Notably, patients with IBS perceive balloon distention at much lower volumes of inflation than do normal subjects; they also describe the sensation of distention as more painful (Fig. 4.3) than do their healthy counterparts. In addition to visceral hypersensitivity, some patients with IBS also suffer from allodynia, mistakenly interpreting normal physiological events as painful.

IBS and CNS Processing

Abnormal sensory processing outside of the ENS is also a phenomenon seen in patients with IBS. A comparative study of CNS activation measured by positron

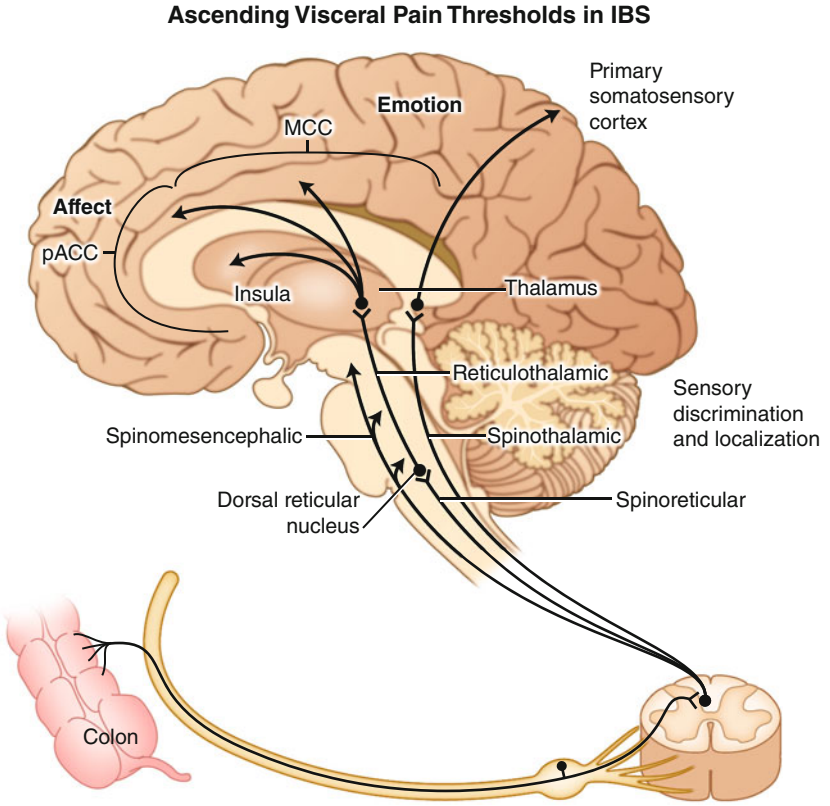

Fig. 4.4 Ascending visceral pain pathways in IBS. *Source*: Drossman DA. *Clin Gastroenterol Hepatol*. 2004; 2:353–365

emission tomography (PET) distinguished patients with IBS from their healthy controls during the inflation of a rectal balloon, recording an unusually increased level of activity in the prefrontal cortex—an area associated with anxiety and hypervigilance—and reduced activity in the anterior cingulate cortex—an area regulated by opioid activity—in the patient cohort compared to controls [15]. These findings may not surprise clinicians who are accustomed to the unique intensity with which many IBS patients monitor their symptoms. Similarly, Mertz et al. [16] used functional magnetic resonance imaging (fMRI) to characterize the differences in CNS activity that separate IBS patients from those without the disorder. Specifically, patients with IBS process sensory information from the GI tract in such a way that stimuli, such as stress, anxiety, and depression, may modulate and subsequently influence the perception of abdominal pain (Fig. 4.4).

These and other like findings have significant implications for the clinical course and treatment of IBS—therapy that is focused solely on the GI tract may not be nearly as successful as a multisystem approach that treats the GI tract, the CNS, and any psychosocial component of the disorder in parallel.

Infection as a Cause of IBS

Infection of the GI tract has been clearly linked to the development of IBS in some patients, yielding a diagnosis of "post-infectious IBS." For instance, a prior history of infectious gastroenteritis increases the likelihood that a patient will develop IBS later in life [17–19]. Clinically, many patients recall the persistence of bloating, abdominal pain, and altered bowel habits after an acute infectious illness (e.g., traveler's diarrhea). Although the precise mechanism underlying post-infectious IBS is unknown, several possibilities exist. An infectious process may transiently or permanently injure the ENS, impairing its ability to coordinate peristaltic activity within the GI tract. In the setting of recurrent exposure to a previously benign substance, a new immune hypersensitivity may induce inflammation in the GI tract and alter motility. Some experts also believe that an infectious agent can initiate a cycle of chronic mucosal inflammation that eventually alters gut motility. Although post-infectious IBS is more likely to be associated with IBS-D, a prior viral or bacterial infection can clearly predispose a patient to develop symptoms of any subtype of IBS.

Abuse and IBS

A history of physical, emotional, and/or sexual abuse may play a role in the development of IBS. In a retrospective analysis of etiological factors, Drossman et al. [20] found a higher prevalence of physical or sexual abuse in patients (primarily women) with IBS than in control groups without IBS. An abuse history is important to consider in all patients with functional bowel disorders; ideally, this issue should be raised during the initial evaluation. The timing of this discussion, however, is critical and depends on both the patient and the physician, who should have sufficient time and resources at hand to complete and then address what is undoubtedly a sensitive conversation.

Small Intestine Bacterial Overgrowth and IBS

Considerable energy has been directed towards characterizing the relationship between the gut microbiome and IBS. Small intestinal bacterial overgrowth (SIBO), a state of excessive bacteria in the upper GI tract, is frequently implicated as the cause of chronic diarrhea and malabsorption, and its symptoms (bloating, distention, abdominal cramps, and diarrhea) are frequently confused with those of IBS. In a landmark study, Pimentel et al. [21] found that 78% of 202 patients who met Rome I criteria for IBS had an abnormal lactulose breath test, suggestive of SIBO. These preliminary results generated a considerable amount of excitement in the field of IBS, since they raised the hope that IBS could be "cured" with antibiotics. Pimentel et al. [22] then more rigorously evaluated this relationship with a blinded,

randomized study, which found that 84% of IBS patients (Rome I) had an abnormal lactulose breath test consistent with SIBO, compared to 20% of healthy controls.

Although these promising results have been confirmed elsewhere [23], other research groups have failed to replicate the strong association between IBS and SIBO. Parisi et al. [24] evaluated a cohort of 85 consecutive IBS patients (Rome II)—none were positive for SIBO using glucose breath testing. Walters and Vanner [25] identified 10% of IBS patients (Rome II) as having SIBO using the lactulose breath test; similarly, Posserud et al. [26] found that the prevalence of SIBO measured with jejunal aspirates was no greater in IBS patients than in healthy volunteers—approximately 4%.

Given the uncertain role of SIBO in the development of IBS, Ford et al. [27] conducted a meta-analysis involving 12 studies and 1,921 subjects to estimate the prevalence of SIBO in patients with IBS. They found that the prevalence of SIBO depended upon the test and diagnostic criteria used to define a positive result, highest with lactulose or glucose hydrogen breath testing (54% and 31%, respectively), and lowest with a jejunal aspirate and culture (4%). Obviously, the role of SIBO in IBS remains unclear.

In summary, there is a small but significant subset of IBS patients who likely have an imbalance between species in their indigenous colonic flora, which could produce symptoms of gas, bloating, and distention. Given the association between SIBO and conditions like chronic diarrhea, an overgrowth or imbalance in the gut microbiome is more likely in patients with the diarrhea subtype of IBS.

Colonic Dysbiosis and IBS

Disruption of the normal intestinal microbiota has been connected to alterations in intestinal function and the development of functional GI disorders such as IBS. The natural flora of the colon, or the "gut microbiome," consists of approximately 1,000 species of bacteria in greater number than live cells present in the rest of the human body combined (approximately 10^{13}). It serves a variety of normal functions, including improvement in intestinal barrier function, modulation of the mucosal immune system, suppression of pathogenic bacteria, assistance with digestion and absorption of nutrients, vitamins, and minerals, and the synthesis of nutritional factors (e.g., short-chain fatty acids).

Comparative microbiological investigation indicates that the composition of the intestinal microbiota in IBS patients is different from that found in healthy people [28]. Furthermore, preliminary research appears to show that the intestinal microbiota may even be different in patients with IBS-C than patients with IBS-D, especially in those who have post-infectious IBS [29]. However, since most of the bacteria in the human intestine are still unknown, specific alterations in the composition of the gut microbiome between different disordered states are not yet well characterized; therefore, it is not yet clear whether these ecological differences are a cause of IBS symptomatology, or rather a secondary consequence of pathophysiologic factors related to IBS.

Celiac Disease and IBS

Symptoms of celiac disease can mimic those of IBS—bloating, abdominal distention, and diarrhea [30]. Although the prevalence of celiac disease in the United States is much lower than that of IBS (0.41–0.75% or 1 in 133 to 1 in 200) [31, 32], there was initially some speculation that celiac disease might be a causative disease state for IBS, given that there appeared to be an unusually elevated overlap between the two GI conditions. However, larger prospective studies have not identified any relationship between celiac disease and IBS [33, 34]. Rather than screening all patients with IBS for celiac disease, it is clinically appropriate to consider celiac disease in patients with IBS-D who experience persistent symptoms that are refractory to standard therapies. A more detailed discussion of the clinical approach to and management of IBS patients is included below.

Clinical Presentation

IBS is a syndrome, defined by a constellation of symptoms. Each patient may present with a unique collection of symptoms that vary in number and severity; however, two characteristic symptoms are prerequisite to the diagnosis of IBS-C: pain and disordered defecation. Abdominal pain or discomfort is the cardinal symptom of all subsets of IBS. Both "pain" and "discomfort" are important words in making this diagnosis, since some patients will insist that they do not have abdominal pain per se, just a sense of discomfort. The absence of pain makes the diagnosis of IBS untenable (Fig. 4.5).

Pain associated with IBS is typically located in the lower abdomen, but may vary from patient to patient; location is not specified in any definition of IBS. Patients

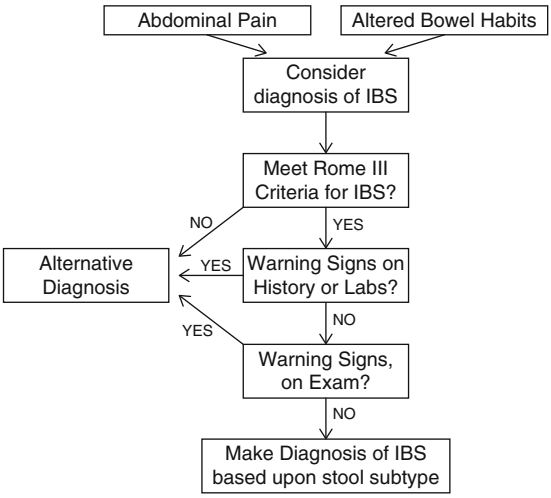

Fig. 4.5 Diagnostic algorithm for the diagnosis of IBS

Table 4.1 Common conditions associated with IBS

Migraine headaches
Fibromyalgia
Insomnia
TMJ syndrome
Functional dyspepsia
GERD
Pelvic floor dysfunction
Interstitial cystitis
Dyspareunia

often characterize IBS pain as "squeezing" or "crampy" or "twisting," finding it difficult to localize. Generally, IBS pain is episodic and unpredictable, although it is more likely to occur in the postprandial period (this is especially true in those patients with IBS-D, as they often have a heightened gastrocolic reflex). It is not solely related to urination, menstruation (although many women note a worsening of symptoms during their menstrual cycle), or physical activity, nor is it relieved by over-the-counter analgesics (e.g., acetaminophen, aspirin), or any type of anti-inflammatory agent. Unsurprisingly, abdominal pain is the primary reason patients with IBS see a healthcare provider.

In addition to abdominal pain, most patients with IBS will present with disordered defecation. Patients may describe symptoms of constipation (e.g., hard stool, straining at stool, feelings of incomplete evacuation, infrequent bowel movements), symptoms of diarrhea (loose stools, urgent bowel movements, more frequent stools) or both. Bowel habits can be unpredictable in IBS patients, which understandably add to their frustration. Although it was originally thought that IBS patients' bowel habits do not change, it is now widely recognized that they may experience multiple IBS subtypes (based on predominant bowel habit) over time. Variable bowel habits like these are not warning signs and should not elicit further diagnostic testing.

Patients with IBS often report a number of other gastrointestinal symptoms, notably including upper abdominal symptoms of burping, belching, reflux, and dyspepsia and lower abdominal symptoms of gas, bloating, distention, urgency, straining, and occasional episodes of fecal incontinence. IBS patients are also more likely to report chronic somatic symptoms, like chronic fatigue, jaw pain, chronic urinary issues, chronic muscle and joint pain, and migraine headaches [35] (Table 4.1).

Diagnosis and Evaluation

Diagnosing IBS need not be a difficult or prohibitively expensive process. However, when first evaluating a patient with multiple gastrointestinal symptoms, IBS is one of many options in a broad differential diagnosis (Table 4.2). A thorough and thoughtful interview, augmented by a careful physical examination, enables most providers to diagnose IBS at the first office visit. In some patients, simple laboratory

Table 4.2 Differential diagnosis of irritable bowel syndrome

Differential diagnosis	Clinical clues	Diagnostic tests
Small intestinal bacterial overgrowth (SIBO)	Previous abdominal surgery Bloating and diarrhea in diabetes mellitus or scleroderma	Lactulose breath test Glucose breath test Quantitative duodenal aspirate culture Trial of antibiotic therapy
Lactose intolerance	Diarrhea, abdominal pain, and flatulence after ingestion of milk or milk containing products	Trial of lactose-free diet Lactose breath test
Celiac disease	Diarrhea, weight loss, anemia, iron deficiency, gluten intolerance	Serology for celiac antibodies (tTG antibodies) Duodenal biopsy
Inflammatory bowel disease (Crohn's and ulcerative colitis)	Nocturnal symptoms, weight loss, blood and mucus in the stools, anemia	Colonoscopy Small bowel capsule study Laboratory tests
Infectious diarrhea (e.g., Giardia, parasites in endemic areas)	History of travel, history of exposure	Stool microscopy, culture; Laboratory tests
Colon cancer	Family history of colon cancer, rectal bleeding, weight loss, recent change in bowel habits in patients over >50 age	Colonoscopy

tests may be required to confirm the diagnosis; however, guidelines suggest that without alarm signs and symptoms, a definitive diagnosis may be made without further testing. When these simple guidelines are followed, the accuracy of a diagnosis of IBS is 97% [36].

IBS should not be a diagnosis of exclusion, nor should the patient be told, or led to believe, that "it is all in your head." Several steps in the clinical encounter ensure an accurate diagnosis of IBS: (1) take a careful history; (2) look for warning signs or "red flags"; (3) use the Rome III definition of IBS [37]; (4) perform a physical examination; and (5) consider targeted diagnostic studies.

Step 1. Take a History

IBS patients most commonly complain about abdominal pain and altered bowel habits, emphasizing whatever is most disturbing to them at the time of presentation. Symptom patterns vary considerably between affected individuals, but remain fairly consistent in a given patient, fluctuating only in intensity and frequency. IBS symptoms are typically intermittent, often absent for periods of days; however, some patients will experience symptoms daily without remission.

The presence of abdominal pain or discomfort is required for a diagnosis of IBS [37]. *If abdominal pain or discomfort is not present, the patient does not have IBS*. Timing is also an important component of an IBS history, given that IBS is a chronic disorder with an insidious onset (see definition for specific parameters below). Intervals of abdominal pain related to IBS should be associated with disordered defecation, and abdominal pain should be temporally related to defecation in some way. Pain related only to urination, menstruation, or exertion suggests an alternative diagnosis. The quality and location of abdominal pain varies between IBS patients, but remains relatively stable over time in individual patients. Some describe the pain as "crampy," whereas others describe it as sharp or burning. Common descriptions for pain in IBS include gurgling, churning, gnawing, stabbing, crampy, queasy, bloating, gassy, and urge to go but can't.

At this point the patient should be asked three key questions:

1. Is your abdominal pain (or discomfort) relieved by defecation?
2. At the onset of the abdominal pain or discomfort, are your stools looser or harder?
3. When the abdominal pain (or discomfort) begins, do you have more (or less) frequent stools?

An affirmative answer to two or more of these questions indicates that this patient likely fulfils the Rome III criteria for IBS. Although these criteria have yet to be validated, they appear to function perfectly well in practice.

Next, questions should focus on patients' bowel habits. Patients can find it difficult or even embarrassing to describe the appearance of stool. In practice the best way to obtain a consistent description of stool form is to use the Bristol Stool Chart (see Fig. 1.5). Questions can elicit information related to diarrhea-predominant, constipation-predominant, or mixed IBS based on the stool form. If patients do not reflect the characteristics of IBS-C, IBS-D, or IBS-M, a fourth category, labeled unsubtyped IBS, is now a recognized subtype of the disorder.

Normal patterns of defecation range from 3 bowel movements per week to 3 per day [38]. Many IBS patients prone to diarrhea find that the first stool in the morning is of normal consistency; however, subsequent bowel movements become increasingly loose and are associated with significant urgency, abdominal cramps, and flatulence. Fecal urgency and cramps are temporarily relieved by the passage of stool, but quickly return to precipitate repeated bowel movements. As bowel evacuation ends, the stools are primarily liquid or mostly mucus, and some patients are left feeling drained. By contrast, patients with IBS-C often report the passage of rocky hard, pellet-like stools (scybala) and may describe straining and the sensation of incomplete evacuation. Mucus may cover the stool or be passed without the presence of stool.

Fecal incontinence (usually slight staining of the undergarments) is more common in patients with IBS compared with the general population and may result from reflex relaxation of the sphincter muscles in association with repetitive colonic contractions. Although not well-studied, fecal incontinence is more likely to occur in patients with IBS-D or alternating constipation and diarrhea than in those with IBS-C.

IBS patients frequently report feelings of bloating and abdominal distention, which can be attributed either to increased amounts of abdominal gas, or more

Table 4.3 Common conditions that mimic IBS

Lactose intolerance
Fructose intolerance
Celiac disease
Small intestinal bacterial overgrowth (SIBO)
Colonic inertia (slow transit constipation)
Complicated diverticular disease
Pelvic floor dysfunction
Chronic intestinal pseudoobstruction (CIP)

likely, increased sensitivity to normal amounts of intestinal gas [39]. Lactose or fructose intolerances increase gas production, which can exacerbate underlying visceral hypersensitivity, as do large amounts of dietary fiber and legumes (e.g., beans) that contain stachyose or raffinose. As noted previously, SIBO has also been invoked as a cause of bloating in patients with IBS [20, 22, 40].

Finally, query the patient's past medical history, current medical conditions, and circumstances that might explain the etiology of the patient's discomfort. IBS patients often present with constitutional symptoms, such as fatigue, myalgia, arthralgia, insomnia, and headache; these symptoms are commonly caused by comorbid conditions like fibromyalgia, arthritis, or hypothyroidism, rather than IBS (Tables 4.2 and 4.3). Elicit a travel history for indications of a recent bacterial or parasitic infection, including giardiasis and amebiasis. Pay attention to the patient's family history, especially regarding GI malignancy and autoimmune conditions, and be sure to ask specific questions about food intolerances, anxiety and depression, sleep quality, medication use, alcohol consumption, and exercise, as these are all factors that can exacerbate or ameliorate IBS symptoms.

Step 2. Look for Warning Signs ("Red Flags")

The abdominal pain and altered bowel habits associated with IBS are frustrating and uncomfortable for patients, who often describe a significant decrease in their quality of life over the course of the disorder. Despite the apparent chronicity and severity of IBS, the disorder does not predispose patients to increased risk of malignancy or other life-threatening GI conditions. Therefore, it is important to distinguish IBS from other conditions, benign and serious, which can cause similar abdominal complaints (e.g., SIBO, lactose intolerance, celiac sprue, inflammatory bowel disease (IBD), and colorectal cancer).

To confirm the diagnosis of IBS, ask questions to investigate any alarm symptoms—all should be absent in the patient's history (Table 4.4). Standard questions evaluating alarm symptoms include:

– Do you know if you are anemic or have a history of anemia or iron deficiency?
– Have you had any gastrointestinal bleeding? (e.g., bloody bowel movements or vomiting of blood?)

Table 4.4 Alarm features that should alert you to the possibility of other diagnoses

Alarm features	Possible diagnosis	Tests recommended
Rectal bleeding	Colon cancer, inflammatory bowel disease	CBC, colonoscopy
Unintentional weight loss (>5–10% of body weight)	Colon cancer, celiac disease, other malabsorption syndromes	Upper endoscopy, duodenal biopsy, colonoscopy; Laboratory tests
Persistent nausea and vomiting	Bowel obstruction	Cross-sectional abdominal imaging; Laboratory tests
Anemia or iron deficiency	Celiac disease, colon cancer, inflammatory bowel disease	Upper endoscopy, duodenal biopsy, colonoscopy; Laboratory tests
Family history of other GI conditions	Colon cancer, inflammatory bowel disease, celiac disease	Upper endoscopy, duodenal biopsy, colonoscopy, celiac serology
Fever	Diverticulitis, abscess, inflammatory bowel disease	Abdominal CT scan; Laboratory tests
Abdominal mass	Colon cancer, Crohn's disease	Abdominal CT scan; Laboratory tests
Age >50	Colon cancer	Colonoscopy

- Do you have symptoms of recurrent nausea and vomiting?
- Have you had documented fevers with your symptoms of pain and altered bowel habits?
- Is there a family history of IBD, celiac disease, or any type of gastrointestinal cancer?
- Have you had symptoms consistent with a bowel obstruction?
- Any unintentional weight loss?
- Are you over the age of 50?

Weight loss (>10%), *occult blood in the stool*, *anemia*, *or other evidence of a GI bleed are not consistent with the diagnosis of IBS*. A positive answer to any query regarding alarm symptoms, or the presence of any alarm signs on physical examination (below), should prompt careful consideration of alternative diagnoses. Alarm symptoms ("red flags") raise the pretest probability that there is underlying structural disease; however, most patients with one alarm feature will not be found to have a serious organic explanation for their symptoms during subsequent evaluation [41]. The investigation of alarm features depends on the findings; usually blood work [e.g., complete blood cell count (CBC), erythrocyte sedimentation rate (ESR)] followed by a colonoscopy are the first tests considered. In the United States, preventive medicine guidelines recommend that all patients 50 years and older be offered a colonoscopy (if not previously performed) or an alternative test to screen for colon cancer. These screening tests should be performed 5 years earlier, at age 45 in African-Americans. In the setting of IBS, polyps or even an incidental cancer found on colonoscopy usually mean that the patient has the disorder plus the colonic pathology—*IBS symptoms are not sensitive markers of colorectal cancer*.

Table 4.5 Diagnostic criteria for IBS

Rome III

1. Symptom onset at least 6 months prior to diagnosis
2. Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with two or more of the following:
   - Improvement with defecation
   - Onset associated with change in stool frequency
   - Onset associated with change in stool form (appearance)
3. One or more of the following symptoms on at least a quarter of occasions for subgroup identification
   - Abnormal stool frequency (<3/week)
   - Abnormal stool form (lumpy/hard)
   - Abnormal stool passage (straining, incomplete evacuation)
   - Bloating or feelings of abdominal distension
   - Passage of mucous
   - Frequent, loose stools

ACG definition of IBS

1. Abdominal discomfort associated with altered bowel habits
2. Symptoms of constipation include infrequent stools, straining, feelings of incomplete evacuation, difficult evacuation, passage of rocky, hard stools

From Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology*. 2006;130(5):1480–1491, with permission

When evaluating patients for suspected IBS, physicians can be inclined to routinely order a battery of investigative tests out of fear of missing a more serious condition before committing the patient to a diagnosis of IBS. This is neither economical nor clinically appropriate [36] and is a practice that should be reserved for only those patients who are identified by affirmative alarm features.

Step 3. Use the Rome III Definition of IBS

Clinically, IBS is currently defined using the latest iteration of the Rome criteria (Rome III). See Table 4.5 for a description of these criteria. What should be considered if the patient does *not* fulfil Rome criteria? These criteria are specific but not sensitive for the diagnosis of IBS; the absence of the criteria does *not* mean the patient does not have the disorder. Alternatively, clinicians can use The American College of Gastroenterology (ACG) IBS Task Force definition of IBS, which more broadly identifies the disorder as abdominal pain or discomfort associated with altered bowel habits over a period of at least 3 months, in the absence of warning signs or "red flags" suggestive of organic disease [42]. ACG criteria are sensitive, but not particularly specific; if a patient fails to fulfil Rome criteria, a more detailed clinical evaluation will exclude other potential etiologies before confirming the diagnosis of IBS (see Table 4.2).

Step 4. Perform a Physical Examination

A thorough physical examination serves a dual purpose in the diagnostic evaluation of IBS and should be performed during the initial clinical encounter: (1) a careful physical exam reassures patients that the clinician has listened to their complaints and takes their discomfort seriously. A physical exam is important for this reason even if the patient presents with classic symptoms of IBS that have been present for many years without alarm features or warning signs. (2) A physical exam might uncover comorbid, overlapping, or causal disease processes that exist in addition to or in place of the patient's IBS and is a helpful barrier to some physicians' tendency to prefer a single, unifying diagnosis for each patient. Suffice it to say—it is not uncommon for several disease processes to simultaneously shape a patient's illness experience.

Findings on physical examination are generally unremarkable in IBS patients, including vital signs, the head and neck, heart, lungs, skin, and cranial nerves. The abdominal examination may reveal some tenderness or firmness, especially in the left lower quadrant over the sigmoid colon. Don't confuse abdominal wall pain (which increases with tensing the abdominal wall muscles; a positive Carnett's sign) with deep tenderness sometimes found in IBS. The sigmoid colon often contains stool and can be palpated, regardless of whether the patient has IBS. Signs of rebound and guarding should be absent in IBS; their presence suggests alternative diagnoses. The physician also should look for evidence of masses in the abdomen, check for bruits, listen for a succussion splash (heard in patients with gastroparesis) prior to palpation, and the liver and spleen should be carefully examined.

A digital rectal examination should be considered in all patients. An anal fissure may explain a history of rectal bleeding, especially in patients with constipation and straining. A fistula or significant perianal disease raises the possibility of Crohn's disease. Some tenderness is often noted in the rectum of patients with IBS as a consequence of visceral hypersensitivity, rectal spasms, and muscular contractions; however, significant tenderness, evidence of a mass, or blood in the rectum warrants further investigation.

Step 5. Consider Targeted Diagnostic Studies

As with all diagnoses, the goals of testing in suspected IBS are to establish the diagnosis as early as possible, identify or rule out coexisting/alternative diagnoses, and avoid unnecessary studies. No further diagnostic evaluation is necessary in younger patients who meet system-based criteria for IBS, have normal findings on physical examination, and do not present with alarm signs or symptoms [36, 37, 42]. However, many IBS patients are reassured by results from an objective test that rule out serious organic disease [43], and many physicians cannot confidently diagnose IBS without the same objective tests, especially in an era of increasing medical malpractice suits [44, 45].

With these parameters in mind, we suggest consideration of a safe, cost-effective set of tests when indicated. Thyroid-stimulating hormone levels (TSH) may be

checked in patients with IBS-C. Tests might also include a CBC and an ESR or C-reactive protein (CRP) if they have not recently been performed (<6 months prior). The latter are especially useful in patients with IBS-D to exclude IBD. Test stool samples for fecal leukocytes in patients with diarrhea predominance, and if present, test for routine culture, ova and parasites, and *Clostridium difficile*. Reserve serologic tests for celiac disease for patients with persistent IBS symptoms (especially those with IBS-D); a cost-effective approach to celiac starts with serum tissue transglutaminase (TTg) antibody and serum immunoglobulin A, if indicated. Flexible sigmoidoscopy is usually recommended for patients younger than 40 years with a change in bowel habits or rectal discomfort, and colonoscopy is warranted in all patients 50 years of age or older (45 and older in African-Americans), and in those who are anemic or have a strong family history of IBD, or colorectal cancer (Fig. 4.5).

Management of IBS with Constipation

The management of patients with IBS and constipation does not follow a rigid algorithm. Rather, optimal treatment is tailored to each patient's symptom complex and is modified by symptom severity. For instance, lifestyle modifications and dietary changes may greatly improve very mild symptoms, whereas persistent or severe symptoms tend to benefit from additional therapeutic interventions (Table 4.6). In all cases, reassurance and education are the foundation of successful management of IBS.

Education

Patient education increases patient compliance with recommended treatment plans, enhances satisfaction with the healthcare system, and improves physician–patient interactions. Unfortunately, many patients with IBS report that they are insufficiently informed about their condition [46]. Healthcare providers should be educators at heart, and physicians offer their IBS patients great comfort and reassurance by making time each visit to answer questions, provide online and printed resources, and encourage patients to be honest about their confusion and fears. The latter is especially important—ideal patient education encompasses a bidirectional exchange of information, which accounts for each individual's understanding of IBS and its implications. Patient education should be specifically tailored to the level of education and most useful learning strategies that characterize each clinical relationship.

Reassurance

Many patients with IBS are needlessly fearful about their diagnosis. Nearly 20% are convinced that IBS will turn into cancer; another 30% believe that IBS increases the

Table 4.6 Treatment options for constipation symptoms in patients with IBS-C

Fiber supplements
Calcium polycarbophil (Equalactin, FiberCon)
Guar gum, partially hydrolyzed (Benefiber)
Coarse bran or ispaghula husk
Chloride channel activators
Lubiprostone (Amitiza)
Guanylate cyclase C activators
Linaclotide (Linzess)
Stool softeners
Docusate sodium (Colace)
Osmotic agents and unabsorbed sugars
Magnesium hydroxide (Phillips Milk of Magnesia, Freelax)
Magnesium citrate
Polyethylene glycol (Miralax)
Lactulose (Chronulac, Kristalose)
Sorbitol
Stimulant laxatives
Bisacodyl (Dulcolax, Gentlax)
Senna, sennosides (Senokot, Ex-Lax, Swiss-Kriss)
Aloe
Cascara
Combination agents
Docusate sodium and sennoside (Senokot-S)
Docusate sodium and casanthrol (Peri-Colace)
Herbal agents
Aloe vera (*Aloe barbadensis*)
Buckthorn (*Rhamnus catharticus*)
Cascara sagrada (*Rhamnus purshianus*)

likelihood of developing IBD (neither are true) [44]. For this reason, the importance of communication in the care of IBS patients cannot be overemphasized. Patients should be asked specifically about their fears and concerns at the start of the discussion regarding an individualized treatment plan. It would not be surprising for a patient to relate that he or she is concerned that he or she will develop colon cancer because of their IBS or that IBS can never be treated. All strategies should be employed to support patient honesty as an opportunity to eliminate future fear and distress. The provider's availability, good communication, and sufficient education can correct common misconceptions like these.

Lifestyle Modifications

Fortunately for patients with IBS-C, education, reassurance, and therapeutic lifestyle modifications can significantly alleviate their symptoms—patients with mild

IBS-C might find that this triad is all that is required. Patients should be queried about their diet, exercise plan, routines, and sleep, looking for small changes that can make a difference. For instance, although there is nothing magical about drinking eight glasses of water per day, and in fact no data to support that hydration is effective, nevertheless, some patients who drink very little liquid note some improvement in constipation symptoms when better hydrated. Patients should be counseled to consume foods with natural fiber (to a goal of approximately 25 g/day) if they are fiber deficient. However, if the patient is already ingesting 25 g of fiber per day, adding more fiber to the daily diet will not help constipation symptoms and likely will only worsen gas and bloating. Many IBS patients find that a daily routine improves their bowel habits, and an effective strategy includes timed toileting, meaning that a regular, convenient time be set aside for a bowel movement each day. Notably, many patients find that a daily morning regimen of fiber cereal along with fruit high in fiber and fructose and strong coffee or tea followed by routine scheduled bathroom time is all that is required to improve their symptoms. Finally, there is some evidence that exercise improves IBS symptoms [47]. Whether exercise directly affects the GI tract (e.g., change in motility), improves gas and abdominal distension, or simply increases patients' sense of well-being is unknown. Nonetheless, a daily or 4–5 times weekly exercise program will likely improve overall the general sense of well-being and IBS symptoms.

Medications

Fiber

Although fiber supplements are a safe, intuitive selection in the treatment of IBS-C, their therapeutic benefit is equivocal. Fiber supplements are categorized by their solubility in water (soluble fiber products include psyllium or ispaghula, calcium polycarbophil, and guar gum; insoluble fiber products include corn bran and wheat bran) and act as hydrophilic agents which bind water in the colon, preventing excessive dehydration of colonic contents. Over the course of three decades, only three studies have demonstrated that supplemental fiber significantly benefits IBS treatment plans—one for polycarbophil and two for ispaghula husk [48]. In a recent meta-analysis of 12 studies, Ford et al. [49] determined that IBS patients treated with fiber were only slightly less likely to have persistent IBS symptoms ($n = 591$; 52%), compared to those treated with placebo or a low-fiber diet (57%; $p = 0.05$), and estimated that 11 patients needed treatment with fiber to demonstrably improve symptoms. When treating patients with IBS-C, remember that fiber supplements are not effective if the patient is already taking in a normal fiber diet, that these products do not relieve abdominal pain, and that at least 30% of patients taking them experience significant bloating and abdominal distention.

Stool Softeners

Like fiber, stool softeners, such as docusate sodium, are historically significant agents in the treatment of IBS-C. Mechanistically, stool softeners are emollients that increase the water content of stool by 2–3%. Limited data available in the chronic constipation (CC) literature found that stool softeners are generally no better than placebo at improving constipation symptoms [50, 51]. No randomized, controlled studies have been performed in patients with IBS-C and thus, although safe, they cannot be recommended.

Stimulant Laxatives

Laxatives (e.g., bisacodyl) improve symptoms of constipation by stimulating the large intestine, thereby increasing intestinal transit. However, these agents generally worsen cramps, spasms, and pain in patients with IBS. No randomized, controlled studies have been performed in patients with IBS-C and thus cannot be recommended.

Osmotic Agents

Osmotic agents are widely available over-the-counter for the treatment of constipation. Lactulose, polyethylene glycol (PEG), and magnesium hydroxide or magnesium citrate are the most widely used agents in this class. Lactulose is a nonabsorbable, synthetic disaccharide composed of the sugars, D-galactose and D-fructose, which are fermented in the colon by bacteria to organic acids. These fermentation products (e.g., lactic acid and small-chain fatty acids) increase the osmotic load to the gut, thus stimulating peristalsis. Lactulose may improve symptoms of constipation, but will not help abdominal pain or discomfort and may worsen bloating (Fig. 4.6).

PEG is a nonabsorbable, non-metabolized osmotic agent that retains water in the stool, softening the stool and increasing the number of bowel movements (Fig. 4.7). It is approved for the treatment of transient constipation, but is not FDA approved for the treatment of IBS with constipation—no large prospective studies have been performed to evaluate the efficacy of PEG in IBS-C patients. Nevertheless, PEG appears to be widely used clinically to treat constipation symptoms in patients with IBS-C, even though it does not improve abdominal pain or bloating.

Magnesium hydroxide, in either liquid or pill form, is also an option for mild cases of constipation, but, once again, generally does not relieve abdominal pain and bloating. *The long-term use of magnesium hydroxide can be dangerous in patients with renal insufficiency or renal failure*.

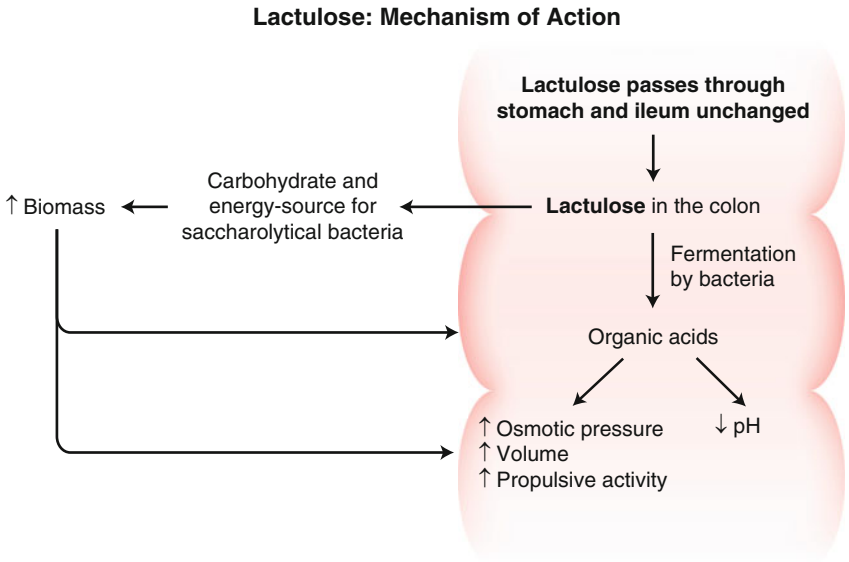

Fig. 4.6 Mechanism of action of lactulose

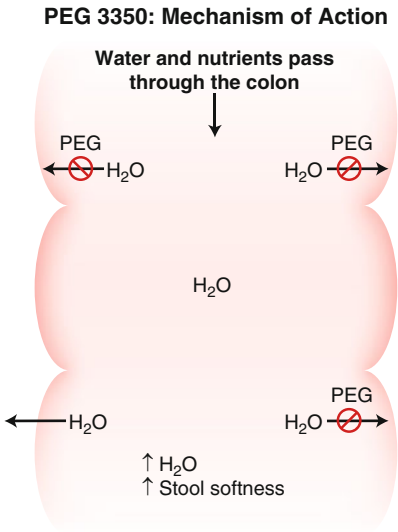

Fig. 4.7 Mechanism of action of PEG 3350 (glycolax)

Finally, magnesium citrate can be used on a p.r.n. basis to help with constipation, but it is not recommended for long-term use and will not help the abdominal pain that characterizes IBS.

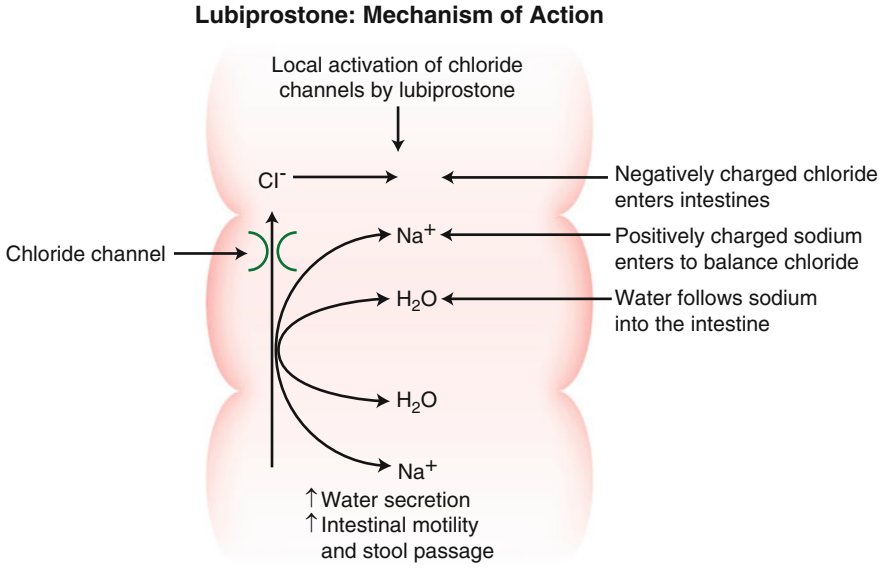

Fig. 4.8 Mechanism of action of lubiprostone

Lubiprostone

Lubiprostone, a bicyclic fatty-acid derivative that activates chloride channels within the lumen of the GI tract (Fig. 4.8), improves symptoms of chronic constipation in both men and women and was approved for the treatment of chronic constipation by the FDA in January 2006 [52]. These encouraging results naturally led researchers to evaluate the efficacy of lubiprostone in the treatment of IBS and constipation [53]. In a 2007 study, 1,171 adults diagnosed with IBS-C using the Rome II criteria were randomized to receive either 12 weeks of lubiprostone (8 μg) or placebo given twice daily [54]. Most patients were women (91.6%), and most were between the ages of 18 and 65 (91.7%). The primary efficacy variable was a global question rating overall IBS symptoms, while a 7-point balanced scale was used to rate changes in individual symptoms. The authors reported that patients receiving lubiprostone were nearly twice as likely as those receiving placebo to achieve overall response (17.9% vs. 10.1%; $p=0.001$). Secondary end points, including abdominal pain, bloating, straining, stool consistency, and constipation, all were significantly improved in the lubiprostone group compared with the placebo group ($p<0.05$ for all end points). Lubiprostone was generally well tolerated. The most common treatment-related side effects were nausea (8% vs. 4% in placebo) and diarrhea (6% vs. 4% in placebo).

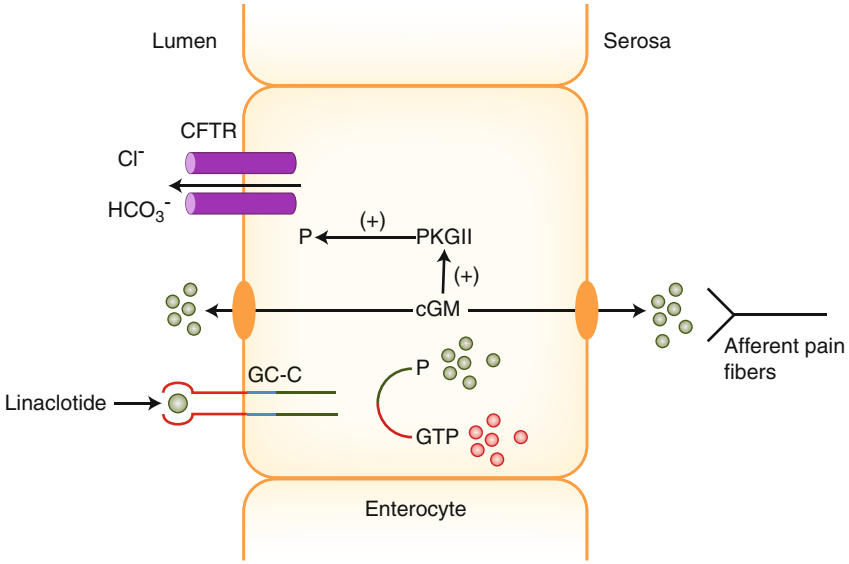

Fig. 4.9 Mechanism of action of linaclotide

Linaclotide

Linaclotide is an acid-stable, protease-resistant 14-amino acid peptide that stimulates intestinal guanylate cyclase type C (GC-C) receptors [55]. Linaclotide mimics the action of the endogenous intestinal peptides guanylin (15 amino acids) and uroguanylin (16 amino acids), activating cGMP-dependent protein kinase II pathways via the GC-C receptor on human colonic epithelial cells, which it binds with high affinity and independent of pH [56–59] (Fig. 4.9). Phosphorylation activates the cystic fibrosis transmembrane conductance regulator (CFTR), which increases the flow of electrolytes (HCO_3^- and Cl^-) and water into the lumen of the GI tract, accelerating the transit of its contents.

Linaclotide appears to be quite acid-stable [56]. Similar results were reported when linaclotide was exposed to pepsin [30]. The parent compound is broken down by removing the C-terminal tyrosine, leaving a 13 amino acid compound that appears to have full biologic activity; the metabolite appears to be completely broken down within several hours. In animal studies (mice), linaclotide has been shown to be minimally absorbed with bioavailability of approximately 0.10% [58]. Bioavailability in humans is also thought to be very low; in healthy volunteers linaclotide, at doses up to 1,000 μg, could not be detected in serum [60, 61]. Linaclotide is broken down within the lumen of the GI tract; a small amount may be recovered intact in feces.

The effects of linaclotide in women with IBS-C were first evaluated in a 5-day colonic transit study [62]. Thirty-six women with IBS-C (Rome II criteria; mean age = 39) were randomized to receive either placebo or one of two doses of daily linaclotide (100 or 1,000 μg) for 5 days. All study patients had documented slow colonic transit (defined by a geometric center ≤2.65 at 24 h or ≤3.0 at 24 h and ≤3.9 at 48 h). Patients with evacuation disorders were excluded. Analysis showed a significant effect of linaclotide on ascending and overall colonic transit at 48 h, but not 24 h, with the 1,000 μg dose, but not the 100 μg dose, compared to placebo (ascending $p=0.015$ and total $p=0.020$). Secondary outcomes that improved and were statistically significant compared with placebo include the time to the first bowel movement, stool frequency, stool consistency, and improved ease of stool passage. No serious adverse events were reported. These encouraging results led to two large prospective clinical trials which led to the FDA approval in August 2012 of linaclotide for the treatment of IBS-C.

Johnston et al. [63] conducted a phase IIb dose-ranging study to evaluate the efficacy and safety of linaclotide in patients with IBS-C. Men and women, age 18 and older, who met Rome II criteria for IBS with <3 spontaneous bowel movements (SBM) per week were eligible for the study. The primary efficacy endpoint was the change from the baseline period in weekly complete spontaneous bowel movements (CSBMs). Four hundred and twenty patients (92% women, mean age 44.4 years; 80% Caucasian) with IBS-C were randomized to receive either daily placebo or one of four doses of linaclotide (75, 150, 300, or 600 μg) for 12 weeks in a double-blind, multicenter study. Three hundred and thirty-seven patients completed the study (81%). The primary endpoint (mean change in CSBM compared to baseline) was met for all doses of linaclotide. CSBM rates for linaclotide (75, 150, 300, and 600 μg doses, respectively) were 2.90, 2.49, 3.61, and 2.68, compared to 1.01 for placebo ($p<0.01$ for all doses). SBM rates also improved for all doses of linaclotide compared to placebo ($p<0.001$), as did stool consistency and straining ($p<0.001$ for each). Abdominal pain was significantly better with 31.1–38.7% of linaclotide patients reporting improved abdominal pain compared to 22.7% for placebo ($p\leq0.01$ for 300 and 600 μg, $p\leq0.05$ for 75 μg). Abdominal pain returned to baseline levels after linaclotide was stopped and approached levels of pain found in the placebo group. Diarrhea was the most common AE and was the only dose-dependent AE, occurring in 11.4, 12.2, 16.5, and 18% of patients on 75, 150, 300, and 600 μg of daily linaclotide, respectively, compared to placebo (1.2%). The authors did not report any clinically significant differences in EKG recordings, electrolytes, vital signs, or physical examination for those patients on linaclotide compared to those on placebo.

Most recently, Rao et al. [64] conducted a phase III randomized, double-blind, placebo-controlled 12-week trial of linaclotide 290 μg in 800 IBS-C patients (mean age: 43.5 years; 90.5% women), followed by a 4-week randomized washout (RW) period. A significant number of linaclotide-treated patients reported clinical improvement of >30% in their abdominal pain (50.1% vs. 37.5% placebo, $p=0.0003$), and an increase in CSBM >1 from baseline (same week; 48.6% vs. 29.6% placebo, $p<0.0001$), consistent with FDA endpoint criteria for therapeutic drug approval. Patients were re-randomized following the 12-week trial; those

previously on linaclotide who were randomized to continue the therapy showed continued clinical improvement. Those randomized back to placebo returned to baseline symptoms, but without worsening of pretrial symptoms relative to baseline. Diarrhea was the most common adverse drug reaction (ADR).

Future Directions

Prucalopride

Prucalopride is an orally administered dihydrobenzofurancarboxamide derivative shown to be a potent, selective, high-affinity agonist at the 5-HT_4 receptor. The safety and efficacy of prucalopride for the treatment of chronic constipation has been evaluated in three large studies [65–67]. No large prospective studies have been performed in patients with IBS-C; however, given prucalopride's mechanism of action, and the prior success of both tegaserod and lubiprostone for the treatment of patients with both chronic constipation and IBS-C, it seems likely that prucalopride should improve constipation symptoms in patients with IBS-C. It should be noted that tegaserod, a 5-HT_4 agonist, was approved in 2002 for IBS-C, but removed from the market in 2007 related to concerns of cardiovascular side effects.

All three trials were similarly designed—12-weeks in duration, multicenter, randomized (2 vs. 4 mg vs. placebo), double-blind, placebo-controlled, and parallel group. Patients were defined as having chronic constipation if they had two or fewer CSBMs each week for a minimum of 6 months before the screening visit. Patients also had to have very hard or hard stools, or straining with at least 25% of bowel movements. The primary efficacy endpoint was the proportion of patients having three or more spontaneous, complete bowel movements per week, averaged over the 12-week period, using an intention-to-treat analysis. The main secondary endpoint was the percentage of study patients with an average increase of one or more CSBMs per week. Other secondary endpoints included the median time to the first CSBM, changes in stool consistency and straining at stool, and satisfaction with bowel habits.

Camilleri et al. [65] included 620 patients with chronic constipation (88% women; mean age = 48 year) in the study analysis. The primary endpoint (three or more CSBM/week) was reached by 31% of those on 2 mg of prucalopride, 28% of those on 4 mg, and 12% of those on placebo ($p<0.001$ for both study groups). During the 12-week study period, more patients treated with prucalopride had an increase of one or more CSBM/week when treated with either 2 mg (47%) or 4 mg of prucalopride (47%) compared to placebo (26%; $p<0.001$ for both doses).

Tack et al. [66] enrolled 720 chronic constipation patients, finding that most patients met the primary end point on treatment with prucalopride (both 2 and 4 mg daily) compared to placebo during the 12-week study period. Patients treated with prucalopride were more likely to rate their treatment as quite effective or extremely effective (35–36%), compared to placebo (19%; $p<0.001$).

Similar to the Camilleri et al. [65] and Tack et al. [66] studies, Quigley et al. [67] found that chronic constipation patients treated with prucalopride were more likely to rate their treatment as effective compared to those treated with placebo (37–39% vs. 20%; $p<0.001$) in a trial drawn from 41 US sites. No deaths were reported in any of these studies. Diarrhea was the most common adverse event.

Plecanatide

Plecanatide (SP-306) is an experimental 16 amino-acid GC-C agonist presently in Phase II/III trials for both chronic constipation (CC) and IBS-C. Structurally and functionally, it is nearly identical to the human hormone uroguanylin save for an extra methylene residue [68]. Binding of uroguanylin or plecanatide to transmembrane enteric receptors stimulates increased production of intracellular cyclic guanosine monophosphate (cGMP) which activates the CFTR and increases the secretion of fluid and ions into the gastrointestinal lumen. Data from a study involving patients with chronic constipation appears to support plecanatide's mechanism of action. In an unpublished study reported in January 2013, a 12-week randomized, double-blind, placebo-controlled, multicenter study involving 951 patients found that 3 mg of daily plecanatide was significantly more effective than placebo at improving symptoms of chronic constipation. A large multicenter trial is currently underway to evaluate the safety and efficacy of plecanitide in IBS-C patients.

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