ETIOLOGY AND PATHOPHYSIOLOGY OF IRRITABLE BOWEL SYNDROME AND CHRONIC CONSTIPATION

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ABSTRACT

Functional gastrointestinal (GI) disorders are collections of symptoms attributable to the GI tract in the absence of mucosal, structural, or biochemical disease. Two of the most common disorders, chronic constipation and irritable bowel syndrome (IBS), have common etiopathogenetic features—notably psychosocial disturbances, dysmotility, and heightened sensitivity. In some patients with IBS, there is an association with a postinfective state. In constipation, transit disorders and abnormal evacuation represent disturbances of function that are amenable to therapy. This review is an update of the mechanisms and pathophysiology of these disorders. IBS and constipation are defined, and control of gut motility and sensation and their disturbances in these disorders are reviewed along with the mechanisms and pathophysiology of IBS and constipation. (Adv Stud Med. 2005;5(10B):S955-S964)

Functional gastrointestinal (GI) disorders are defined as collections of functional symptoms that are not attributable to structural, mucosal, or biochemical diseases of the GI tract. Symptoms include indigestion, abdominal pain, bloating, distension, and symptoms of disordered defecation. The most common functional bowel disorders are functional dyspepsia, irritable bowel syndrome (IBS), and chronic constipation. These are biopsychosocial disorders in which psychosocial factors, prior gastroenteritis, abnormal motility, gas retention, and heightened sensation interact to induce symptoms.

IBS is the most common functional bowel disorder and is characterized by chronic or recurrent symptoms that are thought to arise in the small bowel or colon. Symptoms have been embodied in the Manning4 or Rome II1,2 criteria and include lower abdominal pain related to bowel movements, changing bowel habit (eg, diarrhea, constipation, or alternating between the two), abdominal bloating, a sense of incomplete rectal evacuation, and passage of mucus.

Constipation is variably defined, but usually refers to persistent difficult, infrequent, or seemingly incomplete defecation. Diagnosis often is arbitrary and may depend on the patient’s perception of what is abnormal. The prevalence of constipation depends on the definition and the population studied. Individual patients’ symptoms must be analyzed in detail to ascertain what is meant by “constipation” or “difficulty” with defecation (Figure 1). Patients also may perceive incorrectly that they are constipated. When formally evaluated via daily diary during a 4-week period, only 20 out of 44 patients who perceived they were constipated had reduced stool frequency (ie, <3 bowel movements per week). The perception of hard stools or excessive straining is more difficult to assess objectively, though instruments such as the Bristol Stool Form Scale may be helpful. The need for enemas or digital disimpaction is a clinically useful marker to corroborate the patient’s perceptions of difficult defecation.

PATHOPHYSIOLOGY AND MECHANISMS IN IRRITABLE BOWEL SYNDROME

In addition to classical concepts of the pathophysiology of IBS, this section addresses current understanding of the role of inflammation in IBS and the potential of novel mechanisms, serotonin, genetics, and intraluminal
factors. Intrinsic and extrinsic neural influences modulate the motor and sensory functions of the gut (Figure 2).

**CLASSICAL PATHOPHYSIOLOGY**

The pivotal mechanisms involved in the pathophysiology of IBS are altered psychosocial function, motility, and hypersensitivity. Psychosocial aspects are important determinants of the emotional response to visceral stimulation, and they influence the time to presentation as well as the severity of disease—and provide the rationale for treatment with antidepressants and other behavioral approaches.

Important motor dysfunctions include prominent symptoms and colonic contractions after feeding in diarrhea-predominant IBS (D-IBS) and poor colonic response in constipation-predominant IBS (C-IBS) or functional constipation associated with slow transit. Disturbances of transit profiles reflect the predominant bowel dysfunction, and gas transit also is demonstrable experimentally and is related to bloating sensation. An associated evacuation disorder (eg, puborectalis spasm) may result in an overlap with symptoms of C-IBS. Epidemiologic studies document overlap with upper functional disease, specifically dyspepsia or upper abdominal pain, which occurred in 80% of IBS patients in one study.

Overlap of IBS with celiac disease may merely reflect the concurrence of 2 relatively common disorders in the same person and the limited repertoire of symptoms of diverse gut disorders. Screening for celiac disease is important in susceptible populations; however, population-based studies in a community with a predominant northern European extraction suggest that serologic screening does not identify significant numbers of patients with celiac disease among individuals with IBS and dyspepsia.

Visceral hypersensitivity and hyperalgesia are well documented in IBS, and the rectal sensory threshold for pain of 32 mm Hg has relatively high sensitivity and specificity for identifying hypersensitivity. The increased activation of the limbic or emotional motor system in IBS patients during rectal distension has been confirmed in several studies.

**DOES INFLAMMATION PLAY A KEY ROLE IN IRRITABLE BOWEL SYNDROME?**

Several lines of evidence address this question. First, epidemiologic studies suggest an association between inflammation as a result of earlier infection and...
the persistence of IBS symptoms. The interdependence of prior infection and psychologic status also has been consistently documented, and may raise questions as to the role of persistent inflammation as an independent risk factor. Alternatively, the data are interpreted as evidence of the importance of psychoneuroimmune interactions; it is unclear whether inflammation is a common final pathway to nonspecific psychologic influence on gut function and the prior infection potentially unrelated, other than as an initiator of the cascade of events. However, a summary of the epidemiology data also shows that the prevalence of postinfectious IBS (PI-IBS) is no higher than IBS in the general population.

In addition, several studies have documented increased numbers of CD3, CD25, or mast cells in ileal, colonic, or rectal biopsy specimens, but the differences in lymphocyte counts between controls and IBS are small, with predominant overlap in the counts between the 2 conditions. A few outliers seem to be exceptions, and it is unclear whether these higher immune cell counts have functional significance (eg, influence sensitivity or permeability).

Differences in ileal mast cell numbers between IBS and controls appear to be more substantial and consistent, and there is now evidence of functional correlates in the significant association between mast cells in close proximity to nerves and severity and frequency of abdominal pain. Nevertheless, it is significant that only 1 of 5 markers of mast cell morphology was associated with IBS, sample size was small, and the correlation is influenced by the fact that 3 out of 13 patients with IBS had no pain (which, based on current criteria, raises the question of whether they indeed had IBS).

The third line of evidence to be examined is the response of IBS to anti-inflammatory treatment. A controlled trial has shown that, among carefully selected patients with PI-IBS, a 30-mg dose of prednisone taken twice daily was not significantly better than placebo and that, whereas placebo resulted in the customary significant 30% change in median symptom score relative to baseline, no change in score was noted in the prednisone treatment group. Controlled studies with other anti-inflammatory agents are needed.

**NEW MECHANISTIC INSIGHTS IN IRRITABLE BOWEL SYNDROME**

**WHAT IS THE ROLE OF SEROTONIN?**

Some have suggested that IBS is a disorder of serotonin, quoting recent evidence that modulation of serotonergic mechanisms significantly impacts the manifestations of IBS. In some respects, this is a borrowed concept, as serotonin is a key player in the secretion and dysmotility of the carcinoid syndrome, in which 5-hydroxytryptamines (5-HT3) antagonists reduce the colonic response to feeding, diarrhea, and the need for rescue anti diarrheal agents. There are other more direct lines of evidence to address the potential role of serotonin. First, plasma 5-HT levels are elevated in patients with IBS. Postmeal symptoms can be prominent in IBS patients, and Houghton et al attempted to correlate postprandial symptoms and increased plasma 5-HT. However, it appears that the peak in plasma 5-HT levels does not coincide with the time (60 to 90 minutes after a meal) at which patients with IBS typically experience pain, diarrhea, and urgency.

Second, enteroendocrine cells in rectal biopsies of PI-IBS patients show significantly increased numbers of 5-HT–containing cells. These quantitative differences were more impressive in one study than in a subsequent study from Spiller’s group; and overlap with numbers in disease control groups or non–PI-IBS suggests that prior infection may not be a key factor.

A third line of study assessed factors involved in the control of 5-HT in IBS via examination of mucosal biopsy specimens from patients with IBS, healthy patients without IBS, and disease controls (who had ulcerative colitis). Coates et al showed that the number of enteroendocrine E cells containing 5-HT was normal, in contrast to other studies, and the release of 5-HT from mucosal biopsy specimens under baseline conditions or in response to stimulation was normal. However, the mucosal content of the 5-HT reuptake protein, serotonin transporter (SERT), was reduced, as shown by SERT messenger RNA content and immunohistochemistry. These changes paralleled the findings in nonsevere ulcerative colitis, and it is unlikely that the diarrhea itself induced the changes, because results were similar in D-IBS and C-IBS. The mechanisms causing these changes and their functional importance remain the subject of continued research. Certainly, differences in SERT function appear to influence the response to therapy in IBS, and further studies are forthcoming.

Fourth, serotonergic agents, including 5-HT3 antagonists and 5-HT4 agonists, are effective in the treatment of multiple symptoms of IBS.
WHAT IS THE ROLE OF GENETICS IN IRRITABLE BOWEL SYNDROME?

Three lines of evidence suggest there may be a role for genetics in IBS, but the data are inconclusive at present. First, familial aggregation studies suggest that family members of individuals with IBS are more likely to suffer from IBS than are their spouse controls.\(^{51,52}\)

Second, twin studies also document a difference between risk of IBS in monozygotic twins compared with dizygotic twins\(^{53,54}\); however, the fact that mothers of mono- and dizygotic twins have similar prevalence of IBS suggests that heredity and social learning or other environmental factors interact as risk factors in development of IBS. One study from the United Kingdom did not confirm increased IBS prevalence in twins.\(^{55}\)

Third, genetic epidemiology studies provide some evidence of a genetic association in IBS. However, these data are to be viewed as preliminary and the pitfalls of such association studies, which may be underpowered, should be kept in mind.

Fewer IBS patients have high interleukin (IL)-10 producer (G/G) genotype than do controls.\(^{56}\) Reduced IL-10 production in these patients may lead to an inability to down-regulate inflammation, which may be a factor in the development of IBS.

Holtmann et al have shown that a polymorphism in the gene for the G protein involved in mediating the effects of several neurotransmitters and hormones, G-protein β subunit gene (GNβ3 C825T) genotype, is significantly associated with the report of dyspepsia and, to a lesser extent, IBS in patients presenting to a clinic in Germany.\(^{57}\)

Adrenergic and serotonergic genotypes were investigated in 276 IBS patients and 120 community controls. A 44-base pair deletion in the gene for the promoter for SERT (SERT-P) previously has been shown to influence the function of the SERT protein produced.\(^{58}\) Thus, the wild-type L/L polymorphism results in normal function, whereas the presence of the short allele (S/L or S/S) results in impaired function.\(^{58}\) Kim et al\(^{59}\) showed in 90 C-IBS patients a significant association with α2A adrenoceptor polymorphism, and the combination of the α2 adrenoceptor and SERT-P polymorphism was associated with high somatic scores in patients with lower functional GI disorders (FGIDs). SERT-P alone was not a risk factor for D-IBS in the Mayo Clinic study,\(^{60}\) and a summary of studies to date\(^{61}\) suggests there is no significant association with IBS or its subtypes in studies from North America and Korea.\(^{62,63}\) A positive association with D-IBS in Turkey\(^{64}\) should be viewed with caution, given the ethnic differences in the genetic distribution of the polymorphism and the small sample studied (n=18). In summary, the reduced mucosal SERT in C-IBS and D-IBS observed by Coates et al\(^{65}\) does not appear to be genetically determined, based on reports in the literature to date.

“IRRITATED BOWEL” SYNDROME

Changes in the intraluminal milieu may result in symptoms that may be alleviated by treatments directed at the intraluminal factors.

Symptom overlap exists between idiopathic bile acid catharsis and rapid ideal transit that results in failure of bile acid absorption. Bile salt retention is reduced in patients who have functional diarrhea with or without associated pain.\(^ {66}\) Patients with IBS show higher intestinal secretion in response to perfused bile acids in the ileum, compared with controls.\(^ {55}\) Retarding transit with loperamide reduces the risk of bile salt loss.\(^ {66}\) It therefore is not surprising that bile salt binding with cholestyramine may be effective in the treatment of IBS with diarrhea.

Perfusion of the mammalian or human colon with di-α-hydroxy bile acids such as chenodeoxycholic acid or short-chain fatty acids results in high-amplitude propagated contractions or rapid transit in a healthy colon.\(^ {67-70}\) Studies have not been conducted in IBS patients. However, the relatively low concentrations of bile acid (1 mmol/L) required to induce highly propulsive propagated sequences\(^ {71}\) suggest that relatively modest levels of malabsorption may be sufficient to perturb colonic motility. The concentrations of long-chain fatty acids (eg, oleic acid) required to accelerate colon transit are relatively high, but certainly would be in the range associated with moderate fat malabsorption.\(^ {72}\) Such colonic concentrations of longer-chain fatty acids are unlikely to be achieved in patients with IBS, although formal studies with long- and short-chain fatty acids are required.

DOES A CHANGE IN INTRALUMINAL MILIEU OR BACTERIAL ECOCASY IN THE INTESTINE IMPROVE BOWEL FUNCTION AND SYMPTOMS OF IRRITABLE BOWEL SYNDROME?

Small studies suggest that probiotics or antibiotics aimed at changing bacterial counts may indeed alter symptoms, although the mechanism is still unclear. Nobaek et al showed that alteration of intestinal microflora via probiotics was associated with reduction in abdominal bloating and pain in patients with IBS.\(^ {72}\)
Similarly, Kim et al showed that, in patients with IBS, the combination probiotic, VSL#3, resulted in improvement of the symptoms of bloating and flatulence in 2 separate studies, but there was no other symptom or global relief. In the second study, there was a slight, but significant retardation of colonic transit without significant alteration of bowel function. Quigley et al have preliminarily reported a benefit with *Bifidobacteria* but not with *Lactobacillus*-containing probiotics. This benefit was associated with restoration of normal IL-10/IL-12 ratios in plasma, suggesting that the probiotic normalized immune function in these patients.

Finally, change in the bacterial ecology with the non-absorbable antibiotic, neomycin, results in short-term improvement in the composite score for IBS and bowel dysfunction. These effects were observed in a 7-day trial. Interestingly, patients whose lactulose-hydrogen breath test normalized had greater improvement than those with no response in breath hydrogen. The author’s interpretation is that this represents an effect on bacterial overgrowth in the small bowel in IBS. Whereas this interpretation may be questioned and longer-term studies and outcomes of treatment with bacterial modification need to be evaluated, the role of the intestinal milieu and the effects of bacteria and endogenous factors such as bile acids and fatty acids in the mechanisms and treatment of IBS deserve further study.

Although there is increasing evidence that IBS represents an enteric neurologic disorder that alters bowel sensation, secretion, and motility, it is important to continue to study inflammation and the potential for intraluminal factors resulting in dysregulation of those functions. Central mechanisms may enhance visceral sensation or the interpretation of ascending visceral signals as unpleasant because of the disturbances in the limbic system, which is involved in the affective response to pain. At this time, the role of genetics is uncertain. These data suggest that therapies should continue to be directed at these pathophysiologic mechanisms in the gut and central control. However, it is conceivable that further understanding of the bowel ecology in health and disease may open new avenues for treatment of IBS.

**CHRONIC CONSTIPATION**

Constipation is a common symptom affecting between 2% and 27% of the population in Western countries and between 10% and 15% in the United States. In the United States, it results in more than 2.5 million visits to physicians, 92,000 hospitalizations, and laxative sales of several hundred million dollars a year. Constipation is more prevalent in women than in men, in nonwhite than in white persons, in children than in adults, and in older than in younger adults. Severe constipation (eg, bowel movements only twice a month) is seen almost exclusively in women. Physical inactivity, low income, limited education, a history of sexual abuse, and symptoms of depression all are risk factors for constipation.

There is no single definition of constipation. Most patients define constipation as having 1 or more of the following symptoms: hard stools, infrequent stools (typically fewer than 3 per week), the need for excessive straining, a sense of incomplete bowel evacuation, and excessive time spent on the toilet or in unsuccessful defecation. An epidemiologic study of constipation in the United States identified the condition as an inability to evacuate stool completely and spontaneously 3 or more times per week. A consensus definition of constipation (the Rome II criteria) used in current research is provided in Table 1.

**CAUSES AND PATHOPHYSIOLOGY**

Constipation frequently is multifactorial and can result from systemic or neurologic disorders or medications. Constipation can be classified into 3 broad categories: normal-transit constipation, slow-transit constipation, and disorders of defecatory or rectal evacuation. More than 1 mechanism may contribute to constipation. In a study of more than 1000 patients with chronic constipation (CC), normal transit through the colon was the most prevalent form (occurring in 59% of patients), followed by defecatory disorders (25%), slow transit (13%), and a combination of defecatory disorders and slow transit (3%).

**NORMAL-TRANSIT CONSTIPATION**

Normal-transit constipation (or “functional” constipation) is the most common form of constipation that clinicians see. In patients with this disorder, stool traverses at a normal rate through the colon and the stool frequency is normal, yet patients believe they are constipated. In this group of patients, constipation is likely to be the result of a perceived difficulty with evacuation or the presence of hard stools. Patients may experience bloating and abdominal pain or discomfort, and they may exhibit increased psychosocial distress; some may have increased rectal compliance, reduced rectal sensa-
tion, or both. Symptoms of constipation typically respond to therapy with dietary fiber alone or with the addition of an osmotic laxative.

Lack of a response to these therapies may reflect a disturbance of evacuation or transit that requires further management.

DEFECATORY DISORDERS

Defecatory disorders are most commonly the result of dysfunction of the pelvic floor or anal sphincter. Other terms used to describe defecatory disorders include anismus; pelvic-floor dyssynergia; paradoxical pelvic-floor contraction; obstructed constipation; functional rectosigmoid obstruction; the spastic pelvic floor syndrome; and functional fecal retention in childhood. Functional fecal retention in children may result in secondary encopresis as a result of leakage of liquid stool around impacted stool, which can lead to an initial misdiagnosis of diarrhea. Prolonged avoidance of the pain associated with either the passage of a large, hard stool or an anal fissure or hemorrhoid may result in defecatory disorders. Structural abnormalities, such as rectal intussusception, rectocele, obstructing sigmoidocele, and excessive perineal descent, are less common causes of defecatory disorders. Some patients with defecatory disorders have a history of sexual or physical abuse or an eating disorder. Failure of the rectum to empty effectively may be the result of an inability to coordinate the abdominal, rectoanal, and pelvic-floor muscles during defecation.

These dysfunctions can be identified clinically and with the use of defecography as reduced descent of the perineum (less than 1 cm) and a reduced change in the anorectal angle (usually less than 15 degrees) during simulation of straining to defecate (Table 2). Ignoring or suppressing the urge to defecate may contribute to the development of mild constipation before the evacuation disorder becomes severe.

SLOW-TRANSIT CONSTIPATION

Slow-transit constipation occurs most

### Table 1. Rome II Criteria for Constipation*

<table>
<thead>
<tr>
<th>Adults</th>
<th>Infants and Children</th>
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<td>2 or more of the following for at least 12 weeks (not necessarily consecutive) in the preceding 12 months:</td>
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<td>• Straining during &gt;25% of bowel movements</td>
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<tr>
<td>• Lumpy or hard stools for &gt;25% of bowel movements</td>
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<tr>
<td>• Sensation of incomplete evacuation for &gt;25% of bowel movements</td>
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<tr>
<td>• Sensation of anorectal blockage for &gt;25% of bowel movements</td>
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<tr>
<td>• Manual maneuvers to facilitate &gt;25% of bowel movements (eg, digital evacuation or support of the pelvic floor)</td>
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<tr>
<td>• &lt;3 bowel movements per week</td>
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<tr>
<td>• Loose stools not present, and insufficient criteria for IBS</td>
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**Infants and Children**

- Pebble-like, hard stools for a majority of bowel movements for at least 2 weeks
- Firm stools <2 times per week for at least 2 weeks
- No evidence of structural, endocrine, or metabolic disease


### Table 2. Diagnostic Findings in Patients With Defecatory Disorders

#### History

- Prolonged straining to expel stool
- Unusual postures on the toilet to facilitate stool expulsion
- Support of the perineum, digitation of rectum, or posterior vaginal pressure to facilitate rectal emptying
- Sensation of incomplete evacuation for >25% of bowel movements
- Manual maneuvers to facilitate >25% of bowel movements (eg, digital evacuation or support of the pelvic floor)
- <3 bowel movements per week
- Loose stools not present, and insufficient criteria for IBS

#### Rectal examination (with patient in left lateral position)

- Anus pulled forward while the patient is bearing down
- Anal verge descends <1.0 cm or >3.5 cm (or beyond the ischial tuberosities) while the patient is bearing down
- Perineum balloons down while the patient is bearing down, and rectal mucosa partially prolapses through anal canal
- Palpation
- High anal-sphincter tone at rest
- Anal-sphincter pressure during voluntary contraction is only slightly higher than tone at rest
- Perineum and examining finger descend <1.0 cm or >3.5 cm while patient simulates straining during defecation
- Puborectalis muscle is tender on palpation through the rectal wall posteriorly, or palpation produces pain
- Palpable mucosal prolapse during straining
- Defect in anterior wall of the rectum, suggestive of rectocele

#### Anorectal manometry and balloon expulsion (with patient in left lateral position)

- Average tone of anal sphincter at rest, >80 cm water (or >60 mm Hg)
- Average pressure of anal sphincter during contraction, >240 cm water (or >180 mm Hg)
- Failure to expel balloon

commonly in young women who have infrequent bowel movements (1 or fewer per week). Often, this condition begins in puberty. Associated symptoms are an infrequent urge to defecate, bloating, and abdominal pain or discomfort. In patients with a minimal delay in colonic transit, dietary and cultural factors contribute to symptoms. In these patients, a high-fiber diet may increase stool weight, decrease colon-transit time, and relieve constipation. Patients with more severe slow-transit constipation have a poor response to dietary fiber and laxatives. Such patients have more delayed emptying of the proximal colon and fewer high-amplitude peristaltic contractions after meals, which normally induce movement of content through the colon. Colonic inertia, a related condition, is characterized by slow colonic transit and the lack of an increase in motor activity after meals or after the administration of bisacodyl, cholinergic agents, or anticholinesterases such as neostigmine.

Histopathologic studies in patients with slow-transit constipation have shown alterations in the number of myenteric plexus neurons expressing the excitatory neurotransmitter, substance P, abnormalities in the inhibitory transmitters, vasoactive intestinal peptide, and nitric oxide, and a reduction in the number of interstitial cells of Cajal, which are thought to regulate gastrointestinal motility (Figures 3 and 4).

Hirschsprung’s disease is an extreme form of slow-transit constipation with similar enteric neuropathologic features. In Hirschsprung’s disease, ganglion cells in the distal bowel are absent, a result of an arrest in the caudal migration of neural-crest cells through the gut during embryonic development; and the bowel narrows at the area that lacks ganglion cells. Though most patients with this disorder present in infancy or early childhood, some patients with a relatively short segment of involved colon do not show symptoms until later in life. Hirschsprung’s disease is associated with mutations in the RET proto-oncogene or the gene for the endothelin-B receptor.

The role of colonic absorption of fluids and electrolytes in the etiopathogenesis of constipation is unclear. Sodium-hydrogen and sodium-potassium exchanges occur in the proximal and distal colon under mineralo-
corticoid control; however, there appear to be no reports of disturbances in these exchanges or the related aquaporins in common constipation disorders. On the other hand, fluid and electrolyte handling in the colon is extremely important in determining stool consistency. The colon has a vast capacity to reabsorb water and electrolytes.\(^{39,100}\) Conversely, patients with constipation tend to benefit from fiber, osmotic laxatives, stool softeners, and stimulant laxatives (eg, bisacodyl). In disease states such as carcinoid diarrhea, small intestinal secretion may contribute to the accelerated emptying of the proximal colon.\(^{40}\) The induction of small intestinal secretion via osmotic or pharmacologic agents appears to result in acceleration of small bowel or colonic transit, such as with lactulose\(^{101}\) or lubiprostone, a novel chloride channel activator.\(^{102}\) This combination of secretion and accelerated transit is associated with relief of chronic constipation.\(^{106}\)

**CONCLUSION**

IBS and constipation are commonly encountered clinical disorders; their pathophysiology and mechanisms are more clearly understood, and novel treatments based on this greater understanding will lead to optimized treatment.

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