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The Brain-Gut Axis: From Basic Understanding to Treatment of Irritable Bowel Syndrome and Related Disorders

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Introduction

The objectives of this review are to describe advances in understanding the mechanisms, and provide an update of current and promising therapy directed at the gut or the brain in the treatment of irritable bowel syndrome (IBS).

The diagnosis of IBS is typically based on identification of symptoms, such as the Rome III criteria for IBS in adults and children (1,2). The criteria are similar in children and adults (Table 1). The focus of this review is the bowel dysfunction associated with IBS. Therefore, readers interested in treatment of functional abdominal pain (FAP) syndrome are referred to a recent review (3); there are no recently approved drugs for the treatment of FAP.

Pathophysiology

There are three main pathophysiological mechanisms associated with IBS (4): psychosocial factors, altered motility and altered sensation. In addition, research in the last decade has identified other factors that contribute to the development of the syndrome, including prior gastroenteritis, genetics, luminal irritants, changes in the microbial flora, mucosal inflammation or local immune activation, disorders of evacuation of stool or gas, and certain transmitters and transporters, such as serotonin. These mechanisms are reviewed extensively elsewhere (4–7). The bidirectional communication and neuroanatomical regions involved between the brain and the gut are illustrated in Figure 1 from a recent review by Mayer and Tillisch (7), to which the reader is referred for in depth analysis of the brain-gut axis in abdominal pain syndromes.

Whereas visceral hypersensitivity was considered a potential biological marker of IBS (8), results from several centers (9–13) have not replicated the 95% prevalence of rectal hypersensitivity or hyperalgesia in the original report, and the range is as low as 21%, and rectal hyposensitivity has even been reported in adults. In addition, the interpretation of original reports that suggested activation of the prefrontal cortex and the anterior cingulate cortex in IBS (14) and visceral pain is complex, since several other centers of activation and

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deactivation are described (15) and because of appreciation that differences in regional gray matter density in the brain may reflect anxiety or depression (e.g. prefrontal cortex) and that the cognitive/evaluative centers are apparently more specific for IBS (16).

Rectal hypersensitivity in children with IBS has been reported by at least 4 centers (17–20). It was noted that a rectal sensory threshold for pain of 30mmHg had a sensitivity rate of 89% and a specificity rate of 83% for diagnosis of IBS and that children with IBS had abnormal pain referral after rectal distension (19). However, Vlieger et al. observed only 23% with rectal hypersensitivity among children with functional abdominal pain or IBS, and there were no significant differences in sensation thresholds in IBS and FAP (21). It has also been reported that “emotional instability”, a highly prevalent personality characteristic of children with IBS, seems to modulate the perception response to visceral stimulations (20). Brain imaging studies are still in their infancy in pediatrics, and no information is currently available about central nervous system activation in children with IBS.

Altered motor function of the colon and the pelvic floor is increasingly recognized in patients with IBS and related symptoms. For example, 48% of adults with diarrhea-predominant IBD (IBS-D) and about 20% of those with constipation-predominant IBS (IBS-C) had accelerated or slow colonic transit respectively (13), and there are increased numbers of postprandial colonic high amplitude colonic contractions that are associated with colonic mass movements in patients with IBS-D (22,23). Children with IBS were found to have a disturbed rectal contractile response to a meal (17). A valid noninvasive transit test goes a long way in identifying these disturbances of colonic motility. One such test is the radiopaque marker transit Metcalf method (24); using this protocol, about one-third of adults with unexplained chronic constipation or chronic diarrhea had demonstrably abnormal transit (25). Among children, the method of Bouchoucha et al. is often preferred (26). A single abdominal radiograph is taken following six successive daily ingestions of the same number of identical radiopaque markers (26).

Such a simple, noninvasive, inexpensive test has the potential to guide treatment by selecting for pharmacotherapy those patients who have abnormal transit. Even among children with constipation, 50% have colonic transit time within the normal range (27). Colonic transit measurement may also identify the predominant bowel dysfunction (13) in adult patients with alternating bowel function (IBS-M); in one study, colonic transit by scintigraphy demonstrated that patients presenting with IBS-M had significantly accelerated transit at 48 hours, relative to healthy controls.

Differential Diagnosis of IBS

There are several commonly encountered conditions that mimic IBS; indeed, the symptoms of IBS are not specific (28). In addition to exclusion of mucosal disease and malignancy, especially in older patients or in those with recent onset symptoms or presence of alarm symptoms (such as rectal bleeding or weight loss), several benign conditions need to be sought in the appropriate clinical setting, as their diagnosis leads to specific and effective therapies.

The *conditions that mimic IBS-D* include: sugar maldigestion (such as lactase and sucrase-isomaltase deficiency), celiac disease, gluten intolerance without celiac disease, pancreatic exocrine insufficiency, small bowel bacterial overgrowth, microscopic colitis, and bile acid malabsorption (BAM). There seems to be evidence that, among these, BAM appears to be the most prevalent, with an estimated 25% of patients with chronic, otherwise unexplained diarrhea being attributable to BAM (29).

Two recent advances have provided information about the mechanisms associated with alterations in bile acid synthesis that result in chronic diarrhea or accelerated colonic transit in some patients with IBS-D. First, there is a deficiency in the synthesis of the hormone fibroblast-growth factor 19 [FGF-19 (30)]. Normally, the enterohepatic circulation of bile acids (BA) down-regulates BA biosynthesis. Bile acids traversing the ileal enterocyte activate farnesoid X receptor (FXR), the nuclear receptor for bile acids. FXR activation promotes the synthesis of FGF-19, a protein that exits the ileal enterocyte and travels to the liver in the portal blood. FGF-19 interacts with the dimeric receptor fibroblast-growth factor receptor 4 (FGF-R4)/Klotho- β on basolateral surface of hepatocytes. The activated receptor initiates a phosphorylation cascade that represses the gene encoding cholesterol 7- α hydroxylase, the rate-limiting enzyme in BA biosynthesis. In patients with idiopathic BAM, ileal bile acid transport is unimpaired. FGF-19 release from the ileal enterocyte is impaired for unknown reasons, leading to increased hepatic BA biosynthesis that, in turn, causes diarrhea (31). A second mechanism is a genetic variation in the hepatocyte receptor protein Klotho- β , to which FGF-19 binds (32). A functional genetic variation in the Klotho- β gene that results in impaired protein synthesis ultimately prevents FGF-19 binding to the combined Klotho- β -FGFR4 receptor on the hepatocyte, and this reduces the FGF-19 feedback inhibition of hepatocyte synthesis of bile acids, resulting in more bile acids reaching the bowel and potentially causing diarrhea.

The main *conditions that mimic IBS-C* in adults include the rectal evacuation disorders: anismus, pelvic floor dyssynergia or puborectalis spasm, and descending perineum syndrome (33). In children, functional constipation is the main condition which presents with symptoms overlapping IBS-C. Among adults, the current consensus criteria for IBS, functional constipation and rectal evacuation disorders cannot distinguish these conditions (34); for example, Prott et al. identified several features suggestive of pelvic floor dyssynergia among patients with non-diarrhea IBS (35). Therefore, it is therefore essential to screen for symptoms of evacuation disorder (e.g. excessive straining, anal or vaginal digitation to facilitate defecation in adults, overflow incontinence in children), and to perform appropriate testing to exclude these eminently treatable conditions (33). It is important to note that, in adults, symptoms attributable to IBS such as abdominal pain and bloating respond very well to pelvic floor re-training for evacuation disorders (36). Evidence of benefit for biofeedback therapy in children with IBS or evacuation disorder remains elusive (37).

Abdominal bloating in IBS may be a manifestation of sugar maldigestion or celiac disease; however, it may also result from the types of evacuation disorders described above (38). A classical clinical feature of patients with evacuation disorder causing bloating is that the distension gets worse throughout the day, with visible distension by the evening, and the abdomen is reported to be flat on awakening the following morning. Studies with a device called a bloatermeter (39) have shown that such patients evacuate gas during sleep reducing the abdominal girth by morning.

What is the Role of Immune Activation and Barrier Function in IBS?

Ohman and Simren have summarized a vast literature documenting the evidence in support of inflammation or immune activation in intestinal or colonic mucosa, as well as in circulating blood in at least some subsets of patients with IBS (40). These data, in addition to the clinical observation of post-infectious IBS, overall support a role of immune activation and altered bowel barrier function in a subgroup of IBS patients. Support for this overall hypothesis is also provided from studies of the interaction between the host and genetic factors (41) that determine responses, and intraluminal dietary factors, endogenous irritants and the microbiome.

These are a few pertinent examples from this vast literature:

- a. Genetic susceptibility to inflammation: Among 30 Crohn's disease susceptibility loci (42) that are associated with epithelial transport, barrier function, bacterial recognition, autophagy, prostaglandin production, and Th17 lymphocyte differentiation, Zucchelli et al. identified statistically significant association between *TNFSF15* and IBS phenotype in separate populations of Swedish and American patients (43). Villani et al. (44) reported 4 genes associated with post-infectious IBS patients in Walkerton, Ontario, and these susceptibility loci included *TLR9*. Camilleri et al. identified univariate associations between 4 genes that also included *TLR9* and colonic transit in patients with IBS (45).
- b. Wahnschaffe et al. (46) reported that patients with IBS who carried the HLA-DQ2 or 8 genotype were five times as likely to respond to gluten withdrawal as those who were not carriers.
- c. Kassinen et al. (47) and Malinen et al. (48) reported qualitative differences in fecal microflora in patients with IBS.

Spiller et al. (49) showed that patients with IBS with increased T lymphocytes in rectal mucosa had evidence of increased colonic mucosal permeability. Several other studies have documented increased small bowel and/or colonic mucosal permeability in vivo, or in mucosal biopsies in vitro; moreover, fecal supernatants from patients with IBS increase the permeability of Caco2 monolayers. The adult literature on the alterations in permeability in IBS has been reviewed by Rao et al. (50). Shulman et al. demonstrated that children with IBS have evidence of increased proximal gut and colonic permeability and low-grade inflammation (51). Saps et al. have reported a variety of early childhood inflammatory conditions are associated with the development of several functional GI disorders later in childhood, including IBS (52–55).

What Is in the Arsenal, Specifically for IBS? What Actually Works?

Several treatments have been sanctioned for the treatment of IBS in adults on the basis of expert opinion, predominantly as a result of systematic reviews and meta-analyses (56). These include fiber, smooth muscle relaxants, peppermint oil, antidepressants, probiotics, alosetron, behavioral therapy and hypnotherapy (57,58). For several of these classes of treatments (e.g. antidepressants and peppermint oil), the number needed to treat is ~4. Some meta-analyses are also reported to demonstrate funnel plot asymmetry suggestive of publication bias. Although all of these medications are used and many are endorsed in national guidelines, a critical analysis (59) has shown that the evidence of efficacy of these different classes of approved or available drugs, including antispasmodics and antidepressants, is weak. The reader is referred to the analysis of Camilleri and Mayer for an in-depth analysis of efficacy and meta-analyses that suggest efficacy of the available medications (59).

In adults and children (60) with IBS, there is a proportion of patients who respond to placebo; the proportion of responders to placebo and active treatment in phase III trials depends on the stringency and the nature of the endpoint. Placebos administered without deception may also be effective in the treatment of IBS (61).

The pediatric trials regarding the use of antidepressants are conflicting, with one study showing a mild benefit (62) Possible mtg. w/Ryan Mc Clellan/Takeda) and one showing equivalency to placebo (63). A Cochrane review concluded that amitriptyline does not appear to provide any benefit for the treatment of functional GI disorders in children and adolescents (64). Among trials of behavioral and psychotherapy, one study in adults showed

significant benefit relative to waiting-list control of a more cost-effective 4-session, patient-administered cognitive behavioral therapy that is as efficacious as 10 sessions with a therapist (65). Pediatric data suggest that hypnotherapy is a very effective intervention for children with IBS (66). Self administered audio-recorded guided imagery treatment also seemed to be helpful in reducing functional pain in children (67). A Cochrane review of the pediatric literature concluded that cognitive behavioral therapy may be a useful intervention in children with recurrent abdominal pain and IBS (68).

On the other hand, it also appears that in a meta-analysis of such therapies, efficacy is center-dependent and this highly specialized treatment may not be easily applied across centers. However, the inclusion of trials of different designs with different doses of medications, different mechanisms of action in the same class (e.g. SSRI and TCA antidepressants), and different sample sizes in individual trials raised questions as to whether the conclusions of these analyses were sufficiently robust to result in treatment guidelines (59). It has been proposed that meta-analyses should only be used for hypothesis generation (69).

Chloride secretagogues can drive intestinal secretion and with it cation and water secretion that loosen stool consistency and stimulate transit. The cellular mechanisms involved in chloride secretion are illustrated in Figure 2. The chloride channel opener, lubiprostone, is approved for the treatment of adult patients with IBS-C. Chloride ions are actively transported together with potassium and sodium ions through the basal domain of the enterocyte (70), and lubiprostone activated chloride secretion results in relief of constipation and relief of abdominal pain (71).

Although the 5-HT₃ antagonist, alosetron, is only available on a restricted prescription program because of concerns regarding the risks of significant constipation and ischemic colitis, the clinical trials indicate its consistent efficacy in males and females with IBS-D (72). Similar efficacy was demonstrated for the nonapproved cilansetron.

Rifaximin, a nonabsorbed antibiotic, is used off label in patients with IBS. Its efficacy was demonstrated in two large randomized, controlled trials (73); efficacy relative to placebo appears to persist for 8 weeks following cessation of treatment. Rifaximin has also been tested in children with chronic abdominal pain and abnormal lactulose breath test (LBT); treatment with 10 days of rifaximin has low efficacy in normalizing LBT in children (74).

Several meta-analyses also have evaluated the approximately two dozen individual trials of probiotics in adults. Conclusions in these analyses vary, but, in general, it has been claimed that *Bifidobacteria* or the mixture of *Escherichia coli* (DSM 17252) and *Enterococcus faecalis* (DSM 16440) are efficacious for treatment of abdominal pain in IBS, and probiotics in general appear to aid bloating and flatulence in IBS (75–80). Data in pediatrics are similarly heterogeneous, but there seems to be a benefit for the use of *Lactobacillus rhamnosus* GG and VSL#3 in children with pain-predominant functional GI disorders, especially in those with the phenotype of IBS-D (81,82).

Future Treatments of IBS

There is a rich pipeline of medications that are in development for the treatment of patients with lower functional gastrointestinal disorders (Table 2). So far, these agents have been tested only in adults, but, considering the similarities between IBS in adults and in children, there is no reason to believe that their efficacy will differ when used in pediatrics.

Novel 5-HT₃ Antagonist: Ramosetron

In experimental animal models, ramosetron inhibited stress or corticotrophin releasing factor-induced water secretion, accelerated colonic transit, and reduced stress-induced colonic nociception. Two randomized, controlled trials (83,84) in patients with IBS-D assessed the efficacy of 5 and 10µg once daily, or 5µg once daily. In the first trial, a global relief of IBS symptoms was achieved more frequently with ramosetron than with placebo. In the second trial, 5µg once daily compared to placebo was effective and well tolerated in the treatment of abdominal pain, discomfort and bowel habits. The safety profile of ramosetron relative to ischemic colitis needs to be carefully assessed.

Tryptophan Hydroxylase Inhibitor: LX-1031

Given reports that IBS-D is associated with high circulating levels of serotonin, LX-1031, a long-acting inhibitor of 5-HT synthesis restricted to the gut [not acting on the brain 5-HT levels (85,86)], is being tested in non-constipation IBS. A first trial assessed 250 and 1000mg qid versus placebo for 28 days in a double-blind, randomized, controlled trial (87). LX-1031 (1000mg qid) was superior to placebo in global assessment of relief of pain/discomfort weekly for 2 of 4 weeks of treatment, and improved stool consistency. Correlation with reduction of urine 5-HIAA suggests that the proposed mechanism of action was achieved. This medication needs to be tested using more rigorous endpoints over 12-week trials.

New Generation 5-HT₄ Agonists

A new series of compounds in this class are being developed. The safety and efficacy of these agents have been reported in greater detail elsewhere (88). In summary, whereas 5-HT receptors may modify vascular function and the delayed rectifier potassium current in the heart leading to tachyarrhythmias, and these are considered to have been responsible for adverse events leading to withdrawal of cisapride (Ikr) and tegaserod (5-HT_{2B}, 5-HT₇), the new drugs in this class (e.g. prucalopride, velusetrag and ATI-7505) have proven great selectivity for the 5-HT₄ receptor over other receptors (e.g. 5-HT_{2B}, 5-HT₇) and channels (e.g. Ikr). In addition, safety has been demonstrated through thorough studies of their arrhythmogenic potential and effects on QTc interval.

The agent most thoroughly studied in this group is prucalopride which accelerated pan-gut and regional transit in patients with chronic constipation (89), relieved symptoms, and was associated with satisfactory symptom relief in patients with severe, chronic constipation who were treated over 12 weeks (90). Prucalopride is commercially available in several European countries. The approved and recommended doses are 2mg/day in adults and 1mg/day in the elderly (over 65 years). Prucalopride, like other 5-HT₄ agonists, is sometimes associated with headache as an adverse effect. The main adverse effects, reflecting prucalopride's pharmacological actions, are diarrhea, nausea and abdominal pain. Most of these adverse effects are confined to the first day of treatment, since excluding the first day experience shows that the incidence of these adverse effects is similar to placebo. Prucalopride is also efficacious in the elderly; testing in a sample of ~80 nursing home residents, most of whom were taking other medications for cardiovascular problems, proved safe (91). Open-label prucalopride treatment involving an estimated 1000 patient-years showed that satisfaction with bowel function is maintained for up to 18 months of treatment with prucalopride. Gastrointestinal events and headache have caused discontinuation of prucalopride treatment in ~5% of patients (92).

Velusetrag induced dose-related acceleration of gastric and colonic transit in healthy volunteers (93) and resulted in relief of chronic constipation over a 4-week trial (94).

Intestinal Secretagogues by Guanylate Cyclase-C Agonists

Guanylate cyclase-C receptors are located on the luminal aspect of the enterocytes. Endogenous ligands such as guanylin and uroguanylin secreted from goblet cells stimulate GC-C receptor, which is also the receptor responsible for the diarrheagenic effects of the *E. coli* heat stable enterotoxin (95). When the GC-C receptor is activated, intracellular cascades of messengers ultimately activate the cystic fibrosis transmembrane regulator (CFTR), resulting in secretion of Cl^- and HCO_3^- and water from enterocytes.

Two drugs that are GC-C agonists are in development. Linaclotide has been shown to accelerate colonic transit and improve stool consistency in patients with IBS-C (96). In several large phase IIB and III trials, linaclotide has been efficacious in relief of constipation, abdominal pain, discomfort and bloating (97–99), including in repeated treatment and 6-month efficacy and safety studies. The optimal linaclotide dose appears to be 266mcg/day.

A new GC-C agonist, plecanatide, has been tested in a 14-day trial in patients with chronic constipation and also appears to be promising (100).

Bile Acid Modulation

Diarrhea results from passage of increased concentrations of endogenous bile acids into the colon (101). The bile acid sequestrant, colestevlam, slowed colonic transit in patients with IBS-D (101). Conversely, administration of delayed-release chenodeoxycholate, 1g/day, to the colon of healthy volunteers (102) and patients with IBS-C (103) accelerated colonic transit, loosened stool consistency, and reduced straining over a short-term trial. An extension of this principle is to deliver more endogenous bile acids to the colon by inhibiting the ileal bile acid transporter (104). This agent has been tested in phase IIA and IIB trials in patients with chronic idiopathic constipation and functional constipation, and all studies provide concordant information: acceleration of colonic transit; increased stool frequency, and relief of symptoms associated with constipation such as discomfort and bloating (105–107). An additional potential benefit is that this medication reduced plasma cholesterol levels, as it likely depletes the bile salt pool when administered over a prolonged time (107).

Visceral Analgesic Therapy

Asimadoline is a kappa-opioid agonist that reduced colonic pain induced by balloon distension in healthy volunteers (108). In addition, it resulted in adequate relief of pain and discomfort in patients with IBS-D and IBS-A when it was administered consistently over a three-month period (109). It was ineffective when tested as an on-demand treatment for acute episodes of pain in IBS (110).

Pregabalin is an $\alpha\delta$ ligand that is approved for treatment of somatic pain due to fibromyalgia and painful diabetic neuropathy. It binds voltage-gated calcium channels, reducing depolarization associated with Ca^{2+} influx at the nerve terminals and reducing effects of transmitters such as glutamate, noradrenaline, substance P, and calcitonin gene related peptide [CGRP (111)]. A first study of the effects of pregabalin, 200mg tid, in IBS patients showed it increased sensation thresholds, but this was associated with significant changes in rectal compliance (112). More recently, pregabalin, 200mg, was shown to reduce gas and pain sensation ratings over 4 distension pressures in healthy subjects with no significant effect on colonic compliance, suggesting a direct effect on visceral sensory pathways (113).

Glucagon-like peptide 1 (GLP-1) inhibits small intestinal migrating motor complexes (114). The GLP-1 analog, ROSE-010, was administered subcutaneously during acute attacks of pain in IBS, and it increased the proportion of responders and reduced the time to meaningful pain relief (115). The main challenge to its use may be nausea, which is a known adverse effect of GLP-1 and its analogs.

Novel Neurokinin Antagonist

While the selective neurokinin (NK)-3 antagonist, talnetant, was not efficacious in IBS (116), a novel neurokinin 1,2,3 receptor antagonist, DNK333, has shown promise on the basis of two clinical trials conducted in 315 women with IBS-D (117). There was reduced IBS-related pain/discomfort, relief of global IBS-D symptoms, and reduced abdominal bloating (117).

N-methyl-D-aspartate (NMDA) Antagonist

A pharmacodynamic study shows that, when compared to the control diphenhydramine (50mg), the N-methyl-D-aspartate antagonist, dextromethorphan, 60mg, reduced temporal summation of second pain (called wind-up) in response to a series of heat pulses in the subset of patients with IBS who show this phenomenon (118,119).

Anti-inflammatory Therapy

Two approaches of anti-inflammatory therapy that have been addressed in clinic trials are mast cell stabilization and a 5-amino salicylate (5-ASA).

The **mast cell stabilizer, ketotifen**, decreased visceral hypersensitivity and improved intestinal symptoms and health-related quality of life in patients with IBS who had evidence of visceral hypersensitivity (120). It is unclear whether the effect was secondary to the mast cell stabilization by ketotifen or whether the lack of selectivity, including histamine (H1) receptor antagonism, remains to be elucidated.

The **5-ASA agent, mesalazine**, 800mg tid, compared to placebo for 8 weeks, significantly reduced rectal biopsy mast cells, circulating levels of IL-1 β , histamine and tryptase, and improved general well-being, but it did not affect specific IBS symptoms in a 20-patient, pilot study of IBS (121).

Conclusions

Advances in understanding of the pathophysiology and mechanisms associated with IBS have led to several promising treatments of IBS in adults and children. Well-structured, clinical trials conducted in children and adults are now needed to explore these promising treatments. As clinical trials in children have involved only few children, future studies warrant national or international collaborative studies.

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Abbreviations

GI gastrointestinal

IBS irritable bowel syndrome

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Figure 1.

Cortical modulation of homeostatic afferent input to the central nervous system. Prefrontal regions modulate activity in limbic and paralimbic regions, subregions of the anterior cingulate cortex, and hypothalamus, which in turn regulate activity of descending inhibitory and facilitatory descending pathways through the periaqueductal gray and pontomedullary nuclei. Activity in these corticolimbic pontine networks mediates the effect of cognitions and emotions on the perception of homeostatic feelings, including visceral pain and discomfort. Reproduced from ref. 7, Mayer and Tillisch. *Annu Rev Med* 2011;62:381–96.

Figure 2.

Cl^- transport in intestinal epithelial cells. At the basolateral membrane, Cl^- enters the cell from blood across the $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter. Na^+ is expelled by the Na^+ pump, and K^+ leaves via a K^+ channel. Na^+ is shown crossing the cell layer via a paracellular pathway, but Na^+ channels also exist (not shown). Both cystic fibrosis transmembrane regulator (CFTR) and CIC-2 Cl^- channels are present on the apical membrane and can allow Cl^- to exit the cell. Reproduced from ref. 122, Cuppoletti J, Malinowska DH, Tewari KP, et al. SPI-0211 activates T84 cell chloride transport and recombinant human CIC-2 chloride currents. *Am J Physiol* 2004;287:C1173–83.

Table 1

Symptom Criteria for IBS in Adults [A (ref. #1)] and Children [B (ref. #2)]

A.	Recurrent abdominal pain or discomfort for at least 3 days per month in the last 3 months associated with 2 or more of the following:
1.	Improvement with defecation
2.	Onset associated with a change in frequency of stool
3.	Onset associated with a change in form (appearance) of stool
B.	Must include all of the following:
1.	Abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with 2 or more of the following at least 25% of the time:
a.	Improved with defecation
b.	Onset associated with a change in frequency of stool
c.	Onset associated with a change in form (appearance) of stool
2.	No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms

Table 2**Medications in Development for Treatment of Lower Functional Gastrointestinal Disorders**

New generation serotonergic agents
For IBS-D: ramosetron, LX-1031
For IBS-C: new generation 5-HT ₄ agonists
Secretagogues: guanylate cyclase C agonists: linaclotide, plecanatide
Bile acid modulation: IBAT inhibitor, A3309
Peripheral analgesic: asimadoline, pregabalin, GLP1
Central visceral analgesic: NMDA antagonist
Anti-inflammatory: 5-ASA, mast cell stabilizers