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REVIEW

# Treating irritable bowel syndrome: overview, perspective and future therapies

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This article summarizes the ongoing challenges in irritable bowel syndrome and the exciting opportunities for development of novel therapies for this common, enigmatic condition. The challenges include insufficient understanding of mechanisms, lack of specificity of symptoms, differentiation from other conditions, and lack of availability of noninvasive tests to identify dysfunctions. However, significant opportunities are reflected by the advances in clinical trial design and, particularly, clinically relevant end points for such trials, and the increasing understanding of basic neuroenteric science. The latter has delivered two new medications to the practice (alosetron and tegaserod), and other candidate therapies (other serotonergic, tachykininergic, opioid, cannabinoid modulators) are being carefully appraised as potential drugs for the future.
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**Keywords:** Colonic diseases; functional; treatment; challenges; opportunities

**Abbreviations:** α, alpha; CCK, cholecystokinin; C-IBS, constipation-predominant irritable bowel syndrome; CRF, corticotrophin-releasing factor; CT, computed tomography; D-IBS, diarrhea-predominant irritable bowel syndrome; GI, gastrointestinal; 5-HT, serotonin; IBS, irritable bowel syndrome; ICCs, interstitial cells of Cajal; κ, kappa; μ, mu; NK, neurokinin; SNRIs, serotonin and norepinephrine reuptake inhibitors; SPECT, single photon emission computed tomography

## Introduction

The irritable bowel syndrome (IBS) is a highly prevalent disorder (Talley *et al*., 1991). The role of motility and sensory dysfunction in IBS and a growing understanding of the roles of neurotransmitters and hormones in the control of gastrointestinal (GI) motility and secretion and sensation (Goyal & Hirano, 1996; Cooke, 2000; Grundy, 2002) provide a basis for more effective therapies. Why has this burgeoning science not been translated to clinical effectiveness and impact of the novel therapies? The objectives of this article are: to provide a review of the challenges facing academic and clinical gastroenterologists engaged in the management of patients with the irritable bowel syndrome (Drossman *et al*., 2002) and to look to the future for new therapies to build on the successes represented by the approval and introduction to patient care of two serotonergic agents, alosetron and tegaserod.

Sir Winston Churchill (1874–1965) was asked to predict what Russia would do before the start of the World War II. His response seems an apt summary of the challenges associated with the conundrum that is IBS: 'It is a riddle wrapped in a mystery, in an enigma'! From my experience as an academic and clinical gastroenterologist, my perspectives in this field can be summarized as 10 challenges. However, it would be wrong to dismiss the tremendous opportunities for development of future therapies, based on significant advances in enteric neuroscience.

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## Challenges in IBS

### *Challenge # 1: The lack of a realistic animal model of IBS*

Though much has been written about this (Mayer & Collins, 2002), many still consider that models such as maternal separation, water avoidance, stress, induction of colonic inflammation and knockout of the serotonin transporter in mice are not realistic models for the 'wild-type' IBS seen in patients. This is partly due to the protean manifestations, associations and overlap symptoms of IBS. Education of physicians (e.g. in the Rome criteria) has focused on appropriate use of the IBS diagnosis instead of the wastebasket approach, where all symptoms that were unassociated with a definable structural, endoscopic or histological abnormality were diagnosed as IBS. This clearer characterization of patients with IBS has been useful, but many regard this as a largely academic exercise, given the fact that there are no outstanding breakthroughs in understanding the mechanisms of IBS.

### *Challenge # 2: The lack of a thorough understanding of the mechanisms controlling gut function in health and functional GI diseases*

The mechanisms responsible for the induction of symptoms in functional GI diseases are relatively poorly understood (Drossman *et al*., 2002). While the biopsychosocial model provides a reasonable framework, this does not specifically identify the main 'actors' responsible for symptoms in an individual. The practitioner has to determine what factors are

at play in the patient in the clinic. Is the prior history of abuse relevant 20 years later, when the patient seems so well adjusted? Is the prior history of 'turista' the cause of IBS now or is it simply a coincidence? Does 'turista' predispose to constipation-predominant IBS (C-IBS)? Does prior exposure to infection provide a clue that there are plasticity changes in the neurosensory mechanisms, or is there an ongoing paucicellular inflammatory response that should be amenable to treatment with anti-inflammatory agents (Spiller, 2003)? How does the latter situation differ from mild forms of inflammatory bowel disease (Podolsky, 2002) or chronic intestinal pseudo-obstruction (Tornblom *et al*., 2002; Figure 1)? If there are some inflammatory cells on the rectal biopsy (Macintosh *et al*., 1992), are the patient's symptoms of chronic diarrhea and tenesmus due to IBS or microscopic colitis (Pardi *et al*., 2002)?

Herein lies another dilemma: What causes microscopic colitis (Goff *et al*., 1997; Pardi *et al*., 2002), and is it an extreme expression of IBS? Is it a manifestation of the surface-active or detergent properties of the bile acids or fatty acids (Gaginella *et al*., 1977; Chadwick *et al*., 1979) spilled into the colon in higher concentrations due to rapid small bowel transit? Or, is there a defect in the active transport process for bile acids, so called 'bile acid catharsis' (Poley & Hoffman, 1976)? When should the practitioner use agents that retard small or large intestinal transit, and when is it appropriate to bind bile acids with a sequestrant agent (Hofmann & Poley, 1969; Poley & Hoffman, 1976)? The $^{75}$SeHCAT method (Merrick *et al*., 1985) to identify low bile acid retention is available in many centers in Europe, but not in other countries including the Unites States. Stool measurements of bile acid and the $^{14}$C-cholyglycine breath test seem to be relics of a distant past when function tests were an essential part of the diagnostic process (Hofmann, 1976). The gastroenterologist may try to choose therapy based on underlying mechanisms, but there are multiple potential mechanisms and a broad range of symptoms.

### *Challenge # 3: The seemingly protean manifestations of IBS*

The practitioner is faced with a syndrome in which symptoms vary greatly between individuals and over time within the same individual. It is difficult to comprehend that a condition can present with diarrhea one time and constipation another time!

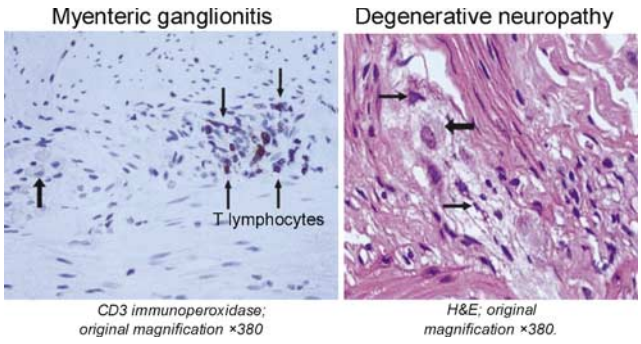


**Figure 1** Inflammatory and degenerative neuropathy in 'severe IBS'. Reproduced from Torblom *et al*., 2002.

It is not surprising that physicians are more comfortable dealing with defined bowel dysfunctions (with attendant transit disorders) with symptomatic treatment than trying to correct the underlying mechanisms that could result in such diverse symptoms.

Other IBS symptoms, such as bloating, are incompletely understood. Does bloating result from bacterial fermentation of products of digestion or does it represent a failure of normal transit of gas through the bowel (Serra *et al*., 2001)? Is there any utility in distinguishing upper from lower abdominal bloating? Can bloating be measured (Reilly *et al*., 2002; Basilisco *et al*., 2003)? Does upper abdominal bloating result from retained gastric content or alterations of gastric tone/relaxation? Or, is upper abdominal bloating the result of retardation of transit of residue through the transverse colon? Even when bloating (a secondary endpoint) responds to treatment with a prokinetic such as tegaserod, it is unclear whether this results from motor effects in the stomach, small bowel or colon.

The practice of evidence-based medicine using targeted therapy requires a more clear understanding of the underlying pathophysiology in the individual patient. Studies of GI motor and sensory functions have been proposed as surrogate or even biological markers of IBS (Mertz *et al*., 1995; Bouin *et al*., 2002). Measurements must also identify dysfunctions in extracolonic organs in IBS, such as the stomach, small bowel and pelvic floor. The relative inaccessibility of the small bowel to quantitative measurements of motor and sensory functions remains a significant problem. Even when a noninvasive method such as scintigraphy can be applied, the very large coefficient of variation among transit measurements negates their practical use and 'diagnostic value' (Argenyi *et al*., 1995; Cremonini *et al*., 2002). Other tests such as barium follow-through, a CT enterography, or invasive methods such as GI manometry may be indicated in patients with intractable symptoms and evidence of bowel dilatation to identify obstruction or neuromyopathy (Narducci *et al*., 1987; Spiller *et al*., 1987; O'Brien *et al*., 1996; Choi *et al*., 1997; Coulie & Camilleri, 1999; Chey *et al*., 2001).

### *Challenge # 4: Lack of specificity of symptoms*

The GI tract has a limited repertoire of symptoms and the features of IBS are certainly not specific. Indeed, practitioners have only partly embraced the idea of using positive symptom evaluation for the diagnosis of IBS. This may occur because clinical experience will provide the occasional surprise (e.g. the patient with 'classical' IBS symptoms who turns out to have right-sided colon cancer). Physicians also assume a more defensive posture in a litigious environment. Thus, IBS is still regarded by many as a diagnosis of exclusion, given the lack of any 'diagnostic test'. In specialized centers, tests of GI function are available and can provide support for the diagnosis of IBS. However, the results of such tests are certainly not specific, for example, patients with diarrhea from carcinoid tumors present with features suggestive of IBS with diarrhea, and demonstration of rapid transit (von der Ohe *et al*., 2003) would not identify the presence of the tumor. The irritable bowel syndrome, therefore, remains a diagnosis of exclusion, and clinicians have persistent doubts in their minds. Are they perhaps missing an alternative diagnosis, especially when

symptoms recur or there is insufficient response to therapy prescribed?

Features in the history are helpful in the evaluation of patients with diarrhea or constipation (for exclusion of an evacuation disorder), as shown in Tables 1 and 2 (Camilleri, 1997; Lembo & Camilleri, 2003).

### *Challenge # 5: Overlap of functional GI disorders with other conditions that require different management*

Clinical experience shows two common examples of this principle. The presentation of diarrhea-predominant IBS may be very similar to that of lactose intolerance or celiac disease; in some patients, both conditions may co-exist and contribute to the presentation (Sanders *et al*., 2001; Wahnschaffe *et al*., 2001). Clearly, treatment may be required for both the conditions if the patient is to obtain relief.

The clinician is faced with a challenging question: which patients should be investigated? What is the likelihood of finding an alternative diagnosis? The literature provides some guidance: Among patients meeting symptom-based criteria for IBS, the pretest probability of inflammatory bowel disease, colorectal cancer, or infectious diarrhea is less than 1%. Currently, recommended diagnostic tests rarely identify organic GI disease in patients fulfilling symptom-based criteria for IBS. However, the pretest probability of celiac disease in patients meeting symptom-based criteria for IBS was 10 times higher than the prevalence of celiac disease in the general population (Cash *et al*., 2002). Screening of serum for tissue transglutaminase seems worthwhile in patients with diarrhea-predominant IBS (D-IBS).

A second more frequent and under-recognized example is the concurrence of constipation-predominant IBS and obstructed defecation due to pelvic floor dysfunction. Both conditions present with a symptom complex of: constipation, sense of incomplete evacuation, abdominal discomfort when constipated, relief of the discomfort after bowel movements, and bloating. Features in the history that suggest an evacuation disorder are shown in Table 2.

Yet, clinical experience suggests that colonic prokinetics may not relieve and may actually aggravate the abdominal pain of patients with obstructed defecation. Optimal selection of patients in clinical trials may not translate to selection of patients for treatment in clinical practice, and this results in a negative experience for the prescribing physician who receives the report from the patient that the symptoms are much worse! This reinforces the practitioner's bias that IBS is a challenge and an enigma.

**Table 1** Identifying key issues on diarrhea in the clinical history

1. Is the consistency of the stool altered or are stools of normal consistency passed more frequently?
2. Does the patient have diarrhea or incontinence? Is incontinence at daytime or nighttime?
3. Does the diarrhea alternate with constipation?
4. What is the diurnal frequency and periodicity of the symptom?
5. Does the patient pass blood per rectum with or without diarrhea?
6. Are there features suggestive of steatorrhea (oily, undigested food, difficult to flush, or weight loss)?
7. Are there other features to positively diagnose irritable bowel syndrome: relationship with abdominal pain, sense of incomplete rectal evacuation?
8. Medications, past medical/surgical history.
9. Relationship of diarrhea to meals or dietary factors.
10. Symptoms referable to skin, eyes, joints.

**Table 2** Identifying key issues on constipation in the clinical history: factors that suggest a defecatory disorder

1. Prolonged straining to expel stool
2. Assuming unusual postures on the toilet to facilitate stool expulsion
3. Support of the perineum, digitations of the rectum, posterior vaginal pressure to facilitate rectal emptying
4. Inability to expel enema fluid
5. Constipation after subtotal colectomy for constipation

### *Challenge # 6: The lack of generally applicable methods to evaluate pathophysiology in clinical practice*

Tertiary care centers have developed and validated noninvasive or minimally invasive methods such as scintigraphy for transit (Cann *et al*., 1983; Proano *et al*., 1990; Vassallo *et al*., 1992), stable isotope breath tests for gastric emptying (Lee *et al*., 2000a; Viramontes *et al*., 2001a), electrogastrography for gastric dysrhythmias (Parkman *et al*., 2003), SPECT imaging for measurement of gastric volumes (Bouras *et al*., 2002), satiety tests for gastric sensitivity (Tack *et al*., 1998; Camilleri *et al*., 2002), and anorectal manometry with balloon expulsion for exclusion of evacuation disorders (Lembo & Camilleri, 2003). However, most, if not all, of these tests are not available for the vast majority of practitioners evaluating and treating patients with IBS. Radiopaque marker transit measurements are useful and have been validated for identifying slow transit (Metcalf *et al*., 1987), but there has not been sufficient validation in diarrheal diseases. Thus, it is conceivable that an X-ray of the abdomen 5 days after marker ingestion (Arhan *et al*., 1981) would not provide useful information: the absence of any markers in the colon would not distinguish whether the colonic transit time was less than 4 h or less than 120 h!

Hence, clinical management strategies have traditionally been based on appraisal of symptoms and empirical choice of therapy, rather than targeting treatment to the underpinning mechanism or pathophysiology.

### *Challenge # 7: 'Is it all in the brain after all?'*

After a decade of educating physicians to avoid telling patients that 'It's all in the head', it seems that this may be incorrect after all! Recent research and some opinion leaders point to the central role of the brain and the psyche in the causation and manifestations of IBS. Unpleasantness of visceral sensations may be related to increased blood flow in the anterior cingulate cortex and its subregions (Mertz *et al*., 2000; Silverman *et al*., 2000).

While the role of the brain in conscious perception and the association of psychological disorders with IBS cannot be dismissed, it is clear that the symptoms originate in the gut and that disturbances of gut motor, sensory or secretory functions

are key. The emphasis on central modulation has had three unintended consequences: First, it reinforced, with some physicians and patients, the concept that the symptoms of IBS are 'in the head' after all; second, it has de-emphasized the important advances in therapy (e.g., alosetron, tegaserod) that have resulted from targeting peripheral mechanisms or pathophysiology; and third, it may have resulted in a 'flight' of young investigators away from this field of study, given the challenges associated with the vagaries of higher brain functions with which gastroenterologists are not usually facile. Gastroenterology fellows seem reluctant to commit to a field of study that is perceived to be likely to lead to an under-appreciated and less lucrative practice compared to the lure of the procedural practice of gastroenterology or the glamour of liver transplantation.

### *Challenge # 8: Lack of consensus on optimal experimental and trial designs for IBS*

There is a high placebo response rate in IBS (Spiller, 1999), and it persists even in 12 week trials (Figure 2). With the experience obtained in the alosetron and tegaserod trials, which showed significant improvement over placebo within 4 weeks of onset of therapy, there is a renewed enthusiasm to change the 'dogma' that proving the efficacy of a medication in IBS requires 12-week-long clinical trials. Interestingly, the European agency for drug evaluation has recommended that IBS medications be tested over 4-week periods and that the efficacy should be demonstrated with repeated episodes of treatment (http://www.emea.eu.int/pdfs/human/ewp/078597en.pdf; Corazziari *et al*., 2003). In a previous review, the lessons learned from the recent, large, multi-center clinical trials were summarized, with insights provided on the enrichment of the study population, end points, conduct and analysis of these studies (Camilleri, 2002). While there are still considerable challenges in optimal trial design, this is an area where the partnering of academia and industry has been very effective in the last decade.

### *Challenge # 9: Single or multiple therapies for IBS?*

Many physicians are accustomed to treating with combination therapy medical conditions such as asthma, angina, hypertension or inflammatory bowel disease. Even reflux esophagitis is sometimes treated with a double dose of a proton pump inhibitor and an additional dose of an H-2 receptor antagonist at bedtime! Clinicians are accustomed to treating D-IBS with a centrally acting agent, such as a tricyclic antidepressant, and a peripherally acting agent, such as loperamide. Given the redundancy of mechanisms controlling neurosensory and neuromuscular functions, it is not inconceivable that more than one mechanism may need to be modulated by peripherally active medications to achieve higher levels of symptom control.

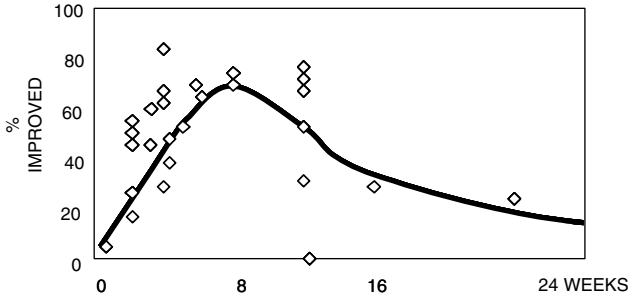


**Figure 2** Placebo response rates in irritable bowel syndrome and relationship with study duration. Reproduced from Spiller, 1999.

It is worth noting that even the best results from large multicenter studies with approved agents (e.g. tegaserod or alosetron) achieved primary clinical end points in $<70\%$ of patients (Camilleri *et al*., 2000; Muller-Lissner *et al*., 2001; Cremonini *et al*., 2003). What would it take to increase the proportion of responders? Phase IIB studies did not suggest that higher or lower doses would increase the likelihood of response. Rather, it is likely that the mechanisms underpinning symptoms in IBS may differ from one patient to another, and that it may be necessary to consider using multiple therapies. Examples of combinations might include a 5-$HT_4$ agonist with a neurokinin (NK)-1 agonist, or a motilide or a $\mu$-opiate antagonist for slow transit, or a 5-$HT_3$ antagonist and a NK-2 or -3 antagonist or a $\kappa$ opioid agonist for patients with significant diarrhea and abdominal pain.

There are several practical challenges to combination therapies: these agents are typically tested through large multi-center, industry-funded trials with single agents and they are not all approved for use in treatment of IBS. There is a significant fiscal disincentive for pharmaceutical sponsors to conduct comparator trials between these agents or combination trials and, hence, the clinician tends to use each medication alone without the potential benefits of combined therapy. As basic and applied studies provide improved understanding of the pathobiology of IBS, combinations of medications may be tested together in the future. New regulatory perspectives would be required to rapidly translate basic and applied science on the potential benefits of combination therapies to clinical practice after the medications are individually approved. High levels of safety are key to evaluation of drug combinations that are proposed for approval based on mechanistic studies, but it seems that necessitating proof of additional efficacy of the combination over the individual agents would require such large sample sizes as to present insurmountable challenge. The alternative to new regulatory approaches to combination therapy approval is for physicians to continue to fumble their way through off-label use of medications in combination, without regulatory guidance or reassurance that the combinations are actually safe.

### *Challenge # 10: Pharmacogenomics: one size does not fit all*

Inter-individual differences in responses to medications are genetically determined. These are potentially most relevant in the metabolism of the medication to the active moiety. Thus, for example, codeine is metabolized to morphine by the CYP2D6 enzyme system. It is considered that morphine is the active metabolite that delays GI and colonic transit. In a previous report in the literature (Hawkes *et al*., 2001), a low dose of codeine of 30 mg b.i.d. had variable effects on GI transit, and this could conceivably have resulted from different rates of metabolism of codeine influenced by the CYP2D6 activity. Similarly, the effect of oral codeine on orocecal transit

was significantly prolonged in extensive metabolizers, but not in poor metabolizers (Mikus *et al*., 1997).

Genetic variation may also influence the response to therapy in IBS. To date, this has been most convincingly demonstrated for the *SLCA4* long polymorphism, which encodes for a normally functioning promoter for the serotonin transporter protein. This polymorphism is associated with greater response of colonic transit to alosetron in D-IBS (Camilleri *et al*., 2002).

The challenge presented by pharmacogenomics is that a medication may be effective but may not help all patients at the dose approved because of inter-individual variations in metabolism or action. This raises a specific challenge in drug development programs: Should pharmacogenomic studies be included in phase IIB or phase III studies with the potential restrictions in the application of the medication in practice? Confident that the financial disincentives will lead pharmaceutical sponsors to answer that question will be a resounding 'no', one can only remind clinicians that individual patients respond differently to standard doses of medications prescribed according to regulatory guidelines.

## Future pharmacotherapy in IBS: opportunities for improvements

Assuming that one is permitted to quote a famous personality twice in one article, I feel it is important to reflect the significant optimism in this field. In a speech delivered at Harrow School in 1941, at the height of the destruction, doom and gloom of the Second World War, Sir Winston stated: 'These are not dark days: these are great days—the greatest days our country has ever lived.' The same can be said about the current state of the IBS field. Never before has the impact of basic science, applied physiology and pharmacology been so promising, and the clinician scientists so prepared to translate those advances to the care of the patient (Camilleri, 2001). Unashamedly, one can express confidence and satisfaction in the achievements of the past 5 years: development of IBS study methodology and the marketing of a 5-$HT_3$ antagonist (alosetron) and a 5-$HT_4$ agonist (tegaserod) for the treatment for diarrhea- or constipation-predominant irritable bowel syndrome, respectively. These medications have proven effective repeatedly in well-controlled studies (Tougas *et al*., 2002; Cremonini *et al*., 2003; Kellow *et al*., 2003); they impact on patients' symptoms in the short and medium term (up to 6 months). There is also evidence, for the first time, that medications may impact on patients' quality of life. In a controlled study of psychotherapy and paroxetine, both were superior to treatment as usual in improving the physical aspects of health-related quality of life (Creed *et al*., 2003).

### *What is in the medication pipeline for IBS?*

The fundamental processes that are being explored as therapeutic targets stem for an understanding of the factors that are believed to contribute to the development of the syndrome (Figure 3). Given the success of loperamide, laxatives, alosetron and tegaserod in controlling the bowel dysfunction in IBS, future therapeutic advances are likely to be based on the treatment of visceral pain. The anatomical substrate for relief of pain is reflected in the neural centers and pathways involved in pain sensation (Figure 4). Medications

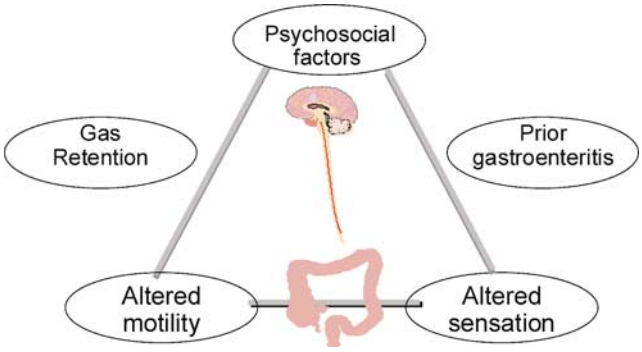


**Figure 3** Pathophysiology of irritable bowel syndrome.

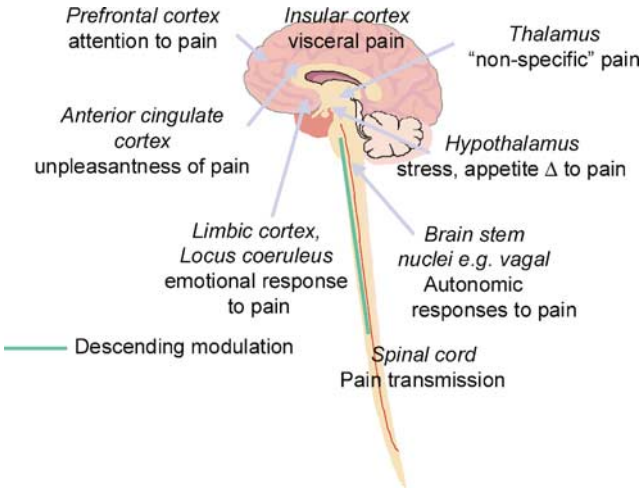


**Figure 4** Neuro-anatomical centers involved sensation of visceral sensation.

may be directed to central processes to reduce the perception of pain or activate centers that are involved in the down-regulation of pain sensation or descending pathways that reduce the ability of the dorsal horn neuron to activate ascending pathways that bring afferent signals to conscious sensation.

The following is a summary of the potential new medications that are being tested or developed for the treatment of IBS (Figure 5).

### *Newer serotonergic agents*

*5-$HT_3$ agonist* These receptors are located in the motor and sensory apparatus of the rodent gut (Hillsley & Grundy, 1998; Glatzle *et al*., 2002; Hicks *et al*., 2002; Mazzia *et al*., 2003). 5-$HT_3$ receptors occur on intrinsic sensory neurons in the rat colon, and on extrinsic sensory nerve fibers that innervate the colon. These receptors are the targets for anti-emetic medications, as well as are being antagonized by alosetron and cilansetron in the treatment of IBS. Interestingly, a recent study has shown that an agonist at this receptor, MKC 733, slightly delays stomach emptying of liquids and transfer of solids from the proximal stomach, but it significantly accelerates small bowel transit in healthy volunteers (Coleman *et al*., 2003). The presumed mechanism of action is activation of cholinergic neurons to stimulate contractions. MKC 733

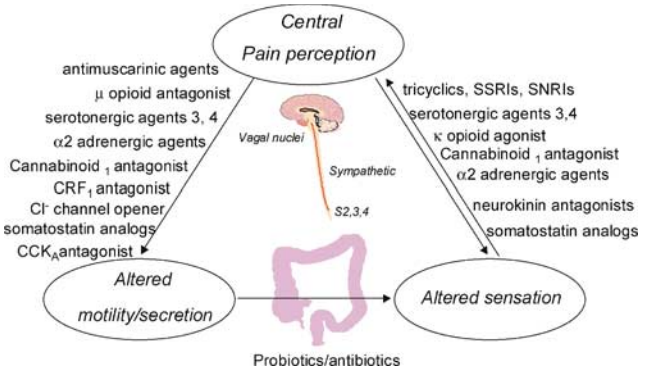


**Figure 5** The pipeline in IBS. Candidate medications and possible mechanisms of action.

increased the number of migrating motor complexes recorded in the antrum and duodenum ($P<0.001$), but had no effect on postprandial motility in healthy volunteers (Coleman *et al*., 2003). Effects on colonic transit and further investigations in IBS are awaited.

*5-$HT_3$ antagonist, cilansetron* Cilansetron follows on from alosetron with the same presumed mechanism of action, that is inhibition of cholinergic neurons and of visceral sensory mechanisms (peripherally or centrally). Recent data from Mayer's group suggest that this class of drug has the ability to change the areas of the brain that respond to visceral pain. Moreover, activation of areas associated with descending modulation may result in reduced sensitivity of the dorsal horn neuron to the incoming afferent signals (Berman *et al*., 2002; Mayer *et al*., 2002). As with alosetron, there is evidence that this 5-$HT_3$ antagonist is also effective in IBS without constipation (Caras *et al*., 2001), and the benefit–risk ratio will require further appraisal.

*5-$HT_4$ agonist/5-$HT_3$ antagonist renzapride* The presumed mechanism of action of renzapride is the activation of 5-$HT_4$ receptors in cholinergic neurons to stimulate GI contractions; it also has 5-$HT_3$ antagonist activity, which may have opposite effects on GI or colonic transit to those expected from a 5-$HT_4$ agonist. As a 5-$HT_3$ antagonist, renzapride may also reduce visceral sensation.

Evidence for a potentially favorable outcome in the treatment of IBS with renzapride is based on phase IIb trials in IBS-C or mixed symptom IBS. Preliminary data have been presented recently (Meyers *et al*., 2002; George *et al*., 2003). Moreover, a pharmacodynamic study at Mayo Clinic shows that 4 mg renzapride accelerated the ascending colon emptying and there was a significant dose-related acceleration of colonic transit in C-IBS patients in whom an evacuation disorder was excluded. The acceleration of transit was associated with an improvement ion stool consistency and ease of stool passage during a 2-week treatment period (Camilleri *et al*., in press).

*5-$HT_{1A}$ agonist* Data from studies with buspirone suggest that it may have beneficial effects on rectal sensorimotor function (Coulie *et al*., 1998). In a subsequent study, these effects were not observed during colonic distension and no effects on colonic tone and compliance were observed (Chial *et al*., 2003b). Formal studies in IBS are awaited.

*5-$HT_{2B}$ antagonist* In an intriguing study of the longitudinal muscle that runs between the taenia coli in the human colon, it was demonstrated that the predominant receptors involved in inhibiting contractile responses to 5-HT were of the 5-$HT_{2B}$ type (Borman *et al*., 2002). The significance of this finding requires further investigation.

*Reuptake inhibitors of serotonin and norepinephrine* - Serotonin reuptake inhibitors tend to accelerate small bowel transit (Gorard *et al*., 1994; Chial *et al*., 2003a). Recent data suggest that the combined serotonin and norepinephrine reuptake inhibitors alter colonic tone (preventing the tonic response to feeding), and reduce colonic sensation in response to distension pressures that are in the noxious range, as well as satiation after feeding (Chial *et al*., 2003a, b). Other SNRIs are being considered for treatment of fibromyalgia and chronic pain syndromes.

### *NK modulators*

Substance P is a peptide (tachykinin) that is the ligand for the NK1 receptor; both substance P and NK1 receptor are widely distributed in the central nervous system: cortex, basal ganglia, amygdala, hippocampus, hypothalamus, locus coeruleus, dorsal raphe, and habenula. Substance P is also co-localized with norepinephrine and 5-HT in neurons in the central nervous system. Substance P and NK1 receptor are also expressed on small-diameter sensory somatic visceral fibers and enteric sensory neurons. Hence, there is considerable potential for NK modulation in the treatment of sensory or motor disorders in IBS.

*NK1 antagonist* The presumed mechanism of action of this class is the antagonism of NK1 receptors, which are the preferential receptors for substance P in myenteric neurons and afferent pathways. $NK_1$ receptors are expressed by a number of neuronal and non-neuronal cells involved in gut motility. Tachykinergic NK1 transmission to the circular muscle may be mediated by receptors located both on ICCs and smooth muscle cells. NK1 receptor blockade inhibits peristalsis. This effect is probably mediated by the inhibition of post-junctional NK1 receptors.

One of the compounds tested was TAK 637, which is a selective antagonist of smooth muscle NK1 receptors that activate intestinal muscle contraction. Additionally, TAK-637 inhibits neuronal NK1 receptors involved in the 'local' motor response to stimulation of capsaicin-sensitive primary afferents (Venkova *et al*., 2002). TAK 637 dose-dependently reduced abdominal contractions in response to colorectal distension in rabbits by antagonizing tachykinin NK1 receptors, mainly in the spinal cord (Okano *et al*., 2002), and reduced colonic transit and defecation in a Mongolian gerbil model of IBS (Okano *et al*., 2001). However, its development was stopped because of lens abnormalities developed in two animal species.

Selective NK1 antagonists, SR-140333, and MEN-10930, inhibit colonic propulsive activity induced by NK1 agonists in an *in vitro* preparation (Onori *et al*., 2003).

Evidence of the promise of this class of compounds comes from the efficacy of the NK1 antagonist aprepitant in the relief of chemotherapy-induced delayed emesis (Chawla *et al*., 2003; Poli-Bigelli *et al*., 2003), suggesting significant inhibition of vagal afferents, and the preliminary data suggesting that the

IBS patients were less angered by the distension of a balloon in the rectum after treatment with the NK1 receptor antagonist CJ-11974 (Lee *et al*., 2000b).

This class of medication may also have other beneficial effects in IBS. For example, through central effects and interactions with serotonin, substance P antagonists might alleviate anxiety and major depression, at least in part, by enhancing the degree of activation of some 5-HT receptors in the forebrain (Haddjeri & Blier, 2001). Secondly, they have effects on bowel inflammation (Stucchi *et al*., 2000) or anti-secretory action (Moriarty *et al*., 2001).

*NK2 antagonism* The presumed mechanism of action of this class of compounds reflects the preferential binding of the ligands, NK A/B, to NK2 receptors, which are predominantly on sensory neurons. However, intravenous NK A ($9\,nmol\,kg^{-1}$) stimulated GI motility in unanesthetized dogs, suggesting motor effects too.

Nepadutant (NK2 receptor antagonist also called MEN 11420) at $0.1\,\mu mol\,kg^{-1}$ suppressed the stimulant effects of NK A, but up to a dose of $10\,\mu mol\,kg^{-1}$ did not produce significant changes in the basal migrating motor complexes. In experimental models, prototype NK2 antagonists, like saredutant, dose-dependently reduced agonist-induced fecal excretion, and reduced fecal water excretion, and abdominal contractions in response to colorectal distension. However, there was no effect demonstrable on colonic transit in stressed rats (Mclean *et al*., 1997). Studies in healthy humans and patients with IBS are awaited.

*NK3 antagonism* The presumed mechanism of action of this class of compounds reflects the preferential binding of the NK ligands to NK3 receptors, which are predominantly on sensory neurons. NK3 receptors are present on spinal terminals of capsaicin-sensitive neurons and within intrinsic neurons of the spinal cord. Intrathecal NK3 receptor antagonist SR 142,801 reduced rat behavioral response to noxious colorectal distension.

Data also suggest a *peripheral* role for the NK3 receptor in the mechanisms of intestinal nociception (Fioramonti *et al*., 2003). Thus, both NK3 receptor antagonists, talnetant (which crosses the rat blood–brain barrier) and SB-235375 (which does not cross the barrier), reduce colonic sensation (abdominal contractions in response to colorectal distension) without altering colonic compliance (Fioramonti *et al*., 2003).

## *Opioids*

*μ and nonspecific opioid antagonists. Opioid compounds on enteric motility, secretion, neurotransmission and inflammation* μ Opioid receptors are located in the enteric nervous system (Sternini, 2001) as well as on nociceptive pathways conducting pain to the central nervous system (reviewed in Kurz & Sessler, 2003). Clearly, an effective μ opiate such as fentanyl (Lembo *et al*., 2000) is capable of blunting the pain induced by colonic distension, but the central, euphoric, and addictive potential makes this an impractical therapy except in emergencies.

A study compared naloxone *versus* placebo, and showed no significant improvement in the scores for pain, bloating, straining, and urgency in the naloxone group (Hawkes *et al*., 2002). However, larger clinical trials are needed to evaluate the usefulness of opioid antagonism in constipation-predominant IBS.

Naltrexone is a nonspecific opioid antagonist whose presumed mechanism of action is as an antinociceptive and antimotility agent. While its potential role in narcotic bowel dysfunction has been observed (Foss, 2001), formal studies of this or similar compounds (such as the μ opioid antagonist, alvimopan (Taguchi *et al*., 2001)) are required in IBS before their potential role can be appraised.

Combination of opiate medications with other agents has been proposed based on experimental studies, but these have not really been adequately tested in humans (Foxx-Orenstein *et al*., 1998).

*K-opioid agonist, asimadoline* The presumed mechanism of this agent is as an antinociceptive with predominantly peripheral action (Ozaki *et al*., 2000; Su *et al*., 2000); recent data suggest that its action may be at least partly through blockade of sodium channels. Two pharmacodynamic studies have been published suggesting that it can reduce colonic sensation at subnoxious levels of distension and it also reduces gastric sensation after a satiating meal (Delgado-Aros *et al*., 2003a, b). Evidence for promise is also provided by a study conducted in IBS-C, in which pharmacodynamic end points of colonic compliance, tone, and sensory thresholds were investigated, and there was a reduction of colonic sensation in response to colonic distensions (Delvaux *et al*., 2002).

## *CRF-1 antagonist*

The presumed mechanism of action is to antagonize the effects of the stress hormone CRF on colonic motor and possibly on sensory function. A prototype compound is NBI 34041. The evidence for the promise of this class of compounds in IBS is based on: first, a study by Fukudo *et al*. (1998) of the effects of i.v. CRH on colonic motility in humans; second, the effects of CRH on colon functions in animals (Maillot *et al*., 2003), and pharmacodynamic study of inhibition of colonic transit in a stressed animal model of IBS, and the dose-dependent relief of experimentally induced visceral discomfort (Martinez & Tache, 2001; Martinez *et al*., 2002; Miampamba *et al*., 2002). A CRF antagonist, astressin, injected into the CSF at low doses (1–10 μg) has an antagonistic action against CRF and stress-related alterations of GI motor function (Martinez *et al*., 1997). Endogenous CRF in the brain plays a significant role in the central nervous system mediation of stress-induced inhibition of upper GI and stimulation of lower GI motor function through activation of brain CRF receptors. The inhibition of gastric emptying by CRF may be mediated by interaction with the CRF-2 receptor, while CRF-1 receptors are involved in the colonic and anxiogenic responses to stress. Endogenous serotonin, peripherally released in response to stress, seems to be involved in stress- and central CRF-induced stimulation of colonic motility by acting on 5HT-3 receptors (Monnikes *et al*., 2001).

## *Alpha-2 adrenergic agonist*

There is good pharmacodynamic evidence that clonidine reduces colonic pain sensation in response to distension and relaxes colonic compliance and tone (Bharucha *et al*., 1997; Malcolm *et al*., 2000; Viramontes *et al*., 2001b). A single-center, preliminary study of clonidine in IBS with diarrhea suggests that 0.1 mg clonidine b.i.d. may be associated with an

improvement in the proportion of patients achieving satisfactory relief of IBS and an improvement in overall bowel function (Camilleri *et al*., 2003); more definitive studies are required. However, it is clear that excessive somnolence or postural hypotension is dose limiting with clonidine and more gut selectivity would be advantageous with this class of medication.

### *CCK-A antagonist*

The presumed rationale for this class of compounds is that CCK is involved in gastric relaxation and colonic contractile responses to feeding. After initial promise, it was decided to discontinue development in the U.S. of dexloxiglumide for constipation-predominant irritable bowel syndrome, based on the outcome of two completed placebo-controlled Phase III clinical studies involving over 1400 women and 12 weeks of treatment (http://www.prnewswire.com/cgibin/stories.pl?ACCT=105&STORY=/www/story/10-01-2003/0002027991). Although a numeric trend was observed in favor of dexloxiglumide in both studies, the difference compared to placebo was not statistically significant. On theoretical grounds, one may question whether the choice of the subgroup of IBS patients with predominant constipation was an optimal choice given the evidence that loxiglumide mimics the effects of atropine on muscle tension of colonic muscle strips (Chey *et al*., 2001).

### *Chloride channel openers*

These channels are extensively reviewed elsewhere (Farrugia, 1999). A new approach to the treatment of C-IBS is to evoke a controlled intestinal secretory state; the presumed mechanism of action of chloride channel openers is an increase in the intestinal secretion of water and electrolytes. However, chloride channels (ClC-2) modulate GI neuromuscular functions *in vitro*. The role of chloride channels in sensory functions in the GI tract is unclear; however, there are reports that suggest that chloride channels modulate afferent function in the ear, laryngeal mucosa, and in proprioceptive afferents.

One chloride channel (ClC-2 selective) activator, RU-0211, is also a prostaglandin E1 analog that is active after oral administration (Johanson *et al*., 2003). This effect is at least in part due to an effect on chloride secretion, and the effect on motor function in humans is unclear. However, given the effects of prostaglandin E1 and F2 alpha analogs on colonic motility and transit, and the documented effects of prostaglandins on motor function elsewhere (stomach, small bowel, and gall bladder), it is important to evaluate the effect of these compounds on motor function of the gut using validated methods in humans.

### *Cannabinoid receptor modulation*

Cannabis has been used for centuries in the medicinal treatment of GI disorders. Endogenous cannabinimimetic substances such as 2-arachidonylglycerol have been isolated from gut homogenates and CB1-cannabinoid-binding sites have been identified in small intestine. CB1-cannabinoid receptors (CB1-R) were immunohistochemically localized within the enteric nervous system of the pig, an omnivorous species whose digestive tract is functionally similar to humans. CB1-R are present in cholinergic neurons in the porcine ileal and colonic enteric nervous system (Kulkarni-Narla & Brown, 2000).

Cannabinoid CB1 receptors are functionally present in the human ileum and colon; their pharmacological activation apparently results in inhibition of excitatory cholinergic pathways subserving smooth muscle contraction (Manara *et al*., 2002). Activation of enteric cannabinoid CB1 receptors inhibits motility in the small intestine; endogenous cannabinoids (anandamide and 2-arachidonylglycerol) acting on myenteric CB1 receptors tonically inhibit colonic propulsion in mice (Pinto *et al*., 2002). The competitive cannabinoid receptor antagonist SR 141716A enhanced both tonic and phasic motor activities in the colonic longitudinal smooth muscle, suggesting that CB1 receptor antagonists could act either through antagonizing the effect of endogenous CB1 receptor agonist or by an agonist effect on these receptors (Mancinelli *et al*., 2001).

Thus, cannabinoid receptors may alter intestinal motility and, in view of the fact that CB1r mediates the anti-emetic action of cannabinoids in the dorsal vagal complex, other effects on visceral afferent pathways are also being explored (Van Sickle *et al*., 2001). Synthetic cannabinoids such as CT-3 are being explored in the treatment of chronic neuropathic pain with hyperalgesia or allodynia (Karst *et al*., 2003).

## Conclusions

Clinical gastroenterologists remain baffled by this enigmatic disorder, IBS. There needs to be a concerted effort to enhance basic and applied research in this field and an increased commitment by federal agencies, foundations and pharmaceutical companies to these disorders of GI function, because of the magnitude of the burden to individuals and to society. Clinicians need to continue to develop clinically applicable tools to appraise the mechanisms of IBS in patients seen in practice. Regulatory agencies have a key role in protecting patients from harm; they also can help relieve the burden of illness by providing further guidance on the approval process and the standards for safety, for example, in the case of combined therapies. Ultimately, clinicians respond to the developments in basic science; however, there is still a credibility gap in the disorders of GI function since the animal models of disease still do not reflect accurately the 'wild-type' disease seen in the clinic. The clinician investigator is, therefore, essential for significant advancement in this field.

The combined efforts of basic scientists and clinician investigators have led to the potential innovations in therapy. In the last 5 years, the focus has been on serotonergic agents and significant improvement in patients' lives has resulted from the development and marketing of the 5-$HT_3$ antagonist alosetron and the 5-$HT_4$ agonist tegaserod, despite much initial concern about the safety of these compounds. In the near future, there will likely be second-generation agents in these two classes. However, with the basic understanding of the processes underpinning the motor and sensory dysfunctions of IBS, it is likely that several other classes of medications will be brought to the clinic. These may include NK antagonists, CRF antagonists, $\mu$ opiate antagonists, and $\kappa$ opiate agonists. Clinicians and patients have reason for optimism: significant help is on the way.

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