Neurogastroenterology & Motility

Neurogastroenterol Motil (2015) doi: 10.1111/nmo.12524

REVIEW ARTICLE

Irritable bowel syndrome: an integrated explanatory model for clinical practice

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Key Messages

- We elucidated an integrated explanatory model (EM) for irritable bowel syndrome (IBS) that utilizes the main strands of knowledge about the origin and perception of IBS symptoms. This easily communicable EM may aid diagnosis, communication, and management in IBS.
- We aimed to elucidate an EM for IBS from the existing literature to provide a conceptual understanding of the disorder for pragmatic use in the clinical setting.
- Systematic literature searches and supplementary exploratory searches were conducted to identify publications on IBS and EMs. Data from identified studies were synthesized using a narrative approach.
- An integrated EM was elucidated that takes into account known underlying mechanisms which constitute explanations for IBS symptoms. The EM consists of three main components: altered peripheral regulation of gut function; altered brain–gut signaling, and psychological distress.

Abstract

Background *Although irritable bowel syndrome (IBS) is a symptom-based diagnosis, clinicians' management of and communication about the disorder is often hampered by an unclear conceptual understanding of the nature of the problem. We aimed to elucidate an integrated explanatory model (EM) for IBS from the existing literature for pragmatic use in the clinical setting.* ***Methods*** *Systematic and exploratory literature searches were performed in PubMed to identify publications on IBS and EMs.* ***Key Results*** *The searches did not identify a single, integrated EM for IBS. However, three main hypotheses were elucidated that could provide components with which to develop an IBS EM: (i) altered peripheral regulation of gut function (including sensory and secretory mechanisms); (ii) altered brain–gut signaling (including visceral hypersensitivity); and (iii) psychological dis-*

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Received: 30 August 2014
Accepted for publication: 13 January 2015

tress. Genetic polymorphisms and epigenetic changes may, to some degree, underlie the etiology and pathophysiology of IBS and could increase the susceptibility to developing the disorder. The three model components also fit into one integrated explanation for abdominal symptoms and changes in stool habit. Additionally, IBS may share a common pathophysiological mechanism with other associated functional syndromes. ***Conclusions & Inferences*** *It was possible to elucidate an integrated, three-component EM as a basis for clinicians to conceptualize the nature of IBS, with the potential to contribute to better diagnosis and management, and dialog with sufferers.*

Keywords *explanations, explanatory models, irritable bowel syndrome, mechanisms.*

Abbreviations: 5-HT, 5-hydroxytryptamine; CNS, central nervous system; EM, explanatory model; HPA, hypothalamic–pituitary–adrenal; IBS, irritable bowel syndrome; TRPV1, transient receptor potential cation channel subfamily V member 1.

INTRODUCTION

Understanding and explaining the causes and nature of irritable bowel syndrome (IBS) remains a problem in the clinical setting. As a functional disorder, IBS is defined essentially by symptoms, without the presence of abnormal anatomy or universally applied pathophysiological explanations. The literature provides hypotheses on causes, triggers, and possible underlying mechanisms, but there is much reiteration of relatively sparse original data. Published study data from animal IBS models or human volunteers and patients with IBS are complex and potentially confusing, especially for those who are not experts in IBS. The lack of comprehension about the underlying explanations for IBS is a handicap in clinical practice, hindering diagnosis, communication, and management.

The absence of a single, easily explainable model for IBS probably contributes to the sense of inadequacy that many clinicians, including primary care physicians, have in diagnosing and managing IBS. Such a situation is likely to be associated with clinicians being uncomfortable about giving a diagnosis of IBS until other possible explanations for a patient's symptoms have been ruled out ('diagnosis of exclusion').[1,2] This is despite Rome III criteria indicating that a diagnosis of IBS can usually be made based on symptoms, with limited laboratory evaluations, and that needless investigation may undermine the patient's confidence in the diagnosis and the clinician.[3] Diagnostic testing can heighten patients' concern about their symptoms, thereby complicating their subsequent acceptance of an IBS diagnosis. For example, individuals with chronic gastrointestinal disorders who were participating in focus groups in the USA described their frustration with hearing varying notions and ideas about the possible etiologies of their conditions, and they noted that what they needed to know was what was actually happening to them.[4]

Sometimes, there is a mismatch between the patient's and the clinician's perceptions of IBS and its etiology that troubles the patient–clinician relationship and has a negative impact on IBS disease outcomes.[2,5] As emphasized at a recent Rome Foundation–World Gastroenterology Organisation symposium on IBS, differences in perspective need to be reconciled for a successful therapeutic outcome.[6] Agreement about an integrated, easy-to-understand explanatory model (EM) of IBS would help clinicians and patients to communicate better about the disorder, and help to support disease management and adherence to treatment.[7]

This article reviews the literature on IBS with the aim of elucidating a possible integrated EM for the disorder. Firstly, the literature regarding the history of EMs is explored, to ascertain the meaning and value of an integrated model. Using available data, this work then creates a picture about IBS that clinicians, including primary care physicians, can bear in mind when communicating with patients about their IBS. This paper briefly describes features common to IBS and to other functional syndromes with regard to an EM, but the focus is on IBS.

METHODS

Systematic literature searches were conducted in PubMed to June 2014 to identify publications on IBS and EMs and were independently verified by a second reviewer. The search string used was: ('conceptual model' OR 'conceptual models' OR 'explanatory model' OR 'explanatory models' OR 'disease model' OR 'disease models' OR paradigm) AND (IBS OR 'irritable bowel syndrome'). Search filters were used to limit studies to those published in English. Relevant publications were identified by manual screening of the search results and by supplementary exploratory searches using the identified search results as starting points. Data from identified studies were synthesized using a narrative approach.[8]

RESULTS

A total of 258 publications were identified by the systematic literature search, of which 64 were included in this review to elucidate EMs for IBS. Papers were excluded if they were not about IBS or IBS etiology (n = 37), not published in English (n = 8), or described animal studies or models (n = 149); animal studies were assessed for supplementary information about

biophysiological concepts. Supplementary exploratory searches identified a further 56 publications.

Explanatory models: what are they and do we need them?

The concept of EMs arose in the late 1970s as a way to explain ill health, including cause(s) and symptoms and their timing, the bodily processes generating the symptoms, and the course and severity of an illness episode.[7,9] As originally described for the social sciences by Kleinman, EMs are 'the notions about an episode of sickness and its treatment that are employed by all those engaged in the clinical process'.[7,9] Kleinman argued that discrepant lay and professional explanations of ill health could lead to problems with patient–clinician communication and with treatment adherence, because patients who do not understand or agree with a medical or scientific rationale are unlikely to adhere to a treatment regimen. Kleinman recommended that clinicians should elicit patients' views early in management, and then point out and explain discrepancies with the professional perspective and identify expectations and goals. To help with this process, he developed questions that investigated the patient's views about the etiology, onset, consequences, prognosis, and treatment of their ill health (Table 1).

The concept of EMs arose in response to what was perceived as a rapid rise in the use of medical technology and the resulting fears that clinicians were taking a reductionist approach toward caregiving.[10] Kleinman built on ideas by Engel, who postulated that a new model of disease was needed because the traditional, biomedical model conceptualized disease in terms of anatomical and biochemical principles and excluded all that could not be explained in this way.[11] Initially, Kleinman drew a clear distinction between patients' focus on the ever-changeable experience of symptoms and ill health in the social and cultural context of their daily lives ('illness') and clinicians' quest to diagnose and treat abnormalities in the structure and function of body organs and systems ('disease'). Later, he held that the illness/disease distinction inappropriately separated subjectivity from physiology, noting that such a strict division was untenable within an integrated biosocial framework.[10] This more recent, assimilated approach fits with that originally taken by Engel, who believed in the need for a single EM that includes psychosocial, behavioral and biological data without sacrificing the advantages of the biomedical perspective.[11]

An integrated EM combines the patients' symptom experiences with the etiology of the disease or disorder. The importance of the patients' perspective on their ill health is much better recognized today than it was in the 1970s, and patient-reported outcomes, including measures of symptoms and health-related quality of life, are now routinely used in research and clinical

Table 1 Explanatory model of illness: Kleinman's targeted questions and patients' and clinicians' models for IBS

Dimension	Explanatory model of illness: targeted questions [7]	Patients' explanatory models for IBS [5]	Clinicians' explanatory models for IBS [2]
Etiology	• What do you think has caused your problem?	• Patients had very little to say about causes of IBS. • The disorder was sometimes seen as part of a person's character or personality	• Clinicians thought of IBS as a combination of symptoms with no explained organic cause and with a putative psychosomatic nature
Onset	• Why do you think it started when it did?	• Patients often attributed the onset of IBS to a specific event (e.g., pregnancy, illness, accident requiring strong analgesia). • Stress and certain foods were listed as symptom triggers	• Some clinicians noted that infection could be a possible trigger for the onset of IBS. • Stress, tension, diet, and lifestyle habits (e.g., smoking) were listed as symptom triggers
Consequences	• What do you think your sickness does to you? How does it work? • What are the chief problems your sickness has caused for you?	• Patients said that they tried to get on with their lives, without let ting the IBS take over. • The need for taking certain precautions (e.g., having a toilet	• Clinicians saw the unpredictability of IBS (i.e., when symptoms occur) as the most difficult part of living with the disorder

Table 1 Continued

Dimension	Explanatory model of illness: targeted questions [7]	Patients' explanatory models for IBS [5]	Clinicians' explanatory models for IBS [2]
		always readily accessible) was noted as important	
Prognosis	• How severe is your sickness? Will it have a short or long course? • What do you fear most about your sickness?	• Most patients were relieved that the diagnosis was IBS and not cancer. • There was anxiety about the possible long-term effects of irregular bowel activity	• Clinicians reassured their patients that IBS is not a serious or life-threatening disease. • It was thought that patients needed to learn to live with the disorder
Treatment	• What kind of treatment do you think you should receive? • What are the most important results you hope to receive from this treatment?	• Patients described receiving prescription medication and advice for self-management (e.g., diet, stress-management) • There was anxiety about the possible effects of long-term medication use	• Clinicians viewed treatment for IBS as a trial-and-error process

practice. The significance of the concept of an integrated EM for clinical practice is that it has the potential to enhance the patient–clinician relationship and the patients' adherence to and satisfaction with their treatment, with a consequent improvement in general health management and outcomes. As is the case with scientific hypotheses, EMs fit with the data available at the time and can change and evolve as knowledge and perceptions change.

Does an explanatory model exist for IBS?

Explanations for the etiology and symptoms of IBS have been sought for decades, and they include Drossman's unifying concept using the biopsychosocial model in gastrointestinal illness.[12] Studies conducted in the 1950s showed that stress affects colonic function and leads to increased contractility in healthy individuals and those with an 'irritable bowel'. In the 1970s and 1980s, various stressors were shown to lead to increased motor reactivity, and individuals with IBS were shown to be more sensitive than healthy individuals to colonic distension.

Despite the long history of research into IBS etiology, there is a lack of an underlying, integrated EM that illustrates the etiology of IBS and its symptoms. An interview study conducted in the UK and Netherlands highlighted the lack of knowledge about IBS among patients and clinicians (Table 1).[2,5] Most patients with IBS had little to say about what causes IBS, focusing instead on the identification of symptom triggers, an approach that may be related to the paucity of clear pathophysiological explanations for IBS.[5] Similarly, most clinicians who participated in the study did not have a mental picture of what causes IBS: many described it as a psychosomatic disorder and took into account patient characteristics, such as psychosocial background and personality, when diagnosing IBS.[2] This mismatch in patients' and clinicians' views can lead to differences in expectations regarding treatment options and outcomes.[2,5]

Identified components for an integrated explanatory model of IBS

The systematic literature searches did not identify a published, integrated EM for IBS. However, three main hypotheses about the etiology and pathophysiology of IBS were elucidated that could provide components with which to develop an IBS EM: (i) altered peripheral regulation of gut function (including altered peripheral sensory and secretory mechanisms); (ii) altered brain–gut signaling (including visceral hypersensitivity); and (iii) psychological distress. These components also provide hypotheses to explain the differences between IBS with diarrhea (IBS-D) and IBS with constipation (IBS-C) and, to some extent, also mixed IBS (IBS-M), although a paucity of research pertaining specifically to IBS-M means that this common type of IBS remains poorly characterized.[13] Genetic polymorphisms and epigenetic changes may, to some degree, underlie the etiology and pathophysiology of IBS and may increase susceptibility to developing the disorder.[14–17]

Altered peripheral regulation of gut function Altered peripheral regulation of gut function is caused by changes in local neurotransmitter signaling, gut inflammation, and changes in microbiota, and provides a hypothesis to explain IBS and the differences between IBS-D and IBS-C (Fig. 1).[17–24] Susceptibility to altered peripheral gut regulation may be increased by underlying gene mutations, polymorphisms and changes in mRNA expression.[14–17,24] As part of an integrated EM, the picture would be of the gut not regulating itself properly, resulting in diarrhea or constipation. Much literature is available around the role of gut 5-hydroxytryptamine (serotonin, 5-HT) in IBS, and is, in part, associated with interest in drug development.[20,25] The neurotransmitter is released from mucosal enterochromaffin cells in the gut in response to elevated intraluminal pressure during normal digestion. Release of 5-HT initiates the activation of gut motor and secretory reflexes, and the signal is terminated with the help of serotonin-selective reuptake transporters that are located in the epithelial cells lining the gut lumen.[18] Irritable bowel syndrome pathophysiology could thus be shaped by changes in the availability of 5-HT, including its production and release, the number of available reuptake transporters, and the number of enterochromaffin cells in the gut. Increased availability of 5-HT would inappropriately enhance gut peristalsis and secretory activity, thereby leading to IBS-D, whereas decreased availability of 5-HT would dampen peristalsis and secretion, thereby leading to IBS-C.[26] In support of this model, different phenotypes of tryptophan hydroxylase 1, an enzyme needed for 5-HT biosynthesis in enterochromaffin cells, have been shown to correlate with IBS subtypes,[27] and a polymorphism in the 5-HT_3 receptor is associated with severity of IBS symptoms.[28]

Altered gut 5-HT signaling as part of an IBS EM model provides a possible explanation for the symptoms of abdominal discomfort and changes in gut motility because serotonin also targets extrinsic nerves in the gut, which are able to transmit sensations of discomfort to the central nervous system (CNS).[29] In addition, reduced peristalsis could also lead to bacterial overgrowth and excess gas production in the gut, leading to discomfort and bloating.[30] Altered central responses to serotonin have been found in individuals with IBS,[31] and patients with IBS have anxiety responses to a change in tryptophan load (a proxy for serotonergic functioning) that are different from controls.[32] Gene mutations or polymorphisms leading to altered 5-HT signaling may form an interface between the 5-HT and psychological distress models of IBS: i.e., mutations or polymorphisms in the 5-HT transporter gene could cause independent susceptibilities to anxiety/depression (via brain 5-HT[33]) and IBS symptoms (via gut 5-HT[20,25]), which would in turn enhance each other. Although 5-HT is the prototype mediator of intestinal secretion,[22] other neurotransmitters, such as acetylcholine and substance P, also affect gut peristalsis. Peptides and polypeptides that have been impli-

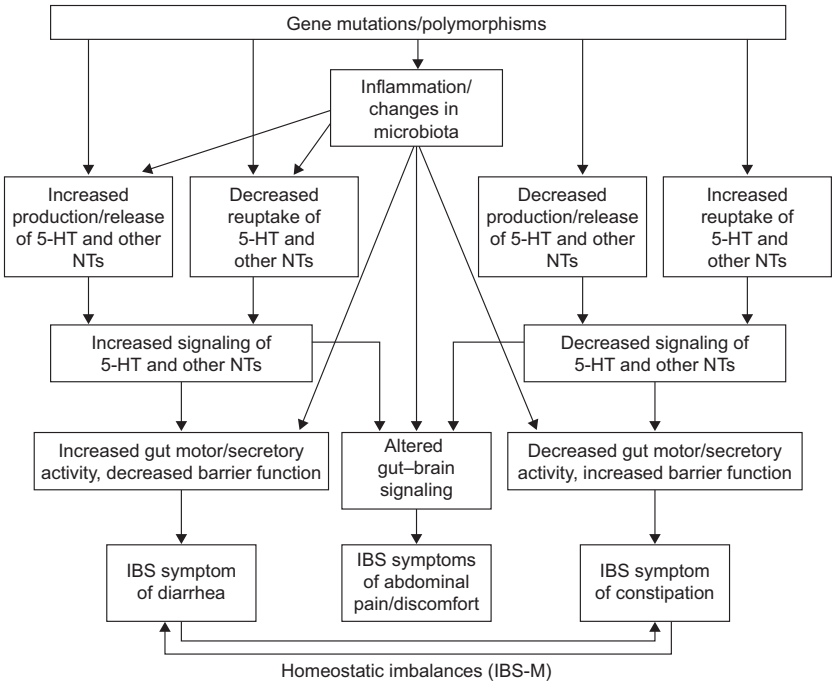

Figure 1 Schematic representation of peripheral regulation of the gut as a component of an explanatory model for irritable bowel syndrome (IBS). 5-HT, 5-hydroxytryptamine; IBS-M, mixed IBS; NTs, neurotransmitters.

cated in IBS include the hormone somatostatin, peptide YY, and neuropeptide Y, all of which increase fluid absorption, and the chromogranin polypeptides, which are involved in intestinal secretory mechanisms that affect gut motility.[22]

Gut inflammation and changes in microbiota have been described in patients with IBS and are possible triggers of increased or decreased gut motility.[19,25,34–43] Low-grade inflammation and immune activation may also cause increased permeability of the intestinal mucosa, leading to altered nerve signaling in the gut.[44] Genetic polymorphisms in pro-inflammatory cytokines have been observed in individuals with IBS,[20,21,45] and data indicate that gut microbiota can affect the host immune system via epigenetic mechanisms.[14] A link between infection and peripheral regulation of gut function is suggested by the inhibition of serotonin transporter activity by enteropathogenic *Escherichia coli* infection[46] and by raised levels of 5-HT-containing enterochromaffin cells following bacterial gastroenteritis.[25] The reported incidence of new-onset IBS after intestinal infection ranges from 4% to 36% among exposed individuals, and up to 17% of patients with IBS believe that their disorder developed from an episode of gastroenteritis.[25,30,47] It may be that a persistent, low-grade, postinfection rise in intraepithelial inflammatory cells increases the likelihood of developing IBS in susceptible individuals,[25] but this area of research still requires further exploration. There are some data to suggest that probiotics and prebiotics may improve IBS symptoms and immune function, although overall efficacy is generally modest.[48–52]

Peripheral motility, sensory, and secretory mechanisms The importance of altered peripheral sensory and secretory mechanisms in IBS was recently reviewed by Camilleri.[17,22] Gut motility, secretory, and barrier functions are altered by local reflexes in response to changes in the microbiome, intraluminal irritants (such as excess bile acids and short-chain fatty acids) and immune/inflammatory pathways, aided by aberrant function of transporters for bile acids, serotonin, and ions.[17,22] Gut function may also be affected by dietary factors such as maldigestion of complex carbohydrates (the FODMAP theory): although the prevalence of celiac disease in patients with IBS is similar to that in healthy controls, gluten withdrawal improves bowel function in some patients with IBS-D, potentially by affecting small bowel permeability.[17,53] Changes in intestinal barrier function may contribute to IBS, including symptoms of visceral pain, although a causal relationship remains to be established.[54] When supernatants from colonic biopsies of patients with IBS-D, but not IBS-C, were applied to mouse dorsal route ganglia neurons, neuronal excitability was increased, resulting in enhanced nociceptive signaling.[55] The effect was absent in mice lacking the protease activated receptor 2 (PAR2), suggesting a role of PAR2 signaling in enhanced visceral nociceptive signaling.[55] Differences have also been observed in the immune profile of peripheral blood mononuclear cell supernatants from patients with IBS-D and IBS-C, and from healthy individuals, with distinctly different effects when applied to mouse gut sensory nerves.[56]

Bile acids are endogenous laxatives that stimulate gut motility. Low bile acid retention values, caused by bile acid malabsorption and/or overproduction, have been observed in individuals with IBS-D and IBS-M, compared with healthy controls and patients with IBS-C, and are associated with accelerated colonic transit time, frequent or loose bowel movements, and increased intestinal permeability.[23,57,58] A reduction in stool frequency (although not a change in consistency) was demonstrated with open-label treatment with a bile acid sequestrant, supporting a role for bile acids in the pathophysiology of IBS-D, but low bile acid retention values were not associated with abdominal pain, discomfort, or bloating.[57] In patients with chronic diarrhea, bile acid malabsorption has been observed to be less common in individuals with than without IBS-D symptoms, and IBS-D symptoms were seen to be more prevalent in individuals with mild than with moderate or severe bile acid malabsorption.[59] These observations suggest that increased colonic bile acid exposure affects bowel habits but not abdominal symptom generation in IBS-D. Changes in the microbiota involved in bile acid transformation were demonstrated in individuals with IBS-D and correlated with bowel habits.[60] Gut microbiota provide the exclusive metabolic pathway for biotransformation of primary into secondary bile acids, and differences in the proportions of primary and secondary unconjugated fecal bile acids between patients with IBS-C and IBS-D, compared with healthy controls, support a relationship between the gut microbiome and IBS.[61]

Altered brain–gut signaling The altered brain–gut signaling hypothesis proposes that individuals with IBS have a perceptual hypersensitivity to gut signals (Fig. 2).[34,62–64] Such hypersensitivity could arise via increased signaling from the gut (visceral hypersensitivity) and/or via central dysregulation,[63,65–70] and assessing the contribution of peripheral *vs* central factors is an area of ongoing research.[71] Increased sympathetic and decreased parasympathetic nervous system activity has been observed in individuals with

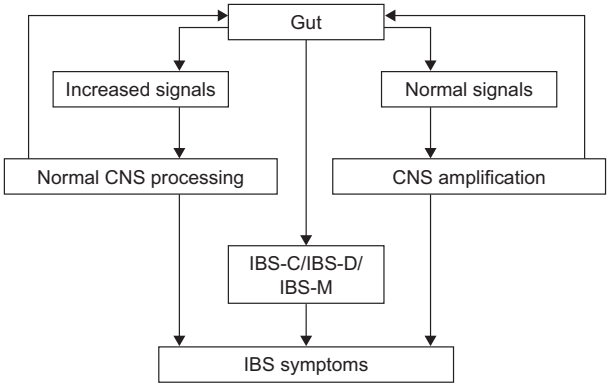

Figure 2 Schematic representation of altered brain–gut signaling as a component of an explanatory model for irritable bowel syndrome (IBS). CNS, central nervous system; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, mixed IBS.

IBS, suggesting that altered brain–gut signaling in IBS may be mediated in part by the autonomic nervous system.[72] Ischemia in the microvasculature of the brainstem lateral medulla has been proposed as a cause of autonomic dysfunction in IBS and other pain disorders.[73] Altered brain–gut communications in IBS can also occur through dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, a system that is activated in particular in response to stress.[44] Patients with IBS may have an enhanced stress response, possibly because of changes in the HPA axis.[44]

As part of an integrated EM, visceral hypersensitivity can be pictured as impaired transmission of communications between the brain and the gut that leads to an over-amplification of signals, resulting in the patient's subjective symptom experience.[64] Heightened awareness of symptoms can be envisaged approximately as a large number of symptoms and 'niggles' that can be noticed when one focuses on one's body, which are overlooked in daily life. Using this analogy, healthy people may be more likely to 'blunt' their symptoms, whereas those with IBS may be more likely to 'monitor' their bodies.[74] Altered brain–gut signaling as a component of an integrated EM would provide an explanation for symptoms of abdominal pain and discomfort in IBS, but would need to be expanded to include causal explanations for the altered stool frequency and/or consistency. A bidirectional nature of the signaling pathway between the CNS and the gastrointestinal tract may help to account for these alterations in stool habits.

Support for visceral hypersensitivity comes from rectal balloon distension studies, which show a lower pain threshold in individuals with IBS compared with healthy individuals.[63,75] Among individuals with IBS, women show a greater perceptual sensitivity than men to rectal distension,[76,77] suggesting that the importance of visceral hypersensitivity in the etiology of IBS may differ between the sexes. Although rectal hypersensitivity may not generally be demonstrable in patients with IBS-D, there is some evidence that patients with IBS-D show a lower threshold for the urge to evacuate than those with IBS-C in response to phasic rectal balloon distension.[78] Visceral hypersensitivity may thus account for some differences between subgroups of patients with IBS. Among patients with IBS-C with or without the urge to evacuate, there is an increased sensitivity to rapid phasic rectal distension compared with healthy individuals, but only patients who have IBS-C without the urge to evacuate show decreased sensitivity to slow distension.[79]

Altered expression or sensitivity of transient receptor potential cation channel subfamily V member 1 (TRPV1), a receptor that mediates responses to noxious stimuli, has been implicated in visceral hypersensitivity in IBS. Compared with rectal biopsies of healthy controls, those of patients with IBS show increases in sensory fibers expressing TRPV1.[80] Increased pain perception to rectal capsaicin application was observed in patients with IBS who had visceral hypersensitivity compared with healthy controls, and both peripheral and central factors were involved[81]; no upregulation of TRPV1 was observed in this study, but increased sensitivity of the receptor to noxious stimuli was postulated as an alternative mechanism for increased pain perception *vs* controls.[81] Colonic visceral perception in patients with IBS has been shown to be reduced by agonists that increase epithelial cyclic guanosine monophosphate production.[82]

Abnormal CNS processing may not occur in all patients with IBS, but this concept nevertheless provides a model for the syndrome. Perceptual hypersensitivity may arise via CNS amplification of normal (or even reduced) signals from the gut.[64] Such central dysregulation is supported by brain images that show changes in the degree of connectivity between different brain regions in individuals with IBS compared with healthy controls, suggesting a structural reorganization of chronic pain pathways.[83] A bidirectional nature of visceral hypersensitivity and central dysregulation is suggested by an increase in functional brain network connectivity in patients with IBS undergoing rectal balloon distension.[84] Aberrant central functional responses of the brain have also been observed in this setting.[85] Brain imaging data show heightened responses to painful visceral stimuli in patients with IBS compared with healthy controls,[86] and differences in brain responses between women and men with IBS.[87] Individuals with visceral hypersensitivity show

a relative decrease in gray matter compared with healthy controls in regions of the brain involved in cognitive and evaluative functions (the prefrontal and posterior parietal cortices), and this difference remains when controlling for anxiety and depression.[88] A study conducted in healthy individuals showed that decreases in gray matter in pain-relevant regions of the brain correlate with an increase in lower rectal visceral sensitivity.[89]

Psychological distress The psychological distress hypothesis postulates that mental functions, behavioral patterns, and childhood occurrences can come together to produce or worsen IBS symptoms.[12,90] How psychological distress may manifest as IBS symptoms can be visualized approximately as the abdominal sensations experienced in response to exam stress, which individuals may see as a normal part of life and not an expression of underlying illness. However, in the presence of psychological distress, these bodily sensations are interpreted or amplified as physical symptoms of disease (somatization). An increased sensory sensitivity and tendency to scan the body for symptoms (hypervigilance) may also mean that minor symptoms become more noticeable, and the belief that the symptoms are a sign of serious underlying disease (catastrophizing) may create a vicious circle by causing more stress.

As part of an integrated EM, psychological distress can be pictured as impaired interpretation by the brain of signals from the gut. Support for this hypothesis comes from studies showing that individuals with IBS are more likely than those without IBS to show signs of hypervigilance, catastrophizing, and somatization,[34,91] that catastrophizing and somatization exacerbate IBS,[91,92] and that psychosocial factors, including somatization, negatively affect self-ratings of health in individuals with IBS.[93] Hypervigilance has been linked to an over-reporting of symptoms,[34] which may explain the observation that increased colonic pain sensitivity can be due to an increased tendency to report pain rather than an actual decrease in pain thresholds in IBS.[94] Compared with controls, patients with IBS also have an increased response to expected abdominal pain.[95] Patient-reported IBS severity correlates with the belief that 'something is wrong with the body',[96] and education about the link between IBS and emotions can improve IBS symptoms.[97] Individuals with IBS are more likely than those without the disorder to have comorbid anxiety, depression, and chronic stress.[44,98–100] The heightened awareness of symptoms has been used to explain the (high) prevalence of psychological and psychiatric disorders observed in patients with IBS, although this association has been seen mostly in severe cases in secondary care and may thus be, at least partly, due to referral bias.[98,99,101]

Early adverse life events, including physical and mental abuse, are more commonly reported in individuals with IBS than in those without the disorder.[102,103] It may be that these events are indirectly associated with future development of IBS, by increasing the likelihood of developing a component of the psychological distress model. Controlling for psychological and somatic symptoms weakens the association, but recollection of early life events still has some independent association with IBS,[102] suggesting that such events (or their recall) are independently linked with other factors, such as hypervigilance, which increase susceptibility to IBS. Nonadverse life events could have a part in the future development of IBS. Excessive parental attention may reinforce symptoms in children, potentially causing them to evaluate discomfort as threatening and to establish long-lasting illness behavior.[104] Among patients with IBS, social support can affect symptoms, with those with supportive family relationships tending to have lower IBS activity than those with family conflict.[105]

An EM incorporating psychological distress would explain symptoms of abdominal pain and discomfort. Combining it with the altered brain–gut signaling component and the altered peripheral regulation component would help to account for the changes in stool frequency and/or consistency in IBS. This combined model approach is supported by studies showing long-term changes in constituent parts of brain–gut signaling in response to early life stress experiences.[106,107] Stress has also been shown to lead to visceral hypersensitivity, low-grade inflammation, and epithelial changes in the intestine.[108–110] Psychological distress, including stress, anxiety, depression, and recent adverse life events, is associated with an increased risk of developing postinfection IBS.[25] In a study conducted in rodents, stress was shown to lead to long-lasting changes in signaling pathways in afferent sensory neurons and to hyperalgesia.[111] In rats that experienced neonatal maternal deprivation, exposure to a novel environment or acute stress in adulthood resulted in significantly enhanced colonic motility (based on fecal pellet output) compared with their non-deprived counterparts.[112]

Overlapping models in IBS

Symptom overlap between IBS and functional pain syndromes, including fibromyalgia, migraine, chronic fatigue, non-specific low-back pain, and urological pain

syndromes, is more common than would be expected by chance.[113–120] Although these may be extradigestive IBS manifestations, there is speculation that functional disorders may represent different manifestations of a common, as-yet unidentified pathophysiological mechanism.[113–115,121] Central sensitization (hypersensitivity to painful stimuli and reduced endogenous pain inhibition) is being proposed as a candidate underlying mechanism,[115,122–125] although this remains controversial.[126] In a cross-sectional survey study, patients with functional disorders (chronic fatigue, chronic wide-spread pain, oro-facial pain, or IBS) were more likely than controls to report sleep disturbance, anxiety, depression, and recent adverse life events.[127]

A possibly common connective tissue abnormality has been suggested by the high prevalence of functional gastrointestinal disorders in individuals with joint hypermobility syndrome.[128] Overall, there is, as yet, no definitive evidence to support or refute a common underlying mechanism for all functional disorders.

The effects of food, food intolerance, and, more recently, the microbiome have added to controversies around the causes and management of IBS. Although food and eating may not cause IBS, changes in diet might improve symptoms. Guidance on IBS from the UK National Institute for Health and Care Excellence recommend a review of diet and nutrition for individuals with IBS, including discouraging patients from eating insoluble fiber and 'digestion-resistant' starch.[129] Diet can also influence the gut microbiota, and specific probiotics can help reduce overall symptoms and abdominal pain in some patients with IBS.[52]

DISCUSSION

An integrated EM needs to combine the patient's symptoms with the presumed etiology of the disorder. In clinical practice, an integrated EM has the potential to aid earlier diagnosis and enhance management of the disorder and patient adherence with treatment. Explanatory models necessarily evolve with time—the discovery of the etiology of duodenal ulcers being a prime example—and functioning in an explanatory vacuum creates limitations. No single integrated EM for IBS was identified by our literature searches. We produced a theoretical model and the next stage would be to test the effectiveness of this theoretical EM in clinical practice.

In establishing an integrated EM, we identified three main hypotheses on IBS etiology and pathophysiology, which comprise three components: the brain, the gut, and signaling between these two centers. These components can fit together into one integrated EM based on impaired transmission and interpretation of brain and gut communications (Fig. 3). Altered peripheral regulation of gut function leads to motility, sensory or secretory changes, triggering IBS-C or IBS-D, respectively, and to changes to extrinsic signal transmission to the CNS, leading to abdominal symptoms. Inflammatory mediators can induce visceral hyperalgesia when released by the gut mucosa and can also increase pain perception centrally by vagal activation of limbic brain regions.[64] Altered brain–gut signaling may lead to amplification of normal signals on their way from the gut to the brain; IBS-D or IBS-C is then triggered when the CNS reacts to these abnormal signals in an erroneous attempt to re-establish homeostasis. Attempts at homeostatic fine-tuning could results in oscillations around the targeted set-point, leading to IBS-M. Psychological distress, whether historic or current, produces or worsens the IBS symptoms of abdominal pain and discomfort.

Merging the three hypotheses about IBS into one integrated EM provides an explanation for abdominal pain/discomfort and changes in stool habit, and would be able to differentiate between IBS-D and IBS-C.

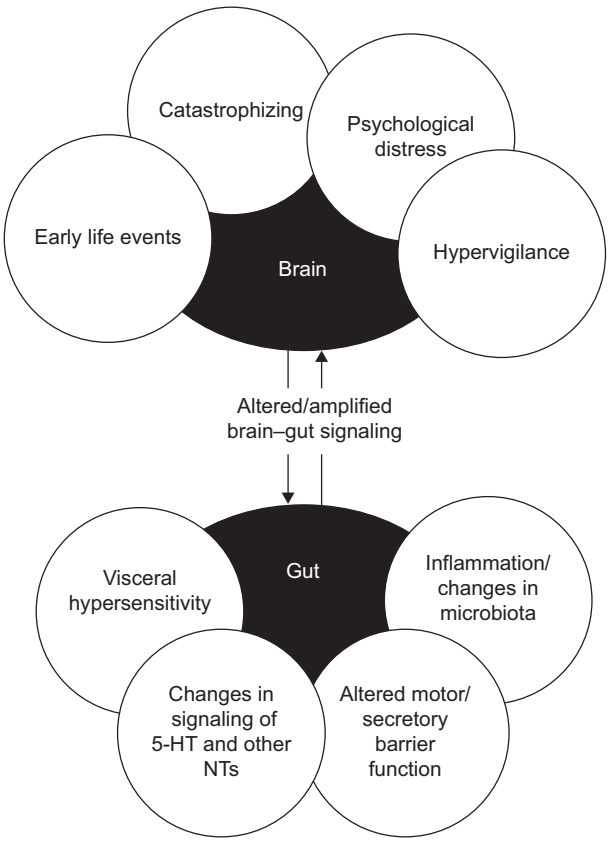

Figure 3 Schematic representation of the three components of an integrated explanatory model for irritable bowel syndrome (IBS). 5-HT, 5-hydroxytryptamine; NTs, neurotransmitters.

However, IBS is a heterogeneous disorder and the relevance of individual model components in the etiology of IBS is likely to vary between different individuals. Although an integrated model may be relevant in some patients, it is likely that single strands of the model will apply to others. The EM provides a basic understanding and explanation for IBS and has the potential to enhance communication with patients, many of whom will also have their own theories and explanations for their symptoms. The integrated EM also provides a useful guide for future avenues to explore for IBS interventions and clinical management, including patient education, counseling, and caregiving. New research into the genetics and epigenetics of IBS may in future be able to elucidate a common underlying mechanism to link the different facets of the IBS etiology, including familial clustering, childhood trauma, stress, and gastrointestinal infection and inflammation.[14–16] In the wider context of the functional syndromes, it remains to be explored whether IBS should be approached as a separate entity or as part of an overarching EM that includes these other syndromes as well.

The three-component explanation of IBS offers a pragmatic opportunity for a deeper understanding and meaningful dialog for clinical practice, by translating the etiology and the pathophysiology of the disorder into a visual model that can help clinicians to communicate with patients (Fig. 3). The model is relatively straightforward to explain, visualize, and understand, thereby enabling a match between the patients' and clinicians' expectations and clinical practice. For patients with unexplained medical symptoms, a diagnosis of IBS can open up a path that consolidates their symptom experiences. However, such a path also requires a patient–clinician dialog based on current knowledge. The model provides a basis from which clinicians can explain IBS to their patients in lay terms (see Box 1). Having their symptoms explained and accepted by their clinician legitimizes patients' illness experiences and is likely to contribute to the patient–clinician partnership, the essential part of care in IBS.[130]

Examples of lay language for communicating with patients

- The brain sends signals in such a way that they are over-interpreted by the bowel.
- The bowel is receiving signals over-sensitively.
- The bowel is processing signals over-sensitively and this affects function.
- The function of the bowel is affected by the nervous system.
- The bowel sends signals in such a way that they are over-interpreted by the brain.
- The brain is receiving or processing signals too sensitively.
- The brain is misinterpreting normal signals from the body as signs of disease.
- Food, bacteria, or substances found in the gut can sometimes cause the gut to malfunction and trigger symptoms.

ACKNOWLEDGMENTS

The clinician authors of this paper are members of the Rome Primary Care Committee and we would like to thank the members of the Rome Foundation for their support.

FUNDING

Oxford PharmaGenesis™ Ltd, Oxford, UK, collaborated for this project with the School of Medicine, Pharmacy and Health (SMPH), Durham University, UK. Funding was provided from a departmental grant from the SMPH.

CONFLICTS OF INTEREST

A Pali S Hungin has been an advisory board member and speaker for Reckitt Benckiser, Danone, Almirall, and Novartis. Anja Becher is a contracted employee of Oxford PharmaGenesis™ Ltd, Oxford, UK. Greg Rubin has provided consultancy advice and has developed educational materials for Almirall. Andrew Russell, Bill Cayley, Joel J Heidelbaugh, Jean WM Muris, Bohumil Seifert, and Niek de Wit have no personal interests to declare.

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