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Overlap between functional GI disorders and other functional syndromes: what are the underlying mechanisms?

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Abstract

Background—Irritable bowel syndrome and other gastrointestinal (GI) and non-GI disorders such as functional dyspepsia, fibromyalgia, temporomandibular joint disorder, interstitial cystitis/painful bladder syndrome, and chronic fatigue syndrome are known as functional pain syndromes. They commonly coexist within the same individual. The pathophysiologic mechanisms of these disorders are not well understood, but it has been hypothesized that they share a common pathogenesis.

Purpose—The objective of this review is to discuss the proposed pathophysiologic mechanisms, which have been similarly studied in these conditions. These mechanisms include enhanced pain perception, altered regional brain activation, infectious etiologies, dysregulations in immune and neuroendocrine function, and genetic susceptibility. Studies suggest that these functional disorders are multifactorial, but factors which increase the vulnerability of developing these conditions are shared.

Keywords

chronic fatigue syndrome; fibromyalgia; functional dyspepsia; interstitial cystitis/painful bladder syndrome; irritable bowel syndrome; temporomandibular joint disorder

INTRODUCTION

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder (FGID) that has a worldwide prevalence. The pathophysiology of this disorder is complex and not fully understood. Proposed pathophysiologic mechanisms of IBS include, but are not limited to,

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brain-gut axis dysregulation,[1] enhanced visceral perception,[2] altered intestinal microbiota,[3] post infectious changes in gastrointestinal (GI) function,[4] and enhanced immunologic reactivity (Fig. 1).[5] Currently, there is no reliable diagnostic biomarker for IBS and therefore, IBS has been generally considered "functional" in etiology due to the lack of consistent anatomic or biochemical abnormalities to explain the symptoms.[6] Similarly, there are other symptom-based disorders, which have been labeled "functional," as their pathophysiologic mechanisms are yet to be clearly defined (see Table 1). These conditions include other GI disorders such as functional dyspepsia (FD) and non-GI disorders including fibromyalgia (FM), chronic fatigue syndrome (CFS), interstitial cystitis/painful bladder syndrome (IC/PBS), and temporomandibular joint disorder (TMD).

Several observations support that these conditions share a common pathophysiology. For example, there is significant overlap between IBS and these other functional disorders (Table 2).[7-10] This overlap may be seen with two syndromes, or even three with various combinations of comorbidities such as IBS, CFS, and IC/PBS[11] or IBS, FM, and IC/PBS.[12] For example, one study noted health-care provider diagnoses of comorbid conditions of TMD, FM, and CFS within an IBS group from a tertiary care outpatient clinic to be 16%, 59%, and 36%, respectively. When examining symptoms, it is commonly found that IBS is associated with non-GI symptoms that are commonly seen in other somatic syndromes such as FM, CFS, IC/PBS, and TMD. For example, sleep disturbance was observed in 28–74% of IBS patients,[13-15] whereas urinary symptoms (i.e., frequency, urgency, nocturia, incomplete bladder emptying sensation) were found approximately in 50% of IBS patients.[14]

Furthermore, stress and other psychosocial factors appear to play a role in the development or the symptom exacerbations of these conditions (Fig. 2). Depression, anxiety, and other psychiatric comorbidities can frequently coexist with these functional syndromes particularly in more severe cases, although the prevalence can vary among studies (Table 2).[16,17] A study conducted in the Netherlands noted that 30% of Rome II positive IBS patients had anxiety symptoms and 22% had depression symptoms based on the Hospital Anxiety and Depression (HAD) Scale.[18] A study conducted in FD patients found that a coexistent anxiety disorder existed in 28.5% patients,[16] while another study evaluating FD patients at a tertiary outpatient clinic found that 30.4% had a comorbid depression disorder.[17] In FM, the prevalence of an anxiety disorder ranged between 20% and 80% and the prevalence of depression ranged between 13% and 63.8%.[19] Furthermore, one survey study found that 57% of FM patients reported symptoms of posttraumatic stress disorder (PTSD).[20] The prevalence of depression and anxiety based on DSM-IV criteria within a CFS population in the United Kingdom were each 14%, with coexistent depression and anxiety in 18%.[21] However, a large United States survey study noted the lifetime prevalence of having a diagnosis of depression in a CFS population was as high as 57%.[22] With respect to TMD patients, a US study demonstrated that the lifetime prevalence of a depressive disorder, which was diagnosed by a psychiatrist or a clinical psychologist, was 41%.[23] In a study of IC/PBS female patients at a tertiary urology clinic setting, 5% had a diagnosis of depression, 11% had positive depression symptoms, and 14% had a panic disorder.[24] However, this study noted that a "masking" effect was a confounder because patients who were taking an antidepressants or anxiolytics were unaccounted for. In contrast, based on a large community-based sample of IC/PBS patients, the probable diagnosis of depression was 34.8% and panic attacks were 52%.[25] In summary, there are many studies conducted in these functional pain syndromes that demonstrate a significant comorbidity with psychological symptoms or psychiatric disorders with depression and anxiety being the more common diagnoses. However, studies varied in the type of patient population (tertiary vs community sample), geographic region, diagnostic criteria, and medication use.

Another common observation in these functional somatic syndromes is a female predominance that is likely multifactorial. These factors include estrogen-related enhancement in pain sensitivity,[26] increased pain amplification of sensory stimuli in women compared to men,[27] gender differences in stress reactivity, and sociocultural differences in reaction to pain/coping mechanisms,[28,29] and increased health-care seeking behavior in women.

Lastly, these functional syndromes are often treated similarly, such as with antidepressants and cognitive behavioral therapy. Thus, it can be hypothesized that these conditions have a unifying pathophysiology. The objective of this review is to discuss the overlap of IBS with these other functional syndromes and explore shared pathophysiologic mechanisms.

FUNCTIONAL GASTROINTESTINAL DISORDERS (FGIDS)

Irritable bowel syndrome

Irritable bowel syndrome is one of the most common FGIDs and affects between 10% and 15% of the US and European populations.[30] Irritable bowel syndrome is associated with a female predominance although this is more evident in the clinic populations than in the general community.[31] Currently, IBS is diagnosed using symptom-based criteria, such as the Rome III criteria,[30] which is defined as the presence of abdominal pain or discomfort for at least 3 days per month in the last 3 months with two or more of the following features: (i) onset in relation to a change in frequency of stool, (ii) onset associated with a change in form of stool, and/or (iii) improvement with defecation.[30]

Functional dyspepsia

Dyspepsia is defined as “persistent or recurrent upper gastrointestinal symptoms, predominantly pain or discomfort localized in the epigastric region.”[32,33] FD is a very common disorder, with a worldwide prevalence ranging from 11.5% to 29.2%.[34] The Rome III diagnostic criteria for FD are at least 3 months or more of: (i) discomforting postprandial fullness, (ii) early satiation, (iii) epigastric pain, and/or (iv) epigastric burning for at least 3 months with the onset at least 6 months ago and no evidence of structural disease to explain all symptoms. In addition, FD is further subcategorized into epigastric pain syndrome and postprandial distress syndrome, which can also coexist. This subcategory is mainly to distinguish differences between dyspeptic symptoms induced by ingestion vs those that are not.[35] Usually a negative endoscopy in the presence of dyspeptic symptoms confirms the diagnosis of FD.[36]

NON-GI FUNCTIONAL DISORDERS

Fibromyalgia

Fibromyalgia is defined by chronic widespread somatic pain and is typically associated with fatigue, anxiety, sleep disturbances, and/or cognitive dysfunction.[37] It is prevalent in about 2–5% of the population.[38,39] There is a higher prevalence in women that increases with age: 2% in women between the ages of 30 and 39 years and 7% in women between the ages of 60 and 69 years.[39] Fibromyalgia is currently diagnosed using the modified 2010 American College of Rheumatology that utilizes two scales, the Widespread Pain Index (WPI) and the Symptom Severity (SS) scale. The diagnosis is based on meeting three criteria: (i) WPI ≥7 (0–19) and the SS score ≥5 (0–12) or a WPI of 3–6 and a SS is ≥9; (ii) a persistent similar level of symptoms for at least 3 months; and (iii) absence of another disorder to explain the pain.[37]

Temporomandibular joint disorder

Temporomandibular joint disorder is comprised of clinical symptoms related to pain of the masticatory musculature and/or the temporomandibular joint and associated structures.[40] Temporomandibular joint symptoms are seen in 6-12% of the US population.[41] Although imaging studies of temporomandibular joint can be done, TMD remains mainly a clinical diagnosis.[40] The Research Diagnostic Criteria for temporomandibular disorders has a two-axis method of diagnosing TMD.[42,43] Axis I focuses on the physical diagnosis of TMD, whereas Axis II assesses behavioral, social, and psychological factors associated with TMD.[42,43]

Interstitial cystitis/painful bladder syndrome

While some disagree, IC and PBS have been commonly used together, although they are sometimes used interchangeably. Interstitial cystitis was traditionally diagnosed using the National Institute for Diabetes and Diseases of the Kidney (NIDDK) criteria, which included bladder pain or urinary urgency, cystoscopic findings of either glomerulations or Hunner's ulcers, and the lack of exclusion criteria.[44] In 2002, the International Continence Society preferred the term PBS over IC and defined PBS in less restrictive terms as "suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and nighttime frequency in the absence of proven urinary infection or other obvious pathology."[45] The diagnosis of IC requires typical cytoscopic and histological features. Prevalence varies depending on the diagnostic criteria used, but it is between 0.002% and 0.1%.[46]

Chronic fatigue syndrome

Chronic fatigue syndrome is characterized by "intense fatigue of an unknown cause, which is permanent and limits the patient's functional capacity producing various degrees of disability."[47] Chronic fatigue syndrome has a prevalence ranging from 0.1% to 1.0%.[48] Diagnostic criteria have been established by The Centers for Disease Control and the CFS International Study Group where patients must have persistent chronic fatigue for at least 6 months, or unexplained relapsing intermittent fatigue that is not secondary to exertion, does not improve with rest, and results in remarkable reduction from previous normal activity.[49] Other medical and psychiatric disorders that can explain CFS symptoms must be excluded.[49]

PROPOSED PATHOPHYSIOLOGIC MECHANISMS

There are multiple factors that may contribute to the development of functional somatic syndromes and their symptom expression (Fig. 2). Relatively greater contribution from peripheral factors, such as afferent excitation and upregulation of afferent pathways, may be observed in patients with mild to moderate symptoms. Moderate to severe symptoms may be due to disinhibition at the level of central modulation of pain leading to lack of pain inhibition at the peripheral afferent level. Contributory factors may be life stressors, psychiatric diagnoses, poor coping skills, and abuse. Common pathophysiologic mechanisms that have been proposed in functional pain syndromes will be discussed in this review.

Enhanced pain perception

Enhanced visceral perception, also referred to as visceral hypersensitivity, has been demonstrated in IBS, and has been proposed as a biomarker for the diagnosis or treatment response in a subset of IBS patients.[50] Studies utilizing an electronic computerized barostat distention device report that enhanced visceral hypersensitivity can be observed in 30–40% of IBS patients.[51,52] Proposed pathophysiologic mechanisms underlying enhanced visceral

perception in IBS patients are as follows: (i) altered central processing of visceral afferent sensory input,[53] (ii) peripheral sensitization of sensory afferents, (iii) increased intestinal membrane permeability associated with altered expression of colonic microRNAs,[50] and (iv) psychological tendency to report pain and urgency.[54] In a study where rectal perceptual thresholds were compared in IBS, IBS with coexistent FM (IBS+FM), and healthy controls, both the IBS and IBS+FM groups had significantly lower discomfort thresholds to rectal distention (increased visceral sensitivity) compared to controls.[55]

Somatic pain perception has also been measured in IBS and IBS with comorbid FM (IBS +FM). Originally, studies showed that IBS patients had somatic hyposensitivity.[56] In one study, pressure stimuli were applied to the skin with increasing tension in IBS, IBS+FM, and healthy controls.[57] Irritable bowel syndrome patients demonstrated somatic hypoalgesia and IBS+FM patients had somatic hyperalgesia compared to controls.[56] In contrast, subsequent studies have shown somatic hypersensitivity in IBS.[55,58] In a study done by Calderella *et al.*,[55] IBS patients had normal skin sensitivity to electrical stimuli, but lowered pain thresholds at the subcutis and muscle when compared to healthy controls. However, patients with IBS+FM and FM alone had significantly lower pain thresholds to controls at all three sites.[55] In another study by Moshiree *et al.*,[59] IBS+FM patients had enhanced thermal sensitivity compared to IBS only patients during foot immersion in hot water.[59] These studies support that IBS patients have visceral hyperalgesia and may also have somatic hypersensitivity depending on the presence of comorbid FM or greater illness severity.

Enhanced pain perception has also been demonstrated in FD.[60,61] Balloon distention studies have demonstrated visceral hypersensitivity involving the stomach, but not the rectum.[60,62] In a study by Tack *et al.*,[62] gastric hypersensitivity was found in a subset of FD patients and was associated with symptoms of belching, postprandial epigastric pain, and weight loss.[62] Similarly, in another study by Mertz *et al.*,[60] reduced thresholds to discomfort, fullness, or pain was observed in FD patients compared to healthy controls and organic dyspeptic patients (dyspepsia associated with tissue injury/irritation).[60] Studies have evaluated visceral perception in patients with coexistent FD and IBS (FD+IBS). In a study by Corsetti *et al.*,[61] gastric perception to barostat-administered balloon distension was assessed during a meal in FD and FD+IBS patients.[61] FD+IBS patients showed lower gastric thresholds (increased sensitivity) for first perception and discomfort compared to patients with FD only.[61] In another study by Holtmann *et al.*,[63] patients with FD and/or IBS collectively demonstrated lower thresholds for first perception and maximum tolerated pressure to small intestinal distension compared to controls.[63] There were no differences between the FD only, IBS only, and FD+IBS groups. Similar to IBS, enhanced pain perception in FD is thought to be due to several factors including central and peripheral sensitization.[60]

Enhanced pain perception and persistent pain are the main defining features of FM.[64] A number of studies have demonstrated enhanced pain perception in FM. A study employing self-reported surveys of daily lives of FM patients, rheumatoid arthritis patients, and healthy controls revealed increased generalized sensory hypersensitivity to somatic (tactile) and non-somatic (olfactory, taste, auditory) stimuli in FM patients compared to the other two groups.[65] Other studies have demonstrated that FM patients have lowered thresholds to painful electrical stimuli of the hand and arm,[66] and to thermal stimuli given via a CO_2 laser stimulator to the dorsum of hand, and tender and nontender points compared to healthy controls.[67] In a study by Chun *et al.*,[68] patients with FM perceived pain at rectal phasic distension pressures that were intermediate between patients with IBS and healthy controls. Rectal pain thresholds in FM patients were no different from those in IBS patients or controls.[68] However, the number of subjects within each group was small. The mechanisms of increased multisensory perception are postulated to be due to central sensitization and

increased sensory processing of painful stimuli.[67] However, peripheral involvement in the maintenance of central sensitization has been observed as well.[69]

Increased pain perception has also been demonstrated in patients with TMD.[70,71] Lowered thresholds to various painful stimuli, such as thermal, mechanical, or ischemic pain were found in TMD patients compared to patients without TMD.[70,71] One of these studies examined pain sensitivity at a symptomatic (i.e., oropharynx) and an asymptomatic site (i.e., upper extremity), and both sites showed increased pain sensitivity in TMD patients compared to controls.[70] This finding suggests a generalized upregulation of central processing to sensory stimuli,[70] similar to what has been postulated in FM.

In IC/PBS, somatic and visceral pain perception has been studied. In a small study, Ness *et al.*[72] demonstrated enhanced hypersensitivity in IC/PBS patients, using multisensory stimuli. Thermal stimuli was delivered through a contact heat probe applied to the forearm, deep tissue stimuli was applied to the upper trapezius, masseter, and ulna using a handheld algometer, and ischemic stimuli was induced using a modified tourniquet on the arm. Furthermore, bladder distension pain was measured by intravesicle infusion of normal saline. These multisensory stimuli induced higher sensory ratings in IC/PBS patients compared to healthy subjects.[72] In another study, IC/PBS patients reported increased pain compared to baseline during intravesicle instillation of ice water compared to patients with neurogenic detrusor overactivity and stress urinary incontinence.[73] Increased pain sensitivity was thought to be due to an increased expression of immunoreactive nerve fibers, known as TRPM8.[73] Central factors have been shown to play a role as well. Ness *et al.*[72] found that IC patients had greater catastrophizing and vigilance to sensory stimuli than controls.

Persistent and widespread pain is notable in CFS patients[74] and thus, the theory of enhanced pain perception has been postulated.[75] Past studies showed enhanced pain perception or lowered pain thresholds to multiple types of sensory stimuli such as electrical, mechanical pressure, and heat to various regions of the body, including the skin and muscle tissue in CFS patients compared to healthy controls.[75,76] The etiology of enhanced pain perception in CFS is not clear, but dysfunction in pain inhibitory control ("anti-nociceptive") pathways within the CNS,[75,77] dysfunction in afferent sensory input,[75] decreased antioxidants with increased oxidative stress,[76] and altered brain activation patterns[78-80] have been proposed as mechanisms of this phenomenon.

In summary, patients with these functional pain syndromes demonstrate evidence of enhanced perception at sites associated with their predominant symptoms. However, when patients have coexistent conditions, they may have more widespread hypersensitivity.

Altered brain activation patterns

Irritable bowel syndrome has been commonly associated with altered brain-gut interactions. The brain-gut axis is comprised of bidirectional neural pathways linking the enteric, autonomic, neuroendocrine, and central nervous systems.[81,82] It is still not completely clear which areas of the brain-gut axis are consistently dysregulated in IBS, as there could be sensitization at the level of the afferent enteric neurons,[83] dysregulated processing of sensory information at the spinal or supraspinal level, abnormal brain modulation of sensory or nociceptive input from the gut,[82,84] and/or failure to sufficiently activate descending pain inhibitory pathways or activation of pain facilitatory pathways.[85] To further delineate the brain-gut axis and its role in IBS, neuroimaging studies have been performed. Although there are brain regions, which were similarly activated in response to rectal distension, there were also areas, which were differentially activated in IBS patients compared to controls[86,87] and patients with inflammatory bowel disease.[85] These differentially activated areas included somatosensory processing regions (e.g., thalamus, insula) and cognitive and

affective processing regions (e.g., anterior cingulate cortex [ACC]), and limbic and paralimbic regions (e.g., amygdala).[82,87] Interestingly, altered central activation patterns were similar in response to actual and expected but undelivered rectal distensions in IBS patients compared to healthy controls.[87] The ACC has been a region of interest in IBS. Studies demonstrated greater activation of ACC in IBS patients compared to healthy controls.[58,86,88] In a recent study, Larsson *et al.*[88] found that IBS patients with visceral hypersensitivity (based on perceptual thresholds to rectal distension) had greater activation of the insula and reduced deactivation of the perigenual ACC during noxious rectal distensions compared to normosensitive patients and healthy controls.[88]

Neuroimaging studies conducted in FD patients support the presence of altered brain-gut interactions.[89,90] Brain imaging during the resting state as well as during gastric distension has been performed in FD patients.[91,92] A positron emission tomography (PET) study measuring resting state brain activity in FD patients showed increased activation of the ACC, insula, thalamus, cerebellum, and middle cingulate cortex compared to healthy controls.[93] Significant positive correlations between dyspepsia symptom severity and activation of the ACC, insula, thalamus, cerebellum, and middle cingulate were seen, although significantly negative correlations between dyspepsia-specific quality of life and these regions were noted.[93] Another neuroimaging study was performed during proximal stomach distension in FD patients and healthy controls.[92] This study revealed that hypersensitive FD patients (had lower gastric distension pressures) showed significant brain activations in regions not noted in healthy subjects and normosensitive FD patients.[92] Interestingly, this study failed to show activation of the medial pain system, i.e., insula, ACC, and thalamus, which suggests that in FD patients, there may be a dysfunction in activating the descending anti-nociceptive pathways of the medial pain system, and/or no additional cortical activity volume recruitment as distension increases.[92] These findings support the presence of aberrant brain activity in FD patients and its possible role in symptom severity and global outcome, with some similarities observed between FD and IBS in terms of areas of brain activation (i.e., insula, ACC and thalamus).

In FM, there is also evidence of altered central activation patterns compared to controls.[94] In a functional magnetic resonance imaging (fMRI) study conducted by Gracely *et al.*,[95] FM patients had increased activations of the primary and secondary somatosensory cortex, insula, and ACC compared to “pain free” subjects using non-painful and painful thermal stimuli as well as painful pressure stimuli.[95,96] In a PET study conducted in FM patients with and without coexistent IBS, increased regional cerebral blood flow to the midcingulate cortex was seen in response to noxious somatic stimuli in FM patients with IBS and to visceral stimuli in IBS-only patients.[97] This study suggests that stimulus-specific enhancement of midcingulate responses to sensory stimuli occurs in both FM and IBS and may be associated with cognitive enhancement of either visceral (IBS) or somatic (IBS+FM) sensory input. Studies utilizing a dopamine receptor antagonist and opioid receptor agonists in FM patients suggest that a possible dysfunction in the central dopaminergic and opioidergic systems exist that results in ongoing widespread pain.[98] In addition, neuroimaging studies postulate dysregulation of the central nervous system and its sensory pathways with exaggerated neural responses to afferent sensory stimuli, augmented sensory processing, and/or increased anticipation, attention, and memories from pain derived from abnormal cognitive and sensory processing.[96]

Neuroimaging studies have also been performed in TMD patients. A small study used voxel-based morphometry and MRI of the brain to assess changes in the brain structure or morphology in TMD patients. Decreased gray matter volume in regions, including the left ACC, right anterior insular cortex, and superior temporal gyrus were found.[99] In addition, decreased white matter volume in the prefrontal cortex was noted. These findings signify

possible alterations of the central pain system as a contributing cause of TMD.[99] Jiang *et al.*[100] conducted a fMRI study to assess brain activation patterns during evoked clenching in three sets of patients: TMD patients, patients with atypical facial pain, and healthy subjects. Patients with TMD and atypical facial pain showed different areas of brain activation: TMD patients showed activation of the postcentral gyrus, cingulate gyrus, and prefrontal cortices, whereas atypical facial pain patients had activation of the thalamus and ACC. This study noted that different pain pathways are activated even when the same stimulus is applied,[100] suggesting a possible intrinsic dysfunction of the pain pathway or central processing of pain. Furthermore, magnetoencephalography was performed in TMD patients and demonstrated evidence of altered brain responses to innocuous tactile stimulation above the masseter muscle compared to healthy controls.[101] These findings support the presence of abnormal central pain processing in TMD.

Neuroimaging studies are limited in IC/PBS. Using an acoustic startle paradigm, increased central nervous system excitability in response to a visceral-related threat was seen in female PBS/IC patients compared to healthy controls.[102] In a similarly designed paradigm, comparable findings were found in IBS patients compared to controls.[103]

In CFS patients, low perfusion of the brainstem was observed compared to healthy controls using brain single-photon emission computed tomography (SPECT) imaging.[78] In another study, PET scans of the brain demonstrated decreased metabolism in the right mediofrontal cortex and brainstem in CFS patients compared to healthy controls.[79] Another brain perfusion imaging study was conducted in CFS patients without current depressive symptoms, patients with depression, and healthy controls. Both CFS and depression patients had increased perfusion to the right thalamus, pallidum and putamen, while CFS patients also had increased perfusion to the left thalamus.[104] Despite the limitations that depression patients were taking tricyclic antidepressants and that a high proportion of CFS patients had a prior history of depression and were on antidepressants, this study suggested a possible role of an overactive thalamus associated with hypervigilance and hyperattentiveness in CFS patients.[104] However, neuroimaging studies have reported contradictory results in CFS,[105,106] and therefore the role of structural or functional changes in the brain in the pathogenesis of CFS is not yet well understood.

In summary, brain imaging is an innovative research tool to study the role of CNS alterations in IBS and other functional somatic syndromes. Neuroimaging modalities, analytical methodology, and types of stimuli differed in many of these studies. However, in response to painful stimuli, there were similar brain regions, which were activated in the different functional pain syndromes. These included sensory processing regions (i.e., thalamus, insula), and cognitive and affective processing regions (i.e., ACC). Therefore, these studies suggest there are shared alterations in central circuits involved in sensory perception that may contribute to the etiology of these syndromes.

Peripheral immune activation

There are multiple components within the immune system such as T lymphocytes, mast cells, cytokines, and toll-like receptors (TLR) that have been postulated to play a role in pathophysiology of IBS. Mediators released by immune cells, such as mast cells, have been proposed to increase the sensitivity of primary sensory afferents in IBS patients and to lower the pain threshold. Barbara *et al.*[107] found that the mean area of colonic mucosa occupied by mast cells in close proximity to sensory neurons was significantly greater than that in controls. Furthermore, they also showed that the number of mast cells in the vicinity of nerve fibers positively correlated with severity and frequency of abdominal pain/discomfort in IBS patients.[108] In addition, soluble factors, such as proteases, histamine, and serotonin, released from mucosal biopsies of IBS patients were shown to excite human submucosal

neurons.[109] However, in a study by Klooker *et al.*,[110] both hypersensitive and normosensitive IBS patients had fewer mast cells in the rectum and descending colon compared to healthy controls. In addition, tryptase and histamine release in the supernatant of rectal biopsies were similar among IBS patients with visceral hypersensitivity, IBS patients with visceral normosensitivity, and controls.[110]

While elevated levels of certain cytokines from serum or stimulated peripheral blood mononuclear cells have been reported in IBS patients compared to controls, proinflammatory cytokines in the colonic mucosa are not significantly elevated although lower levels of the anti-inflammatory cytokine interleukin, IL-10, have been reported.[111] In one study, IBS patients had increased plasma levels of IL-6 and IL-8, whereas those with IBS and comorbid conditions such as FM, premenstrual dysmorphic disorder, and CFS also had increased plasma levels of IL-1 β and TNF-α.[112] Other recent studies found increased mRNA expression of TLR 3,4, and 5 in the colonic mucosa of rats with colonic hypersensitivity exposed to early life stress.[113] Compared to healthy controls, IBS patients had increased mRNA expression of TLR 4 and 5 and decreased expression of TLR 7 and 8 in the colonic mucosa.[114] Taken together with the finding of increased fecal levels of human β-defensin-2 in IBS patients compared to healthy controls,[115] the innate immune system may play a role in IBS pathogenesis.[114] Chronic stress has been postulated to induce immunologic responses in IBS patients that in turn can lead to altered gut function, including sensory, motor, and secretory changes.[113] Differing views on the role of immunologic responses in pathophysiology of IBS suggest that IBS is a heterogenous condition and there are likely phenotypic subgroups primarily characterized by different biologic mechanisms.

Immune system involvement in the pathogenesis of FD has been studied.[116,117] Eosinophils were found in higher concentrations in the duodenal mucosa of patients with FD compared to healthy controls, but there was no difference in the amount of eosinophils in the stomach.[118] A proposed mechanism of the pathophysiologic role of eosinophils in FD is immune activation with cytokine release that can result in pain, neural excitation, and muscle spasm.[116] For example, when an allergen or infection disturbs the duodenum, eosinophils are activated, which in turn, release cytokines and other degranulation products such as nerve growth factors and major basic proteins.[119] These degranulation factors can directly act on sensory nerves and muscarinic receptors that can lead to neurologic dysfunction and increased smooth muscle contractions.[119] In addition, immune system dysfunction following an infectious gastroenteritis has also been associated with FD. Duodenal biopsies showed increased macrophages and areas of focally concentrated T-cells in “post-infectious FD.”[120] These studies suggest that immune dysregulation exists in FD, although further studies are needed.

Although limited, immune system dysfunction has also been studied in FM.[121,122] A study by Blanco *et al.*[121] demonstrated evidence of tissue injury from skin biopsies in FM patients, including the presence of proinflammatory cytokines, increased mast cells, IgG deposits, and expression of nociceptive glutamate NMDA receptors. They postulated a potential role of mast cells in releasing proinflammatory products that then results in “CNS hypersensitivity” along with fatigue, pain, and other local and systemic symptoms of FM.[121] Another study hypothesized that corticotropin-releasing hormone (CRH) and substance P trigger the release of mast cells resulting in an enhanced inflammatory state.[122] Although there are studies that support the presence of elevated cytokines and immune dysfunction in fibromyalgia,[123-126] other studies do not.[127] Additional elucidation is needed.

In TMD, immune dysfunction has been hypothesized to play a pathophysiologic role.[128,129] The presence of elevated levels of immunoglobulins in temporomandibular joint synovial

fluids was thought to result in an inflammatory reaction where complement activation ultimately leads to articular cartilage damage through increased blood vessel permeability, which allows entry of lysosomal enzymes.[128] Another study found a positive correlation between joint effusion at the tempormandibular joint and levels of cytokines, such as IL-1, IL-6 and tumor necrosis factor (TNF) receptors I and II, in TMD patients suggesting that joint effusions in TMD are inflammatory.[129]

Immune system involvement, particularly that involving mast cells, has been proposed in IC/PBS.[130,131] Mastocytosis, or increased mast cells, has been shown in the bladder of a subset of patients with IC.[130,132] Mastocytosis has been more commonly demonstrated in IC/PBS with Hunner's ulcers than IC/PBS without ulcers, however, this discrepancy may be due to methodological differences.[131] Two studies demonstrated increased mast cells in the bladder of IC/PBS patients although there were differences in location (detrusor, submucosal layer) and type of IC/PBS.[133,134] It has been speculated that mast cells within the bladder uroepithelium can release neurotransmitters and neuropeptides, which then activate C-fiber afferent sensory nerves, which ultimately results in visceral hypersensitivity and hyperalgesia.[131] Another proposed mechanism is that mast cells release granules (i.e., IL-6, glycoprotein-like substances), which cause vasodilatation, inflammation, muscle contraction, and inflammation.[133,135]

Chronic fatigue syndrome has also been associated with mast cells and immunologic dysfunction.[77,136] Overproduction of proinflammatory cytokines (e.g., TNF-α),[137] other inflammatory markers (i.e., C-reactive protein [CRP], beta2-microglobulin),[74] and reduction of natural-killer cells have been demonstrated in CFS compared to healthy controls. These immune system markers are thought to be associated with the flu-like symptoms and fatigue seen in CFS.[136,138] However, other studies demonstrated that when body mass index and other patient factors (age, depression, etc.) were taken into account, there were no major differences in levels of inflammatory markers (i.e., CRP, IL-6) between controls and CFS patients.[139,140] Interestingly, in a subset of patients with CFS, IBS, and FM, no IgE-mediated food hypersensitivity was found.[141]

In summary, the immune system seems to play a pathophysiologic role in at least a subset of patients with these functional somatic syndromes. Common immune markers of interest are mast cells and proinflammatory cytokines such as TNF-α, IL-1 and IL-6. Although enhanced immune activation has been hypothesized to have a pathophysiologic role in symptom development, further studies demonstrating a convincing causal association between immune markers and symptom expression are needed.

Post-infectious etiology

Post-infectious IBS (PI-IBS) is by description the onset of IBS symptoms following an infectious gastroenteritis.[142] This form of IBS is more commonly characterized by non-constipation predominant IBS with findings of elevated immune cells in rectal biopsies.[142] In a recent review, the patient reported incidence of PI-IBS ranged from 4% to 36%.[143] PI-IBS has been reported following bacterial infections, such as Salmonella, Shigella, and Campylobacter, although it has also been associated with viral[144] and parasitic infections.[145] Proposed risk factors for PI-IBS include female gender, severe infection, and chronic stress at the time of the infection.[146]

Although there is less extensive data than in IBS, infectious agents have also been associated with the onset of FD.[117,147,148] Suzuki *et al.*[147] proposed that *H.* pylori-associated FD is due to abnormal ghrelin or leptic secretion, altered expression of muscle-specific microRNAs, and duodenal inflammatory cell infiltration. However, the association between *H.* pylori and FD has been questioned because some studies do not show eradication of FD symptoms

after *H. pylori* eradication.[149,150] *Giardia lamblia* infection has been also associated with FD.[148] Patients who experienced a *G.* lamblia infection completed structured surveys and questionnaires 12–30 months later and 24% patients met Rome II diagnostic criteria for FD.[148] Another study conducted in Spain found a five-fold increase in the incidence of dyspepsia following Salmonella gastroenteritis.[151] The mechanism underlying postinfectious functional dyspepsia is still not clear, but persistent T-cell aggregates, increased duodenal macrophages, immune activation, and impaired gastric accommodation with dysfunction in gastric nitrergic neurons have been hypothesized to have etiologic roles.[117]

The onset of FM has also been associated with infection.[152] Associations between FM and hepatitis C, HIV, parvovirus, and chronic Lyme disease have been reported.[153-156] However, other studies failed to demonstrate a relationship between infections such as hepatitis C and FM.[157,158] Despite reported associations between infection and FM, no definite causal–effect relationship has been described.

Studies assessing a relationship between infection and TMD are limited. Case reports of tuberculosis in the temporomandibular joint has been reported,[159,160] although it is not known if this infection is associated with the persistent pain observed in the TMD patients.[159,161] In pediatric patients with TMD (from infancy to 18 years of age), approximately 18.4% had a prior history of infection of the surrounding structures of the temporomandibular joint such as chronic otitis media, staphylococcus infection, or parotid gland infection leading to septic arthritis.[162] Furthermore, TMD symptoms in HIV patients receiving antiviral treatment has been reported,[163] suggesting a possible association between HIV and TMD. As most studies are small and limited, more information is needed to demonstrate if a “post-infectious TMD” syndrome exists.

Although IC/PBS is clinically diagnosed in the absence of a urinary tract infection, an association with prior urinary tract infections has been found.[164,165] Furthermore, gynecological infections have also been demonstrated in patients with IC/PBS.[166] In a study by Berger *et al.*,[165] bacteriuria was found in IC/PBS, although no symptom improvement was seen with resolution of bacteriuria with antibiotics and symptom flares were not associated with episodes of bacteriuria.[165,167] Thus, a clear etiologic link between infection and IC/PBS has not been confirmed.

Infectious agents, including bacteria, protozoa, and viruses, have long been suspected as playing a causal role in CFS, which has also been labeled “post-infectious fatigue syndrome.”[168,169] Mycoplasma infection has been associated with CFS.[170] Postulated pathophysiologic mechanisms to explain this relationship include dysregulation of the synthetase/RNase L antiviral pathway and immune system dysregulation (e.g., mycoplasmas acting as T- and B-cell activators).[170] Also, viruses such as human herpes virus and a xenotropic murine leukemia related virus have been shown to be associated CFS. Viruses are hypothesized to cause CFS in part due to their damaging effects on T-cell memory function.[171,172] In addition, about 5% of patients who have had Giardia enteritis subsequently developed a post-infectious fatigue syndrome. Similar to that observed with PI-IBS, these patients were found to have experienced more stressful life events prior to getting the Giardia infection.[173] Another study showed increased risk of having CFS and IBS after following a cohort of a population exposed to acute giardiasis outbreak, with relative risk of having both CFS and IBS post exposure as 6.8 (95% CI 5.3-8.5).[174] However, not all studies were able to find a close association between infection and CFS.[175] Therefore, although it may be still premature to state that there is a causal relationship, an association appears to exist.

In summary, infection has been proposed as a pathophysiologic factor contributing to the development of these functional somatic syndromes. It appears that infectious source can be bacterial, viral, or parasitic.

Neuroendocrine dysregulation

Given the stress-sensitive nature of IBS and other functional pain syndromes, hypothalamic-pituitary-adrenal (HPA) axis function at basal states and in response to hormone challenge or stress have been studied. Although alterations in HPA axis activity have been reported in IBS patients, some studies report an increased response whereas others show no or a blunted response at baseline or provoked by stress or hormone challenge,[176] In one study evaluating the basal circadian rhythm of ACTH and cortisol in women with IBS (with or without FM) and healthy women, both IBS and IBS+FM patients demonstrated blunted ACTH and elevated cortisol levels suggesting a dysregulated HPA axis compared to controls.[177] In patients with IBS and healthy controls, early adverse life events, such as childhood abuse and parental loss, were associated with an enhanced cortisol response to a visceral stressor.[178]

In FD, studies evaluating neuroendocrine dysregulations have been performed.[179] In a relatively small study by Bohmelt *et al.*,[179] HPA axis function was compared in patients with IBS, non-ulcer dyspepsia, or IBS with coexistent non-ulcer dyspepsia, and healthy controls. Results suggested attenuated pituitary and adrenocortical activity in the patient group who had lower salivary cortisol levels and a less robust response to CRH.[179] In a study by Mutsuura *et al.*,[180] a relationship between HPA axis function and mood was reported in FD and other functional syndromes (patients had a diagnosis of either FD, IBS, chronic tension headaches, CFS, chronic pain, or other functional GI disorder) compared to healthy controls. In the patient group, there was a negative correlation with depressive mood and morning free salivary cortisol although a positive correlation was observed in healthy controls.[180] Although these studies showed some evidence of HPA axis dysregulation in FD patients, limitations included combining FD with other functional syndrome, differences in medications used by these patients, and underlying comorbid depression/anxiety/or stress state, which may affect cortisol levels.

In FM patients, abnormalities in the HPA axis have been more extensively studied.[181,182] For example, in a recent study, free salivary cortisol levels were measured at multiple times of the day in FM patients and healthy controls, who also completed questionnaires assessing psychophysiological measures, such as sleep disturbances and perceived stress. FM patients demonstrated significantly lower cortisol levels throughout the day as well as higher scores on the psychophysiological assessments (i.e., more perceived stress, sleeping problems).[182] Although some studies showed blunted cortisol levels in FM patients, other studies did not demonstrate statistically significant decreased cortisol levels.[183,184] Differences in methodology, patient characteristics, and other factors could explain the contrary results.

Studies have investigated the role of the HPA axis in TMD, although to a lesser extent than IBS and FM. Elevated cortisol levels were observed in TMD patients.[185,186] However, in another study, morning free salivary cortisol levels did not differ between TMD patients and healthy controls.[187]

In IC/PBS, HPA axis function involvement has been studied as well. In a study by Lutgendorf *et al.*,[188] 24-h urine cortisol and free salivary cortisol were measured at various times of the day and did not differ between IC/PBS patients and healthy controls. However, within the IC/PBS group, there was a negative correlation between cortisol level and urinary symptoms, particularly urinary urgency.[188] Interestingly, cats with naturally occurring IC demonstrated smaller adrenal gland size at autopsy with decreased adrenal reserve and

increased CRF activity, suggesting enhanced negative feedback of glucocorticoids at the adrenal level.[189,190]

There has also been interest in HPA axis function in CFS, because symptoms of fatigue are shared by CFS and Addison's disease and are explained in part by low cortisol levels.[191,192] Papadopoulos and Cleare[191] summarized the four main features of low cortisol levels in CFS: a mild degree of hypocortisolism, attenuated diurnal variation of cortisol, enhanced negative feedback, and blunted HPA axis responsiveness.

Basal and stimulated HPA axis functions are highly dynamic and affected by a multitude of factors, and thus, it is not entirely surprising that results can be inconsistent. However, studies overall suggest that HPA axis dysregulation exists in IBS and other related functional syndromes. It is possible that early dysregulation of the HPA axis results in elevated HPA axis hormone levels, whereas more prolonged dysregulation leads to ultimately blunted cortisol levels due to ineffective HPA axis responsiveness.

Genetic factors

A genetic disposition to developing IBS or other chronic functional pain syndromes has been advocated. Multiple candidate genes are being studied, but those that have been linked to IBS include genes that encode for serotonin-related proteins (e.g., SERT, $5HT_3$-receptor), noradrenergic signaling markers (e.g., alpha-adrenergic receptor), and immunologic markers (e.g., IL-10).[193-195] Relatives of IBS patients are two to three times more likely to have IBS than others.[196] Furthermore, family case studies of IBS patients have shown a familial aggregation of IBS, however, these studies were limited by confounding factors such as environmental exposure and shared disease susceptibility genes for other IBS risk factors (e.g., depression, anxiety).[193] Although a few candidate gene polymorphisms may be associated with IBS, studies are limited by relatively small sample sizes, lack of reproducibility in larger studies, and the heterogeneity and lack of reliability of the clinical phenotype of IBS.[196]

In FD, genetics involvement in the pathophysiology is also being studied. Interleukin and migratory inhibiting factor genes were found to be associated with the FD subset of patients with *H.* pylori.[197] Other genes of interest in FD are serotonin receptor promoter genes, catechol-o-methyltransferase (COMT), cyclooxygenase-1, and G protein activated MPA kinase pathway (GNβ3).[198] However, a clear link between specific genetic polymorphisms and FD symptoms has yet to be demonstrated.

Genetic factors have been studied in FM. Proposed genes of interest include those associated with COMT, serotonin receptors, and mu-opioid receptor (OPRM1).[199,200] Gene x experience interactions were found with genetic polymorphisms of COMT and OPRM1. Specific genotypes were associated with changes in daily positive affect regardless of increased daily pain ratings.[199]

Investigations attempting to identify a cluster of genes, which play a role in pain syndromes, particularly TMD, are ongoing. Genes of interest include those that encode for COMT,[201] beta-2 adrenergic receptor,[202] and estrogen receptor.[203]

In IC/PBS, familial clustering[204] and twin studies[204] suggest that a genetic susceptibility to developing IC/PBS exists. Although there are concerns for confounding factors in genetic association studies in IC/PBS, the presence of a greater concordance of IC/PBS in monozygotic compared to dizygotic twins supports that genetic factors play a role in IC/PBS and that not all of the inheritance pattern is attributed to environmental factors or comorbid conditions.

There are various genes of interest in FM and CFS, such as those linked to COMT and glucocorticoid and mineralocorticoid receptors.[205] Also, glutamate receptor genes involved in the circadian rhythm have been studied in CFS.[206] In a recent meta-analysis, 11 genes were identified, which may be associated with CFS symptoms.[207] For example, the symptom of fatigue in CFS has been hypothesized to be associated to the gene WAVE3, which is involved in regulation of brain cytokines.[207] One limitation of gene association studies in CFS is the presence of co-morbidities that may confound results.[208-210]

Currently, genetic studies suggest that individual genes have relatively small effects and multiple genes combined with environmental and developmental factors may collectively increase the vulnerability to developing these functional pain syndromes.

CONCLUSION

In summary, defining the exact pathophysiologic mechanisms underlying IBS and other functional pain syndromes still remains elusive. Various mechanisms such as enhanced pain perception, altered brain activation, dysregulations in immunologic and neuroendocrine function, and genetic factors appear to be involved to some extent. Whether one proposed mechanism predominates over another, and whether there is one unifying mechanism explaining these functional disorder requires further study. However, when examining some of the GI and non-GI functional disorders, key unifying features can be observed. First, these functional disorders tend to overlap within the same individual. Second, studies have demonstrated common pathophysiologic disturbances, such as the presence of central sensitization associated with enhanced pain perception. Third, these disorders are often responsive to similar treatment interventions, such as antidepressants and psychological and behavioral therapies. Studies are increasingly supportive of the possibility that these disorders are multifactorial and patient populations may cluster into phenotypic subgroups that are characterized by a unique set of pathophysiologic mechanisms and treatment responses.

Abbreviations

ACC	anterior cingulate cortex
CFS	chronic fatigue syndrome
FD	functional dyspepsia
FGID	functional gastrointestinal disorders
FM	fibromyalgia
fMRI	functional magnetic resonance imaging
GI	gastrointestinal
IBS	irritable bowel syndrome
IC/PBS	interstitial cystitis/painful bladder syndrome
IL	interleukin
PET	positron emission tomography
SPECT	single photon emission computed tomography
TMD	temporomandibular joint disorder
TNF	tumor necrosis factor

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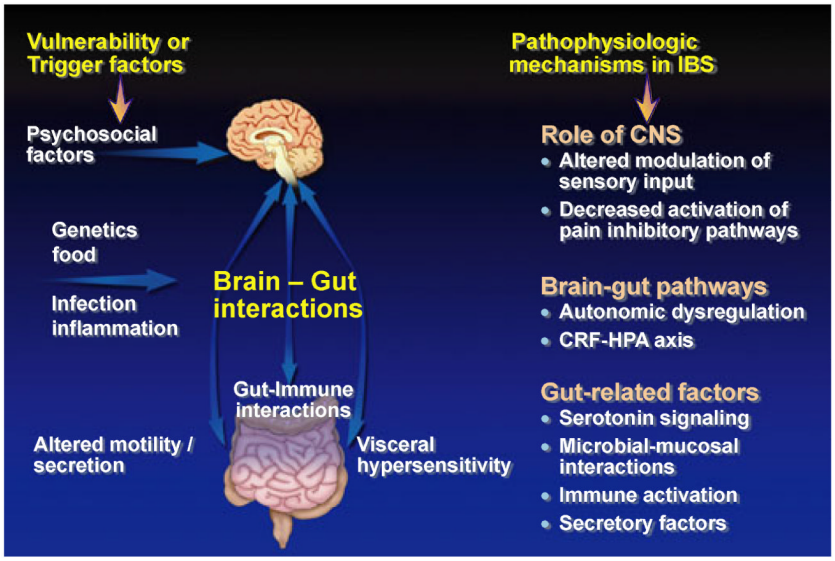

Figure 1.

Factors that increase the vulnerability of developing irritable bowel syndrome (IBS) or trigger symptom onset include psychosocial symptoms, genetic factors, and infection. The physiological effects of psychological and physical stressors on gut function and brain–gut interactions are mediated by outputs of the autonomic, neuroendocrine, and pain modulatory responses. Patients show an enhanced responsiveness of this system manifesting in altered modulation of gastrointestinal motility and secretion and in alterations in the perception of visceral events. Pathophysiologic mechanisms reported in IBS include alterations in central processing and modulation of sensory input, autonomic and neuroendocrine responses, and gut-related factors. Functional brain imaging techniques are beginning to identify brain circuits involved in the perceptual alterations. Adapted from[229]. This figure has been reproduced with permission of the International Association for the Study of Pain ® (IASP ®). The figure may not be reproduced for any other purpose without permission.

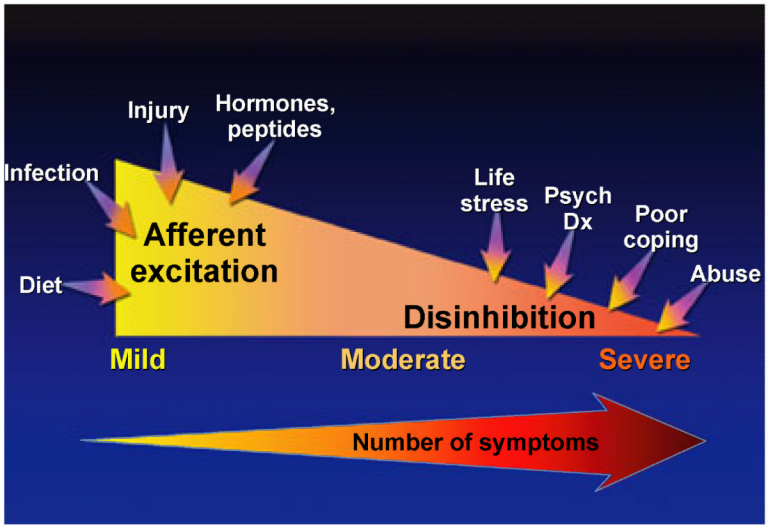

Figure 2.

Peripheral and central influences on severity of functional pain syndromes. This figure depicts multiple factors which may contribute to pain symptoms in functional pain syndromes. Afferent excitation and thus upregulation of afferent pathways may be observed in patients with mild to moderate symptoms with contributory factors being diet, infection, injury, hormones, and peptides. Moderate to severe symptoms may be due to disinhibition at the level of central modulation of pain leading to a lack of inhibitory effects at the peripheral afferent level. Contributory factors associated with increasing severity include life stressors, greater psychosocial disturbances, poor coping skills, and abuse. Concurrently, there is an increase in symptom reporting. Adapted from[229]. This figure has been reproduced with permission of the International Association for the Study of Pain ® (IASP ®). The figure may not be reproduced for any other purpose without permission.

Table 1

Selected functional pain disorders

	IBS	FD	FM	CFS	TMD	IC/PBS
Definition	A functional bowel disorder in which abdominal pain or discomfort is associated with defecation or a change in bowel habit, and with features of disordered defecation[30]	Presence of symptoms thought to originate in the gastroduodenal region, in the absence of any organic, systemic, or metabolic disease that is likely to explain the symptoms[211]	Chronic widespread somatic pain and is typically associated with fatigue, anxiety, sleep disturbances, and/or cognitive dysfunction[37]	Intense fatigue of an unknown cause, which is permanent and limits the patient's functional capacity producing various degrees of disability[47]	Pain of the masticatory musculature and/or the temporomandibular joint and associated structures[40]	Suprapubic pain related to bladder filling, with other symptoms such as increased daytime and nighttime frequency in the absence of proven infection or other pathology[45]
Prevalence (%)	10–15[6]	11–29[15]	2–5[24,25]	0.1–1[40]	6–12[30]	0.002–0.1[46]
Female : male ratio	1.5–2 : 1[30,212]	1–1.5 : 1[34,213]	7–9 : 1[214]	3 : 1[215]	4 : 1[216]	5–10:1[46]
Usual age of onset or at time of diagnosis (years)	29–33[212]	15 and up[34]	25–60[214]	40–56[217]	~14[218]	42–46[219]

Table 2

Overlap between irritable bowel syndrome (IBS) and other functional pain disorders

Disorder	Prevalence of IBS in patients with the disorder	Prevalence of the disorder in patients with IBS
Gastrointestinal		
Functional dyspepsia	11–37%[8]	32%[220]
Non-gastrointestinal or somatic		
Fibromyalgia	30–70%[221,222]	32%[223]
Chronic fatigue syndrome	35–92%[224,225]	14%[10]
Temporomandibular joint disorder	64% *[9]	16% *[9]
Interstitial cystitis	30.2–40%[226,227]	35% †[228]

* Based on one study.

† Includes all pelvic pain disorders.