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SPECIAL REPORTS AND REVIEWS

Systematic Review of the Comorbidity of Irritable Bowel Syndrome With Other Disorders: What Are the Causes and Implications?

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Background & Aims: **Comorbid or extraintestinal symptoms occur frequently with irritable bowel syndrome and account for up to three fourths of excess health care visits. This challenges the assumption that irritable bowel is a distinct disorder. The aims of this study were to (1) assess comorbidity in 3 areas: gastrointestinal disorders, psychiatric disorders, and nongastrointestinal somatic disorders; and (2) evaluate explanatory hypotheses.** ***Methods:*** **The scientific literature since 1966 in all languages cited in Medline was systematically reviewed.** ***Results:*** **Comorbidity with other functional gastrointestinal disorders is high and may be caused by shared pathophysiological mechanisms such as visceral hypersensitivity. Psychiatric disorders, especially major depression, anxiety, and somatoform disorders, occur in up to 94%. The nongastrointestinal nonpsychiatric disorders with the best-documented association are fibromyalgia (median of 49% have IBS), chronic fatigue syndrome (51%), temporomandibular joint disorder (64%), and chronic pelvic pain (50%).** ***Conclusions:*** **Multivariate statistical analyses suggest that these are distinct disorders and not manifestations of a common somatization disorder, but their strong comorbidity suggests a common feature important to their expression, which is most likely psychological. Some models explain the comorbidity of irritable bowel with other disorders by suggesting that each disorder is the manifestation of varying combinations of interacting physiological and psychological factors. An alternative hypothesis is that the irritable bowel diagnosis is applied to a heterogeneous group of patients, some of whom have a predominantly psychological etiology, whereas others have a predominantly biological etiology, and that the presence of multiple comorbid disorders is a marker for psychological influences on etiology.**

Patients with irritable bowel syndrome (IBS) are about twice as likely as comparison groups to be diagnosed with a variety of other, nongastrointestinal somatic disorders (Table 1). Herein, we discuss the most common of these disorders to see what light they may shed on the etiology of IBS. Before we do so, however, it is important to appreciate the sheer number of these comorbid symptoms and disorders, as well as their impact on quality of life and health care costs:

1. Levy et al.[1] reported that IBS patients make twice as many health care visits per year as age-matched controls, and as Figure 1 shows, 78% of the excess health care visits are for nongastrointestinal somatic complaints. Drossman et al.[2] also reported that IBS patients make 3 times as many nongastrointestinal health care visits as control subjects.
2. Approximately 50% of IBS patients from primary care and gastroenterology clinics have at least 1 comorbid somatic symptom.[3] So common is the reporting of nongastrointestinal comorbid complaints in IBS patients that 1 group of investigators has suggested that this reporting be used as a diagnostic criterion for IBS.[4]
3. IBS patients also incur more than twice the health care costs of non-IBS patients; 66% of these excess costs are for nongastrointestinal indications.[5]
4. Patients with 1 or more comorbid somatic disorders report more severe IBS symptoms,[6,7] more anxiety and depression,[8] greater impairment in quality of life,[3,9] and more illness-related absenteeism[3] than IBS patients without comorbid disorders.

Investigating the origins of comorbidity in IBS is important, because this may provide clues to reducing

Abbreviations used in this paper: ANS, autonomic nervous system; CFS, chronic fatigue syndrome; CNS, central nervous system; IBS, irritable bowel syndrome; TMJ, temporomandibular joint disorder.

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Table 1. Prevalence of Comorbid Medical Conditions in IBS

Study	Methods	Subjects	Findings	IBS criteria and comments
Sperber et al. 1999[9]	Physical testing for FM and questionnaires	79 IBS, 72 non-IBS controls, 100 FM	31.6% of IBS (OR, 7.5) had FM, 32% of FM pts had IBS	Rome criteria, IBS + FM worse physical functioning and quality of life than IBS only or FM only
Sperber et al. 2000[7]	Questionnaire	75 IBS 69 matched CONT	33.3% of the IBS pts had FM[a]	Rome criteria, Bowel disease severity IBS + FM > IBS only
Jones et al. 2001[40]	Questionnaire	3912 GI pts; including 270 IBS	IBS had higher prevalence of several self-reported disorders compared to GI pt controls: HA 51% (OR: 1.46), BP 38% (OR: 1.41), PMS 18% (OR: 2.25), TMJ 16% (OR: 2.0), CFS 14% (OR: 2.0), DM 10% (OR: 2.0)	Criteria: Pt. report of past diagnosis
Barton et al. 1999[19]	Physical testing for FM and sicca complex	46 IBS, 46 CONT	28% of IBS pts had FM (OR: 2.54)	Rome criteria
Veale et al. 1991[20]	Interview, physical exam, sigmoidoscopy	20 IBS 20 FM 20 IBD 20 inflammatory arthritis 20 CONT	65% of IBS had FM (OR: 5.4); 70% of FM pts had IBS (OR: 7.0)	Criteria: Other
Kennedy et al. 1998[51]	Community survey (England)	3169 respondents including 546 with IBS, 442 with BHR, and 539 with GERD	22.7% of IBS pts had BHR (OR, 1.9), 28% of individuals with BHR had IBS[a]	Manning criteria
Walker et al. 1996[8]	Interview	60 IBS, 26 IBD	35% of IBS reported CPP (OR, 2.54)	Rome criteria
Yunus et al. 1989[21]	Physical testing for FM and interview	113 FM, 77 RA, 67 CONT	36% of FM pts had IBS (OR, 6.8)	Criteria: Other
Prior & Whorwell, 1989[44]	Interviews with 1-year follow-up	80 gynecology pts. with CPP	52% of CPP had IBS-type symptoms[a] IBS symptoms associated with symptom persistence at follow-up and less objective findings	Criteria: Other No control group
Alagiri et al. 1997[48]	Survey of IC pts	2405 pts with interstitial cystitis	30.2% of IC patients reported diagnosis of IBS	Criteria: Self-reported diagnosis No control group
Aaron et al. 2000[30]	Questionnaire, physical exam	25 CFS 22 FM 25 TMJ 22 healthy CONT	Lifetime history of IBS found in 92% of CFS pts (OR, 5.1), 77% of FM pts (OR, 4.3), 64% of TMD pts (OR, 3.6), and 18% of CONT	Pt. report of past diagnosis
Korszun et al. 1998[35]	Chart review, questionnaire	93 pts with FM, CFS, or FM + CFS	46% reported IBS diagnosis	Criteria: Pt. report of past diagnosis
Gomborone et al. 1996[36]	Questionnaire	1797 CFS	63% of CFS pts met IBS criteria over past year	Manning criteria
Goldenberg, 1987[28]		118 FM	52% of FM had IBS	Criteria: Other
Hudson et al. 1992[31]	Interview	33 female FM pts, 205 CONT	52% (OR, 26.0) lifetime prevalence of IBS in FM	Criteria: Thompson et al. 1989
Walker et al. 1991[41]		CPP	79% of CPP had IBS symptoms	Criteria: Other
Endicott, 1998[37]	Interview + physical work-up for CFS	46 CFS, 92 physically healthy CONT, 46 unselected controls	35% of CFS (OR: 3.5) had history of IBS diagnosis	Criteria: Pt. report of past diagnosis. All groups psychiatric samples
Zondervan et al. 1999[42]	Tracking of course of disease	5051 CPP patients	29.1% of CPP patients received IBS diagnosis	Criteria: Diagnosis documented in medical records
Aaron et al. 2001[52]	Questionnaire	127 CFS with 127 non-CFS healthy co-twins	59% of CFS had IBS (OR, 6.6)	Criteria: Pt. Report of past diagnosis

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Table 1 (continued). Prevalence of Comorbid Medical Conditions in IBS

Study	Methods	Subjects	Findings	IBS criteria and comments
Prior et al. 1989[44]	Questionnaire	798 gynecology referrals vs. 321 dermatology and ENT CONT	IBS identified in 52.4% of dyspareunia (OR, 1.9), 50% of dysmenorrhea (OR, 1.8), 44.4% of urinary symptom presenters (OR, 1.6), 40% of nonmenstrual bleeding (OR, 1.44)	Manning criteria
Longstreth et al. 1990[43]	Interview	86 CPP laparoscopy pts., 172 hysterectomy pts, 172 CONT	47.7% of CPP met criteria for IBS (OR, 1.49)	Criteria: Other
Yunus et al. 1981[21]		50 FM, 50 CONT	34% of FM pts had IBS (OR, 4.25)	Criteria: Other
Sivri et al. 1996[24]	Questionnaire	75 FM, 50 CONT	41.8% of FM pts had IBS (OR, 2.6)	Criteria: Drossman et al. 1982
Triadafilopoulos et al. 1991[29]	Questionnaire	125 FM, 54 degenerative joint disease, 46 CONT	60% of FM pts had IBS[b]	Criteria: Drossman et al. 1982
Morriss et al. 1999[39]	Interview	77 CFS-only, 42 CFS + depression, 26 depressed non-CFS	49% of CFS-only pts had IBS[a]	Rome criteria
Romano, 1988[26]	Questionnaire, history, physical exam	100 primary FM, 100 secondary FM, 100 arthritis controls	49% of primary FM, (OR, 5.4) 19% of secondary FM (OR, 2.1) had IBS	Criteria: Other
Yunus et al. 2000[23]	Questionnaire and FM physical testing	469 female FM, 67 male FM, 36 male CONT	IBS identified in 38.9% of female FM[a] and 13.8% of male FM[b]	Criteria: Other
Wolfe et al. 1990[16]	Questionnaire	293 FM, 265 CONT	36% of FM met IBS criteria (OR, 2.8)	Criteria: Other
Wolfe et al. 1995[17]	Community telephone survey	60 FM	48% of FM met IBS criteria (OR, 2.5)	Criteria: Other
Campbell et al. 1983[27]	Questionnaire	22 FM, 22 CONT	50% of FM had IBS (OR, 10)	Criteria: Other

[a]Odds ratio could not be calculated as there was no appropriate control group, or control group statistic was not reported.
[b]Odds ratio could not be calculated as none of the CONT subjects had IBS.
BHR, bronchial hyper-responsiveness; CFS, chronic fatigue syndrome; CONT, control subjects; CPP, chronic pelvic pain; DM, dysmenorrhea; FM, fibromyalgia; HA, headache; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; PMS, premenstrual syndrome; TMJ, temporomandibular joint disorder.

health care costs and treating IBS more effectively. More fundamentally, however, the extent of comorbidity challenges the concept that IBS is a distinct diagnostic entity rather than a variant of a psychiatric[10,11] or a neuroendocrine[12,13] disorder. In this review, we begin by examining the disorders and the symptoms that overlap with IBS at greater than chance levels to see whether they share any common pathophysiologic or psychological mechanisms with IBS. We then review studies that examine the comorbidity of IBS with multiple other symptoms or disorders to test the hypothesis that IBS is not a distinct diagnostic entity, but rather part of a general somatoform disorder. Finally, we review hypotheses that attempt to provide a unitary explanation for the comorbidity of IBS with other disorders, and we offer our own view.

Methodologic Considerations

We searched the world medical literature indexed in Medline from 1966 to the present for the following terms: irritable bowel syndrome, IBS, functional bowel, and colonic disorders–functional, in conjunction with the terms comorbidity, comorbid disorder, psychiatric illness, psychiatric disorder, mental disorder, somatoform disorder, anxiety, anxiety disorder, depression, depressive disorder, panic, panic disorder, somatization, fibromyalgia, chronic fatigue syndrome, headache, temporomandibular joint, TMJ, temporomandibular joint dysfunction /disorder, TMD, pelvic pain, and interstitial cystitis. Articles in any language were included if they (1) examined the prevalence of IBS and at least 1 other disorder (somatic, gastrointestinal, or psychiatric) and (2) contained sufficient detail to evaluate how representative

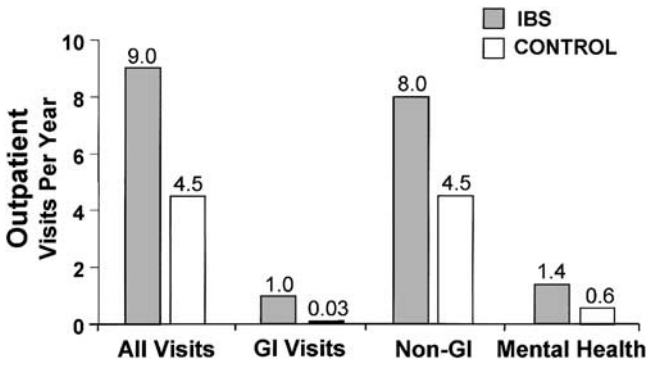

Figure 1. Annual outpatient visits by IBS patients and control subjects. (Data from Levy et al.[1])

the sample was and how diagnosis or classification was made. We also examined the reference section of the articles that we found to identify additional references, and examined abstracts from *Digestive Disease Week 2000*. Books were not included. Review articles were examined for explanatory hypotheses and for additional references. This was a systematic review, not a meta-analysis.

The comorbidity of IBS with other somatic disorders has been the topic of several recent publications, but systematic reviews have not been conducted. Azpiroz et al.[14] reported the consensus of an international working team who concluded that "attempts to lump together different functional syndromes lack any solid base, and only constitute vain speculative exercises based precisely on the absence of information regarding the different conditions" (p. 71). Mayer et al.[15] hypothesized that the extraintestinal symptoms of IBS are caused by unique characteristics of the afferent innervation of the viscera. Most visceral afferents do not follow separate pathways to the brain, but rather converge on dorsal horn cells in the spinal cord that primarily receive afferent information from somatic structures. Visceral afferent fibers from each organ diverge, projecting to multiple spinal segments with resulting overlap. These 2 phenomena render the sensations associated with visceral stimulation vague or "fuzzy" and lead to the referral of visceral pain to other somatic organs. Neither of these articles presented a detailed review of the literature on comorbidity.

It must be acknowledged at the outset that a review of this nature is hindered by the diversity of methods that have been used in this research domain. Studies differ in how they define IBS and other health conditions, and study samples are often drawn from medical subspecialty clinics. General conclusions can be made across studies, because each study assesses cases and controls using the same methodology, but absolute prevalence estimates may not be comparable.

For the purposes of the review, we found it necessary to depart from conventional terminology regarding coexisting symptoms. Gastroenterologists have usually referred to comorbid somatic symptoms as "extraintestinal" symptoms of IBS. This terminology implies that IBS is the primary disorder and that comorbid somatic disorders, such as fibromyalgia, are expressions of IBS. We avoided this rather narrow perspective by using the term "comorbid" somatic symptoms or disorders.

Specific Comorbid Somatic Conditions

Fibromyalgia. Fibromyalgia is a chronic condition of diffuse musculoskeletal pain associated with specific tender points on examination.[12,16] It affects an estimated 2% of the population.[17] The association between IBS and fibromyalgia has been studied more than any other IBS comorbidity. Fibromyalgia occurs in approximately 32.5% (range, 28%–65%) of IBS patients[7,18–21] (Table 1), and IBS occurs in an estimated 48% (range, 32%–77%) of patients with fibromyalgia.[16,18,21–31]

Chronic fatigue syndrome. Chronic fatigue syndrome (CFS) is defined as persistent or prolonged fatigue for more than 6 months causing more than 15% impairment, without medical or psychiatric conditions that can account for the symptoms.[32,33] The prevalence of CFS in the general population has been estimated as 0.4%.[34] Six studies have examined the presence of IBS in patients with chronic fatigue and reported a high degree of overlap, ranging from 35% to 92% (median, 51%).[30,35–39] The only study to date to report on the prevalence of CFS in IBS patients found that 14% reported a CFS diagnosis.[40]

Chronic pelvic pain. Fourteen percent of women report experiencing pelvic pain of more than 6 months at some time.[41] Five studies of patients reporting pelvic pain have shown IBS to be a common comorbid condition, affecting 29%–79% (median, 49.9%) of women with chronic pelvic pain.[8,41–44] Walker et al.[8] similarly found that 35% of women with IBS reported chronic pelvic pain (odds ratio, 2.54).

Temporomandibular joint disorder. Temporomandibular joint disorder (TMJ) is characterized by orofacial pain, restricted jaw movement, and noise in the jaw.[45] It affects 21% of people,[46] but only 5% seek medical care.[47] Aaron et al.[30] reported that IBS was present in 64% of 25 TMJ patients, and Jones et al.[40] found a self-reported TMJ diagnosis in 16% of 270 IBS patients.

Other disorders. Individual reports have suggested significant comorbidity between IBS and a number of other physical conditions, but these isolated findings need to be replicated. IBS was reported

by 30.2% of 2045 survey respondents with interstitial cystitis,[48] compared with a prevalence of IBS in the population of 9.4%.[49] Jones et al.[40] found that 38% of IBS patients self-reported back pain, 18% reported premenstrual syndrome, and 10% reported dysmenorrhea; all of these incidence rates are significantly higher than those in other gastrointestinal patients. Prior et al.[50] found IBS to be common among gynecologic referrals with dyspareunia (52.4%), dysmenorrhea (50%), urinary symptoms (44.4%), and nonmenstrual bleeding (40%). The overall IBS rate in this sample of 798 gynecology patients was 37.3%, significantly higher than that seen in dermatology and ear, nose, and throat clinic patients. Kennedy et al.[51] identified IBS in 22.7% of individuals who had bronchial hyperresponsiveness.

Comorbid nongastrointestinal symptoms. Table 2 lists the nongastrointestinal symptoms (not diagnoses) that are reported significantly more often by IBS patients than by controls. Many of these are musculoskeletal pain symptoms and fatigue symptoms that are consistent with the comorbid diagnoses listed in Table 1. However, Table 2 shows that urinary symptoms consistent with detrusor hyperreflexia (i.e., increased frequency of micturition, urinary urgency, nocturia) or bladder outlet dysfunction (i.e., urinary hesitancy, incomplete bladder emptying) are also common in patients with IBS.

Do the Comorbid Disorders Share Pathophysiologic Mechanisms With Irritable Bowel Syndrome?

The 4 nongastrointestinal conditions just described that are strongly associated with IBS share some clinical features: They are all substantially more common in women, may be triggered or exacerbated by stress, and are associated with fatigue, sleep difficulties, anxiety, and depression. Furthermore, these 4 disorders all have a high degree of overlap with each other.[30,52] It would seem likely that disorders with so many similarities and excess overlap would share a common etiology; however, the evidence to support such a common etiology is unconvincing. The pathophysiologic mechanisms believed to account for the symptoms of IBS include:

1. visceral hypersensitivity[53–55]
2. autonomic nervous system dysregulation[56]
3. smooth muscle hyperreactivity, characterized by exaggerated motility responses to a variety of provocative events[54,57]
4. abnormalities in the levels of neurotransmitters such as serotonin or the receptors for these neurotransmitters[58]
5. sustained activation of the immune system after infection,[59–61] stress, or other psychological factors[62,63]

Table 2. Comorbid Nongastrointestinal Symptoms Significantly More Common in IBS Than Controls and Their Prevalence (% in IBS Patient Samples)

Symptom	Whorwell et al. 1986[101] (n = 100)	Zaman et al. 2001[100] (n = 606)	Jones et al. 2001[40] (n = 88)	Maxton et al. 1991[4] (n = 107)	Nyhlin et al. 1993[173] (n = 128)	Fass et al. 1997[163] (n = 266)
Headache	31	23.1	34	45		
Back pain	61	27.6	44	81		
Low back pain		37.1		88		
Fatigue	63	36.3	47			
Poor sleep	30					
Decreased sex drive		13.4				26.9
Fever (subjective)			6			
Shortness of breath			25			
Wheezing						
Muscle aches or soreness		36.3	29			
Sensitivity to heat or cold			14			
Dyspareunia	42					9.3
Urinary frequency	61	20.5	32	56	41	
Urinary urgency	60					
Urinary hesitancy/difficulty			11			
Nocturia	53					
Incomplete bladder emptying	50					
Pruritis	32					
Bad breath/unpleasant taste in mouth	58	16.3		65		
Palpitations/heart pounding	44		27		13	
Tummy butterflies					13	
Dizziness			27		11	
Stiffness		27.1				

6. sexual trauma history[64–66]

We first considered whether any of these pathophysiologic mechanisms are common to one or more of the nongastrointestinal somatic disorders that overlap with IBS.

Visceral hyperalgesia. Pain sensitivity has been most thoroughly investigated for fibromyalgia and IBS, and the data do not support a common hypersensitivity to pain as the explanation for comorbidity. Although two thirds of IBS patients have lower visceral pain thresholds,[55] their somatic pain thresholds are normal[67] or higher than in normal controls.[68] In contrast, patients with fibromyalgia have decreased somatic pain thresholds but normal visceral pain thresholds.[69,70] It is only the subgroup of patients who have both IBS and fibromyalgia who appear to have both visceral and somatic hypersensitivity.[69]

Autonomic nervous system dysfunction. Tougas[56] speculated that autonomic dysfunction could be the common pathophysiologic mechanism accounting for comorbid symptoms associated with IBS. More than a dozen studies have assessed autonomic nervous system (ANS) activity in IBS, but they have shown inconsistent results, e.g., increased or decreased sympathetic activity[71–75] and/or parasympathetic activity,[76–79] or specific ANS functional abnormalities only in particular symptom subgroups.[74,78,80] ANS function has also been studied in CFS and fibromyalgia, but here also results have been inconsistent, with some studies showing no difference from healthy controls[81–83] but others suggesting elevated sympathetic activity and/or parasympathetic withdrawal.[84–89] In fibromyalgia, studies generally point to elevated sympathetic and decreased parasympathetic activity.[90–92] Little is known about autonomic activity in TMJ. In summary, autonomic abnormalities have been described in 3 of these 4 common comorbid conditions, but the findings are nonspecific (e.g., shift in autonomic balance toward sympathetic predominance), and they characterize a minority of the patients with these disorders; thus, these findings do not suggest a specific physiologic mechanism linking these disorders to IBS.

Hyperreactive smooth muscle. A specific type of ANS dysfunction, smooth muscle hyperreactivity, is seen in IBS[54,93] and may also contribute to detrusor instability and bronchospasm. However, no data are available on such dysfunction in the other IBS comorbid disorders, and smooth muscle dysfunction is unlikely to explain the comorbidity of IBS with musculoskeletal disorders.

Immune dysfunction. Postinfectious IBS occurs in approximately 25% of patients with a new onset of gastroenteritis,[59,60] and a similar etiologic mechanism has been proposed for CFS.[94] However, postinfectious IBS is thought to occur only after gastrointestinal inflammatory reactions, whereas postinfectious CFS is thought to be specific to systemic viral infections. It is not clear how this hypothesis could account for the overlap of IBS with CFS, or how it could account for the comorbidity of IBS with other somatic disorders listed in Table 1.

Serotonin hypothesis. Serotonin is involved peripherally in the regulation of motility and sensation in the gut,[95,96] whereas in the central nervous system (CNS) it is involved in mood disorders.[11] Antidepressants that modify central serotonin levels and possibly also peripheral serotonin levels benefit patients with various chronic pain syndromes[97] including IBS.[98] Similarities in response to antidepressants are consistent with a common pathophysiologic basis for IBS and these other disorders,[97] but this evidence is indirect. No data directly link any of these disorders, except possibly IBS,[58] to abnormalities in serotonin.

Stress reactivity and psychological symptoms. For most of the disorders listed in Table 1, one third to one half of patients are depressed or anxious or they report that their symptoms are worsened by stress and/or they have a psychiatric diagnosis.[99] Moreover, there is some indication that patients with 2 or more of these disorders are more anxious and depressed than patients with only a single diagnosis.[8,18] This suggests that psychological distress may be an etiologic factor common to all of them. However, the psychological symptoms associated with IBS are diverse, and the possible mechanisms linking psychological symptoms to somatic complaints are still speculative. Moreover, when anxiety and depression are entered into regression models to explain comorbidity of IBS with other somatic disorders, they do not explain nearly all the variance.[40,100,101]

Sexual and physical abuse. A history of sexual abuse, and to a lesser degree physical abuse, is more common in IBS than in patients with other gastrointestinal disorders.[65–66,102,103] Sexual abuse is also more common in TMJ,[104–105] CFS,[106] fibromyalgia,[107–108] and chronic pelvic pain,[108–109] and patients with a history of abuse score higher on scales measuring somatization (i.e., the tendency to report multiple somatic symptoms).[110–112] Thus, somatization may be the mediating variable that places individuals with a history of abuse at increased risk for developing both IBS and its most frequently coexisting medical conditions. Consistent with this speculation, Walker et al.[108] found that patients who had both IBS and chronic pelvic pain had significantly higher scores on somatization scales than

those who had only IBS, and logistical regression analysis demonstrated that the mean number of somatization symptoms was the best predictor of which patients had chronic pelvic pain in addition to IBS rather than IBS alone.

Overlap With Other Functional Gastrointestinal Disorders

The comorbidity of IBS with other functional gastrointestinal disorders is even more striking than its overlap with nongastrointestinal somatic conditions; compare Table 3 with Table 1. However, this may have a very different explanation, as follows:

1. It may occur because there is an overlap in the symptoms used to diagnose these disorders; for example, abdominal pain is common to IBS, functional dyspepsia, noncardiac chest pain, and functional anorectal pain.[113]
2. Visceral hyperalgesia is seen throughout the gastrointestinal tract in IBS,[114] including the esophagus,[115] stomach,[116] duodenum,[117] ileum,[118] and colon.[53] This appears to represent a common pathophysiologic mechanism that also contributes to noncardiac chest pain,[119] functional dyspepsia,[120] and possibly levator ani syndrome.[121]
3. Pangastrointestinal motility abnormalities may also contribute to the overlap of functional gastrointestinal disorders. In IBS patients, motor abnormalities have been recorded in the stomach,[122,123] proximal small intestine,[124] and ileum,[125] as well as in the colon and rectum, and there are well-described long reflex pathways that serve to coordinate the transit of nutrients and the elimination of toxins.[126]

So striking is the overlap among the functional gastrointestinal disorders that some have proposed that one term, such as "irritable gut," be used for all of them,[127] and that drugs that are effective for 1 of these disorders may be effective for others as well.[128] However, factor analysis studies continue to show that independent clusters of symptoms correspond to most of the functional gastrointestinal disorders[129–133]; this suggests that they are distinct diagnostic entities despite a high degree of overlap.

Overlap With Psychiatric Disorders

More than 20 studies have assessed the overlap between IBS and psychiatric disorders in the last 3 decades and have found that 54%[134] to 94%[135,136] of IBS patients meet criteria for at least 1 primary (axis I) psychiatric disorder. Most studies show the prevalence of psychiatric disorders in IBS to be 90% or better.[135–140] Drawing conclusions about the prevalence of individual psychiatric conditions based on a review of the literature is fraught with problems, because the most common diagnostic categories–anxiety, depression, and somatization disorders–are known to overlap in medical populations.[141,142] Empirical reports rarely take this factor into account, tabulating prevalences individually for each diagnosis, and several of the studies in this area have not assessed all 3 domains. Furthermore, many of these studies are limited by small sizes and self-selected groups of patients recruited from gastroenterology clinics. Despite these limitations, certain generalizations are possible:

1. Most IBS patients presenting in medical clinics,[135–140] and approximately 18% of people with IBS seen in the community,[143] have 1 or more psychiatric disorders.
2. No single psychiatric disorder is uniquely associated with IBS. However, the psychiatric diagnoses most commonly associated with IBS are major depression, followed by generalized anxiety disorder.
3. Although much attention has been given to the association between IBS and panic disorder, a relatively modest 30% (range, 15%–41%)[41,134–137,140] of IBS patients (modest by comparison with major depression) meet diagnostic criteria for panic disorder. The association between panic disorder and IBS may be overestimated, because the transitory diarrhea and abdominal pain that normally occur during panic attacks (extreme anxiety) may be mistaken for the chronic intermittent symptoms of IBS.
4. Somatization disorder is diagnosed in one fourth to one third of IBS patients. However, the prevalence of somatization disorder is probably underestimated, because the standardized Diagnostic Interview Schedule[144] is known to underestimate the prevalence of this disorder. Furthermore, somatization disorder is only one of several psychiatric diagnoses in the current DSM-IV-TR classification of mental disorders[145] that are collectively called "somatoform disorders"; this list also includes such problems as conversion disorder, pain disorder, and hypochondriasis. Therefore, reported statistics on the association of somatization disorder with IBS represent only a portion of the psychiatric spectrum of somatization.

It is important to distinguish between somatization disorder, which is a psychiatric diagnosis defined by

Table 3. Comorbidity of IBS With Other Gastrointestinal Disorders

Study	Methods	Subjects	Findings	IBS Criteria and Comments
Kennedy et al. 1998[51]	Community survey	3169 respondents including 546 with IBS, 442 with BHR, and 539 with GERD	46.5% of IBS pts had GERD, and 47% of GERD pts had IBS (reported OR for the association: 2.72). 57.5% of subjects had dyspepsia (OR, 2.92)	Manning criteria
Fass et al. 1998[163]	Questionnaire	683 pts with IBS, dyspepsia or both	37.1% of IBS had dyspepsia, 64.9% of dyspepsia pts had IBS	Manning criteria
Caballero-Plasencia et al. 1999[164]	Community survey (Spain)	264 respondents, including 36 IBS and 63 dyspepsia	56% of IBS had dyspepsia (OR, 2.97) and 32% of those with dyspepsia had IBS (OR, 4.0)	Rome criteria
Porcelli et al. 1998[165]	Interview	127 functional GI outpts, 163 gallstone disease	57% of IBS had dyspepsia and 47% of dyspepsia pts had IBS	Rome criteria
Scott et al. 1993[166]	Questionnaire	387 NCCP, 93 CCP, 81 CONT	IBS more prevalent in NCCP than in CCP or CONT	Criteria: Other
Svedlund et al. 1985[167]		101 IBS pts	87% of IBS had dyspeptic symptoms	Criteria: Other
Talley & Piper, 1985[168]	Interview	327 dyspepsia patients	23% of FD+ diagnosed with IBS (42% including those who were also GERD+)	
Sloth & Jorgensen, 1989[169]	Questionnaire	37 pts with nonorganic upper GI pain tracked	54% of FD pts reported IBS symptoms initially, and 35% had IBS symptoms at 5–7 year follow-up	Criteria: Other
Talley et al. 1992[170]	Community survey (USA)	835 respondents	29% of IBS were FD+, 29% of FD were IBS+	Rome criteria
Crean et al. 1994[171]	Questionnaire	1540 GI pts; 22% had FD and 15% had IBS	23% of IBS were FD+, 13% of FD were IBS+	Criteria: Physician diagnosis
Agreus et al. 1996[127]	Community survey (Sweden)	1059 respondents, of which 12.5% had IBS and 14% had dyspepsia	87% of FD were IBS+	Criteria: Other
Whitehead, 1996[172]	Community survey (USA)	Drossman et al., 1993 sample (see below)	28% of FD were IBS+	Rome criteria
Talley et al. 1998[133]	Community survey (Australia)	730 respondents, of which 11.8% had IBS and 11.5% FD	57% of IBS were FD+ (OR, 5.0), and 40% had frequent heartburn	Rome criteria; OR calculated based on FD community prevalence data including IBS
Drossman et al. 1993[49]	Community survey (USA)	5430 respondents; 11.6% had IBS and 13% had dyspepsia	Among respondents meeting IBS criteria, 21.1% had fecal incontinence (OR, 2.7), 34.3% had anorectal pain (OR, 3.0), 42.4% had dyschezia (OR, 3.1), and 28.4 had FD (OR, 2.2). IBS was found in 30.2% of fecal incontinence pts (OR, 2.6), 33.1% of anorectal pain pts (OR, 2.85), 38.9% of dyschezia pts (OR, 3.4), and 37.6% of FD pts (OR, 3.2)	Rome criteria; Odds ratio calculated based on FD community prevalence data including IBS

CCP, cardiac chest pain; FD, functional dyspepsia; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; NCCP, noncardiac chest pain; OR, odds ratio.

explicit criteria,[145] and the behavioral tendency to report multiple somatic complaints, which is what psychological tests of somatization measure. Somatization trait can be defined as a predisposition to experience and report many somatic symptoms that have no pathophysiologic explanation, to misattribute them to disease, and to seek medical attention for them.[146] These 2 concepts are related; somatization disorder is diagnosed when the tendency to report multiple somatic complaints is extreme, involving at

least 3 organ systems and beginning before age 30.[145] However, less severe forms of this behavior are common and are known to have a profound influence on health care utilization.[142,147] The origin of somatization trait is poorly understood, but it appears to be related to modeling and reinforcement of illness behavior during childhood,[1,148,149] stress or anxiety,[150] and early sexual and physical trauma.[110–112]

Is IBS a Distinct Entity or Part of a Global Disorder?

This important question has been addressed by 3 types of studies: measurement of somatization, factor analysis, and multivariate statistical analysis.

Measurement of Somatization

Talley et al.[151] tested the hypothesis that IBS and functional dyspepsia are due to the trait of somatization by administering the Psychosomatic Symptom Checklist to 5 groups of patients: 82 IBS patients, 33 functional dyspepsia patients, 99 patients with organic gastrointestinal disorders, 37 patients with somatoform disorder who were recruited from a pain clinic, and 143 healthy controls. The Psychosomatic Symptom Checklist is a list of 17 diverse symptoms that patients are asked to rate with respect to frequency and intensity. The authors found that the group of patients with somatoform disorder endorsed significantly more items on the Psychosomatic Symptom Checklist than the healthy controls; but the IBS patients were not significantly different from controls. They interpreted this as evidence that IBS and functional dyspepsia are not due to somatization. However, the results are ambiguous, because the IBS group was intermediate between the somatoform group and the healthy controls and not significantly different from either.

Factor Analysis

Whitehead et al.[129–131,152] and Talley et al.[132,151] used exploratory factor analysis to show that gastrointestinal symptoms aggregate together in discrete clusters, providing support for the independence of IBS from functional dyspepsia and other functional gastrointestinal disorders. Robins and Kirmayer[153] used confirmatory factor analysis to show that IBS is associated with a cluster of symptoms that are independent of fibromyalgia, CFS, anxiety, and depression. However, there is moderately high overlap among the patients who endorse these 5 distinct clusters of symptoms, which muddies the waters somewhat.

Multivariate Statistical Analysis

Other investigators[40,100,101] have used multiple regression or analysis of covariance to determine whether the comorbidity of IBS with nongastrointestinal symptoms is explained by psychological traits such as anxiety, depression, and somatization. Statistically adjusting for psychological symptoms reduced the differences between IBS patients and controls in amount of comorbidity but did not eliminate those differences.[40,100,101]

The 3 studies described in this section have limitations and should be replicated. However, they suggest that any adequate theory of what accounts for comorbidity must take 3 characteristics into account:

1. The disorders listed in Table 1 are relatively independent entities. They probably have independent etiologic mechanisms, and they are not different aspects of 1 disorder, such as somatization.
2. However, these disorders overlap much more frequently than would be expected by chance. This suggests that the patients who have these disorders have something in common that is relevant to the expression of all these disorders.
3. The common factor is most likely to be psychological and to involve stress reactivity and/or a tendency to selectively attend to somatic sensations and to amplify their intensity and significance.

Hypotheses to Explain the Comorbidity of IBS With Other Somatic Disorders

Diagnostic Ambiguity

All of the disorders that are comorbid with IBS are characterized by vague, sometimes overlapping symptoms,[154] and Mayer et al.[15] suggested that there is a physiologic basis for this vagueness: visceral afferents converge with somatic afferents on the same dorsal horn cells in the spinal cord, and the spinal segments to which visceral afferents project are overlapping. Wessely et al.[155] further suggested that classification of these somatic symptoms into discrete diagnoses may be an artifact of medical subspecialization: that is, confronted with the same patient's history, a gastroenterologist might diagnose IBS, whereas a gynecologist might diagnose chronic pelvic pain syndrome or dysmenorrhea, and a rheumatologist might diagnose fibromyalgia. This hypothesis could explain at least some of the comorbidity of IBS with other somatic disorders (Table 1). However, the symptoms associated with headache and TMJ are so different from those of IBS and the afferent projections of those target organs are so far removed that it seems

unlikely this explanation could fit all cases. No data directly support the diagnostic ambiguity hypothesis.

Affective Spectrum Disorder

Hudson and Pope[11] carried out a systematic review of the literature to identify all disorders that showed a consistent response to 2 or more classes of antidepressants. (The classes of antidepressants considered were tricyclics, monoamine oxidase inhibitors, serotonin reuptake inhibitors, and atypical agents.) They reasoned that disorders that respond to the same treatments probably share common etiologic elements. Their review identified 8 such disorders: major depression, bulimia, panic disorder, obsessive-compulsive disorder, attention deficit disorder with hyperactivity, cataplexy, migraine, and IBS. Subsequent experience suggests that other disorders listed in Table 1 also respond to antidepressants and are likely to meet Hudson and Pope's criteria for inclusion when more clinical trials have been published.

Further evidence for the affective-spectrum hypothesis comes from the mammoth multinational study of depression and somatization by Simon et al.[142] Of 25,916 primary care patients from 15 primary care centers representing 14 countries, 10% met criteria for major depression, and 50% of these patients reported 3 or more unexplained somatic symptoms. Unfortunately, the percentage of patients with 3 or more unexplained somatic symptoms who did not have major depression was not provided. Limitations of the affective spectrum hypothesis include that not all patients with the disorders listed in Table 1 are depressed, and not all of them respond favorably to antidepressants. Moreover, antidepressants down-regulate peripheral nociceptive pathways,[156] and this peripheral action may account for some of their benefits.

Neuroendocrine-Immune Hypothesis

Investigators concerned primarily with understanding fibromyalgia and explaining its associations with other disorders[12,13] have proposed that there is a common CNS abnormality in all of these disorders characterized by a neuroendocrine-immune dysfunction, possibly related to deficient levels of serotonin or by excessive amounts of CRH[157] in the CNS. The emotional motor system proposed by Mayer[158] as a way of conceptualizing the multiple CNS and endocrine circuits involved in the response of the gut to stress could also be used to explain comorbidity of other disorders with IBS. These are both conceptual models that have not yet been directly supported by data.

Somatization

The trait of somatization is believed by some to explain IBS and its association with other functional somatic disorders. The somatization hypothesis allows for some differentiation among different functional disorders based on 3 mechanisms:

1. Childhood social learning contributes to symptom reporting and the learning is relatively specific; people tend to report the disorders and symptoms that their parents modeled and reinforced during childhood.[1,148]
2. There may be biologic differences between people in the types of somatic sensations they experience, and these differences can become amplified by psychological processes.
3. Physical events (e.g., serendipitous gastroenteritis) may direct the somatization tendency toward particular organ systems. For example, Gwee et al.[159] found that individuals high in the traits of somatization, anxiety, depression, and neuroticism were the ones most likely to develop persistent IBS symptoms 6 months after a confirmed episode of gastroenteritis.

The limitations of the somatization hypothesis were discussed earlier. There is evidence that IBS, CFS, and fibromyalgia are independent disorders,[153] and statistically controlling for psychological traits, such as somatization and depression, does not explain away all of the comorbidity of IBS with other somatic disorders.[40,100,101]

Multivariate Models

Various physiologic and psychological mechanisms have been shown to be relevant to understanding IBS, but no 1 of these mechanisms accounts for more than two thirds of patients, and most account for less than half. These etiologic mechanisms include visceral hypersensitivity, ANS dysfunction, postinfectious IBS, and psychosocial influences. There is evidence that these different mechanisms may interact; for example, psychological stress predicts which patients with gastroenteritis will develop postinfectious IBS,[59] and abnormal gastrointestinal motility can interact with a low sensory threshold to determine when patients experience abdominal pain.[160] This body of data has led to the biopsychosocial model of IBS,[161] which holds that (1) many factors or influences contribute to symptom development, (2) no 1 of these factors is necessary to the development of the disorder, and (3) these factors interact in different combinations. This biopsychosocial model may also apply to the other disorders listed in Table 1.

A different multivariate model has been proposed by Naliboff et al.[162] Like the biopsychosocial model, this model emphasizes that there are many possible interactions between physiologic and cognitive/psychological processes that can give rise to IBS symptoms.

These multivariate models provide a way of understanding how the diverse disorders listed in Table 1 may exist as separate entities and yet share common pathways, which could lead to comorbidity. If all of these disorders result from interactions between psychological and physiologic factors, then some of these factors may be common to multiple disorders, whereas others are unique to specific disorders. Examples of etiologic influences that are common to many disorders include:

1. hyperalgesia occurring throughout the gastrointestinal tract and contributing to both IBS and functional dyspepsia
2. stress, which causes increased autonomic activity and increased physiologic arousal
3. the psychological trait of somatization, which acts like a nonspecific amplifier that magnifies the severity and the significance of any somatic sensations present.

Examples of etiologic influences that are specific to single disorders include genetically determined patterns of physiologic reactivity (e.g., 1 child is a gut responder, whereas another is innately a cardiovascular responder) and childhood social learning in the form of selective reinforcement and modeling of illness behavior by parents, which may lead the child to become selectively attentive to specific types of somatic sensations and to interpret these sensations as symptoms of disease.

The principal limitation of these multivariate models is that they are amorphous. They imply that there are no etiologic factors necessary or sufficient to explain IBS or any other disorder, and thus it is difficult to identify testable mechanistic hypotheses and specific targets for treatment.

Heterogeneity of Irritable Bowel Syndrome: A Dual-Etiology Hypothesis

All of the hypotheses reviewed here that have been proposed to explain the comorbidity of IBS with other disorders assume that IBS is a homogeneous entity; there may be different ways to get there, as proposed by the biopsychosocial model, but all patients diagnosed with IBS are presumed to have the same disease or disorder. An alternative hypothesis is that a heterogeneous group of patients is currently labeled IBS, some whose symptoms primarily have a biological basis and others whose symptoms primarily have a psychological basis, and comorbidity with other disorders and excessive general somatic symptoms are markers for somatization and identify the group with a predominantly psychological IBS etiology, whereas patients with no comorbid conditions and few general physical complaints are more likely to have a biologic basis for IBS symptoms.

This dual-etiology hypothesis has several advantages. It is more parsimonious and easier to understand than the multivariate models, because it proposes only 2 etiologic pathways to IBS rather than many. It has direct implications for the choice of treatment if patients can be classified into these 2 categories (i.e., predominantly physiologic or predominantly psychological). It generates some very specific predictions that are easily testable:

1. The *relative* prevalence of different comorbid disorders in IBS patient samples will reflect the relative prevalence of these disorders to each other in the rest of the population, although the absolute prevalence of these disorders is greater in IBS. If confirmed, this would suggest that these disorders do not share a common pathophysiologic mechanism with IBS, but instead the excess incidence of these disorders in IBS patients is caused by amplification by a somatization process, such as selective attention and/or increased disease attribution.
2. The number of comorbid somatic disorders and nongastrointestinal symptoms reported by IBS patients will be correlated with psychometric measures of depression, anxiety, stress, and/or parental modeling of illness behavior, because comorbidity is a consequence of, and thus a marker for, somatization trait.
3. IBS patients with no comorbid somatic disorders will be more likely to exhibit putative biological markers for IBS, such as visceral hyperalgesia or motility disturbances, in contrast to IBS patients with multiple comorbid disorders, who would be expected to lack biological markers for IBS.

By implying that there are only 2 etiologic mechanisms for IBS (psychological and biological) that act independently of each other, the dual-etiology hypothesis is likely to be an oversimplification. There is good evidence for the interaction of, for example, stress and immune factors,[59] and more than 1 biological mechanism may be involved in the development of IBS. However, the dual-etiology hypothesis emphasizes that there may be a subgroup of patients whose IBS symptoms result from *predominantly biological* processes and another subgroup whose IBS symptoms reflect *predominantly psychological* etiologies; not all IBS patients are alike.

If supported by research, the dual-etiology hypothesis would help address some of the greatest challenges in interpreting research on the nature and treatment of IBS. First, it would help explain why all of the specific and measurable characteristics of IBS patients, whether autonomic dysfunction, motility disturbance, or visceral hyperalgesia, are absent in one half (or at least a substantial proportion) of patients evaluated. Second, it would explain to some degree why most efforts to treat IBS, whether pharmacologic or psychological, benefit only about one half of the patients receiving the intervention.

Patients with a predominantly psychological basis for their IBS symptoms are likely to respond to a different class of treatments than patients with a predominantly biological basis for their symptoms. If the 2 proposed etiologic subgroups can be reliably identified by as simple a process as counting the number of comorbid somatic symptoms, then it may be possible to offer patients more appropriate and effective treatment. There will inevitably be patients who do not fit into these 2 (or more) boxes and whose symptoms will seem to reflect the interaction between psychological and physiologic processes, but it is not clear how large this residual group will be.

Study Limitations

The studies reviewed here have a number of limitations, including the following:

1. Few of them are based on representative samples; most come from subspecialty clinics, which are affected by patient self-selection for treatment and other forms of ascertainment bias.
2. The case definitions for IBS and the other disorders of interest vary greatly across studies, and also have changed over time.
3. Many of the studies involve very small samples.
4. The criteria for diagnosis vary from patient self-report on questionnaires to clinical diagnosis by unspecified symptom criteria or patient self-report, to rather restrictive research criteria. Aaron and Buchwald[52] pointed out that as more restrictive criteria are applied, the prevalence rates for the disorders decline, as does the amount of overlap that is seen.
5. The list of candidate comorbid symptoms or diagnoses investigated varies from study to study; most studies have focused on the overlap between only 2 specific disorders. These limitations make an accurate estimation of the degree of overlap between conditions problematic.

Future Research Directions

Comorbid Disorders

Future work should assess large samples from either the general population or general medical patients, such as primary care patients; measure in the same samples all the commonly known comorbid conditions; and use well-defined clinical criteria for each of the disorders assessed.

Dual-Etiology Hypothesis

This hypothesis has implications for the kinds of experiments investigators might want to conduct on the pathophysiology and treatment of IBS. It suggests that it may be more productive to look for subgroups of patients who fit a particular pathophysiologic mechanism (e.g., postinfectious etiology, hyperalgesia, or stress reaction) or who respond to a specific treatment, rather than assuming that 1 etiology and 1 treatment must characterize all patients.

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