Irritable Bowel Syndrome, Anxiety, and Depression: What Are the Links?

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Irritable bowel syndrome (IBS) is a common and potentially disabling functional gastrointestinal disorder characterized by abdominal pain and altered bowel patterns. A significant amount of clinical and research data suggest the importance of the brain-gut interaction in IBS. This review examines the observed high prevalence of psychiatric disorders in patients with IBS. The published literature indicates that fewer than half of individuals with IBS seek treatment for it. Of those who do, 50% to 90% have psychiatric disorders, including panic disorder, generalized anxiety disorder, social phobia, posttraumatic stress disorder, and major depression, while those who do not seek treatment tend to be psychologically normal. Both physiologic and psychosocial variables appear to play important roles in the development and maintenance of IBS. Recent information suggests that the association of IBS and psychiatric disorders may be more fundamental than was previously believed. A brain-gut model for IBS is presented, and the role of traumatic stress and corticotropin-releasing factor as modulators of the brain-gut loop is discussed. Finally, the rationale for the use of psychotropic agents in the treatment of IBS with or without psychiatric symptoms is presented.

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Irritable bowel syndrome (IBS) is a common, potentially disabling functional bowel disorder with an estimated prevalence of 8% to 17% in the general population.[1–4] The diagnostic criteria for IBS have recently been modified.[5,6] The key features include continuous or recurrent abdominal pain or discomfort associated with a change of bowel frequency or consistency and usual relief with defecation in the absence of physical or laboratory abnormalities indicative of an organic etiology. Other symptoms are used as additional descriptors (Table 1).

In both clinical and population-based samples, women are twice as frequently affected as men.[6–9] The onset of IBS is most often in the younger age group (15–34 years) but can occur earlier or in late life.[10] The course of the illness is typically chronic, with intermittent exacerbation by stress.[7–9] Symptom severity of IBS varies within and between individuals, and can range from mild to incapacitating.[2,10] The majority of individuals who seek treatment for their IBS symptoms exhibit significant IBS-related emotional distress and functional impairment.[9,10] IBS has been estimated to rank second only to the common cold as a cause for work absenteeism.[11] The economic burden of IBS in the United States is estimated at approximately $8 billion per year.[12]

PSYCHIATRIC DISORDERS AND IBS

Clinical Samples

Fewer than half of individuals who meet diagnostic criteria for IBS seek treatment for it.[9,13–15] The bulk of the published literature indicates that individuals seeking treatment for IBS have high levels of neuroticism or other abnormal psychological traits, exhibit more illness behavior, use ineffective coping styles, consume more health services, and have an increased prevalence of psychiatric disorders and sexual and physical abuse than individuals with IBS symptoms who do not become patients.[9,13,16] Theoretical explanations for the high prevalence of psychiatric disorders in IBS patient samples and methods used for assessment of psychological/psychiatric abnormalities in IBS patients have varied widely. The most commonly observed psychiatric disorders found in IBS patients are major depression, panic disorder, social phobia, generalized anxiety disorder, posttraumatic stress disorder, and somatization disorder (Table 2).[17–33] Some evidence suggests that anxiety may be more prominent early in the course of IBS, whereas depression is more common in patients suffering from chronic IBS symptoms.[21] Conversely, psychiatric patients with anxiety and mood disorders have a significantly increased prevalence of IBS.[34–37] Panic disorder and IBS coexist frequently in both psychiatric and IBS patient

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Table 1. Diagnostic Criteria for Irritable Bowel Syndrome (IBS)[a]

Rome I IBS Criteria[4]	Rome II IBS Criteria[5]
Continuous or recurrent symptoms of abdominal pain that have one or more of the following features:	Twelve weeks or more in the past year of abdominal discomfort or pain that has 2 of the following features:
Relieved with defecation	Relieved with defecation
Associated with a change in frequency of stool	Onset associated with a change in frequency of stool
Associated with a change in consistency of stool	Onset associated with a change in consistency of stool
Two or more of the following features present on at least 25% of occasions or days:	Supportive symptoms of IBS (not diagnostic criteria) if present on at least 25% of occasions or days:
Abnormal stool frequency (> 3 bowel movements per day or < 3 per week)	Abnormal stool frequency (> 3 bowel movements per day or < 3 per week)
Abnormal stool form (lumpy/hard or loose/watery stool)	Abnormal stool form (lumpy/hard or loose/watery stool)
Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation)	Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation)
Passage of mucus	Passage of mucus
Bloating or feeling of abdominal distension	Bloating or feeling of abdominal distension

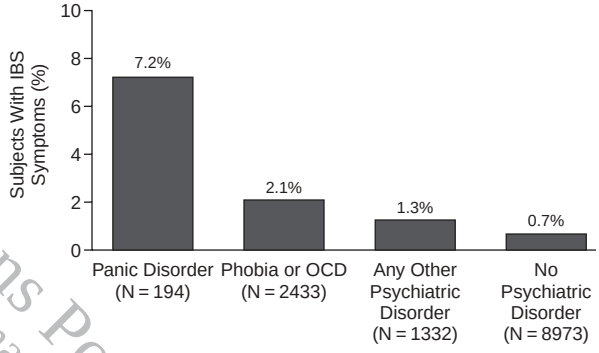
[a]Based on Drossman et al.[4] and Drossman.[5]

Table 2. Percentage of Treatment-Seeking Irritable Bowel Syndrome Patients With Current DSM-III-R or DSM-IV Psychiatric Disorders[a]

		Psychiatric Disorder					
Study	Patients (N)	MDE	Dysthymia	Panic Disorder	GAD	Social Phobia	Somatization Disorder
Blewett et al.[38]	63	17	5	16	5	N/A	N/A
Irwin et al.[32]	50	18	N/A	18	4	10	N/A
Walker et al.[31]	71	15	39	28	58	N/A	17[b]
Lydiard et al.[25]	36	23	9	26	26	26	12
Walker et al.[26]	19	21	N/A	7	11	11	32[c]
Blanchard et al.[39]	44	6	4	0	88	7	1

[a]Abbreviations: GAD = generalized anxiety disorder, MDE = major depressive episode, N/A = not available. Total percentage may exceed 100%, since some patients have > 1 disorder.
[b]Excludes gastrointestinal symptoms.
[c]Lifetime, not current.

Figure 1. The Co-Occurrence of Psychiatric Disorders and Unexplained Gastrointestinal Symptoms in a Community-Based Sample[a]



[a]Data from Lydiard et al.[40] Abbreviations: IBS = irritable bowel syndrome, OCD = obsessive-compulsive disorder.

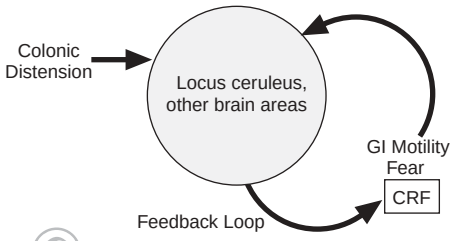
samples.[26,28,38,39] In individuals with both psychiatric disorders and IBS, psychiatric disorders are more likely to precede or begin at about the same time as IBS.[25,28]

Nonclinical Samples

Assessment of the overlap of psychiatric disorders and IBS in a community-based, nonclinical sample avoids the potential bias of subjects' self-selection due to psychiatric disorders or neuroticism. My colleagues and I assessed the prevalence of medically unexplained gastrointestinal (GI) symptoms in a large epidemiologic sample (N = 13,537) of individuals surveyed as part of the National Institute of Mental Health Epidemiologic Catchment Area (ECA) study.[40] The aim of this post hoc analysis was to examine the potential association of panic disorder with medically unexplained GI symptoms included in the somatization disorder diagnostic module of the structured psychiatric interview that was used in the ECA survey. An "IBS-like" cluster of GI symptoms (abdominal pain, diarrhea or constipation, and abdominal bloating) was used as a basis for identifying individuals with GI symptoms that were most similar to IBS.

Respondents with panic disorder (N = 194) were significantly more likely to endorse the IBS-like cluster of GI symptoms than were the remainder of the sample (N = 13,163), followed by respondents with other anxiety disorders, but not panic disorder (N = 2433), and then by those with other psychiatric disorders, excluding anxiety (N = 1332). IBS-like symptoms were least common among those with no psychiatric disorder (N = 8973) (Figure 1). Walker et al.[41] had previously reported very similar findings from an analysis of the same data set. The population-based methods used and the size of our sample distinguish it from previously published studies[9,13] of nonclinical samples. Our results support the hypothesis that the high coprevalence of psychiatric disorders and IBS may not necessarily represent self-selection due to psychiatric disorders. However, an important weakness of our study was that the GI symptoms were assessed in a structured psychiatric interview that was not designed to diagnose IBS.

Figure 2. Brain-Gut Loop Model for Irritable Bowel Syndrome[a]



[a]Abbreviations: CRF = corticotropin-releasing factor, GI = gastrointestinal.

My colleagues and I subsequently conducted a prospective U.S. community survey sample (N = 3911) that included validated diagnostic tools for both functional GI and psychiatric disorders. Preliminary results indicate that lifetime psychiatric disorders are significantly more common in individuals meeting diagnostic criteria[4] for IBS (63%) than in those without IBS (24.8%) ($p < .00001$); IBS sufferers were more likely to have more than 1 psychiatric diagnosis than those without IBS ($p < .00001$). The prevalence and types of psychiatric disorders detected were nearly identical in those respondents with IBS who had received treatment for IBS and those who had not, while both IBS groups were markedly different from those without IBS.[42] This community survey provides empirical support of the association of IBS and psychiatric disorder, which appears to be independent of treatment-seeking status.

SEXUAL AND PHYSICAL ABUSE AND IBS

Drossman and colleagues[43] studied the prevalence of sexual and physical abuse in 206 women attending a GI specialty clinic for GI complaints. They reported that women with functional GI disorders reported substantial previous physical and sexual abuse at a significantly higher rate than women with comparably severe GI illness of organic etiology. Walker and colleagues[44] reported a similarly high rate of sexual abuse in patients with IBS (55%) compared with those with inflammatory bowel disease of similar severity (5%). In that study, IBS patients also had more psychiatric disorders and unexplained physical symptoms (non-GI) than inflammatory bowel disease patients.

Several other groups have confirmed rates of sexual and physical abuse in IBS patient samples attending health maintenance organizations, family practice clinics, or other tertiary care facilities ranging from 40% to over 60%,[32,45–47] and a community sample of IBS sufferers yielded a rate of 22% of subjects with significant prior abuse.[48] In a review of the association of traumatic stress and IBS, Stam et al.[49] concluded that "trauma might play a role in the etiology or perception of IBS," and further noted that functional GI disorders "are a common occurrence in patients with posttraumatic stress disorder." Previous sexual or physical abuse is associated with increased undiagnosed symptomatic pain complaints, health care utilization and cost, functional impairment, and poor treatment outcome.[43,50–57] It should be noted that not all investigators have concluded that abuse increases the likelihood of physician visits. Talley et al.[48] reported a 22% endorsement rate of prior physical and sexual abuse in an Australian community sample of IBS sufferers. However, increased health care utilization was not predicted by abuse but by the severity of abdominal pain, suggesting that the role of victimization requires further investigation in IBS.

"BIG BRAIN" AND "LITTLE BRAIN"

The enteric nervous system (ENS) has been called the "little brain," at least in part because central nervous system (CNS) and ENS neurons share a common embryonic neural crest origin.[58–60] Like the CNS, the ENS contains many interneurons, a myenteric-blood barrier (analogous to the blood-brain barrier), and glia (vs. Schwann cells usually found on peripheral nerves); exhibits adaptive neuronal plasticity; and contains similar types of neurotransmitters and neuropeptides.[60]

Several brain nuclei that modulate normal GI function also coordinate emotional, physiologic, and fear-conditioning reactions to perceived danger as components of the innate "fear circuit."[61] Dysregulation of homeostatic intermodulation of these limbic and paralimbic nuclei is believed to play a prominent role in the etiology of pathologic anxiety states such as panic disorder and posttraumatic stress disorder.[62] Relevant brain structures include the locus ceruleus (LC), amygdala, parabrachial nucleus, nucleus tractus solitarius, periaqueductal gray paraventricular nucleus of the hypothalamus dorsal motor nucleus, and, possibly, Barrington's nucleus.[61–74] Several of the nuclei in the fear-circuit pathway receive rich afferent input from the gut.[75–76]

One of the best-characterized brain-gut pathways is a vagal afferent pathway from the distal colon to the nucleus LC.[75,77] Experimentally induced colonic distension increases the firing rate of the LC, which, in turn, mediates increases in sympathetic outflow and CNS arousal.[62] A cycle between the brain and the gut has been proposed as a model for IBS (Figure 2). In this model, individuals with increased CNS arousal could experience GI distress and increased GI motility via CNS-mediated sympathetic outflow. Afferent input via the ENS back to the LC might potentially create an uncontrolled positive-feedback cycle of GI distress and CNS arousal. The model is also consistent with the theory that GI symptoms (cramping, pain) cause CNS arousal via the afferent input to the LC (and probably other important brain areas). Thus, pathologic events in either the CNS, the ENS, or both could initiate the hypothesized uncontrolled positive-feedback cycle.

Normalization of hyperreactivity of the LC, amygdala, and other discrete brain areas to afferent input is one of the proposed mechanisms of action of anxiolytics and antidepressants in reducing arousal associated with anxiety and mood disorders.[34,35,78,79] The limited literature regarding the use of psychopharmacologic agents in IBS suggests that a substantial percentage of IBS patients, even those with no apparent psychiatric disorder, derive benefits from treatment.[42] Also consistent with this model is the emerging evidence that cognitive-behavioral therapy, which includes self-monitoring techniques aimed at reducing hyperreactivity to visceral and emotional stimuli, has beneficial effects as a treatment for IBS.[80,81]

CORTICOTROPIN-RELEASING FACTOR: A NEUROBIOLOGICAL LINK?

Corticotropin-releasing factor (CRF), a neuropeptide with potent anxiogenic properties, serves a primary role in mediating arousal and in activating the hypothalamic-pituitary-adrenal axis during stress. CRF appears to play an active role in the homeostatic interregulation of the fear circuit and in mediating brain-gut interactions. The amygdala is densely innervated by CRF neurons, which exert excitatory influences on various fear-circuit brain nuclei, including the LC,[62,65] which is sensitive to experimental CRF administration.[71,82] Stress-induced GI motility is mediated by both CNS and peripheral CRF effects.[72,83–85] For example, during a "fight-or-flight" response, the delay in gastric emptying and increased distal colonic motility is mediated via 2 distinct CRF-receptor subtypes.[84] Individuals with anxiety disorders, depression, and stress-related disorders may exhibit autonomic arousal, GI distress, or misinterpretation of visceral stimuli,[28,85–90] all of which are commonly observed in patients with IBS.[42] Gender differences in the regulation of CRF theoretically could confer an increased risk for developing both psychiatric and functional GI disorders.[91] For example, there is evidence that the reactivity of the hypothalamic-pituitary-adrenal axis to experimental stress is greater and lasts longer in women than in men; these observations may be related to the documented effects of estrogen on the CRF system.[91]

Finally, CRF may play a role in pain perception in IBS. The analgesic effect of CRF in acute inflammatory paradigms has been well described, and the available evidence suggests that CRF may also have a significant role in chronic pain syndromes associated with hypothalamic-pituitary-adrenal axis abnormalities.[92] Like the CNS, ENS neurons can be permanently sensitized to various stimuli by either stress or noxious stimulation.[49,92–96] For example, both animals and humans exhibit increasing sensitivity to repetitive, noxious, chemical, or mechanical stimuli to the gut. This increased sensitivity persists over time.[49,94–96] Numerous investigators have confirmed that IBS patients have a lower threshold for abdominal discomfort or pain during experimental distension of the lower colon; the discomfort or pain becomes more exaggerated with repeated colonic distension.[95,97–101] Amplification of visceral sensations due to sensitization of gut nociceptors may explain some clinical observations in IBS. IBS patients who are victims of repeated traumatic stimulation associated with sexual abuse could experience amplification of visceral sensations via trauma-related sensitization of peripheral nociceptors.[94,98,100,101] Consistent with this hypothesis is the observation of unexplained pelvic complaints associated with IBS. Chronic pelvic pain and painful intercourse often co-occur with IBS.[55,102,103] Unexplained pelvic pain symptoms are more frequently reported by women with IBS who have histories of childhood sexual abuse than those without abuse histories.[102] While it is not yet entirely clear at this point, abuse-related alterations in peripheral and CNS pain perception might be a factor.

IMPLICATIONS FOR TREATMENT OF IBS WITH PSYCHOTROPIC MEDICATIONS

The literature regarding psychopharmacologic treatment of IBS is limited, and many methodological issues preclude direct comparison of the available studies. The majority of the published literature shows that treatment with psychotropic agents benefits IBS sufferers with or without psychiatric disorders (Table 3).[34,35,42,78,105–107] If present, concomitant psychiatric disorders do not adversely affect treatment outcome of IBS with psychotropics, and usually both IBS and psychiatric symptoms improve.[104]

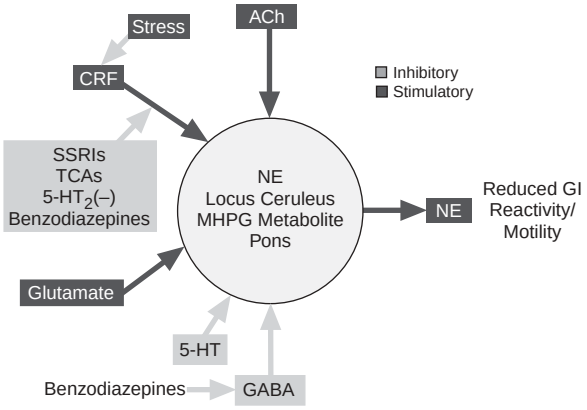
In our experience, both the older tricyclic antidepressants and the newer agents such as the selective serotonin reuptake inhibitors (SSRIs) appear to have therapeutic effects in IBS.[78,106] The accruing evidence suggests that important brain-gut interactions in IBS and perhaps other functional GI disorders may be mediated by chronic CRF overactivity. In the brain-gut model discussed earlier, there are several potential sites of action at which psychotropic agents might produce beneficial effects in patients with IBS (Figure 3). Antidepressants and benzodiazepines, which have been shown to relieve IBS symptoms, effectively antagonize CRF effects via different mechanisms. Newer therapeutic agents such as the CRF-receptor antagonists, which could directly antagonize CRF effects in the CNS and ENS, might theoretically prove to be useful in both psychiatric disorders and IBS. For the many individuals with both psychiatric disorders and IBS, the newer agents could prove to be an important therapeutic tool. The use of the antidepressants (SSRIs and others) has shown promise, but has not been adequately investigated. Although many clinicians treat IBS with psychotropic medications, and the brain-gut model presents a rationale for why they might be effective, treatment trials that in-

Table 3. Psychopharmacologic Treatment in Irritable Bowel Syndrome (IBS)[a]

Study	Study Population	Patient Characteristics	Study Design	Drug	Results
Steinhart et al[108]	Psychiatric site (N = 14)	Spastic colon syndrome	Double-blind, crossover	Amitriptyline (50 mg/d) and placebo	Improvement in IBS symptoms at low doses
Greenbaum et al[109]	Gastroenterology site (N = 28)	Diarrhea predominant in 19 patients, constipation in 9 patients	Double-blind, crossover	Desipramine, atropine, and placebo	Desipramine improved pain, GI distress, and ADL in the diarrhea-predominant subgroup
Rajagopalan et al[110]	Gastroenterology site (N = 40)	No comorbid medical or psychiatric condition	Double-blind, placebo-controlled	Amitriptyline (75 mg/d)	Significant global improvements in well-being and abdominal pain
Heefner et al[111]	Medical site (N = 31)	21 patients with depression (Zung Self-Rating Depression Scale ratings)	Double-blind, placebo-controlled	Desipramine (150 mg/d)	Moderate improvements in pain, activities of daily living, and depression compared with placebo
Myren et al[112]	Medical site (N = 428)	No details supplied	Double-blind, placebo-controlled	Trimipramine (30–50 mg/d)	50% symptom reduction compared with placebo
Lancaster-Smith et al[113]	Medical site (N = 38)	GHQ indicated "probable psychiatric condition" in 22 patients	Double-blind, placebo-controlled	Fluphenazine (1.5 mg/d) and nortriptyline (30 mg/d)	Significant effects on diarrhea and abdominal pain, but "probable psychiatric conditions" adversely affected short-term outcome
Tanum and Malt[114]	Psychiatric site (N = 47)	Functional GI disorders, 28 patients with IBS	Double-blind, placebo-controlled	Mianserin (120 mg/d)	Improvement in abdominal pain, GI symptoms, and functional disability
Noyes et al[36]	Psychiatric site (N = 30)	Panic disorder patients, 5 diagnosed with IBS	Double-blind, placebo-controlled	Diazepam (10–40 mg/d) or alprazolam (1–4 mg/d)	Improvement in IBS and anxiety symptoms in all patients
Tollefson et al[35]	Psychiatric site (N = 32)	Comorbid GAD	Single-blind	Alprazolam (up to 4 mg/d)	Improvement in both GAD and IBS symptoms
Clouse et al[115]	Gastroenterology site (N = 138)	No other GI problem diagnosed	Review of up to 5 sequential trials	Low-dose antidepressants, mostly tricyclic antidepressants	Bowel symptoms improvement in 89% of patients, and complete remission in 61% of patients
Lydiard et al[78]	Psychiatric site (N = 5)	Comorbid panic disorder	Case histories	Alprazolam or antidepressants	Simultaneous improvement in panic and GI symptoms

[a]Abbreviations: ADL = activities of daily living, GAD = generalized anxiety disorder, GHQ = General Health Questionnaire, GI = gastrointestinal.

Figure 3. Potential Sites of Action for Psychotropic Agents in Irritable Bowel Syndrome Patients With or Without Psychiatric Disorders[a]



[a]Abbreviations: 5-HT = serotonin, ACh = acetylcholine, CRF = corticotropin-releasing factor, GABA = γ-aminobutyric acid, GI = gastrointestinal, MHPG = 3-methoxy-4-hydroxyphenylglycol, NE = norepinephrine, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

clude IBS patients with and without psychiatric disorders are now indicated to test the hypotheses we presented here.

CONCLUSIONS

IBS is a common and potentially debilitating illness in which significant brain-gut interaction is evident. Both physiologic and psychosocial variables appear to play important roles in the development and maintenance of IBS. The association of anxiety, depression, and stress with IBS may be due to a combination of neurobiological factors, including abnormalities of CRF regulation, which may be inherited, induced, or both. The available data suggest that there are common neurobiological factors involving brain-gut interactions, anxiety, and depression.[86] The model is consistent with the theory that aversive GI symptoms (cramping, pain, and others) can cause CNS arousal via vagal afferent feedback to the LC and other key nuclei in the CNS. Thus, pathologic levels of CNS arousal or aversive GI symptoms, or both, could activate the hypothesized positive-feedback cycle. The rationale for the use of

psychopharmacologic medications as a treatment for IBS that may affect both ENS and CNS functioning is presented.

Drug names: alprazolam (Xanax and others), amitriptyline (Elavil and others), atropine (Donnatal and others), desipramine (Norpramin and others), diazepam (Valium and others), nortriptyline (Pamelor and others), trimipramine (Surmontil).

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