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

R. Bruce Lydiard, M.D., Ph.D.

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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samples. In individuals with both psychiatric disorders and IBS, psychiatric disorders are more likely to precede or begin at about the same time as IBS.

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.

Twelve weeks or more in the past year of abdominal discomfort or pain that has 2 of the following features:
- Relieved with defecation
- Onset associated with a change in frequency of stool
- Abnormal stool frequency
- (> 3 bowel movements per day or < 3 per week)
- Abnormal stool form (lumpy/hard or loose/watery stool)
- Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation)
- Passage of mucus
- Bloating or feeling of abdominal distension

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 form (lumpy/hard or loose/watery stool)
- Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation)
- Passage of mucus
- Bloating or feeling of abdominal distension

Table 1. Diagnostic Criteria for Irritable Bowel Syndrome (IBS)*

<table>
<thead>
<tr>
<th>Rome I IBS Criteria</th>
<th>Rome II IBS Criteria</th>
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<tr>
<td>Continuous or recurrent symptoms of abdominal pain that have one or more of the following features: Relieved with defecation Associated with a change in frequency of stool Associated with a change in consistency of stool Two or more of the following features present on at least 25% of occasions or days: Abnormal stool frequency (&gt; 3 bowel movements per day or &lt; 3 per week) Abnormal stool form (lumpy/hard or loose/watery stool) Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation) Passage of mucus Bloating or feeling of abdominal distension</td>
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</tr>
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Table 2. Percentage of Treatment-Seeking Irritable Bowel Syndrome Patients With Current DSM-III-R or DSM-IV Psychiatric Disorders*

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (N)</th>
<th>Panic Disorder</th>
<th>Social Somatization Disorder</th>
</tr>
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<tbody>
<tr>
<td>Blewett et al.</td>
<td>63</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Irwin et al.</td>
<td>50</td>
<td>18</td>
<td>N/A</td>
</tr>
<tr>
<td>Walker et al.</td>
<td>71</td>
<td>15</td>
<td>39</td>
</tr>
<tr>
<td>Lydiard et al.</td>
<td>36</td>
<td>23</td>
<td>9</td>
</tr>
<tr>
<td>Walker et al.</td>
<td>19</td>
<td>21</td>
<td>N/A</td>
</tr>
<tr>
<td>Blanchard et al.</td>
<td>44</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

*Abbreviations: GAD = generalized anxiety disorder, MDE = major depressive episode, N/A = not available. Total percentage may exceed 100%, since some patients have > 1 disorder.

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

Data from Lydiard et al. Abbreviations: IBS = irritable bowel syndrome, OCD = obsessive-compulsive disorder.
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 for IBS (63%) than in those without IBS (24.8%) (p < .0001); IBS sufferers were more likely to have more than 1 psychiatric diagnosis than those without IBS (p < .0001). 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.

Several other groups have confirmed rates 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 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%, and a community sample of IBS sufferers yielded a rate of 22% of subjects with significant prior abuse. In a review of the association of traumatic stress and IBS, Stam et al. 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. It should be noted that not all investigators have concluded that abuse increases the likelihood of physician visits. Talley et al. 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. 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.

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.” 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. 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. Several of the nuclei in the fear-circuit pathway receive rich afferent input from the gut.

One of the best-characterized brain-gut pathways is a vagalfferent pathway from the distal colon to the nucleus LC. Experimentally induced colonic distension increases the firing rate of the LC, which, in turn, mediates increases in sympathetic outflow and CNS arousal. A cycle between the brain and the gut has been proposed as a model for IBS. 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.

**Figure 2. Brain-Gut Model for Irritable Bowel Syndrome**

![Brain-Gut Model for Irritable Bowel Syndrome](image-url)  

**Abreviations:** CRF = corticotropin-releasing factor, GI = gastrointestinal.
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.

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.

Stress-induced GI motility is mediated by both CNS and peripheral CRF effects. 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. Individuals with anxiety disorders, depression, and stress-related disorders may exhibit autonomic arousal, GI distress, or misinterpretation of visceral stimuli, all of which are commonly observed in patients with IBS.

Gender differences in the regulation of CRF theoretically could confer an increased risk for developing both psychiatric and functional GI disorders. 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.

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. Like the CNS, ENS neurons can be permanently sensitized to various stimuli by either stress or noxious stimulation. 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.

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. 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.

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. Unexplained pelvic pain symptoms are more frequently reported by women with IBS who have histories of childhood sexual abuse than those without abuse histories. 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). 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-
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, anxiety, and depression. 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 hypothalamic positive-feedback cycle. The rationale for the use of

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Patient Characteristics</th>
<th>Study Design</th>
<th>Drug</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steinhart et al^108</td>
<td>Psychiatric site (N = 14)</td>
<td>Spastic colon syndrome</td>
<td>Double-blind, crossover</td>
<td>Amitriptyline (50 mg/d) and placebo</td>
<td>Improvement in IBS symptoms at low doses</td>
</tr>
<tr>
<td>Greenbaum et al^109</td>
<td>Gastroenterology site (N = 28)</td>
<td>Diarrhea predominant in 19 patients, constipation in 9 patients</td>
<td>Double-blind, crossover</td>
<td>Desipramine, atropine, and placebo</td>
<td>Desipramine improved pain, GI distress, and ADL in the diarrhea-predominant subgroup</td>
</tr>
<tr>
<td>Rajagopalan et al^110</td>
<td>Gastroenterology site (N = 40)</td>
<td>No comorbid medical or psychiatric condition</td>
<td>Double-blind, placebo-controlled</td>
<td>Amitriptyline (75 mg/d)</td>
<td>Significant global improvements in well-being and abdominal pain</td>
</tr>
<tr>
<td>Heefner et al^111</td>
<td>Medical site (N = 31)</td>
<td>21 patients with depression (Zung Self-Rating Depression Scale ratings)</td>
<td>Double-blind, placebo-controlled</td>
<td>Desipramine (150 mg/d)</td>
<td>Moderate improvements in pain, activities of daily living, and depression compared with placebo</td>
</tr>
<tr>
<td>Myren et al^112</td>
<td>Medical site (N = 428)</td>
<td>No details supplied</td>
<td>Double-blind, placebo-controlled</td>
<td>Trimipramine (30–50 mg/d)</td>
<td>50% symptom reduction compared with placebo</td>
</tr>
<tr>
<td>Lancaster-Smith et al^113</td>
<td>Medical site (N = 28)</td>
<td>GHQ indicated “probable psychiatric condition” in 22 patients</td>
<td>Double-blind, placebo-controlled</td>
<td>Fluphenazine (1.5 mg/d and nortriptyline (30 mg/d)</td>
<td>Significant effects on diarrhea and abdominal pain, but “probable psychiatric conditions” adversely affected short-term outcome</td>
</tr>
<tr>
<td>Tanum and Malt^114</td>
<td>Psychiatric site (N = 47)</td>
<td>Functional GI disorders, 28 patients with IBS</td>
<td>Double-blind, placebo-controlled</td>
<td>Mianserin (120 mg/d)</td>
<td>Improvement in abdominal pain, GI symptoms, and functional disability</td>
</tr>
<tr>
<td>Noyes et al^116</td>
<td>Psychiatric site (N = 30)</td>
<td>Panic disorder patients, 5 diagnosed with IBS</td>
<td>Double-blind, placebo-controlled</td>
<td>Dizepam (10–40 mg/d or alprazolam (1–4 mg/d)</td>
<td>Improvement in IBS and anxiety symptoms in all patients</td>
</tr>
<tr>
<td>Tollefson et al^117</td>
<td>Psychiatric site (N = 32)</td>
<td>Comorbid GAD</td>
<td>Single-blind</td>
<td>Alprazolam (up to 4 mg/d)</td>
<td>Improvement in both GAD and IBS symptoms</td>
</tr>
<tr>
<td>Clouse et al^118</td>
<td>Gastroenterology site (N = 138)</td>
<td>No other GI problem diagnosed</td>
<td>Review of up to 5 sequential trials</td>
<td>Low-dose antidepressants, mostly tricyclic antidepressants or alprazolam or antidepressants</td>
<td>Bowel symptoms improvement in 89% of patients, and complete remission in 61% of patients</td>
</tr>
<tr>
<td>Lydiard et al^119</td>
<td>Psychiatric site (N = 5)</td>
<td>Comorbid panic disorder</td>
<td>Case histories</td>
<td>Alprazolam or antidepressants</td>
<td>Simultaneous improvement in panic and GI symptoms</td>
</tr>
</tbody>
</table>

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

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

*Abbreviations: 5-HT = serotonin, ACh = acetylcholine, CRF = corticotropin-releasing factor, GABA = γ-aminobutyric acid, GI = gastrointestinal, MHPG = 3-methoxy-4-hydroxyphenylglycol, NE = norepinephrine, SRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.
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 (Donaatall and others), desipramine (Norpramin and others), diazepam (Valium and others), nortriptyline (Pamelor and others), trimipramine (Surmontil).

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