Anxiety and the Irritable Bowel Syndrome: Psychiatric, Medical, or Both?

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The association between the irritable bowel syndrome (IBS) and psychiatric disorders is well-known to most clinicians, but the nature of the relationship is far from clear. There is an increased prevalence of psychiatric illness in IBS patients and an increase in IBS in psychiatric patients. Whether this association exists outside of treatment-seeking populations (i.e., in IBS sufferers who do not seek treatment) has not been well investigated. This paper will selectively review the existing literature regarding the association of IBS and psychiatric illness in both patient and nonpatient samples. A model of the brain-gut interaction will be presented, as will practical implications of this model for treatment of individuals with IBS.

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Functional gastrointestinal (GI) disorders occur in up to 69% of the U.S. population, according to a recent community household survey.[1] Among individuals who seek treatment for functional GI disorders, especially irritable bowel syndrome (IBS), the available literature indicates that there is a high prevalence of concurrent psychiatric morbidity—predominantly anxiety and mood disorders. Recent studies have provided additional support for the hypothesis that there is an intimate interaction between the central nervous system (CNS) and the enteric nervous system (ENS). The brain and the gut communicate via established neuronal (both efferent and afferent) pathways and can mutually influence one another. This concept is important in the evaluation of patients with functional GI disorders and may help guide treatment decisions. This review will examine the association of IBS and psychiatric illness in treatment-seeking patient samples. Additionally, recent information regarding the prevalence of medically unexplained GI symptoms in a community sample who were also screened for psychiatric disorders will be presented. A model of the brain-gut interaction that will provide a rationale for the use of psychopharmacologic agents in the treatment of IBS will be presented.

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IBS AND PSYCHIATRIC DISORDERS

Irritable bowel syndrome is the most common functional GI disorder and can have debilitating effects in the 8% to 17% of the general population who are sufferers.[1] Diagnostic criteria for IBS have been recently established by an international committee of experts. The hallmark feature of IBS is abdominal pain or discomfort. Table 1 shows the important diagnostic features of IBS.

By definition, this functional GI disorder is not characterized by any physical findings or laboratory abnormalities and is diagnosed mainly by exclusion of possible organic etiologies. Irritable bowel syndrome is a chronic condition that commonly begins in early adulthood and affects females approximately twice as often as it does males. IBS is associated with significant morbidity.

For example, a recent survey of IBS sufferers conducted by The International Foundation for Bowel Dysfunction indicates that 30% of individuals with IBS lose at least 1 day of work per month on average and 88% had seen a physician for IBS in the past year.[2] In fact, only the common cold outranks IBS as a cause of absenteeism from work. The annual direct (medical visits, procedures, and treatment) and indirect (impairment or inability to work) financial loss due to IBS may be as much as $1 billion per year.[3] Sandler et al.[4] reported that over half of a sample of individuals in a nonpatient population who met criteria for a functional bowel disorder had never consulted a doctor. Those not seeking health care had better coping patterns and fewer abnormal personality patterns and experienced less disruption due to their symptoms. Several investigators have identified factors that may contribute to health care seeking behavior; these include psychological and psychosocial factors.[4–10]

Table 1. Irritable Bowel Syndrome Characteristics*

Recurrent symptoms (at least 3 months):
Abdominal pain
typically relieved with defecation
change in frequency or consistency of stool; and/or
Disturbed defecation three or more of the following at least 25% of the time):
change in stool frequency
change in stool form (hard or loose/watery)
change in stool passage (straining or urgency, feeling of incomplete evacuation)
mucous passage
bloating or sensation of abdominal distention
Additional laboratory investigation (e.g., complete blood count, erythrocyte sedimentation rate) and a sigmoidoscopy (fiber-optic) should be completed to assure that inflammatory bowel or other pathology is not present.

*Data from reference 1. Additional tests, if any, are based on clinical indications.

Table 2. Number and Percent of 35 IBS Patients With Axis I DSM-III-R Diagnosis*

DSM-III-R Diagnosis	N	%
Panic disorder	11	31
with agoraphobia[a]	7	20
Generalized anxiety disorder	12	34
Social phobia	10	29
Major depression	16	46
Dysthymic disorder	5	14
Current anxiety disorder	23	66
Current mood disorder	12	34

*Data from reference 16.

[a]Subgroup of the patients with panic disorder and not an additional group.

PSYCHIATRIC DISORDERS IN IBS PATIENTS

Of the published studies to date that assessed psychiatric diagnoses in patients with IBS and used standardized interview techniques, to date only a few have applied the DSM-III-R[11] criteria.[12] Prior to the use of DSM-III-R, there was a diagnostic hierarchy that excluded the mutual diagnoses of anxiety and depression. Lydiard et al. reported several years ago the common occurrence of prominent GI symptoms in patients suffering from panic disorder,[13] which are similar to those described in DSM-IV.[14] In that report, we noted an unusually high prevalence (42%) of anxiety-related discomfort, cramping, and diarrhea in patients with panic disorder. Five patients with panic disorder who were diagnosed and treated for IBS experienced apparent resolution of IBS and panic disorder symptoms with effective antipanic treatment. Our group subsequently conducted structured psychiatric interviews on a series of patients with IBS, by utilizing a Structured Clinical Interview for DSM-III-R (SCID).[15]

Our group found that 94% of the patients had a lifetime history of a major psychiatric illness (Table 2).[16] Over 80% were currently psychiatrically ill, primarily with anxiety and mood disorders; many of these patients were unaware of their psychiatric diagnosis. A recent report by Walker and colleagues[17] reported findings in a blinded study comparing patients with inflammatory bowel disease (ulcerative colitis and Crohn's disease) with patients who had IBS. Similar to our group's findings, in that sample, over 90% of the patients with IBS had a lifetime prevalence of psychiatric disorder, predominantly mood and anxiety disorders. Interestingly, they found a 29% prevalence of panic disorder in that sample. In contrast, Blanchard and colleagues[12] found less psychopathology in a treatment-seeking group of IBS patients presenting to a psychology-based stress management center. It appears, then, that treatment-seeking IBS patients who present to medical centers often suffer from concomitant psychiatric conditions and that panic disorder is common in this population.

POSTTRAUMATIC STRESS DISORDER AND IBS

Recent reports indicate that there is a significant association between sexual and physical abuse and IBS, as well as other functional bowel disorders. Sexual and physical assault history have been identified as a second potentially important determinant of health care seeking behavior in IBS patient samples. Drossman and colleagues[18] administered a self-report questionnaire to 206 patients at a university-based gastroenterology clinic and found that patients with functional GI disorders, particularly IBS, had a significantly higher rate of physical and sexual trauma in childhood or later in life than a comparable sample with organic illness. A second report by Felitti[19] reviewed records from a health maintenance organization. The author found that individuals who had answered affirmatively to a screening question inquiring about rape or sexual molestation were significantly more likely to have IBS than a comparison group who answered negatively to the question on sexual trauma. Several others have reported findings consistent with the association of victimization and IBS.[20–22] Our group recently reported the prevalence of posttraumatic stress disorder (PTSD) in treatment-seeking patients with IBS.[23] The survey, which included structured interviews for major psychiatric disorders, including PTSD, revealed a 36% rate of PTSD. The most common histories included sexual (26%) and/or physical (22%) abuse as the identified stressors initiating the disorder. It is important to note that this is a conservative estimate of the abuse history of these patients, since only those who satisfied DSM-III-R diagnostic criteria were included; those with a history of victimization but without PTSD were not represented. Whether health care seeking is higher in PTSD victims than those with victimization who do not meet diagnostic thresholds for PTSD is an important, but unanswered, question. It appears that a history of victimization may be an important determinant of health care seeking behavior. Individuals

with a history of abuse were more likely to have surgery with normal findings, visit a physician, or be hospitalized.[24–28] Because history of sexual or physical abuse is associated with health care seeking and utilization, as is suggested by these studies, the importance of recognizing patients with an abuse history is an important part of the evaluation of individuals with functional GI disorders. This would be particularly important in the evaluation of the treatment-resistant patients for whom psychopharmacologic intervention is being considered.

IBS IN OTHER PSYCHIATRIC PATIENTS

We surveyed 68 patients who met DSM-III-R criteria for panic disorder with or without agoraphobia who were entering treatment studies in our Anxiety Disorders Program, by applying the criteria noted in Table 1 for IBS.[26] No additional laboratory or endoscopic evaluations that had not already been completed were obtained. Of these, 28 (41%) met diagnostic criteria for IBS. Improvement in GI symptoms closely paralleled improvement in panic symptoms. Similarly, Noyes and colleagues[27] recently reported that a group of patients with panic disorder exhibited a high frequency of IBS-like symptoms, which abated when patients were effectively treated for panic. Tollefson and colleagues[25] recently described an unexpectedly high prevalence of IBS in patients with generalized anxiety disorder (GAD) (37%) and in patients with major depression (29%) relative to normal controls (11%). They also described improvement in psychiatric symptoms in conjunction with IBS-like symptoms when patients were effectively treated for the psychiatric disorder. Thus, in both treatment-seeking IBS patients and in treatment-seeking psychiatric patients, particularly those with panic disorder, there appears to be a diagnostic overlap between GI symptoms and psychiatric illness.

Recent data have confirmed that IBS appears to be quite common in patients with anxiety disorders. Olden et al.[28] reported a 44% prevalence of IBS in patients with obsessive-compulsive disorder. More recently, Johnson et al.[29] reported a high prevalence of IBS in patients with panic disorder (44%), social phobia (20%), and generalized anxiety disorder (20%) versus 8% of normal controls. Given the high prevalence of IBS in anxious patients, it is noteworthy that the limited data suggest that treatment of the psychiatric disorder often results in improvement in GI symptoms.

PSYCHIATRIC DISORDERS AND GI SYMPTOMS IN A NONPATIENT SAMPLE: FINDINGS FROM THE NIMH EPIDEMIOLOGIC CATCHMENT AREA PROJECT

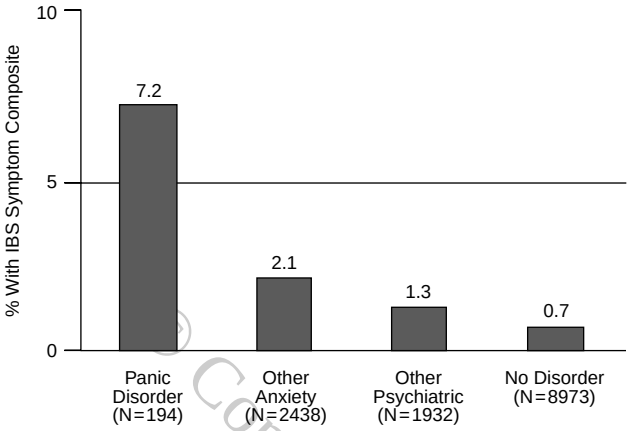
Studies[28] to date suggest a tendency for individuals with psychological/psychiatric distress to seek treatment, while those with similar functional GI symptoms without psychological distress and better coping skills did not become patients.[30] Since we had found a consistently high rate of IBS in treatment-seeking patients with panic disorder, we were interested in whether there was a similar association in a non-treatment seeking sample of individuals with panic disorder compared with other psychiatric disorders.[31]

To assess medically unexplained GI symptoms in a nonpatient, community-based sample, we surveyed[30] the prevalence of GI symptoms in individuals with panic disorder, other anxiety disorders, other psychiatric disorders, or no psychiatric disorders obtained in a national community survey. At four sites of the National Institute of Mental Health (NIMH) Epidemiologic Catchment Area (ECA) project DSM-III, the prevalence of psychiatric diagnoses was determined by using the Diagnostic Interview Schedule (DIS) for 13,537 respondents. Gastrointestinal symptoms were assessed from the somatization[32] disorder section of the DIS. Such an approach would allow for examination of this association without the potential confounding effect of "treatment-seeking bias" that has been thought to underlie the high prevalence rates of anxiety and other psychiatric disorders in treatment-seeking samples of IBS patients.

The ECA study is an epidemiologic survey of the rates and risks of psychiatric disorders conducted from 1980 to 1984. The DIS is a highly structured questionnaire that is designed to be used by lay interviewers in epidemiologic studies and that generates DSM-III diagnoses of psychiatric disorders. Also included in the DIS are questions about the occurrence of several GI symptoms in the somatization disorder section (e.g., "Have you ever had a lot of trouble with [non-menstrual] abdominal or belly pain?") Similar questions were asked for frequent vomiting, nausea without vomiting, diarrhea, constipation, abdominal or stomach bloating, and becoming sick from certain foods. My colleagues and I also assessed[30] the proportion of subjects who endorsed the combination of symptoms that approximated the diagnostic criteria for IBS (i.e., abdominal pain, diarrhea and/or constipation, abdominal bloating). It should be noted that these symptoms may not necessarily have occurred concurrently in those individuals endorsing this IBS composite.

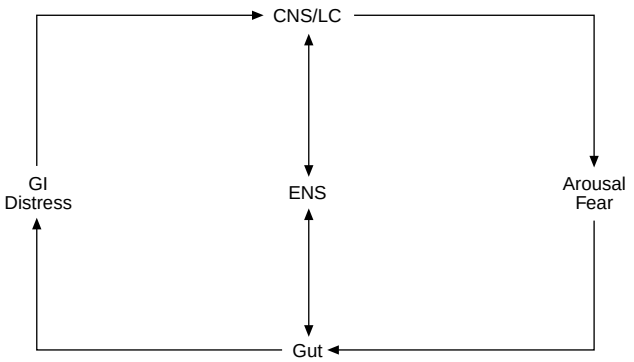
A total of 194 persons from the four sites had a lifetime DIS/DSM-III diagnosis of panic disorder (a weighted mean rate of 1.5%). A total of 2438 persons had another anxiety disorder such as phobia or obsessive-compulsive disorder (a weighted mean rate of 15.3%); 1932 persons had another psychiatric disorder, excluding panic, phobia, and obsessive-compulsive disorder (a weighted prevalence of 15.8%); and 8973 persons never had a psychiatric disorder (a weighted prevalence of 67.4%). The lifetime prevalence of the GI symptoms in the respondents were as follows: abdominal pain, 6.2%; vomiting, 1.8%; nausea,

Figure 1. Prevalence of IBS Symptoms in ECA Respondents*



*Abbreviations: IBS = irritable bowel syndrome, ECA = Epidemiologic Catchment Area.

Figure 2. Brain-Gut Interaction*



*Abbreviations: CNS = central nervous system, ENS = enteric nervous system, LC = locus ceruleus.

4.2%; diarrhea, 3.5%; stomach bloating, 6.8%; sick from certain foods, 2.8%; constipation, 6.9%; and IBS-like symptoms, 0.8%. The general demographic profile of a person endorsing any unexplained GI item was that of a white, married female, in the mid-socioeconomic range, aged 18 to 44 years.

Persons with panic disorder had the highest rate of unexplained GI symptoms compared with the other diagnostic classifications. The rates of unexplained GI symptoms in persons with panic disorder versus no panic disorder were statistically significant for all of the GI symptoms except for "sick from certain foods."[30] Notably, there was a 4.7-fold increased risk for persons with panic disorder to report nausea without vomiting compared with persons without panic disorder; there was a 4.6-fold increased risk for persons with panic disorder to have the IBS-like composite of symptoms compared with persons without panic disorder.

We[30] are aware of the numerous limitations to this study, most of which are obvious. Within these limitations, however, a survey of a large, well selected, nonclinical sample of subjects suggests that GI symptoms are reported significantly more frequently by subjects with panic disorder. The analysis did not include specific examination of the other psychiatric disorders, but Figure 1 suggests that the lowest prevalence was in individuals who were never psychiatrically ill and was the highest in patients with anxiety disorders in general. Our data[30] suggest that the coexistence of panic disorder and psychiatric IBS may represent true diagnostic overlap between these two disorders. The data also suggest that IBS-like symptoms are more common in individuals with psychiatric disorders than in those without psychiatric disorders. There is evidence that treatment of a coexisting psychiatric disorder in individuals with IBS results in alleviation of both psychiatric and GI symptoms in many patients. Therefore, discerning the presence of a psychiatric disorder in patients with IBS and other functional GI disorders may provide important clues for treatment planning.

THE BRAIN-GUT CONNECTION

Advances in our understanding the brain-gut interaction have provided new insights into this "psychosomatic" loop. It is clear that neuronal pathways between the brain and the gut interact in a coordinated fashion to exchange information on a regular basis (Figure 2). For example, anxiety/stress responses, which involve the septohippocampal area, amygdala, and midbrain central grey areas, send information to the hypothalamus, which integrates the input and sends autonomic output to the gut via both the sympathetic and parasympathetic pathways.[33–35]

The ENS is an elaborate neuronal network in the gut. It has been called the "little brain." Most vagal fibers connecting the gut and brain are afferent. The ENS can maintain reflex and other sophisticated activities when connections with the CNS are disrupted.[36,37] There are distinct similarities between the ENS and CNS. These include the presence of interneurons, a myenteric-blood barrier (like the blood-brain barrier), glial cell sheaths (Schwann cells usually surround peripheral nerves), and the same array of neurotransmitters and neuropeptides as found in the CNS.[38]

A potentially important CNS-GI link involves the locus ceruleus (LC), which mediates, in part, aspects of fear and arousal.[39,40] The LC receives afferent input from the gut during distention of bowel or stomach, which in turn causes increased firing of the LC.[40] This model provides a way to understand how patients with anxiety disorders could experience GI distress during pathologic arousal (with excessive sympathetic discharge) followed by afferent input from the gut back to the LC (and probably other

important CNS areas). This model suggests that a potentially vicious positive feedback loop may be initiated and maintained by pathologic anxiety and arousal. Like IBS patients, individuals suffering from anxiety or depression experience excessive autonomic symptoms, suggesting some common pathophysiology, perhaps in part at the level of the LC.[17] Many anxiolytic or antipanic agents (tricyclic antidepressants [TCAs], monoamine oxidase inhibitor [MAOI] antidepressants, benzodiazepines) appear to reduce the sensitivity of the LC response to afferent input.[41] This model may also help explain why anxiety symptoms frequently accompany unexplained GI symptoms.[17,42] Abnormal CNS function may affect the GI system via neuronal and neurohumoral pathways with resulting GI motility alteration and GI distress; via feedback to arousal centers at the CNS, GI distress could theoretically cause or worsen psychiatric symptoms such as anxiety. Finally, both anxiety/arousal and GI distress may occur simultaneously and mutually exacerbate each other.[17,42] Since the cells for both the ENS and CNS derive from the same embryonic cells, it is not surprising that ENS and CNS dysfunction might co-occur frequently.

This theoretical model of the interplay between the gut/ENS and brain/CNS is clearly an oversimplification. However, this model provides a conceptual framework for explaining how psychoactive agents (which reduce the sensitivity of the LC to afferent input) may have a place in treatment of IBS patients with or without psychiatric disorders. It is feasible that neuroactive agents, which presumably restore normality to neuronal functioning in the brain, may also exert similar effects on the ENS.

APPLICATION OF THE BRAIN-GUT MODEL: PSYCHO-ENTERO-NEUROPHARMACOLOGY?

In general, nonpharmacologic treatments are the first choice for individuals with moderate IBS symptoms. Patient education, dietary hygiene, stress management techniques, and bulk fiber products are the usual initial treatments. Drossman has suggested several other important therapeutic points.[7,30] Regular follow-up visits indicate interest on the part of the clinician as well as commitment to the patient. Education about IBS as a chronic or intermittent condition, often requiring long-term management, helps to generate reasonable patient expectations and goals such as improvement in functioning rather than complete relief from all symptoms. Providing information about IBS and making a "positive" diagnosis can help reassure patients that they do not have a life-threatening illness. Psychotherapy may be indicated for some patients with severe psychosocial stressors.

A substantial percentage of patients, however, particularly those with clinically significant anxiety or mood symptoms, often achieve only partial relief from the first-line treatments. Some clinically useful strategies may be suggested. It appears from the limited data reviewed earlier that psychopharmacologic treatment of psychiatric disorder/symptoms may also lead to improvement in GI symptoms. In such patients, pharmacotherapy may be quite useful. If a patient with IBS has a psychiatric disorder, I believe that this is an indication for treatment. In the following section, the limited literature on the treatment of IBS is reviewed.

Almost all studies of treatment of IBS with psychotropics are methodologically flawed,[43] but most support the clinical impression that neuroactive medications are helpful. Due in part to varying methods, the specific benefits reported in the studies varied. Greenbaum et al.[44] used desipramine or placebo in IBS patients. It was effective for improving abnormal motility in diarrhea-predominant IBS patients but not in the group as a whole. Also, the order in which the treatments were used had a significant effect. Importantly, in the desipramine group, pain symptoms and interference in the activities of daily living from symptoms were significantly improved relative to those of the controls.

Aside from the studies reviewed earlier, treatment of IBS patients with benzodiazepines has occurred only in conjunction with other treatments. In one study,[45] benefits from various combinations of benzodiazepines, bulk, and antispasmodics were reported. However, the placebo response rate in that study was reportedly 0%, leaving open questions about the methods employed. Even though there is a significant body of published evidence indicating that treatment-seeking IBS patients commonly suffer from psychiatric disorders, attention to psychiatric diagnosis has been essentially absent from IBS treatment studies published to date. Since the likelihood that a psychiatric disorder coexists is, conservatively, 70%, the treating clinician should make every attempt to detect if a psychiatric disorder is present; if there is recognizable psychiatric distress, the treatment should be targeted appropriately with consideration of the most tolerable side effect profile for that patient. The scientifically rigorous literature assessing the treatment of coexisting psychiatric disorders and IBS is extremely limited. No double-blind, placebo-controlled studies that assess IBS patients by both IBS subtype and psychiatric diagnosis have been reported. Following is a summary of the existing literature, supplemented by the clinical experience of the author.

IBS AND GAD

Many IBS patients (15%–55%) also have GAD. To date, there are no double-blind, placebo-controlled treatment studies in patients with both GAD and IBS. Clinical experience suggests that anxiolytic agents such as buspirone may be helpful in relieving GAD symptoms and also GI symptoms. Initial doses of 5 mg t.i.d. increasing to the

therapeutic range of 30 to 60 mg daily as tolerated is recommended. Our clinical experience also suggests that IBS patients with subdiagnostic syndromes (similar to DSM-IV mixed-anxiety depressive disorder)[14] may also benefit from azapirone treatment. It is important to use an adequate dose of buspirone (usually 30 mg/day or more) for a sufficient period of time (at least 4 weeks). Because of the relatively low incidence of GI motility effects of buspirone, it is relatively well tolerated by IBS patients. Benzodiazepines are clearly effective for GAD and appear to have some direct effects on the gut as well as in the CNS. Enthusiasm is somewhat limited by the lack of antidepressant properties and the probability of physical dependence over the long term. Despite these limitations, the benzodiazepines are a safe and effective treatment choice for nondepressed patients with GAD. Adinazolam, a low-potency triazolobenzodiazepine, has been shown in an open study to be effective in relieving both anxiety and GI symptoms in patients with combined GAD and IBS.[46] Many clinicians prefer the high-potency agents such as clonazepam (0.25–2.0 mg b.i.d.) or alprazolam (0.5–2.0 mg up to t.i.d.), but most benzodiazepines should be effective as well. TCAs (for example, imipramine or desipramine, 50–250 mg/day) have been shown to be effective in GAD and represent a useful alternative, particularly for diarrhea-predominant IBS patients. Trazodone, a triazolopiperidine, is effective in treating GAD, and the new antidepressant in that chemical class, nefazodone, also appears to have clinically significant anxiolytic properties. These agents may be particularly useful in patients with constipation-predominant IBS or alternating diarrhea and constipation, since the effects of these agents on GI motility appear to be modest in most patients. The newer agents (serotonin selective reuptake inhibitors [SSRIs]), paroxetine, fluoxetine, sertraline, and fluvoxamine, and the atypical agent venlafaxine, can be useful in some patients as well.

IBS PATIENTS WITH PANIC DISORDER

About one fourth of treatment-seeking IBS patients will also suffer from panic disorder. These patients may also have significant avoidance behavior related to fear of loss of bowel control and anticipated embarrassment. It may be strategically helpful to inquire about patient concerns regarding limitations imposed by the IBS symptoms and encourage patients who may be reluctant to take medication to comply with suggested interventions.

For patients with coexisting panic disorder, the traditional antipanic agents may be particularly useful. The strategy is to initiate low dosages in all patients and increase as tolerated until the desired antipanic effect is achieved. These treatments include high potency benzodiazepines such as alprazolam, which has been shown to be effective in panic disorder[47] and specifically in panic patients with IBS-like symptoms,[27] or clonazepam, a long-acting potent benzodiazepine. Dosage requirements for alprazolam in panic disorder range from 0.5 mg to 2.0 mg t.i.d. and for clonazepam, 0.25 to 2.0 mg b.i.d. Of course, other benzodiazepines are also useful in equipotent doses. Since patients with panic disorder often experience concomitant depression, antidepressants are also useful—or even preferable. For IBS patients with predominant diarrhea, imipramine or desipramine may be started at dosages of 10 mg daily and increased as tolerated. Because these patients are often activated by antidepressants, it is important to explain in advance that jitteriness may occur and to initiate treatment at very low dosages. Dosages in excess of 200 mg daily may be needed, but many patients will respond to lower dosages. For patients with sensitivity to anticholinergic effects (such as those with predominant constipation), the SSRIs have been useful. These agents, like the TCAs, can cause jitteriness upon initiation of treatment, and a low starting dose is recommended: initial fluoxetine dose is 2.5 mg/day (usual therapeutic range, 20–40 mg/day); initial sertraline dose is 25 mg/day (usual therapeutic range, 50–200 mg/day); and initial fluvoxamine dose is 25 mg/day (usual therapeutic range, 150–200 mg/day). Paroxetine (now approved by the Food and Drug Administration [FDA] for panic disorder) has mild anticholinergic effects and may be useful for individuals with diarrhea-predominant IBS or alternating constipation and diarrhea. An initial dose of 10 mg/day, which is titrated to 30 to 50 mg/day, has shown positive effects in our experience. Nefazodone, which has been clinically reported to have some antipanic effects, may also be useful; begin dosing at 50 mg q.h.s. and increase gradually to 300 to 500 mg given in two daily doses. Venlafaxine may also be useful, but experience is limited in the IBS population.

IBS PATIENTS WITH PTSD

PTSD is a chronic anxiety disorder characterized by a variety of symptoms of anxiety and depression, including trauma-related intrusive images, sleep disturbance, depression, phobic avoidance, panic attacks, and often chronic, pathologic arousal. Of course, pharmacologic treatment represents only a part of standard PTSD treatment plans (for review see reference 48). Treatment is targeted toward attenuation of intrusive symptoms, improvement of avoidance behaviors, normalization of hyperarousal, treatment of depression, and improvement of impulse control. Only a few double-blind, placebo-controlled studies have been completed in PTSD, and evidence is accruing that pharmacologic treatment can significantly reduce bothersome symptoms. Since victimization appears to be common in this patient group, amelioration of trauma-related symptoms may be critical for some patients. The accrued literature indicates that the TCAs amitriptyline and imipramine (these may be benefi-

cial in patients with diarrhea-prone IBS) and monamine oxidase inhibitors (such as phenelzine) can effect modest improvement in some symptoms of PTSD.[49] Recent studies and several anecdotal reports support the clinical use of the SSRIs as a treatment for PTSD.[49] Van der Kolk et al.[50] recently reported that fluoxetine was significantly more effective than placebo in reducing symptoms of PTSD in a mixed combat and civilian PTSD patient sample. The SSRIs have a broad spectrum of effectiveness against a variety of anxiety and depressive symptoms and may be the pharmacologic treatment of choice for PTSD. In particular, individuals with constipation-predominant IBS may benefit from the lack of anticholinergic effects, while clomipramine, which shares properties of both the TCAs and the SSRIs, may be useful for those with diarrhea-predominant IBS.

IBS PATIENTS WITH SOCIAL PHOBIA

Social phobia is common in IBS patients and has been studied in nonmedical populations to date, but the data suggest that social phobia will respond to both medication and cognitive-behavioral treatments. Currently, the SSRIs are often used as a first-line treatment for social phobia.[49] The SSRI dosage requirement appears to be up to twice the dosage needed for depression in some patients. Benzodiazepines (same dosage range for social phobia as for panic disorder) are useful, but do not reliably provide treatment for or protection against depression. TCAs are believed to be ineffective for social phobia. The MAOIs phenelzine and tranylcypromine are effective in the treatment of social phobia, but require a restricted tyramine diet and have significant short- and long-term side effects.

IBS PATIENTS WITH MOOD DISORDERS

As was noted earlier, almost two thirds of IBS patients in most reported treatment-seeking samples have current major depression or dysthymia. The suggested strategy is to tailor side effects of the antidepressant to the patient as closely as possible. For patients with diarrhea-predominant IBS, TCAs with anticholinergic properties, as noted above, are particularly useful (imipramine or desipramine in antidepressant dosages); paroxetine may also be useful for some patients. Patients with constipation-predominant IBS may tolerate agents with fewer anticholinergic effects such as fluoxetine, sertraline, paroxetine, fluvoxamine, nefazodone, trazodone, venlafaxine, or bupropion.

IBS PATIENTS WITHOUT PSYCHIATRIC DISORDER

IBS patients without a clinically significant psychiatric disorder may benefit from psychopharmacologic agents. As was discussed above, these agents appear to attenuate the postulated positive feedback cycle between the gut and the brain at the level of the LC and probably other CNS sites and potentially the ENS.

As was mentioned earlier, these agents theoretically may have effects in the ENS, or "little brain," as well as the CNS. Clouse et al.[51] reported the results of a treatment study of 138 treatment-refractory IBS patients referred to a university-based gastroenterology practice. On the basis of results from a semistructured psychiatric interview, they estimated that nearly half of these patients had no apparent psychiatric disorder. Despite the apparently low (50%) rates of psychiatric disorder, over 90% of the 138 IBS patients benefited from sequential treatment of up to five different agents, including low-dose antidepressants (TCAs or trazodone for the majority of patients) or benzodiazepines. A few patients who were given low-dose thioridazine showed some improvement. Because of the risk of inducing tardive dyskinesia, this would not be a treatment my group would recommend. In this study, 92% of patients improved, 56% experienced complete remission of their IBS symptoms, and 44% experienced remission after the first medication trial. The reason for a favorable response to psychotropic agents in individuals with IBS who have no psychiatric illness is unclear. Attenuation of a pathologically activated "brain-gut" feedback loop at the CNS or ENS level may be one possible mechanism. Distinct from this mechanism, a second possibility is a reduction in afferent pain signals from the viscera; both are potential mechanisms. Finally, since psychiatric syndromes (e.g., anxiety or mood disorders) that were "sub-diagnostic" may have existed in some of these individuals, those disorders may have been positively affected by treatment as well.

CONCLUSION

It appears that treatment-seeking patients with functional GI disorders frequently present with concomitant psychiatric disorders. Findings to date suggest that knowledge about coexisting psychiatric illnesses in patients with IBS and other functional GI disorders may enhance our ability to treat them more effectively. A model has been offered that suggests that, in patients without psychiatric disorders, neuroactive medications may be a useful tool in improving functioning in individuals with functional GI disorders who have not responded to standard, conservative treatments. Neuroactive medications may be useful in treating patients with IBS, particularly those with coexisting psychiatric illness. As more is learned about the interaction between the brain and the gut, additional helpful treatments will surely result.

Drug names: adinazolam (Deracyn), alprazolam (Xanax), amitriptyline (Elavil and others), bupropion (Wellbutrin), buspirone (BuSpar), clomi-

pramine (Anafranil), clonazepam (Klonopin), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), nefazodone (Serzone), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), thioridazine (Mellaril and others), tranylcypromine (Parnate), trazodone (Desyrel and others), venlafaxine (Effexor).

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