Common Psychological Disorders in Inflammatory Bowel Disease and Implications for Disease Management

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ABSTRACT

• **Objective:** To review and describe the relationship between mood disorders and inflammatory bowel disease (IBD), considering the evidence for prevalence and comorbidity, as risk factors for disease course, and for psychological interventions in IBD disease management.

• **Methods:** Review of the clinical literature, with a primary focus on human studies and English language reports in the last decade to serve as an update to prior reviews.

• **Results:** Studies suggest that mood disorders are more prevalent in IBD. Anxiety and depression that pre-date IBD onset may be a risk factor for disease. Mood disorders can adversely affect the course of IBD, including more frequent relapses and greater risk of surgery. Active or more severe disease and poorer socioeconomic status are risk factors for the development of a mood disorder in IBD. Antidepressant medication and psychological therapy can improve anxiety and depression in IBD, but the evidence for direct improvement of IBD outcomes with these 2 therapy approaches is still preliminary.

• **Conclusion:** The psychological health of the IBD patient is relevant in disease management given the relationship of mood disorders with disease outcomes. GI practitioners are encouraged to screen for depression and anxiety and to initiate or refer for pharmacologic or psychological treatment when indicated. There is potential for these interventions to positively affect disease course directly in addition to mitigating distress and improving quality of life.

**Crohn’s disease (CD) and ulcerative colitis (UC), collectively described as inflammatory bowel disease (IBD), are chronic, spontaneously relapsing and remitting inflammatory disorders of the gastrointestinal tract. These diseases are as common as type 1 diabetes and twice as common as multiple sclerosis, given prevalence rates conservatively estimated at 150 per 100,000 [1], and there is some indication that prevalence rates may be rising [2]. Approximately 30% of those with IBD are diagnosed before the age of 21 [3], making IBD the most significant chronic disease of childhood and adolescence, and a disease of lifelong struggle.**

The current etiologic hypothesis of IBD suggests the disease is triggered by an abnormal immune response to microbial agents that reside in the gut [4,5]. These chronic inflammatory disorders are painful, embarrassing, and socially and physically limiting, and can persist throughout one’s lifetime [6]. Characterized by exacerbations and remissions, symptoms typically include abdominal pain, diarrhea, weight loss, and a variety of extraintestinal symptoms. Disease management is accomplished through a range of medications, including the use of steroids, immunomodulators, and the newer biologic agents; as well, surgery is often required. Management goals include achieving symptomatic remission, suppressing inflammation and achieving mucosal healing, controlling or minimizing complications, and maintaining remission. Overall, the long-term course of IBD can include hospitalization, surgery, and costly medications, as well as a reduced quality of life (QOL) [7].

In addition to the clinical burden of the disease for the patient, there is evidence of significant psychiatric comorbidity that not only can add to the distress of the patient experience but may also directly affect the course
of the disease [8]. This paper will review the recent clinical findings regarding mood disorders and IBD, and consider implications and directions for intervention when treating the IBD patient.

**Prevalence of Mood Disorders in IBD**

Anxiety and depression have been commonly reported in patients with IBD. A recent clinical study comparing IBD patients (n = 103) and healthy controls (n = 124) reported significantly higher anxiety and depression scores on a validated symptom self-report measure than the healthy control sample [9]. In a population-based study using case controls, Lerebours et al [10] compared 241 incident cases of IBD to 225 blood donor community controls. They found that those with IBD had significantly higher levels of depression than the community controls, with similar findings for anxiety. A larger case-control study compared rates of depression and anxiety in patients with IBD relative to rates in 800,000 controls admitted to a hospital for minor medical reasons [11]. Results indicated higher rates of both anxiety and depression in the IBD patients that were especially evident early in the disease course. For those with CD, the rates of anxiety or depression were 5 times higher than for the controls, and for those with UC the rate of anxiety was 4 times higher and that of depression was twice as high as controls. The Manitoba IBD cohort study is the largest study, and one of only 2, to use a structured clinical diagnostic interview to assess prevalence rates when comparing mood disorders in those with IBD versus controls [12]. They reported higher lifetime rates of depression in the IBD population-based sample (27% vs. 12%), and they noted lower rates of social anxiety in IBD compared with the community controls (6% vs. 11%).

When rates of mood disorders in IBD have been compared with rates in other chronic diseases, CD patients were found to have a higher prevalence of depressed mood relative to those with erosive esophagitis, (25.4% vs. 8.2%) [13]. Both UC and CD patients had similar levels of anxiety as those with chronic liver disease [14]. The chronic liver disease patients had higher depression levels than the IBD patients, which may relate to treatment side effects with interferon for chronic liver disease and/or may reflect the higher rates of substance abuse and associated depression often found in a chronic liver disease population [14]. Generally, however, depression is more likely to co-occur with chronic conditions characterized by pain, such as IBD [15].

There has been little attention to suicide risk with depression in IBD, but one small study of CD patients (n = 69) specifically queried this and found 13% acknowledged feeling suicidal due to their IBD [16]. These results were supported by a larger national study that reported 17% of those with major depression and IBD had considered suicide at some point in the previous year [17].

All of these studies provide very strong support for a higher prevalence of mood disorders in IBD compared with the general community. Disease activity may play a role, in light of the findings that depression and anxiety levels were significantly higher for CD and UC patients with active disease than matched healthy controls, but were not significantly different for those in remission [14], paralleling earlier findings in a population-based study of psychological functioning in IBD [18].

**Depression and Anxiety as Risk Factors for IBD Onset**

Epidemiologic research has suggested that those with depression are at a greater risk of subsequent development of a variety of chronic diseases, including hypertension (hazard ratio [HR] 1.6, 95% confidence interval [CI] 1.2–2.2), arthritis (HR 1.7, CI 1.3–2.2) and asthma (HR 1.8, CI 1.3–2.5) [19], although the relatively lower base rate of IBD may make it more difficult to discern a downstream etiological relationship in epidemiologic studies. A population-based Canadian study found that depression antedated IBD diagnosis by at least 2 years in 54% of those with a lifetime history, and that 79% of people with IBD and a lifetime history of an anxiety disorder had a first episode more than 2 years prior to the IBD diagnosis [12]. This time frame might still be considered concurrent to disease onset though, given the lengthy period of 2 to 3 years that it can take to establish a diagnosis. However, Kurina and colleagues [11] found higher rates of depression 5 years prior to an IBD diagnosis, compared with the general population. Similarly, the Nurses Health Study, which has tracked more than 150,000 women since 1992, reported that a higher level of depressive symptoms at baseline was associated with a greater risk of subsequently developing CD (OR 1.62), although an increased risk for UC was not evident [20].

While the studies do not conclusively support an etiological role for mood disorders in IBD onset, they highlight the possibility that anxiety and depression may in themselves be risk factors for IBD.
Mood Disorders and IBD Disease Course

Several studies have observed that anxiety and depressive symptoms are likely to be more prominent in times of increased disease activity and to improve when the disease activity is reduced [21]. Goodhand and colleagues used a cross-sectional design to examine the relationships between demographic, clinical and phenotypic factors, and mood in patients with UC, CD, and healthy controls, focusing specifically on the association between disease activity and mood [9]. They found that for both UC and CD patients, anxiety and depression scores were higher than for controls. In UC, anxiety was associated with perceived stress and a new diagnosis of IBD, and depression was associated with stress, inpatient status and active disease. In CD, anxiety was associated with perceived stress, abdominal pain, lower socioeconomic status, and active disease (as measured by fecal calprotectin and/or serum CRP), while depression was associated with perceived stress and increasing age [9].

While associations cannot clarify causal direction, several prospective studies have suggested that mood disorders can negatively influence disease course in IBD. A small 2-year study tracking CD patients every 2 to 3 months found that higher depression scores were associated with subsequent elevated clinical disease scores (ie, Crohn’s Disease Activity Index (CDAI) scores) in the following time period [22]. In a study on the impact of depression and anxiety on IBD relapse in CD and UC patients, Mittermaier and colleagues [23] found that depression levels at baseline were significantly correlated with the total number of relapses in the subsequent 18 months. Higher anxiety at baseline was also related to more frequent relapses. They also found that the time to first relapse was significantly shorter for patients who were depressed at baseline compared with those who were not (97 vs. 362 days).

Using a large electronic medical record (EMR) database of over 10,000 IBD patients, Ananthakrishnan et al [24] identified that CD patients with a diagnosis of depression or anxiety were 28% more likely to require surgery than those without psychiatric comorbidity, after adjusting for demographic and clinical disease factors. They did not find the same outcome for UC patients, although surgery rates tend to be lower for UC compared with CD patients, which may be a confounder.

Depression may also interfere with effects of medication or through adherence more generally as other avenues to impact disease course. In a prospective study of CD patients, major depression was a risk factor for failure to achieve remission with infliximab [25]. While it was unclear whether adherence was the relevant mechanism in the infliximab study, depression is associated with lower behavioural adherence to treatment regimens in chronic disease [26]. Poorer adherence to treatment in IBD has been associated with a variety of demographic, clinical and psychological factors, such as male gender, young age, and mild disease, with adherence tending to be lower in those suffering from anxiety or depression [27]. A recent study on adherence in adolescents with IBD found that higher anxiety and depression symptoms were associated with lower adherence, playing a moderating role with specific barriers to adherence [28]. However, a large survey study of over 1000 members of a national IBD association in France, found that self-reported nonadherence increased with anxiety and moodiness, but was not associated with depression [29].

There has been some exploration of coping as a mediator of the impact of mood in IBD, although it has been difficult to delineate these relationships. Dorrian and colleagues examined the relative contribution of illness perceptions and coping strategies to explain adjustment to IBD, assessing adjustment in terms of psychological distress, quality of life and functional independence [30]. In this study, coping did not independently predict these aspects of adjustment once illness perceptions were controlled for. A recent study assessed the relationship among IBD knowledge, coping, and medication adherence [31]. They found that individuals with IBD who had greater disease knowledge and who were better informed about their IBD were more likely to endorse adaptive coping strategies, such as the use of more problem-focused coping and less emotion-focused coping, however they did not assess disease outcomes.

While a self-management approach has been incorporated into the management of many chronic diseases, it is unclear whether outcomes with these types of approaches in IBD are influenced by comorbid mood disorders. A review of self-management and educational interventions in IBD found 10 out of 18 studies had incorporated 1 or more measures of psychological well-being [32]. Three studies showed a reduction in anxiety with self-management interventions, 2 of which involved CD patients, and 1 involving UC patients. The study of UC patients implemented a “comprehensive lifestyle modification program” that included stress management training, disease education, and self-care. They found...
improvement in anxiety after 3 months, but no long-term mood benefits 12 months after completion [33]. Overall, however, none of these studies assessed mood in a mediating or moderating role, but rather mood was included as a secondary outcome.

**Risk Factors for Development of Mood Disorders in IBD**

The risk of clinical depression or anxiety has been found to be high in the year following an IBD diagnosis in particular, with estimates of 4 to 5 times increased risk compared with population base rates [11]. Loftus and his colleagues [34] evaluated the risk of developing anxiety or depression in children (ie, < 18 years old) with Crohn’s disease using a 1:5 case-matched design, and found a significantly elevated risk as well after the CD diagnosis compared to non-IBD controls (HR 2.28 for anxiety; HR 1.74 for depression). It is only recently, though, that factors associated with developing one of these mood disorders in IBD have been specifically explored.

An association with disease activity has consistently been observed, such that those with active disease were more likely to experience depression or anxiety [9,13,14,35]. This association intuitively make sense as the challenges of managing active symptoms and medications in a chronic disease with an unpredictable course can be daunting for many patients.

The largest study to date to assess risk factors for psychological comorbidity surveyed 1663 IBD patients and examined clinical disease and socioeconomic factors [35]. Multivariate analyses indicated that disease flares, severe disease, self-reported poorer treatment adherence, being unemployed, and socioeconomic deprivation were each independently associated with anxiety for IBD patients. Depression in IBD was associated with the sociodemographic factors of age, unemployment, and social deprivation, as well as disease flares. A small Korean study similarly reported lower socioeconomic status as a risk factor for depression in IBD [36]. Other risk factors for IBD patients that have been identified include family history of depression (risk for anxiety [13]), and concurrent stress (risk for anxiety and depression [9]). However, all of these studies used cross-sectional designs which do not allow determination of causality. The associational relationships could as readily be reflecting an effect of mood disorders on disease and adherence for example, as reflecting the opposite, namely that active disease is a risk factor for the development of mood disorders.

One prospective study examined onset of anxiety or depression following IBD hospitalization or surgery, and evaluated risk factors for the development of mood disorders at that time [37]. Using the EMR database described previously, for this study, Ananthakrishan and his group first excluded all patients with a diagnosis of depression or anxiety prior to or within 30 days of an IBD-related surgery or hospitalization. They found a significantly greater risk of depression following surgery for both UC and CD, compared to IBD patients who had never had surgery, with a median onset of depression 2.5 years post-surgery. They reported similar findings for anxiety, although the risk of anxiety post-surgery was smaller than the risk for depression, compared to the IBD patients who had never had surgery. There was also a significant risk of depression or anxiety 5 years after an IBD-related hospitalization, with a nearly twofold greater risk of depression than for those with IBD who never needed hospitalization.

Overall, these findings imply that active disease, and in particular a more severe disease course as evidenced by the need for surgery or hospitalization, may predispose to psychological morbidity.

**Why are Mood Disorders Co-occurring with and Adversely Affecting IBD?**

The studies reviewed in the previous sections suggest that mood disorders may both affect and be affected by IBD. A bidirectional influence in the brain-gut pathway has been supported through prospective work with the functional gastrointestinal disorders. Koloski et al [38], in a study assessing 1775 participants, concluded that psychological disorders both preceded and followed onset of irritable bowel syndrome and functional dyspepsia. They found that higher anxiety levels at baseline for those with no evident functional GI disorder independently predicted the development of these functional GI disorders 12 years later. Similarly, those who had either IBS or functional dyspepsia but no elevated depression or anxiety at baseline were much more likely to have clinically elevated anxiety and depression when assessed 12 years later.

The complex interactions in the brain-gut axis have been broadly studied, spanning interconnections among the psycho-neuro-endocrine-immune systems implicated in the pathogenesis and pathophysiology of IBD [39]. Multiple factors that might drive neuroimmune modulation in IBD have been identified and include psychological factors such as stress and depression, with
potential pathways via inflammation and/or autonomic imbalance. Studies modeling colitis and depression in mice found that depression increased susceptibility to experimental colitis [40] and worsened colitis severity, regardless of whether it was induced prior to inducing the colitis or following the colitis onset [41,42]. Depression in the mice was found to exacerbate the colitis by interfering with the actions of the vagus nerve that serve to counter inflammation [41]. These findings affirm that depression can negatively affect the course of intestinal inflammation. There is also evidence to support directional influence the other way, namely that inflammation may precipitate depression [43]. Elevated proinflammatory cytokines have been identified in depressed individuals even in the absence of any comorbid inflammatory disease, and it is now recognized that proinflammatory cytokines can access the brain through humoral, neural and cellular pathways and alter cerebral function [44].

The gut microbiome, which collectively refers to all the microbes residing in the gut, may be another pathway through which mood disorders and IBD interact, although the work in this area is still in its infancy [45]. Research is converging to suggest that intestinal microbes might be involved centrally in modulating behavior and brain biochemistry, and that environmental influences such as stress can affect the microbial balance in the gut [46]. Bercik and colleagues [47] altered the gut bacterial composition in a strain of timid mice through application of antibiotics and observed significant behavior changes from shy to bold tendencies. They also colonized bacteria from opposite strains of mice (ie, timid and bold) and observed parallel changes in behavior, noting that the bolder mice became more hesitant and anxious. In another study, this group induced inflammation through parasitic infection resulting in increased anxious behavior, which subsequently abated when the mice were treated with a beneficial gut microbe [48].

Collectively, the knowledge from these animal models of the brain-gut axis provides insight into mechanisms and common pathways. These findings may also highlight new targets for intervention, and they support, at a conceptual level, that treating one component of the mood-disease interrelationship may help to address the other component.

Psychological Health and Implications for Treatment

Overall, the current evidence underscores that psychological health should be a clinical consideration in disease management for IBD. With an emerging model suggesting a bidirectional relationship between mood disorders and inflammatory bowel disease, assessment and treatment of psychological concerns, in addition to management of bowel symptoms and inflammation, may decrease distress, improve quality of life for the IBD patient, and potentially improve disease course [49,50]. IBD specialty clinics in multiple countries have adopted more of a biopsychosocial approach in their management of IBD patients [51]. However, this approach is not yet common or standard practice, despite consensus guidelines calling for more routine screening and treatment of anxiety and depression [52]. A study in the Netherlands found that less than 20% of IBD patients with current significant anxiety or depressive symptoms had recently received any intervention, either psychological or psychiatric [53], suggesting undertreatment of comorbid mental health needs parallel to the concerning under-treatment of depression in the general population [54].

Anxiety and depression are very treatable conditions, and have been responsive to both pharmacological and psychological treatment approaches. The most widely used antidepressant medications are the second generation serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) [55]. The cognitive behavior therapies also have extensive empirical support for treating mood disorders [56]. The efficacy of these 2 approaches to treatment has been examined in IBD, with some evaluation of impact on psychological outcomes as well as IBD outcomes, albeit with varying quality of study methodology.

Pharmacotherapy

While randomized controlled animal studies have found that antidepressant therapy can attenuate induced colitis in mice [40,41], the handful of human studies that have examined the use of antidepressants in IBD consist mainly of case studies [57], with 1 open-label trial [58], 1 recent case-control study [59] and 1 small randomized controlled trial (RCT) [60]. A systematic review of the case studies and the open-label trial concluded that the targeted anxiety or depression generally responded to treatment (primarily paroxetine or buproprion), and most of the studies found a positive effect on IBD disease activity [57]. Goodhand and colleagues [59] used retrospective case review to assess the disease course of 29 patients in the year before and after they were started...
on antidepressants for a comorbid mood disorder, comparing them to matched IBD controls who were not on antidepressant medication. Eight different antidepressants were used across the cases, with the most common being citalopram and fluoxetine. They found both an improvement in mood symptoms and improvement in IBD disease course, reporting significantly fewer IBD relapses and less use of steroids for those using antidepressant medication. The only RCT involved 50 UC patients tracked prospectively for 8 weeks, half of whom were treated with imipramine [60]. They reported improved mood and decreased disease severity in the treated group, however they did not randomize based on mood status, resulting in baseline differences between groups.

This early stage data suggests antidepressant medications may positively affect IBD disease course in addition to treating comorbid mood disorders. It is not clear from the studies done to date whether any IBD improvement is a result of treating the depression, or is more directly impacting brain-gut processes relevant in IBD. Carefully controlled studies are needed to examine whether this treatment approach might improve IBD in the absence of psychiatric comorbidity. Studies in non-IBD samples have shown that antidepressant treatment has been associated with decreases in inflammatory markers [61], providing some support for the potential of these medications as an adjunct for disease management in IBD. However it is important to treat depression and anxiety regardless of whether there is a direct positive effect on the IBD, as these psychiatric disorders contribute to significant suffering and disability in their own right.

Psychotherapy
As with pharmacotherapy, there are 2 outcomes of interest when considering the utility of psychological therapies in IBD—psychological functioning and impact on IBD symptoms and course. A number of recent reviews, including a Cochrane review, have evaluated the efficacy of psychological treatments in IBD [8,49,50,62–64], with mixed conclusions. However, most included any nonpharmacological interventions rather than considering only evidence-based psychotherapy interventions for mood disorders and assessing their efficacy with comorbid mood disorders in IBD. For example, the Cochrane review [62] concluded there was little support for the efficacy of psychological therapy in IBD for either psychological or IBD outcomes, but they included studies of patient education and supportive psychotherapies, which have not been established as efficacious for primary depression or anxiety. In contrast, studies that have used cognitive behavioral therapy (CBT) for depression or stress management interventions based on CBT strategies, have more consistently reported significant improvements in the targeted anxiety or depression, and quality of life for IBD patients [65–69].

CBT and stress management interventions have had only modest effects on disease outcomes in IBD [64]. Of the studies noted previously with significant psychological functioning improvements, most also measured outcomes for IBD and did not find any effect on disease course [65,66,68,69]. However, improvements in IBD symptoms post-treatment, including constipation fatigue, pain, and abdominal distension, have been reported in a few randomized controlled studies [70–72]. In addition, a retrospective case-control study found that patients who received psychological counseling had fewer relapses, fewer outpatient visits, and decreased used of steroid medication and other relapse-related IBD medications in the year following counseling relative to the year prior, with no differences in outcomes for the control group [73].

The studies to date suggest that empirically supported psychological interventions, and in particular CBT, can be applied to mood disorders in IBD with positive effect, similar to what has been found for the use of antidepressant medication in IBD. However, the direct impact on IBD outcomes for patients with or without a concurrent mood disorder has not been clearly established. Recent controlled studies suggest that psychological therapies hold promise as a useful adjunct to IBD management, but methodological issues such as inclusion of non–evidence-based therapies, unselected IBD patients, or patients in remission with little elevated distress or disease activity need to be addressed.

Other Novel Therapies
Hypnotherapy has been reported as an effective intervention for irritable bowel syndrome, but has only recently been applied to inflammatory bowel disease. A controlled experimental study of UC patients with active disease demonstrated significant improvements in both systemic and rectal mucosal inflammatory responses following hypnosis compared to the control group [74]. Two small uncontrolled clinical studies using hypnotherapy found improvements in IBD symptoms. One study provided gut-directed hypnotherapy to 15
medication-refractory IBD patients [75]. They found that the majority of IBD patients experienced improved symptoms (reclassified from severe to mild or moderate), improved quality of life, and decreased use of corticosteroids, with results sustained for an average 5 year follow up. The second study reported significant improvement in disease-specific quality of life for 8 UC patients in remission [76]. A further controlled study by the same group, comparing hypnotherapy to an active attention control for UC patients, reported that the treated group was less likely to have a disease flare in the subsequent 12 months [77].

Bonaz and his group have explored the role of vagal nerve inhibition in anti-inflammatory processes, given the link between the hypothalamus-pituitary-adrenal axis and stress in IBD. Their preliminary findings showed vagus nerve stimulation improved colitis in rats, and they are now piloting this novel approach in patients with CD [39].

Conclusions

There is increasing recognition that chronic disease management optimally involves attention to psychological processes as well. This is becoming particularly evident in IBD, as depression and anxiety are highly prevalent. It may be that these mood disorders are consequences of the challenges of coping with an illness that is defined by an unpredictable course, fears of disease progression, and painful and embarrassing symptoms. These disorders in turn can worsen disease activity. The heterogeneity of the inflammatory bowel diseases, in terms of disease type (ie, CD, UC), disease activity, phenotype and genotype, add complexity when discerning outcomes and interrelationships with psychiatric illness, as many studies do not distinguish IBD subgroups across all of these dimensions. Nevertheless, the weight of evidence for an adverse impact of these psychological factors on IBD supports the call for more routine screening and care in the regular course of health care provision (Table). The IBD patient may be best served by a review of symptoms and functioning that includes queries regarding mental health, as has been initiated with other chronic disease populations such as heart disease and diabetes [78,79]. The time around IBD diagnosis and during periods of active disease may be especially vulnerable periods for development of or exacerbation of these psychological disorders, but routine review and intervention when indicated could potentially mitigate the adverse effects to some degree. While more rigorous studies of antidepressants and psychological therapies are needed to determine the impact on physiological and symptom outcomes for IBD, their effectiveness with mood disorders is well-established. Perhaps it is time to integrate these approaches more fully into the arsenal for IBD disease management.

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Mood Disorders and IBD


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