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Psychiatric Comorbidities in Inflammatory Bowel Disease

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Abstract: Inflammatory bowel disease (IBD) classically consists of ulcerative colitis and Crohn's disease, which are typically characterized by progressive cyclical attacks of abdominal pain, diarrhea and fatigue. Other highly prevalent clinical features of IBD include psychiatric disorders such as mood and anxiety, which may occur in 60-80% of patients during relapse. Stressful live events seem to precipitate IBD diagnosis, and are related to a significantly increased risk of disease relapse. Alternatively, an IBD diagnosis itself is associated with an increased risk for the development of anxiety and depression. These conditions lead to significantly worsened prognosis, increased risk of relapse, increased healthcare utilization, and decreased quality of life. Risk factors known to predict anxiety and depression in patients with IBD include female gender, presence of other medical comorbidities, severe and active disease, and socioeconomic deprivation. Thus, increased clinical suspicion for comorbid mood or anxiety disorders must be made once a diagnosis of inflammatory bowel disease is established, with appropriate followup. This review summarizes the literature regarding the relationship between IBD and the development of psychiatric disorders.

Keywords: Anxiety, crohn's disease, depression, inflammatory bowel disease, mood, ulcerative colitis.

1. INTRODUCTION

Inflammatory bowel disease (IBD) classically encompasses two clinically related illnesses: Crohn's disease (CD) and Ulcerative Colitis (UC). These disorders share similar manifestations such as abdominal pain, diarrhea and fatigue [1]. Less common symptoms include weight loss, hematochezia, short stature, delayed puberty, anorexia, and fever (Table **1**). IBD has a chronic course, where asymptomatic periods are followed by a constellation of symptoms that may initially present in patients at a young age. Approximately 25% of patients with IBD present during childhood or adolescence [2]. The location and extent of inflammation differentiate CD from UC. Crohn's disease is characterized by transmural inflammation at any point along the digestive tract with "skip lesions" located in the colon. Strictures, colonic granulomas, and perianal fistulas with chronic drainage may also be present in CD. Ulcerative colitis is characterized by contiguous mucosal inflammation between the rectum and the proximal colon with "pseudopolyps" of regenerating mucosa interspersed between atrophic colonic tissue. Extraintestinal findings in IBD include rashes such as pyoderma gangrenosum and erythema nodosum, uveitis, nephrolithiasis, cholelithiasis, sclerosing cholangitis, and ankylosing spondylitis. There is no cure for IBD, but symptoms are controlled with medical management until surgical intervention is indicated. Approximately two thirds of CD patients ultimately require surgery, while approximately one third of UC patients require surgery [3]. In CD, even after surgical intervention, pathology can recur whereas surgery is seen as curative in UC. However, the rates of major abdominal surgery including colectomy for CD and UC have been decreasing in the post-biological therapy era [3, 4]. Another important clinical feature of IBD is the significant likelihood of comorbid psychiatric disease, primarily depression and anxiety. An excellent review by Mikocka-Walus *et al.* delineates several currently existing controversies relating to the marked occurrence of psychiatric disorders in patients with IBD, chief among them is the interface between mood and anxiety and gastrointestinal disease progression [5]. This review summarizes the literature regarding the relationship between IBD and the development of psychiatric disorders.

2. EPIDEMIOLOGY OF IBD

The prevalence of IBD varies in different geographical regions of the world. This difference is likely multifactorial and a result of the psychosocial influences believed to affect progression of the disease. The Rochester Epidemiology Project, a major ongoing population-based study in the United States using a medical records linkage system in Olmsted County, Minnesota, determined that the annual incidence rates for UC and CD were 7.9 and 8.8 cases per 100,000 people, respectively [6]. The same study determined the prevalence of UC and CD were 214 and 174 cases per 100,000 people, respectively. In comparison, the worldwide prevalence of IBD varies from 37 to 246 cases per 100,000 for UC and 26 to 199 cases per 100,000 for CD [7]. It is

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Table 1. Disease manifestations of Ulcerative Colitis and Crohn's Disease[a].

Feature	Ulcerative Colitis	Crohn's Disease
Region	Colon	Along entire GI tract
Distribution	Continuous	Skip lesions
Hematochezia	Often	Occasionally
Mucus in stool	Often	Occasionally
Fistulas	Absent	Present
Strictures	Rarely	Often
Intestinal inflammation	Mucosal	Transmural
Pseudopolyps	Often	Rare
Granulomas	Absent	Present
Vitamin malabsorption	Absent	Occasionally
Intestinal obstruction	Rarely	Frequently
Toxic megacolon	Yes	No
Reoccurrence after surgery	No	Yes
Malignant potential	No	Yes

[a]Adapted from S Friedman, RS Blumberg [73].

estimated that in the United States, more than 593,000 people have UC, and more than 565,000 people have CD [8]. While IBD rates in the United States appear to be stabilizing in adults, the incidence of IBD in developing countries appear to be increasing over the last several decades and the incidence may approximate North American rates in coming years [9]. Reasons for lower disease incidence in the developing world are unclear, but may be due to lower clinical suspicion or a misdiagnosis of presenting symptoms as secondary to an infectious etiology. As modernization continues, including improved hygiene and alterations in pathogen exposure, diagnosis of IBD rates in these countries are likely to continue to increase, stressing the need for improved management of these disorders.

3. DEMOGRAPHICS OF IBD

Males have a slightly higher incidence of UC than females (10.8 vs 7.0 per 100,000, respectively), while the incidence for CD is approximately equal between the genders [6]. Caucasians and Jews are historically more frequently diagnosed with IBD [10]. In the United States, Caucasians and African Americans are more likely to have CD, while Mexican Americans are more likely to have UC [11]. Manifestations of IBD may also vary between ethnic groups. For example, arthritis and uveitis are significantly more common in African Americans with CD than in Caucasians with CD. The mean age of diagnosis for CD in North America is in the late 30s, while the peak incidence of UC is between 15 and 40 years [12, 13]. A second peak in UC incidence is reported between 50 and 80 years. The strongest environmental factors associated with the development of CD and UC are smoking and appendectomy [14]. Smoking is a risk factor for CD, but appears to be protective in UC. Appendectomy for confirmed appendicitis appears to be protective against UC, but studies in CD are less clear. One recent meta-analysis demonstrated an increased risk for CD during the first 4 years following appendectomy before a subsequent return to baseline risk, leading the authors to conclude that this may be an effect of increased vigilance for the diagnosis of gastrointestinal disorders post-appendectomy, including the early detection of CD [15]. However, this cannot explain the decreased risk for UC following an appendectomy. Other risk factors for IBD include dietary and hygiene changes due to urbanization as well as increased use of antibiotics that may adversely affect the intestinal flora.

4. PATHOPHYSIOLOGY OF IBD

Inflammatory bowel disease is believed to develop in a genetically susceptible host in response to an environmental trigger. Unfortunately, a definite etiological agent has not yet been identified. Possible inciting events include infections or medications that may alter the permeability of the intestinal epithelium, allowing increased passage of bacterial contents. The underlying pathophysiology of IBD is complex but is believed to be related to chronic inflammation due to an exaggerated immune response in predisposed patients. Several lines of evidence support this theory including murine models of inflammation, epidemiological data, and genome-wide association studies. Specifically, mutations in *CARD15* have been the most strongly implicated polymorphisms involved in the development of CD to date. *CARD15* encodes NOD2, which is an intracellular pattern recognition receptor that leads to downstream NF-κB signaling involved in the innate immune system [16, 17]. Loss of function mutations in *CARD15* variants result in altered cellular responses to toll-like receptor signaling and reduced expression of proinflammatory cytokines. Carriers of one high-risk variant of *CARD15* are associated with a 2.4 fold increased risk for developing CD, while carriers of at least two high-risk variants are associated with a 17.1 fold increased risk for developing CD [18]. Carriers of these variants are also more likely to develop CD at a younger age and involve the terminal ileum. While further studies are needed, these analyses provide the greatest association yet for the role of genetics in the pathogenesis of CD. Weaker genetic linkages have been associated with the development of UC [19].

5. ROLE OF STRESS AND DEPRESSION IN THE PATHOGENESIS OF IBD

There is a striking relationship between IBD and comorbid psychiatric disorders, initially leading George Engel to mischaracterize IBD as primarily a psychosomatic disease [20]. Psychiatric disorders, especially anxiety, depression and panic disorder, have been found in 30-50% of patients with inactive IBD [21-23]. This is higher than the rate of psychiatric disorders found in cohorts of other chronically ill patients, such as patients with diabetes or chronic hepatitis. A large, population-based cohort study on the prevalence of mood disorders in patients with IBD showed 45% lifetime prevalence of mood or anxiety

disorders in respondents, including 22% prevalence during the past 12-months (Table **2**). Another study found that during IBD relapse, depression may be present in up to 60% of patients, while anxiety may be present in up to 80% of patients [24]. Patients with CD have a higher number of psychiatric comorbidities than patients with UC [22, 25]. In support of Engel's biopsychosocial model of IBD and other similar theories that emphasize how the role of behaviors and emotions play in the pathophysiological process of disease, stressful life events seem to precipitate the onset of IBD diagnosis [26-30]. In patients with inactive IBD, the risk of relapse is significantly increased in patients with higher scores on the Beck Depression Inventory, greater perceived stress, and a negative affect [31, 32]. More recent stressful life events, as determined by self-reports using the Perceived Stress Scale, are associated with shortened time until relapse in patients with inactive IBD [33]. Long-term stress is more indicative of disease exacerbation in UC than short-term stress, which may be due to the negative effects of stress on immune function [34]. Interestingly, depression was even shown to be a predictor of CD treatment failure with infliximab, which may be due to increased production of pro-inflammatory cytokines during severe depressive episodes [35]. Animal models of inflammation provide evidence for the mechanism through which stress may aggravate IBD. These models show that chronic stress may cause inflammation by altering the hypothalamo-pituitary axis and mast cell activity in the gut, causing defects in the epithelial lining of the intestine [36]. Stress has also been shown to cause reactivation of colitis in rat models of IBD [37]. Stress activates hypothalamic pathways that control the pontomedullary nuclei involved in control of the autonomic nervous system. For instance, patients with IBD have been shown to have clinical evidence of altered autonomic function by exhibiting increased autonomic nervous hyperreflexia [38]. Objective measures of autonomic dysfunction in IBD patients have been shown to be associated with decreased QOL and higher utilization of healthcare resources [39]. In a stress protocol of patients with inactive UC, patients with greater social support, as determined by the Social Support Questionnaire, reported greater parasympathetic involvement on heart rate variability. This lead the researchers to conclude that social support decreases inflammatory activity *via* the autonomic nervous system [40]. However, more recent studies have provided conflicting evidence for the role that stressful life events may have on developing IBD, suggesting that these early studies were biased by anxiety and depression [41, 42]. While the precise role that stress and depression play in the development of CD and UC is still unclear, it is likely to manifest through inflammatory, hormonal and neurological mechanisms.

Table 2. Prevalence (%) of mood and anxiety disorders in patients with IBD during the past 12 months and lifetime, according to the Manitoba IBD cohort [23][a].

	12-month	Lifetime
Mood disorders		
Major depressive disorder	9.1	27.2
Dysthymia	0.6	2.0
Bipolar I and II	1.1	1.7
Any mood disorder	10.5	29.9
Anxiety disorders		
Panic disorder	3.7	8.0
Agoraphobia without panic	0.6	1.1
Specific phobia	9.7	14.8
Social anxiety disorder	2.6	6.0
Generalized anxiety disorder	3.7	13.4
Post-traumatic stress disorder	4.0	7.7
Obsessive-compulsive disorder	1.0	2.8
Any anxiety disorder	17.9	31.6
Any mood or anxiety disorder	22.2	45.3

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From a psychodynamic perspective, patients with IBD may have greater difficulty expressing feelings of anger, resentment, or rage. Acute episodes of object loss, narcissistic wounding, or bitter disappointment, along with a sense of helplessness may be particular stressors associated with worsening symptoms of IBD and UC in particular [43]. Internally, IBD patients may view their illness as a threat, and when they do, the illness might be a metaphor for all of the disappointments and losses that have occurred creating a feeling of helplessness and lack of control that might generally characterize their lives [44]. IBD patients with a comorbid depression and anxiety may also be more prone to use maladaptive, neurotic defenses such as isolation of affect, repression, turning anger inward, and somatization, all which may lead to worsening inner conflict and IBD symptoms.

6. ROLE OF IBD IN THE DEVELOPMENT OF PSYCHIATRIC DISORDERS

In addition to evidence that psychological factors may contribute to development of IBD, the diagnosis of IBD itself may result in an increased risk for the development of psychiatric disorders. Newly diagnosed IBD patients, especially CD patients, report significant negative effects on physical and social functioning on health-related QOL questionnaires [45, 46]. Symptoms of anxiety and depression significantly increase following the diagnosis of IBD and adversely affect disease recovery [21, 47-49]. Patients with active disease who completed a clinical interview and self-reported questionnaires on psychological functioning were found to have significantly increased levels of perceived stress and decreased levels of social support and disease-specific QOL versus patients with inactive disease [50]. Moreover, a worsening course of gastrointestinal symptoms has been shown to increase anxiety and depression in patients with IBD completing the Hospital Anxiety Scale (HADS-A) and Hospital Depression Scale (HADS-D) [51]. In one study that investigated the effect that surgery has on

the development of depression and anxiety in patients with IBD, patients without depression had a significantly higher incidence of depression 5 years after surgery than patients who did not undergo surgery [52]. Female gender and the presence of other medical comorbidities are the only risk factors shown to predict depression in both UC and CD. Specifically in patients with IBD, other risk factors for the development of anxiety and depression include severe and active disease and socioeconomic deprivation [24]. Younger patients with IBD are also more likely to be prescribed psychotropic medications such as antidepressants, anxiolytics and benzodiazepines, as well as to develop long-lasting anxiety and depression [53]. Patients with greater levels of perceived stress, as determined by the Perceived Stress Questionnaire, have significantly greater levels of CD exacerbation [54]. The hypothesis is that these effects are mediated through the adverse results stress has on anxiety and depression [54, 55].

Biopsychosocial factors have been shown to significantly affect disease progression. For instance, patients with IBD believe that stress and psychosocial events affect the course of their illness [28, 56]. In addition, patients with psychiatric disorders such as depression significantly overreport the burden of their gastrointestinal disease than patients without depression. Patients with both IBD and psychiatric conditions have a significantly greater number of subjective symptoms of gastrointestinal distress than IBD patients without psychiatric disorders, despite no difference in objective measures of IBD disease severity such as use of medications or the number of physician visits [57]. In this study, the authors conclude that patients with psychiatric disorders perceive their level of illness with greater severity than patients with similar objective measures of illness who do not have diagnosed psychiatric disorders. The reasons for this are unclear but are believed to be due to an inability of psychiatric patients with recent onset of IBD to properly adapt to their new diagnosis. This "amplification of symptoms" is also described in patients who have both depression and other chronic medical conditions, such as hepatitis and diabetes [58, 59]. Depression is also a known risk factor for medical noncompliance [60]. Therefore, patients who report a worsening disease course despite appropriate medical therapy should be investigated for the presence of psychiatric comorbidities. Indeed, up to a third of patients with IBD ultimately request psychological intervention, which is significantly greater than in patients with other chronic inflammatory disorders [61].

7. EFFECT OF IBD AND COMORBID MOOD DISORDERS ON QUALITY OF LIFE

Inflammatory bowel disease is a chronic illness that produces significant impairment in normal functioning and reduces patient QOL. Psychiatric comorbidities can further precipitate this decline. Patients with IBD have poorer psychological health and view their health status more negatively than patients without IBD [62]. A large epidemiological study by Walker *et al.* used a structured diagnostic interview to compare rates of psychiatric disorders in IBD patients with matched controls from the Canadian Community Health Survey, and found significantly lower QOL and earlier onset of IBD symptoms in patients with anxiety than patients without anxiety [23]. Patients are more likely to have a reduced QOL during active episodes of IBD than during disease remission. Patients are also more likely to improve their QOL with a fluctuating disease course than with consistent IBD activity [50, 63]. A study by Israeli *et al.* found that major depression in patients with IBD was more strongly correlated with disability and reduced QOL than a history of IBD-related surgeries or hospitalizations, as determined by validated measures including the World Health Organization Disability Assessment Schedule v2.0 (WHODAS) and the Comprehensive International Diagnostic Interview (CIDI) [64]. This underscores the critical role that vigilance and prompt treatment of mental health disorders play in the long-term management of IBD patients. Anxiety itself is associated with disability and poorer QOL, as determined using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) [65]. Patients with IBD are also more likely to miss work and report unmet healthcare needs on the Canadian Community Health Surveys (CCHS) [66]. A randomized control trial in young patients with IBD who had mild to moderate symptoms of depression showed significant improvement in global psychosocial functioning at long-term followup if they underwent Primary and Secondary Control Enhancement Training (PASCET, a type of cognitive behavioral therapy), in addition to treatment as usual [67, 68]. These studies suggest that an emphasis on psychosocial treatment in young patients with mild symptoms of depression and concurrent IBD may assist in the long-term maintenance of global functioning.

8. PSYCHOTHERAPEUTIC AND PSYCHOPHARMACOLOGIC TREATMENT OF IBD

Both therapeutic and medical management have been used to treat the comorbid psychiatric symptoms in patients with IBD. While psychotherapy, including short term psychodynamic therapy, cognitive behavioral therapy, relaxation training, and group therapy, has not been shown to alter disease course, these therapies have been shown to decrease the length of hospital stays, decrease hospital admissions, and improve patient QOL [69, 70]. Data on the effectiveness of psychopharmacologic agents is minimal. However, case reports suggest that paroxetine, phenelzine, and bupropion are effective against depression in IBD [71]. Interestingly, bupropion has been demonstrated to lower tumor necrosis factor levels and alter disease activity [72]. Randomized clinical trials using antidepressant medications in patients with IBD are therefore needed.

9. CONCLUSION

IBD is a chronic medical condition with a high level of associated morbidity. An often overlooked feature of IBD is the psychological aspect of the disease, especially during severe presentations with comorbid mood disorders. Psychological disorders may precede the diagnosis of IBD or develop soon after, and are associated with a significantly worsened prognosis, increased risk of relapse, and increased healthcare utilization. Psychiatric comorbidities that are not addressed in patients with IBD can lead to a significantly deteriorating QOL. The risk of the development of mental

health issues stresses the need for a heightened physician suspicion for psychiatric screening in patients with IBD. Improved medical and surgical therapies have certainly improved the course of IBD, but more attention is needed regarding the role that psychiatric interventions can have on patient QOL.

10. DISCLOSURE

The views expressed in this article are those of the author(s) and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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