Influences and Impact of Anxiety and Depression in the Setting of Inflammatory Bowel Disease

Seyedehsan Navabi, MD,[*] Venkata Subhash Gorrepati, MD, MPH,[†] Sanjay Yadav, MD,[‡] Jaykrishna Chintanaboina, MD,[*] Sarah Maher, MD,[†] Peter Demuth,[†] Benjamin Stern, MD,[†] August Stuart,[*] Andrew Tinsley, MD,[*] Kofi Clarke, MD,[*] Emmanuelle D. Williams, MD,[*] and Matthew D. Coates, MD, PHD[*]

Background: Individuals with inflammatory bowel disease (IBD) are at increased risk of developing anxiety or depression (A&D). Crohn's disease (CD) and ulcerative colitis (UC) with comorbid A&D are both more challenging to manage. IBD providers need to better understand the causes and impact of A&D in order to improve care for IBD patients. We sought to identify clinical factors that influence development of A&D and healthcare utilization in IBD.

Methods: This is a retrospective analysis using an IBD natural history registry from a single tertiary care referral center. Presence of A&D was determined based upon responses to the Hospital Anxiety and Depression Scale. Demographic and clinical factors were abstracted to evaluate for significant associations.

Results: Four hundred thirty-two IBD patients (132 UC, 256 CD, and 44 indeterminate colitis) were included in this study. One hundred ninety-two (44.4%) had anxiety or depression or both, and most were female (59.4%, $P < 0.05$). History of surgery ($P < 0.05$), female gender ($P < 0.05$), smoking ($P < 0.05$), and extra-intestinal manifestations ($P < 0.01$) were each independently predictive of A&D. Inflammatory bowel disease patients with A&D more often underwent imaging studies (53.6% vs 36.7%, $P < 0.05$), visited the ED (30.7% vs 20.8%, $P < 0.05$), or were hospitalized (31.7% vs 21.7%, $P < 0.05$). They were also more frequently prescribed corticosteroids (50.5% vs 36.7%, $P < 0.01$) and biologic medications (62.5% vs 51.3%, $P < 0.05$). Finally, they were more likely to have had at least 1 "no-show" (29.2% vs 16.7%, $P < 0.01$) and had a higher mean number of "no-shows" (0.69 +/- 0.1 vs 0.30 +/- 0.1, $P < 0.01$) over the study period.

Discussion: Anxiety and depression are common in the setting of IBD and are strongly associated with surgical history, disease complications (including extra-intestinal manifestations), smoking, and female gender. Inflammatory bowel disease patients with A&D are also more likely to require therapy and to utilize healthcare resources. This study refines our understanding of A&D development and its impact in IBD and provides additional considerations for management in this setting.

Key Words: anxiety, Crohn's disease, depression, inflammatory bowel disease, ulcerative colitis

INTRODUCTION

Previous studies have demonstrated that individuals with inflammatory bowel disease (IBD) are more likely to develop a variety of psychiatric disorders, including anxiety and depression (A&D), when compared with their age-matched counterparts.[1–3] These disorders are as common as any other psychiatric conditions in IBD, and many investigators have found the prevalence of A&D in IBD to be twice or more of that seen in the general population.[2, 4–9] This association has been recognized almost as long as ulcerative colitis (UC) and Crohn's disease (CD) have existed as recognized clinical entities.[10–12] In spite of this, there remains significant uncertainty regarding how these conditions affect one another.

It is critical for providers to gain an improved understanding of how IBD and A&D influence one another for several reasons. Management of both UC and CD is more challenging in the setting of A&D. Inflammatory bowel disease patients with A&D are more likely to report problematic symptoms (even in the absence of significant inflammation).[13–15] Development of A&D in these patients may potentiate disease flares or complications[16] and can reduce the likelihood of therapeutic success.[17] These populations also consistently demonstrate lower quality of life scores.[14, 18–22] Additionally, there is at least circumstantial evidence suggesting that A&D may incur more significant healthcare-related costs in the setting of IBD.[23, 24]

As not all patients with IBD develop anxiety or depression, investigators have sought to determine how these conditions

Received for publications October 26, 2017; Editorial Decision February 26, 2018.

From the *Penn State Hershey Medical Center, Department of Medicine, Division of Gastroenterology & Hepatology, Hershey, Pennsylvania, USA; †Penn State Hershey Medical Center, Department of Medicine, Hershey, Pennsylvania, USA; ‡Penn State Hershey Medical Center, Department of Psychiatry, Hershey, Pennsylvania, USA

Conflicts of interest: The authors have no conflicts of interest to disclose.

Supported by: This research was supported by the Peter and Marsha Carlino Early Career Professorship in Inflammatory Bowel Disease and the Margot E. Walrath Career Development Professorship in Gastroenterology.

Address correspondence to: Matthew Coates, Penn State University Hershey Medical Center, Division of Gastroenterology and Hepatology, E-mail: mcoates@pennstatehealth.psu.edu.

doi: 10.1093/ibd/izy143
Published online 17 May 2018

develop in this setting. A variety of clinical variables have been implicated as risk factors for A&D in the setting of IBD, including increased disease activity, disease complications, advanced age, and female gender.[2, 3] But not all studies are in agreement about the influence of these factors.[17, 25] In order to improve our ability to care for IBD patients suffering with A&D, we need to have a better understanding for the underlying drivers of these disorders and their influence on resource utilization in this population.

The primary aim of this study was to perform a more comprehensive analysis to identify the clinical factors associated with A&D in IBD. Our secondary aims were to determine how A&D influence patient IBD symptom experience and to evaluate how A&D impact healthcare utilization in this population.

METHODS

Study Population

We performed a retrospective analysis using information derived from consecutive patients consented to participate in the Intestinal Diseases Natural History Database at Pennsylvania State University Hershey Medical Center (PSHMC) between January 1, 2015, and August 31, 2016. This database includes clinical and research information related to the encounters of IBD patients receiving clinical management at PSHMC, a tertiary care referral hospital with a dedicated IBD center that cares for approximately 5000 patients with these disorders. This study was performed with the oversight and permission of the Pennsylvania State University College of Medicine Institutional Review Board (IRB#'s PRAMSHY98-057 and 00000934).

Definitions and Data Abstraction

In order to be included in this study, patients had to have an established diagnosis of CD, UC, or IBD colitis of indeterminate nature, based upon standard clinical criteria routinely used to identify IBD as previously described.[26] Presence of a state of anxiety or depression or both was determined based upon responses to the Hospital Anxiety and Depression Scale (HADS)[27] completed at the time of the first clinical encounter recorded within this study period, using a score of 8 or greater in the anxiety or depression subscore in order to optimize sensitivity and specificity.[28] Age, gender, IBD duration, IBD extent (eg, organ involvement), disease complications (including abscess and stricture development), extra-intestinal manifestations (EIM), physician global assessment (PGA), endoscopic severity, Harvey Bradshaw Index (total score and symptom subscores), Simple Clinical Colitis Activity Index (SCCAI, total score and symptom subscores), medication use (including antidepressant, anxiolytic, corticosteroid, mesalamine, immunomodulator, and biologic therapy), surgical history, laboratory values (sedimentation rate, ESR), C-reactive protein (CRP), vitamin D, zinc, vitamin B_{12}, ferritin, folate), opiate and tobacco use (active and former), and the number of emergency department (ED) visits, clinic "no-shows," hospitalizations, and imaging studies associated with IBD during the study period were also abstracted from the electronic medical record. Presence of "significant inflammation" was defined as moderate to severe activity based upon findings during endoscopic evaluation within 3 months of the clinic visit (using a Mayo endoscopy subscore ranging from 0–3, with 0 as no disease and 3 as severe disease).

Statistics

Data was extracted and analyzed using SAS Version 9.4 (Cary, NC). Initially, demographic, clinical, and healthcare utilization variables (eg, ED visits, hospitalizations, imaging studies, clinic "no-shows") were compared using univariate analysis (eg, student t test, χ^2 test or Fisher exact test, as appropriate) between 2 distinct cohorts: 1) IBD patients with A&D, and 2) IBD patients without A&D. A multivariate logistic regression model was then performed incorporating each significant variable to examine the odds of developing A&D. A binary logistic regression was used with Fischer's scoring for optimization. These statistical approaches were also used to evaluate for potential associations between A&D and key demographic and clinical factors within the CD and UC subcohorts. Multivariate analyses were also employed to assess for predictors of anxiety and depression states in each of these IBD subtypes in patients who had undergone endoscopic evaluation within 3 months of survey completion (see below). The primary endpoint was presence of an A&D (as defined below). Values listed represent means +/- standard error of the mean (SEM) unless indicated otherwise. P values less than 0.05 were considered to be statistically significant. Of note, although individuals with indeterminate colitis were included in the analyses associated with the total IBD cohort, we did not perform subcohort analyses of indeterminate colitis patients due to their limited sample size.

RESULTS

Prevalence and Predictors of Anxiety and Depression in IBD

One hundred ninety-two of 432 IBD patients (44.4%) were found to have significant anxiety or depression scores. Most of these individuals (59.4%) were female (Table 1). One hundred seventy individuals (39.4%) had symptoms that were consistent with anxiety, while 108 patients (25.0%) were found to have depression. Of note, 86 patients were found to have both anxiety and depression. White blood cell count (WBC) and sedimentation rate (ESR) were slightly higher, and extra-intestinal manifestations were more common in IBD patients with A&D (42.7% vs 29.2%, $P < 0.01$). Vitamin B_{12} levels were also lower in those with A&D (Table 1). Patients with A&D were also more likely to have been administered anti-TNF therapy (62.5% vs 51.3%, $P < 0.01$) or steroids (50.5% vs 36.7%, $P < 0.01$) and to

TABLE 1: Characteristics of The Entire IBD Cohort

Variable	Cohort	No AD	AD	*P*
Sample (% women)	432 (52.8%)	240 (47.5%)	192 (59.4%)	<0.05
Age (yrs)	42.3 ± 0.6	43.1 ± 1.1	41.3 ± 1.0	0.25
BMI	27.5 ± 0.6	27.8 ± 0.8	27.2 ± 0.9	0.90
Disease Type	UC-132	85	47	<0.05*
	CD-256	130	126	0.45*
	Indet-44	25	19	
Disease Duration (yrs)	12.6 ± 0.5	13.1 ± 0.7	12.0 ± 0.7	0.25
Significant Inflammation (No. colonoscopies)	95 (296)	49 (161)	46 (135)	0.50
History of EIM	152	70	82	<0.01
Harvey-Bradshaw Index		5.6 ± 0.3	9.2 ± 0.7	<0.0001
SCCAI		2.2 ± 0.1	5.5 ± 0.3	<0.0001
Laboratory Studies				
Albumin (mg/dL)	4.4 ± 0.1	4.4 ± 0.1	4.3 ± 0.1	0.18
WBC (K/dL)	8.4 ± 0.2	7.5 ± 0.3	8.7 ± 0.4	<0.05
ESR (mm/hr)	12.9 ± 1.1	11.6 ± 1.3	16.2 ± 1.8	<0.05
CRP (mg/dL)	1.3 ± 0.1	1.3 ± 0.1	1.3 ± 0.1	0.67
Vitamin D (mg/dL)	33.5 ± 1.1	34.3 ± 1.4	32.6 ± 1.4	0.14
Vitamin B12 (mg/dL)	491 ± 24.7	545 ± 35.1	437 ± 26.6	<0.05
Therapy (Since 1/15)				
Corticosteroid	185	88	97	<0.01
Immunomodulator	133	76	57	0.67
Anti-TNF	243	123	120	<0.01
Mesalamine	162	91	71	0.84
Tobacco Use	54	19	35	<0.01
Opiate Use (Current)	82	32	50	<0.001
Healthcare Use (Since 1/15)				
Emergency Room Visits	0.66 ± 0.1	0.44 ± 0.1	0.95 ± 0.2	<0.05
Hospital Admissions	0.47 ± 0.1	0.36 ± 0.1	0.60 ± 0.1	<0.05
Imaging Studies	0.98 ± 0.1	0.77 ± 0.1	1.23 ± 0.2	<0.05
Surgeries	0.49 ± 0.1	0.30 ± 0.1	0.69 ± 0.1	0.06

*compared with CD subcohort

have used tobacco (18.2% vs 7.8%, $P < 0.01$) or opiates (26.0 vs 13.2%, $P < 0.001$).

Employing a multivariate logistic regression analysis involving patients with endoscopic evaluation of their IBD within 3 months of the clinic visit (n = 283), history of prior surgery ($P < 0.05$), female gender ($P < 0.05$), extra-intestinal manifestations ($P < 0.01$), and tobacco use ($P < 0.05$) were each independently predictive of A&D (Table 2).

We also evaluated the CD and UC subcohorts separately. Presence of A&D was more common in CD when compared with the UC population (49.2% vs 35.6% respectively; $P < 0.05$). Demographic and clinical characteristics of each subcohort are described in Supplementary Tables 1 and 2. When we performed multivariate analyses to evaluate for predictors of A&D in CD and UC (Supplementary Tables 3 and 4), we found that presence of EIMs ($P < 0.05$) and tobacco use ($P < 0.05$) were independently associated with CD, while reduced disease duration ($P < 0.05$) was associated with UC. Of note, CD patients with A&D were significantly more likely to use immunomodulators (IMM) ($P < 0.05$), while UC patients with A&D were significantly less likely to use IMM ($P < 0.01$).

We performed multivariate logistic regression analyses evaluating for predictors of anxiety or depression in the separate IBD cohorts (Supplementary Tables 5 and 6). Presence of EIMs ($P < 0.05$ and $P < 0.001$ for anxiety and depression, respectively) and tobacco use ($P < 0.05$ each) were both independently associated with anxiety and depression. Additionally, history of surgery ($P < 0.01$) was independently associated with anxiety in IBD, while corticosteroid use ($P = 0.06$) trended toward an association with coincident depression.

TABLE 2: Predictors of Anxiety and Depression in IBD

Variable	Odds Ratio	95% Confidence Interval	*P*
Significant Inflammation	1.18	0.67–2.09	0.56
Age	1.00	0.98–1.01	0.59
Disease Duration	0.97	0.94–1.00	0.02
Female Gender	1.82	1.09–3.04	0.02
Mesalamine Use	1.38	0.76–2.52	0.29
Immunomodulator Use	1.11	0.63–1.94	0.72
Anti-TNF Use	0.97	0.53–1.76	0.92
Corticosteroid Use	1.14	0.67–1.95	0.62
History of Surgery	2.10	1.16–3.79	0.01
History of EIM	2.15	1.19–2.84	0.01
History of Tobacco Use	1.90	1.07–3.38	0.03
History of Opiate Use	1.62	0.85–3.10	0.14

Two hundred eighty-three IBD patients who had undergone a colonoscopy within 3 months of completing the HADS questionnaire were included in this analysis. "Significant inflammation" was defined as a Mayo endoscopy subscore of 2 or greater.

Anxiety, Depression, and Symptoms in IBD

Key reported symptoms were evaluated using responses to individual questions in the Harvey-Bradshaw Index (HBI) and Simple Clinical Colitis Activity Index (SCCAI). Abdominal pain frequency (64.6% vs 30%, $P < 0.0001$) and intensity ($P < 0.0001$) were both more severe in the setting of A&D. Every other symptom evaluated was also significantly more common in IBD patients with A&D, including fatigue (88.5% vs 47.5%, $P < 0.0001$), excess gas (46.9% vs 18.3%, $P < 0.0001$), fecal urgency (76.6% vs 52.9%, $P < 0.01$), blood in the stool (39.1% vs 20.8%, $P < 0.01$), nocturnal stooling (51.6% vs 28.3%, $P < 0.01$), and difficulty maintaining weight (56.8% vs 29.2%, $P < 0.01$). They also had a higher mean endoscopic inflammatory score, PGA, CRP and ESR levels (each $P < 0.05$). The prevalences of each symptom were not significantly different between the CD and UC subcohorts.

Anxiety, Depression, and Healthcare Utilization in IBD

Inflammatory bowel disease patients with A&D were more likely to undergo imaging studies (53.6% vs 36.7%, $P < 0.05$), visit the ED (30.7% vs 20.8%, $P < 0.05$), and be hospitalized (31.7% vs 21.7%, $P < 0.05$). During the study period, patients with A&D also underwent more imaging studies ($P < 0.05$), emergency room visits ($P < 0.05$), and hospitalizations ($P < 0.05$). They were also more frequently prescribed corticosteroids (50.5% vs 36.7%, $P < 0.01$) and biologic medications (62.5% vs 51.3%, $P < 0.05$) and demonstrated a trend toward undergoing more surgery ($P = 0.06$) (Table 1). Finally, they were more likely to have had at least 1 "no-show" to clinic (29.2% vs 16.7%, $P < 0.01$) and had a higher mean number of "no-shows" (0.69 +/- 0.1 vs 0.30 +/- 0.1, $P < 0.01$) over the study period.

When comparing CD patients with UC patients, we found that CD patients were more likely to have been hospitalized (32.8% vs 18.2%, $P < 0.01$), undergone an imaging study (53.9% vs 31.1%, $P < 0.0001$), undergone surgery (59.4% vs 32.6%, $P < 0.05$) and had a "no-show" to clinic (27.7% vs 16.7%, $P < 0.05$). CD patients were also more likely to have been prescribed corticosteroids (48.4% vs 35.6%, $P < 0.05$) and biologic medications (70.7% vs 40.2%, $P < 0.0001$) during the study period.

Finally, we compared healthcare utilization between IBD patients with only anxiety (n = 86) and only depression (n = 22) and found no statistically significant differences in any of the parameters described previously.

DISCUSSION

This study demonstrated once again that anxiety and depression are very common in the setting of IBD. The respective rates of each of these psychiatric conditions in our cohort were relatively high but within previously reported ranges involving IBD study populations.[8] We also demonstrated that A&D were more common in CD patients, similar to what has been demonstrated in previous studies.[8] Notably, CD patients were significantly more likely to have required IBD-related hospitalization, testing, or therapy (both medical and surgical), and so it is possible that increased disease-related stressors or financial burden related to these factors drove an increased incidence of these psychological symptoms. Our investigation also identified a number of independent risk factors for A&D in IBD, including some that were uncovered in previous studies, such as female gender. Perhaps unsurprisingly, other independent predictors of A&D in IBD included extra-intestinal manifestations of IBD, prior IBD-related surgery, and tobacco use (the latter in CD but not UC, as might be expected based upon the differential impact that smoking appears to have on these disorders[29]). Other factors that may play a role include micronutrient deficiencies (eg, vitamin B_{12}, vitamin D), but further study is required to verify this interaction. Interestingly, despite higher mean WBC, ESR, HBI, and SCCAI scores, we found no significant association between moderate-severe IBD activity (as determined by endoscopic evaluation) and the presence of anxiety or depression.

Exactly how anxiety and depression influence and are influenced by IBD has been a topic of controversy. Psychiatric maladies have previously been conjectured as both a cause and result of IBD.[1, 30] Early prevailing theories held that psychosomatic drivers actually caused CD and UC.[31–33] Although other influences (including genetic, environmental, and immunological factors) have subsequently been implicated to play a major role in the pathogenesis of IBD, several recent studies have suggested that psychiatric illness and stress can increase the risk of

flares in IBD patients.[16, 34, 35] Animal models of colitis have also indicated that psychological stressors may have the capability to induce gut inflammation. Alternatively, several studies have implicated systemically available inflammatory mediators as potential causes of mental illness.[36, 37] These may be associated with a chronic inflammatory disorder such as IBD or not. Data supporting the use of anti-inflammatory therapeutic strategies in the setting of isolated A&D are mixed,[38] but there is strong evidence suggesting that controlling IBD disease activity (as well as that associated with other chronic inflammatory disorders) can be effective in mitigating coexistent psychiatric symptomatology.[39–41] In our study cohort, IBD patients with A&D were more likely to use anti-TNF agents and corticosteroids, but we could not make clear determinations about any cause and effect relationship from the data presented here. It is quite possible, though, that there is a bidirectional relationship between the inflammatory mediators of IBD and A&D.

Our study also made it clear that IBD patients dealing with anxiety and depression also experience more disease-related complications and more often engage in counterproductive behaviors and utilize medical therapies with problematic side effects. Specifically, we demonstrated that they are more likely to manifest extra-intestinal manifestations of IBD, and they carry a significantly more severe symptom burden. Although not necessarily surprising, these are relatively novel findings that may provide explanation for development of comorbid psychiatric symptoms in at least some patients. IBD patients with A&D were also found to use more testing, visit the ED, and be hospitalized more often, and so incur more healthcare costs. These results are consistent with those of other studies demonstrating that comorbid psychiatric disorders are among the most important predictors of resource utilization in IBD.[42] Our study showed that these patients are also more likely to rely on therapies associated with significant side effects and toxicity (eg, corticosteroids and opiates), particularly in the setting of IBD.[43, 44] Finally, we demonstrated that IBD patients with A&D more frequently engage in detrimental lifestyle choices, such as smoking, while being more likely to miss clinic visits. All of the findings described previously significantly complicate the ability of IBD providers to effectively manage their patients and make it harder for individuals with IBD to remain healthy.

There are several strengths of this investigation. This is one of the largest studies to have evaluated potential interactions between A&D and IBD, and it is one of the only studies to examine healthcare resource utilization while factoring these conditions together. We also defined IBD activity using endoscopic assessments performed at a dedicated IBD center, associated with stereotypical clinical episodes of disease flares or states of quiescence. This helped to confirm the actual inflammatory state and burden of most of the study participants. This study also incorporated several key variables previously shown to modify risk for the development of A&D in IBD and other chronic inflammatory disorders, including age, gender, disease duration, disease and symptom burden, nutritional status, tobacco use, and medication administration (eg, corticosteroid use). The data were also analyzed using a multivariate logistic regression model to help control for potential confounding effects.

One of the larger limitations to this study is that it was conducted in a single tertiary care center evaluating a predominantly Caucasian population. Thus, these findings may not be relevant to every patient population. The data were also collected in a retrospective manner, so some relevant clinical information may have been missed. Beyond this, while the HADS survey has been used as a screening tool for anxiety and depression in certain settings, it is not designed to provide an actual diagnosis of these disorders. Additionally, although the HADS survey has been validated in outpatient clinical settings[45] and previously used in IBD populations,[3, 19, 46–48] it has not yet been completely validated for use in IBD patients. There has been some concern raised over the possibility of "criterion contamination" in this setting due to the similarity of at least some of the tool's self-reported symptoms with those reasonably expected to occur in the setting of IBD (eg, abdominal sensation).[49] Thus, it would have been helpful to have more formalized, coincident psychiatric assessments for anxiety and depression in each of our study subjects. As indicated previously, this design also precludes our ability to determine whether a cause-and-effect relationship exists among the major study variables. We also did not have data relating to the exact timing of A&D development for many members of the study cohort. As a result, it was impossible to determine whether the psychiatric symptoms preceded the IBD diagnoses or vice versa. Although this is one of the largest studies of its kind, it is quite possible that we needed a bigger study population to elucidate potential contributors to A&D in IBD (eg, vitamin D) and to more effectively evaluate for differing influences on symptoms, patient lifestyle choices, and healthcare resource utilization that CD, UC, anxiety, and depression may have each had. Finally, we also did not have information related to some known risk factors of A&D (eg, childhood trauma or abuse) that could have played a role in this setting.

Despite the shortcomings described previously, findings from this research can be used to develop additional strategies to identify and help manage A&D in the setting of IBD. Based upon the results of this investigation, providers should strongly consider incorporating strategies early in the care of IBD patients that screen for and intervene on A&D, regardless of IBD disease activity state. Previous research suggests that a significant portion of IBD patients with established mood disorders do not receive formal psychiatric care.[7] IBD providers should strongly consider psychiatric consultation as early as possible in the disease course in patients with coexistent A&D, particularly when 1 or more of the risk factors mentioned previously are identified. Improving accessibility and ensuring timely referrals of patients to appropriate

psychiatric resources could have a variety of positive impacts on IBD patient care. These interventions could help reduce the risk of disease progression and flares, address patient quality of life, improve continuity of care, and reduce potentially inappropriate healthcare resource utilization and harmful lifestyle choices.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

REFERENCES

1. Kurina LM, Goldacre MJ, Yeates D, et al. Depression and anxiety in people with inflammatory bowel disease. *J Epidemiol Community Health*. 2001;55:716–20.
2. Panara AJ, Yarur AJ, Rieders B, et al. The incidence and risk factors for developing depression after being diagnosed with inflammatory bowel disease: a cohort study. *Aliment Pharmacol Ther*. 2014;39:802–10.
3. Goodhand JR, Wahed M, Mawdsley JE, et al. Mood disorders in inflammatory bowel disease: relation to diagnosis, disease activity, perceived stress, and other factors. *Inflamm Bowel Dis*. 2012;18:2301–09.
4. Addolorato G, Capristo E, Stefanini GF, et al. Inflammatory bowel disease: a study of the association between anxiety and depression, physical morbidity, and nutritional status. *Scand J Gastroenterol*. 1997;32:1013–21.
5. Fuller-Thomson E, Sulman J. Depression and inflammatory bowel disease: findings from two nationally representative canadian surveys. *Inflamm Bowel Dis*. 2006;12:697–707.
6. Kessler RC, Berglund P, Demler O, et al.; National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the national comorbidity survey replication (NCS-R). *Jama*. 2003;289:3095–105.
7. Bhandari S, Larson ME, Kumar N, et al. Association of inflammatory bowel disease (IBD) with depressive symptoms in the United States population and independent predictors of depressive symptoms in an IBD population: a NHANES study. *Gut Liver*. 2017;11:512–9.
8. Neuendorf R, Harding A, Stello N, et al. Depression and anxiety in patients with inflammatory bowel disease: a systematic review. *J Psychosom Res*. 2016;87:70–80.
9. Mikocka-Walus A, Knowles SR, Keefer L, et al. Controversies revisited: a systematic review of the comorbidity of depression and anxiety with inflammatory bowel diseases. *Inflamm Bowel Dis*. 2016;22:752–62.
10. Goldberg DP. A one-year survey of the prevalence of psychiatric illness in patients with disease of the small intestine. *Gut*. 1968;9:725.
11. McKell TE, Tuthill SW, Sullivan AJ. The affective response of a patient with chronic ulcerative colitis to cortisone. *Gastroenterology*. 1951;17:20–4.
12. Sajadinejad MS, Asgari K, Molavi H, et al. Psychological issues in inflammatory bowel disease: an overview. *Gastroenterol Res Pract*. 2012;2012:106502.
13. Coates MD, Lahoti M, Binion DG, et al. Abdominal pain in ulcerative colitis. *Inflamm Bowel Dis*. 2013;19:2207–14.
14. Simrén M, Axelsson J, Gillberg R, et al. Quality of life in inflammatory bowel disease in remission: the impact of IBS-like symptoms and associated psychological factors. *Am J Gastroenterol*. 2002;97:389–96.
15. Isgar B, Harman M, Kaye MD, et al. Symptoms of irritable bowel syndrome in ulcerative colitis in remission. *Gut*. 1983;24:190–2.
16. Mittermaier C, Dejaco C, Waldhoer T, et al. Impact of depressive mood on relapse in patients with inflammatory bowel disease: a prospective 18-month follow-up study. *Psychosom Med*. 2004;66:79–84.
17. Persoons P, Vermeire S, Demyttenaere K, et al. The impact of major depressive disorder on the short- and long-term outcome of crohn's disease treatment with infliximab. *Aliment Pharmacol Ther*. 2005;22:101–10.
18. Farrokhyar F, Marshall JK, Easterbrook B, et al. Functional gastrointestinal disorders and mood disorders in patients with inactive inflammatory bowel disease: prevalence and impact on health. *Inflamm Bowel Dis*. 2006;12:38–46.
19. Iglesias-Rey M, Barreiro-de Acosta M, Caamaño-Isorna F, et al. Psychological factors are associated with changes in the health-related quality of life in inflammatory bowel disease. *Inflamm Bowel Dis*. 2014;20:92–102.
20. Kim ES, Cho KB, Park KS, et al.; Daegukyungbook Gastrointestinal Study Group (DGSG). Predictive factors of impaired quality of life in Korean patients with inactive inflammatory bowel disease: association with functional gastrointestinal disorders and mood disorders. *J Clin Gastroenterol*. 2013;47:e38–44.
21. Vidal A, Gómez-Gil E, Sans M, et al. Health-related quality of life in inflammatory bowel disease patients: the role of psychopathology and personality. *Inflamm Bowel Dis*. 2008;14:977–83.
22. Zhang CK, Hewett J, Hemming J, et al. The influence of depression on quality of life in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2013;19:1732–9.
23. de Boer AG, Sprangers MA, Bartelsman JF, et al. Predictors of health care utilization in patients with inflammatory bowel disease: a longitudinal study. *Eur J Gastroenterol Hepatol*. 1998;10:783–9.
24. Park KT, Colletti RB, Rubin DT, et al. Health insurance paid costs and drivers of costs for patients with Crohn's disease in the united states. *Am J Gastroenterol*. 2016;111:15–23.
25. Gracie DJ, Williams CJ, Sood R, et al. Poor correlation between clinical disease activity and mucosal inflammation, and the role of psychological comorbidity, in inflammatory bowel disease. *Am J Gastroenterol*. 2016;111:541–51.
26. Sands BE. From symptom to diagnosis: clinical distinctions among various forms of intestinal inflammation. *Gastroenterology*. 2004;126:1518–32.
27. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67:361–70.
28. Bjelland I, Dahl AA, Haug TT, et al. The validity of the hospital anxiety and depression scale. An updated literature review. *J Psychosom Res*. 2002;52:69–77.
29. Calkins BM. A meta-analysis of the role of smoking in inflammatory bowel disease. *Dig Dis Sci*. 1989;34:1841–54.
30. Bannaga AS, Selinger CP. Inflammatory bowel disease and anxiety: links, risks, and challenges faced. *Clin Exp Gastroenterol*. 2015;8:111–7.
31. Whybrow PC, Kane FJ Jr, Lipton MA. Regional ileitis and psychiatric disorder. *Psychosom Med*. 1968;30:209–21.
32. Feldman F, Cantor D, Soll S, et al. Psychiatric study of a consecutive series of 34 patients with ulcerative colitis. *Br Med J*. 1967;3:14–7.
33. Keefer L, Keshavarzian A, Mutlu E. Reconsidering the methodology of "stress" research in inflammatory bowel disease. *J Crohns Colitis*. 2008;2:193–201.
34. Bitton A, Sewitch MJ, Peppercorn MA, et al. Psychosocial determinants of relapse in ulcerative colitis: a longitudinal study. *Am J Gastroenterol*. 2003;98:2203–8.
35. Mawdsley JE, Macey MG, Feakins RM, et al. The effect of acute psychologic stress on systemic and rectal mucosal measures of inflammation in ulcerative colitis. *Gastroenterology*. 2006;131:410–9.
36. Liu CS, Adibfar A, Herrmann N, et al. Evidence for inflammation-associated depression. *Curr Top Behav Neurosci*. 2017;31:3–30.
37. Felger JC, Lotrich FE. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. *Neuroscience*. 2013;246:199–229.
38. Raison CL, Rutherford RE, Woolwine BJ, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry*. 2013;70:31–41.
39. Kappelmann N, Lewis G, Dantzer R, et al. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. *Mol Psychiatry*. 2018;23:335–43.
40. Strober B, Gooderham M, de Jong EMGJ, et al. Depressive symptoms, depression, and the effect of biologic therapy among patients in psoriasis longitudinal assessment and registry (PSOLAR). *J Am Acad Dermatol*. 2018;78:70–80.
41. Uguz F, Akman C, Kucuksarac S, et al. Anti-tumor necrosis factor-alpha therapy is associated with less frequent mood and anxiety disorders in patients with rheumatoid arthritis. *Psychiatry Clin Neurosci*. 2009;63:50–5.
42. Limsrivilai J, Stidham RW, Govani SM, et al. Factors that predict high health care utilization and costs for patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol*. 2017;15:385–92.e2.
43. Burr NE, Smith C, West R, et al. Increasing prescription of opiates and mortality in patients with inflammatory bowel diseases in England. *Clin Gastroenterol Hepatol*. 2017. doi: 10.1016/j.cgh.2017.10.022.
44. Lichtenstein GR, Abreu MT, Cohen R, et al; American Gastroenterological Association. American gastroenterological association institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology*. 2006;130:940–87.
45. Herrero MJ, Blanch J, Peri JM, et al. A validation study of the hospital anxiety and depression scale (HADS) in a spanish population. *Gen Hosp Psychiatry*. 2003;25:277–83.
46. Mikocka-Walus A, Pittet V, Rossel JB, et al; Swiss IBD Cohort Study Group. Symptoms of depression and anxiety are independently associated with clinical recurrence of inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2016;14:829–35.e1.
47. Deberry JJ, Bielefeldt K, Davis BM, et al. Abdominal pain and the neurotrophic system in ulcerative colitis. *Inflamm Bowel Dis*. 2014;20:2330–9.
48. Porcelli P, Leoci C, Guerra V, et al. A longitudinal study of alexithymia and psychological distress in inflammatory bowel disease. *J Psychosom Res*. 1996;41:569–73.
49. Hopkins CWP. Inflammatory bowel disease, the hospital anxiety and depression scale and criterion contamination. *Inflamm Bowel Dis*. 2017;23:E54.