The emerging role of mood disorders in inflammatory bowel diseases

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Abstract

Inflammatory bowel diseases (IBD) are chronic, devastating conditions of the gastrointestinal tract characterized by a complex pathogenesis, increasing worldwide prevalence, a wide spectrum of extraintestinal manifestations, and a reduced health-related quality of life (HRQoL). Furthermore, mood disorders, specifically anxiety and depression, are more prevalent among IBD patients compared to the general population. The connection between mental disorders and IBD is compound, bidirectional and still not fully understood. The IBD may impact psychological health, whereas anxiety and depression are associated with a more aggressive course of IBD. The inflammation process, gut microbiota alterations and drug side effects are factors that influence the mental state of patients with IBD. Importantly, despite the high prevalence of depression and anxiety in IBD, many of the current guidelines do not include clear recommendation for assessment of mental problems in patients and further management. Therefore, monitoring for mood disorders should become a part of the multi-disciplinary and holistic approach to patients with IBD. This review is based on current literature searched in PubMed, mainly considering publications from the last 10 years.

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

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Introduction

Inflammatory bowel diseases (IBD), encompassing ulcerative colitis (UC) and Crohn's disease (CD), are chronic, devastating conditions of the gastrointestinal tract, characterized by a relapsing course with periods of flares and remissions and the presence of the wide spectrum of extraintestinal manifestations (EMs).¹ The prevalence of IBD is increasing worldwide, especially in highly developed countries, where about 0.3% of the population is already suffering from them, and in newly industrialized regions of the world.² For instance, in Canada, one of the countries with the highest incidence of IBD, it is estimated that 0.9% of the population will be affected in 2025, whereas in China there will be over 1.5 million cases of IBD by that time.^{3,4} Furthermore, the etiopathogenesis of IBD has not been fully elucidated. The key role in the development of the disease is played by the interaction of genetic, immunological, microbiological, and environmental factors. Consequently, there are no single diagnostic tests, and despite the introduction of novel biological treatment strategies, effective therapy remains unavailable. Additionally, it has repeatedly been demonstrated that the health-related quality of life (HRQoL) of IBD patients is significantly reduced. For example, a recently published meta-analysis, which encompassed 7154 patients, demonstrated that in all 19 studies included, the QoL levels in IBD patients compared to healthy controls were poorer in at least 1 aspect.⁵ Furthermore, almost 40% of IBD patients in remission suffer from fatigue, which has a negative impact on HRQoL⁶ independently of disease activity. Last of all, anxiety and depression disorders are more prevalent in IBD patients compared to the general population, and the interrelation between the conditions is unclear. The gut–brain axis and interference of numerous agents in communication between the gut and the brain seem to play a crucial role. Among the suggested mechanisms are activation of the inflammatory response in the brain, compromised blood–brain barrier integrity and the impact of gut microbiota.⁷ The results of studies on the impact of mental disorders on IBD onset and course are inconclusive. Additionally, in a recently published study it was demonstrated that patients with anxiety, depression and immune-mediated disorders (including IBD, multiple sclerosis and rheumatoid arthritis) had reduced cognitive function.⁸ Moreover, 1/3 of IBD patients with depression and 2/3 of those with anxiety remained undiagnosed.⁹ It also has to be emphasized that all the aforementioned factors, along with the fact that the onset of IBD is associated with young age, indicate not only the necessity of further research, but above all the importance of including the mental aspects in IBD patients' care.

Epidemiology of depression and anxiety disorders in patients with IBD

Patients with IBD have a 2- to 4-fold greater risk of developing depressive disorders and a 3- to 5-fold of greater risk of developing anxiety disorders than the general population.¹⁰ Many cases of psychiatric disorders remain undiagnosed.¹¹ Many studies have repeatedly demonstrated that psychological problems are more common in patients with active disease compared to those in remission; that patients with CD are at higher risk than those with UC; and that women are affected more often than men.^{12,13} However, the occurrence of depression and anxiety in IBD is similar or even less frequent than their occurrence with other chronic disorders (Table 1).^{14,15}

Table 1. Factors related to the prevalence of anxiety and depression disorders in IBD patients

Depression and anxiety in IBD patients		
IBD	>	general population
IBD	≤	other chronic diseases
CD	>	UC
flare	>	remission
woman	>	man

IBD – inflammatory bowel diseases; CD – Crohn's disease; UC – ulcerative colitis.

Furthermore, in a large study conducted in Canada, the prevalence and incidence of depression, anxiety, bipolar disorders, and schizophrenia were higher in IBD individuals than in a matched cohort of the general population. The study, comprising more than 6000 IBD patients, showed that women were more often affected by depression and anxiety than men. However, the authors also observed that the incidence of psychiatric disorders was higher in individuals aged 18–24 years, in urbanites and in individuals of lower socioeconomic status.¹⁶ There is a growing body of evidence that the prevalence of mental health problems in IBD patients is increasing. For instance, in a cohort of more than 60,000 US veterans with IBD, the annual age-standardized prevalence rates of depression and anxiety increased respectively 3.75-fold and 5-fold in the years 2001–2015.¹⁷

Selected studies evaluating the prevalence of anxiety and depression disorders and associated factors among IBD patients are presented in Table 2.

Gut microbiota

Gut microbiota is involved in IBD pathogenesis and is simultaneously among the crucial factors interfering with the gut–brain axis. Therefore, the gut microbiome can be a link between IBD and mental disorders. Characteristic

Table 2. Prevalence of anxiety and depression disorders in IBD patients

Author, year	Number of IBD patients	Prevalence of anxiety	Prevalence of depression	Associated factors
van den Brink et al., 2020 ¹⁸	374	28.3%	2.9%	female sex, disease activity, disease duration
Choi et al., 2019 ¹⁹	15569	CD – 11.5%* UC – 16.7%*	CD – 8%* UC – 10.8%*	medication use, comorbid medical conditions
Lewis et al., 2019 ⁹	242	40.1%	30.6%	female sex for depression
Bhamre et al., 2018 ²⁰	70	18.6%	34.3%	disease activity
Navabi et al., 2018 ²¹	432	39.4%	25%	female sex, extra-intestinal manifestations of IBD, prior IBD-related surgery, tobacco use in CD
Byrne et al., 2017 ²²	327	21.2%	25.8%	female sex, disease activity
Chan et al., 2017 ²³	200	27%		
Bennebroek Evertsz' et al., 2012 ²⁴	231	42.6%		disease activity

*6 years after diagnosis; IBD – inflammatory bowel diseases; CD – Crohn's disease.

differences in the abundance of individual microbiota species in IBD patients with associated anxiety and depression disorders as well as reduced HRQoL have been identified.²⁵ Dysbiosis is associated with abnormal metabolism of tryptophan, which under normal conditions passes through the blood–brain barrier and becomes a precursor of serotonin. In an alternative pathway, especially intensified in the case of intestinal inflammation, tryptophan can be metabolized to kynurenine and its derivatives, leading to the development of depressive disorders both by the direct action of these substances on neuronal transmission and indirectly by decreasing serotonin levels.²⁶ In addition, through fermentation of dietary fibers, gut microbiota is responsible for the production of short chain fatty acids (SCFAs), which control the inflammation process of the intestines. In IBD, the amount of SCFAs is reduced, so the concentration of some of their metabolites is also reduced. One of them, gamma-aminobutyric acid, is inhibitory neurotransmitter involved in the development of anxiety and depression.^{27,28} This connection may be the starting point for creating a future therapeutic strategy based on selective manipulation of microbiota species to modify the course of both IBD and associated mental disorders. However, even if the results of preliminary studies on the influence of gut microbiota modulation on depression and anxiety in IBD patients are promising, there is not enough evidence to apply it in clinical practice.²⁹

Ingesting certain microorganisms can influence human brain activity in specific regions modifying behavior, emotions and cognition. Additionally, it can lead to decreases in the concentration of stress hormones. These findings mean that some probiotic species, which in this context are termed 'psychobiotics', may be usable as a treatment option. Interestingly, microbiome alterations may be significant in psychiatric pharmacotherapy, because some drugs currently prescribed by psychiatrists or neurologists

were used as antibacterial agents in the past. However, as already mentioned, scientific evidence is still insufficient to recommend psychobiotics as a form of therapy.^{30,31}

The impact of depression and anxiety disorders on IBD onset

The influence of mental disorders on the development of IBD remains unclear. It is suggested that abnormalities in mental functioning may occur several years before the diagnosis of intestinal disease. For instance, a Canadian study demonstrated that anxiety disorders and mood disorders were diagnosed in respectively 80% and 54% of patients with IBD on average 2 years before the IBD diagnosis. Additionally, patients with depression and anxiety disorders were diagnosed with the disease earlier (34.9 years on average) than those without these disorders (37.8 years on average).¹³ In subsequent studies, it was found that the interval between the deterioration of mental functioning and the diagnosis of intestinal disease may be even longer, and could be up to 5 years.³²

Impact of anxiety and depression disorders on the course of IBD

Depression and anxiety associated with IBD may directly affect its course. The correlation between intestinal disease activity and worsened mental condition is particularly evident in patients who believe that psychological stress contributes to exacerbations.³³ It was observed that IBD patients with accompanying mental disorders have increased likelihoods of surgical interventions, extended diagnostics with additional examinations, such as computer tomography (CT) or multiple colonoscopies, as well as a need for

corticosteroids, immunomodulators or anti-tumor necrosis factor (TNF) therapy.³⁴ The presence of depressive symptoms can worsen the course of IBD and may be considered a predictor of aggressive, recurrent disease.^{35,36}

One of the suggested mechanisms explaining how depression can influence the activity and severity of IBD is its impact on the inflammatory process. For instance, in about 80% of severely depressed patients, hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis is observed. The resulting chronic hypercortisolemia leads to elevation of pro-inflammatory mediators.³⁷ Moreover, depression is associated with decreased parasympathetic activity of the autonomic nervous system (ANS), which causes inhibition of macrophage activation through the cholinergic anti-inflammatory pathway. As a result, depression clearly influences the Crohn's Disease Activity Index score in CD patients, can lead to exacerbations of IBD and increases the rate of failure during infliximab treatment. In a study of 100 people with CD, it turned out that patients with major depressive disorder (MDD) found it harder to achieve remission. Persistent MDD after adequate treatment of CD with infliximab is a risk factor for the need of early retreatment.^{38,39}

Interestingly, a study of a small group of women with depression showed that treating them with behavioral-cognitive therapy resulted in a decrease in the concentration of interleukin 6 (IL-6), which is one of the major pro-inflammatory cytokines in IBD.⁴⁰ According to another meta-analysis, behavioral-cognitive therapy in patients with IBD has limited and short-term effectiveness in treating depressive symptoms and improving HRQoL, without affecting anxiety, stress levels or disease activity.⁴¹

Regarding pharmacotherapy of depression and anxiety disorders in IBD, although antidepressants are commonly used by these patients with (based on previous research) apparently beneficial effects, it is not possible to determine conclusively whether pharmacotherapy affects the course of IBD.⁴² Central neuromodulators may be used in painful IBD as supplements to peripheral agents, like in the management of functional disorders. In cases of major psychiatric problems, consulting with a psychiatrist to optimize therapy is recommended.⁴³ The previously described potential benefits of using antidepressants may be associated with a reduction in inflammatory processes or simply with mood improvement.⁴⁴ For now, it is only known that the use of certain antidepressants reduces the risk of intestinal disease in the future.⁴⁵ Properly conducted randomized controlled trials are necessary to accurately define their efficacy.

The impact of IBD on anxiety and mental disorders

Depressive disorders are accompanied by elevated concentrations of pro-inflammatory mediators such as C-reactive protein (CRP), IL-6, IL-1, IL-12, and TNF- α .^{38,46} It has

been suggested that CRP levels might be used to predict the severity and recurrence of depression.⁴⁷ Consequently, patients with CD who received anti-inflammatory therapy with anti-TNF agents (infliximab or adalimumab) reported rapid improvement in depressive disorders. Most importantly, this was not associated solely with clinical improvement of their IBD.^{48–50}

Sleep disorders observed in patients with IBD, which are closely related to depression, may be a marker of subclinical inflammation or persistent histologic disease activity. It has been suggested that elevated levels of circulating cytokines contribute to sleep disturbances, even in clinical remission. Injection of pro-inflammatory IL-1 or TNF in animal models suppresses rapid-eye movement (REM) sleep and alters sleep patterns. Additionally, administration of IL-6 increases non-rapid eye movement (NREM) sleep and reduces slow-wave sleep during the 1st half of the sleep cycle.⁵¹ Interestingly, some studies have shown that CD patients who have impaired sleep quality while in clinical remission have a greater risk of disease flare-ups. This is why sleep disturbances, potentially modifiable risk factors for IBD relapse, should be considered for routine assessment in patients.^{52–54}

Depression as a side effect of IBD treatment

Drugs used in the treatment of IBD may also influence the occurrence of depression and anxiety disorders. It is known that long-term use of glucocorticosteroids negatively affects the mood of patients.⁵⁵ Interestingly, in previous randomized clinical trials and observational studies, adverse psychiatric effects (APE) during biological treatment were very rare or absent. However, the exact frequency of them among biologically treated patients is difficult to assess, because many studies do not consider adverse effects of the drug on the patient's psychological state. It is not known whether the authors did not observe such effects or whether they did not collect data related to this aspect.⁵⁶

Depression and anxiety disorders in the guidelines

In the recent guidelines of the European Crohn's and Colitis Organization (ECCO) regarding the management of CD (2019) and UC (2017), there are no recommendations concerning assessment of the patients' mental state and possible therapeutic interventions.^{57,58} Such recommendations appeared in the 2018 Nurses' European Crohn's and Colitis Organization (N-ECCO) consensus regarding the role of nurses in caring for patients with IBD. According to this document, nurses should be aware of more frequent depression and anxiety disorders among

the patients than in the general population, and, if necessary, should refer selected patients to a specialist.⁵⁹ The British Gastroenterology Association also took a position on this matter in guidelines issued in 2019. The British recommendations suggest supportive behavioral therapy, hypnotherapy or mindfulness meditation for interested patients. Similarly, the German Clinical Practice Guideline on IBD emphasizes the significance of accompanying psychiatric symptoms. So far, no reliable studies have been conducted in patients with IBD and depression or anxiety disorders that may provide a basis for recommending antidepressants.^{60,61}

Conclusions

The risk of depression and anxiety disorders in patients with IBD is significantly higher than in the general population, so both family physicians and gastroenterologists should consider them in patients under their care, as they can negatively impact the course of the disease. Nevertheless, the current guidelines refer to this problem only to a limited extent at best. Considering the close relationship between depression and anxiety and the degree of disease activity, optimization of IBD treatment should include psychiatric, psychological and social support. Due to the steadily increasing incidence of IBD, a holistic approach is needed, both to avoid the development of depression-related disabilities and to improve HRQoL and patient–doctor compliance.

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References

- Vavricka SR, Schoepfer A, Scharl M, Lakatos PL, Navarini A, Rogler G. Extraintestinal manifestations of inflammatory bowel disease. *Inflamm Bowel Dis*. 2015;21(8):1982–1992. doi:10.1097/MIB.000000000000000392
- Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: A systematic review of population-based studies. *Lancet*. 2017;390(10114):2769–2778. doi:10.1016/S0140-6736(17)32448-0
- Coward S, Clement F, Williamson T, et al. The rising burden of inflammatory bowel disease in North America from 2015 to 2025: A predictive model. *Am J Gastroenterol*. 2015;110:S829.
- Kaplan GG. The global burden of IBD: From 2015 to 2025. *Nat Rev Gastroenterol Hepatol*. 2015;12(12):720–727. doi:10.1038/nrgastro.2015.150
- Knowles SR, Graff LA, Wilding H, Hewitt C, Keefer L, Mikocka-Walus A. Quality of life in inflammatory bowel disease: A systematic review and meta-analyses – Part I. *Inflamm Bowel Dis*. 2018;24(4):742–751. doi:10.1093/ibd/izx100
- Romberg-Camps MJL, Bol Y, Dagnelie PC, et al. Fatigue and health-related quality of life in inflammatory bowel disease. Results from a population-based study in the Netherlands: The IBD-South Limburg cohort. *Inflamm Bowel Dis*. 2010;16(12):2137–2147. doi:10.1002/ibd.21285
- Abautret-Daly Á, Dempsey E, Parra-Blanco A, Medina C, Harkin A. Gut–brain actions underlying comorbid anxiety and depression associated with inflammatory bowel disease. *Acta Neuropsychiatr*. 2018;30(5):275–296. doi:10.1017/neu.2017.3
- Whitehouse CE, Fisk JD, Bernstein CN, et al. Comorbid anxiety, depression and cognition in MS and other immune-mediated disorders. *Neurology*. 2019;92(5):e406–e417. doi:10.1212/WNL.0000000000006854
- Lewis K, Marrie RA, Bernstein CN, et al; CIHR Team in Defining the Burden and Managing the Effects of Immune-Mediated Inflammatory Disease. The prevalence and risk factors of undiagnosed depression and anxiety disorders among patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2019;25(10):1674–1680. doi:10.1093/ibd/izz045
- Graff LA, Walker JR, Bernstein CN. Depression and anxiety in inflammatory bowel disease: A review of comorbidity and management. *Inflamm Bowel Dis*. 2009;5(7):1105–1118. doi:10.1002/ibd.20873
- Marafini I, Longo L, Lavasani DM, et al. High frequency of undiagnosed psychiatric disorders in inflammatory bowel diseases. *J Clin Med*. 2020;9(5):1387. doi:10.3390/jcm9051387
- 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(8):802–810. doi:10.1111/apt.12669
- Walker JR, Ediger JP, Graff LA, et al. The Manitoba IBD cohort study: A population-based study of the prevalence of lifetime and 12-month anxiety and mood disorders. *Am J Gastroenterol*. 2008;103(8):1989–1997. doi:10.1111/j.1572-0241.2008.01980.x
- Mikocka-Walus A, Knowles SR, Keefer L, Graff L. Controversies revisited: A systematic review of the comorbidity of depression and anxiety with inflammatory bowel diseases. *Inflamm Bowel Dis*. 2015;22(3):752–762. doi:10.1097/MIB.0000000000000620
- 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(8):1732–1739. doi:10.1097/MIB.0b013e318281f395
- Bernstein CN, Hitchon CA, Walld R, et al. Increased burden of psychiatric disorders in inflammatory bowel disease. *Inflamm Bowel Dis*. 2019;25(2):360–368. doi:10.1093/ibd/izy235
- Thakur ER, Sansgiry S, Kramer JR, et al. The incidence and prevalence of anxiety, depression and post-traumatic stress disorder in a national cohort of US veterans with inflammatory bowel disease. *Inflamm Bowel Dis*. 2019;26(9):1423–1428. doi:10.1093/ibd/izz280
- van den Brink G, Stapersma L, Plug LE, et al. Clinical disease activity is associated with anxiety and depressive symptoms in adolescents and young adults with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2018;48(3):358–369. doi:10.1111/apt.14832
- Choi K, Chun J, Han K, et al. Risk of anxiety and depression in patients with inflammatory bowel disease: A nationwide, population-based study. *J Clin Med*. 2019;8(5):654. doi:10.3390/jcm8050654
- Bhamre R, Sawrav S, Adarkar S, Sakaria R, J Bhatia S. Psychiatric comorbidities in patients with inflammatory bowel disease. *Indian J Gastroenterol*. 2018;37(4):307–312. doi:10.1007/s12664-018-0870-9
- Navabi S, Gorrepati VS, Yadav S, et al. Influences and impact of anxiety and depression in the setting of inflammatory bowel disease. *Inflamm Bowel Dis*. 2018;24(11):2303–2308. doi:10.1093/ibd/izy143
- Byrne G, Rosenfeld G, Leung Y, et al. Prevalence of anxiety and depression in patients with inflammatory bowel disease. *Can J Gastroenterol Hepatol*. 2017;2017:6496727. doi:10.1155/2017/6496727
- Chan W, Shim HH, Lim MS, et al. Symptoms of anxiety and depression are independently associated with inflammatory bowel disease-related disability. *Dig Liver Dis*. 2017;49(12):1314–1319. doi:10.1016/j.dld.2017.08.020
- Bennebroek Evertsz F, Thijssens NAM, Stokkers PCF, et al. Do inflammatory bowel disease patients with anxiety and depressive symptoms receive the care they need? *J Crohns Colitis*. 2012;6(1):68–76. doi:10.1016/j.crohns.2011.07.006
- Humbel F, Rieder JH, Franc Y, et al; Swiss IBD Cohort Study Group. Association of alterations in intestinal microbiota with impaired psychological function in patients with inflammatory bowel diseases in remission. *Clin Gastroenterol Hepatol*. 2019;18(9):2019–2029.e11. doi:10.1016/j.cgh.2019.09.022
- Waclawiková B, El Aidy S. Role of microbiota and tryptophan metabolites in the remote effect of intestinal inflammation on brain and depression. *Pharmaceuticals (Basel)*. 2018;11(3):63. doi:10.3390/ph11030063
- Oligschläger Y, Yadati T, Houben T, Condello Oliván CM, Shiri-Sverdllov R. Inflammatory bowel disease: A stressed “gut/feeling.” *Cells*. 2019;8(7):659. doi:10.3390/cells8070659

28. Lydiard RB. The role of GABA in anxiety disorders. *J Clin Psychiatry*. 2003;64(Suppl 3):21–27.
29. Kilincarslan S, Evrensel A. The effect of fecal microbiota transplantation on psychiatric symptoms among patients with inflammatory bowel disease: An experimental study. *Actas Esp Psiquiatr*. 2020;48(1):1–7.
30. Skonieczna-Żydecka K, Marlicz W, Misera A, Koulaouzidis A, Łoniewski I. Microbiome: The missing link in the gut-brain axis. Focus on its role in gastrointestinal and mental health. *J Clin Med*. 2018;7(12):521. doi:10.3390/jcm7120521
31. Jacobs JP, Mayer EA. Psychobiotics: Shaping the mind with gut bacteria. *Am J Gastroenterol*. 2019;114(7):1034–1035.
32. Marrie RA, Walld R, Bolton JM, et al; CIHR Team in Defining the Burden and Managing the Effects of Psychiatric Comorbidity in Chronic Immunoinflammatory Disease. Rising incidence of psychiatric disorders before diagnosis of immune-mediated inflammatory disease. *Epidemiol Psychiatr Sci*. 2019;28(3):333–342. doi:10.1017/S2045796017000579
33. Araki M, Shinzaki S, Yamada T, et al. Psychologic stress and disease activity in patients with inflammatory bowel disease: A multicenter cross-sectional study. *PLoS One*. 2020;15(5):e0233365. doi:10.1371/journal.pone.0233365
34. Ananthakrishnan AN, Gainer VS, Perez RG, et al. Psychiatric co-morbidity is associated with increased risk of surgery in Crohn's disease. *Aliment Pharmacol Ther*. 2013;37(4):445–454. doi:10.1111/apt.12195
35. Kochar B, Barnes EL, Long MD, et al. Depression is associated with more aggressive inflammatory bowel disease. *Am J Gastroenterol*. 2018;113(1):80–85. doi:10.1038/ajg.2017.423
36. Moulton CD, Pavlidis P, Norton C, et al. Depressive symptoms in inflammatory bowel disease: An extraintestinal manifestation of inflammation? *Clin Exp Immunol*. 2019;197(3):308–318. doi:10.1111/cei.13276
37. Leonard BE. Inflammation and depression: A causal or coincidental link to the pathophysiology? *Acta Neuropsychiatr*. 2018;30(1):1–16. doi:10.1017/neu.2016.69
38. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. *Psychosom Med*. 2009;71(2):171–186. doi:10.1097/PSY.0b013e3181907c1b
39. 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(2):101–110. doi:10.1111/j.1365-2036.2005.02535.x
40. Gazal M, Souza LD, Fucolo BA, et al. The impact of cognitive behavioral therapy on IL-6 levels in unmedicated women experiencing the first episode of depression: A pilot study. *Psychiatry Res*. 2013;209(3):742–745. doi:10.1016/j.psychres.2013.03.002
41. Gracie DJ, Irvine AJ, Sood R, Mikocka-Walus A, Hamlin PJ, Ford AC. Effect of psychological therapy on disease activity, psychological comorbidity and quality of life in inflammatory bowel disease: A systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2017;2(3):189–199. doi:10.1016/S2468-1253(16)30206-0
42. Macer BJD, Prady SL, Mikocka-Walus A. Antidepressants in inflammatory bowel disease: A systematic review. *Inflamm Bowel Dis*. 2017;23(4):534–550. doi:10.1097/MIB.0000000000001059
43. Sobin WH, Heinrich TW, Drossman DA. Central neuromodulators for treating functional GI disorders: A primer. *Am J Gastroenterol*. 2017;112(5):693–702. doi:10.1038/ajg.2017.57
44. Tynan RJ, Weidenhofer J, Hinwood M, Cairns MJ, Day TA, Walker FR. A comparative examination of the anti-inflammatory effects of SSRI and SNRI antidepressants on LPS stimulated microglia. *Brain Behav Immun*. 2012;26(3):469–479. doi:10.1016/j.bbi.2011.12.011
45. Frolkis AD, Vallerand IA, Shaheen AA, et al. Depression increases the risk of inflammatory bowel disease, which may be mitigated by the use of antidepressants in the treatment of depression. *Gut*. 2019;68(9):1606–1612. doi:10.1136/gutjnl-2018-317182
46. Anisman H, Merali Z. Cytokines, stress and depressive illness: Brain-immune interactions. *Ann Med*. 2003;35(1):2–11. doi:10.1080/07853890310004075
47. Liukkonen T, Silvennoinen-Kassinen S, Jokelainen J, et al. The association between C-reactive protein levels and depression: Results from the Northern Finland 1966 Birth Cohort Study. *Biol Psychiatry*. 2006;60(8):825–830. doi:10.1016/j.biopsych.2006.02.016
48. Minderhoud IM, Samsom M, Oldenburg B. Crohn's disease, fatigue, and infliximab: Is there a role for cytokines in the pathogenesis of fatigue? *World J Gastroenterol*. 2007;13(14):2089–2093. doi:10.3748/wjg.v13.i14.2089
49. Loftus EV, Feagan BG, Colombel JF, et al. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: Patient-reported outcomes of the CHARM trial. *Am J Gastroenterol*. 2008;103(12):3132–3141. doi:10.1111/j.1572-0241.2008.02175.x
50. Guloksuz S, Wichers M, Kenis G, et al. Depressive symptoms in Crohn's disease: Relationship with immune activation and tryptophan availability. *PLoS One*. 2013;8(3):e60435. doi:10.1371/journal.pone.0060435
51. Rohleder N, Aringer M, Boentert M. Role of interleukin-6 in stress, sleep and fatigue. *Ann N Y Acad Sci*. 2012;1261:88–96. doi:10.1111/j.1749-6632.2012.06634.x
52. Ananthakrishnan AN, Long MD, Martin CF, Sandler RS, Kappelman MD. Sleep disturbance and risk of active disease in patients with Crohn's disease and ulcerative colitis. *Clin Gastroenterol Hepatol*. 2013;11(8):965–971. doi:10.1016/j.cgh.2013.01.021
53. Marinelli C, Savarino EV, Marsilio I, et al. Sleep disturbance in inflammatory bowel disease. Prevalence and risk factors: A cross-sectional study. *Sci Rep*. 2020;10(1):507. doi:10.1038/s41598-020-57460-6
54. Ali T, Madhoun MF, Orr WC, Rubin DT. Assessment of the relationship between quality of sleep and disease activity in inflammatory bowel disease patients. *Inflamm Bowel Dis*. 2013;19(11):2440–2443. doi:10.1097/MIB.0b013e3182a0ea54
55. Ou G, Bressler B, Galorport C, et al. Rate of corticosteroid-induced mood changes in patients with inflammatory bowel disease: A prospective study. *J Can Assoc Gastroenterol*. 2018;1(3):99–106. doi:10.1093/jcag/gwy023
56. Jain A, Marrie RA, Shafer LA, et al. Incidence of adverse psychiatric events during treatment of inflammatory bowel disease with biologic therapies: A systematic review. *Crohn & Colitis 360*. 2020;2(1):53. doi:10.1093/crocol/otz053
57. Torres J, Bonovas S, Doherty G, et al. ECCO Guidelines on therapeutics in Crohn's disease: Medical treatment. *J Crohns Colitis*. 2020;14(1):4–22. doi:10.1093/ecco-jcc/jjz180
58. Magro F, Gionchetti P, Eliakim R, et al; European Crohn's and Colitis Organisation (ECCO); Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: Definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. *J Crohns Colitis*. 2017;11(6):649–670. doi:10.1093/ecco-jcc/jjx008
59. Kemp K, Dibley L, Chauhan U, et al. Second N-ECCO consensus statements on the European nursing roles in caring for patients with Crohn's disease or ulcerative colitis. *J Crohns Colitis*. 2018;12(7):760–776. doi:10.1093/ecco-jcc/jjy020
60. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut*. 2019;68(Suppl 3):s1–s106. doi:10.1136/gutjnl-2019-318484
61. Mikocka-Walus A, Clarke D, Gibson P. Can antidepressants influence the course of inflammatory bowel disease? The current state of research. *European Journal of Gastroenterology and Hepatology*. 2009;5:48–53.