Psychosocial Support of the Inflammatory Bowel Disease Patient

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KEYWORDS

• Psychological impacts • Inflammatory bowel disease • Depression • Anxiety

KEY POINTS

- Inflammatory bowel disease (IBD) is a chronic, debilitating disease whose effects spread far beyond the gut.
- IBD does not generally result in excess mortality; health care providers should thus focus their efforts on improving health-related quality of life and minimizing associated morbidity.
- A bidirectional relationship exists between IBD and psychiatric conditions; chronic inflammation can produce neuromodulatory effects with resultant mood disorders, and the course of IBD is worse in patients with anxiety and depression.
- Screening for the early signs of depression or anxiety and initiating appropriate treatment can lead to improved functioning and positively impact disease course.

INTRODUCTION

Inflammatory bowel disease (IBD), namely Crohn's disease (CD) and ulcerative colitis (UC), afflicts 1.5 million people in the United States and 28 million worldwide.[1,2] The chronic, unpredictable, disabling, and progressively destructive nature of IBD gives rise to substantial psychosocial implications.[3]

There has been a great deal of speculation over the years on the importance of psychiatric and social factors in IBD; however, it is only in the last decade or so that studies with stronger designs have been available to clarify the nature of this relationship. And although there is no conclusive evidence for anxiety, depression, and psychosocial stress contributing to the risk for IBD onset, they have been found to impact the course of IBD patients, including risk of relapse.

The purpose of this review is to shed light on the complex relationship between mental health and IBD, highlighting the various associations and risk factors for

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psychiatric disorders, and clinical recommendations for the detection, screening, and management of these conditions in patients with IBD, bolstering a more patient-centered approach with improving outcomes.[2,4–6]

PSYCHIATRIC DISORDERS IN INFLAMMATORY BOWEL DISEASE

Chronic medical conditions in general are associated with higher rates of anxiety and mood disorders compared with the general population; the stress associated with these conditions may trigger or intensify a psychiatric condition. Newer insight, however, has linked depression and anxiety specifically to inflammatory conditions, like IBD, possibly via induced immunoregulatory circuit dysfunction.[3] This section considers recent evidence on the prevalence of anxiety and depressive disorders in IBD, the role of these disorders as a risk factor for IBD onset, the degree to which they affect its course. Screening for psychiatric illness and management strategies is also discussed.

Four population-based studies consistently demonstrated a clear relationship between IBD and depression and higher levels of anxiety.[7–9] The largest of these studies found patients with CD to be 5 times more likely than controls to have anxiety or depression, whereas patients with UC were 4 times as likely to have anxiety and twice as likely to be depressed than matched controls.[7] Overall, the mean prevalence of depression in patients with IBD is estimated to be 20%,[10] and abnormal anxiety levels are found in up to 40% of patients with IBD.[11]

In an attempt to establish a temporal relationship between IBD and depression/anxiety, a prospective, population-based study found UC to be at least twice as common in patients with anxiety and depression compared with controls without these conditions years before the onset of IBD.[12] This, however, was likely reflective of reactive anxiety or depressive symptoms related to early signs of IBD. Also, increased levels of inflammatory mediators seen in patients before the onset of IBD symptoms may play a role in initiating mood disorders.

Currently, there is no conclusive evidence to suggest that anxiety, depression or psychosocial stress play an etiologic role in the onset of IBD.[4,5,13] Nevertheless, evidence does suggest that the course of IBD is worse in patients with anxiety and depression and that patients with active disease or symptoms demonstrate higher levels of anxiety or depression than those in remission.[14–16] A 2-year study that assessed a small sample of CD patients at 2- to 3-month intervals found that higher depression scores were associated with higher Crohn's Disease Activity Index scores in the subsequent time period. Mittermaier and colleagues[17] reported similar findings in patients with UC.[16] Severe active and aggressive disease seems to be the primary risk factor for depression and anxiety disorders.[18] Psychological stress, advancing age, surgery and stoma, and poor socioeconomic status have all been reported as well.

PATHOPSYCHOLOGY OF DEPRESSION AND ANXIETY DISORDERS IN INFLAMMATORY BOWEL DISEASE

The etiology of mood disorders in patients with IBD seems multifactorial. Recently, there has been considerable interest in the combined role of inflammatory and stress biomarkers to cause changes in brain structure and function, with resultant mood disorders.[6,19–21] Most of the evidence that links inflammation to depression comes from 3 observations:

- One-third of patients with major depression show elevated peripheral concentrations of inflammatory biomarkers, namely C-reactive protein, tumor necrosis factor-α and interleukin (IL)-6, even in the absence of medical illness.[22,23]

- Patients with IBD with higher levels of acute phase reactants have a higher incidence of depression compared with those with normal inflammatory marker levels. A recent metaanalysis found treatment with selective serotonin reuptake inhibitors produced a decrease in IL-1b and IL-6 levels that paralleled improvement in depressive symptoms.[24]
- Patients treated with cytokines are at greater risk of developing major depressive illness.[25]

Proposed mechanisms include the direct effects of proinflammatory cytokines on monoamine levels, dysregulation of the hypothalamic–pituitary–adrenal axis, pathologic microglial cell activation, impaired neuroplasticity, and structural and functional brain changes.[26]

Targeting specific immune markers, for example, tumor necrosis factor-α inhibitors, however, has had little effect on psychiatric morbidity. This is likely to the complex multifactorial nature of "brain–gut" interactions in IBD. A holistic approach would potentially target underlying inflammation, and in turn this would decrease the excitability of sensitized afferent pathways and alter emotional and/or cognitive functions, ultimately enabling more effective management of both inflammation and depression in patients with IBD.

Visceral hyperalgesia also seems to play a role in IBD associated mood disorders. Pain is the presenting symptom in up to 70% of patients with IBD.[27,28] The relationship between chronic pain and depression, like the brain–gut axis, is bidirectional. The brain–gut axis is a communication between the central and autonomic nervous system, the hypothalamic–pituitary–adrenal axis, and the intestinal response.[5,29,30] Depression can present itself as chronic abdominal pain, and patients with pain are at increased risk for depression independent of disease activity.[29,31]

Chronic inflammation, as seen in IBD, induces persistent sensitizing effects in the sensory afferent pathways and leads to an altered processing of pain by the central nervous system, with downstream alterations in the emotional and cognitive processing of this increased visceral input.[5,6,29]

Medications used in the treatment of IBD have also been linked to mood disorders. Results from -analyses have suggested that more than one-quarter of patients on corticosteroids may experience adverse psychiatric effects.[32,33] Fardet and colleagues[33] found that 10% of patients on greater than 20 mg of daily prednisone for 3 months required hospitalization for either mania or severe depression. In 1 survey, psychiatric symptoms were second only to "moon facies" as the most distressing side effect of corticosteroids. The incidence of psychiatric disorders seems to be related directly to medication dosage. Patients with a prior history of steroid-induced psychiatric symptoms are also at greater risk. With the widespread use of steroid alternatives, especially biologics, steroids now are relatively small contributors to the overall prevalence of psychiatric disorders in patients with IBD.

SCREENING FOR PSYCHIATRIC DISORDERS IN INFLAMMATORY BOWEL DISEASE

Given the frequency and impact of psychiatric disorders in IBD, updated consensus guidelines for the management of IBD have included a recommendation for routine screening for these disorders. Ensuring that patient are screened routinely for common psychiatric symptoms can help those patients most likely to benefit from assistance, especially considering that most patients are reluctant to voice such concerns.

Both anxiety disorders and depression are criterion-based diagnoses (**Table 1**). The former is characterized by symptoms of excessive fear and worry that are difficult to control, a state of hyperarousability, and resultant behavioral disturbances (typically,

Table 1
Anxiety and depression are criterion-based diagnoses

Depression	Anxiety
Persistently depressed mood[a]	Excessive anxiety or worry, difficult controlling worry
Diminished interest or pleasure[a]	—
Significant weight loss, or change in appetite[a]	—
Insomnia or hypersomnia	Sleep disturbance[b]
Psychomotor agitation or retardation[a]	Muscle tension[b], irritability[b]
Fatigue or loss of energy[a]	Fatigue or loss of energy[b]
Feelings of worthlessness or inappropriate guilt[a]	Feelings of restlessness, or keyed up or on edge[b]
Diminished ability to think or concentrate[a]	Diminished ability to think or concentrate[b]
Recurrent suicidal ideation[a]	—

[a] Five or more symptoms for 2 or more weeks.
[b] Three or more symptoms occurring more days than not for at least 6 months.
Data from Diagnostic and statistical manual of mental disorders. 5th edition. Washington, DC: American Psychiatric Association; 2013.

avoidance of source of fear). Depression is characterized by a sad or depressed mood affect, with cognitive and somatic symptoms that cause significant distress or impairment in social, occupational, or other important areas of functioning. Symptoms of both disorders must be persistent and are not secondary to direct physiologic effects of a substance (eg, a drug of abuse, a medication) or a general medical condition.

Patient-based screening forms and health care provider administered brief standardized questions are simple, valid psychosocial screening instruments frequently used in patients with IBD.

The 5-item Anxiety and Depression Detector is an example of a self-report scale[34]; its questions focus on eliciting information regarding depression and anxiety. Its high sensitivity and specificity combined with its relative ease of use (yes/no responses, simple language, can be completed while patient is in the waiting room) make it favorable. Clinician-administered scales, such as the Luebeck Interview for Psychosocial Screening in Patients with IBD, are not only useful in identifying patients with manifestations of illness, but also help to identify social support mechanisms, distress caused by IBD, and the patients interest in receiving psychological care. It has shown good interobserver reliability and correlates with other psychometric measures. Two approaches have been used in the management of psychiatric conditions in IBD patients. This is usually done in collaboration with mental health professionals (**Table 2**).[5,6,13]

PHARMACOLOGIC TREATMENTS

Selective serotonin reuptake inhibitors, such as citalopram, fluoxetine, and sertraline, and serotonin norepinephrine reuptake inhibitors, such as venlafaxine, are both safe and effective in the treatment of anxiety and depressive disorders,[4,5,13] with a significant percentage of IBD patients with anxiety or depression reporting a favorable response. In addition to controlling symptoms of anxiety and depression, both selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors have been reported to decrease pain, gut irritability, and urgency of defecation.[35,36] Goodhand and colleagues[37] stated that patients reported fewer clinical IBD relapses

Table 2
Screening instruments for patients with IBD

The Anxiety and Depression Detector	LIPS – IBD*
Did you ever have a spell or an attack when all of a sudden you felt frightened, anxious, or very uneasy? Yes/No	With whom do you live together? Do you have children? Is anyone available for you who supports you with your problems? *Social support* 1 2 3 4 5
Would you say that you have been bothered by nerves or feeling anxious or on edge? Yes/No	During the last months, did you feel sad, depressed, or hopeless? Were you at least interested in activities you used to enjoy? *Depression* 1 2 3 4 5
Would you say that being anxious or uncomfortable around other people is a problem for you in your life? Yes/No	During the last months, did you often feel restless? Did you worry a lot? Did you sometimes experience sudden feelings of worry or anxiety? *Anxiety* 1 2 3 4 5
Did you have a period of 1 week or more when you lost interest in most things like work, hobbies, and other things you usually enjoyed? Yes/No	How much do you feel stressed by your IBD? *Impact of disease* 1 2 3 4 5
Some people have terrible experiences happen to them, like being attacked or threatened with a weapon, being in a fire or a bad traffic accident, being sexually assaulted, or seeing someone being badly injured or killed. Has anything like this ever happened to you? Yes/No	—

Abbreviation: IBD, inflammatory bowel disease; LIPS, Luebeck Interview for Psychosocial Screening.
Adapted from Means-Christensen AJ, Sherbourne CD, Roy-Byrne PP, et al. Using five questions to screen for five common mental disorders in primary care: diagnostic accuracy of the Anxiety and Depression Detector. Gen Hosp Psychiatry 2006;28(2):108–18; and Kunzendorf S, Jantschek G, Straubinger K, et al. The Luebeck interview for psychosocial screening in patients with inflammatory bowel disease. Inflamm Bowel Dis 2007;13(1):33–41.

after receiving antidepressants for 1 year. This may explained by the fact that patients in better psychological health report fewer functional gastrointestinal symptoms. A recent survey found almost 80% of gastrointestinal specialists had prescribed antidepressants as an adjunctive therapy, especially for pain and sleep difficulties. Patients should be made aware that clinical benefit is generally not seen for at least 2 to 4 weeks after start of treatment, and that side effects are not unusual and can be problematic (namely weight gain and sexual dysfunction). Up to 50% of patients discontinue treatment within the first weeks or months, often because of side effects, limiting the effectiveness of the treatment. The dose of these medications should be adjusted or altered to ensure maximum therapeutic benefit while minimizing side effects. Relapse is common after discontinuation of treatment; maintenance of treatment gains requires long-term treatment in patients who demonstrate a good response to therapy.

NONPHARMACOLOGIC PSYCHOTHERAPY

Cognitive–behavioral therapy has been found to be effective in the treatment of both anxiety and depression. In patients with IBD, a randomized controlled trial reported significantly decreased depression and improved global functioning after

cognitive–behavioral therapy. For those who also had a comorbid anxiety disorder, there was a significant decrease in anxiety as well.[38,39] Similar findings were reported in adults in a Spanish randomized controlled trial after a structured cognitive–behavioral therapy program that included relaxation training, distraction, and cognitive restructuring.[40] The benefits in both studies were maintained at 12-month follow-up. A recent Cochrane review however found the evidence supporting psychological therapy in adult patients with IBD to be inconclusive.[41]

Psychological treatment, however, is not indicated for all patients with IBD. In patients with no evidence of depression or anxiety, evidence that psychological interventions help patients to cope with disease is lacking. In a large pooled analysis of unselected adult patients with IBD, psychotherapy was ineffective in improving quality of life (QOL), emotional problems, and disease activity.[41] Validated treatments should thus only be used in high-risk subgroups with comorbid psychiatric conditions. In addition, cognitive–behavioral therapy is less readily available, costlier, and more labor/time intensive than pharmacologic treatment.

Importantly, health care providers must be aware of compliance issues in patients with depression. Overall, the reported rate of non-compliance in patients with IBD was 30% in 1 report, comparable with that of patients with other chronic illnesses.[42] Depression and psychological distress are both predictors of nonadherence, with 1 series citing those with IBD and depression are 3 times less likely to comply with treatment compared with nondepressed counterparts.[13] Approaches such as improving the physician–patient relationship, individualized therapy, providing patient information and support, self-management programs and practical memory aids can increase the likelihood of adherence and prolonged remission rates.[43]

Last, physicians treating IBD patients should be vigilant about expressions of suicidal ideation or signs and symptoms of self-harm. Studies have demonstrated an increased rate of suicide among patients with CD and UC, even after adjusting for confounders.[44,45]

HEALTH-RELATED QUALITY OF LIFE

Health-related QOL (HRQoL) is defined as "a quantitative measurement of subjective perception of ones' health state, including physical, emotional and social functioning."[42] It provides important insight into patients' perception of their health and the effect of treatments. Various QOL measures have been developed and used by researchers and health care providers. These measures can be either generic or disease specific; the former being useful to compare HRQoL across different disease states, whereas disease specific measures are more sensitive to changes in a patient's health state.

A recent systematic review of HRQoL measures found the Inflammatory Bowel Disease Questionnaire (IBDQ) to be the most widely used IBD-specific measure of HRQoL.[46] Several studies have confirmed its reliability, validity, and internal consistency. The IBDQ questionnaire, originally composed of 32 items, has been shortened to 10 (Short IBDQ, **Box 1**) and 9 items (IBDQ-9).

In a recent survey by the European Federation of Crohn's and Ulcerative Colitis Associations (n = 5576 participants), 75% of patients reported symptoms affected their ability to enjoy leisure activities, and two-thirds felt that their symptoms affected their ability to perform at work. Interestingly, nearly one-half (n = 2666; 47.8%) reported that their doctor does not ask about the impact of symptoms on their QOL.[3] In another survey, almost 50% of patients reported IBD had negatively affected their performance in educational settings, and 24% had received unfair comments about their work performance, mainly owing to absenteeism.[47]

Box 1
Colitis: short Inflammatory Bowel Disease Questionnaire

Bowel

Frequency of bowel movements compared with when disease is stable

Frequency of distress from abdominal cramps

Systemic

Feelings of fatigue, or being "worn out"

Energy

Emotion

Worried about possibility of surgery

Fear of not finding a toilet

Free of tension

Mood irritability

Social

Limitation of leisure or sports activity secondary to disease

Limitation of sexual activity secondary to disease

DETERMINANTS OF HEALTH-RELATED QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE

Numerous studies have found that patients with active disease have significantly impaired HRQoL compared with patients in remission.[6–8,48–51] This is owing to the fact that patients with active IBD tend to have more bowel symptoms that interfere with daily activities, as well as more disease-related worries, perceived stress, and emotional distress.[51] Conversely, achievement of disease remission in Crohn's disease, whether by pharmacologic or surgical means, is associated with improved HRQoL.[52] Importantly, poor HRQoL is not restricted to active episodes; rather, it persists even when the disease is inactive. Newer treatments have come with a greater ability to induce and maintain remission; this in turn has resulted in greater improvements in HRQoL. However, improving social support systems and even patient–physician interactions are necessary in view of their ability to positively impact HRQoL.[53–55] Treating concomitant anxiety and depression also seems to improve HRQoL, an added benefit of identifying those likely to benefit from psychiatric treatment of these conditions.[9]

Gender, socioeconomic status, and ethnicity have also been shown to be determinants of HRQoL. Several reports suggest that females report more disease-related concerns than males, particularly regarding self-image and relationships. In adults with CD, poorer HRQoL was reported in black compared with white patients. Self-esteem also was found to be a predictor of HRQoL.

Factors that are not direct effects of IBD can also diminish QOL in IBD patients, including stress, sleeping problems, depression, pain, and conflicts at work or home. Numerous studies have found unemployed people to exhibit poorer QOL; estimated unemployment rates among patients with IBD range from 25% to 39%.[55] One study found long-term active disease and the presence of psychiatric comorbidity, particularly depression, to be major determinants of work-related disability.[55] Even personality traits such as neuroticism and alexithymia (inability to describe feelings)

have been reported to predict HRQoL, likely owing to effects on coping and adjustment.

COPING WITH INFLAMMATORY BOWEL DISEASE

The unpredictable, chronic, and debilitating nature of IBD gives rise to significant psychological concerns, including loss of control of bowel function, fatigue, impairment of body image, a fear of sexual inadequacy, feelings of social isolation, and dependency.

Table 3
Psychosocial factors shown to improve QOL

Strategy	Rationale
Education/self-management	Having inadequate information about a patient's own disease process been found to result in poorer reported QOL.[59,60] Self-management training has also been shown to improve HRQoL.[61]
Exercise and sleep	Exercise may help counter stress and psychiatric disturbance associated with IBD. A randomized trial found significant improvement in QOL in IBD patients randomized to light exercise, with no adverse effect on disease activity.[62] A survey of 200 IBD patients found poor sleep quality to be significantly associated with poor HRQoL. Patients with self-reported poor sleep quality are also 3 times as likely to have active IBD as compared with patients who reported good sleep quality.[63,64]
Psychotherapy	Several studies have found CBT to positively affect QOL. This effect is most likely secondary to improvements in coping mechanisms, as well as treatment of coexisting anxiety/depression.[65,66]
Hypnotherapy	Hypnotherapy seems to be effective in diseases with a psychosomatic component. In one study, patients with severe IBD refractory to corticosteroids reported an 80% improvement in QOL after 12 sessions of hypnotherapy. Such benefits likely stem from its ability to control emotional symptoms, and possibly improve pain.[67,68]
Social support	Family and social support has been reported by patients as being helpful with managing IBD, particularly with respect to coping and stress management.[69]
Pharmacotherapy	Several RCTs have found the biologics infliximab, adalimumab, certolizumab, and natalizumab to be associated with significant and sustained improvements of HRQoL in IBD patients compared with placebo. This is likely owing to their ability to induce and sustain remission, a factor that has been associated with improved QOL.[70–74] In a recent survey, almost 75% of patients receiving biologics reported QOL improvements.[15] Medication nonadherence can increase the risk of surgery and result in more severe disease with detrimental effects on QOL.[75] Physicians should thus focus their efforts on educating patients, simplifying regimens, and identifying barriers to adherence.

Abbreviations: CBT, cognitive–behavioral therapy; IBD, inflammatory bowel disease; HRQoL, health-related quality of life; QOL, quality of life.

Adapted from Karwowski CA, Keljo D, Szigethy E. Strategies to improve quality of life in adolescents with inflammatory bowel disease. Inflamm Bowel Dis 2009;15(11):1755–64; with permission; and *Data from* Refs.[59–74]

These are all constant and real concerns that can result in loss of feelings of self-worth. How one responds to and copes with IBD seems to be an important determinant of QOL as well as psychiatric comorbidity and disability.

Coping may be broadly defined as the "cognitive and behavioral efforts to manage specific external or internal demands that are appraised as taxing or exceeding the resources of a person."[56] Although coping strategies do not necessarily affect the disease process itself, the use of coping strategies can decrease the extent of disease-related emotional, social, and physiologic distress. Coping has been shown to be an important determinant of outcomes in a number of chronic diseases, including rheumatoid arthritis and sickle cell disease. The relationship between coping and outcome in patients with IBD, however, is variable. A systemic review of all published literature regarding coping strategies of IBD patients found no consistent relationship between coping and psychological outcomes. There was, however, a trend toward better outcomes with problem-focused coping (ie, to alter or eliminate the source of stress) compared with emotion-focused coping (aims to reduce the emotional distress caused by the situation).[57] Not surprisingly, maladaptive behavior such as self-pitying, musing, social withdrawal, and feelings of helplessness contribute to a reduced QOL.[58]

IMPROVING QUALITY OF LIFE IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

The main psychosocial factors shown to improve QOL are summarized in **Table 3**.[51]

SUMMARY

IBD is a chronic, debilitating disease whose effects spread far beyond the gut. An illness that does not generally result in excess mortality, patients spend many years coping with their condition and its associated morbidity. Screening for the early signs of depression or anxiety and the initiation of pharmacologic or psychological treatment when appropriate can lead to improved functioning and positively impact the course of disease. HRQoL is a major outcome in patients with IBD and can be influenced by a myriad of factors. Factors that seem to have the greatest impact are social and emotional, not physical.[76] A multidisciplinary, evidence-based approach involving psychosocial and medical interventions is of paramount importance to provide optimal care in managing these patients.[77]

REFERENCES

1. Ananthakrishnan AN. Epidemiology and risk factors for IBD. Nat Rev Gastroenterol Hepatol 2015;12(4):205–17.
2. Schoultz M, Atherton I, Hubbard G, et al. Assessment of causal link between psychological factors and symptom exacerbation in inflammatory bowel disease: a protocol for systematic review of prospective cohort studies. Syst Rev 2013;2(1):8.
3. Ghosh S, Mitchell R. Impact of inflammatory bowel disease on quality of life: Results of the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) patient survey. J Crohns Colitis 2007;1(1):10–20.
4. Filipovic BR, Filipovic BF. Psychiatric comorbidity in the treatment of patients with inflammatory bowel disease. World J Gastroenterol 2014;20(13):3552.
5. Sajadinejad M, Asgari K, Molavi H, et al. Psychological issues in inflammatory bowel disease: an overview. Gastroenterol Res Pract 2012;2012:106502.
6. Mackner LM, Greenley RN, Szigethy E, et al. Psychosocial issues in pediatric inflammatory bowel disease: a clinical report of the North American Society for

Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2013;56(4):449.
7. Kurina L, Goldacre M, Yeates D, et al. Depression and anxiety in people with inflammatory bowel disease. J Epidemiol Community Health 2001;55(10):716–20.
8. Lerebours E, Gower-Rousseau C, Merle V, et al. Stressful life events as a risk factor for inflammatory bowel disease onset: a population-based case–control study. Am J Gastroenterol 2007;102(1):122–31.
9. Fuller-Thomson E, Sulman J. Depression and inflammatory bowel disease: findings from two nationally representative Canadian surveys. Inflamm Bowel Dis 2006;12(8):697–707.
10. Graff LA, Walker JR, Bernstein CN. Depression and anxiety in inflammatory bowel disease: a review of comorbidity and management. Inflamm Bowel Dis 2009;15(7):1105–18.
11. Association AP. Diagnostic and statistical manual of mental disorders, (DSM-5®). American Psychiatric Pub; 2013.
12. Rosenkranz MA. Substance P at the nexus of mind and body in chronic inflammation and affective disorders. Psychol Bull 2007;133(6):1007.
13. Häuser W, Moser G, Klose P, et al. Psychosocial issues in evidence-based guidelines on inflammatory bowel diseases: a review. World J Gastroenterol 2014;20(13):3663.
14. Angelopoulos N, Mantas C, Dalekos G, et al. Psychiatric factors in patients with ulcerative colitis according to disease activity. Eur J Psychiatry 1996;10(2):87–99.
15. Mikocka-Walus AA, Turnbull DA, Moulding NT, et al. Does psychological status influence clinical outcomes in patients with inflammatory bowel disease (IBD) and other chronic gastroenterological diseases: an observational cohort prospective study. Biopsychosoc Med 2008;2:11.
16. Mardini HE, Kip KE, Wilson JW. Crohn's disease: a two-year prospective study of the association between psychological distress and disease activity. Dig Dis Sci 2004;49(3):492–7.
17. 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(1):79–84.
18. Panara A, Yarur A, 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):802–10.
19. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. Psychol Bull 2014;140(3):774.
20. 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(1):31–41.
21. Horst S, Chao A, Rosen M, et al. Treatment with immunosuppressive therapy may improve depressive symptoms in patients with inflammatory bowel disease. Dig Dis Sci 2014;60(2):465–70.
22. Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. Biol Psychiatry 2010;67(5):446–57.
23. Liu Y, Ho RC-M, Mak A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. J Affect Disord 2012;139(3):230–9.
24. Hannestad J, DellaGioia N, Bloch M. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. Neuropsychopharmacology 2011;36(12):2452–9.

25. Bonaccorso S, Puzella A, Marino V, et al. Immunotherapy with interferon-alpha in patients affected by chronic hepatitis C induces an intercorrelated stimulation of the cytokine network and an increase in depressive and anxiety symptoms. Psychiatry Res 2001;105(1):45–55.
26. Krishnadas R, Cavanagh J. Depression: an inflammatory illness? Journal of Neurology. Neurosurg Psychiatry 2012;83(5):495–502.
27. Aghazadeh R, Zali MR, Bahari A, et al. Inflammatory bowel disease in Iran: a review of 457 cases. J Gastroenterol Hepatol 2005;20(11):1691–5.
28. Wagtmans M, Verspaget H, Lamers C, et al. Crohn's disease in the elderly: a comparison with young adults. J Clin Gastroenterol 1998;27(2):129–33.
29. Srinath AI, Goyal A, Zimmerman LA, et al. Predictors of abdominal pain in depressed pediatric inflammatory bowel disease patients. Inflamm Bowel Dis 2014;20(8):1329–40.
30. Mayer EA, Tillisch K. The brain-gut axis in abdominal pain syndromes. Annu Rev Med 2011;62:381–96.
31. Zimmerman LA, Srinath AI, Goyal A, et al. The overlap of functional abdominal pain in pediatric Crohn's disease. Inflamm Bowel Dis 2013;19(4):826–31.
32. Lewis DA, Smith RE. Steroid-induced psychiatric syndromes: a report of 14 cases and a review of the literature. J Affect Disord 1983;5(4):319–32.
33. Fardet L, Kassar A, Cabane J, et al. Corticosteroid-induced adverse events in adults. Drug Saf 2007;30(10):861–81.
34. Means-Christensen AJ, Sherbourne CD, Roy-Byrne PP, et al. Using five questions to screen for five common mental disorders in primary care: diagnostic accuracy of the Anxiety and Depression Detector. Gen Hosp Psychiatry 2006;28(2):108–18.
35. Mikocka-Walus AA, Turnbull DA, Moulding NT, et al. "It doesn't do any harm, but patients feel better": a qualitative exploratory study on gastroenterologists' perspectives on the role of antidepressants in inflammatory bowel disease. BMC Gastroenterol 2007;7:38.
36. Mikocka-Walus AA, Gordon AL, Stewart BJ, et al. A magic pill? A qualitative analysis of patients' views on the role of antidepressant therapy in inflammatory bowel disease (IBD). BMC Gastroenterol 2012;12:93.
37. Goodhand JR, Greig FI, Koodun Y, et al. Do antidepressants influence the disease course in inflammatory bowel disease? A retrospective case-matched observational study. Inflamm Bowel Dis 2012;18(7):1232–9.
38. Szigethy E, Whitton SW, Levy-Warren A, et al. Cognitive-behavioral therapy for depression in adolescents with inflammatory bowel disease: a pilot study. J Am Acad Child Adolesc Psychiatry 2004;43(12):1469–77.
39. Szigethy E, Youk AO, Gonzalez-Heydrich J, et al. Effect of 2 Psychotherapies on Depression and Disease Activity in Pediatric Crohn's Disease. Inflamm Bowel Dis 2015;21(6):1321–8.
40. Díaz Sibaja MA, Comeche Moreno MI, Mas Hesse B. [Protocolized cognitive-behavioural group therapy for inflammatory bowel disease]. Rev Esp Enferm Dig 2007;99(10):593–8.
41. Timmer A, Preiss JC, Motschall E, et al. Psychological interventions for treatment of inflammatory bowel disease. Cochrane Database Syst Rev 2011;(2):CD006913.
42. Tabibian A, Tabibian JH, Beckman LJ, et al. Predictors of health-related quality of life and adherence in Crohn's disease and ulcerative colitis: implications for clinical management. Dig Dis Sci 2015;60(5):1366–74.
43. Robinson A. Review article: improving adherence to medication in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2008;27(s1):9–14.

44. Gradus JL, Qin P, Lincoln AK, et al. Inflammatory bowel disease and completed suicide in Danish adults. Inflamm Bowel Dis 2010;16(12):2158–61.
45. Gibson PR, Weston AR, Shann A, et al. Relationship between disease severity, quality of life and health-care resource use in a cross-section of Australian patients with Crohn's disease. J Gastroenterol Hepatol 2007;22(8):1306–12.
46. Alrubaiy L, Rikaby I, Dodds P, et al. Systematic review of the health related quality of life (HRQoL) measures for inflammatory bowel disease. J Crohns Colitis 2015; 9(3):284–92.
47. Lonnfors S, Vermeire S, Greco M, et al. IBD and health-related quality of life – discovering the true impact. J Crohns Colitis 2014;8(10):1281–6.
48. Larsson K, Lööf L, Rönnblom A, et al. Quality of life for patients with exacerbation in inflammatory bowel disease and how they cope with disease activity. J Psychosom Res 2008;64(2):139–48.
49. Nordin K, Påhlman L, Larsson K, et al. Health-related quality of life and psychological distress in a population-based sample of Swedish patients with inflammatory bowel disease. Scand J Gastroenterol 2002;37(4):450–7.
50. Bernklev T, Jahnsen J, Schulz T, et al. Course of disease, drug treatment and health-related quality of life in patients with inflammatory bowel disease 5 years after initial diagnosis. Eur J Gastroenterol Hepatol 2005;17(10):1037–45.
51. Karwowski CA, Keljo D, Szigethy E. Strategies to improve quality of life in adolescents with inflammatory bowel disease. Inflamm Bowel Dis 2009;15(11):1755–64.
52. Wright EK, Kamm MA. Impact of drug therapy and surgery on quality of life in Crohn's disease: a systematic review. Anxiety 2014;63:66.
53. Moradkhani A, Beckman LJ, Tabibian JH. Health-related quality of life in inflammatory bowel disease: psychosocial, clinical, socioeconomic, and demographic predictors. J Crohns Colitis 2013;7(6):467–73.
54. van der Have M, van der Aalst KS, Kaptein AA, et al. Determinants of health-related quality of life in Crohn's disease: A systematic review and meta-analysis. J Crohns Colitis 2014;8(2):93–106.
55. Israeli E, Graff LA, Clara I, et al. Low prevalence of disability among patients with inflammatory bowel diseases a decade after diagnosis. Clin Gastroenterol Hepatol 2014;12(8):1330–7.e2.
56. Folkman S. Stress, appraisal, and coping. New York: Springer Publishing Company LLC; 1984.
57. McCombie AM, Mulder RT, Gearry RB. How IBD patients cope with IBD: a systematic review. J Crohns Colitis 2013;7(2):89–106.
58. Mussell M, Böcker U, Nagel N, et al. Predictors of disease-related concerns and other aspects of health-related quality of life in outpatients with inflammatory bowel disease. Eur J Gastroenterol Hepatol 2004;16(12):1273–80.
59. Moser G, Tillinger W, Sachs G, et al. Disease-related worries and concerns: a study on out-patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol 1995;7(9):853–8.
60. Waters BM, Jensen L, Fedorak RN. Effects of formal education for patients with inflammatory bowel disease: a randomized controlled trial. Can J Gastroenterol 2005;19(4):235–44.
61. Kennedy A, Nelson E, Reeves D, et al. A randomised controlled trial to assess the effectiveness and cost of a patient orientated self management approach to chronic inflammatory bowel disease. Gut 2004;53(11):1639–45.
62. Ng V, Millard W, Lebrun C, et al. Low-intensity exercise improves quality of life in patients with Crohn's disease. Clin J Sport Med 2007;17(5):384–8.

63. Ranjbaran Z, Keefer L, Farhadi A, et al. Impact of sleep disturbances in inflammatory bowel disease. J Gastroenterol Hepatol 2007;22(11):1748–53.
64. Ananthakrishnan AN, Long MD, Martin CF, et al. Sleep disturbance and risk of active disease in patients with Crohn's disease and ulcerative colitis. Clin Gastroenterol Hepatol 2013;11(8):965–71.
65. von Wietersheim J, Kessler H. Psychotherapy with chronic inflammatory bowel disease patients: a review. Inflamm Bowel Dis 2006;12(12):1175–84.
66. Jantschek G, Zeitz M, Pritsch M, et al. Effect of psychotherapy on the course of Crohn's disease: results of the German prospective multicenter psychotherapy treatment study on Crohn's disease. Scand J Gastroenterol 1998;33(12): 1289–96.
67. Miller V, Whorwell PJ. Treatment of inflammatory bowel disease: a role for hypnotherapy? Int J Clin Exp Hypn 2008;56(3):306–17.
68. Mawdsley JE, Jenkins DG, Macey MG, et al. The effect of hypnosis on systemic and rectal mucosal measures of inflammation in ulcerative colitis. Am J Gastroenterol 2008;103(6):1460–9.
69. Drossman DA, Patrick DL, Mitchell CM, et al. Health-related quality of life in inflammatory bowel disease. Dig Dis Sci 1989;34(9):1379–86.
70. Vogelaar L, Spijker AV, van der Woude CJ. The impact of biologics on health-related quality of life in patients with inflammatory bowel disease. Clin Exp Gastroenterol 2009;2:101.
71. Feagan BG, Reinisch W, Rutgeerts P, et al. The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. Am J Gastroenterol 2007;102(4):794–802.
72. Loftus EV, Feagan BG, Colombel J-F, 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):3132–41.
73. Rutgeerts P, Schreiber S, Feagan B, et al. Certolizumab pegol, a monthly subcutaneously administered Fc-free anti-TNFα, improves health-related quality of life in patients with moderate to severe Crohn's disease. Int J Colorectal Dis 2008; 23(3):289–96.
74. Feagan BG, Sandborn WJ, Hass S, et al. Health-related quality of life during natalizumab maintenance therapy for Crohn's disease. Am J Gastroenterol 2007;102(12):2737–46.
75. Kane S. Systematic review: adherence issues in the treatment of ulcerative colitis. Aliment Pharmacol Ther 2006;23(5):577–85.
76. Han S-W, Gregory W, Nylander D, et al. The SIBDQ: further validation in ulcerative colitis patients. Am J Gastroenterol 2000;95(1):145–51.
77. Panés J, O'Connor M, Peyrin-Biroulet L, et al. Improving quality of care in inflammatory bowel disease: what changes can be made today? J Crohns Colitis 2014;8(9):919–26.