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TOPIC HIGHLIGHT

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Psychiatric comorbidity in the treatment of patients with inflammatory bowel disease

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Abstract

Ulcerative colitis and Crohn's disease, commonly known as inflammatory bowel disease (IBD), draw attention from specialists of various disorders, including gastroenterology, psychiatry, and radiology. The involvement of a cortical influence in the brain-gut axis as well as the interaction of the hypothalamic-pituitary-adrenal axis and the peripheral nervous system provide an initial explanation of the psychological symptoms associated with IBD. The involvement of structures the limbic system, such as the anterior cingulate cortex, the prefrontal cortex, and the amygdala, paves the way for the discovery of the mechanisms underlying depression depression, anxiety, alexithymia, personality traits, and other psychological impairments following the onset of IBD. Psychiatric therapy in IBD patients is almost as important as the gastroenterological approach and consists of pharmacological treatment and psychotherapy. Neither of the available psychiatric treatment methods is considered the golden standard because both methods have side effects, and psychotropic medication can provoke the worsening of IBD symptoms. Thus, both approaches must be applied with awareness of the possibility of side effects. We suggest that psychiatrists and gastroenterologists work together to reach a consensus on IBD therapy to ensure success and to reduce side effects and relapse to the lowest possible rates.

Key words: Inflammatory bowel disease; Psychiatry; Treatment; Personality traits; Depression; Anxiety

Core tip: The involvement of a dysfunction of brain-gut interactions in the pathogenesis of inflammatory bowel disease (IBD) is represented by a dysfunction of the autonomic nervous system, an abnormal hypothalamic-pituitary-adrenal axis and cholinergic anti-inflammatory pathway, a deleterious effect of stress and depression, an abnormal coupling of the prefrontal cortex-amygdaloid complex, and an abnormal relation between the microbiota and the brain as pro-inflammatory factors. New investigations have provided a critical link between forebrain changes and abdominal pain independent of active disease and drug treatment, providing a potential basis for an explanation of the psychological symptoms and brain influence in the pathogenesis of IBD.

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ANATOMICAL BASIS FOR THE PSYCHIATRIC CHANGES IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) results from an inap-

propriate inflammatory response to intestinal microbes in a genetically susceptible host. In recent reports, authors[1,2] have discussed the involvement of a dysfunction of brain-gut interactions in the pathogenesis of IBD as represented by a dysfunction of the autonomic nervous system, an abnormal hypothalamic - pituitary - adrenal axis and cholinergic anti-inflammatory pathway, a deleterious effect of stress and depression as well as an abnormal coupling of the prefrontal cortex-amygdaloid complex and an abnormal relation between the microbiota and the brain as pro-inflammatory factors. The New investigations have provided a critical link between forebrain changes and abdominal pain independent of active disease and drug treatment because all patients examined in the morphometric evaluation were in remission and suffered from ongoing abdominal pain. Investigators observed decreased gray matter volumes in the dorsolateral prefrontal cortex and the anterior midcingulate cortex (aMCC), and the disease duration was negatively correlated with volumes in the subgenual anterior cingulate (sACC), the posterior MCC (pMCC), the ventral posterior cingulate (vPCC), and the parahippocampal cortices. The aMCC has a role in feedback-mediated decision making, and specific cognitive tasks that differentiate the aMCC and pMCC can be used to evaluate defects in Crohn's disease (CD). The sACC is an important area because it has impaired functions in major depression. Because depressive symptoms are a feature in a subset of patients with active inflammatory diseases, including IBD, treatment targeting this subregion should prove efficacious. Finally, the vPCC has a role in ongoing self-monitoring of the personal relevance of sensory stimuli, including visceral signals *via* the sACC. This pathway may be interrupted by vPCC atrophy in CD. Cingulate atrophy in CD requires the targeting of chronic pain and psychiatric symptom therapies *via* neuronal circles involved in the cingulum. These therapies include psychotherapy, guided imagery and relaxation training, analgesic dosages of morphine or antidepressants, and hypnosis. Thus, a new generation of novel treatments may emerge from drug and non-traditional therapies for CD in this formative area of research[3,4]. Nevertheless, a certain level of caution should remain: the same areas have been found to be susceptible to changes in temporal epilepsy[5], and it remains unclear whether the volume alterations in these areas are specific to IBD or if they overlap with other diseases.

The white matter is not spared from damage in IBD patients. The number of such lesions is significantly higher in IBD patients compared to controls (12.75 ± 19.78 *vs* 3.20 ± 2.90, $P < 0.05$). However, there are no significant differences between UC and Crohn's disease patients with regard to magnetic resonance imaging (MRI) findings. In addition, the incidence of white matter lesions and other brain parenchymal lesions, sinusitis, and otitis-mastoiditis does not differ significantly with disease activity ($P > 0.05$ for all)[6].

Scheid *et al*[7] (2007) proposed the following three possible mechanisms for peripheral and central nervous system involvement in ulcerative colitis (UC): cerebrovascular conditions due to thromboembolic events, systemic and cerebral vasculitis, and neuropathy and cerebral demyelination due to immune-related mechanisms. In contrast, white matter lesion is a frequent finding in patients with IBD on MRI, and the development of these lesions has been attributed to ischemic mechanisms (atherosclerotic or vasculitic) or demyelination[8-10]. Thus, early identification of these lesions may be clinically helpful as an early indication of neurological involvement because they may represent another extra intestinal manifestation of the disease[10].

Studies performed by functional magnetic resonance imaging for both, patients and control subjects suffering from irritable bowel syndrome, which is also a psychosomatic disease, and control subjects, rectal distention stimulation increased the activity of the anterior cingulate cortex (number of positive answers to the stimulation/total number of patients: 35/37), the insular cortex (37/37), the prefrontal cortex (37/37), and the thalamus (35/37) in most cases. In patients with inflammatory bowel sydrome (IBS), the average percentage area of regions of interest increased in parallel with rectal distention volumes in the insular cortex, the prefrontal cortex, and the thalamic region. However, only the prefrontal cortex was statistically significant ($P < 0.05$). In controls, this tendency to increase only occurred in the anterior cingulate cortex. At 120 mL rectal distention, the average percentage area of regions of interest (ROI) and the average percentage change in MR signal intensity of ROIs in the insular cortex, the prefrontal cortex, and the thalamic region were significantly greater in patients with IBS than in control subjects[11,12].

PSYCHOLOGICAL SYMPTOMS IN IBD

There is consistent evidence that psychological factors play a role in the pathophysiology and the course of IBD and in how patients cope with IBD[12]. One prospective study in a population-based cohort of individuals with IBD ($n = 552$) evaluated whether the presence of a stressful event and the perception of stress as well as other factors (*i.e.*, nonsteroidal anti-inflammatory drugs, antibiotics, or infections) believed to contribute to triggering flares of IBD were, in fact, associated with symptomatic flares[13]. Subjects completed surveys on health issues every 3 mo for 1 year. In any 3-mo period, approximately 50% of subjects experienced some type of stress, and the majority of subjects reported the stresses were everyday life stresses. Family stress was the most commonly reported stress, followed by work or school and financial stress. Subjects were grouped by disease activity over time. Significantly more individuals in the persistently inactive disease group indicated they experienced no stressful events compared with individuals in the persistently active disease group. In terms of the association between variables experienced in one 3-mo period and a symptomatic flare in the next 3-mo period, only psychological factors, including the occurrence of a major life event, high perceived stress, and high negative mood during a previous 3-mo period, were significantly

associated with the subsequent occurrence of a flare. This study complements the growing evidence from experimental as well as clinical studies that stress exposure, including stressful events and perceived stress (the individual's view of his or her own level of demand relative to resources), may contribute to relapse risk in IBD[14-18]. In fact, using multivariate logistic regression analyses of these variables, only high perceived stress (adjusted OR = 2.40; 95%CI: 1.35-4.26) was associated with an increased risk of flare. This finding speaks to the bidirectional relationship between stress and symptomatic disease. Being symptomatic may exacerbate or even incite stress, whereas being stressed may trigger symptomatic disease. Recent reports have shown that brain derived neurotrophic factor (BDNF) levels are highly dynamic in response to stress. BDNF levels not only vary across brain regions but also fluctuate rapidly, both immediately after a stressor and over the course of a chronic stress paradigm. However, BDNF alone is not sufficient to effect many of the changes observed after stress. Glucocorticoids and other molecules have been shown to act in conjunction with BDNF to facilitate both the morphological and molecular changes that occur, particularly changes in spine density and gene expression[19].

Although discrete personality traits have been studied in IBD patients, no specific personality type matches this disease. It is recommended that future research consider the discrete personality traits observed in these patients and integrate them in such a way that the traits will be addressed to include new personality types, such as types C and D[20,21], which are well matched with the unregulated immune and hormonal systems that are characteristics of IBD. Type C individuals are introverted, perfectionistic, sensitive, and thoughtful. Individuals with a type D personality have the tendency to experience increased negative emotions across time and situations and tend to not share these emotions with others because of a fear of rejection or disapproval. It is believed that depression and anxiety are dominant in patients with IBD[22]. These patients also have a higher prevalence of anxiety and depressive disorders than the general population but a lower prevalence of these disorders than patients with a functional bowel disorder. The prevalence (21%-35%) is similar to that found in other patients with chronic physical illness. Depressive disorder appears to be more common in older patients and individuals with a previous history of a psychiatric disorder[23,24]. Patients suffering from IBD take more medications than the healthy population: the use of antidepressants (OR = 1.44, 95%CI: 1.28-1.61), anxiolytics (OR = 1.52, 95%CI: 1.31-1.78), oral bisphosphonates (OR = 6.08, 95%CI: 4.56-8.11), cardiovascular medications (OR = 1.38, 95%CI: 1.24-1.54), antibiotics (OR = 4.01, 95%CI: 3.57-4.51), proton pump inhibitors (OR = 3.90, 95%CI: 3.48-4.36), and nonsteroidal anti-inflammatory analgesics (OR = 1.17, 95%CI: 1.07-1.28) is significantly more common in IBD patients than in controls. Individuals who use antidepressants, anxiolytics, or analgesics have significantly impaired health-rated quality of life (HRQOL) ($P < 0.001$)[25].

Both depression and anxiety precede ulcerative colitis significantly more often than would be predicted from the control population's experience[24]. The association is strongest when the two psychiatric disorders and ulcerative colitis are diagnosed in the same year, although the association between depression and ulcerative colitis is also significant when depression precedes ulcerative colitis by five or more years. Neither depression nor anxiety precedes Crohn's disease more often than expected by chance, although the study involved fewer cases with Crohn's disease than ulcerative colitis. Two prospective clinical studies of patients with IBD appear to produce conflicting results. During a 6-mo follow-up period, one study found a strong association between the change in disease activity and anxiety level and a weaker association with depressive symptoms. Changes in disease activity seemed to lead to changes in anxiety and depression. Beck Depression Inventory scores at baseline predicted the number and timing of relapses during an 18-mo follow-up period[26,27].

Nevertheless, the origin of depression and anxiety in patients with IBD remains at least insufficiently explained. In a review of psychotherapeutic approaches to IBD, Prasko *et al*[28] (2010) emphasized that higher scores of neuroticism, depression, inhibition, and emotional instability are typical for many patients with chronic diseases and nonspecific for chronic gastroenterological disorders. More directly, anxiety and depression are consequences of IBD symptoms, such as frequent stools with evidence of blood, pain in the abdominal region, and bloating.

Because anxiety and mood disorders are the most common mental health concerns in the community, these disorders are usually the focus of screening efforts. The typical symptoms of anxiety disorders include high levels of physiological arousal, excessive worries about the future, avoidance of feared situations (including, in some cases, medical appointments and procedures)[29,30], and difficulty coping with unfamiliar situations. Depression typically presents with a constellation of affective, cognitive, and somatic symptoms, including a sad or depressed mood; a loss of interest in normal activities; feelings of guilt, worthlessness, or hopelessness; difficulties with concentration; reduced energy; changes in appetite and sleep; and withdrawal from usual activities. When these clusters of symptoms persist beyond a few weeks and begin to significantly interfere with daily functioning, they are typically considered to reach a clinical threshold[31]. The incidence of IBD in adolescents has been reported to be an increasing trend, especially in the Northern parts of Europe (Finland, Schotland)[32-34]. According to parent reports, adolescents with IBD have more emotional, social, and thought problems and lower competence than their healthy peers[35]. The disease disturbs adolescents' quality of life[25,36,37], may have negative consequences for education and school functioning[38,39], and may be a cause of difficulties in employment, such as finding or maintaining a desired job[40-42]. Furthermore, adolescents with severe IBD have disturbed sleep and are overtired

more often than their healthy peers[43].

Some studies have shown alexithymia to be another common personality characteristic in IBD patients. Patients with alexithymia have difficulties in recognizing and verbalizing emotions, and their ability to regulate emotions and express them to others is usually reduced[44,45]. Numerous studies[46-50] have shown that IBD patients have higher scores for alexithymia than controls. In a study conducted by Jones *et al*[46] (2006), the scores of 74 IBS patients, 55 healthy control subjects, and 48 IBD patients were compared on the Toronto Alexithymia Scale. The results showed that IBS and IBD patients had higher scores on measures of alexithymia than the controls, but they did not differ from one another. In an epidemiological study, Porcelli *et al*[50] (1999) compared 121 functional gastrointestinal disorder patients, 116 IBD patients, and a group of 112 healthy subjects using the Toronto Alexithymia Scale. Their results showed that the FGID group was significantly more alexithymic than the IBD group, and the scores of the two gastrointestinal groups were higher than the normal healthy group. Even after controlling for the influence of education, gender, anxiety, depression, and gastrointestinal symptoms, these differences remained significant. Moreno-Jiménez *et al*[47] (2007) did not use a control group. In their sample comprising 60 UC and 60 CD patients, they attempted to address the question of which personality factors may predict HRQOL in IBD patients. They showed that difficulty in describing one's feelings was significant for predicting two dimensions of HRQOL, systemic symptoms and social functioning. Difficulty in describing one's feelings negatively predicted systemic symptoms and social functioning. Patients experiencing more difficulty in describing their feelings reported lower HRQOL. Although alexithymia may not be specific to IBD, it may lead patients to communicate their psychological distress through somatic and behavioral symptoms rather than verbal communication. This may occur particularly when patients have limited perceived social support or personality traits such as introversion. Regardless of whether alexithymia is specific to IBD, it has been reported that affected patients have greater difficulty in describing their feelings to others, poorer disease outcome, lower psychological functioning, and worse HRQOL[12,47,51].

Adolescents with IBD have mild cognitive problems compared to the same population with juvenile idiopathic arthritis, particularly in the acute phase. Adolescent patients with IBD produced more perseverative errors than patients with non-acute juvenile idiopathic arthritis. Perseveration in the California Verbal Learning Test may be related to a momentary loss of alertness in the tiresome and long verbal memory test. However, no other differences in cognitive functioning between the study groups were detected. These findings indicate that adolescents with active IBD may have some mild problems in verbal memory but no major cognitive deficits. Prior studies in adults with IBD found deficits, particularly in verbal functioning, suggesting that in the clinical evaluation of young patients with IBD, it may be relevant to pay attention to even minor cognitive problems that may be aggravated during the growth process[43,52,53].

PSYCHIATRIC THERAPY IN IBD

Psychiatric treatment of patients with IBD involves two types of approaches: (1) psychotropic medication; (2) psychotherapy; and (3) psychotropic medication.

Anxiety and depression, the most common psychiatric symptoms in IBD patients, are highly treatable conditions. The interventions that are the most widely used and have been evaluated the most extensively for anxiety and depressive disorders are specific pharmacological agents [particularly selective serotonin reuptake inhibitors (SSRIs), such as citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline, and the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine] and specific psychological treatments (particularly cognitive behavioral therapies). The SSRI and SNRI medications are second-generation antidepressants that have been well established in the literature as being similarly effective for anxiety and depression[54].

In humans, it has been observed that although antidepressants improve both the mental and somatic status of IBD patients, the low quality of available research provides significant barriers to making a definitive statement on their efficacy or lack thereof[55]. Animal models, however, have found a positive impact of desipramine and fluoxetine on inflammation in models of IBD. When doctors' perspectives on antidepressants in IBD were examined, it was reported that gastroenterologists commonly treat IBD patients with antidepressants for pain, anxiety and/or depression, and insomnia. Gastroenterologists reported that antidepressants were successful in reducing pain, gut irritability, and urgency of defecation. In the most recent retrospective case-note audit of 287 patients, 83 (28.9%) patients had used an antidepressant at some time in their life[56-59]. Nonetheless, the design of the study does not allow a firm statement to be made about whether antidepressants improved the course of IBD. The recent study in this area conducted by Goodhand *et al*[60] (2012), which examined the disease course one year before and one year after the commencement of antidepressants, showed that patients reported fewer relapses and steroid treatment in the year after starting an antidepressant than in the year before. This effect was not observed in the control group. Although this report of decreased symptoms may simply reflect the report of fewer functional gastrointestinal symptoms when patients are in better psychological health[61,62], it may also indicate an inflammation-specific benefit from antidepressants. Thus, it is clear that randomized controlled trials are justified and needed to provide a definitive answer regarding the efficacy of antidepressants in IBD.

Amitriptyline is an antidepressant drug that is widely used for the treatment of IBD and gastrointestinal disorders[55,63]. It is effective for treating psychological and somatic symptoms in patients suffering from IBD[55]. Other studies have shown the anti-inflammatory effects

of antidepressants by different mechanisms[64,65]. Amitriptyline also acts on α1-adrenoceptors to produce anti-inflammatory effects[64]. Due to its effects on the inhibitory cytokine interleukin-10, amitriptyline has been reported to suppress neuroinflammation[66]. Furthermore, antidepressants have anti-inflammatory effects by considerably decreasing the production of nitric oxide (NO) and umor necrosis factor-alpha (TNFα) in microglia and astrocyte cultures at mRNA levels[65]. They can inhibit the degradation of IκB, the nuclear translocation of the p65 subunit of NF-κB. Therefore, NF-κB cannot transmigrate into the nucleus to bind with DNA to promote the expression of gene regions[66]. Antidepressants can also inhibit the phosphorylation of p38 mitogen-activated protein kinase in lipopolysaccharide-stimulated microglia cells[65]. This phosphorylation can induce the associated inflammatory gene expression to produce the proinflammatory cytokines and NO, which may be attenuated or inhibited by antidepressants[66]. NO can also induce ROS; therefore, it can increase intestinal damage and, with cytokine production, prolong the development of IBD. Based on these studies, the NF-κB pathway has been considered to play an important role in the inflammatory process. Therefore, investigators have hypothesized that the antidepressant-like effects of amitriptyline, *via* the modulation of this pathway, may be more effective for treating and suppressing the development of IBD through its anti-inflammatory actions[67].

Some authors have argued that antidepressants may, in fact, cause tolerance and present problems when tapering off medications[68,69]. Significant numbers of patients no longer need an antidepressant for their mental health problems, yet they suffer unbearable withdrawal effects when discontinuing the medication and thus remain on the treatment[58]. Patients participating in a study by Mikocka-Walus *et al*[58] (2012) reported antidepressants to be a medication worth recommending to fellow IBD sufferers as long as the decision for their use was taken into consideration. Although studies exploring attitudes toward antidepressant use in larger samples or in samples recruited in primary care (and thus with possibly better-controlled IBD) are not available, studies conducted in the general population in primary care have shown a less receptive attitude toward antidepressants. For example, a survey of 1054 primary care users showed that over 20% of individuals did not disclose depressive symptoms to their doctors due to fear that antidepressants would be prescribed[70]. Other studies have reported non-adherence to treatment with antidepressants due to patient beliefs or misconceptions about this type of medication[71,72]. In light of these findings, the positive attitudes toward antidepressants identified in previous studies should be interpreted with caution and confirmed by larger quantitative studies with more representative IBD samples.

A systematic review of SSRIs indicated that although the medications were similar in efficacy, there were meaningful differences in their side effect profiles. These differences may guide decisions concerning the best choice for a particular patient[73]. Nevertheless, studies report serious adverse effects of selective serotonin reuptake drugs. Gastrointestinal side effects can be of particular concern to the IBD patient and have been reported for many antidepressant medications. These side effects are generally dose related and tend to decrease over the first weeks of treatment[74]. Nausea and vomiting are more frequent with the one SNRI evaluated (venlafaxine) compared to the SSRIs as a group (fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram; 34% *vs* 22%). Diarrhea is reported more often with sertraline than with the other SSRIs. Other side effects that have been cited as problematic when patients decide to discontinue antidepressant medication early in the course of treatment include drowsiness/fatigue (10%), anxiety (6%), headache (6%), insomnia (2.7%), and dizziness (2.7%)[75]. Weight gain has been found to be a more significant problem with paroxetine and mirtazapine[74], but it remains a concern with all SSRI medications[76]. In some cases, there may be weight loss early in treatment and weight gain later[74]. Decreased sexual functioning is a relatively common dose-related side effect of antidepressant medications and may be a concern for IBD patients, given the disease-related difficulties with intimacy and sexual functioning[77]. It has been found that 60% to 70% of patients report reduced sexual functioning on SSRIs or SNRIs that does not improve with longer periods on the medication. Buproprion has the lowest rates of sexual dysfunction relative to other antidepressants[76], and it is usually recommended as a substitute for SSRIs in case of side effects. Kast *et al*[78] (2001) reported two patients who achieved long-lasting remission of Crohn's disease while using bupropion. These investigators hypothesized that this outcome may have resulted from decreased TNFα, which is known to play a vital role in Crohn's disease. Phenelzine and bupropion increase intracellular cyclic adenosine mono phosphate[79], which, in turn, decreases TNFα. Because phenelzine may cause a hypertensive crisis, bupropion is suggested to be a safer therapeutic option than phenelzine. Interestingly, phenelzine and other monoamine oxidase inhibitors have been noted to induce remission of rheumatoid arthritis, a disease in which, as in Crohn' s disease, TNFα has a central role[80]. Kast[81] (2003) compared the use of bupropion and mirtazapine in patients with Crohn's disease. He speculated that both of these antidepressants have the potential to affect inflammatory responses: bupropion by lowering TNFα and mirtazapine by increasing its level. Therefore, according to the hypothesis of Kast[81] (2003), there are theoretical reasons for recommending bupropion and cautioning against mirtazapine when treating depression in patients with Crohn's disease. Although Kast's explanations appear logical and are supported by other investigators[82], their practical effectiveness needs to be experimentally confirmed in appropriate clinical studies[55].

With regard to the risk of severe side effects, recent reports have raised the possibility of a greater risk of upper gastrointestinal (GI) bleeds with the use of certain antidepressants[83-85]. Large-scale studies have found a moderately increased risk of GI bleeds with SSRIs as well as with

the SNRI venlafaxine[86-88]. The use of acid-suppressing agents mitigated the higher risk, whereas the use of non-steroidal anti-inflammatory drugs (NSAIDs) increased the risk[86]. The absolute risk of taking SSRIs was low, however; 2000 patients per year would need to be treated with SSRIs for one case of upper GI tract bleeding to be attributed to such drugs. The risk is higher when SSRIs and NSAIDs are taken together, with one patient in 250 experiencing a GI bleed that could be attributed to that combination[86].

PSYCHOTHERAPEUTIC APPROACH

The first study regarding the effectiveness of psychotherapy for ulcerative colitis was conducted half a century ago[89], but it was methodologically problematic. The effect of psychodynamic psychotherapy on patients with Crohn's disease was investigated in a randomized, multicenter study[90]. The psychotherapeutic intervention consisted of psychodynamic psychotherapy (26 sessions) and autogenic training (17 sessions). After 2 years, relapse was not experienced by 23% of the control group and 30% of the therapy group. Twenty-nine percent of the control group and 17% of the therapy group had to undergo surgery. The therapy group had better somatic data than the control group, but this was not significant. Nevertheless, a meta-analysis was necessary for this review article given that the authors analyzed a respectable number of investigations addressing the subject of interest, such as the use of psychotherapy in IBD patients[91,92]. Twenty-one studies were included in the analysis. Four studies did not report results in detail and could not be included in any of the pooled analyses. These 4 studies included a controlled trial on hypnosis in ulcerative colitis[93], a trial on the effects of a multicomponent behavioral therapy package in 22 patients with IBD[94], and a trial examining the effects of support meetings[95].

Given its chronic nature and frequently reported poor quality of life for many patients, IBD is often associated with anxiety and depression. In addition to medical treatment, psychological intervention may be a crucial component of the treatment of IBD patients[96,97]. Prior research has found that the disease course is gender dependent and that females may have a higher risk of disease activity relapse than males[22,98]. Therefore, females may have more psychological symptoms. Furthermore, females more frequently become ill from Crohn's disease. Second, patients are stratified by treatment center. A distinction must be made between an academic setting and a peripheral setting. We expect that an academic hospital would treat more severe cases of IBD than a peripheral setting. Finally, the disease type is also used as a stratification factor. Previous research has found that CD patients undergo more surgical interventions and experience more disease exacerbations than ulcerative colitis patients[99]. This finding indicates that CD is a more complex disorder than UC. In addition, CD patients report poorer quality of life and more anxiety symptoms than UC patients[99,100]. Therefore, it is important that UC and CD patients are distributed evenly in the experimental group and the waiting list control group[101]. Of all psychotherapeutic interventions, cognitive behavioral therapy appears to be the most effective[102]. This therapy posits that an individual's biased information processing leads to restrictive thoughts, feelings, and behaviors that can culminate in anxiety and depressive symptoms and, eventually, in psychiatric disorders. Cognitive behavioral therapy offers a well-developed intervention protocol that has been found to enhance quality of life and to decrease psychological distress. Its positive effect has been emphasized in individuals with other chronic somatic illnesses, such as chronic obstructive pulmonary disease, diabetes, and cancer[103,104].

Cognitive behavior therapy was evaluated in an open trial of adolescents with major depression[105,106] and a randomized controlled trial (RCT) of adolescents with subsyndromal depression[107]. In all studies, treatment significantly reduced depression and improved global functioning. For individuals with a comorbid anxiety disorder, there was also a significant reduction in anxiety. The open trial did not find any change in illness severity posttreatment. The RCT reported a decrease in the number of individuals with moderate to severe disease posttreatment (29% pre-treatment *vs* 15% post-treatment), but the decrease was not significant. In an RCT of adults with IBD, a Spanish group reported clinically significant reductions in anxiety and depression following a structured cognitive-behavior therapy program that included components such as relaxation training, distraction, and cognitive restructuring[108].

Reviews considering the overall effectiveness of psychological therapies for IBD patients not selected for anxiety or depressive disorders have reached a more modest conclusion: there may be some clinical benefit related to psychological functioning, with little support at this point for a significant direct impact on disease parameters[109-111]. These studies incorporated a broad range of treatments (*e.g.*, psychodynamic therapy, supportive therapy, and cognitive behavioral therapies), some of which are not as well supported empirically. Further, the studies often involved unselected IBD patients or patients in remission with little elevated distress[112,113], resulting in the potential for floor effects. Thus, unsurprisingly, psychological treatment is not indicated for all patients with IBD[114]. The results of well-conducted studies imply that validated treatments should be targeted to high-risk subgroups, such as individuals with comorbid psychiatric conditions or elevated stress[110,111]. Certainly, IBD patients may be quite susceptible to psychological treatment. Among individuals reporting high distress, there is a strong level of interest in receiving support for these concerns[115]. A structured measure of desire for psychological care comparing patients with IBD and rheumatoid arthritis found that 2 to 3 times the number of IBD patients (31%) expressed an interest in receiving assistance compared to individuals with rheumatoid arthritis (13%)[116]. Other indicators of receptivity included positive evaluations of treatment[113] and low dropout rates despite the expectation of active participation[104,106].

The appropriate choice of medication depends on many factors that are best tailored to the individual patient. Different galenic preparations are released at different sites and may have local activity [such as mesalazine (5-ASA) preparations, budesonide, or types of enemas]. The choice is influenced by the balance between drug potency and side effects, previous response to treatment (especially when considering treatment for a relapse or treatment for corticosteroid-dependent or corticosteroid-refractory disease), and the presence of extraintestinal manifestations (indicating the need for systemic therapy) or complications. Despite general agreement that treatment decisions for active Crohn's disease should be based on the site as well as the activity and behavior of the disease, the sample size is too small for statistically valid conclusions to be drawn from therapeutic trials when patients are stratified according to the site of disease[117].

For mildly active IBD, budesonide 9 mg/d is favored because it is superior to both placebo (OR = 2.85, 95%CI: 1.67-4.87)[118,119] and 5-ASA 4 g/d (OR = 2.8, 95%CI: 1.50-5.20)[120], and it achieves remission in 51%-60% of individuals over 8-10 wk[119,121-123]. Budesonide is preferred to prednisolone for mildly active CD because it is associated with fewer side effects, although a Cochrane systematic review has shown budesonide to be somewhat less effective than prednisolone (pooled OR for the five trials 0.69, 95%CI: 0.51-0.95)[119]. For corticosteroid-related adverse effects, budesonide showed no difference from the placebo (OR = 0.98, 95%CI: 0.58-1.67)[118,119] but had fewer side effects than prednisone (pooled OR = 0.38, 95%CI: 0.28-0.53).

When IBD is estimated as moderately active, budesonide or prednisolone are appropriate. Prednisolone is associated with a good clinical response (92% remission within seven weeks at a high dose of 1 mg/kg), but it commonly causes more side effects than budesonide[117,124,125]. The dose of prednisolone is adjusted to the therapeutic response over a period of weeks. More rapid reduction is associated with early relapse. The consensus does not favor sole nutritional therapy, antibiotics (unless septic complications are suspected), infliximab (IFX) (until more data are available), or surgery for moderately active ileal CD as the first line therapy[122].

Prednisolone or intravenous hydrocortisone is appropriate for the initial treatment of severe ileal CD. Azathioprine (AZA) (or mercaptopurine) should be added for individuals who have relapsed because it has a corticosteroid-sparing effect (NNT 3) and is effective at maintaining remission[126,127]. Methotrexate should be considered an appropriate alternative if thiopurines cannot be tolerated, but it has specific contraindications, such as pregnancy. IFX is best reserved for patients who do not respond to initial therapy and for whom surgery is considered inappropriate. This does not mean that surgery takes precedence over IFX. IFX has emerged as a conservative option for cases with severe inflammatory activity, and it is in these cases that primary surgery will often be inappropriate. Surgical options should, however, be considered and discussed with the patient as part of an overall management strategy. The stage at which IFX is introduced may change if it can be established whether early therapy changes the pattern of disease. The threshold for surgery for localized ileocecal disease is lower than for disease elsewhere, and some experts advocate surgery over IFX for disease in this location. Other experts advocate resection if medical therapy is not effective within two to six weeks. It may sometimes be difficult to distinguish between active disease and a septic complication, but antibiotics should be reserved for patients with a fever or focal tenderness or in whom imaging has indicated an abscess. Adding ciprofloxacin and metronidazole to budesonide has been shown to have no advantage over budesonide alone in active CD[127,128].

BIOLOGICAL THERAPY

Regular infusions of IFX 5 or 10 mg/kg every eight weeks are effective at maintaining an IFX-induced response in nonfistulating CD (EL1b). Patients in a scheduled treatment strategy with regular infusions of IFX seem to fare better in many (but not all) clinical end points compared with patients in an episodic (on-demand) strategy[129,130].

CONCLUSION

The psychopathological impact in IBD patients is evident, and the most common symptoms of depression and anxiety may affect the success of the desired gastroenterological therapy. Personality traits, cognitive impairment, and sleep deprivation are the tip of the iceberg of psychological problems in patients with IBD. The worsening of psychological problems is often followed with the same trend in GI symptoms of IBD and vice versa; that is, relapse of IBD symptomatology, such as blood in the stool, bloating, and pain, may increase psychological problems. This "vicious cycle" could be broken by involving a trained psychiatrist in the IBD treatment team. Nevertheless, some measures of precaution should be taken, such as avoiding bias in the group selection for both psychotropic medication and psychotherapy and an awareness of the possible side effects of antidepressant therapy, especially SSRIs, such as more frequent liquid stools, addiction, or sexual dysfunction problems. Finally, we suggest that psychiatrists and gastroenterologists work together to determine the final consensus of the IBD therapy to ensure success and to reduce side effects and relapse to the lowest possible rates.

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