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Depression and Its Treatment in IBD



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The prevalence of depression in inflammatory bowel disease (IBD) is double that in the general population. Mood disorders are more common in Crohn's disease than in ulcerative colitis and when patients' IBD is in relapse. The association between depression and IBD may not simply reflect a response to chronic gastrointestinal symptoms, since recent animal data suggest that intestinal inflammation may precipitate mood disorders by directly altering cerebral function. Whether depression has a detrimental effect on the course of IBD remains controversial. Conversely, while psychotherapy, antidepressants and other modalities can improve patients' psychological state, their effect on the natural history of IBD is not yet clear. Nevertheless, as part of holistic management of IBD, gastroenterologists should be alert to depression and other mood disturbances in their patients with IBD, and at the least establish prompt routes of referral to colleagues with expertise in the treatment of psychological disorders.

INTRODUCTION

Although the etiology of the inflammatory bowel diseases (IBD), Crohn's disease and ulcerative colitis (UC) has yet to be fully elucidated, it

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appears to involve a complex interaction between poorly defined environmental and genetically determined factors regulating mucosal tolerance to intestinal microflora. Historically IBD was classified as a psychosomatic disorder with early studies reporting a close association between IBD and psychiatric diagnoses. Recent studies have re-affirmed the high prevalence of depression and other types of psychological distress in patients with IBD, leading researchers to re-examine its role as an etiological factor and therapeutic target in IBD. Here, we review not only these topics, but also outline very recent evidence that mucosal inflammation may itself induce psychological disturbance.

WHAT IS DEPRESSION?

The diagnosis of depression is made by recognition of subjective core symptoms which include depressed mood, anhedonia (reduced ability to experience pleasure), irritability, difficulties in concentrating, and abnormalities in appetite and sleep. In addition to suicidal thoughts, depressed patients report reduced health-related quality of life and significant psychosocial disability (1). Depression is common, affecting in 1:6 of the population. Heritability, as in IBD, is estimated at about 40%, but genetic association studies, unlike in other chronic medical conditions including IBD, have failed to identify specific genetic risk variants (2). Environmental precipitant factors include stressful life events, chronic medical illness and the side effects of medications; however, most cases are idiopathic (1).

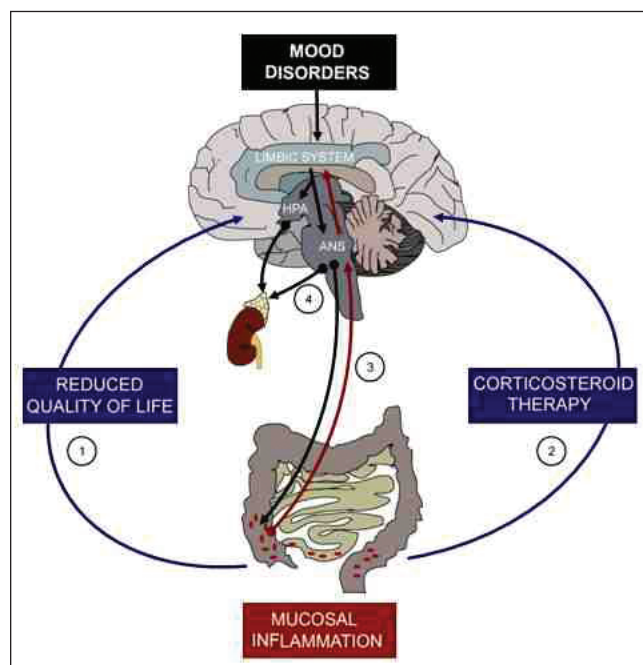


Figure 1. Interacting pathways between the brain and the gut. Factors potentially aggravating depression in patient's with active IBD include; reduced quality of life as a result of gastrointestinal symptoms (1), corticosteroid therapy (2) and vagal sensory inputs to the nucleus solitarius provoked by mucosal inflammation (3). Conversely, depression and other mood disorders may adversely affect gut inflammation via the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal axis (HPA) (4).

PREVALENCE OF DEPRESSION IN IBD

Unfortunately, many of the early studies examining the relationship between depression and IBD were designed sub-optimally. Few were prospective or defined the diagnosis, disease activity or extent of patients' IBD adequately. Outcome measures relied on self-reported symptom scores containing items that could be influenced by either psychological state or IBD activity (for example, well-being, fatigue, sleep disturbance, appetite and weight changes).

However, data from recent well-designed studies estimates the prevalence of depression in IBD at 25%–35%, double that of the healthy population and significantly greater than in other chronic inflammatory conditions, such as rheumatoid arthritis [for review see (3)]. Most studies suggest that psychological disorders are more common in Crohn's disease than UC. Although the heterogeneity of the studied populations does not allow direct comparison, depression and anxiety seem to be more prevalent during relapse of IBD. In support of this contention, in patients with Crohn's disease, depression sub-scores improved more in the treatment than placebo arms in controlled trials of infliximab (4) and adalimumab (5).

WHY IS DEPRESSION MORE COMMON IN IBD?

As indicated earlier, it is possible that the burden and chronicity of symptoms in IBD, particularly when it is active, causes a reactive depression in predisposed patients (Figure 1). Additionally, some of the medications used to treat IBD, can cause mood disturbances.

For example, short-term therapy with corticosteroids, especially in high dose, is often associated with euphoria and even hypomania; disturbances in sleep, cognition, and frank psychosis are also well recognized. Conversely, long-term "maintenance" therapy with steroids tends to induce depressive symptoms (6); fortunately, long-term use of these drugs in patients with IBD is now rarely necessary. Qualitative surveys suggest that patients taking immunosuppressants are more depressed and report worse quality of life scores than healthy controls. However, while thiopurines, methotrexate and biologics are not usually considered to cause mood disorders, neuropsychiatric disturbances including depression occasionally occur with cyclosporine.

Other reasons for an association between depression and IBD include the possibilities that, on the one hand, intestinal mucosal inflammation directly precipitates psychological distress (7), and, that, on the other, psychological disturbances intensify mucosal inflammation (8–10).

CAN IBD WORSEN DEPRESSION?

In an intriguing series of experiments, mice challenged with *Campylobacter jejuni* appeared more anxious and displayed less exploratory behavior than saline-treated controls. The mice did not show a serum inflammatory response, suggesting a direct non-humoral link from the gut to the brain. Immunohistochemical staining for the neuronal activation marker, c-fos, suggested that during the first six hours after infection the gut signals directly to the brain through vagal sensory fibres. Brain imaging studies confirmed activation of the nucleus solitarius, the site of termination of vagal afferents, as well as of the paraventricular hypothalamus, the amygdala and the bed of the stria terminalis, areas classically activated in mood disorders [for review see (7)].

CAN DEPRESSION WORSEN IBD?

Whether depression has a detrimental effect on the outcome of IBD, has been examined prospectively in two recent studies. The first study enrolled 47 patients with Crohn's disease and 13 with UC in remission and followed them up for 18 months. At baseline, depression was found in 28% of patients. Regression analysis showed a significant correlation between depression scores at baseline and the total number of relapses and the time until first relapse (11). In contrast, in a similar study comparing IBD, IBS and patients with chronic hepatitis C over a period of 12 months, no relationship was found between relapse and psychological status; active disease at recruitment was the only predictor of relapse (12). While the contradictory results of these studies are at first sight at variance with the increasing acceptance that psychological stress increases the risk of relapse in patients with IBD (8–10), it has to be remembered that perceived stress has a wide range of causes, of which depression is only one.

ROLE OF PSYCHOLOGICAL TREATMENT IN IBD

If depression and anxiety do have a significant impact on disease activity in IBD, then treatments directed primarily at the mood disorder could in theory prove a useful addition to the therapeutic armamentarium against IBD itself. Unfortunately, placebo-controlled studies using non-pharmacological psychological interventions are difficult to blind and published results are therefore hard to interpret. A lack of funding has meant that studies of pharmacological treatments are scarce. Lastly, the need to individualize psychological therapy according to the patient's specific requirements (Table 1), makes it hard to design or conduct trials using single treatment modalities of large groups of patients. Despite these limitations, several studies suggest that there may be a role for psychological therapies in patients with IBD.

Psychotherapy is an interpersonal relational intervention between patient and therapist that employs a range of techniques designed to improve coping mechanisms and thereby mental health (13). In a review of ten heterogeneous studies involving several types of psychotherapy (including cognitive behavioural therapy, counselling, and group therapy), this modality did not appear to affect the course of patients' IBD (14). In some cases, however, it did positively influence the patient's psychological state, improving depression, anxiety, health-related quality of life and their ability to cope. Patients with psychological problems, especially if pertaining to their IBD, or associated with maladaptive coping, might therefore benefit from a psychotherapeutic approach, although which type is not clear.

Anti-depressants are probably the most widely used treatment for depression but they are successful in relieving the psychological symptoms in only about 30% of patients (1,15).

Most gastroenterologists will have had experience in treating functional gastro-intestinal disorders with antidepressants. However, there is a paucity of studies to guide the use of such drugs in IBD. Data from a single open label study of paroxetine (20–40 mg) in eight depressed IBD patients reported a significant improvement in depression and social disability scores and an unspecified positive effect on IBD activity after eight weeks of treatment (16). At Digestive Disease Week in 2008, the results of a randomized controlled trial in

Table 1.

An approach to selecting the appropriate psychological treatment (adapted from Maunder, et al [25]) in patients with IBD. Interventions are selected according to the stage of adjustment and degree of psychological distress associated with IBD.

<i>Stage of adjustment to IBD</i>	<i>Psychological intervention</i>
Uncertainty about illness	Education, peer-counseling
Residual uncertainty	Supportive counseling
Distress	Relaxation, exercise, hypnosis, supportive psychotherapy, antidepressants
Suffering	Ensure IBD maximally treated, stress reduction, antidepressants

patients with ulcerative colitis using imipramine were presented. Unfortunately, the encouraging findings were compromised by several aspects of trial design, the most important of which was that clinical response was assessed using symptom scores depending heavily on bowel frequency (17).

Other approaches: Encouraging physical exercise is moderately effective in depression (18). Moderate but not severe exhaustive exercise is reported to improve well-being and possibly disease activity in patients with mild-moderately active IBD (19). Relaxation exercises are easy to learn and have been shown to ameliorate chronic pain in ulcerative colitis (20). Alternative therapies are used widely by patients with IBD and depression. In a recent trial of 84 depressed patients, depression scores were significantly improved and sustained over one year in a cohort of patients treated with hypnotherapy and cognitive behavioral therapy (CBT) compared with CBT alone (21). Hypnotherapy has an established role in patients with irritable bowel syndrome and experimentally reduces some measures of the inflammatory response systemically and in rectal mucosa in ulcerative colitis (22): whether relaxation-inducing gut-focused hypnosis is beneficial in IBD, and whether any response found is dependent on mood prior to treatment, awaits formal controlled evaluation. Social support and close networks with friends and family are associated with happiness (23) and conversely social isolation is linked with depression and poor health. Attempting to strengthen patients' exogenous coping resources by manipulating their social environment is extremely

difficult. Despite being unproven as a way of improving coping strategies and disease course, a supportive relationship between patients, whether in groups or as individuals, and their IBD team is likely to be important, as may be links with patient bodies such as the Crohn's and Colitis Foundation of America (CCFA).

CONCLUSIONS

Patients suffering with IBD vary dramatically in their psychological response to the illness: despite significant morbidity from their IBD, most are heroically resilient. For those who develop or already have associated depression, or other mood disturbances, management should be holistic. A recent qualitative survey using the ADAPT (Assessment of the Demand for Additional Treatment) questionnaire showed that a third of patients with IBD want psychological support (24), a demand which far exceeds supply in most countries. The reasons for the apparent under-provision of psychological support to patients with IBD are likely to include a failure by gastroenterologists to recognize concurrent mood disorders, a perceived lack of benefit from psychological treatments and in the UK at least, a shortage of health care funding.

It is clear therefore, that at the same time as optimizing conventional treatment of their IBD, physicians should look out for mood disorders and be ready and able to offer patients psychological treatment. At the very least, they should ensure that they have in place routes for prompt referral of their patients to colleagues with expertise in the management of psycho-

logical disorders. What remains unclear is which of the wide range of available interventions is most appropriate for individual patients with IBD who have associated psychological illness: further formal randomized controlled trials are urgently needed. ■

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