Depression and anxiety in inflammatory bowel disease:

A review of comorbidity and management

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Abstract: While there has been a great deal of speculation over the years on the importance of emotional factors in inflammatory bowel disease (IBD), it is only in the last decade or so that studies with stronger designs have been available to clarify the nature of this relationship. This review 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 the course of the IBD, and the contribution of corticosteroid treatment to psychiatric symptom onset. There is evidence that anxiety and depression are more common in patients with IBD and that the symptoms of these conditions are more severe during periods of disease activity. The few studies that address the issue of anxiety and depression as risk factors for IBD do not yet provide enough information to support definite conclusions. There is evidence, however, that the course of the disease is worse in depressed patients. Treatment with corticosteroids can induce mood disorders or other psychiatric symptoms. The second part of the review focuses on patient management issues for those with comorbid anxiety or depression. Practical approaches to screening are discussed, and are recommended for routine use in the IBD clinic, especially during periods of active disease. We review evidence-based pharmacological and psychological treatments for anxiety and depression, and discuss practical considerations in treating these conditions in the context of IBD, to facilitate overall management of the IBD patient.

Key Words: Crohn's disease, ulcerative colitis, Anxiety, Depression, Mood disorders

The etiology of Crohn's disease (CD) and ulcerative colitis (UC) is not well delineated, but is currently understood to relate to the complex interaction between genetic and environmental variables resulting in an inappropriate and exaggerated intestinal inflammatory response in vulnerable individuals.[1-3] The chronic clinical course often results in reduced quality of life.[4] Given that the disease has both early life onset and does not typically contribute to shortened life span, addressing how the individual manages with and is impacted by the disease is an important aspect of care.

The presence of a chronic medical condition is often associated with higher rates of anxiety and mood disorders compared to the general population.[5-7] Potentially, there are reciprocal influential processes, such that the experience of the disease is sufficiently stressful to trigger or intensify the psychiatric condition or conversely anxiety or depression may be sufficient to trigger or exacerbate the health condition.[8-10] Alternatively, there has been significant discussion about potential common pathways, particularly between depression and inflammatory conditions such as IBD, related to dysfunctioning immunoregulatory circuits.[11-13]

Regardless, the comorbidity can complicate functioning as well as disease outcomes.[7,14,15] A great deal of disability and functional impairment that occurs in chronic health problems is associated with anxiety and depression moreso than the features of the disease.[14,15] Depression has been projected to be the second leading cause of disability world-wide by 2020,[16] and yet it often goes unrecognized and untreated.

This review considers the most recent literature on the nature of the relationship between IBD and two common psychiatric disorders, depression and anxiety. It emphasizes these disorders rather than more general distress or stress impact, in order to more consistently link the psychiatric condition to appropriate clinical intervention. We examine the evidence on co-

occurrence, the potential contribution of these psychiatric conditions as risk factors for IBD onset and disease course, and summarize the converse relationship of psychiatric symptoms as an adverse outcome of IBD treatment. Finally, we discuss strategies for screening and treating anxiety and depression in the context of IBD, considering both evidence-based pharmacological and nonpharmacologial interventions.

RELATIONSHIP OF ANXIETY AND DEPRESSIVE DISORDERS AND INFLAMMATORY BOWEL DISEASE

Reviews in the 1990s OF IBD and co-occurring psychiatric disorders challenged the long-held belief that IBD was primarily a psychosomatic illness, concluding that there was little support for the role of psychological factors in the development of UC or CD.[17-20] The reviews were highly critical of early research, which was comprised primarily of case studies, psychiatric referral samples, noncontrolled samples, and studies with poor measurement of IBD and/or psychiatric disorder. When the few studies with more adequate methodology were examined,[21-23] it was concluded that there was no indication of higher rates of psychiatric disorder for those with UC.[17] CD was found to be associated with higher rates of anxiety and depression across some controlled studies,[23,24] however the relationship was often explained by the greater severity of the disease.[22,25]

Research over the past decade has endeavoured to further clarify questions of clinical interest regarding the relationship between IBD and psychiatric disorders.[26-28] That is, (a) do psychiatric disorders occur at a higher level in IBD than base rates might project; (b) do psychiatric disorders contribute to greater risk of disease onset, and (c) do psychiatric disorders affect disease relapse or disease management. A search of this recent literature, identifying

studies that used validated measures of anxiety or depression (rather than more generic distress or personality scales), sufficient samples, control or comparison groups, and prospective designs where appropriate, suggests there have been some improvements to address methodological flaws of prior work. The next three sections describe studies regarding rates of comorbidity, risk related to onset, and risk related to disease course. The number of studies that met the above criteria was surprisingly low given the interest and need for further information in this area.

The Presence of Anxiety and Depression in IBD

There were eight controlled studies that were appropriate to include based on the above criteria. The most recent comprehensive review of anxiety and depression in IBD was unable to come to a conclusion about psychiatric disorder levels in IBD relative either to community base rates or in relation to other medically ill patients,[29] however the timing of the review meant it did not include five of the eight studies that were subsequently published and have been included here. Of the eight studies, half used clinic samples of IBD patients, and included either healthy or patient controls; only two of these attempted any matching with the control sample.[30,31] Four studies used population-based IBD samples with community controls or case comparisons.[32-35]

One of the only studies to use a structured psychiatric diagnostic interview, considered the gold standard for identifying anxiety and depressive disorders, was done by Walker and colleagues in 1995.[36] They compared 40 IBD and 71 irritable bowel syndrome (IBS) patients presenting consecutively at a tertiary care clinic for the presence of a range of psychiatric concerns. The IBS patients had consistently higher current and lifetime prevalence rates of mood disorders than the IBD patients, which is not surprising in light of the numerous studies that have identified a psychological overlay for those with IBS who seek treatment.[37] However, the

lifetime prevalence of the selected disorders for the IBD patients (65%) was still high when considering reported rates of 42% using the same diagnostic interview in community samples with other chronic medical illnesses.[38] There was no difference in rates between the CD and UC patient groups.

A Hungarian study using matched samples of tertiary clinic IBS and IBD patients and healthy controls found the IBD patients had significantly higher levels of anxiety and depression symptoms than the healthy control group based on validated symptom measures.[31] Similarly, a study from Italy matched 79 IBD clinic patients with 36 healthy controls, and used validated symptom patient-report measures to assess anxiety and depression symptoms.[30] They found that, for both CD and UC, the IBD patients had higher anxiety and depression levels than the control group. Filipovac and colleagues assessed newly diagnosed IBD and colon cancer patients with no previous psychiatric history, selecting those groups because of similarity of presenting GI symptoms.[39] A structured psychiatric interview determined that the IBD patients had a higher level of both depression and anxiety than those with cancer, although a potential confounding issue was the markedly older age in the cancer group.

The advantage of using clinic samples is that it allows for confidence in the IBD diagnosis; all the above studies used multiple methods to confirm the IBD diagnosis including, typically, clinical assessment, and endoscopic and histological investigation. However, these studies can potentially inflate the levels of psychiatric disorders, as those seeking treatment may be more symptomatic than community samples.[40,41]

Nevertheless, the four population-based studies also consistently indicated a clear relationship between IBD and depression, with some support for higher levels of anxiety as well. Lerebours and colleagues using a case control design, identified 241 incident cases of IBD

through a regional IBD registry, and compared them to 255 blood donor community controls.[33] Based on validated symptom self-report measures, both those with CD and UC had higher levels of depression than the community controls, but had similar levels of depression to each other. Anxiety levels were higher for both the CD and UC cases compared to the community controls, although the difference was only significant for those with CD. A much larger nested case-control study that examined hospital and outpatient records for diagnosed cases of IBD (> 12,000), depression (>41,000) and anxiety (>12,000), compared those with IBD for expected rates of depression and anxiety and vice versa, relative to rates for 800,000 controls admitted to hospital for minor medical procedures or conditions.[32] Higher rates of anxiety and depression were found for those with IBD compared to those without IBD, and were particularly pronounced in the early period around the IBD diagnosis. For CD patients, anxiety or depression occurred five times more often than for controls, and for UC patients, anxiety occurred almost four times as often and depression twice as often as for controls.

A Canadian study based on two nationally representative health surveys extracted IBD cases from the samples and examined depression rates.[34] Depression was diagnosed using a contemporary structured diagnostic interview, and similar 12-month depression prevalence rates of 14% and 16% were found across both survey samples for the IBD cases. The rate was approximately triple that of the Canadian population. The drawback with this study, unfortunately, was the lack of precision regarding the IBD cases. Cases were included based on the respondent's report of "a bowel disorder such as Crohn's disease or colitis" that has lasted longer than six months and been diagnosed as such by a health professional. While the authors suggest that it was reasonable to conclude that the sample primarily included those with IBD, the prevalence of IBD according to this definition was at least twice as high as the prevalence

determined using more rigorous methods.[42] There was no ability to cross-check clinical records or to definitively exclude other gastrointestinal conditions such as irritable bowel syndrome.

Our group completed a study that aimed to address the above shortcomings, comparing a population-based cohort of IBD cases with diagnoses confirmed on chart review to a matched sample of community controls from a population-based national health survey who did not have IBD. Diagnosis of lifetime and recent anxiety or depressive disorders was determined using the structured diagnostic interview used in the national study.[35] There was a significantly higher lifetime prevalence of major depression for the IBD cases compared to the community cases (27% vs 12%). Twelve month prevalence rates were also almost twice as high for IBD (9.1 % vs 5.5%), with a trend to significance (Odds Ratio (OR) 1.53, 95% confidence interval (CI) 0.96-2.45). Rates for anxiety disorders were similar for both the IBD and nonIBD community cases, with a higher lifetime prevalence of social anxiety for those in the community, and a trend to a higher lifetime prevalence of panic disorder for those with IBD (8.0% vs 4.7%, OR 1.59, 95% CI 0.96-2.63).

Collectively, these controlled clinic and community-based studies suggest greater comorbidity of anxiety and depression in IBD than in those without IBD. Conservatively, the rates for depression in particular may be at least twice the rate of those in the general community. The studies which considered CD and UC separately generally indicated that both subtypes were associated with higher rates or elevated symptoms of anxiety and depression. The national health surveys using population-based controls discussed above did not specifically screen out other chronic illness and nevertheless noted higher rates for IBD. However, the higher rates of these psychiatric disorders are not necessarily unique to IBD.[7] Research that has established rates of psychiatric disorders in medically ill groups using community-based samples suggests that

rates for IBD are quite similar to rates for those with health issues such as rheumatoid arthritis[43] and diabetes[44], and may be even higher compared to conditions such as heart failure.[45]

Anxiety and Depression as Risk Factors for IBD Onset

Ideally, prospective tracking of individuals with diagnosed anxiety or depression and a matched control group to assess rates of subsequent IBD would help to delineate whether these psychiatric conditions contribute to onset. No studies like this have been published to date, as the low rate of occurrence for IBD makes them impractical and costly.

Three controlled studies were identified that address this issue to some extent, however.[23,32,35] A small study of 51 IBD patients in remission and 28 community controls reported a higher lifetime prevalence of anxiety and depressive disorders for CD patients than for the controls,[23] with a significant proportion of the CD patients meeting diagnostic criteria prior to the IBD diagnosis, for panic disorder in particular. Unfortunately, the study did not report the time between the psychiatric and IBD diagnoses, which is relevant given the lag time from IBD symptom onset to diagnosis.[46,47] The recent Walker study[35] was also able to identify first onset of psychiatric disorder through diagnostic interview. Almost two thirds of those with an anxiety disorder (65%) and over half of those with a mood disorder (54%) had first onset two years or more before the IBD diagnosis. Epidemiological data[48] suggests that base rates and typical early age of onset for anxiety and mood disorders may account in part for the prior onset of these disorders. However, the age of onset of IBD symptoms was earlier in those with a lifetime anxiety or mood disorder compared to those without (29 vs. 33 years, p=.01) and there was a trend for age at IBD diagnosis to be younger also (35 vs. 38 years, p=0.06), raising the

possibility that anxiety or mood problems are contributing to risk. Both of these studies were based on retrospective recall of symptoms and historical chronology, which can introduce bias.

The large health records study in southern England (described previously) was able to examine temporal relationships without potential recall bias, although it was limited to those who obtained treatment for depression or anxiety.[32] They found that CD patients did not have any higher rates of depression and anxiety before the IBD diagnosis than expected. In contrast, depression and anxiety occurred at two and three times higher rates, respectively, than expected prior to UC diagnosis. The association was strongest when onset for the psychiatric disorder was within a year of IBD diagnosis, which could reflect reactive anxiety or depressive symptoms related to early signs of IBD. A significant association was also found between depression and UC (OR = 1.49, 95% CI 1.12-1.93) when the depression predated UC by more than 5 years, which is unlikely to be influenced by initial IBD symptom presentation.

In sum, there is no conclusive support for anxiety and depression contributing to risk for IBD onset, but the findings of these few relevant studies do suggest that the possibility of an etiological role cannot be ruled out. Alternatively, if the lag phase before IBD is diagnosed is longer than expected,[47] perhaps there are reciprocal effects of the brewing inflammatory state that initiate a mood disorder.[11] At the very least, there is evidence that depression can significantly antedate the diagnosis of IBD at a higher rate than one would expect from comparative base rates.

Anxiety and Depression as Risk Factors for Disease Exacerbation

The relationship between psychiatric disorders and the course of IBD has been more extensively examined, using comparative cross-sectional or prospective studies. The

comparative studies have typically reported higher levels of anxiety or depression for those who had active disease or symptoms than those in remission or in comparison to a normative sample.[49-52] A recent study had contradictory results, concluding that anxiety and depression levels were similar regardless of disease activity status.[53] The authors noted that anxiety and depression scores were relatively low in this study, potentially restricting the ability to distinguish any differences relative to disease activity.

A prospective design can provide clearer understanding of the influence of a psychiatric disorder on IBD course. Six studies prospectively examined this relationship, using validated measures of anxiety or depressive symptoms, although none of them included the gold standard measure of a structured diagnostic interview.[54-59]

Two studies noted a clear temporal association between disease activity and levels of symptoms. In a small sample of 25 UC clinic patients, Angelopoulos et al. found higher levels of depression and anxiety during an active disease phase, with symptoms diminishing once the IBD was in remission.[54] Disease activity was found to be closely paralleled by anxiety and depression levels in a clinical sample of 104 CD and UC patients followed for six months, such that improved disease was mirrored by a drop in anxiety, worsening disease was accompanied by a large increase in anxiety, and ongoing disease activity had parallel stable anxiety, with a similar pattern seen for depression.[55] In a third study, Mikocka-Walus and colleagues[56] reached a different conclusion when they assessed 59 CD and UC patients at two time points, reporting similar levels of anxiety and depression at baseline and 12 months later. However, they did not consider separately those who had different disease activity patterns (e.g., those in remission who had subsequently relapsed versus those in active or inactive disease for the whole period), potentially confounding any interpretation.

Three prospective studies provide support for a more direct negative impact of depression on IBD, two of them related to disease relapse and one related to detrimental impact on treatment course. A two-year study that assessed a small sample of CD patients in 2-3 month intervals found that higher depression scores were associated with higher CDAI scores in the subsequent time period.[57] Mittermaier and colleagues[59] enrolled 60 CD and UC patients with clinically inactive disease and assessed them every three months for a year and a half. Depression level at baseline was significantly correlated with total number of relapses. They also found the median time until first relapse was much shorter for patients with depression (md=97 days) compared to the group who were not depressed at baseline (md=362 days; $p < .05$). Higher anxiety at baseline was also related to more frequent relapses in the follow up period.

A prospective study of the relationship between depression and treatment response tracked 100 CD clinic patients refractory to usual treatments who were given infliximab.[58] They were followed for up to nine months until the next flare or the end of the observation period. Those with major depressive disorder or higher anxiety symptoms at baseline were less likely to achieve remission with the infliximab, with multivariate regression analyses confirming depression was an independent determinant of failure to achieve remission in these patients. Further, the presence of a major depressive disorder at baseline was significantly associated with a shorter time to re-treatment.

Overall, these studies suggest that anxiety and depressive symptoms are more likely to be elevated around periods of active disease. There is some indication that symptoms may remit as the IBD symptoms settle, but the nature of the measurement and study designs in the current literature do not provide a clear clinical picture or allow ready prediction of who may still require clinical care for the psychiatric symptoms. The prospective work, while limited, consistently

points to a role for depression in disease exacerbation, and may be an important consideration when initiating IBD treatment.

Anxiety and Depression as Adverse Effects of IBD Treatment

Psychiatric issues arise in another context with IBD, namely as potential adverse effects of medications commonly used in the course of disease management. Medical intervention for the IBD patient can include aminosalicylates, corticosteroids, immunomodulators, biologics, and less commonly antibiotics, which variously aim to settle active symptoms and maintain remission by reducing inflammation and promoting mucosal healing. Corticosteroids have been most closely associated with psychiatric side effects generally, as well as specifically in IBD.[60-63]

While morphological changes such as the 'moon face' were found to be most distressing to patients, psychiatric symptoms were the second most distressing side effect of corticosteroids.[64] Most available empirical data on corticosteroids support an association with depressive symptoms or other psychiatric effects, including mania and psychosis, across a range of inflammatory conditions.[60,61,64-67] Fardet and colleagues[64] assessed consecutive patients on $\geq$ 20 mg of daily prednisone in the first 3 month period of therapy and found that 52% of the sample developed psychiatric symptoms, of which 12% of those were serious enough to require hospitalization for either mania or severe depression. A controlled study tracking patient psychiatric symptoms on daily low-dose (7.5 mg) long-term (6 month) prednisone therapy reported that 60% of the corticosteroid patients had had a current or past mood or anxiety disorder related to corticosteroid therapy. In marked contrast, none of the controls had a history of prednisone-induced psychiatric conditions, despite having the same medical conditions.[68]

Results from meta-analyses have suggested that over a quarter of patients on corticosteroids may experience adverse psychiatric effects, with almost 6% having a severe reaction.[69] The most significant risk factor appears to be dose related, with higher doses associated with higher incidence rates.[70] However, the adverse effects remain difficult to predict in terms of onset, severity or type.[71,72] There are little data to suggest that prior history of psychiatric disorder increases risk,[60,61] although a recent review of adverse effects with the elderly concluded that there was a higher risk in this group if corticosteroids had previously induced psychiatric symptoms.[73] Psychiatric outcomes such as mania are more likely to occur early in treatment, potentially within the first week of therapy.[61,74] Depressive symptoms typically occur later in the course of treatment or may be evident during the tapering phase of therapy.[61,62]

The majority of IBD patients are not taking corticosteroids at any given time, and typically patients are on prednisone for the shortest time possible to achieve the therapeutic goal. These considerations suggest that adverse effects of medication are a relatively small contributor to the overall prevalence of psychiatric disorders in this patient population, but nevertheless warrant clinical attention.

MANAGING COMORBID ANXIETY AND DEPRESSION IN IBD

Particularly vulnerable times for IBD patients regarding depression or anxiety are around the period of onset and diagnosis,[32,33,39] as well as during disease flares.[54,55] There is evidence to suggest depression in particular can have a detrimental impact on disease course,[28,28-59] IBD treatment outcomes,[58] and overall quality of life for IBD patients.[75,76] The relationship between depression and disease course may be influenced in part by the effect of the disorder on

treatment adherence, as there is significantly poorer adherence to treatment regimens by those with a comorbid psychiatric disorder.[77,78] Finally, 17% of those with a major depressive disorder and IBD had considered suicide in the previous 12 months,[34] raising a concern about the mortality risks associated with comorbid depression.

The weight of the evidence for a negative impact of these psychiatric factors on IBD patients supports the calls for more routine screening of patients,[27,53,58,79-81] particularly as anxiety and depression often go unrecognized in IBD.[82] Recent consensus guidelines for CD management include recommendations to assess for anxiety and depression and identify appropriate treatment if needed.[83] The concerns about psychiatric impact and need for intervention have been recognized in other chronic illness populations as well, with recent advisories recommending routine screening for depression for those with heart disease or diabetes.[84,85]

Screening for Psychiatric Disorders in IBD

Given the frequency and relevance of psychiatric disorders in IBD, it is most effective to identify patients with these disorders as a part of routine primary or specialist care. Fortunately, there are a several approaches to screening that are able to identify a high proportion of those with significant mental health problems. As anxiety and mood disorders are the most common mental health concerns in the community, these are usually the focus of screening efforts. 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),[86,87] and difficulty coping with unfamiliar situations. Depression typically presents with a constellation of affective, cognitive and somatic symptoms including sad or depressed mood, 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 normal activities. When these clusters of symptoms persist beyond a few weeks and begin to interfere significantly with daily functioning, they are typically considered to reach a clinical threshold.[88]

Screening approaches to detect clinical anxiety or depression in everyday practice may use self-report forms, which can be completed while the patient is in the waiting room, or use brief standardized questions administered by the health care provider. Previous research suggests that even very short scales can be effective in flagging problems such as depression.[89] One example of a patient-based screener is the five-item Anxiety and Depression Detector,[90] which was recently developed for application in primary care settings. The questions elicit information regarding common anxiety problems such as panic disorder, generalized anxiety, social anxiety disorder and post-traumatic stress disorder, as well as depression. The items have simple wording and dichotomous yes/no responses so they can readily be understood. The overall scale has high sensitivity (i.e., good ability to identify persons meeting the criteria for a diagnosis of anxiety or depression) and reasonable specificity (i.e., lower rate of false positives that would identify people as likely positive who do not meet the criteria for a diagnosis). The screening measure was found to have adequate validity across genders and racial groups.

A screening measure developed more specifically for IBD, the Luebeck Interview for Psychosocial Screening in Patients with IBD,[91] was validated in a specialty GI service in Germany. This clinician-administered scale provides a broader scope of information for patient management, covering areas including social support, depression, anxiety, distress caused by IBD, and interest in receiving psychological care, but still only takes an average of 5 to 10 minutes to administer. Clinicians can be quickly trained to use the scale. The screening

interview had good levels of interobserver agreement based on physician review of videotaped interviews, and satisfactory correlations with other measures of the various dimensions. Further evaluation is needed to confirm the extent of its validity and applicability, but it shows promise as a useful clinical tool.

As an alternative to using one of the structured approaches to screening described above, the clinician can incorporate a brief series of questions into the clinical setting, such as those shown in Table 1. Ensuring that every patient is asked routinely about common psychiatric symptoms can be key to identifying those who may benefit from assistance for problems with anxiety and depression, particularly since many patients are reluctant to volunteer information about these concerns.[92]

Treatment of Anxiety and Depression

Most people who are experiencing difficulty with anxiety and depression do not obtain treatment and this often results in unnecessary disability or high use of other health care resources.[93,94] Some are reluctant to consider treatment because of their preference to cope independently, their concerns about the cost and time involved in treatment, or concerns about stigma related to seeking help for a mental health problem.[95]

Many who are treated pharmacologically are seen in primary care,[96] although patients are more likely to receive an adequate trial of medication in a specialty mental health service.[94] Given the high prevalence of anxiety and depression, it can be challenging to provide appropriate services in a timely fashion.[93,94,97]

Anxiety and depression are highly treatable conditions. The interventions that are most widely used and have been evaluated most extensively for anxiety and depressive disorders are

specific pharmacological agents (particularly the selective serotonin reuptake inhibitors (SSRI) such as citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline, and the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine) and specific psychological treatments (particularly the cognitive behavior therapies). The SSRI and SNRI medications are second generation antidepressants that have been well established in the literature as being similarly effective for both anxiety and depression.[98] Cognitive behavioral therapies have also had extensive empirical support for treatment of these disorders, with active treatment components typically including education about the interactions among thoughts, feelings and behavior, development of more adaptive thinking patterns, problem solving, exposure to anxiety-provoking situations, and active coping strategies.[99] Studies have found similar changes in functional brain activity following treatment with either pharmacological or psychological treatment, suggesting similar pathways for symptom relief.[100] Meta-analytic studies indicate that these medication and cognitive behavioral treatments are equally effective when provided by appropriately trained mental health professionals[101-104] or primary care staff.[105] Either medication or cognitive behavior therapy can be considered as first line treatment of anxiety or depression.

Decisions regarding treatment may hinge on practical considerations such as availability and cost, and should be guided more broadly by the patient's preference for or tolerance of one type of treatment over the other. Screening for anxiety and depression, and discussing treatment options for these disorders validates for the patient that this is an important aspect of their health. Patients with IBD are routinely screened for malnutrition, anemia, and even osteoporosis, and there is no evidence that any of those conditions necessarily impact on quality of life to any greater extent than these psychiatric conditions.

Knowledge of the advantages and disadvantages of the most common treatment approaches can help to guide discussion with the patient. Table 2 highlights key considerations for evidence-based pharmacological and psychological treatments for depression and anxiety. A major advantage of medication treatments is their higher level of availability through primary care settings whereas a significant disadvantage is the high rate of relapse when medication is discontinued. Patient concerns about side effects and use of multiple medications can also negatively influence adherence with pharmacological treatments, including for IBD.[106,107] A major advantage of the psychological treatments is the lower rate of relapse post-treatment,[108] and the low rate of side effects. However, timely access to a trained clinician who is experienced with evidence-based treatments of anxiety and depression can be problematic.

While it is often recommended as desirable to routinely combine pharmacological and psychological treatments, the data supporting this approach is limited, and in fact combining treatment often does not improve outcome.[108-110] There is some indication that the lower relapse rate typically found with psychological treatments can erode in a combined approach, at the point when the medication is discontinued.[108-110] As well, the cost of combined treatment is higher. An alternative to routinely combining medication and psychological treatment is a patient-focussed strategy, in which the treatment options and any contraindications are reviewed with the patient and a trial of the treatment approach preferred by the patient is planned. The other treatment modality may be added at a later point if there is not sufficient response to the selected first line of treatment. If medication is initiated as the first intervention step, subsequent psychological treatment has been found to reduce the rate of relapse from pharmacological treatments, especially if the psychological intervention is provided around the time that the psychiatric medication is discontinued.[108]

Reviews of patient treatment preferences suggest that many patients have strong views regarding the type of treatment they would rather use. Interestingly, in many settings, a larger proportion of patients indicate a preference for psychological over pharmacological treatment,[95] although many patients are also receptive to medication. There appear to be advantages to providing the preferred form of care when it is available, as this can facilitate adherence to treatment recommendations.[95,97,111] This process of reviewing treatment choices with the patient and then following up on treatment decisions is outlined in Tables 1 and 3. Table 3 emphasizes the importance of following up after treatment has been implemented to monitor response to the planned intervention.

Pharmacological Treatment

There is very little research assessing pharmacological treatment of anxiety or depression specifically in IBD patients, so practice guidance needs to come from the more general clinical literature. A recent systematic review of clinical studies identified only 12 studies since 1990 addressing the use of antidepressants in IBD, none of which were randomized controlled trials.[82] Based on the available literature, including an open-label study and six case reports, it was found that the targeted anxiety or depression in IBD patients was generally responsive to pharmacological treatment. In addition, there was a positive effect on disease activity in the majority of the reports, which primarily involved use of the antidepressants paroxetine or buproprion. However, any conclusions regarding direct benefit of antidepressant medication on IBD over and above the impact on the psychiatric condition is significantly restricted as findings were based on only 20 patients collectively. Preliminary work in animal studies, however, has

suggested a protective role for antidepressants in mouse models of colitis[13,112] holding out the possibility that antidepressants may affect the disease process directly.

A qualitative study assessing use of antidepressant medications for IBD patients in gastroenterology practices found that the majority of GI specialists (78%) had treated their patients with antidepressants as an adjunctive therapy, especially for pain or sleep difficulties.[113] Half had specifically treated depression or anxiety in their patients, whereas the remainder more typically referred depressed patients to a mental health specialist or the patient's family practitioner for care. Most did not believe antidepressant medications influenced the IBD directly, but observed that treatment of the comorbid disorder improved the patient's quality of life and improved their ability to manage the IBD.

The clinical literature on antidepressants suggests they are safe and are similarly effective for both anxiety and depressive disorders.[98,114,115] Newer generation antidepressants (SSRIs, SNRIs) currently in widespread use have been found to be better tolerated than the previous generation of tricyclic antidepressant medications and monoamine oxidase inhibitors.[116,117] Despite those improvements, however, studies in primary care settings suggest that many patients do not fill the first prescription. Of those who do, 40 to 50% discontinue treatment within the first weeks or months, often because of side effects, limiting effectiveness of the treatment particularly given recommendations that medication treatment continue for at least a year.[116,117]

Patients may be better able to manage side effects or tolerate them during the initiation of treatment if they are aware of the potential side effects, as well as the potential benefits of persisting until they have adapted to the medication. While this is particularly relevant for corticosteroid medications and adverse psychiatric side effects,[61,118] education about side effects

can also help patients to persist with antidepressant medication. A systematic review of SSRIs indicated that, while the medications were similar in efficacy, there were meaningful differences in side effect profiles and that these might guide decisions concerning the best choice for a particular patient.[119] Gastrointestinal side effects can be of particular concern to the IBD patient, and have been reported with many of the antidepressant medications. These side effects are generally dose related and tend to decrease over the first weeks of treatment.[120] Nausea and vomiting were more frequent with the one SNRI evaluated (venlafaxine) compared to the SSRIs as a group (fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram; 34% vs 22%). Diarrhea was reported more often with sertraline than with the other SSRIs.

Other side effects that are 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%).[121] Weight gain has been found to be a more significant problem with paroxetine and mirtazapine,[120] but it remains a concern with all of the SSRI medications.[122] In some cases there may be weight loss early in treatment and weight gain later.[120]

Decreased sexual functioning is a relatively common dose-related side effect of the antidepressant medications, and may be of particular concern for IBD patients given disease-related difficulties with intimacy and sexual functioning.[81] Sixty to 70% of patients report reduced sexual functioning on SSRIs or SNRIs that does not improve with longer periods on the medication. Buproprion has had the lowest rates of sexual dysfunction relative to other antidepressants.[122]

With regard to risk of severe side effects, recent reports have raised the possibility of a greater risk in upper GI bleeds with the use of certain antidepressants.[123-125] Large-scale studies

found a moderately increased risk of GI bleeds with the SSRIs as well as an SNRI, venlafaxine.[126-128] Use of acid-suppressing agents mitigated the higher risk, while the use of NSAIDs increased the risk.[126] The absolute risk in taking SSRIs was low, however, such that 2000 patients per year would need to be treated with SSRIs in order for 1 case of upper GI tract bleeding to be attributed to such drugs. The risk was higher when SSRIs and NSAIDs were taken together, with 1 patient in 250 experiencing a GI bleed that could be attributed to that combination.[126]

In conclusion, there is a range of effective medications for these psychiatric disorders, and they can readily be considered for the IBD patient when needed. As there is similar effectiveness of many of the second generation antidepressants for both anxiety and depression, treatment choices are best made in consultation with the patient (see Tables 1,2,and 3), considering factors such as side effect profile and cost, as well as the physician's familiarity with particular antidepressants.[129] Educating the patient concerning the recommended duration of treatment and the need to persist until benefits are achieved, which often is a number of weeks after the treatment is initiated, will make it more likely that the patient will be able to follow treatment recommendations. Gastroenterologists can enhance patient management by familiarizing themselves with a few of the antidepressant medications so that pharmacological treatment could be initiated, if this is the approach the patient prefers, while awaiting primary care, or psychiatric or psychological specialist consultation.

Psychological Treatment

There is an extensive literature that supports the effectiveness of cognitive behavioral therapies for anxiety and depression,[101-103,105] as well as evolving research assessing these

treatments in the context of several chronic illnesses. White[130] describes cognitive behavior therapy for a variety of common health problems, such as cancer, chronic pain, diabetes, heart disease, and surgical issues. Specific treatment components are incorporated in the therapy depending on targeted symptoms and patient presentation.

There have been several studies of psychological intervention with IBD patients, particularly in the last decade.[131-134] However, only a few have directly examined the application of evidence-based treatments in IBD patients with anxiety or depressive disorders. Cognitive behavior therapy was evaluated in an open trial with adolescents with major depression (n=11)[135,136] and a randomized controlled trial (RCT) in adolescents with subsyndromal depression (n=41).[137] In both studies, treatment significantly reduced depression and improved global functioning. For those who also had a comorbid anxiety disorder, there was a significant reduction in anxiety as well. The open trial did not find any change in illness severity post-treatment; the RCT reported a decrease in the number of individuals with moderate to severe disease post-treatment (29% pre- vs 15% post-treatment),but the drop was not significant. In a randomized controlled trial with 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.[138] The improvements in psychiatric symptoms were maintained at 12-month follow up in both the adolescent and adult samples, suggesting good durability of effect. These studies provide support for the utility of evidence-based psychological treatment targeting depression and anxiety in the context of IBD, adding to the evidence for effectiveness in the general clinical literature.

Recent reviews considering the *overall* effectiveness of psychological therapies for IBD patients not selected for anxiety or depressive disorders have reached a more modest conclusion, namely that there may be some clinical benefit related to psychological functioning, with little support at this point for a significant direct impact on disease parameters.[27,28,81,139] The 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, and often involved unselected IBD patients or those in remission with little elevated distress,[134,140] resulting in the potential for floor effects. As such, the conclusion to date is not surprising, and suggests that psychological treatment is not indicated for all patients with IBD. A small study of CD patients found that psychological interventions may have a positive impact through reduced health care utilization, but that preliminary finding has yet to be replicated.[141] Rather, the current research suggests validated treatments should be targeted at high-risk subgroups such as those with comorbid psychiatric conditions or elevated stress.[27,139]

Certainly, IBD patients may be quite receptive to psychological treatment. Among those reporting high distress, there was a strong level of interest in receiving support for these concerns.[91] A structured measure of desire for psychological care comparing patients with IBD and rheumatoid arthritis, found that two to three times the number of IBD patients (31%) expressed an interest in receiving assistance compared to those with rheumatoid arthritis (13%).[142] Other indicators of receptivity included positive evaluations of treatment[140] and low drop out rates, despite the expectation of active participation.[134,137]

In conclusion, effective psychological treatments are available for anxiety and depression. Cognitive behavioral therapies are well accepted by patients in general, and initial evidence suggests that they are accepted and effective in depressed or anxious patients with IBD.

The evidence for psychological interventions to assist the broader range of IBD patients in coping with the disease is more limited, but this area also holds some promise for evidence-based interventions as well.

CONCLUSIONS

As is the case with most chronic illnesses, there is a higher rate of anxiety and depressive disorders in IBD than in the population at large. An important area of future inquiry would be to explore in greater depth whether anxiety or depression may be risk factors for the development of IBD, either through some direct effect or indirectly through a common risk factor such as stress. Coexisting depression predicts a more negative disease course and may be associated with poorer response to treatment. Depression has also been associated with poor treatment adherence in range of other health conditions. Consequently it is recommended that clinicians routinely screen their IBD patients for anxiety and depressive disorders in the regular course of providing care, especially at the time of first diagnosis and during disease flares. Identification of problems with anxiety and depression should be followed by a process of treatment planning with the patient, including review of the range of treatment options. Effective treatment of anxiety or depressive disorders can decrease suffering, and lead to improved functioning and quality of life. Further research is needed to evaluate the most effective approaches to treatment of anxiety and depression in the context of IBD, and to identify modifications to treatment that may be required for these patients. Prospective studies of the impact of treatment on the course of IBD for those patients with comorbid anxiety or depression would be important to establish priorities in managing IBD.

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TABLE 1. Screening and Treatment Planning for Anxiety and Depression in IBD

I) SCREENING

- Routinely screen IBD patients, especially at time of diagnosis and during active disease
- Use brief standardized patient-report or clinician interview measures that are readily administered in clinic

OR

- Screen with 3 key questions: "*Living with IBD can be challenging…*
  a) *Have you been experiencing any difficulties with stress, worry, or anxiety*?
  b) *Have you been feeling nervous, jittery, or tense much of the time?*
  c) *Have you felt down or depressed most of the day OR experienced decreased interest/enjoyment in most things?"*
- If yes to any of the above screening questions, obtain further information on persistence and severity including (e.g.,)
  d) *How long have you been experiencing these difficulties?*
  e) *Have they interfered with your daily functioning such as work, self-care, or home/family responsibilities? OR*
  f) *Have these difficulties (e.g. stress, anxiety, depression) affected the IBD?*

- If significant emotional distress, significant interference in daily functioning, or significant impact on IBD is identified by the patient, and has been present for at least two weeks or more then it is important to initiate discussion of treatment needs

II) TREATMENT PLANNING

When anxiety or depression is identified:

- Explain condition and its common occurrence with acute or chronic illness
- Emphasize importance of dealing with problem, as effective coping can improve health, functioning, and quality of life
- Educate that effective treatment is available and includes pharmacological or psychological approaches
- Discuss patient preferences and choice, reviewing advantages and disadvantages of the treatment options (see Table 2), and patient questions or concerns; patients may need time to consider options and discuss with family members or an insurer.
- Consider management options with patient (see Table 3)
  A) pharmacological treatment initiated by the physician treating the IBD patient , if feasible
  B) referral to primary care physician or mental health specialist for pharmacological treatment
  C) referral to mental health specialist for psychological treatment
- Proceed with the patient to implement the preferred choice

TABLE 2. Advantages and Disadvantages of Evidence-based Treatments for Anxiety and Depression

Pharmacological Treatments (e.g., SSRIs SNRIs)	**Psychological Treatments (e.g. Cognitive Behavior Therapies)**
Advantages: • Demonstrated effectiveness. • Accessible in primary care settings. • Requires less active participation by the patient. • Treatment may be helpful with a range of mental health problems. • Less expensive in short term	Advantages: • Demonstrated effectiveness • Good maintenance of gains after treatment is completed • Treatment is time limited, often 2 to 4 months – reducing cost. • Treatment may be helpful with a range of mental health problems. • Well accepted by patients
Disadvantages: • Relapse common after discontinuation of treatment • Higher cost in medium and long term; medication costs may not be covered in the health system or insurance plan • Side effects can be problematic, including weight gain and reduced sexual functioning • Patients taking medications for IBD may be reluctant to take additional medication.	Disadvantages: • Less readily available than pharmacological treatments. • Higher cost in the short term; costs may not be covered in the health system or insurance plan • Requires more time and effort by the patient. • Adjustments are necessary if the patient has limited education. • Not all counsellors and therapists are trained in evidence-based psychological treatments for anxiety and depression.

SSRI – selective serotonin reuptake inhibitor, SNRI – selective norepinephrine serotonin reuptake inhibitor

TABLE 3. IBD Patient Management for Comorbid Anxiety or Depression

The PHYSICIAN treating the IBD Patient…

A) …Oversees PHARMACOLOGICAL Treatment

- Explore medication options that are familiar to the physician and match best with patient concerns (e.g., cost, side effects)
- Educate patient regarding (a) expected clinical benefit delay of at least 2-4 weeks after start of treatment
- (b) potential side effects, particularly GI, sexual functioning, and weight gain effects
  (c) potential transient nature of the side effects
- Initiate treatment, gradually increasing dose to therapeutic level.
- Schedule brief follow up appointments during first weeks of treatment to facilitate dose or medication type adjustments, monitoring of side effects, and encouragement of patient persistence until clinical benefit is obtained; this can also be facilitated through phone calls with clinic nurse.
- Continue treatment longer-term if there is a good response to ensure maintenance of treatment gains.
- Follow up as per D below.

B) … OR Refers Patient to Primary Care or Specialty Mental Health Service for PHARMACOLOGICAL Treatment

- Developing a consulting relationship with clinicians working in these areas can facilitate the referral process
- Follow up as per D below.

C) … OR Refers Patient to Specialty Mental Health Service for PSYCHOLOGICAL Treatment

- Developing a consulting relationship with clinicians working in these areas can facilitate the referral process
- Follow up as per D below.

D) … AND Follows up with Patient to Ensure that Anxiety or Depression is Managed Effectively

- It is important to review symptoms and functioning within 6 to 8 weeks after an intervention has been initiated.
- Many patients do not implement the first treatment choice. If the patient continues to have significant distress or interference with functioning, further encouragement to consider some form of treatment can be useful at this point.
- About 50 to 60% of patients do well with the first treatment choice; if patient is not responding, consider adjustments to pharmacological or psychological treatments or re-visit the alternate approach.