



Controversies surrounding the comorbidity of depression and anxiety in inflammatory bowel disease patients: a literature review

AUTHOR(S)

Antonina Mikocka-Walus, D A Turnbull, N T Moulding, I G Wilson, J M Andrews, G J Holtmann

PUBLICATION DATE

01-01-2007

HANDLE

[10536/DRO/DU:30091069](https://hdl.handle.net/10536/DRO/DU:30091069)

Downloaded from Deakin University's Figshare repository

Deakin University CRICOS Provider Code: 00113B

Controversies Surrounding the Comorbidity of Depression and Anxiety in Inflammatory Bowel Disease Patients: A Literature Review

Antonina A. Mikocka-Walus, MSc, MA,^{*†‡} Deborah A. Turnbull, BA, MPsych, PhD,^{*}
Nicole T. Moulding, BA, PhD,[†] Ian G. Wilson, MBBS, PhD, FRACGP, FACPsychMed,[§]
Jane M. Andrews, MBBS, FRACP, PhD,[‡] and Gerald J. Holtmann, MD, PhD

(*Inflamm Bowel Dis* 2007;13:225–234)

Abstract: Psychological disorders are highly prevalent in patients with inflammatory bowel disease (IBD). Anxiety and depression are known to independently affect quality of life and may additionally impair quality of life in IBD over and above the IBD itself. Some researchers have further proposed that anxiety and depression may influence the clinical course of IBD. However, despite the potential for anxiety and depression to play an important role in the clinical picture of IBD, there is little prospective well-controlled research in this area. Probably because of this lack of clear data, researchers dispute the actual role of these psychological disorders in IBD, with a number of conflicting opinions expressed. This article reports on a review of the literature in this field. Herein we discuss the five main areas of controversy regarding IBD and the specific psychological comorbidities of depression and anxiety: 1) the relative rate of cooccurrence of these psychological disorders with IBD; 2) the cooccurrence of these psychological disorders with particular phase of IBD; 3) the cooccurrence of these psychological disorders with the specific type of IBD; 4) the rate of these psychological comorbidities compared both to healthy subjects and to other disease states; and 5) the timing of onset of psychological comorbidity with respect to onset of IBD. Methodological weaknesses of the reviewed studies make it impossible to resolve these controversies. However, the results clearly show that anxiety/depression and IBD frequently interact. Given the long-term illness burden patients with IBD face, further prospective, appropriately controlled studies are needed to adequately answer the question of the precise interplay between anxiety/depression and IBD.

Key Words: inflammatory bowel disease, anxiety, depression

Inflammatory bowel disease (IBD) is a generic term used to describe a group of chronic and relapsing inflammatory disorders of the gastrointestinal tract of which Crohn's disease (CD) and ulcerative colitis (UC) are the most common. The disease is characterized by an inappropriate immune response that causes characteristic inflammatory lesions. The prevalence of IBD has been estimated at 200 per 100,000 people,^{1–3} with a total of 43,000 cases in Australia,⁴ and a peak incidence around 20 years of age. While the etiology of IBD is unknown, genetic, immune, and environmental factors are all implicated in its causation.^{5,6} Some researchers also propose that IBD may be partly psychosomatic.^{7–13} While this view is highly controversial, IBD patients have been noted to suffer from psychological disorders more commonly than healthy people. In general, the prevalence of anxiety and depression is noticeably higher in people suffering from gastrointestinal problems than in the wider population, and is estimated to be about 30%.^{14,15} In particular, in IBD the rate of anxiety and/or depression has been estimated at 29%–35% during remission^{16,17} and as high as 80% for anxiety and 60% for depression during relapse.¹⁸ The high prevalence of these psychological comorbidities has been used to support the premise that a patient's psychology may play a role in etiology and/or in the clinical course of IBD. This hypothesis claims additional support from prospective studies in which the researchers observed the relationship between depression, the course of the disease, and the response to standard medical treatment,^{16,19} numerous studies linking stress and disease exacerbations in IBD,^{20–25} as well as from similar data linking poor outcome to psychological comorbidities in other chronic conditions.^{26–28}

Although IBD is only rarely a lethal disease, it significantly impairs health in a substantial proportion of affected patients. Furthermore, as the disease frequently affects young adults, quality of life and psychological well-being have the potential to be profoundly impaired over a lifetime as a

Received for publication June 28, 2006; accepted August 16, 2006.

From the ^{*}School of Psychology, University of Adelaide, Adelaide, SA, Australia; [†]School of Population Health & Clinical Practice, Discipline of General Practice, University of Adelaide, Adelaide, SA, Australia; [‡]Department of Gastroenterology, Hepatology and General Medicine, Royal Adelaide Hospital, Adelaide, SA, Australia; [§]School of Medicine, University of Western Sydney, Sydney, NSW, Australia.

Reprints: Antonina Mikocka-Walus, MSc, MA, PhD candidate, Discipline of General Practice, University of Adelaide, Level 3, Eleanor Harrauld Building, 5005 Adelaide, South Australia, Australia (e-mail: antonina.mikockawalus@adelaide.edu.au).

Copyright © 2006 Crohn's & Colitis Foundation of America, Inc.

DOI 10.1002/ibd.20062

Published online 19 December 2006 in Wiley InterScience (www.interscience.wiley.com).

consequence of systemic symptoms, surgery, and medication side effects. Consistently, both CD and UC have a significant impact on patients' self-image, social relationships, and sexual functioning.^{5,29} Moreover, as the life expectancy of IBD patients approximates that of healthy people,³⁰ improving these patients' quality of life and psychological well-being is imperative.

Although interest in the psychological aspects of IBD has increased in recent years, much of the published material is outside mainstream gastroenterology journals and thus does not necessarily influence clinical practice. Indeed, anecdotal evidence from clinicians suggests that improvements in clinical care derived from integrating the psychological and physical aspects of IBD are often omitted from standard treatment models. Previously, gastroenterologists have been resistant to consider the possible role of psychological factors in IBD. However, as the discrete roles played by neurology versus immunology in the gut are no longer clearly demarcated, as evidenced by "inflammation" discovered in irritable bowel syndrome (IBS),³¹ it seems timely to reexamine the evidence for the possibility that the psyche may also affect IBD. Moreover, as psychological approaches to the treatment of other gastrointestinal illnesses such as IBS and functional dyspepsia have now been demonstrated to be effective in controlled studies,³²⁻³⁴ it is appropriate to review the current state of knowledge regarding psychological comorbidities in IBD.

Because of conflicting data and divergent opinions on the psychological aspects of IBD, we chose to review this literature with a particular emphasis on those areas where published controversies exist. As the role of stress has been previously reviewed³⁵ and is notoriously difficult to both measure and define, we have restricted our review to the more discrete, diagnosable entities of depression and anxiety. Moreover, from a therapeutic viewpoint, stress cannot necessarily be modified; however, accepted therapies exist for anxiety and depression. Thus, if they can be shown to have an impact on IBD, targeted therapeutic interventions may benefit IBD patients beyond standard antiinflammatory therapy. Our purpose was to build a clearer picture of the precise nature of these areas of divergent opinions regarding IBD and anxiety/depression, and to delineate directions for future research, tailored to address these unanswered questions.

METHODS

Initial articles pertinent to the psychological aspects of IBD were published in the 1960s,³⁶⁻³⁸ often in languages other than English; however, the biggest interest in the topic worldwide began in the 1980s. This review therefore includes articles published in PubMed between 1980 and 2005 and available to researchers. Searches were conducted in July and August 2005. Keywords used were: (Inflammatory Bowel Disease OR Crohn's Disease OR Ulcerative Colitis) AND

(Psychological disorders OR depression OR anxiety). The titles and abstracts of all identified articles were examined and included for review if the report was directly related to BOTH psychological disorders AND to IBD, and included: systematic reviews; randomized controlled trials; cohort prospective studies; case-control studies; and cross-sectional studies. We excluded studies with fewer than 10 participants, discussion articles, case reports, letters, and other publications of poor quality. The articles remaining after these exclusions were subsequently reviewed looking at study design, control group, sample size, and "prospectiveness."

RESULTS

Seventeen articles directly related to the comorbidity of psychological disorders with IBD were identified and reviewed (Table 1). Eight studies were controlled (however, not always appropriately), six studies were cross-sectional, two were cohort prospective studies, and one study was a systematic review. No randomized controlled trials were identified. Six studies were conducted in the US, four in the UK, three in Italy, one partly in France, two in Sweden, and one each in Austria and Japan. Six were published in the 1980s, six in the 2000s, and five in the 1990s. Our investigation revealed five consistent areas of controversy that arose in relation to the following questions: Do psychological disorders cooccur with IBD more often than expected by chance? Do psychological disorders appear during relapse or during remission of the disease? Are particular psychological disorders specific to Crohn's disease or ulcerative colitis? Is the frequency of psychological disorders in IBD similar to or higher than in other groups of medically ill patients? Do psychological disorders precede and/or follow onset of the disease?

Do Psychological Disorders Cooccur with IBD More Often than Expected by Chance?

The fact that psychological disorders occur in patients with IBD has been widely discussed in the literature.^{16,18,39,40} While there is general agreement that psychological disorders are common in IBD patients, authors disagree as to whether they cooccur more often with IBD than expected simply by chance. In a pair of case-control studies, Helzer et al^{39,40} found no evidence of association between psychiatric illness and either UC and CD. However, they found some evidence of an excess of psychiatric disorder in CD patients compared with controls. Other studies note a strong association between both UC and CD and psychological disorders.^{16,18} Mittermaier et al,¹⁶ in a longitudinal cohort study, found depression in 28% of patients and showed that depressed mood associated with anxiety was a risk factor for early clinical recurrence of IBD. However, they did not use a control group to address whether psychological disorders are more common in IBD patients than expected by chance. Addolorato et al¹⁸

found higher rates of both anxiety and depression in both UC and CD than in controls; however, they used healthy controls rather than controls with other chronic illness.

Do Psychological Disorders Appear during Relapse or during Remission of the Disease?

Some researchers report that depression and anxiety appear in patients only during relapse, while during remission their mental health is similar to that found in the general population.^{23,41} Using a case-control design, Robertson et al⁴¹ examined 80 IBD patients during different stages of the disease and 40 diabetic controls. They found that anxiety was less common in established IBD than among diabetic controls, and that excess depression occurred only in studied IBD patients during relapse. However, not all authors fully agree with this second conclusion, and some argue that a significant number of patients with IBD is equally vulnerable during both relapse and remission of the disease.^{42,43} In a case-control study, Simren et al⁴³ examined quality of life and psychological wellbeing in 43 UC and 40 CD patients in remission. As a group, compared to normal Swedish controls these IBD patients' psychological well-being was similar to that found in the wider population. However, in the subset of IBD patients with IBS symptoms, levels of psychological well-being were lower, with 33% of UC and 57% of CD patients with concurrent IBS-like symptoms demonstrating higher levels of depression and anxiety. Tanaka and Kazuma⁴² confirmed this result in a cross-sectional survey with 72 ulcerative colitis outpatients.

Are Particular Psychological Disorders Specific to Crohn's Disease or Ulcerative Colitis?

Another point of controversy touches on the question of whether particular psychological disorders are more specific to Crohn's disease or ulcerative colitis. Many researchers have described a link between psychological disorders and CD.^{17,25,40} Other studies show that this association is also present in patients with UC.^{18,23,41,44–46} Still other researchers have observed that the association exists for patients with CD and not generally for UC.^{17,47–49} It may also be that psychological disorders interact differently with CD compared to UC,¹⁷ with psychological disorders occurring equally commonly among the two conditions, but impairing physical recovery only in CD. Nordin et al,⁴⁸ in a cross-sectional investigation with 492 patients (331 UC and 161 CD), confirm a high rate of psychological comorbidity in CD but not UC and hypothesize that this may result from more severe somatic symptoms in CD. North and Alpers,⁴⁷ in a thoroughly conducted systematic review, examined 12 studies (10 controlled), each of more than 10 patients, and concluded that there appeared to be a higher lifetime burden of psychiatric disorders in CD than in UC.

On the other hand, a large nested case-control study

from a database of linked hospital records in Southern England clearly showed that patients with both CD and UC were equally prone to mood disorders.⁴⁴ This finding is supported by the results of a cross-sectional survey of 116 consecutive IBD patients.⁴⁶

Is the Frequency of Psychological Disorders in IBD Similar to or Higher than in Other Groups of Medically Ill Patients?

Researchers have also widely discussed the issue of whether psychological disorders are more common in IBD patients than in other medically ill populations. Some have noted that the rate of psychological disorders in IBD patients is similar to that found in other populations of patients with chronic physical illness.^{17,39,50} Andrews et al¹⁷ conducted a cohort prospective study with 162 consecutive IBD patients attending a clinic for inflammatory bowel disease and found that 34% of UC and 33% of CD patients had suffered from some psychiatric disorder. This study did not include a control group, but other authors report that the prevalence of psychiatric disorders in other chronic medical disorders is $\approx 30\%$.^{51,52} In line with this, in a case-control study with 50 UC participants Helzer et al³⁹ found no difference in the rate of psychological disorders in IBD when compared to a control group of patients with other chronic nongastrointestinal disorders. Finally, Drossman et al⁵⁰ also report similar rates in a cross-sectional random survey with 997 members of the Crohn's and Colitis Foundation of America. This observation is consistent with the generally reported rates for psychological comorbidity in chronic medical illness.

In contrast, other investigators report depression and/or anxiety to be more common in patients with IBD than in other patient groups.^{18,44,45,48,53} In a case-control study with 50 UC patients, Magni et al⁴⁵ noted the presence of psychological disorders in 31 UC patients (62%) compared with four controls (8%), although it should be noted that the controls were patients with only minor urological problems. An increased burden of psychological comorbidity was also found in a large retrospective nested case-control study of almost 12,500 participants.⁴⁴ The control group in this study, however, were patients admitted to the hospital for minor medical and surgical conditions, rather than those suffering from a chronic illness.

Do Psychological Disorders Precede and/or Follow Onset of the Disease?

A further source of controversy lies in the question of whether psychological disorders appear before the onset of IBD, are in fact its sequelae, or both. Of the five areas of controversy, the dispute concerning the time of onset of psychological disorders has been the most intense and long-lasting. In a retrospective nested case-control study with 12,500 participants, Kurina et al⁴⁴ found that depression and

TABLE 1. Features of 17 Studies Describing the Comorbidity of Psychological Disorders with IBD in Alphabetical Order

Name of the study	Sample and source of subjects	Methods	Results
Addolorato et al 1997 (Italy)	79 consecutive IBD patients (43 CD and 36 UC) tertiary referral centre, no steroid therapy, no previous surgery + 36 healthy controls matched for gender, residence, marital and socioeconomic status.	Case-control study; disease activity: sCDAI for CD and Truelove-Witts criteria for UC and a clinical rating scale (CRS); psychological assessment: STAI, Zung Self-Rating Depression Scale.	<ul style="list-style-type: none"> ● The percentage of subjects with state anxiety significantly higher in the CD ($P < 0.001$) and UC ($P < 0.001$) than in controls. ● The percentage of subjects with depression significantly higher in the CD ($P < 0.05$) and UC ($P < 0.05$) than in controls. ● State anxiety and depression significantly associated with physical morbidity and correlated with malnutrition in CD and UC patients.
Andrews et al 1987 (UK)	162 consecutive patients (91 CD and 71 UC) attending IBD clinic, no controls.	Cohort prospective study; physical morbidity measured with CRS; psychological assessment: HADS; in addition a sample interviewed for DSM-III by a psychiatrist blinded to the HADS results.	<ul style="list-style-type: none"> ● Prevalence of psychiatric illness (DSM-III) in UC and CD was 34% and 33% respectively. ● No statistically significant association between the presence of psychiatric illness and the present physical illness in UC. ● Psychiatric illness more common in the physically ill CD patients compared with those who were well: 50% vs. 8% ($P < 0.01$), using HADS criteria 66% vs. 37% ($P < 0.001$). ● The presence of psychiatric illness adversely affected physical recovery. Seventeen percent recovered when psychiatrically ill vs. 53% when psychiatrically well ($P < 0.025$).
Drossman et al 1991 (USA)	997 members of the Crohn's and Colitis Foundation of America (320 UC and 671 CD), no controls.	Cross-sectional random survey; self-administered questionnaire measuring IBD symptoms, psychosocial health, medication use, daily functional status, perceptions of health, and coping styles. Survey included: SIP, SCL-90, and the Ways of Coping-Revised Questionnaire.	<ul style="list-style-type: none"> ● The health status of this population is generally good and may be a result of effective coping styles. ● Patients with CD have more psychosocial difficulties, which appear related to greater symptom severity. ● Both psychosocial and physical health variables are related to number of physician visits, while primarily physical health variables are related to number of hospitalizations and surgeries.
Guthrie et al 2002 (UK)	116 consecutive patients (75 CD, 37 UC, 4 unspecified) attending GI clinic with a special interest in IBD. No controls.	Cross-sectional survey; IBD-related factors questionnaire developed by Drossman et al. (see above), a modified disease activity index, a measure of the severity of IBD symptoms, HADS, and SF-36.	<ul style="list-style-type: none"> ● Thirty patients (25.9%) had probable psychological disorder; Fifty five patients (47.4%) had possible psychological disorder (measured by HADS). ● Both psychological symptoms and disease severity or activity contributed independently to impaired health-related quality of life. ● After severity of disease taken into account, no significant differences between CD and UC in depression scores and health-related quality of life.
Helzer et al 1982 (USA)	50 consecutive CD patients obtained either from the university clinic (22) or a private internist clinic (28) + 50 consecutive controls with chronic medical illnesses of various kinds excluding gastrointestinal disorders obtained from the same sources.	Case-control study; gastroenterological assessment: CDAI, psychiatric assessment: the Renard Research Interview, EPI, and the Paykel Life Events Inventory.	<ul style="list-style-type: none"> ● Compared with controls, a significantly greater number of patients with CD met criteria for some psychiatric disorder at some time in their lives, and a significantly greater number had a diagnosis of depression. ● A greater number of CD patients than controls reported obsessional or phobic symptoms, and the mean number of obsessional symptoms was higher in CD patients than in controls. ● No evidence of an interaction between psychiatric disorder and CD.

TABLE 1. (Continued)

Name of the study	Sample and source of subjects	Methods	Results
Helzer et al 1984 (USA)	50 consecutive UC patients obtained either from the university clinic of gastroenterology (15) or a private internist clinic (37) + 50 consecutive controls with chronic medical illnesses of various kinds excluding gastrointestinal disorders obtained from the same sources.	Case-control study; gastroenterological assessment: barium enemas or x-rays or colonoscopy with biopsy; psychiatric assessment: structured psychiatric interview, EPI, a 90-item self-administered personality inventory, and the Paykel Life Events Inventory.	<ul style="list-style-type: none"> ● No greater frequency of diagnosable psychiatric disorder in UC patients than in controls. ● Those with UC and a psychiatric illness did not appear to have more serious gastrointestinal involvement, nor did severity of the UC predict more frequent or more serious psychiatric disorder. ● Personality profiles similar in UC patients and controls. ● No correlation between the frequency of potentially stressful life events within the 6 months prior to interview and severity of UC at the time of interview. ● Despite the fact that more than a quarter of the UC patients had some diagnosable psychiatric illness, the occurrence of psychiatric disorder was rarely documented.
Kurina et al 2001 (UK)	First study included 12,499 IBD patients (7268 UC and 5231 CD) and 800,000 controls with minor medical conditions not related to the conditions of interest, obtained from the ORLS database of southern England reporting general hospital admissions. Second study included 41,324 patients with depression and 12,687 patients with anxiety and approximately 800,000 controls.	Retrospective nested case-control studies; using a database of linked hospital record abstracts to test whether UC or CD co-occurred with depression or anxiety more often than expected by chance.	<ul style="list-style-type: none"> ● Both depression and anxiety preceded UC significantly more often than would be expected from the studies with controls. ● The associations were strongest when the depression/anxiety was diagnosed shortly before UC. ● The association between depression and UC was also significant when depression preceded UC by five or more years. ● Neither depression nor anxiety occurred before CD more often than expected by chance. ● Depression and anxiety were significantly more common after CD; the associations were strongest in the year after the initial record of CD. ● UC was followed by anxiety, but not by depression, more often than expected by chance and the association was strongest within one year of diagnosis with UC.
Levenstein et al 1994 (Italy)	79 UC patients attending hospital IBD clinic. No controls.	Cross-sectional double-blind study comparing patients with and without symptoms of the disease; disease activity: Truelove and Witts criteria, by endoscopy with biopsy and by barium enema. Psychological assessment: the Paykel Interview for Recent Life Experiences, STAI, CES-D, and PSQ. Six days after psychological testing unprepared rigid proctoscopy performed by the physician blinded to earlier results.	<ul style="list-style-type: none"> ● Among asymptomatic patients, the level of stress over the past 2 years on the General Perceived Stress Questionnaire was higher in the 11 with mucosal abnormalities than in the 35 with a normal rectal mucosa ($P = 0.004$). ● Among the entire population, symptomatic patients were more likely to recall major life events in the previous 6 months than the asymptomatic group ($P = 0.02$). ● The association of perceived stress with rectal mucosal abnormalities in asymptomatic patients is strongly suggestive of a true link between psychological factors and ulcerative colitis activity. ● Symptomatic patients had higher level of perceived stress, trait and state anxiety and depression.

TABLE 1. (Continued)

Name of the study	Sample and source of subjects	Methods	Results
Magni et al 1991 (France and Italy)	50 consecutive UC patients tertiary referral center + 50 controls with urolithiasis or symptomatic varicocele matched with UC patients for sex, age, and marital status.	Case-control study; disease activity: Edwards and Turnlove's classification. Psychological assessment: SAD-L and SCL-90.	<ul style="list-style-type: none"> ● History of psychiatric disturbance found in 11 UC patients (22%) and 8 controls (16%). ● At the time of the interview a psychiatric disturbance was present in 31 UC patients (62%) and four controls (8%). ● The most frequent diagnoses in UC patients were minor depression and generalized anxiety disorder. ● Patients with UC scored significantly higher than the controls on all the different SCL-90 subscales.
Mittermaier et al 2004 (Austria)	60 consecutive IBD patients (47 CD and 13 UC) in remission obtained from tertiary clinic. No controls.	Cohort prospective study with follow-up tests every 3 months for 18 months. Disease activity: CDAI and CAI. Psychological status: BDI, STAI, IBDQ, PSQ, and RFIPC.	<ul style="list-style-type: none"> ● At baseline, depression found in 17 of 60 (28%) patients. ● Thirty-two patients (59%) experienced at least one relapse during the 18 months of follow-up. ● BDI scores at baseline significantly correlated with the total number of relapses after 12 ($P < 0.01$) and 18 months ($P < 0.01$) of follow-up. ● Depression scores at baseline correlated with the time until the first recurrence of the disease ($P < 0.05$). ● Anxiety and low HRQOL also related with more frequent relapses during follow-up ($P < 0.05$ and $P < 0.01$, respectively).
Nordin et al 2002 (Sweden)	492 IBD patients (161 CD and 331 UC) identified by a registry at the university IBD clinic. A population-based sample. No controls.	Cross-sectional self-administered postal questionnaire comprising: SF-36, IBDQ, and HADS. Disease history collected from the register.	<ul style="list-style-type: none"> ● Patients with UC reported higher levels in all dimensions of health-related and disease-specific quality of life than did patients with CD. ● CD patients reported more anxiety and depression than did patients with UC. ● Patients with ileoanal anastomosis were more anxious and depressed than those with ileostomy.
North et al 1994 (USA)	12 articles with 10 subjects (10 out of 12 studies were controlled) on which statistical data were reported from standardized instruments of measure included.	Systematic review of the literature on psychiatric factors in CD with special attention to research methodology.	<ul style="list-style-type: none"> ● Most studies reported a significant association between CD and psychiatric factors. ● Many of the investigative groups reporting such an association in CD had also studied UC and failed to find a similar association in that disease. ● Published data indicate that CD, unlike ulcerative colitis, may be statistically associated with lifetime psychiatric disorders. This association appears to be more modest than in IBS, in which far higher rates of psychiatric disorders are reported than in CD.
Robertson et al 1989 (UK)	80 consecutive IBD patients (44CD and 36 UC) + 22 consecutive new referrals with suggested IBD (16 CD and 6 UC) + 40 controls with diabetes.	Case-control study; disease activity assessment not specified; psychological status: the questionnaire designed to assess patients' adjustment to IBD and their quality of life, EPI, and HADS.	<ul style="list-style-type: none"> ● High neuroticism and introversion scores in IBD patients (both before diagnosis and in established cases) than in controls ($P < 0.05$). ● Introversion scores increased with the duration of disease ($r = 0.51$). ● Depression was uncommon, occurring only in patients with active chronic disease. ● Patients believed there was a close link between personality, stress and disease activity. ● Forty two IBD patients thought the disease was initiated by a stressful life event or a 'nervous personality'.

TABLE 1. (Continued)

Name of the study	Sample and source of subjects	Methods	Results
Schwartz et al 1982 (USA)	46 CD patients seen in psychiatric consultation at the public clinic and hospital.	Cross-sectional retrospective review of clinical records. The researchers analyzed: demographic data, reason for psychiatric visit, duration of contact, history of IBD, current and past medication, history of significant stress (excluding this associated with IBD), and history of traumatic childhood.	<ul style="list-style-type: none"> • The most common reason that psychiatric consultation was requested was depression, followed by pain and narcotic-related problems. • Factors which appeared to contribute to psychiatric morbidity were: duration of CD, frequent hospitalizations and surgical procedures, presence of an ostomy, history of proctocolectomy, current psychosocial stress unrelated to Crohn's disease and a history of traumatic childhood experiences.
Simren et al 2002 (Sweden)	242 IBD patients (110 CD and 132 UC) from the university clinic + controls (normal values for the PGWB, GSRS, and HADS derived from the Swedish population; results of STAI compared with American working adults).	Case-control study; disease activity: by colonoscopy, rigid sigmoidoscopy, and blood tests. Psychological assessment: GSRS, HADS, STAI and PGWB.	<ul style="list-style-type: none"> • The psychological well-being in IBD patients in long-standing remission similar to that of the general population. • CD patients reported more psychosocial dysfunction, reduced well-being, and GI symptoms than UC patients. • Thirty-three percent of UC patients and 57% of CD patients had IBS-like symptoms. • The group with IBS-like symptoms (both UC and CD) had higher levels of anxiety and depression and more reduced well-being than those without. • Anxiety and reduced vitality were found to be independent predictors for IBS-like symptoms in these patients.
Tanaka et al 2005 (Japan)	77 UC consecutive patients obtained from the university internal medicine clinic. No controls.	Cross-sectional survey; assessment: questionnaire measuring patients' perception of difficulties of life, POMS, Jalowiec Coping Scale, the Emotional Support Network scale, and with the use of clinical records.	<ul style="list-style-type: none"> • A relatively large number of patients perceived a "decline of vitality or vigor" despite being in the remission phase. • In the presence of IBS-like symptoms, the scores for 'difficulties of life in society' or 'difficulties concerned with bowel movements' were high.
Tarter et al 1987 (USA)	53 consecutive IBD patients (26 CD and 27 UC) tertiary clinic + 28 normal controls obtained by advertisements.	Case-control study; disease activity: clinical examination; psychiatric assessment: DIS	<ul style="list-style-type: none"> • Compared to normal controls, CD patients manifest an increased prevalence of anxiety, depression and panic disorder occurring at any time in their life. • Only panic disorder had an excess prevalence in CD relative to community dwelling normals prior to the time of disease onset. • Individuals with UC did not demonstrate an increased prevalence of psychiatric disorder before or after disease onset.

BDI, Beck Depression Inventory; BMI, body mass index; CAI, Colitis Activity Index; CD, Crohn's disease; CES-D, the Center for Epidemiological Studies Depression Scale; CRS, Clinical Rating Scale; DIS, the Diagnostic Interview Schedule; EPI, the Eysenck Personality Inventory; GSRS, Gastrointestinal Symptom Rating Scale; HADS, the Hospital Anxiety and Depression Scale; IBD, inflammatory bowel disease; IBDQ, Inflammatory Bowel Disease Questionnaire; IBS, irritable bowel syndrome; PGWB, Psychological General Well-Being Index; POMS, Profile of Mood States; PSQ, the Perceived Stress Questionnaire; RFIPC, Rating Form of Inflammatory Bowel Disease Patient Concerns; SADS-L, the Schedule for Affective Disorders and Schizophrenia; sCDAI, simplified Crohn's Disease Activity Index; SCL-90, Symptom Check List 90; SIP, the Sickness Impact Profile; STAI, State and Trait Anxiety Inventory; UC, ulcerative colitis.

anxiety appeared in UC, but not CD patients, before the onset of the disease. As this was most striking in the year prior to the diagnosis of UC, they hypothesized that either depression or anxiety are causally related to UC, that patients are depressed or anxious because of early signs or symptoms of as yet undiagnosed UC, or even that UC may be partly a psychoneuroimmunological disease. However, the researchers evaluated this last possibility as unlikely, as they would then expect the psychological illness to precede UC by many years. These authors found no excess psychological comorbidity in CD prior to diagnosis, but did find excess anxiety and depression in both groups of IBD patients in the first year after diagnosis.⁴⁴ However, Tarter *et al*⁴⁹ report a discordant finding: with an excess of fearfulness and anxiety in CD patients prior to diagnosis, but no significant excess antecedent psychological disorder in UC. Tarter *et al*'s research involved a case-controlled study with 53 consecutive IBD patients and 28 healthy controls recruited by advertisement. It is difficult to reconcile these two divergent findings, as neither study was appropriately controlled. However, the sample size of the Kurina *et al*'s⁴⁴ group was substantially larger than that of the Tarter *et al*'s.⁴⁹

Other investigators have proposed that psychological disorders in IBD patients are generally a consequence of the disease activity as measured by disease activity indices,^{18,25} or a consequence of a recent new diagnosis, particularly of CD.^{17,44} One study of CD even found that the presence of psychological comorbidity makes physical recovery less likely,¹⁷ and another that depression is a risk factor for early relapse.¹⁶ Some authors have hypothesized that the association between active disease and psychological comorbidities may result from malnutrition, disabling symptoms,¹⁸ frequent hospitalizations and operations, particularly the presence of an ostomy, or proctocolectomy.²⁵ However, this premise is not supported by Andrews *et al*,¹⁷ who found no association between psychological comorbidity and the presence or absence of a stoma.

FUTURE DIRECTIONS

The initial reason for undertaking this review was the literature we discovered when seeking to answer the important question of the effect of anxiety/depression on the IBD course and severity. Unfortunately, the subsequent literature searches revealed little on this topic, as most relevant studies were either cross-sectional or case-controlled and as such were unable to resolve the temporal relationship between these psychological disorders and the somatic condition. Because of that, we decided to conduct such a study and hopefully fill the gap in knowledge. However, our searches did reveal several topics surrounding the comorbidities of anxiety/depression in IBD where divergent opinions have been frequently expressed. These controversies are the focus of this discussion. The main areas of controversy concern the

cooccurrence of psychological disorders with IBD as compared with the general population; the cooccurrence of psychological disorders with particular phase of IBD (remission versus relapse); the specificity of psychological disorders for the type of IBD (CD versus UC); the rate of psychological comorbidity compared with other disease states; and the timing of onset of psychological comorbidity with respect to the timing of onset of IBD.

These ongoing controversies indicate that the role of psychological disorders in IBD is still unclear. However, most available studies do demonstrate a high frequency of common psychological disorders such as depression and/or anxiety in IBD patients. These psychological comorbidities appear to occur at least as frequently in IBD as in other chronic illnesses. This association indicates the potential for a patient's psychology to perhaps play a role in the etiology and/or the course of IBD. Alternatively, IBD itself may increase the risk of patients developing psychological disorders. However, because of weaknesses in study design, selection and inclusion bias, and the use of inadequately matched control groups in the research that has been undertaken in this area to date, it is impossible to draw firm conclusions on these propositions. Moreover, psychological disturbances such as depression and/or anxiety are difficult to discretely assess in IBD patients, as no disease-specific instruments to measure psychological disorders have yet been validated. Many currently used instruments have items that may be influenced by active or poorly controlled disease (e.g., general well-being, fatigue, sleep disturbances, and appetite and weight changes). On the other hand, IBD activity indices also contain many subjective items that may be influenced by psychological, functional, or other concomitant illness of remitting/relapsing nature, rather than purely gastrointestinal inflammation. These items include but are not limited to: general well-being, fatigue, pain, and extraintestinal manifestations. Therefore, until we have better instruments to quantify both the psychological and inflammatory aspects of IBD, it is likely that ongoing controversies regarding the contribution of the psyche to IBD will remain.

Furthermore, Kurina *et al*,⁴⁴ among other investigators, suggest that patients with IBD should be thoroughly screened for psychological disorders and would benefit from specific psychological treatment. Interestingly, this opinion is common among researchers in this field, regardless of their findings with respect to these controversies, and despite the absence of any firm evidence to support this belief. The most appropriate approach to psychological treatment and whether it improves patients' physical or psychological well-being has not been clearly demonstrated to date. In fact, in published work no benefit of psychologically directed treatment has been demonstrated, with randomized controlled trials of psychotherapy⁵⁴⁻⁵⁷ giving negative results thus far.

This review therefore demonstrates that the role of

anxiety and depression in IBD warrants further well-designed and properly controlled research and, more specifically, that longitudinal prospective studies are urgently needed to adequately clarify the temporal relation between these psychological comorbidities and IBD.

ACKNOWLEDGMENTS

The study was funded by the Discipline of General Practice and the School of Psychology at the University of Adelaide, and the Department of Gastroenterology, Hepatology and General Medicine at the Royal Adelaide Hospital from International Postgraduate Research Scholarship. No industry sponsorship was involved. Authors are unaware of any conflicts of interest. However, Professor Deborah Turnbull has received research support from AstraZeneca Pty Ltd, Aventis Pharma Pty Ltd, Bayer Australia Ltd, and Pfizer Pty Ltd. Dr. Jane M. Andrews has been a consultant for Schering Plough and Pharmatel Fresenius Kabi. Professor Gerald Holtmann has been a consultant for Abbott, Altana, AstraZeneca, Takeda, Janssen-Cilag, Steigerwald, Knoll, and Novartis. He has also received research support from Altana, Ardey Pharma, Deutsche Forschungsgemeinschaft, Zeria, and Novartis.

REFERENCES

- Loftus EV Jr, Silverstein MD, Sandborn WJ, et al. Crohn's disease in Olmsted County, Minnesota, 1940–1993: incidence, prevalence, and survival. *Gastroenterology*. 1998;114:1161–1168.
- Loftus EV Jr, Silverstein MD, Sandborn WJ, et al. Ulcerative colitis in Olmsted County, Minnesota, 1940–1993: incidence, prevalence, and survival. *Gut*. 2000;46:336–343.
- Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. *Gastroenterology*. 2004;126:1504–1517.
- Australian Crohn's and Colitis Association. What is IBD? Available at: www.acca.net.au; 2005.
- Rampton D (ed.). *Inflammatory Bowel Disease: Clinical Diagnosis and Management*. London: Martin Dunitz; 2000.
- Lashner BA. Disease Management Project: Inflammatory Bowel Disease. The Cleveland Clinic; 2005.
- Sheffield BG, Carney MW. Crohn's disease: a psychosomatic illness. *Br J Psychiatry*. 1976;128:446–450.
- Lieberz K. Ulcerative colitis. A contribution to the discussion of causes. *Z Psychosom Med Psychoanal*. 1991;37:343–349.
- Scheib P, Wirsching M. Psychosomatic aspects of inflammatory bowel diseases. *Fortschr Med*. 1991;109:258–260.
- Ramchandani D, Schindler B, Katz J. Evolving concepts of psychopathology in inflammatory bowel disease. Implications for treatment. *Med Clin North Am*. 1994;78:1321–1330.
- Smith GJ, van der Meer G, Ursing B, et al. Psychological profile of patients suffering from Crohn's disease and ulcerative colitis. *Acta Psychiatr Scand*. 1995;92:187–192.
- Tocchi A, Lepre L, Liotta G, et al. Familial and psychological risk factors of ulcerative colitis. *Ital J Gastroenterol Hepatol*. 1997;29:395–398.
- Moser G. Ulcerative colitis and psychosocial factors. *Ital J Gastroenterol Hepatol*. 1997;29:387–390.
- Derogatis LR, Wise TN. *Anxiety and Depressive Disorders in the Medical Patient*. Washington: American Psychiatric Press; 1989.
- Härter MC, Conway KP, Merikangas KR. Associations between anxiety disorders and physical illness. *Eur Arch Psychiatry Clin Neurosci*. 2003;253:313–320.
- Mittermaier C, Dejaco C, Waldhoer T, et al. Impact of depressive mood on relapse in patients with inflammatory bowel disease: a prospective 18-month follow-up study. *Psychosom Med*. 2004;66:79–84.
- Andrews H, Barczak P, Allan RN. Psychiatric illness in patients with inflammatory bowel disease. *Gut*. 1987;28:1600–1604.
- Addolorato G, Capristo E, Stefanini GF, et al. Inflammatory bowel disease: a study of the association between anxiety and depression, physical morbidity, and nutritional status. *Scand J Gastroenterol*. 1997;32:1013–1021.
- Persoons P, Vermeire S, Demyttenaere K, et al. The impact of major depressive disorder on the short- and long-term outcome of Crohn's disease treatment with infliximab. *Aliment Pharmacol Ther*. 2005;22:101–110.
- Anton PA. Stress and mind-body impact on the course of inflammatory bowel diseases. *Semin Gastrointest Dis*. 1999;10:14–19.
- Drossman DA. Presidential address: gastrointestinal illness and the biopsychosocial model. *Psychosom Med*. 1998;60:258–267.
- García Vega E, Fernández C. Algunos factores predictores en la enfermedad de Crohn. *Psicothema*. 1998;10:143–151.
- Levenstein S, Prantera C, Varvo V, et al. Psychological stress and disease activity in ulcerative colitis: a multidimensional cross-sectional study. *Am J Gastroenterol*. 1994;89:1219–1225.
- Milne B, Joachim G, Niedhardt J. A stress management programme for inflammatory bowel disease patients. *J Adv Nurs*. 1986;11:561–567.
- Schwartz RA, Schwartz JK. Psychiatric disorders associated with Crohn's disease. *Int J Psychiatry Med*. 1982;12:67–73.
- Lustman PJ, Griffith LS, Freedland KE, et al. The course of major depression in diabetes. *Gen Hosp Psychiatry*. 1997;19:138–143.
- Fifield J, Tennen H, Reisine S, et al. Depression and the long-term risk of pain, fatigue, and disability in patients with rheumatoid arthritis. *Arthritis Rheum*. 1998;41:1851–1857.
- Carney RM, Rich MW, Freedland KE, et al. Major depressive disorder predicts cardiac events in patients with coronary artery disease. *Psychosom Med*. 1988;50:627–633.
- Moody G, Probert CS, Srivastava EM, et al. Sexual dysfunction amongst women with Crohn's disease: a hidden problem. *Digestion*. 1992;52:179–183.
- Andrews JM, Norton I, Dent O, et al. Inflammatory bowel disease: a retrospective review of a specialist-based cohort. *Med J Aust*. 1995;163:133–136.
- Gwee KA, Leong YL, Graham C, et al. The role of psychological and biological factors in postinfective gut dysfunction. *Gut*. 1999;44:400–406.
- Tan G, Hammond DC, Joseph G. Hypnosis and irritable bowel syndrome: a review of efficacy and mechanism of action. *Am J Clin Hypn*. 2005;47:161–178.
- Guthrie E, Creed F, Dawson D, et al. A controlled trial of psychological treatment for the irritable bowel syndrome. *Gastroenterology*. 1991;100:450–457.
- Calvert EL, Houghton LA, Cooper P, et al. Long-term improvement in functional dyspepsia using hypnotherapy. *Gastroenterology*. 2002;123:1778–1785.
- Maunder RG. Evidence that stress contributes to inflammatory bowel disease: evaluation, synthesis, and future directions. *Inflamm Bowel Dis*. 2005;11:600–608.
- Chatterjee K, Johnson ES. Kartagener's syndrome, depression and Crohn's disease. *J Indian Med Assoc*. 1969;52:389–391.
- Hryniewicz L, Kotlarek-Haus S, Gabry's K. Psychiatric aspects of ulcerative colitis. *Psychiatr Pol*. 1967;1:407–413.
- Belov VP. Mental disorders in patients with ulcerative colitis. *Vestn Akad Med Nauk SSSR*. 1963;18:82–90.
- Helzer JE, Stillings WA, Chammass S, et al. A controlled study of the association between ulcerative colitis and psychiatric diagnoses. *Dig Dis Sci*. 1982;27:513–518.
- Helzer JE, Chammass S, Norland CC, et al. A study of the association between Crohn's disease and psychiatric illness. *Gastroenterology*. 1984;86:324–330.
- Robertson DA, Ray J, Diamond I, et al. Personality profile and affective state of patients with inflammatory bowel disease. *Gut*. 1989;30:623–626.
- Tanaka M, Kazuma K. Ulcerative colitis: factors affecting difficulties of

- life and psychological well being of patients in remission. *J Clin Nurs*. 2005;14:65–73.
43. Simren M, Axelsson J, Gillberg R, et al. Quality of life in inflammatory bowel disease in remission: the impact of IBS-like symptoms and associated psychological factors. *Am J Gastroenterol*. 2002;97:389–396.
 44. Kurina LM, Goldacre MJ, Yeates D, et al. Depression and anxiety in people with inflammatory bowel disease. *J Epidemiol Commun Health*. 2001;55:716–720.
 45. Magni G, Bernasconi G, Mauro P, et al. Psychiatric diagnoses in ulcerative colitis. A controlled study. *Br J Psychiatry*. 1991;158:413–415.
 46. Guthrie E, Jackson J, Shaffer J, et al. Psychological disorder and severity of inflammatory bowel disease predict health-related quality of life in ulcerative colitis and Crohn's disease. *Am J Gastroenterol*. 2002;97:1994–1999.
 47. North CS, Alpers DH. A review of studies of psychiatric factors in Crohn's disease: etiologic implications. *Ann Clin Psychiatry*. 1994;6:117–124.
 48. Nordin K, Pahlman L, Larsson K, et al. Health-related quality of life and psychological distress in a population-based sample of Swedish patients with inflammatory bowel disease. *Scand J Gastroenterol*. 2002;37:450–457.
 49. Tarter RE, Switala J, Carra J, et al. Inflammatory bowel disease: psychiatric status of patients before and after disease onset. *Int J Psychiatry Med*. 1987;17:173–181.
 50. Drossman DA, Leserman J, Mitchell CM, et al. Health status and health care use in persons with inflammatory bowel disease. A national sample. *Dig Dis Sci*. 1991;36:1746–1755.
 51. Cavanaugh SV, Clark DC, Gibbons RD. Diagnosing depression in the hospitalized medically ill. *Psychosomatics*. 1983;24:809–815.
 52. Rodin G, Craven J, Littlefield C. Depression in the Medically Ill. An Integrated Approach. New York: Brunner/Mazel; 1991.
 53. Garcia Vega E, Fernandez Rodriguez C, Sanchez Lombrana JL. Behavioral profile of the patient with Crohn's disease. *Rev Esp Enferm Dig*. 1994;86:791–795.
 54. von Wietersheim J, Scheib P, Keller W, et al. The effects of psychotherapy on Crohn's disease patients—results of a randomized multicenter study. *Psychother Psychosom Med Psychol*. 2001;51:2–9.
 55. Keller W, Pritsch M, Von Wietersheim J, et al. Effect of psychotherapy and relaxation on the psychosocial and somatic course of Crohn's disease: main results of the German Prospective Multicenter Psychotherapy Treatment study on Crohn's Disease. *J Psychosom Res*. 2004;56:687–696.
 56. Jantschek G, Zeitz M, Pritsch M, et al. Effect of psychotherapy on the course of Crohn's disease. Results of the German prospective multicenter psychotherapy treatment study on Crohn's disease. German Study Group on Psychosocial Intervention in Crohn's Disease. *Scand J Gastroenterol*. 1998;33:1289–1296.
 57. Schwarz SP, Blanchard EB. Evaluation of a psychological treatment for inflammatory bowel disease. *Behav Res Ther*. 1991;29:167–177.