

Psychiatric Disorders in Patients with Immune-Mediated Inflammatory Diseases: Prevalence, Association with Disease Activity, and Overall Patient Well-being

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ABSTRACT. There has been much speculation on the importance of emotional factors in patients with immune-mediated inflammatory disease (IMID); it is only in the past 10 years that well designed, large-cohort studies have been able to clarify this relationship. This article provides an overview of evidence on the occurrence of depression and anxiety in IMID, and the role of these comorbidities as risk factors for onset of IMID, as well as the degree to which they affect the course of disease and treatment outcomes. (J Rheumatol 2011;38:Suppl 88;31–5; doi:10.3899/jrheum.110900)

Key Indexing Terms:

IMMUNE-MEDIATED INFLAMMATORY DISEASES
INFLAMMATION DEPRESSION ANXIETY

Psychiatric disorders, including anxiety and depression, are very common in the general population, with 1-year prevalence rates of 18% for anxiety and 9% for mood disorders¹. Estimates for lifetime prevalence are 28.8% and 20.8% for anxiety and mood disorders, respectively². This lifetime prevalence is likely to be underreported, however, due to the well known bias against reporting embarrassing behaviors or the fact that many people may simply forget that they had the disorder earlier in their life².

There has been a great deal of interest in the range of causal factors involved in the development of anxiety and depressive disorders. Longitudinal twin studies carried out

over the last 20 years³ have provided strong evidence for genetic factors, childhood adversity, and life stress close to the time of onset of the disorder as important contributors to the development of anxiety and depressive disorders.

The rates of anxiety and mood disorders are higher among individuals suffering from a chronic medical condition compared to the general population^{4,5,6}. Further, depression is more likely to coexist with conditions associated with higher levels of pain (i.e., fibromyalgia and arthritis) than those where pain levels are lower (i.e., heart disease and diabetes)⁴. Community studies also indicate that a great deal of the functional impairment and disability associated with health conditions is related to the presence of anxiety or depression^{7,8}. In a population survey of chronic medical conditions, impairment in work functioning was almost entirely restricted to cases with comorbid psychiatric disorders⁷.

Reciprocal influential processes between chronic medical conditions and anxiety/depression have also been suggested^{9,10,11}. In some instances, the experience of the disease may be stressful enough to set off or intensify the psychiatric condition. On the other hand, anxiety or depression may be sufficient to trigger or exacerbate the health condition^{9,10,11}. In addition, there has been significant debate about potential common pathways, particularly between depression and inflammatory conditions, related to dysfunctioning immunoregulatory mechanisms^{12,13,14}.

Given the prevalence of psychiatric disorders in the community and their potentially adverse influence on many aspects of patient life, it is important to consider the presence of these disorders in persons with immune-mediated inflammatory disease (IMID). However, several confounding factors that complicate this type of research should be noted^{15,16,17}. First, many patients seek treatment only when their condition gets worse and/or when they are experiencing

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ing more distress. This may introduce significant bias into samples that are recruited in clinical settings. Second, limited application of accepted international diagnostic criteria makes comparison between patient populations difficult in some cases. Finally, the lack of comparison groups makes it challenging to compare patients with IMID with the general population in terms of prevalence of anxiety and depressive disorders.

ANXIETY AND DEPRESSION IN INFLAMMATORY BOWEL DISEASE (IBD)

Several studies reported high prevalence rates of anxiety and depression in patients with IBD^{18,19,20,21}. Using a structured psychiatric diagnostic interview, Walker, *et al*¹⁸ compared 40 patients with IBD and 71 with irritable bowel syndrome (IBS) presenting consecutively at a tertiary care clinic for the presence of psychiatric concerns. The patients with IBS had consistently higher current and lifetime prevalence rates of mood disorders compared to patients with IBD. However, the lifetime prevalence of psychiatric disorders for the patients with IBD was still considerably higher compared to reported rates using the same diagnostic interview in community samples with other chronic medical illnesses (65% vs 42%, respectively).

Using a case-control design, Lerebours, *et al*¹⁹ compared 241 incident cases of IBD, identified through a regional IBD registry, to 255 blood donor community controls. Based on validated symptom self-report measures, the investigators confirmed that individuals with IBD had higher levels of depression and anxiety than the community controls.

A much larger nested case-control study, which included hospital and outpatient records, compared patients with IBD for expected rates of depression and anxiety relative to rates for 800,000 controls admitted to hospital for minor medical concerns²⁰. Higher rates of both anxiety and depression were found in patients with IBD compared to controls, especially early in the course of the disease. For patients with Crohn's disease (CD), the rates of anxiety or depression were 5 times higher than for controls. For patients with ulcerative colitis, the rate of anxiety was almost 4 times higher than for controls and the rate of depression was twice as high.

Recently, the Manitoba IBD Cohort Study assessed the prevalence of anxiety and mood disorders in a population-based cohort of respondents with clearly established IBD²¹. Prevalence was compared to a matched non-IBD comparison sample drawn from a Canadian survey of health and psychiatric disorders. There was a significantly higher lifetime prevalence of major depression for individuals with IBD compared to community controls (27% vs 12%; Table 1). Twelve-month prevalence rates were also almost twice as high for IBD (9.1% vs 5.5%). In regard to anxiety disorders, there was a higher lifetime prevalence of social anxiety for those in the community (11% vs 6%), and a trend to a higher lifetime prevalence of panic disorder for those with IBD (8.0% vs 4.7%). The same study found the presence of

a psychiatric disorder to be associated with female sex, lower quality of life (Inflammatory Bowel Disease Questionnaire) and psychological well-being, and higher health anxiety and perceived stress. In a multiple logistic regression analysis with all variables included, only being female or having lower psychological well-being were uniquely associated with the presence of an anxiety or mood disorder within the last 12 months (Table 2).

PSYCHIATRIC DISORDERS AS RISK FACTORS FOR IBD ONSET OR EXACERBATION

Although there is no conclusive support for psychiatric disorders contributing to risk for onset of IBD, the findings from a few relevant studies suggested that this cannot be ruled out. In the Manitoba IBD Cohort Study described above, 79% of people with IBD and a lifetime history of anxiety disorder had a first episode of anxiety more than 2 years prior to the diagnosis of IBD²¹. Similarly, 54% of persons with a mood disorder experienced onset 2 or more years prior to the IBD diagnosis. On the other hand, anxiety disorders most often start during childhood and adolescence and mood disorders are most prevalent during the late teens and early 20s, so the age of onset predates the most common ages of onset of IBD²¹.

Several studies also suggested that anxiety and depressive symptoms are more likely to be elevated during periods of increased disease activity and improve when disease activity is reduced^{22,23,24,25}. There are some indications that symptoms may diminish with the resolution of the IBD, but the current literature does not provide a clear picture to predict who will require clinical care for their psychiatric symptoms. The prospective studies, although limited, consistently indicate that depression plays a role in disease exacerbation, and as such should be taken into consideration when initiating IBD treatment^{22,23}.

According to a small 2-year study that assessed patients with CD at 2–3-month intervals, higher depression scores were associated with higher Crohn's Disease Activity Index scores in the subsequent time period²². Another study found the depression level at baseline correlated significantly with total number of IBD relapses²³. The median time until first relapse was much shorter for individuals with depression (97 days) compared to patients who were not depressed at baseline (362 days; $p < 0.05$). Higher anxiety at baseline was also associated with more frequent relapses in the followup period.

DEPRESSION IN PATIENTS WITH RHEUMATOID ARTHRITIS (RA)

Major depressive disorder is 2–3 times more common in individuals with RA than in the general population, affecting 13%–15% of RA patients²⁴. Similar to depression associated with other painful conditions, RA-associated depression is considered to be a consequence of the experience of chronic pain. Studies in the late 1980s and early 1990s suggested that

Table 1. Prevalence (%) of anxiety and mood disorders in the inflammatory bowel disease (IBD) cohort versus a matched non-IBD community sample, using conditional logistic regression. Adapted with permission from Walker JR, *et al.* Am J Gastroenterol 2008;103:1989-97. Copyright© the authors.

	IBD Cohort	12-Month Community Sample	OR (95% CI)	IBD Cohort	Lifetime Community Sample	OR (95% CI)
N	351	799		351	799	
Panic disorder, %	3.7	2.4	1.41 (0.69–2.89)	8.0	4.7	1.59 (0.96–2.63)
Social anxiety disorder, %	2.6	4.5	0.55 (0.26–1.16)	6.0	11.0	0.52* (0.32–0.85)
Major depressive disorder, %	9.1	5.5	1.53 (0.96–2.45)	27.2	13.3	2.20* (1.64–2.95)

* $p < 0.05$. OR: bivariate odds ratio.

Table 2. Relationship between presence of 12-month anxiety or mood disorder and gender, quality of life, and psychological functioning. Adapted with permission from Walker JR, *et al.* Am J Gastroenterol 2008;103:1089-97. Copyright© the authors.

Variable	OR	(95% CI)	Adjusted OR	(95% CI)
Female/male	2.83*	(1.57–5.11)	2.72*	(1.46–5.06)
IBD quality of life	2.71*	(1.49–4.94)	1.49	(0.72–3.11)
Health anxiety	2.55*	(1.36–4.79)	1.44	(0.68–3.10)
Perceived stress	2.93*	(1.71–5.01)	1.68	(0.87–3.25)
Psychological well-being (lower)	4.24*	(2.34–7.67)	2.60*	(1.24–5.41)

* Statistically significant at $p < 0.05$. Adjusted OR: OR controlling for other variables in the table.

the degree of depression varies in proportion to the level of pain^{25,26,27}. However, more recent studies have shown that depression in RA patients is also associated with physical disability, disease activity, and disease duration^{27,28}.

After controlling for relevant factors, Godha, *et al*²⁹ found patients classified as Class III RA (American College of Rheumatology functional status classification criteria) to be 5.9 times more likely than those in Class I RA to have a high tendency toward depression. Those belonging to Class II RA were 3.8 times more prone to depression than those in Class I (Table 3). Older age (≥ 68 yrs) and physical activity were negative predictors of depression in RA, whereas a higher number of comorbidities showed a significant positive association²⁹. The lower rate of depression found with the most severe class of RA (Class IV) and the oldest age group is not surprising, and is consistent with other studies^{30,31}. It is likely that the adaptation to chronic morbidity not only improves with age and duration, but as people grow older, their perception of the severity of symptoms is reduced due to age-related expectations.

THE EFFECT OF PSYCHOLOGICAL DISTRESS ON DISEASE ACTIVITY AND RESPONSE TO THERAPY IN PATIENTS WITH RA

Similar to IBD, comorbid depression in RA is associated

Table 3. Odds ratio estimates for tendency towards depression in rheumatoid arthritis. Reproduced with permission from Godha D, *et al.* Curr Med Res Opin 2010;26:1685-90. Copyright© 2010 Informa UK Ltd.

	OR (95% CI)
Functional status categories (Class I ^R)	
Class II	3.78 (1.41, 10.09)
Class III	5.92 (2.80, 12.50)
Class IV	2.36 (0.85, 6.61)
Age category (18–48 yrs ^R)	
49–55	1.04 (0.25, 2.52)
56–67	0.42 (0.16, 1.06)
$\geq 68^*$	0.11 (0.03, 0.35)
Physically active (No ^R)	0.46 (0.24, 0.85)
Comorbidity index (0 ^R)	
1	0.59 (0.17, 2.03)
2*	2.82 (1.08, 7.41)
3	1.61 (0.56, 4.61)

* Statistically significant at $p < 0.05$. ^R Reference category.

with worsening of disease activity and severity. Studies have also shown that the Health Assessment Questionnaire score, the most frequently used measure of physical disability, is strongly influenced by depression³¹. Comorbid depression may lead to work disability³² and increased mortality rates in RA³³. Further, depression may also influence response to RA treatment³⁴. A recent study showed that depressed patients had higher Disease Activity Score using 28 joint counts (DAS28) at all timepoints³⁵. In addition, treatment with an anti-tumor necrosis factor (TNF) agent was less effective in reducing DAS28 in patients with persistent depression (> 4 mo) than in those without depression [median interquartile range change in DAS28 1.71 (0–2.6) vs 2.2 (1.5–3.2); $p = 0.005$]. Another study demonstrated that discontinuation on anti-TNF therapy was independently associated with psychological distress³⁶. However, as only a small proportion of nondepressed patients at baseline subsequently developed depression following exposure to anti-TNF therapies, Hider, *et al*³⁵ suggested that anti-TNF does not have significant adverse effects on mood in RA.

RISK OF DEPRESSION AND ANXIETY IN PATIENTS WITH PSORIASIS

A high prevalence of psychiatric disorders in patients with psoriasis has been reported in numerous studies and in many different patient populations^{37,38}. Depression can occur as the sole psychological comorbidity associated with psoriasis, but other psychological symptoms may also be present. Excessive alcohol intake, for example, may further contribute to depression and distress in this patient group³⁹.

A recent population-based cohort study conducted in the United Kingdom evaluated incidence of depression, anxiety, and suicidality in 146,042 patients with mild psoriasis, 3956 patients with severe psoriasis, and 766,950 patients without psoriasis⁴⁰. It was found that patients with psoriasis are at increased risk of depression, anxiety, and suicidality compared to controls. Those with severe psoriasis were significantly more prone to depression and suicidal thoughts than patients with mild disease. The absolute risks of diagnosis of depression, anxiety, and suicidality due to psoriasis were 11.8, 8.1, and 0.4 per 1000 person-years, respectively (Table 4). These rates are likely low estimates because they relied on clinical diagnoses by primary care physicians. Patients with anxiety, depression, and suicidality often do not seek medical attention and they may not be identified unless there is specific screening for these problems.

MANAGING COMORBID DEPRESSION AND ANXIETY IN PATIENTS WITH IMID

Clinical evidence has demonstrated that the periods of disease onset and flares are particularly vulnerable times for patients with IMID regarding development of psychiatric disorders⁴¹. Recent data suggest that psychiatric comorbidities may exacerbate chronic health conditions through a number of mechanisms, including decreased adherence to prescribed treatments⁴², suppressed immune system functioning, and increased autonomic nervous system or hypothalamic-pituitary-adrenal axis activity⁴³. The weight of evidence for the negative effects of depression and anxiety on patients with IMID supports the call for routine screening of

these patients for psychiatric disorders. A few questions about stress and mood during routine clinical visits can usually identify those who are experiencing problems with the most common disorders⁴¹. Both anxiety and depression are highly treatable conditions for which a variety of pharmacological and nonpharmacological options are available. An open discussion with a patient regarding treatment options and his/her agreement and willingness to follow the course of the prescribed treatment are keys to successful outcomes. Effective management of anxiety or depressive disorders can decrease the patient's suffering, and lead to improved functioning and quality of life.

CONCLUSION

As with any chronic condition, there is a high rate of psychiatric disorders in patients with IMID compared to the general population. An important area of future research would be to explore how and to what extent these frequent comorbidities contribute to the course of IMID and their treatment outcomes. Research is also needed to evaluate the most effective approaches to management of anxiety and depression in the context of IMID, and to identify treatment alterations that may be required for these individuals.

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Table 4. Risk* of diagnosis of depression, anxiety, and suicidality attributable to psoriasis. Reprinted from Kurd SK, et al. Arch Dermatol 2010;146:891-5. Copyright© 2010 American Medical Association. All rights reserved.

Variable	Mild Psoriasis	Severe Psoriasis	All Psoriasis
Depression, attributable risk/1000 PY	11.5	25.5	11.8
Anxiety, attributable risk/1000 PY	8.0	8.1	8.1
Suicidality, attributable risk/1000 PY	0.4	0.4	0.4

* Adjusted for age and sex. PY: person-years.

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