

# Mental Comorbidity in Rheumatic Diseases

## Psychische Komorbidität bei rheumatischen Erkrankungen

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### ABSTRACT

In this review, we summarise the most relevant studies in a PubMed Search term “mental disorders and rheumatic disease” in the last 15 years. Mental disorders such as depression and anxiety are common in people with rheumatic diseases. Treating these comorbidities can improve the patient’s quality of

life. The high prevalence of symptoms of psychiatric disorders is a challenge for rheumatologists, especially with regard to the differentiation of possible psychiatric components in rheumatological diseases. Screening for psychiatric problems in patients with rheumatic diseases should be evaluated as soon as possible, as these can have a major influence on the perception of pain and physical functioning status from the outset. Mental health disorders are seen as a risk factor for poor patient outcomes, as patients may not adhere to medical treatments. The potential side effects of biological agents can increase patient anxiety and affect adherence to therapy. Therefore, interdisciplinary care would be of great advantage in the treatment of rheumatic patients with psychological comorbidities.

### ZUSAMMENFASSUNG

In dieser Übersicht wurden die wichtigsten Studien einer PubMed-Suche zum Thema „Psychische Störungen und rheumatische Erkrankungen“ der letzten 15 Jahre zusammengefasst. Psychische Störungen wie Depression- und Angsterkrankungen sind bei Personen mit rheumatischen Erkrankungen häufig. Durch eine Behandlung dieser Komorbiditäten kann die Lebensqualität der Patienten verbessert werden. Die hohe Prävalenz von Symptomen psychiatrischer Störungen ist eine Herausforderung für Rheumatologen, insbesondere im Hinblick auf die Differenzierung möglicher psychischer Komponenten bei rheumatischen Beschwerden. Das Screening auf psychiatrische Probleme bei Patienten mit entzündlich-rheumatischen Erkrankungen sollte so bald wie möglich evaluiert werden, da diese von Anfang an einen großen Einfluss auf die Wahrnehmung von Schmerzen und den körperlichen Funktionsstatus haben können. Psychische Störungen sind als Risikofaktor für ein schlechtes Outcome bei Patienten anzusehen, da die Patienten sich möglicherweise nicht an medizinische Behandlungen halten. Die möglichen Nebenwirkungen von biologischen Wirkstoffen können das Angstniveau der Patienten erhöhen und die Therapietreue beeinflussen. Von daher hätte eine interdisziplinäre Versorgung einen großen Vorteil bei der Behandlung von rheumatischen Patienten mit psychischen Komorbiditäten

## Epidemiology of psychiatric comorbidities in rheumatic diseases

The prevalence of clinical anxiety and clinical depression in rheumatic diseases is about twice the prevalence seen in the general population [1]. At a milder level, the occurrence of psychological distress that does not fulfil diagnostic criteria of anxiety and depression is even higher. Evidence indicates that this high prevalence is multifactorial [2]. In addition, different lines of evidence point to a negative association between rheumatoid arthritis (RA) and schizophrenia (SZ) [3].

### Depression and anxiety

Several studies analysed the prevalence of anxiety and depression in RA patients [4]. Of the patients studied using the Depression Anxiety and Stress Scale (DASS) and the Hospital Anxiety and Depression Scale (HADS), 13.5 % had anxiety only; 6.4 % depression only and 21.8 % had both anxiety and depression [5]. In another study the global distress for RA patients was almost twice as high as for the corresponding group from the general population. In a multiple logistic regression analysis the health assessment questionnaire (HAQ) was positively associated with global distress (odds ratio (OR) 3.63) while the visual analogue scale (VAS) for global disease activity was positively associated with symptoms of depression (OR 1.03). Female RA patients (OR 5.45) appear to have a higher probability for experiencing corresponding symptoms, whereas patients over 60 years appear to have less anxiety than younger patients (OR 0.11) [6]. In addition, demographic and socioeconomic aspects play a role in diagnosing a depressive disorder in RA patients [7].

A further study aimed to explore which factors are associated with self-reported anxiety and depression in Spondyloarthritis (SpA) patients. 3,711 patients from the SpAScania cohort were sent a postal questionnaire to assess health-related quality of life (HRQoL) and physical and mental functioning. In total, 683 (32 %) cases were classified as “possible anxiety” and 305 (14 %) as “possible depression” cases with mean (SD) HADS-A 5.9 (4.3) and HADS-D 4.4 (3.6). There were no differences among the SpA subtypes in HADS-A and HADS-D. HADS-A and HADS-D were associated with lower education, lower physical activity (HADS-D only), chronic pain problems, more fatigue, lower general health, lower HRQoL, lower level of functioning, higher disease activity, and lower self-efficacy. Associations with anxiety and/or depression appear multifactorial in patients with SpA including both personal and disease-related factors [8]. Another nationwide population-based retrospective cohort study was performed to analyze the relationship between ankylosing spondylitis (AS) and the subsequent development of psychiatric disorders. The AS cohort from in the Taiwan National Health Insurance (NHI) Research Database consisted of 2331 patients being compared to matched control patients without AS. The adjusted HR for depressive and anxiety disorders in subjects with AS were significantly higher than those of the controls during follow up [9].

Depression and anxiety are common neuropsychiatric complaints in SLE patients. The prevalence of anxiety and depression

varies substantially between studies due to methodological limitations, heterogeneity in defining anxiety and depression, patient selection, and metrics used. Moreover, there is a lack of studies evaluating the validity, reliability, and interpretability of commonly used screening tools for depression and anxiety in SLE patients [10]. Further comparative analysis of incidence and structure of anxiety-depressive spectrum disorders in patients with various rheumatic diseases was performed. Screening of depressive disorders (HADS-D  $\geq 8$ ) was positive in 29.4 % patients, ranging from 41 % in SLE to 20 % in Behcet's disease (BD) and primary Sjögren's syndrome. Anxiety disorders (HADS-A  $\geq 8$ ) was diagnosed in 44.4 % of the patients, ranging from 52 % in RA patients 38 % in BD [11].

Using Taiwan's National Health Insurance Research Database, patients with newly diagnosed primary Sjögren's syndrome (pSS) were compared with controls and newly diagnosed RA patients. Patients with pSS exhibited a significantly higher risk of developing a depressive disorder (adjusted incidence rate ratio [aIRR] = 2.11,  $p < 0.001$ ) and an anxiety disorder (aIRR = 2.20,  $p < 0.001$ ) when compared with the non-pSS cohort as well as with the RA patients. In particular female patients were found to be at greater risk for developing these comorbidities [12].

Depression is recognized as a risk factor for the development of suicidal behavior. A metaanalysis of 34 studies revealed that both suicidal ideation and completed suicide seems to be more frequent in patients experiencing SLE, fibromyalgia and arthritis. Major determinants were comorbid depression in fibromyalgia and arthritis, and neuropsychiatric disease in SLE [13]. Another metaanalysis of 48 studies in SSc patients demonstrated that negative emotions have very high levels in these patients, compared to both healthy population other chronic rheumatic patients assessed with the same instruments and cutoffs. Depression has been the most widely studied psychiatric comorbidity in systemic sclerosis, followed by anxiety. Despite the fact that anger is a common emotion in these diseases, it is poorly studied. Methodologic issues limited the ability to draw strong conclusions from studies of predictors. Disease-specific symptoms (swollen joints, gastrointestinal and respiratory symptoms and digital ulcers) and factors related to physical appearance were associated with negative emotions [14].

### Bipolar Disorder

Recent data suggests that patients with rheumatic diseases have increased prevalence of bipolar disorder (BD). The risk of developing BD was significantly higher among patients with RA compared to individuals without RA with a pooled relative risk of 2.06 (95 % confidence interval [CI], 1.34–3.17) [15]. A case-control study of 11,782 patients with RA and 57,973 age- and gender-matched controls revealed that the prevalence of BD in RA patients was increased (0.6 and 0.4 %, respectively,  $p = 0.036$ ) [16]. Moreover, another study of a RA cohort from Taiwan demonstrated that the BD incidence was higher in patients with RA (incidence rate ratio (IRR) 2.13, 95 % CI 1.12–4.24,  $P = .013$ ) than in control patients [17].

Otherwise, there are some data for the differential response of BD patients diagnosed with fibromyalgia syndroms (FM) to standard therapies, taking into account the markedly statistically significant increase of its prevalence in the syndrome. Ten percent of

100 most recent FM consultations included patients with an established diagnosis of BD. They had little if no response to traditional FM interventions and appeared to have vague and uncertain tender point examinations. The authors conclude that BD may be associated with a form of chronic musculoskeletal pain complaints that is not FM [18]. One study aims to explore the association between BD and the risk of gout using a nationwide population-based dataset from Taiwan National Health Insurance Research Database. Gout occurred in 16.4 % of the BD patients. After adjusting for potential confounders, the regression analysis showed that the hazard of developing gout during the 6-year follow-up period was 1.19 increased (95 % CI 1.10–1.24,  $P < 0.001$ ) for BD patients than their counterparts in the comparison cohort [19].

## Schizophrenia

Previous studies have documented reduced rates of RA in schizophrenia (SZ) [20]. In one population study from Manitoba, Canada, the incidence and prevalence of SZ was studied in a population-based cohort demonstrating that there was no difference between RA patients and the control group [21]. Moreover, several studies have shown that SZ has a protective effect on RA, with RA occurring less frequently in SZ cases than would be expected by chance, whilst other studies have failed to replicate this. Meta-analysis across studies over the past half-century showed that prevalence of RA in SZ cases was significantly reduced (OR = 0.48, 95 % CI: 0.34–0.67,  $p < 0.0001$ ) [22]. Another population-based study included every individual identified in the Swedish Population Register born in Sweden between 1932 and 1989. The risk for RA in SZ was significantly decreased (hazard ratio [HR] = 0.69, 95 % CI = 0.59–0.80), but similar reductions were noted for osteoarthritis (a noninflammatory joint disorder) and AS. Overall, first-degree relatives of SZ patients were not at reduced risk of RA, but the risk for seronegative RA was significantly decreased in children and siblings of SZ probands (HR = 0.13, 95 % CI = 0.02–0.95 and HR = 0.67, 95 % CI = 0.49–0.92, respectively). The analyses indicated the possibility of an inverse coinheritance of schizophrenia and seronegative RA [23] (► **Tab. 1**).

The purpose of another study was to determine if a history of autoimmune diseases (AD) is associated with an increased risk of later onset of SZ. Taiwan's National Health Insurance Research Database was used to identify a total of 64,817 AD patients and an

equal number of age-matched control patients. The main finding was the discovery of a higher incidence of subsequent SZ in patients with AD (HR 1.72, 95 % CI 1.23–2.4) after adjustment for other demographic characteristics. Specifically, the risk of SZ was observed to be significantly increased in SLE (3.73, 95 % CI 2.07–6.72), dermatomyositis (5.85, 1.32–25.94) and autoimmune vasculitis (2.44, 1.17–5.06). In addition, this study revealed some potential risk factors for developing SZ, including younger age (less than or equal to 50 years) and some comorbidities (hypertension, chronic obstructive pulmonary disease, and alcohol use disorder) [24].

## Inflammation

Inflammation seems to play a role in the pathophysiology of mood disorders. In recent years, several studies have shown increased levels of inflammatory and/or immune markers in patients with mood disorders [25]. Moreover, there is cumulating evidence suggesting potential roles of inflammatory cytokines in the pathogenesis of psychiatric disorders [26]. To clarify findings of elevated cytokine levels in depression, one study aimed to investigate the relationship between serum levels of cytokines, symptoms of depression and antidepressant treatment outcome. At baseline (T0) and 4 weeks following initiation of antidepressant treatment (T1), levels of various cytokines, CRP and depression ratings (Beck Depression Inventory - II) were assessed in patients with major depression and age- and sex-matched controls. The authors conclude that cytokines are not generally pro-depressive but rather relate to a more specific regulation of symptoms and severity in depression [27].

Otherwise, it was shown that pro- and anti-inflammatory cytokines mediate indoleamine 2,3-dioxygenase activity; this enzyme drives metabolism of tryptophan and kynurenine in the central nervous system and degrades serotonin. Alterations of serotonergic, noradrenergic, and glutamatergic neurotransmission have been associated with low-level neuroinflammation, and anti-inflammatory compounds have a therapeutic benefit in major depression and SZ, as shown in meta-analyses [28]. The novel treatment of autoimmune diseases with cytokine-blockers presents a unique strategy to understand the role of cytokines in affective disorder

## Genetic association between rheumatic diseases and psychiatric comorbidities

Genome-wide association studies in SZ and RA indicate genetic correlations, suggesting that there may be shared pathogenesis at the DNA level or downstream. Single nucleotide polymorphisms that conferred risk for both groups were localized solely to the extended HLA region. Among single nucleotide polymorphisms that conferred differential risk for SZ and RA, the majority were localized to *HLA-B*, *TNXB*, *NOTCH4*, *HLA-C*, *HCP5*, *MICB*, *PSORS1C1*, and *C6orf10*. Published functional data indicate that *HLA-B* and *HLA-C* have the most plausible pathogenic roles in both disorders. The genes harboring apparently pleiotropic single nucleotide polymorphisms are closely connected to RA and SZ associated genes through common interacting partners. A separate and independent analysis of the interactomes of RA and SZ genes showed a significant overlap between the 2 interactomes sharing several common pathways [3]. Furthermore, advances in understanding

► **Table 1** Incidence und prevalence of psychiatric comorbidities in patients with rheumatic diseases [5, 10, 16, 21, 22].

	Incidence rate ratio	Prevalence (%)
depression	1.46 [95 % CI] 1.35–1.58]	13.5–29.4
anxiety disorder	1.24 [95 % CI 1.15–1.34]	6.4–44.4
bipolar disorder	1.21 [95 % CI 1.00–1.47]	0.6
schizophrenia	0.48 [95 % CI: 0.34–0.67]	0.25

the genetic basis of RA have shown that much of the genetic liability to this condition is due to risk and protective alleles at the HLA DRB1 locus. These data allow robust testing of the hypotheses that allelic variation at DRB1 pleiotropically modulates the risk of RA and SZ. A systematic review of the literature indicates associations of DRB1 variants: DRB1 \* 04 alleles have been associated with increased risk of RA and autism but decreased risk of SZ, and DRB1 \* 13 alleles have been associated with protection from RA and autism but higher risk of SZ [29]. On the other hand, meta-analysis of genome-wide association studies to investigate the shared association loci between RA and SZ at the genome-wide scale showed a significant peak at the major histocompatibility complex (MHC) locus on chromosome 6 in both RA and SZ. Testing RA- and SZ-associated loci outside the human leukocyte antigen region showed no association with both RA and SZ. The findings are consistent with the role of MHC locus in the genetic correlation between RA and SZ, and suggest that either SZ has an autoimmune basis and/or RA has an active neurological component [30]. The genomics era presents an alternative paradigm for investigating the genetic relationship between 2 uncommon disorders. A study tested genome-wide common single nucleotide polymorphism (SNP) data from independently collected SZ and RA case-control cohorts to estimate the SNP correlation between the disorders. They utilized a genotype X environment (GxE) hypothesis for SZ with environment defined as winter- vs summer-born. The results are consistent with epidemiological observations of a negative relationship between SZ and RA reflecting, at least in part, genetic factors. Results of the month of birth analysis are consistent with pleiotropic effects of genetic variants dependent on an environmental context [31].

### BOX 1

Pathogenesis of psychiatric comorbidities:

1. Inflammation: pro- and anti-inflammatory cytokines mediate indoleamine 2,3-dioxygenase activity; this enzyme drives metabolism of tryptophan and kynurenine in the central nervous system and degrades serotonin
2. Genetic association: shared pathogenesis at the DNA level or downstream; single nucleotide polymorphisms that conferred risk is localized solely to the extended HLA region; allelic variation at DRB1 pleiotropically modulates risk of rheumatic disease and psychiatric comorbidities.

## Impact of psychiatric disorders on rheumatic diseases

In one study of RA patients, a strong association between depression and anxiety and the subjective components of the disease activity score (DAS28) was shown for tender joint count and patient global assessment. After adjusting for age, gender, disease duration, baseline tender joint count and patient global assessment respectively, higher levels of depression and anxiety at baseline were associated with increased tender joint count and patient global assessment scores at 1-year follow-up. Symptoms of depression and anxiety have implications for disease activity, as measured by

DAS28, primarily due to their influence on tender joints and patient global assessment [32].

Moreover, research on patient adherence demonstrated a non-significant association between anxiety and noncompliance. The relationship between depression and noncompliance, however, was substantial and significant (OR 3.03, 95 % CI 1.96–4.89). Compared with nondepressed patients, the odds are 3 times greater that depressed patients will be noncompliant with medical treatment recommendations. Evidence of strong covariation of depression and medical noncompliance suggests the importance of recognizing depression as a risk factor for poor outcomes among patients who might not be adhering to medical advice [33]. Moreover, the social context of individuals with RA affects both their coping strategies and their psychological responses to the disease, and can impair responses to treatment through disruption of patient-physician relationships and treatment adherence [34].

One study in patients with psoriatic arthritis (PsA) revealed that psychosocial burden of PsA negatively affects health-related quality of life (QoL). Patients suffered from sleep disorders, fatigue, low-level stress, depression and mood/behavioral changes, poor body image, and reduced work productivity. Additionally, each patient responds to pain differently, depending on a variety of psychological factors including personality structure, cognition, and attention to pain. PsA is associated with a considerable psychosocial burden and new assessment tools, specific to PsA, have been developed to help quantify this burden in patients. Future management algorithms of PsA should incorporate appropriate assessment and management of psychological and physical concerns of patients. Furthermore, patients with PsA should be managed by a multidisciplinary team that works in coordination with the patient and their family or caregivers [35]. It has been shown that in patients with autoimmune diseases, when depression coexists, the quality of life is worse and medical treatment and management is compromised. Depression-like symptoms, such as fatigue and lack of interest, are also common in inflammatory rheumatic diseases and are often associated with poor quality of life [25].

## Activity of rheumatic diseases and psychiatric disorders

Mental health comorbidities in rheumatic diseases could interact with disease processes, including dysregulation of inflammatory responses, prolonged difficulties with pain and fatigue, and the development of cognitive and behavioural responses that could exacerbate the physical and psychological difficulties associated with rheumatic diseases [34].

One study showed that in RA patients the incidence of depression and anxiety was higher than in patients with osteoarthritis (OA) but they experienced lower levels of pain, which was more expressed in OA patients. With regard to autoimmune disorders, these symptoms may reflect the direct effect of cytokines on the central nervous system. As far as it concerns chronic-degenerative diseases, anxiety and depression are usually considered “reactive” to pain, not “constitutive” [36]. Among rheumatic diseases, SLE reveals the highest frequency of central nervous symptoms. Psychiatric abnormalities of various severity, including anxiety disorders, depressive symptomatology and psychosis are present in over 90 % of the patients. Reactive depression in coping with a chronic disease

is, however, a psychologically plausible factor in addition to specific cerebral lesions [37]. A metaanalysis of 48 studies in patients with SSc revealed that disease-specific symptoms (swollen joints, gastrointestinal and respiratory symptoms and digital ulcers) and factors related to physical appearance were associated with negative emotions and development of psychiatric disorders [14]. Another population-based study between 1989 and 2012 aimed to determine whether the incidence of psychiatric disorders is increased in the 5 years before the diagnosis of some autoimmune diseases (AD). As early as 5 years before diagnosis, the incidence of depression (IRR 1.54; 95 % CI 1.30–1.84) and anxiety disorders (IRR 1.30; 95 % CI 1.12–1.51) was elevated in the AD cohort. In addition, the incidence of BD was elevated beginning 3 years before AD diagnosis (IRR 1.63; 95 % CI 1.10–2.40) [20].

## BOX 2

Possible interactions of psychiatric disorders and rheumatic diseases

- a. psychiatric disorders associated with:
  - subjective components of DAS28 primarily due to influence on tender joints and patient global assessment
  - possible noncompliance
  - disturbed pain perception, cognition, and attention to pain
  - coping strategies and the psychological responses to the disease
  - disturbed patient-physician relationship
  - negative effects on health-related quality
- b. activity of rheumatic disease may lead to:
  - exacerbation of psychological difficulties due to prolonged pain and fatigue development followed by cognitive and behavioral responses
  - negative emotions and development of psychiatric disorders due to disease-specific symptoms (swollen joints etc.) and factors related to physical appearance

## Impact of antirheumatic therapy on psychiatric disorders

### Steroids

In animals, stress and corticosteroids can be associated with both reversible and irreversible changes in the hippocampus. Changes in memory and hippocampal structure, perhaps in part due to cortisol elevations, are reported in some patients with mood disorders. Minimal data are available on the effects of long-term exposure to corticosteroids on the human hippocampus. In patients with rheumatic diseases receiving long-term prednisone therapy, greater depressive symptom severity, poorer memory and smaller hippocampal volumes was noted compared to controls. In this report, patients and controls were assessed a mean of 4 years after the first assessment to determine if depressive and manic symptoms and cognition changed over time. Follow-up MRIs for hippocampal volume analysis were available in prednisone-treated participants. With the exception of an increase in depressive symptoms in those receiving prednisone, participants and controls did not show significant changes in mood or cognition from the initial

assessment. Of interest, one participant discontinued prednisone and showed improvement in psychiatric symptoms and cognition. Hippocampal volumes showed inconsistent findings. Although preliminary in nature, the results suggest that long-term prednisone therapy is associated with initial changes in mood, memory and hippocampal volume that appear to stabilize over time. However, in this study the results were not adjusted for disease activity [38]. In addition, one study found that steroid use was a potential protective factor for the development of SZ [23]. Furthermore, corticosteroid drugs may be effective in alleviating mild psychiatric symptoms as well [37].

### Allopurinol

Since bipolar disorder (BD) seems to be associated with purinergic system dysfunction, allopurinol might be effective in treating symptoms of mania. A systematic review and meta-analysis of 5 randomised placebo-controlled trials (RCTs) analysed the effects of adjunctive allopurinol on BD symptom. Participants with allopurinol had a significantly greater decrease in mania symptoms than those with placebo ( $P = 0.007$ ), especially in people with the most severe forms of mania. Remission rates were significantly higher among individuals receiving allopurinol, whereas there was no difference for discontinuation and side-effects [39]. Another double blind, placebo-controlled study included BD patients during acute mania were randomly assigned either to a treatment (sodium valproate 15–20 mg/kg + 300 mg allopurinol twice a day) or to a control condition (sodium valproate 15–20 mg/kg + placebo). Compared to the control group, uric acid levels and symptoms of mania decreased significantly over time in the treatment group. Probability of remission after 4 weeks was 23 times higher in the treatment group than in the control group and lower uric acid levels after 4 weeks were associated with symptom improvements. Allopurinol using as an augmentation agent to mood stabilizers or anti-psychotics was tested only for 4 weeks (information about of side effects of the relative high doses of allopurinol was not available) [40].

### NSAID

Clinical trials with non-steroidal anti-inflammatory drugs (NSAID) in patients with psychiatric disorders demonstrated positive effects and it has been proposed to be of clinical use in the treatment of psychiatric disorders [24]. For example, Cyclooxygenase- (COX) inhibitors not only reduce the levels of proinflammatory cytokines, but also affects glutamatergic neurotransmission and tryptophan/kynurenine metabolism. Several studies have been performed with celecoxib in SZ; the studies found a therapeutic effect, mainly in the early stages of the disorder. In addition, a statistically significant therapeutic effect of celecoxib on depressive symptoms was detectable in a study with patients with major depression [27]. A meta-analysis appears to support the use of NSAIDs in acute depression; the effects of celecoxib for which the best evidence exists to date mainly bias the overall effect. Efficacy data of non-selective COX inhibitors on depressive symptoms are limited and out of 6 studies, only a retrospective analysis shows positive results for a non-selective COX inhibitor. The main problematic factor is that current evidence rests on trials in acute depression. Because of the dynamic nature of depression, it is important to explore if NSAIDs and other anti-inflammatory treatments may have a preventive

role in early stages of depression and for relapse prevention [41]. Furthermore, 5 RCTs (4 unipolar depression studies and one bipolar depression study) were meta-analyzed. The add-on celecoxib group had a statistically significant decrease in means of the HADS score at week 4 (pooled difference in means = 3.3, 95% CI 1.2–5.3,  $p = 0.002$ ) and week 6 (pooled difference in means = 3.43, 95% CI 1.9–4.9,  $p < 0.0001$ ). The add-on celecoxib group also showed higher response (OR 6.6, 95% CI 2.5–17,  $p < 0.0001$ ) and remission rates (OR 6.6, 95% CI 2.7–15.9,  $p < 0.0001$ ) compared with the placebo group [42]. However, results with NSAIDs have been mixed in human observational studies, with both better and worse depression outcomes reported. Four small (pooled  $N = 160$ ) randomized controlled trials suggest that celecoxib (200–400 mg/d) as co-medication of an antidepressant therapy improves 4–6 week outcomes in major depressive disorder. The most recent metaanalysis included 26 RCTs suggesting that anti-inflammatory agents reduced depressive symptoms (SMD -0.55, 95% CI -0.75 to -0.35,  $I^2 = 71\%$ ) compared with placebo. Higher response (RR 1.52, 95% CI 1.30 to 1.79,  $I^2 = 29\%$ ) and remission rates (RR 1.79, 95% CI 1.29 to 2.49,  $I^2 = 41\%$ ) were seen in the group receiving anti-inflammatory agents than in those receiving placebo [43]. There are no data, however, to support the use of celecoxib or other NSAIDs in antidepressant-resistant depression. There are also concerns about adverse events associated with NSAID treatment and about pharmacodynamic drug interactions between these drugs and serotonin reuptake inhibitors [44]. The possible impact of anti-inflammatory treatments on immune changes in different phases of depression warrants caution for a wide and preventive use of anti-inflammatory agents in depression-associated inflammation [41].

### DMARDs

Increased concentrations of inflammatory biomarkers predict antidepressant nonresponse, and inflammatory cytokines can sabotage and circumvent the mechanisms of action of conventional antidepressants. Therefore, a study was performed with medically stable outpatients with major depression who were either on a consistent antidepressant regimen ( $n = 37$ ) or medication-free ( $n = 23$ ) for 4 weeks or more and who were moderately resistant to treatment as determined by the Massachusetts General Hospital Staging method. The patients received 3 infusions of the TNF antagonist infliximab (5 mg/kg) ( $n = 30$ ) or placebo ( $n = 30$ ) in a 12-week trial. There was no overall difference in the Hamilton Depression Scale (HAM-D) scores between treatment groups over time. However, there was a significant interaction between treatment and biomarker for inflammation. Increased hs-CRP concentration at baseline was correlated with a better response to infliximab ( $P = 0.01$ ). A treatment response ( $\geq 50\%$  reduction in HAM-D score at any point during treatment) was observed in 62% patients (8 of 13) of infliximab-treated patients with elevated CRP vs. 33% patients (3 of 9) in the placebo group. In addition, baseline concentrations of TNF and its soluble receptors were significantly higher in infliximab-treated responders vs. non-responders ( $P < 0.05$ ), and infliximab-treated responders exhibited significantly greater decreases in hs-CRP from baseline to week 12 compared with placebo-treated responders ( $P < 0.01$ ). This proof-of-concept study suggests that TNF antagonism does not have generalized efficacy in

treatment-resistant depression but may improve depressive symptoms in patients with high baseline inflammatory biomarkers [45].

Furthermore, another study was performed to investigate the prevalence of depression in RA patients starting anti-TNF therapy and how mood alters after exposure to anti-TNF. Patients starting anti-TNF therapy were assessed for depression using the Hospital Anxiety and Depression Scale (HADS-D). Change in mood was assessed together with disease activity parameters for 12 months. Patients who remained persistently depressed at 4 months had their clinical case notes reviewed to determine whether their low mood had been recognized or treated. Depression was common in this cohort. Depressed patients had higher DAS28 scores at all time points, and patients with persistent depression had smaller reductions in DAS28 ( $P = 0.005$ ). Only 57% (13/23) patients with persistent depression at 4 months had their depression recognized or managed within the rheumatology clinic. Depression is common but under-recognized in RA patients starting on anti-TNF therapy. Patients with persistent depression tended to respond less well to anti-TNF with smaller reductions in DAS28 [46].

A systematic review of the literature regarding the efficacy of anti-inflammatory drugs in major depressive disorder (MDD), SZ and BD patients was performed. The results indicated that COX-2 specific inhibitors showed effectiveness in SZ. Again, anti-TNF-alpha showed effectiveness in resistant MDD with blood inflammatory abnormalities [47].

In patients with rheumatic diseases, few studies have been published focusing on psychiatric disorders. One study included 105 RA patients who were treated with methotrexate, leflunomide, hydroxychloroquine and biologics. The patients using methotrexate and leflunomide reported lower scores on suicidal ideation than those using hydroxychloroquine and biologics. Greater scores for depression, as a comorbidity in RA, increased the rate of suicidal ideation. Patients taking biologics had the highest rates of depression, anxiety and suicidal ideation among all patients studied. In general, it has to be taken into account that there is a bias concerning disease activity and severity between the medications studied. However, psychiatric aspects such as depression, anxiety and even suicide ideation should be addressed in patients with rheumatic diseases [48]. It has also been noted that there are distinct configurations of conditions conducive to anxiety and depression in both anti-inflammatory and biologic agent groups. The observed constellation of dependencies between variables indicates that the choice of treatment scheme differentiates pain levels. This confirms the assumption that pain intensity, coping strategies, and resilience depend on the severity of anxiety and depression [49].

On the other hand, patients with RA and comorbid psychiatric disorders had poor persistence of MTX and TNF therapies. The results suggest that earlier discontinuation and low adherence to therapy among patients with RA with these psychiatric comorbidities may contribute to worse disease outcomes. Mechanisms by which these comorbidities contribute to lower adherence deserve further investigation and may lead to targeted interventions to improve disease outcomes [50]. Furthermore, the potential side effects of biological agents may increase the anxiety levels of patients and influence not only their desire to use these therapies but also their adherence to treatment. A study of 1134 patients who were using biologics for at least 3 months with a diagnosis of a rheumatic di-

sease revealed that general anxiety levels were elevated. The most common cause for drug-related concerns was the potential side effects of the drugs (59.5%). Among the potential side effects, cancer risk was the most common cause for concern (40.1%), followed by the risk of tuberculosis activation (30.7%). Anxiety levels were higher in patients who experienced side effects than in other patients and this difference was statistically significant ( $P < 0.05$ ). Anxiety related to biological agents may significantly affect the patients' anxiety levels. Awareness regarding the patients' concerns and expectations related to the drug is important to ensure drug adherence and concordance to treatment [51].

### BOX 3

Treatment of rheumatic disease and psychiatric comorbidities

#### a. Steroids

- greater depressive symptom severity, poorer memory and smaller hippocampal volumes in patients receiving long-term prednisone therapy
- potential protective factor for the development of schizophrenia
- may be effective in alleviating mild psychiatric symptoms

#### b. NSAR

- in particular COX-2 specific inhibitors have positive effects in psychiatric disorders

#### c. DMARDs

- anti-TNF-alpha showed important effectiveness in resistant major depressive disorder with elevated biomarkers for inflammation
- patients with persistent depression tended to respond less well to anti-TNF therapy
- potential side effects of biological agents may increase the anxiety levels of patients and influence treatment adherence

## Conclusion

Rheumatic diseases are long-term disorders significantly impairing the somatic, emotional, and psychological functioning of its sufferers. Affected individuals are characterized by an increased level of psychiatric disorders. Correlational studies suggest that possible factors for psychiatric disorders include the suffering accompanying somatic symptoms, functional limitations, pro-inflammatory cytokines, helplessness due to the uncontrollable, unpredictable and progressive nature of the disease, and other factors associated with having a chronic disease. The high prevalence of psychiatric abnormalities is a challenge for rheumatologists, particularly with respect to the differentiation of possible psychosomatic components in non-inflammatory joint complaints. Impact of psychological interventions to address these difficulties for patients could be useful in clinical praxis.

## Conflict of interest

OS: Lectures and consulting fees from MSD, Pfizer, CB: Lectures and consulting fees from Abbvie, Boehringer, BMS, Gilead, Pfizer, Roche, Sanofi

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