Neuropsychiatric Disease and Treatment

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REVIEW

The Effect of Depression on Disease Activity and Treatment Response in Patients with Inflammatory Arthritis: Results from a Narrative Literature Review

Arav Dagli[1], Rebecca R Lee[2], James Bluett[1,3]

[1]Versus Arthritis Centre for Genetics and Genomics, Centre for Musculoskeletal Research, the University of Manchester, Manchester, UK; [2]Centre for Epidemiology Versus Arthritis, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK; [3]NIHR Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester, UK

Correspondence: James Bluett, Versus Arthritis Centre for Genetics and Genomics, Centre for Musculoskeletal Research, the University of Manchester, Manchester, UK, Email james.bluett@manchester.ac.uk

Background: Inflammatory arthritis refers to a group of diseases that have a common presentation of joint pain, stiffness, and inflammation. Meanwhile, major depressive disorder is a mental health disorder characterized by anhedonia and low mood. Inflammatory arthritis patients have high rates of major depressive disorder, estimated at being up to 38.8%. Depression leads to a significant reduction in patient's health-related quality of life, treatment adherence, and many other measures of health, both subjective and clinical.

Purpose: This literature review explores the effect that depression has on treatment response for the drugs used in inflammatory arthritis.

Methods: A systematic search using PubMed was conducted identifying articles which were each reviewed for relevance and eligibility.

Results: Depression was negatively associated with treatment response to all classes of drugs used to manage inflammatory arthritis, with an increased disease activity and/or number of swollen/tender joints, as well as a reduced rate of remission being recorded for patients with depression compared to those without. However, this effect on treatment response was less clear when conventional synthetic Disease Modifying Anti-rheumatic Drugs were studied, possibly because their anti-inflammatory effects have wide impacts on the whole immune system, whereas biologic Disease Modifying Anti-rheumatic Drugs have very specific targets.

Conclusion: Inflammatory arthritis patients have a significantly lowered response to most drugs when they have depression. Screening and treating depression may attenuate this association. It is recommended that further research focuses on screening for and treating depression in inflammatory arthritis patients.

Keywords: arthritis, inflammation, depression, csDMARD, bDMARD, adherence

Introduction

The inflammatory arthritides are chronic incurable diseases of heterogeneous aetiology that can lead to joint pain, swelling and disability. Inflammatory arthritis is a broad term that encompasses a number of immune-mediated inflammatory diseases that often share common inflammatory pathways and an underlying immune target, the joint. Disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate and the targeted second-line biological DMARDs, are used to control disease activity but response is not universal. Up to 40% of individuals with rheumatoid arthritis, one of the most common inflammatory arthritides affecting 1% of the adult population,[1] will experience a bDMARD failure.[2]

Depression is a common heterogeneous illness that can have a significant effect on an individual's ability to function and be life threatening. Current National Institute for Health and Care Excellence (NICE) guidelines suggest a number of treatment options are available depending on the severity.[3] These options include group exercise, psychotherapy and pharmacological therapies such as selective serotonin reuptake inhibitors (SSRI's). Therapeutic strategies for severe depression include electroconvulsive therapy and transcranial magnetic stimulation.[3–6] Other pharmacological treatments such as ketamine have also been explored.[7,8] A growing body of research shows that depression and inflammatory arthritis (IA) are inextricably

Received: 22 December 2023
Accepted: 22 May 2024
Published: 5 July 2024

connected, with up to 42% of patients living with IA are also living with depression.[9] Depression is significantly more common in IA patients than the healthy population, which was around 10% of UK adults prior to the COVID-19 pandemic.[9,10] A meta-analysis in 2014 found that the prevalence of depression in rheumatoid arthritis (RA) patients is 16.8% according to gold standard testing (which consists of a psychiatric interview/assessment), but the prevalence increases to 38.8% when self-scoring questionnaires such as the Patient Health Questionnaire 9 (PHQ-9) are used. The rate of depression is higher in arthritis than in diabetes (~12%) and Parkinson's (~17%), a further reinforcement that they are significantly linked. The Matcham et al meta-analysis found a significant negative association between age and depression prevalence; younger RA patients had a higher prevalence of depression, suggesting that the phenomenon is not due to the increased chance of older people developing depression.[9] There is, however, significant heterogeneity in prevalence of depression across the inflammatory arthritides and patients with RA have been shown to have lower rates of depression compared to psoriatic arthritis but still significantly higher compared to the general population.[9,11]

Patients with inflammatory arthritis have raised levels of pro-inflammatory cytokines such as TNF-α and IL-6 that may induce neuroinflammation and depression.[12] Despite the knowledge that IA and depression have a strong association, there is a lack of understanding on how depression affects response to IA drugs. This narrative review aims to determine whether depression influences drug efficacy for IA and explore possible mechanisms for this influence. From the findings of this research, further studies can be directed to specifically address this connection and improve the efficacy of treatments for inflammatory arthritis.

Materials and Methods

PubMed was searched using the search string: "depression"[title] AND ("response"[title] OR drug*[title] OR "response"[tiab]) AND "arthritis"[title]. A filter was applied to only include articles from the last 10 years (2013–2023).

Results

After removing duplicate articles, 24 articles were retrieved (Figure 1). 5 more were added through snowballing. 13 papers were excluded because they were irrelevant to this topic. One paper was excluded because it was not written in English. One paper was excluded because it focused on a very specific target population (US army veterans) and one paper was excluded because it was a literature review of only 7 studies. The main findings of the 13 papers retrieved are summarised in Supplementary Table 1.

Discussion

Mechanism of Depression Pathogenesis in IA Patients

There are both inflammatory (biological), psychological and social mechanisms through which depression can develop in IA patients. As seen in other illnesses where chronic pain makes up a large part of the disease burden, the patient's individual response to stress can have a large impact on their mood.[13]

From a neuro-biological perspective, IA and depression share a common pro-inflammatory pathophysiological mechanism and there is a complex interplay between depression, inflammation, DMARD therapy and disease response. Inflammation plays a key role in the pathogenesis of depression, and inflammatory cytokines can influence mood and behaviour in four ways,[14] discussed below.

Decreased Synaptic Availability of Serotonin

The first mechanism is through decreased synaptic availability of serotonin due to the breakdown of tryptophan, one of the serotonin precursors, in the kynurenine pathway.[14] RA patients show a significantly decreased baseline level of tryptophan, and an increased baseline level of kynurenine, a metabolite of tryptophan.[15] Tryptophan is, therefore, being metabolised through this pathway, which leads to reduced serotonin synthesis.[15]

Increased Oxidative Stress

The second is through increased oxidative stress due to the production of reactive oxygen and nitrogen species.[14] T cells/macrophages release TNF-α and IL-1β, which produce reactive oxygen species (ROS).[16] Through positive feedback

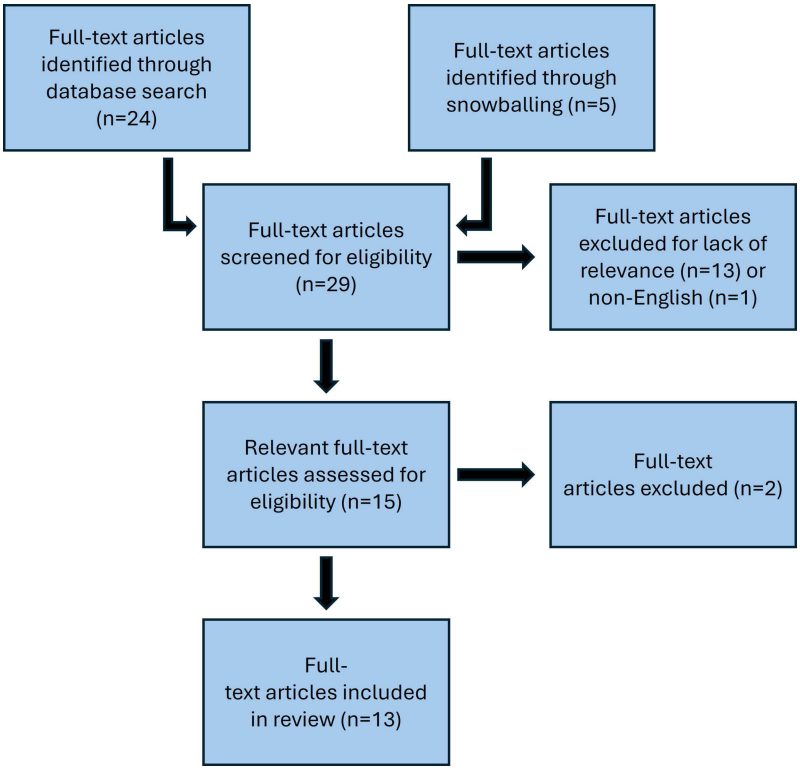

Figure 1 A flow diagram of the literature review process.

mechanisms, the ROS produce more pro-inflammatory cytokines.[16] The pro-inflammatory cytokines activate MAP kinase, which activates NF-κB, a transcription factor that regulates inflammation by increasing the production of the cytokines IL-1 and TNF-α.[16] There are also positive feedback mechanisms further increasing the activation of NF-Kb.[16] Malondialdehyde, a marker of increased oxidative stress, is found in significantly higher levels in patients with depression.[17] Additionally, lower levels of superoxide dismutase, a ROS scavenger, were found in patients with depression.[17] These results suggest that oxidative stress plays a critical role in the pathogenesis of depression.[17]

Increased Synaptic Glutamate

Thirdly, increased synaptic glutamate can lead to excitotoxicity.[14] Rheumatoid arthritis patients show a 52-fold increase in the level of glutamate in synovial fluid, which leads to the activation of AMPA, NMDA, and Kainate glutamate receptors, causing the release of IL-6.[18] When inflammatory markers alter the blood-brain barrier (BBB), it can cause antibodies that the BBB normally blocks to cross the barrier and activate glutamate receptors on glial cells. This leads to excitotoxicity which is linked with the significant behavioural changes associated with depression.[19] IL-6 is specifically connected with depression independent of this effect, with increased levels being seen in the subgenual anterior cingulate cortex of depressed patients compared to control subjects.[20] This area of the brain is important for regulating emotion, and degeneration in this area is associated with anhedonia and depressed mood.[20] Even after accounting for physical health outcomes, anti-IL6 therapies have statistically significant antidepressant effects, further reinforcing that it is a major contributor towards inflammation-derived depression.[21]

Decreased Neurotrophic Factors Causing Decreased Neurogenesis in the Hippocampus

Lastly, decreased neurotrophic factors can lead to decreased neurogenesis in the hippocampus.[14] RA leads to lower levels of brain-derived neurotrophic factor (BDNF) in the brain, but increased levels of BDNF in serum.[22] Depressed patients have lower levels of BDNF in their brains, specifically in their prefrontal cortex/hippocampus.[22] BDNF is responsible for the growth and regeneration of neurons, which may explain the reduced volume of the hippocampus classically seen in depression.[22] The decreased brain BDNF may be due to endothelial dysfunction rather than a direct result of

inflammation.[22] Significant amounts of BDNF are synthesized from the endothelial cells, which are activated by inflammation in RA.[23] This causes the cells to increase the expression of leukocyte adhesion molecules.[24] It is postulated that If this occurs in the brain, it can lead to atherosclerosis and strictures of the capillaries.[24] The link between low BDNF and endothelial dysfunction is further strengthened by the fact that prevention of endothelial dysfunction leads to higher BDNF.[22] Additionally, depressive symptoms in psoriatic arthritis patients have been found to be directly correlated to endothelial dysfunction.[25]

Depression's Effect on IA Patients' Quality of Life

Depression is associated with RA patients being less likely to adhere to exercise programs, which have been noted to improve health outcomes and quality of life.[22] Depression also has a negative effect on the patient's perception of their own treatment and health, as well as their ability to cope with disease exacerbation and high or chronic levels of pain. Due to this, depression may cause lower levels of health-seeking behaviour, which can have manifestations such as missed follow-up visits and lower treatment adherence. Behaviours such as these can exacerbate disease activity, resulting in a lowered quality of life.[26]

Loss of employment, assessed in a study by Callhoff et al, is also of concern in arthritis patients.[27] The Callhoff et al study had a large sample size (n = 528) and assessed patients' work status after 24 months of disease onset, the period when sickness benefits in Germany are withdrawn. The study found that unemployment due to RA increases as disease duration goes on, with 5% of patients unemployed within 2 years and 30% of patients unemployed within 10 years post-onset of RA. 12% of the patients reported moderate to severe depression based on their PHQ-9 results; 10% reported anhedonia for at least half of the days in the previous 2 weeks.[27] A significant association was found between anhedonia and work disability, with 33% of anhedonia-experiencing patients saying they had a work disability compared to only 5% of patients with no issues with mood.[27] Depressive symptoms were found to be strong predictors of a patient applying for work disability than disease burden. Depression also results in a risk of mortality in RA patients that is twice as high as non-depressed RA patients.[28]

Depression's Effect on Disease Activity

Depression in RA is associated with poorer function and poorer self-rated health based on Health Assessment Questionnaire (HAQ) scores. Depressed patients were found to have higher (worse) HAQ scores than non-depressed patients.[29] In a cross-sectional study of 120 RA patients, Kwiatkowska et al also found that RA patients with depression had higher HAQ scores than those without. The study additionally found that depressed RA patients had higher pain scores ($r=0.36$, $p=0$) and disease activity ($r=0.30$, $p=0.001$) than those without depression.[13] Patients with depression also had longer duration of disease compared to those without ($p=0.02$).[13] These results show that depression negatively impacts the patient's perceptions of their health, suggesting a dampened response to treatment. The Kwiatkowski et al study had some limitations, namely that they used self-reporting questionnaires to assess the patients' health status and it was a single-centre study.

Using information collected from both physicians (n=408) and patients (n=1015) in a cohort from the USA and 5 European countries, Peterson et al explored the effect of depression on clinical outcomes allowing them to gain a broader, "big picture" understanding of the impact of depression.[30] Peterson et al found that when compared to RA patients without depression, a lower percentage of RA patients with depression were in remission (40% vs 57% $p<0.001$) and they were more likely to experience disease flare-ups (19.2% vs 9.3% $p<0.001$; Figure 2). The study also noted that RA patients with depression faced significantly more impairments in activities of daily living. However, when selecting patients for the study, physicians were asked to select patients who came for appointments consecutively from a specific date. In other words, the first n patients from the start date whom the physician saw would be considered for the study. This may have biased the study more towards frequently visiting patients, who are likelier to have more severe disease and therefore would not represent the general population of RA patients. Additionally, whether or not the patient was in remission was determined by asking the physician rather than analyzing objective measures of disease, which may have led to inaccuracies.[30]

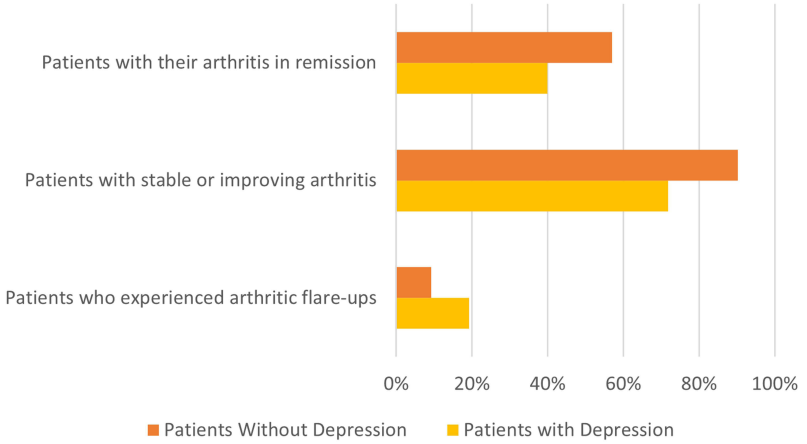

Figure 2 The differences in clinical outcomes for rheumatoid arthritis patients with and without depression.
Note: Data from Peterson et al.[30]

Disease Activity Score 28 (DAS28; Supplementary Figure 1) is a composite score to measure the severity of RA; the number 28 signifies the 28 joints that this examination assesses for swelling and tenderness. Using data from an observational cohort study of patients (n=159) with active RA commencing anti-TNF therapy in the UK, Hider et al measured depression using the validated Hospital Anxiety and Depression Scale (HADS-D). The study demonstrated that depression was common in this cohort at baseline (47.5%), and patients with depression had higher baseline DAS-28 scores representing more active disease and that patients with persistent depression had lower changes in DAS-28 despite treatment.

Depression's Effect on Conventional DMARD Treatment Response

Conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), such as methotrexate, are the first-line treatments for RA in UK[31] and European guidelines.[32] As part of a secondary analysis of a randomised clinical trial, Matcham et al (2016) explored the effect of depression, measured using the EQ-5D, and treatment response in 379 patients commencing a csDMARD with corticosteroid therapy. The study found that patients with baseline depression had significantly reduced odds of clinical remission, measured using DAS-28 (OR=0.50, p=0.02).[33] An additional study by Pinho et al showed that patients taking csDMARDs had far lower rates of depression, anxiety, and suicidal ideation than those taking bDMARDs.[34]

Depression's Effect on Treatment Response to bDMARDs

Biologic DMARDs (bDMARDs) are targeted therapies that are more effective in treating rheumatoid arthritis compared to csDMARDs.[35] A study by Matcham et al (2018) concluded that overall, RA patients with depression were less likely to have a good treatment response to bDMARDS 1 year after starting treatment. 3 different methods of classifying depression were used, allowing more patients with mental health issues to be identified. This resulted in a large sample size of 18,421 patients. The study looked specifically at how depression affected treatment response to bDMARDS 1 year after treatment was initiated. When using the EQ5D health questionnaire to evaluate depression, the study found no significant difference in the odds of having a good treatment response between patients with no depressive symptoms and those with moderate depressive symptoms. However, those with severe depressive symptoms were far less likely to have a good treatment response after 1 year (44.7% vs 26.4%, p=0.005). There were no significant differences between depressed and non-depressed patients in baseline levels of DAS28 before treatment was started. Although they did improve, patients with a history of depression had smaller improvements in the DAS28 and erythrocyte sedimentation rate compared to those without (β_{adj} −0.07 P=0.011 and β_{adj} −0.10 P<0.0001, respectively) at the 1-year follow-up. These results reinforce the findings of Peterson et al by showing that depression at baseline was associated with lower long-term chances of achieving remission. Importantly, reduced improvements in both objective and subjective measures of disease

were found in similar magnitudes. The study noted that this refuted previous evidence, which suggested that depression did not have as much of an impact on biological and inflammatory disease markers as it did on the patient's subjective perceptions of their health. This may be due to the study's very large sample size, which could make smaller effects, which are unobservable in smaller datasets, more noticeable.[36]

Conversely, a study by Rathbun et al published in 2016 suggests that depression does not have a significant impact on remission, disease activity, and most importantly, on treatment response. The authors found that previous studies failed to consider that rather than depression being a co-morbidity of IA which exerts its own influence on inflammatory arthritis, it may simply be a sign of severe IA. If this is the case, poor treatment response would be more common in patients with depression, but not connected with depression itself. Instead, it would be because severe arthritis is, by nature, harder to treat than less severe arthritis. The study only had one method of evaluating whether a patient had depression or not; a one-item tick box that asked patients whether they had ever had depression. This may have resulted in many false positives; by asking whether the patient had ever had depression, the question fails to establish whether the depression was truly related to the IA. The study also failed to assess the severity of depression in its subjects.[37] Due to this, and the wealth of research suggesting that depression and IA have bi-directional links (whereby each condition worsens the other), this review is of the belief that the study's findings need to be reproduced with stronger study design to disprove the other research cited in this review.

Due to the key role of TNF-α in the inflammatory processes of IA, it is worth further evaluating the effect of depression on TNF-α inhibitor (TNFi) response. Hider et al found that after 3 months of TNFi therapy, patients with depression had a significantly lower improvement in their DAS28 score than patients without depression (1.7 vs 2.2, p=0.005). The Hider et al paper demonstrates that depression has an adverse effect on treatment response to TNFi. It is important to note that, in agreement with Matcham 2016 et al, there was reduced improvement in both objective and subjective measures, suggesting that depression's effect on the response to TNFi worsens both the inflammation itself as well as the perception of pain.[38]

Zhao et al explored TNFi response in patients with axial spondyloarthritis (axSpA) and depression.[39] The composite score Ankylosing Spondyloarthritis Disease Activity Score (ASDAS) was used to measure disease activity with low disease activity classified as <2.1. The study found that patients with moderate to severe depressive symptoms were ~50% less likely to achieve low disease activity on TNFi's as those without depressive symptoms. Patients with moderate to severe depressive symptoms had ASDAS scores that were 0.8 units higher than patients with no depressive symptoms at 6 months. Using the HADS scale rather than a previous diagnosis of depression was a justified decision, as only 29% of patients with moderate-severe depressive symptoms had a pre-existing diagnosis of depression. This and the large sample size of the study (n=742) make this study an invaluable contributor to the understanding on mental health's impact on treatment response in non-rheumatoid IA.

A recent, large (n=5502) analysis of five randomised clinical trials from 2022 conducted by Manning-Bennett et al found results suggesting that regardless of whether treatment was with bDMARDs or csDMARDs, remission rates for RA were lowered at similar rates. It found that depressed RA patients, regardless of the type of DMARD commenced, had a 40% lower chance of being in remission at any given time. The study did not find any difference between depressed and non-depressed patients in the time taken to reach C-reactive protein (CRP) levels of ≤1, leading the study authors to speculate that perhaps patients and doctors had unintentionally conflated the symptoms of depression and RA.[40] Table 1 summarises published studies assessing the impact of depression on treatment response to drugs for inflammatory arthritis. The majority of studies grouped drugs together with different mechanisms of action, it is therefore not possible to delineate which specific drugs are associated with an impaired treatment response in inflammatory arthritis patients living with depression. There was also significant study heterogeneity of the timing of outcome measures in relation to treatment start and measurement of depression. This is a major limitation of the current literature.

Mechanisms for Depression's Impact on Treatment Response

One possible mechanism for depression's effect on treatment response is the anatomical link between depression and pain.[41] Emotions are processed in areas of the brain which include the hypothalamus, the amygdala, and the anterior cingulate gyrus.[41] All these areas relay signals to the periaqueductal grey matter and the ventromedial medulla, which are

Table 1 A Summary Table Regarding the Studies That Were Analyzed to Determine the Impact of Depression on Treatment Response to Drugs for Inflammatory Arthritis

Study	Disease	Drug	Definition of Depression	Sample Size	Results
Kwiatkowska et al[13]	RA	Study was not specific to one drug/class of drug	Mild/Moderate: BDI Score 0–9 Moderate/SevereBDI score 10–29 Severe: BDI score 30–63	120	Depressed RA patients HAQ, pain and DAS28 scores were significantly higher than in non-depressed patients
Peterson et al[30]	RA	Study was not specific to one drug/class	EuroQol self-reported	1015	Depressed patients less likely to be in remission (40% vs 57%, P < 0.001) or stable or improving (71.8% vs 90.2%, P < 0.001) compared to non-depressed patients. Depressed patients also had higher DAS28 scores (4.0 vs 3.4, P < 0.001).
Matcham et al[33]	RA	Ciclosporin/ methotrexate/ prednisolone	Moderate: EuroQol self-reported Extreme: EuroQol self-reported	379	Moderate depression/anxiety caused 50% reduction in odds of remission.
Pinho et al[34]	RA	Cs/bDMARDs	HADS-D score ≥8	105	Patients taking bDMARDs had significantly higher rates of depression, anxiety, and suicidal ideation than those taking csDMARDs.
Matcham et al[36]	RA	bDMARDs	1) Previous or current treatment for depression 2) SF36 mental health domain score: ≤40 3) EuroQol self-reported	18,421	Depressed patients had smaller improvements in DAS28, swollen/tender joint counts, and erythrocyte sedimentation rate at 1-year follow up, and a lower likelihood of remission, compared to non-depressed patients.
Rathbun et al[37]	RA	bDMARDs	Self-reported	2551	Depressed patients had no less likelihood of remission at 12 months (OR=0.83; 95% CI: 0.43, 1.60), depression had no effect on low disease activity.
Hider et al[38]	RA	TNF-α inhibitor	HADS-D score ≥8	159	Depressed patients had smaller improvements in DAS28 after 3 months of anti-TNF treatment (1.71 vs 2.20, P = 0.005) compared to non-depressed patients.
Zhao et al[39]	AxSpA	TNF-α inhibitor	Moderate: HADS-D score 8–10 Severe: HADS-D score ≥11	742	Depressive symptoms were associated with a slower and smaller reduction in the ASQOL score (11.8 to 6.4 vs 12.6 to 12.3 in 6 months) in response to TNF-α inhibitor therapy in AxSpA patients.
Manning-Bennett et al[40]	RA	Tocilizumab and csDMARDs	Clinician reported	5502	Depression is associated with 40% reduction in remission rate of RA, regardless of whether treatment was with csDMARD or bDMARD.

Abbreviations: ASQOL, Ankylosing Spondylitis Quality of Life; AxSpA, axial spondyloarthritis; b, biologic; BDI, Beck Depression Inventory; Cs, conventional synthetic; DAS-28, Disease Activity Score 28; DMARD, disease modifying anti-rheumatic drug; HADS-D, Hospital Anxiety and Depression Scale-Depression subscale; HAQ, Health Assessment Questionnaire; RA, rheumatoid arthritis; SF36, 36-item Short Form Survey; TNF-α, Tumor Necrosis Factor.

https://doi.org/10.2147/NDT.S456231

both involved in the modulation of pain signals.[41] Further reinforcing this neuroanatomical link is the fact that the anterior cingulate gyrus shows structural and functional changes in both depression and chronic pain, most notably a reduced volume.[41]

Another possible mechanism is the neurochemical link between depression and pain. Monoamines, namely serotonin and noradrenaline, are involved in both depression and pain modulation. Serotonin neurons are specifically involved in the transfer of pain signals through the pons. These monoamines are known to be depleted in depressive disorders.[41]

Lastly, patients with depression are more aware of their pain and may be more likely to react to it.[41] When depressed subjects anticipate pain, their amygdala shows increased activation compared to the same stimulus in a non-depressed subject. Interestingly, the anterior cingulate gyrus is linked with neuronal discharge in depressed patients when they expect pain from a stimulus, even when the stimulus is not actually painful.[41] Pain is a huge part of inflammatory arthritis and the burden it puts on the patient, and as such, it is reasonable that patients expect it as part of the disease.[41]

Researched Methods to Treat Depression in IA

A major challenge in treating disease is to first recognise and diagnose it. Depression is poorly identified and managed in rheumatology clinics. Hider et al found that 43% of depression cases were not diagnosed and treated, despite multiple appointments with the rheumatology clinics.[38] Further clinician training in the screening of depression may, therefore, be warranted.

Deb et al assessed how treatment with TNF-α affected the incidence of newly diagnosed depression in RA patients. The study found that in those patients who responded to TNFi treatment (39.8% of the patients), there was a 20% lower chance of developing depression. It is important to remember that the study did not have a control group, and causality cannot be proven. One of the limitations of the study is that it was unable to evaluate whether the reduction in risk is directly due to the response to TNFi therapy, or whether it is instead due to an improvement in RA which then stops the possible pathogenesis of depression. However, the end results are the same; a lower risk of depression using TNFi therapy.[28] Further supporting these findings, Hider et al found that very few cases existed where RA patients using TNFi developed depression. Additionally, the percentage of patients on TNFi who remained depressed fell from 24% at 6 weeks of treatment, to 15% at 12 months of therapy.[38]

Kwiatkowska et al found that IA patients treated with bDMARDS had a lower Beck Depression Inventory score, suggesting a lower prevalence of depression symptoms. Corticosteroids did not significantly lower the prevalence of depression symptoms. They also noted that this finding did not change when the dosage and the duration of treatment were changed.[13]

Conclusion

In conclusion, this literature review shows that depression does have a negative association on the efficacy of drugs for inflammatory arthritis and lowers treatment response. However, based on the literature, the evidence for this association specifically regarding csDMARDs and bDMARDs is less clear and identifying these specific associations should be a future research priority. The review demonstrated limited evidence of the association in diseases other than RA. This may be expected due to the lower prevalence of diseases such as Psoriatic Arthritis and axSpA. The inflammatory arthritides are a broad group of diseases that have diverse epidemiological risk factors, comorbidities and management options that limits the review findings to RA and axSpA. The review also highlights mechanisms of pathogenesis for depression within IA and mechanisms for the observed effect on the treatment response.

A recommendation for further research is to continue searching for an anti-inflammatory drug with a dual anti-depressant effect. The use of NMDA antagonists is a possible next step.[23] When administered along dexamethasone (a glucocorticoid drug used for its anti-inflammatory effects), NMDA antagonists have been found to reduce joint swelling and allodynia. This reduction in chronic pain could be very valuable.[42] A randomized controlled trial showed that NMDA antagonists have a safe anti-depressant effect that comes into effect faster than traditionally used SSRIs and SNRIs. It also works better on treatment-resistant depression.[43] Further research should also address the specific needs of people from low socioeconomic backgrounds, as they are at a higher risk of both arthritis and depression.[13] Lastly, research should be done into the best way to screen for and treat depression in IA patients.

Disclosure

JB has received a research grant award from Pfizer and travel/conference fees from UCB, Fresenius Kabi, Pfizer and Eli Lilly. The authors report no other conflicts of interest in this work.

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