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Rheumatoid Arthritis and Mental Health: An In-Depth Review

Wiktoria Oliwia Toczek, ORCID https://orcid.org/0009-0009-3530-6660
E-mail: toczek.wiktoria2@gmail.com
Ludwik Rydygier Specialist Hospital in Cracow, os. Złotej Jesieni 1, 31-826 Kraków, Poland

Klaudia Bogdan, ORCID https://orcid.org/0009-0003-7260-2799
E-mail: klaudiabogdan27@gmail.com
Ludwik Rydygier Specialist Hospital in Cracow, os. Złotej Jesieni 1, 31-826 Kraków, Poland

Mikołaj Jankowski, ORCID https://orcid.org/0009-0009-6542-9143
E-mail: mr.mikolajjankowski@gmail.com
Ludwik Rydygier Specialist Hospital in Cracow, os. Złotej Jesieni 1, 31-826 Kraków, Poland

Magdalena Olszówka, ORCID https://orcid.org/0009-0007-5196-3906
E-mail: magdalenaolszowka2@gmail.com
Stefan Cardinal Wyszyński Provincial Specialist Hospital SPZOZ in Lublin, Lublin, Poland

Urszula Janicka, ORCID https://orcid.org/0009-0001-7324-2137
E-mail: ujanicka.uj@gmail.com
Lower Silesian Center of Oncology, Pulmonology and Hematology, Plac Ludwika Hirszfelda 12, 53-413 Wrocław, Poland

Natalia Ciepluch, ORCID https://orcid.org/0009-0005-1703-4674
E-mail: nw.ciepluch@gmail.com
Municipal Hospital No. 4 in Gliwice, Zygmunta Starego 20, 44-100 Gliwice, Poland

Szymon Stanisław Słomiński, ORCID https://orcid.org/0009-0006-0208-0608
E-mail: szymonslominski085@gmail.com
University Clinical Hospital in Poznań, Przybyszewskiego 49, 60-355 Poznań, Poland
Corresponding Author:
Wiktoria Oliwia Toczek,
E-mail: toczek.wiktoria2@gmail.com

Abstract

Background/Objective: Rheumatoid arthritis (RA) co-occurs with depression and anxiety, driven by shared inflammatory pathways, that impair quality of life and treatment response. This review synthesizes evidence on biological mechanisms, biomarkers, and therapeutic strategies targeting RA-related depression.

Methods: Narrative synthesis of epidemiological, biomarker, pharmacological and lifestyle studies linking RA inflammation to mental health.

Results: Pro-inflammatory cytokines (IL-6, TNF-α) mediate the RA-depression nexus, while elevated IL-6, TNF-α, and CRP levels can be used for predicting depression risk. IL-6 inhibitors, TNF inhibitors and JAK inhibitors demonstrate significant improvement in mental state of the patients. SSRIs/SNRIs provide help in maintaining high-minded mood and pain relief, while Mediterranean diet adherence can halve depression odds. Emerging preclinical data support neuroimmune modulators like aucubin targeting CXCL10/BTN3A2.

Conclusion: Integrated care combining cytokine-targeted therapies, antidepressants, psychological interventions, and anti-inflammatory lifestyle measures optimizes outcomes for RA patients with depression, emphasizing early screening and holistic management.

Key words: rheumatoid arthritis, depression, inflammation, IL-6 inhibitors, JAK inhibitors, TNF inhibitors

1. Introduction

Rheumatoid arthritis is a chronic autoimmune disease that in most cases affects joints, causing inflammation to the synovial membrane, joint erosion and cartilage damage. Because of that patients experience pain, stiffness and swelling which leads to troubles with everyday life. With time the pathological changes can occur not only in musculoskeletal system but also in different body organs causing skin, gastrointestinal, nervous, renal, lungs dysfunction and cardiovascular problems such as pericarditis, myocarditis and congestive cardiac failure[1]. Untreated they may lead to serious disability and even shortening ones lifespan. [2] Among European and North American population 0,5 to even 1% people will develop RA [2].

A lot of studies and articles so far focused on connection between RA and cardiovascular disease. Although it is important, there is also very concerning complication to the chronic diseases such as RA, we all should remember about. It is declining mental health. The definition of mental health from WHO official website is : “Mental health is a state of mental well-being that enables people to cope with the stresses of life, realize their abilities, learn well and work well, and contribute to their community. It has intrinsic and instrumental value and
is integral to our well-being.” [3] According to the studies performed in the last couple of years the RA can cause development of the depression and anxiety, due to chronic pain, reduced mobility, social isolation and the burden of lifelong disease management. [4,5] Moreover mental health status may impact disease activity, response to the treatment and well-being practices. [6].

This article will provide a comprehensive overview of the interconnections between RA and mental health, drawing on current research findings from systematic reviews, meta-analyses, longitudinal studies, and qualitative research. It will discuss the prevalence, risk factors, various treatments method and self-management strategies in the holistic care of RA patients.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

2. Depression and anxiety in RA

Depressive disorders are reported in about 15-40% of the patients [7,8]. In many cases the depression and anxiety coexist, which may increase level of pain, disability and significantly decrease quality of life [9].

3. Biological mechanisms linking rheumatoid arthritis to depression and anxiety

Immune system dysfunction and inflammation are present in not only RA but also in depression. [10]

More and more studies prove that pro-inflammatory cytokines can alter neurotransmitter systems, stress–

response pathways, and brain regions involved in mood and cognition, helping explain why mood symptoms are so tightly linked with disease activity and pain. [11] Some of the cytokines that are responsible for the excessive process of inflammatory response in RA are tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β). [12,13]. Due to the fact that they can pass through or signal across the blood–brain barrier, they are very likely to have impact on depressed mood and anxiety in both RA and primary mood disorders. [11] According to the clinical data the higher level of IL-6 and related inflammatory markers, the more severe depressive and anxiety symptoms can occur. [12] Moreover Inflammatory cytokines can interfere with concentration and function of the neurotransmitters such as serotonin, dopamine, and noradrenaline by affecting their synthesis, release, and reuptake. [12] This could lead to impairment in reward processing and motivation in mesolimbic pathways, which results in anhedonia, low energy, and loss of interest that characterize depression.[14]

4.Bidirectional correlation between pain and depression in RA

There is a strong bidirectional correlation between pain and depression in RA, where greater pain intensity predicts worsening depressive symptoms, and depression amplifies pain perception and persistence. [17].

Up to 70% of the patients with disease in advanced stage had moderate to severe depression. Using visual analog pain scale (VAS) the researchers determined, that patients with more intense depression felt greater pain. [18]. Joint inflammation causes chronic nociceptive and neurophatic pain, which can result in sleep deprivation, fatigue increase that elevates symptoms of depression. [17,19]. Depressed mood can impair pain processing, lower pain threshold and reduce coping mechanisms, establishing situation where depression accounts for higher VAS pain reports. [18-20]

5.Markers of depression in RA

The diagnose of depression in RA is made based on clinical symptoms and screening questionnaires.

The blood markers can only help in identifying patients with high risk of developing depression. No single blood or imaging biomarker is currently accepted as a stand-alone diagnostic test for depression in RA.

5.1Clinical and questionnaire markers

The most fundamental 'marker' for depression is a clinical interview, that covers questions about mood, interest, energy, concentration, sleep, appetite, guilt and suicidal thoughts. [21] After that doctors may usually asks patients to answer some questions in questionnaires such as Patient Health Questionnaire: PHQ-2 (ultra-short), PHQ-9 (full) and Hospital Anxiety and Depression Scale – depression subscale (HADS-D) which shows high sensitivity that is balanced with specificity. [22] Any abnormal score should be followed by detailed diagnosis process.

5.2 Biomarkers

Amongst blood biomarkers Interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) shows the strongest associations with depression severity in RA [23,24]. Regarding IL-6 and TNF correlation with Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI) scales, a Spearman test was conducted. Results showed positive connection for IL-6 with BDI and HDRS ($p < 0.05$) and for TNF- α with HDRS ($p<0,05$). [23] Another marker might be C-reactive protein (CRP) levels (>3 mg/L),which correspond with depression severity and are elevated in 80%+ of depressed RA patients. [25] CRP often follows as a secondary marker reflecting systemic inflammation linked to mood symptoms. [23,25]

Table 1. Ranking of the biomarkers

RANKING OF THE BIOMARKERS BY STRENGTH

PLACE BY STRENGTH	BIOMARKER
1 – strongest	IL-6, TNF-α
2 - moderate	CRP

Source: [23-25]

It is not sure yet if plasma phosphoethanolamine (PEA) could be used as biomarker. Researches show statistically significant differences between depressed and non-depressed RA patients but has weak stand-alone diagnostic performance [26].

5.3 Genes

If correctly indentified particular gene's sequences in our genome can become a valuable tool in diagnostic process or screening. There were 48 differentially expressed genes (DEGs) found in RA that exists with comorbid major depressive disorder (MDD). Through the research six diagnostic markers was selected that are likely related to MDD in RA : AURKA, BTN3A2, CXCL10, ERAP1, MARCO, PLA2G7. Except from PLA2G7 all genes were involved in composition of most immune cells in MDD. Moreover the CXCL10 and MARCO were connected to the diverse immune cells in RA. [27]At present, these biological markers are not used in routine clinical diagnosis.

6. Treatment Strategies for Depression in RA

6.1 Non-Pharmacological Interventions

Psychological interventions such as cognitive behavioral therapy (CBT), mindfulness-based therapies, and patient education show moderate effectiveness in reducing depressive symptoms and improving quality of life in RA patients, when added to standard medical care. [28] CBT and digital therapeutics were recognized to reduce depression and anxiety symptoms, especially in patients with less than 10 years history of RA. [29,30] Another possible methods to improve quality of patient's life are meditation, yoga and mindfulness – mind-body therapies (MBTs). They can create feeling of relaxation, which affects overall health. MBTs can influence mental health, everyday living, and RA activity and symptoms. [31] When it comes to yoga classes participants, they not only showed lower level of anxiety and less symptoms of depression, but also increase in energy levels and mood. [32] MBTs can meaningfully help patients with RA, especially those who suffered from depression. [31]Another solution to decrease symptoms is improving diet. Mediterranean diet, which is rich in omega-3s and fiber, might reduce concentration of IL-6 and CRP, leading to simmering inflammation process in organism. According to study properly applied Mediterranean diet reduces depression risk by almost a half. [33,34]

6.2 Pharmacological interventions

6.2.1 Antidepressants

The most common medications used in depression treatment are Selective Serotonin Reuptake Inhibitors (SSRIs) (sertraline, escitalopram) and Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) (duloxetine). Not only they can lower the level of paint but also influence the inflammatory process by modifying cytokines activity. [35]

Table 2. Comparison of the antidepressants

Feature	SSRIs	SNRIs	TCAs
Efficacy in RA depression	Improves depressive symptoms. Escitalopram may show earlier and greater antidepressant effects compared to sertraline.	SNRIs (e.g., duloxetine) can benefit for pain relief and cognitive symptoms, which may be present in RA	Effective for depression and neuropathic pain. Not as popular as SSRI and SNRI due to side effects
Pain modulation	Limited direct analgesic effect but may improve mood-related pain perception.	Provide analgesia for chronic musculoskeletal pain and fibromyalgia, Duloxetine especially recommended for combined pain and depression.	Strong analgesic properties, helpful in neuropathic and chronic pain conditions
Side effects	Common: nausea, insomnia, sexual dysfunction, headache. Generally well tolerated	Nausea, dry mouth, dizziness, hypertension risk with some SNRIs.	Anticholinergic effects, sedation, weight gain, cardiac risks.
RA considerations	Better side effect profile for physically vulnerable RA patients. Common first choice.	Preferred when pain coexists, especially if fatigue and cognitive deficits prevail.	Less favored unless neuropathic pain prominent and other options fail.

Source: [35-39]

Generally, SSRIs are often the first choice due to less severe side effects, while SNRIs have advantage with treating depression that coexists with RA, because of their pain relief ability. Side effects of the TCAs make them reserved for treatment-resistant and correlated with neuropathic pain cases. Antidepressants might reduce depression and pain, resulting in better life quality.

6.2.2 Biopharmaceutical

Clinical data show that blocking some cytokines (for example with IL-6 inhibitors - tocilizumab or anti-TNF medications - entanercept) can help patients with depression by decreasing its symptoms. [12,15,24] IL-6 inhibitors presents better or equivalent results in the treatment compared to TNF inhibitors in RA patients, especially in anxiety reduction. TNF inhibitors also improve depressive symptoms and emotional health, but IL-6 blockade gives additional advantage which is more effective targeting of neuroinflammatory pathways linked to mood. [39,40]

Table 3. Comparision of IL-6 Inhibitors and TNF Inhibitors

Aspect	IL-6 Inhibitors	TNF Inhibitors
Depression improvement	Significant reductions in depression scores (e.g., HADS-D); lower risk of new-onset depression (RR 0.68).	Improve depressive symptoms and SF-36 mental scores
Anxiety outcomes	Great anxiety relief (HADS-A)	Moderate anxiety improvements, often tied to pain relief.
Mechanistic edge	Directly blocks IL-6, a key cytokine in "inflamed depression"; reverses sickness behavior and HPA dysregulation.	Reduces TNF-α-driven inflammation and pain, indirectly aiding mood; etanercept may outperform adalimumab/infliximab.
Comparative data	Superior to TNFis in RA patients reaching low disease activity/remission for mental health gains; no difference in b/ts-experienced monotherapy for clinical outcomes.	Equivalent or slightly inferior for psychiatric endpoints; better HRQoL in some etanercept studies.
Limitations	Potential paradoxical worsening in low-inflammation cases (rare in RA).	Variable response

Source: [39-42]
Legend:
HADS-D - Hospital Anxiety and Depression Scale – Depression
HADS-A - Hospital Anxiety and Depression Scale – Anxiety
HPA - Hypothalamic-Pituitary-Adrenal
SF36 - 36-Item Short Form Survey
HRQoL - Health-Related Quality of Life

IL-6 inhibitors are preferable for RA patients with prominent depression/anxiety and high IL-6/CRP, while TNF inhibitors suit those prioritizing pain or with IL-6 contraindications. [41]

6.2.3 JAK inhibitors

Janus kinase (JAK) inhibitors can be used in treatment of RA. They reduce inflammation, which is a key factor to improving quality of patient's life both physical and mental. Researches stipulate that patients on JAK inhibitors have higher mental health scores, than those on conventional disease-modifying antirheumatic drugs (cDMARDs) and in some analyses, better than those on TNF inhibitors. JAK inhibitors (tofacitinib, baricitinib, upadacitinib, filgotinib) suppress inflammatory process in RA by blocking intracellular JAK enzymes that pass on signals from cytokine receptors (for example IL-6, interferons) to the nucleus. Thanks to that these medications can modulate neuroinflammation and depression symptoms such as fatigue and decrease emotional state. [43,44]

Table 4. Comparison of JAK kinase inhibitors vs IL-6 Inhibitors and TNF Inhibitors

Aspect	JAK Inhibitors	TNF Inhibitors	IL-6 Inhibitors
Depression/Anxiety Improvement	Strong SF-36 MCS gains, superior to csDMARDs/adalimumab in pooled RCTs. Tofacitinib/upadacitinib lead class.	Moderate SF-36 mental gains, etanercept > infliximab/adalimumab for mood.	Largest anxiety reductions (HADS-A), lower depression risk
Comparative Edge	Equivalent/superior to TNFs	Inferior to JAK/IL-6 in some mental health trajectories.	Equivalent to JAKs, superior to TNFs for psychiatric endpoints.
Speed/Mechanisms	Rapid onset (weeks), blocks multiple cytokines (IL-6, IFN pathways).	Pain-driven mood gains, TNF-α specific.	Direct IL-6 blockade reverses neuroinflammation.
Limitations	Safety concerns (CVT, infections), no depression-specific scales in most trials.	Variable psychiatric response, less neuroinflammatory targeting.	Rare paradoxical mood effects

Source: [39,40,42-46]
Legend:
SF36 - 36-Item Short Form Survey
MCS - mental component score
csDMARDs - conventional synthetic disease-modifying antirheumatic drugs
RCT – randomized control trial
IFN – Interferon
CVT - Cerebral Venous Thrombosis
HADS-A - Hospital Anxiety and Depression Scale – Anxiety
HPA - Hypothalamic-Pituitary-Adrenal
HRQoL - Health-Related Quality of Life

When patients do not respond to first line treatment (for example methotrexate), JAK inhibitors can be prescribed as monotherapy or in coalescence with MTX. [43]

6.2.4Aucubin (AU)

Molecular docking and *in vitro* studies have showed that AU may decrease *CXCL10* and *BTN3A2* gene expression in PC12 cells. [27] CXCL10 was studied for being responsible for cognitive changes in chronic inflammatory response and state of mental well-being, because of its influence in immune cell recruitment and neuroinflammation; The high levels of CXCL10 might cause autoimmune damage in central nervous system.[47] BTN3A2 is related to the immune response and is one of few genes that was associated with RA and MDD. [27] AU is expect to lower pro-inflammatory and immune-activating signals at the neuronal level, by decreasing the expression of CXCL10 and BTN3A2. [48,49] The researches provide informations about reducing oxidative stress, neuroinflammation, and depression-like behavior by AU, in animal models of neurological disease. [48-50] As for now there is no clinical trial to prove AU role in treatment of MDD or RA.

7. Conclusions

Rheumatoid arthritis might be accompanied by depression and anxiety, conditions driven by complex interactions between chronic inflammation, pain, immune-brain signaling and psychosocial stress. Inflammatory cytokines (interleukin-6 and tumor necrosis factor alpha) play critical roles in the pathogenesis of RA-related depression, linking inflammation process to neuropsychiatric symptoms. Biomarkers such as IL-6, TNF-α, and C-reactive protein (CRP) help identify patients at higher risk for depression, although we must remember that clinical assessment remains fundamental. Pharmacologically, IL-6 inhibitors, TNF inhibitors and Janus kinase inhibitors, show promise in improving not only symptoms connected to the RA well-known disease trajectory but also depressive and anxiety symptoms. Antidepressants, such as SSRIs and SNRIs, complement inflammation control by managing mood and pain-related symptoms. Integrated approaches combining pharmacotherapy with psychological interventions, such as cognitive behavioral therapy and mindfulness demonstrate enhanced effectiveness. Adherence to the Mediterranean diet, may further reduce depression risk
in RA through anti-inflammatory and neuroprotective mechanisms. Emerging compounds like aucubin exhibit potential for modulating shared immune and neural pathways involved in RA and depression, though human evidence is pending. Overall, addressing mental health in RA requires a holistic strategy targeting inflammation, psychosocial factors, lifestyle, and psychological care to improve both joint and emotional outcomes, enhancing quality of life for patients with this chronic disease.

Disclossure

Author Contributions :

Conceptualization:Wiktoria Toczek

Formal analysis: Magdalena Olszówka, Natalia Ciepluch

Investigation: Wiktoria Toczek, Klaudia Bogdan

Writing rough preparation: Wiktoria Toczek, Mikołaj Jankowski

Writing review and editing: Szymon Słomiński, Urszula Janicka

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