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TYPES OF PAIN IN RHEUMATOID ARTHRITIS: CENTRALIZATION MECHANISMS, RISK FACTORS, AND TREATMENT APPROACHES

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ABSTRACT

Introduction and aim: One of the main complaints in rheumatoid arthritis (RA) is pain. It may result not only from inflammation and joint damage, but also from neuropathy and central sensitization, leading to nociplastic (central) pain. This type of pain is often overlooked, as it does not correlate with visible musculoskeletal pathology. Its pathogenesis is not fully understood, and both diagnosis and treatment are challenging. The aim of this paper is to review the types of pain in RA, with a particular focus on nociplastic pain—its causes, clinical presentation, diagnostics, and therapy.
Materials and Methods: A review of the available scientific literature on RA was conducted using PubMed, Google Scholar, and Embase databases.
Conclusion: Pain in RA can be nociceptive, neuropathic, or nociplastic. Nociplastic pain is driven by central sensitization, influenced by cytokines (IL-1, IL-6, TNF-α), microglial activation, and synaptic transmission imbalance. Diagnosis relies on questionnaires (e.g., Central Sensitization Index – CSI) and sensory testing (e.g., Quantitative Sensory Testing – QST). Treatment includes pharmacological options (paracetamol, benzodiazepines, opioids, SNRIs, naltrexone, TNF-α inhibitors, pregabalin, gabapentin, Sarilumab, JAK1/JAK2 inhibitors) and non-pharmacological methods: pain neuroscience education (PNE), cognitive behavioral therapy (CBT), stress reduction, and tailored physical activity.

KEYWORDS

Rheumatoid Arthritis, Fibromyalgia, Neuropathic Pain, Chronic Pain, Central Sensitization, Pain Measurement

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Introduction:

Rheumatoid arthritis (RA) is a chronic systemic connective tissue disease characterized by symmetric joint inflammation and a range of extra-articular and systemic symptoms. Its prevalence varies between populations, estimated at 0.5 to 1% [1], with approximately 0.9% in the Polish population [2]. Pain is reported as the primary reason for up to 97% of medical consultations leading to early RA diagnosis (90.4% of these consultations are due to severe pain). Moreover, pain is often the first manifestation of the disease [1]. Despite advances in RA treatment over the last 30 years, pain remains the leading symptom, even in cases of good clinical control. It is important to note that pain in RA is not solely caused by inflammation but also by irreversible joint damage and changes in the nervous system.

Types of pain in RA:

The International Association for the Study of Pain defines pain as"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [3]. It should be remembered that pain, regardless of its causes, is a largely subjective symptom. Many factors influence its perception, ranging from the extent of tissue damage, the presence of comorbidities, to the patient's psychosocial conditions. Conventionally, pain in RA is considered nociceptive, primarily resulting from ongoing inflammation and bone remodeling. However, its etiology is much more complex, involving not only joint pathology but also associated damage to both the peripheral and central nervous systems [4].

Nociceptive Pain

This pain is usually dull, pulsating, or burning and is characterized by a clearly identifiable location, increased intensity during nighttime and morning hours, and accompanying stiffness. It results from the activation of nociceptors (sensory receptors located on nerve endings of fibers involved in detecting mechanical, chemical—including inflammation—and thermal harmful stimuli) due to actual or potential tissue

damage. In rheumatoid arthritis (RA), nociceptive pain is initiated by inflammatory mediators such as prostaglandins, bradykinin, and neurotrophic growth factors released as a result of synovial inflammation [5]. These mediators cause a series of inflammatory changes leading to synovial hypertrophy and destruction of bone and cartilage structure. Cytokines and chemokines like CXCL1 released during inflammation activate and sensitize nociceptors, directly triggering the following pain pathway: the stimulus is transmitted by nerve fibers to the spinal cord and then via the spinothalamic tract to thalamic nuclei. From there, it travels to relevant cortical and subcortical areas such as the amygdala, hypothalamus, periaqueductal gray (PAG), basal ganglia, and cortical areas including the somatosensory cortex, prefrontal cortex (PFC), anterior cingulate cortex (ACC), and insular cortex (IC). These structures collectively form a neural network called the"neuromatrix, " responsible for generating the pain experience [6].

Descending modulatory pathways, both excitatory and inhibitory, originating from the PAG, rostral ventromedial medulla (RVM), and brainstem nuclei such as the locus coeruleus (LC), modulated by noradrenergic and serotonergic neurons, regulate pain perception. These pathways influence sensory information flow to the brain by inhibiting or enhancing sensory neurons [7].

Importantly, chronic inflammation causes changes in the peripheral innervation of the joint, leading to pain [8]. Inflammation also lowers pain thresholds, so that normally non-painful stimuli can evoke pain [4].

The foundation of treating inflammation and thus pain in rheumatoid arthritis is disease-modifying treatment. Disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and leflunomide, as well as non-steroidal anti-inflammatory drugs (NSAIDs), and paracetamol in cases of intolerance, are used. Weak opioids and glucocorticosteroids, mainly for short-term use during flare-ups, are also employed.

Neuropathic Pain

The second type of pain is neuropathic pain, which results from abnormalities or damage to nerves, leading to increased stimulation of the nervous system [9]. It is a consequence of exhausted adaptive capabilities and neuroplasticity. This type of pain cannot be explained by joint damage or the presence of inflammation. It typically affects the area innervated by the damaged nerve and may gradually spread to more distant regions [10]. Neuropathic pain can be caused by damage or disease of either the peripheral or central nervous system. It is classified into peripheral and central forms (e.g., post-stroke or in Parkinson's disease). Neuropathies can also be categorized as polyneuropathy (damage to multiple nerves), mononeuropathy, sensory, motor, mixed, or autonomic neuropathy. In rheumatoid arthritis (RA), peripheral neuropathy may also manifest as small fiber neuropathy (SFN), involving unmyelinated fibers.

Neuropathic pain is typically described as radiating, throbbing, burning, shooting, tingling, numbness, increased sensitivity to heat and cold, swelling, and may also include allodynia, hyperalgesia, or even hypoesthesia.

Importantly, in most patients, significant neurological abnormalities are not observed in the early stages of the disease. Cytokines such as IL-1, IL-6, TNF-alpha, neuropeptides, and nerve growth factor may contribute to the sensitization of peripheral nerves and reduce their excitation threshold [11].

Determining the prevalence of neuropathic pain among RA patients is difficult due to significant discrepancies in study results. In a study by Abdelrazek et al. (2025) involving 586 RA patients, 348 (59.4%) suffered from neuropathy and 48 (8.2%) were in a subclinical stage [12].

Causes of Neuropathic Pain in RA Patients:

Nerve compression – most commonly carpal tunnel syndrome (CTS), resulting from inflammation and swelling compressing the median nerve [13, 14, 15]. In a retrospective cohort study by George et al. (2025) involving 1, 335 RA patients and 1, 331 controls, the prevalence of CTS in those with early-stage RA or shortly before diagnosis was 13%, compared to 6% in non-RA individuals. Based on a median follow-up of 12.8 and 13.8 years, respectively, 154 RA patients developed CTS compared to 102 controls. After adjusting for age and sex, RA patients were found to be 82% more likely to develop CTS [14].

Drug-induced complications related to leflunomide [16, 17]. In a retrospective observational study by Gursimran Kaur et al. (2024) involving 482 patients treated for rheumatic diseases, 23 (4.7%) developed peripheral neuropathy due to leflunomide. Nerve conduction studies confirmed distal, axonal, sensory or sensorimotor peripheral neuropathy in 18 (78.2%) of them [18]. In a prospective cohort study by Richards et al. (2007), participants were divided into a treatment group (receiving leflunomide) and a control group

(receiving other DMARDs). After 6 months, 54% of the treatment group showed increased neuropathic symptoms compared to 8% in the control group. However, this study found no correlation between electrophysiological findings and neuropathic symptoms. In one patient, both neurophysiological and clinical symptoms of neuropathy resolved after discontinuing leflunomide [17].

Vasculitis as a rare complication of RA (estimated prevalence 2–5%), which can restrict blood flow to nerves, leading to damage and causing sensory and motor peripheral neuropathy [19, 20, 21, 22].

Immune system attack on the nervous system [20].

Management:

DMARDs play an indirect role in alleviating symptoms of peripheral neuropathy.

Nonsteroidal anti-inflammatory drugs (e.g., paracetamol) are used. Anticonvulsants such as gabapentin and pregabalin, as well as selected tricyclic antidepressants like amitriptyline, doxepin, or nortriptyline—acting by interfering with pain receptor pathways in the brain and spinal cord—have proven effective [23, 24]. Additionally, serotonin-norepinephrine reuptake inhibitors (SNRIs) such as duloxetine and venlafaxine, and opioids may also be used [23, 25]. Topical treatments like lidocaine and capsaicin are also applied [26, 27]. Cannabinoids have shown promise in symptom relief [28]. Transcutaneous electrical nerve stimulation (TENS) may also help manage pain [29]. In cases of compressive syndromes, surgical decompression is recommended [30].

Nociplastic Pain

According to the International Association for the Study of Pain (IASP), this type of pain is referred to as nociplastic pain. Other terms used by clinicians include neuroplastic pain, central sensitization (CS), central hypersensitivity, and altered pain modulation mechanisms [10]. Nociplastic pain is defined as an amplified response of nociceptive neurons in the central nervous system to normal or subthreshold afferent stimuli [31].

Prevalence

The prevalence of central pain is difficult to determine, with studies reporting varying results. In the study by Filatova et al. (2021), central sensitization was identified in 62.5% of patients with rheumatoid arthritis (RA) [32]. In the study by Mesci et al. (2024), the prevalence was estimated at 48.3% [33], while in another study by Stanislavchuk et al. (2024), the prevalence was reported as 36% [34].

Pathogenesis

Central sensitization refers to a state in which the central nervous system becomes excessively responsive to pain signals, leading to exaggerated pain perception. The mechanisms underlying nociplastic pain are multifactorial and complex, involving changes in neuronal response properties and the integration of nociceptive input in the CNS. The precise pathogenesis remains unclear but likely includes several factors.

Central sensitization primarily affects signal transmission within the dorsal horn of the spinal cord. It reflects changes in neurons responsible for pain regulation [35]. Repeated inflammatory stimulation leads, via neuropeptides and proinflammatory cytokines, to activation of microglia and astrocytes in the spinal cord. These cells enter a state of heightened responsiveness, producing cytokines such as TNF-alpha, IL-1, and IL-6. Spinal cord exposure to these substances can result in hyperalgesia and allodynia [11, 36, 37, 38]. At the synaptic level, excitatory transmission is enhanced while inhibitory control is diminished. Pain signals are more readily transmitted through the CNS, while descending pain inhibition is weakened. As a result, the pain response is amplified in terms of intensity, duration, and spatial extent. Synapses that would normally remain inactive begin to transmit subthreshold signals, activating the pain circuitry [38, 39, 40]. This leads to persistent stimulation of higher brain regions and altered stimulus processing.

At the brain level, studies show that nociplastic pain is associated with increased connectivity between the insular cortex and the default mode network (DMN), which includes regions such as the medial prefrontal cortex (MPFC), posterior cingulate cortex, precuneus, inferior parietal lobule, hippocampal formation, and lateral temporal cortex [41, 42]. In a study by Basu et al. (2018), MRI analysis showed increased insula-DMN connectivity in RA patients with fibromyalgia-type chronic pain, even when inflammation was well controlled. This suggests a CNS rather than inflammatory origin of pain and supports the use of this connectivity increase as a marker of central sensitization [43].

A key concept in central sensitization is Temporal Summation (TS)—a phenomenon in which repeated low-intensity pain stimuli, delivered at short intervals, lead to an escalating CNS pain response [44].

Clinical Manifestations

Nociplastic pain is characterized by pain intensity disproportionate to disease activity as evaluated through physical examination, laboratory tests, imaging, or neurological assessment. Patients often report significant pain despite quiescent inflammatory markers in RA. This pain is not associated with clear inflammatory or structural damage sites, frequently manifesting in regions distant from the primary pain source or spreading beyond it. The origin lies in dysfunctional central pain processing.

Patients typically experience widespread, multifocal pain, often confined to a particular side of the body (e.g., only above the waist or only on the right side). Common features include hyperalgesia and allodynia [45]. Patients often describe the pain using neuropathic terms—burning, tingling, numbness, paresthesias [46]. Accompanying CNS-related symptoms may include fatigue, non-restorative sleep, mood disturbances, cognitive impairment, and memory issues [47, 48, 49].

A chronic pain syndrome strongly associated with RA is fibromyalgia, which exemplifies nociplastic pain [10]. Patients may also show heightened sensitivity to sounds, light, or unpleasant odors [47]. Studies reveal that RA patients with fibromyalgia report higher pain levels, increased fatigue, and more frequent unrefreshing sleep compared to RA patients without fibromyalgia [50]. Other nociplastic-related syndromes include irritable bowel syndrome and chronic migraine.

Risk Factors:

The primary risk factor for centralization of pain in RA is chronic, untreated **inflammation**, which generates prolonged nociceptive input. Sustained stimulation promotes the described changes in central pain processing, leading to sensitization [46].

Comorbidities play a significant role. In a study by Kaplan et al. (2019), RA patients with coexisting fibromyalgia showed more central sensitization symptoms compared to those without this comorbidity [51, 52, 53].

Genetic and hormonal factors are also relevant. Women appear to be more susceptible to pain centralization. Estrogen and testosterone influence different pathways of microglial activation, a key player in central sensitization. Additionally, a microglia-independent pathway involving T-cell recruitment after nerve injury has been described in females [54].

Genetic factors have also been implicated [39].

High stress levels and mood disorders contribute to altered pain modulation. Low physical activity weakens the body's natural analgesic mechanisms, and sleep disturbances reduce pain thresholds and facilitate the development of central sensitization [55].

Importantly, no structural abnormalities are detected in CNS-related clinical, laboratory, or imaging assessments.

Table 1. Comparison of nociceptive, neuropathic, nociplastic pain in RA

Feature	Nociceptive Pain	Neuropathic Pain	Nociplastic Pain
Mechanism of origin	Direct tissue damage and inflammation	Nervous system damage	Disturbed pain processing in the central nervous system (CNS)
Pain location	Limited to affected joints	Often outside the site of inflammation, within the innervation area	Generalized or in atypical locations
Pain characteristics	Dull, throbbing, burning	Burning, shooting, tingling, electric-like	Often hard to describe, chronic diffuse, shifting location
Relation to disease activity	Directly correlated with inflammatory activity	Minimal or no correlation	Minimal or no correlation
Response to treatment	Effective conventional treatment with NSAIDs/DMARDs	Often requires anticonvulsants or antidepressants	Requires a complex approach involving education, psychotherapy, physical activity and CNS pain-modulating medications
Differential diagnosis	Based on clinical evaluation and inflammation assessment	Requires validated questionnaires, tests and neurological examination	Requires validated questionnaires and tests

Pain Diagnostics in Rheumatoid Arthritis (RA):

The foundation of pain diagnostics in RA lies in distinguishing the origin of the pain whether it involves a nociceptive, neuropathic, or nociplastic component. Determining pain intensity is subjective and influenced by various factors. Objectively, the assessment is more straightforward when the pain results from peripheral inflammation. In cases of central sensitization, the pain is not explained by any identifiable damage. Key tools in assessing this type of pain include questionnaires and rating scales.

The **Visual Analogue Scale (VAS)** is the most commonly used and cited scale in literature, where patients mark their pain intensity on a 100 mm line, with higher values indicating more severe pain. Notably, more than 50% of patients report a VAS pain score of ≥30/100 mm despite effective anti-inflammatory treatment, suggesting a source of pain other than nociceptive [56].

The **Central Sensitization Inventory (CSI)**, a 25-item questionnaire covering symptoms associated with central sensitization (pain, fatigue, sleep disturbances, hypersensitivity) is the most important and widely used tools in assessing central pain. A score above 40 points suggests significant central sensitization [57, 58].

The **CAP-RA (Central Aspects of Pain in Rheumatoid Arthritis)** is an 8-item questionnaire specifically designed for RA patients to assess central pain. Its validation and utility have been confirmed in a prospective observational study by Ifesemen et al. (2021) involving 250 adults with active RA [31].

The **Sensory Hypersensitivity Scale (SHS)**, a 25-item questionnaire, has also been identified as a useful screening tool for central sensitization [10, 59].

Quantitative Sensory Testing (QST) methods are also used to assess nociplastic pain. These include pressure pain threshold (PPT), temporal summation, and conditioned pain modulation

(CPM). These tests are well validated and considered important in identifying pain origin in RA. Georgopoulos et al. (2024) demonstrated that these methods can effectively indicate central sensitization in RA [60].

Pressure Pain Threshold (PPT) is measured using an algometer, which applies pressure to specific tender and non-tender points. The threshold at which pressure causes pain is determined. A lowered PPT indicates heightened pain sensitivity. Mesci et al. (2024) found that RA patients with central sensitization had significantly lower PPT values in affected areas (e.g., wrist, trapezius muscle) [33]. Altun Guvenir et al. (2025) also linked lower PPT scores with higher depression scores (HADS-D), suggesting a connection between pain sensitivity and depressive symptoms in RA patients [61].

Temporal Summation involves repeated application of a mechanical or thermal stimulus of constant intensity. In healthy individuals, repeated stimuli do not significantly increase pain perception. In cases of central sensitization, however, perceived pain intensifies over time [62].

Conditioned Pain Modulation (CPM) reflects the body's physiological ability to suppress pain through descending inhibitory pathways. This involves applying two stimuli simultaneously—a test stimulus (e.g., PPT) and a conditioning stimulus (e.g., cold-water immersion of the opposite limb, known as the cold pressor test). In a healthy nervous system, the presence of the conditioning stimulus should raise the PPT of the test stimulus. This test helps identify pain processing dysfunctions and serves as a marker for central sensitization [63].

PainDetect Questionnaire (PDQ) is used to evaluate neuropathic pain, in addition to subjective history and physical examination assessing reflexes, coordination, balance, strength, and sensation. This simple, widely used self-report tool consists of 9 items. A total score above 19 strongly suggests the presence of neuropathic pain. Studies by Yong Gil

Hwang et al. (2017) and Frame confirm the utility of this tool in rheumatic diseases [64, 65].

DN4 (Douleur Neuropathique 4 Questions) is a short screening tool comprising 7 items on subjective symptoms and 3 clinical examination items. A score above 4 points suggests neuropathic pain. However, as noted by Timmerman et al. (2017), false positives may occur due to pain of other etiologies, limiting its specificity in RA [66].

The **LANSS (Leeds Assessment of Neuropathic Symptoms and Signs)** scale includes 5 questions about the patient's subjective symptoms and 2 clinical tests (for hyperalgesia and mechanical allodynia). A score above 12 points indicates a neuropathic component. A key advantage is the combination of questionnaire and physical examination, although misinterpretation is still possible when multiple pain mechanisms coexist [67].

Multidimensional questionnaires assessing quality of life such as the Hospital Anxiety and Depression Scale (HADS) and the Pittsburgh Sleep Quality Index (PSQI) are also used [68, 69]. The Health Assessment Questionnaire Disability Index (HAQ-DI), in conjunction with VAS, and the WHOQOL-BREF questionnaire are important tools for evaluating life impact and functioning in RA patients [70, 71].

Functional MRI (fMRI) is gaining importance in the evaluation of central pain. It visualizes brain morphology, gray matter volume (total and regional), activity, and changes in blood flow and oxygenation—indicating neuroplasticity. It helps visualize changes in brain pain centers. Sandström et al. (2019) used fMRI to demonstrate altered brain activation in RA patients in response to pain stimuli from inflamed areas—supporting central sensitization [72].

When neuropathic pain is suspected but MRI is not feasible, ultrasound may be used to assess nerve damage. Nerve conduction studies and electromyography (EMG) are helpful in evaluating nerve activity [73, 74]. Tissue biopsy may also be performed to confirm the diagnosis [75].

Table 2. Comparison of Scales for Assessing Neuropathic and Nociplastic Pain

Scale	Type of Pain	Tool Description	Diagnostic Threshold	Use in RA
Central Sensitization Inventory (CSI)	Nociplastic	25 questions assessing CNS hyperreactivity symptoms (e.g., fatique, sleep disturbances, irritability)	0-100 points; ≥40 points suggest central sensitization	Frequently elevated in RA patients despite low inflammatory activity - suggests central sensitization (CS) as a cause of pain
Sensory Hypersensitivity Scale (SHS)	Nociplastic	25 items assessing hypersensitivity to sound, touch, light, taste, smell	0-100 points; no established clinical cutoff	Enables identification of central sensitization in RA patients
CAP-RA	Nociplastic / Mixed	Specialized scale designed for RA; assesses sleep, fatigue, pain response	No fixed cutoff; total score is summed	Identifies non-inflammatory pain; currently used more in research than in routine clinical practice
PainDETECT	Neuropathic / Mixed	9 self-assessment questions (pain, attacks, hyperalgesia, cold/heat sensation)	-1 to 38 points; ≥19 = likely neuropathic pain; 13-18 = possible neuropathic pain	Identifies neuropathic pain component in RA; may be difficult to distinguish between neuropathic and nociplastic pain
LANSS	Neuropathic	5 questions + 2 physical exam items (hyperalgesia, pinprick test)	0-24 points; ≥12 points suggest neuropathic pain	Enables objective assessment of neuropathic pain in RA
DN4	Neuropathic	7 questions on symptoms + 3 physical tests (touch, hyperalgesia, pinprick)	0-10 points; ≥4 points = probable neuropathic pain	Assesses neuropathic pain, including when inflammatory components are present

Treatment of Centralized Pain:

Pharmacotherapy:

In the treatment of pain associated with rheumatoid arthritis (RA), disease-modifying antirheumatic drugs (DMARDs) play a key role. They are effective primarily for nociceptive pain, similarly to nonsteroidal anti-inflammatory drugs (NSAIDs). In the context of central pain, they are considered supportive only, as they help dampen peripheral input. For centralized pain, other pharmacological options should be considered. Paracetamol has a potential supportive role due to its described effect on pain modulation [76]. Opioids and benzodiazepines also modulate pain but have a limited role in central pain management and carry risks such as opioid-induced hyperalgesia, addiction, and masking of inflammation, which may delay response to disease flare-ups [11, 28].

Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, sertraline, and citalopram may modulate central pain processing by increasing serotonin levels in the CNS [77].

However, their role in treating central sensitization (CS) in RA appears limited. Serotonin and norepinephrine reuptake inhibitors (SNRIs), such as duloxetine and milnacipran, increase both serotonin and norepinephrine levels, leading to modulation of central pain processing. A study by Lee et al. (2015) showed that milnacipran significantly reduced pain intensity in RA patients with well-controlled inflammation [78]. Nevertheless, both SSRIs and SNRIs are associated with various adverse effects.

Low-dose naltrexone has been reported to influence central pain perception with minimal side effects. Long-term use may reduce the need for other analgesics in RA, likely by inhibiting microglial cell activation, reducing neuroinflammation, and lowering the hyperreactivity of the nervous system, all hallmarks of central sensitization [79].

TNF-alpha inhibitors such as etanercept and infliximab have shown promising results in clinical studies [80]. Neuroimaging has demonstrated that TNF-alpha inhibitors can reduce central pain symptoms by decreasing activity in the somatosensory cortex [81].

Randomized controlled trials (RCTs) have also shown that agents targeting interleukin-6 (IL-6) may help treat both articular and nociplastic pain. Sarilumab, a human monoclonal antibody against the IL-6 receptor, has been shown to alleviate pain that is disproportionate to inflammation or joint damage. This supports the hypothesis of IL-6's role in central sensitization [35]. However, based on the TARGET trial, its use may be associated with adverse effects, including increased infection risk, neutropenia, elevated liver enzymes, and potential cardiovascular events [82].

Janus kinases (JAK1 and JAK2) also play a role in inflammation and potential sensitization. These intracellular messengers transmit signals from the cell membrane, phosphorylating and activating signal transducers and transcription activators (STATs), which influence gene expression and the production of inflammatory mediators. Inhibition of these pathways could impact both inflammation and centralized pain. Baricitinib, a selective and reversible

JAK1/JAK2 inhibitor, has shown efficacy in RA pain treatment. The RA-Begin and RA-Beam trials confirmed baricitinib’s superior or comparable effect on pain compared to adalimumab (a TNF inhibitor) [83]. It reduces pain more effectively due to broader cytokine modulation than TNF inhibitors alone. Baricitinib offers a convenient oral formulation with a relatively favorable safety profile—mainly risk of infections—though this may contraindicate its use in patients with chronic infections. Additionally, baricitinib has been shown to improve general well-being in RA patients [35, 83]. Tofacitinib has demonstrated comparable efficacy, and studies also highlight the benefits of combining methotrexate with filgotinib [84].

Studies have shown that pregabalin and gabapentin may alleviate central sensitization symptoms by modulating central nervous system neuronal activity [85, 86].

Non-pharmacological methods:

Pain Neuroscience Education (PNE) plays a foundational role in non-pharmacological management. This involves explaining pain mechanisms and distinguishing between acute and chronic pain. It reduces fear and catastrophizing while enhancing a sense of control, helping patients understand that pain can be influenced by physical activity, thought patterns, sleep, and lifestyle [87].

Psychotherapy, particularly cognitive-behavioral therapy (CBT), has been shown to improve symptoms of depression, pain, anxiety, and stress—factors believed to contribute to the development of centralized pain [88].

Physical activity also reduces pain intensity. Despite the common belief that physical exertion should be limited in RA, evidence clearly supports that exercise significantly reduces pain in these patients. It is important to avoid high-intensity activities, and transient pain exacerbation during exercise is expected. Notably, patients may initially experience exercise-induced hyperalgesia. Thus, proper education and reassurance that this is a temporary and manageable phase leading to long-term relief is essential [89]. It is crucial to recognize that any exercise is better than none; however, the type, frequency, and intensity should be individualized. Both aerobic (e.g., cycling, swimming) and resistance exercises (e.g., hand-focused activities) are recommended. Complementary techniques such as balneotherapy (warm-water exercises) and whole-body cryotherapy may also be beneficial, improving both pain modulation and mental well-being [11]. Physical activity in some RA patients activates descending pain inhibitory pathways, a mechanism known as exercise-induced hypoalgesia (EIA) [90].

A study by Simonsen et al. (2022) showed that the use of foot orthoses in RA patients helped reduce centralized pain. Pain reduction was observed not only in the treated foot but also in the upper limb joints affected by the disease, suggesting a broader neuromodulatory effect [91].

Conclusions:

As demonstrated in this paper, given the diverse types and underlying causes of pain experienced by patients with rheumatoid arthritis (RA), each type of pain should be treated individually, according to its specific pathophysiological mechanism. It is essential to promote awareness among healthcare professionals treating RA about the various sources of chronic pain, as they differ significantly in both diagnosis and treatment approaches. In the assessment of centralized pain, commonly used tools include the Central Sensitization

Inventory (CSI) and the Self-Report Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS). Additionally, comprehensive quality-of-life questionnaires and functional magnetic resonance imaging (fMRI) are also highlighted as useful diagnostic tools. Unfortunately, current treatment options remain limited, and the available medications are often associated with numerous side effects and suboptimal efficacy. Pharmacological interventions include, among others: paracetamol, benzodiazepines, opioids, serotonin-norepinephrine reuptake inhibitors (SNRIs), low-dose naltrexone, TNF-α inhibitors, pregabalin, gabapentin, sarilumab, and JAK1/JAK2 inhibitors. Among these, the most promising results have been observed with agents targeting Janus kinases (JAKs). Effective management strategies for centralized pain should combine pharmacotherapy with patient-centered pain neuroscience education, psychotherapy, and individually tailored physical activity. However, for many patients, the long-term efficacy of these treatments remains limited.

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