REVIEW ARTICLE

Fatigue as a Feature of Rheumatic and Musculoskeletal Diseases: A Narrative Review for Clinical Practice

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Abstract

Fatigue is a prevalent and debilitating symptom in patients with rheumatic and musculoskeletal diseases (RMDs), yet it remains inadequately addressed in clinical practice. This narrative review synthesises evidence from a comprehensive scoping review of 134 reviews examining fatigue across rheumatoid arthritis, spondyloarthritis, osteoarthritis, and fibromyalgia, supplemented by recent mechanistic, measurement, and intervention studies. No universally agreed definition of fatigue exists, though subtypes include physical and mental fatigue. Twenty-five self-reported measurement instruments have been identified, with PROMIS (Patient Reported Outcomes Measurement Information System) Fatigue most frequently selected by patients (77.9% uptake). Key determinants include pain, physical function, depressive symptoms, female sex, and stress. Fatigue significantly impacts work performance, physical activity, social functioning, and quality of life. Non-pharmacological interventions (exercise, cognitive-behavioural therapy) demonstrate small effect sizes whilst pharmacological interventions in the form of different biologics and JAK inhibitors show clinically meaningful effects. Fatigue in RMDs is a complex, multidimensional phenomenon requiring tailored management approaches. Rheumatologists must recognise fatigue as a cardinal symptom warranting systematic assessment and individualised intervention strategies.

Keywords: Fatigue, Rheumatic diseases, Rheumatoid arthritis, Spondyloarthritis, Patient-reported outcomes

Introduction:

Fatigue represents one of the most prevalent and disabling symptoms experienced by patients with rheumatic and musculoskeletal diseases (RMDs), yet it remains inadequately managed in rheumatological care. Whilst rheumatologists traditionally focus on objective markers of disease activity—joint counts, inflammatory markers, and radiographic progression—patients consistently identify fatigue as a priority symptom that profoundly impacts their quality of life and functional capacity.[1]

The complexity of fatigue in RMDs extends beyond simple tiredness. It encompasses physical exhaustion, cognitive impairment, and emotional depletion that persist despite adequate rest. Unlike transient fatigue experienced by healthy individuals after exertion, fatigue in RMDs is often chronic, unpredictable, and disproportionate to activity levels. This disconnection between patient experience and physician focus has created a significant gap in clinical care.[1]

A comprehensive scoping review of 134 reviews examining fatigue across rheumatoid arthritis (RA), spondyloarthritis (SPA), osteoarthritis (OA), and fibromyalgia (FM) has synthesised the extensive literature on this topic.[1] Combined with emerging mechanistic insights and digital health data demonstrating patient priorities, this evidence provides rheumatologists with an evidence-based framework for understanding and managing this cardinal symptom.[2,3] This narrative review compiles information from the scoping review and evidence gathered from subsequent studies to generate an updated synthesis of the existing scientific literature about fatigue in RMDs.

Definition and Conceptualisation of Fatigue

Despite its prevalence, no universally agreed definition of fatigue exists in rheumatology.[1] This reflects the multidimensional nature of the symptom and challenges in capturing subjective experiences through standardised definitions.

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The most commonly recognised distinction is between physical fatigue (asthenia) and mental fatigue. Physical fatigue is characterised by inadequate energy resources, feeling of having no energy, and need to rest. Patients describe this as "tiredness" that is present continuously, worsens with physical exertion, and increases as the day progresses. Importantly, resting may provide temporary relief but does not fully restore energy levels.[1] Mental fatigue encompasses cognitive difficulties, reduced concentration, and mental exhaustion that may occur independently of physical symptoms.

Some researchers have drawn parallels between fatigue in RMDs and cancer-related fatigue, suggesting shared pathophysiological mechanisms.[3] This conceptualisation emphasises the chronic, debilitating nature of the symptom and its resistance to conventional rest-based management strategies.

Clinically, it is essential to recognise that fatigue in RMDs is not simply a consequence of disease activity or inflammation. Rather, it represents a complex interplay of biological, psychological, and social factors that may persist even when traditional markers of disease activity are well controlled.[1,4] This understanding has important implications for assessment and management.

Pathophysiology

The pathophysiology of fatigue in RMDs is multifactorial, involving inflammatory, neuroendocrine, and psychosocial mechanisms.[1,2,3,5]

Inflammatory Mechanisms: Peripheral inflammatory disease is associated with centrally activated interleukin-1 (IL-1) systems in both humans and animal models [2]. This peripheral-to-central inflammatory signalling represents a key mechanism by which systemic inflammation translates into central nervous system symptoms, including fatigue. Cytokines such as IL-6 play particularly important roles in RA-related fatigue, and the link between chronic inflammation and pain pathways provides additional mechanistic insight.[3,5] The concept of "sickness behaviour"—an evolutionarily conserved response to infection or inflammation characterised by fatigue, reduced activity, and social withdrawal—helps explain why inflammatory diseases produce profound fatigue even when peripheral disease activity appears controlled.

Neuroendocrine Dysregulation: Fatigue in RMDs is associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system.[1,3] These neuroendocrine disturbances may persist independently of peripheral inflammation and contribute to the chronicity of fatigue symptoms.

Central Sensitisation and Pain: The relationship between fatigue and pain in RMDs is bidirectional and complex.[3] Chronic pain contributes to fatigue through multiple mechanisms, including sleep disturbance, reduced physical activity, and psychological distress. Conversely, fatigue may lower pain thresholds and amplify pain perception through central sensitisation mechanisms.

Psychosocial Factors: Depression, anxiety, stress, and poor sleep quality contribute significantly to fatigue in RMDs.[1,4] These factors act both as direct causes of fatigue and as moderators of the relationship between disease activity and fatigue severity.

Recent mechanistic research emphasises that fatigue in RA and other RMDs results from integration of multiple pathophysiological processes rather than a single dominant mechanism.[1,2,3,5] This complexity explains why single-target interventions often produce modest effects and supports the rationale for multimodal management approaches.

Measurement Instruments and Clinical Assessment

Systematic assessment of fatigue is essential for effective clinical management. A comprehensive review identified 25 self-reported measurement instruments for fatigue in RMDs, with several demonstrating strong psychometric properties.[1,6,7,8]

Key Validated Instruments: The most extensively validated instruments include the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), the Short Form-36 Vitality subscale (SF-36 Vitality), the Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire (BRAF-MDQ), the Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale (BRAF-NRS), and the Fatigue Severity Scale (FSS).[8]

The **BRAF instruments** deserve particular attention for clinical practice. The BRAF-MDQ assesses multiple dimensions of fatigue (physical, cognitive, emotional, and living with fatigue), whilst the BRAF-NRS provides a simple 0-10 rating scale suitable for routine clinical use. Both versions demonstrate strong reliability and sensitivity to change.[6]

PROMIS Fatigue has emerged as the most frequently selected instrument by patients in digital health contexts, with 77.9% uptake in longitudinal monitoring studies.[1] The Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue scale offers standardised T-score metrics that facilitate comparison across studies and populations, computerised adaptive testing options, and extensive validation across multiple

rheumatic diseases. Conversion algorithms allow cross-walking between FACIT-F and PROMIS Fatigue scores thereby permitting the comparison of scores obtained across different centres utilizing different scales and thus bringing homogeneity of measurements.[9,10,11]

Clinical Assessment Recommendations: For routine clinical practice, rheumatologists should implement brief fatigue screening using a single-item numerical rating scale (0-10) at each visit. For patients reporting significant fatigue (e”4/10), more comprehensive assessment using a multidimensional instrument such as the BRAF-MDQ or PROMIS Fatigue can guide management planning.[6,8,12] Assessment should extend beyond severity ratings to encompass functional impact, temporal patterns, and potential contributing factors such as sleep quality, mood, and medication side effects.

Determinants of Fatigue

Understanding the determinants of fatigue in RMDs is essential for developing targeted interventions. The scoping review identified numerous disease-related and contextual determinants, with pain, physical function, and depressive symptoms emerging as the most frequently studied disease-related factors, and female sex and stress as the most frequent contextual determinants.[1]

Disease Activity and Inflammation: Whilst inflammatory disease activity contributes to fatigue, the relationship is complex. Longitudinal studies examining fatigue trajectories in patients with established RA starting biologic DMARD therapy found that patient-reported measures (pain, patient global assessment, tender joint counts, anxiety, and depression) predicted persistent fatigue trajectories more strongly than objective markers of peripheral inflammation [4]. This finding has important clinical implications: achieving low disease activity or remission may not fully resolve fatigue, and additional interventions targeting pain, function, and psychological factors may be necessary.

Pain and Physical Function: Pain consistently emerges as one of the strongest determinants of fatigue across RMDs.[1,4,13,14] The bidirectional relationship between pain and fatigue creates a vicious cycle. Physical function limitations similarly contribute to fatigue through multiple mechanisms including deconditioning and reduced activity levels. In patients with ankylosing spondylitis, fatigue associates strongly with disease activity, quality of life, and inflammatory bowel symptoms.[13,14]

Psychological Factors: Depressive symptoms, anxiety, and stress are consistently associated with fatigue severity across RMDs.[1,4] Depression contributes independently to fatigue beyond its association with disease activity, and interventions targeting mood may produce benefits in fatigue even without changes in inflammatory markers.

Sleep and Demographic Factors: Poor sleep quality contributes significantly to fatigue in RMDs, though the relationship is bidirectional.[1] Female sex is consistently associated with higher fatigue severity across RMDs.[1] Other contextual factors including stress, work demands, and social support also influence fatigue.

Importantly, when quantified, associations between fatigue and its determinants are typically small to moderate in magnitude.[1,4] This underscores the multifactorial nature of fatigue and suggests that comprehensive approaches addressing multiple contributing factors simultaneously are more likely to achieve meaningful improvements.

Consequences of Fatigue

Fatigue in RMDs has profound consequences across multiple life domains, significantly impacting work performance, physical activity, social functioning, and overall quality of life.[1,3,14,15,16]

Occupational Impact: Work performance is the most frequently studied consequence of fatigue in RMDs.[1] Fatigue contributes to reduced work productivity, increased absenteeism, and work disability. For patients with ankylosing spondylitis, severe fatigue is associated with significantly reduced occupational participation and quality of life.[16]

Physical Activity and Function: Fatigue creates a vicious cycle with physical activity and function. Fatigue reduces engagement in physical activity, leading to deconditioning, which in turn exacerbates fatigue and functional limitations. In patients with fibromyalgia, fatigue shows complex relationships with physical activity levels and quality of life.[15]

Social Functioning and Quality of Life: Fatigue significantly impacts social roles, relationships, and participation in valued activities.[1] Patients may withdraw from social engagements, reduce participation in family activities, and experience strain in personal relationships. Across all RMDs, fatigue is consistently associated with reduced health-related quality of life.[13,14,15,16] In patients with spondyloarthritis and ankylosing spondylitis, fatigue associates with poorer quality of life, higher disease activity scores, and sleep disturbance.[13,14,16]

The consequences of fatigue extend across all life domains, yet many patients report that their rheumatologists do not

adequately address this symptom or recognise its impact.[1] Systematic assessment of fatigue and its consequences should be integrated into routine rheumatology care.

Management Strategies

Management of fatigue in RMDs requires a comprehensive, individualised approach that addresses multiple contributing factors. Evidence supports both non-pharmacological and pharmacological interventions, though effect sizes are typically modest.[1,17,18,19,20]

Non-Pharmacological Interventions

Cognitive-Behavioural Therapy (CBT): Group cognitive-behavioural programmes specifically designed for RA fatigue have demonstrated efficacy in randomised controlled trials.[18,19] The RAFT (Reducing Arthritis Fatigue by clinical Teams) programme, delivered by nurses or occupational therapists, produces small to moderate sustained improvements in fatigue impact, coping strategies, mood, and some functional outcomes.[19] Qualitative research indicates that patients find CBT approaches acceptable and value the opportunity to develop self-management skills.[21] Mechanisms of benefit include improved coping strategies, cognitive restructuring of unhelpful beliefs about fatigue, activity pacing, and enhanced self-efficacy.

Exercise Interventions: Supervised exercise programmes, including high-intensity interval training, strength training, and sustained aerobic activity, reduce multidimensional fatigue and improve health-related quality of life in RA.[20,22] A recent randomised controlled study demonstrated that high-intensity exercise improves multidimensional fatigue and quality of life in RA, whilst longitudinal studies confirm the sustained role of physical activity in overcoming fatigue.[20,22] Successful implementation requires careful programme design with gradual progression, individualisation based on patient capabilities, and strategies to support adherence.

Pharmacological Interventions

Biologic Therapies: A Cochrane systematic review of biologic response modifiers found small to moderate reductions in patient-reported fatigue compared to placebo across trials, with moderate overall evidence quality.[17] Trial-specific analyses of sarilumab demonstrate clinically meaningful improvements in PROMIS and FACIT-F fatigue scores after treatment.[10,11,23] Anti-TNF therapy has been associated with rapid improvement in fatigue and sleep in active RA in observational studies.[24]

JAK Inhibitors and Targeted Synthetic DMARDs: Emerging evidence suggests that JAK inhibitors may produce meaningful and sometimes rapid fatigue improvements. Conversion studies and patient-reported surveys indicate that baricitinib and other JAK inhibitors can produce clinically significant reductions in fatigue.[9,25]

Integrated Management Approach: Optimal fatigue management typically requires integration of pharmacological and non-pharmacological strategies tailored to individual patient circumstances. Assessment should identify the relative contributions of active inflammation, pain, physical deconditioning, sleep disturbance, mood symptoms, and contextual factors to each patient's fatigue experience. Management plans should then address the most relevant contributing factors through appropriate combinations of disease-modifying therapy, exercise programmes, psychological interventions, sleep management, and other targeted strategies. Regular reassessment using validated instruments allows monitoring of treatment response and adjustment of management plans.[1,17,18,19,20,22]

Patient Perspectives and Digital Health

Understanding patient perspectives on fatigue is essential for delivering patient-centred care. Digital health data provide unique insights into patient priorities and preferences for symptom monitoring.[1]

Patient Priorities: When given the opportunity to select which symptoms to monitor using digital health platforms, patients with RMDs consistently prioritise fatigue above other domains. In longitudinal studies, 77.9% of patients selected PROMIS Fatigue for tracking, making it the most frequently selected single instrument.[1] This high uptake rate demonstrates the sustained importance of this symptom to patients.

Patient-Provider Gap: A significant gap exists between patient priorities and traditional clinical focus. Whilst patients consistently identify fatigue as a top priority, many rheumatologists do not routinely assess or address this symptom.[1] This disconnect contributes to patient dissatisfaction and may undermine the therapeutic relationship. Qualitative research reveals that patients value being heard, having their fatigue validated as a legitimate symptom, and receiving practical strategies for self-management.[21]

Feasibility of Digital Monitoring: Digital health studies demonstrate that remote symptom monitoring via smartphone applications is highly feasible for patients with RMDs.[1] Patients are willing to complete brief assessments (median 30 seconds per instrument) regularly when the measures address symptoms they consider relevant.

Implications for Clinical Practice: Patient perspectives should inform clinical practice in several ways. First, rheumatologists should routinely ask about fatigue and validate it as an important symptom worthy of clinical attention. Second, assessment tools should use simple, patient-friendly language. Third, management discussions should incorporate patient priorities and preferences, recognising that patients may prioritise fatigue management even when traditional disease activity measures suggest good control.[1,21]

Key Messages:

This narrative review has synthesised current evidence to provide specialist rheumatologists with an evidence-based framework for understanding and addressing this complex symptom.

Several key messages emerge from the evidence. First, fatigue in RMDs is multidimensional and multifactorial, resulting from complex interactions among inflammatory, neuroendocrine, psychological, and social factors.[1,2,3,5] This complexity explains why single-target interventions typically produce modest effects and supports the rationale for comprehensive, individualised management approaches. Second, validated measurement instruments are available and should be integrated into routine clinical practice.[6,7,8,9] Third, the determinants of fatigue extend beyond disease activity and inflammation to encompass pain, physical function, mood, sleep, and contextual factors, with patient-reported measures often predicting fatigue trajectories more strongly than objective inflammatory markers. Fourth, the consequences of fatigue are profound and pervasive, significantly impacting work performance, physical activity, social functioning, and quality of life.[1,4,13,14,15,16] Fifth, both non-pharmacological interventions (particularly CBT and exercise) and pharmacological interventions (biologics and JAK inhibitors) demonstrate efficacy for fatigue reduction, though effect sizes are typically modest.[9,10,17-20,22,24,25]

From a clinical practice perspective, several recommendations can be made. Fatigue should be systematically assessed in all patients with RMDs using brief, validated instruments, with more comprehensive evaluation for those reporting significant symptoms.[6,8] Assessment should extend beyond severity ratings to encompass functional impact, temporal patterns, and potential contributing factors. Management should be individualised and multimodal, combining disease-modifying therapies to control inflammation with non-pharmacological interventions addressing behavioural, psychological, and lifestyle factors.[1,17,18,19,202,22] Realistic expectations about treatment outcomes should be established, acknowledging that current interventions produce incremental improvements rather than complete fatigue resolution.

Importantly, clinicians must validate fatigue as a legitimate and important symptom worthy of clinical attention. This validation begins with asking about fatigue, listening to patients' experiences, and acknowledging the profound impact it has on their lives. Patient perspectives consistently identify fatigue as a top priority, yet many patients report that their rheumatologists do not adequately address this symptom. Closing this patient-provider gap requires systematic integration of fatigue assessment and management into routine rheumatology care.[1]

Looking forward, several research priorities emerge. First, improved understanding of fatigue mechanisms is needed to identify novel therapeutic targets.[2,3,5] Second, development and testing of interventions specifically designed to target fatigue are essential. Third, identification of patient subgroups who may respond preferentially to specific interventions could enable more personalised treatment approaches. Fourth, implementation research examining how to effectively integrate systematic fatigue assessment and evidence-based management into routine clinical practice is needed to translate research evidence into improved patient outcomes.

Conclusion:

Fatigue in RMDs is a cardinal symptom that demands systematic attention from rheumatologists. By recognising its importance, assessing it routinely, and implementing comprehensive, individualised management strategies, rheumatologists can better address patient priorities and improve quality of life for the millions of individuals living with debilitating fatigue. The extensive evidence base synthesised in this review provides a foundation for evidence-based practice, whilst patient perspectives remind us that effective care requires not only clinical expertise but also empathy, validation, and partnership with patients in managing this challenging symptom.

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