

# The impact of fatigue in rheumatoid arthritis and the challenges of its assessment

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## Abstract

Fatigue is one of the most important symptoms for patients with RA, and imposes a great burden on patients' lives, being associated with significantly reduced health-related quality of life. Although being recognized by the rheumatology community as a major gap in the current management of the disease, fatigue has not been easy to measure and conceptualize. Part of the problem seems to reside in the multidimensional causality of this phenomenon, which may warrant dedicated measures and interventions. Although there are several instruments available to measure it, no consensus has yet been reached to recommend a 'gold-standard'. This review aims at synthesizing the role of fatigue in the global impact of RA; describing validated instruments and their psychometric properties as measures of fatigue among patients with RA; and finally proposing a clinically meaningful, valid and feasible process to measure fatigue in clinical practice.

**Key words:** arthritis, rheumatoid, fatigue, psychometrics, outcome assessment (health care)

### Rheumatology key messages

- Fatigue is a significant component of the global impact of rheumatoid arthritis (RA).
- Clinicians and researchers should only use valid instruments to measure fatigue in patients with RA.
- Clinicians could screen fatigue in RA with single-item instruments, complemented with multidimensional ones if needed.

## Introduction

Fatigue is a common and persistent problem in musculo-skeletal and rheumatic diseases, including RA [1, 2]. It affects around 40–80% of these patients [3, 4], being defined as severe in about half of the cases [3, 5–7], and has negative impact upon health-related quality of life [8]. Fatigue is experienced as being overwhelming, unpredictable, extreme, not restored by sleep, multidimensional and part of a vicious circle in which fatigue feeds and fosters itself [9, 10]. Coherently, fatigue is considered as one of the most important disease outcomes by patients

[8, 11, 12]. It has received increased attention over the past decade and has been recommended by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group as an important outcome domain that should be assessed in all RA studies, alongside the core set [13].

Despite having been historically considered an extra-articular manifestation of RA, related to disease activity, recent findings support a multifactorial aetiology for fatigue, involving an array of co-morbid factors, such as disability, psychological well-being, social support and 'overall evaluation of health' [14].

The measurement of fatigue in RA entails several challenges due to its subjective nature and close relationship with cognitive and emotional dimensions [15]. Characteristics of the experience and consequences of fatigue are likely to be unique in RA patients, which imposes the need for specific assessment instruments [13]. Generic instruments may, as an example, contain items that in RA would capture the restrictions imposed by inflammation or disability, rather than by fatigue itself, leading to unreliable or misleading results [15]. Previous

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reviews confirmed that the majority of the numerous instruments used to assess fatigue in RA are well validated psychometrically, but lack evidence of their validity in the specific clinical context of RA [16, 17]. This may help explain why no consensus has yet been reached on how to measure it in this disease.

For the purpose of this review, and to further evolve this area, we chose to analyse only the instruments with reasonable evidence of validation for measuring fatigue in RA, diagnosed with established criteria. The aims of this review are: (i) to synthesize the role of fatigue in the global impact of RA, (ii) to describe validated instruments and their psychometric properties as measures of fatigue in patients with RA, and (iii) to propose a clinically meaningful and valid process to measure fatigue in clinical practice.

### Importance of fatigue in the global impact of RA

Fatigue has a significant negative impact on patients' ability to perform daily self-care and socially relevant tasks [18–20], to the detriment of physical and mental or emotional well-being and personal satisfaction [14, 21]. As a consequence of fatigue, patients experience higher levels of interpersonal stress, including with friends and family members [20]. Fatigue has been found to account for 36–44% of role limitations, 52–57% of physical and social functioning problems, 64% of mental health symptoms, and 51% of the general perception of health worsening in RA [21].

Work disability is among the most important consequences of fatigue in RA. In fact, patients have identified this symptom as the principal barrier to employment and reduced productivity [22, 23] and this has been extensively demonstrated by research. In a longitudinal study, the likelihood of absenteeism at 6 and 12 months was significantly higher in those describing more fatigue at baseline (odds ratio (OR) 1.23; 95% CI: 1.02, 1.49). Fatigue was also associated with activity impairment (OR 1.52; 95% CI: 0.79, 2.26) and work productivity loss (OR 4.16; 95% CI: 2.47, 5.85) [22]. Fatigue was also associated with more physicians' consultations and more referrals to therapists over time [24]. This indicates that fatigue is probably associated with considerable additional societal costs in RA although, to our knowledge, this has not been the object of specific publications.

Altogether, these findings can justify why fatigue is considered an important cause in 'difficult to treat' RA patients [25], making the management of RA more challenging and causing greater health care utilization.

Fatigue significantly affects the assessment of disease activity: it has been identified as the main driver of patient self-assessment of global impact of the disease (patient global assessment). This is true even in patients in disease remission, i.e. with good control of the inflammatory process [26, 27]. It has been shown that when fatigue persists, patients will not perceive the achievement of favourable clinical outcomes [28]. Patient global assessment has a significant weight in current disease

activity indices used to guide treatment decisions [27, 29, 30], thus conveying an indirect impact of fatigue in heightened medication cost and risk of overtreatment.

### Instruments and their psychometric properties

The information above underlines the need to accurately assess fatigue both in research and in clinical settings. Clearly, the choice of the instrument to measure fatigue is an essential step and the challenge this represents should not be underestimated. Although several instruments are available for this purpose, two main problems arise. The first is their limited validation. Frequently, publications using these instruments do not include references of validation studies, or do not fully describe the instrument. Therefore, it cannot be ruled out that significant variations in wording of the questions, in time reference (e.g. last week, last month) and even in the number of items may have occurred in different instances of use of the same instrument. This is quite clear with the single-item visual analogue scales, for which several versions were identified [16]. The second problem relates to the use in RA of instruments developed and validated for application in patients with other rheumatic diseases, other diseases, such as cancer [16, 31], or in the general population. The use of such non-specific instruments may entail important issues, namely 'contamination bias', whereby some items may distort the assessment of fatigue by influence of other distinct outcomes in RA: physical function impairment or joints' inflammatory activity. The purpose of fatigue assessment should drive the selection of the instrument and sometimes both RA-specific and non-specific instruments should be used. Whatever the case, clinicians and researchers should consider using only instruments with adequate validation [16, 17], i.e. instruments that have been proven to measure exactly what is purposed (validity) and that provide consistent results at different time points (reliability) or are able to detect relevant changes over time (sensitivity to change) [32].

To select instruments for this narrative literature review we used two criteria: (i) being the most used by clinicians and researchers in patients with RA, according to published reports; and (ii) having reasonable evidence of validation regarding acceptability, validity, reliability and sensitivity to change in RA. Searches were limited to PUBMED and CINAHL, in the English language and without restriction of dates. The search strategy included the following descriptors: fatigue, tiredness, scale, questionnaire, checklist, inventory and psychometrics. One researcher (E.S.) reviewed all abstracts, and then full articles were reviewed to identify the fatigue instrument used and to extract information on their psychometric properties, appraised by all researchers. We have thus identified 12 instruments [16, 33–47], which are presented in Tables 1 and 2. Then, a score was attributed to the psychometric properties of each instrument according to the strength of the available evidence based on its validation studies (strong/good evidence, moderate evidence,

**TABLE 1** Summary of the characteristics of the selected fatigue assessment instruments

Instrument	Information/strengths	Specifically designed for RA	Free to use	Number of items	Time to self-report	Higher score means
BRAF MDQ	Developed with RA patients. Measures multiple dimensions of fatigue	Yes	Yes	20	4–5 min	Higher fatigue
BRAF NRS	Developed with RA patients. Measures severity, impact and coping	Yes	Yes	3	1 min	High severity and effect = higher fatigue; high coping = better
CFQ	Measures severity and uses different subscales	No	Yes	11	2–3 min	Higher fatigue
CIS20R and CIS8R	Used in several long-term conditions	No	Yes	20 or 8	4–5 min	Higher fatigue
FSS	Recommended scale for systemic lupus erythematosus but also used in other rheumatic conditions	No	Yes	9	2–3 min	Higher fatigue
FACIT-F	Used in several rheumatic conditions and in other chronic illnesses	No	Yes, except for commercial studies	13	3–4 min	Better
MAF	Specific for RA but used in other chronic illnesses	Yes	Yes, except for commercial studies	15	5–8 min	Higher fatigue
MFI	Used in several rheumatic conditions and in other chronic illnesses	No	Yes, except for commercial studies	20	4–5 min	Higher fatigue
SF-36 VT	Measures energy and fatigue in general and clinical populations. Widely used	No	No	4	1 min	Better
VAS	Feasible to measure a variety of fatigue constructs. Widely used	No	Yes	Variable	1 min	Higher fatigue
RAID-F	VAS developed with RA patients	Yes	Yes	1	1 min	Higher fatigue
POMS	Although designed to measure mood, the fatigue/inertia scale has been used to assess fatigue experienced by RA patients	No	Yes, except for commercial studies	7	2–3 min	Higher fatigue

BRAF MDQ: Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire; BRAF NRS: Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales for severity, effect and coping; CFQ: Chalder Fatigue Questionnaire; CIS20R and CIS8R: Checklist Individual Strength; FACIT-F: Functional Assessment Chronic Illness Therapy (Fatigue); FSS: Fatigue Severity Scale; MAF: Multi-Dimensional Assessment of Fatigue; MFI: Multi-Dimensional Fatigue Inventory; POMS: Profile of Mood States; RAID-F: Rheumatoid Arthritis Impact of Disease Fatigue Subscale; SF-36 VT: Short Form 36 Vitality Subscale; VAS: Visual Analogue Scales.

low/limited evidence, not applicable) (Table 2). For more details on the psychometric properties and full description of the instruments, readers are advised to appraise their validation studies (last column of Table 2) and/or previous reviews [16, 17].

Based on their characteristics and psychometric properties, all the selected instruments may be considered adequate to measure RA fatigue, depending on the clinical setting and the objectives. However, further studies and cooperative work are required to address specific needs such as the elimination of 'contamination bias', the

consensual adoption of a 'gold standard', the definition of clinically relevant and validated cut-offs to assist in patient care management, and the development and validation of a standardized single-item assessment tool.

The constitution of a task-force with the different stakeholders may be the solution to achieving much-needed progress. A complete systematic review of outcome measurement instruments based on the current guidelines is dearly needed and the use of the COSMIN methodology (<https://www.cosmin.nl/>) is imperative. Furthermore, an update of previous reviews is needed as they considered

**TABLE 2** Summary of psychometric properties of the selected fatigue assessment instruments

Instrument	Psychometric properties							
	Acceptability <sup>a</sup>	Reliability		Validity			Ability to detect change	Validation studies
		Internal consistency	Test-retest	Content validity	Construct validity	Criterion validity		
BRAF MDQ	Strong	Strong	Strong	Strong	Strong	Strong	Good	[33–36]
BRAF NRS	Strong	NA	Severity and effect: strong Coping: moderate	Strong	Strong	Strong, moderate for coping	Good	[33–36]
CFQ	Low	Strong	Strong in other populations	Good	Moderate	Moderate	Good	[37, 38]
CIS20R and CIS8R	Low	Strong	Strong	Moderate	Strong	Strong	Good	[39]
FSS	Moderate	Strong	Strong	Strong	Strong	Strong	Good	[40]
FACIT-F	Moderate	Strong	Strong	Moderate	Strong	Strong	Good	[41]
MAF	Moderate	Strong	Strong	Moderate	Strong	Strong	Good	[42]
MFI	Moderate	Strong	Strong	Moderate	Strong	Moderate and variable	Good	[43]
SF-36 VT	Strong	Strong	Very weak to strong	Moderate	Strong	Moderate to strong	Good	[44]
VAS	Moderate	NA	Strong	No standard format	Strong	Moderate to strong	Good	[16]
RAID-F	Strong	NA	Strong	Strong	Moderate to strong	Strong	Good	[45, 46]
POMS	Moderate	Strong	–	Moderate	Low	Moderate and variable	–	[47]

<sup>a</sup>Based on the ease of reading and understanding, levels of missing data reported and presence of floor or ceiling effects. BRAF MDQ: Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire; BRAF NRS: Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales for severity, effect and coping; CFQ: Chalder Fatigue Questionnaire; CIS20R and CIS8R: Checklist Individual Strength; FACIT-F: Functional Assessment Chronic Illness Therapy (Fatigue); FSS: Fatigue Severity Scale; MAF: Multi-Dimensional Assessment of Fatigue; MFI: Multi-Dimensional Fatigue Inventory; NA: not applicable; POMS: Profile of Mood States; RAID-F: Rheumatoid Arthritis Impact of Disease Fatigue Subscale; SF-36 VT: Short Form 36 Vitality Subscale; VAS: Visual Analogue Scales.

publications until 2004 [16] or not stated ( $\leq 2011$  at best) [17], and further psychometric studies have been published (e.g. on BRAF and RAID) or new instruments developed since these reviews were published.

### Putting the evidence together: a preliminary proposal to measure fatigue in practice

Although fatigue was defined as a core outcome for clinical trials by the ACR/EULAR [48] and was the topic of a study interest group of OMERACT, these leading organizations did not specify/recommend a gold-standard instrument to assess fatigue. The diversity of instruments and their relative advantages and limitations have been the subject of discussion by clinicians and researchers [49].

The arguments for using disease-specific vs generic instruments, or multi-item/multidimensional vs single-item instruments are still open [50]. One large study suggested

that scoring different components of fatigue does not appear to add relevant information to that provided by a single-item instrument [51]. However, this may depend on the intended use of the information (e.g. a self-management intervention or a medication change). Also, a set of qualitative studies have suggested that the RA-specific, multi-dimensional instruments are needed to fully and precisely identify fatigue specific to RA [33, 52, 53].

From the patient's perspective there are three essential aspects of impact of disease that require assessment (the so-called 'Impact Triad'): the severity of an outcome (e.g. fatigue), its importance to the patient (i.e. in comparison with the 'usual' status or with other symptoms), and patient ability to self-manage/cope with that perceived severity. In other words, it is important to consider how symptom severity and self-management may influence patient priorities or the importance of outcomes for an individual person [54]. The development of the BRAF-NRS considered this triad, and this was the instrument

used in a recent randomized controlled trial, which demonstrated that cognitive behavioural intervention had short and long term efficacy on the BRAF-NRS impact but not a similar efficacy in coping with (only in the longer term) or in the severity of fatigue [55].

In the absence of formal recommendations, clinicians and researchers should consider whether their needs are best served by a single-item instrument, a multi-item instrument that explores broader fatigue issues to create a global score, or a multidimensional instrument that produces subscale scores for a range of different domains of fatigue (e.g. cognitive and physical fatigue) [17]. This open choice has, however, the drawback of limiting comparison across studies.

A strategic option for clinical practice may be to use a single-item instrument as a screening tool (e.g. BRAF NRS, RAID-F), which would be supplemented by additional multidimensional assessments, if significant levels of fatigue are identified by screening. This will be particularly useful when the aims are to explore fatigue causality or the efficacy of interventions [17].

Given the multifactorial nature of fatigue, it may be wise to measure other domains of significant impact for patients. In fact, previous studies associated fatigue with specific domains of disease impact (e.g. pain, functional disability and sleep disturbances [12, 56]), suggesting that efficient interventions in these domains may contribute to significant reductions of fatigue levels. In our opinion, the most suitable instrument for this purpose is, currently, the Rheumatoid Arthritis Impact of Disease Score (RAID) [45, 46] which considers seven different domains of impact: pain, functional disability, fatigue, emotional well-being, physical well-being, sleep and coping. RAID was developed and validated as a combined index of overall impact, resulting from the consideration of the seven dimensions (original formulation). The NRS used to assess individual domains of disease impact in RAID are valid, feasible, reliable and sensitive to change in patients with RA [46, 57, 58]. Using the seven scores separately (RAID.7i) offers a feasible tool to analyse impact of disease and to design and monitor individually tailored interventions, targeting the domains of concern, and thus indirectly improving fatigue.

## Conclusions

Fatigue is, undisputedly, an outcome of outstanding importance for patients with RA and, thus, for the conceptualization and achievement of treatment targets.

It should be regularly measured in both research and clinical practice. A number of validated instruments are available to this purpose but there is no consensus definition of gold standard.

The use of a single item tool, followed by multidimensional instruments as appropriate, seems to be a suitable proposal for clinical practice.

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