Fatigue in rheumatic disease: an overview

Fatigue is a common and disabling symptom in a number of rheumatic diseases, including rheumatoid arthritis, ankylosing spondylitis and osteoarthritis. Patients frequently rank fatigue as one of their most disabling symptoms, adversely affecting quality of life and employment opportunities. The aims of this article are to: first, define the concept of fatigue in rheumatic disease, its nature, prevalence and impact; second, describe questionnaires that have been validated as measures of fatigue among people with rheumatic diseases; third, outline the factors which have been identified as influencing fatigue, including disease activity/severity, disability, pain, sleep disturbance, mood, self-efficacy, illness perceptions and coping; and finally, synthesize the sparse evidence currently available regarding the best strategies for managing fatigue in rheumatic disease. Recent research has suggested that disease-modifying antirheumatic drugs and biologic therapies are effective in ameliorating fatigue in both rheumatoid arthritis and ankylosing spondylitis, but the mechanism by which they reduce fatigue is not clear. Tailored exercise and psychological interventions show promise. Further studies are needed to determine the best ways of managing the fatigue associated with rheumatic disease. The assessment of fatigue in rheumatology clinics should be part of standard practice.

KEYWORDS: ankylosing spondylitis ■ fatigue ■ osteoarthritis ■ quality of life ■ rheumatoid arthritis

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Fatigue is a common symptom in many chronic diseases. It can be defined as a state of 'extreme tiredness, typically resulting from mental or physical exertion or illness' [1]. This linguistic definition of fatigue is important because it is likely to form the basis of an individual's understanding of the symptom. Alternative definitions of fatigue were reviewed by Aaronson *et al.*, who recognized the challenges of defining fatigue given the complex interaction of biological and psychological processes, together with the behavioral adaptations that are manifested [2]. Aaronson *et al.* described several published definitions of fatigue, including the comprehensive definition of fatigue as: "A subjective, unpleasant symptom which incorporates total body feelings, ranging from tiredness to extreme exhaustion, creating an unrelenting overall condition which interferes with an individual's ability to function to their normal capacity" [3]. The suggestion that fatigue is a continuum has been challenged by Olson [4]. Fatigue, tiredness and exhaustion have been found to be distinct states with specific clinical meaning at the ends of a continuum of adaptation, where successful adaptation results in tiredness (which can be improved by sleep), and poor adaptation is associated with exhaustion, leading to impaired quality of life and social withdrawal [4].

Attempts have been made to define fatigue in the specific context of arthritis [5], where fatigue is recognized as a complex symptom, with both physical aspects (including need for rest and the experience of weakness in muscles) and psychological aspects (including problems with concentration) [6,7].

This article will address fatigue in three common rheumatic diseases, rheumatoid arthritis (RA), ankylosing spondylitis (AS) and osteoarthritis (OA), where fatigue has a considerable negative impact on quality of life [8,9]. The causes of fatigue are multifactorial [7,10]. Many of the factors leading to fatigue are common to all three conditions; however, the relative influence of contributing factors may differ across these diseases [8].

In undertaking this review, a range of literature databases were searched (including PubMed, PsycINFO, Google Scholar and Web of Science) using terms to identify studies of people with the rheumatic diseases in question (RA, AS, OA), relating to the concept 'fatigue' (or the common antonym 'vitality') and with relevant methodologies (trial, randomized control trial, longitudinal, diary, questionnaire, reliability). Reference lists and key journals (in particular, *Rheumatology*, *Arthritis Care and Research*, *Journal of Rheumatology* and *Musculoskeletal Care*) were also searched by hand.

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The importance of fatigue has recently been recognized by the Outcome Measures in Rheumatology (OMERACT) consortium [11]. OMERACT has endorsed the measurement of fatigue in studies of RA wherever possible, concluding that fatigue is an important symptom that is commonly reported by patients and is often severe. Furthermore, several self-report instruments are available for reliably measuring fatigue, which provide valuable information additional to that obtained from other commonly used outcome measures [12].

Nature of fatigue

The experience of fatigue in individuals with rheumatic diseases is very variable. However, when it is a prominent symptom it occurs on most days and varies in intensity and frequency ranging from heaviness and weariness to exhaustion. Patterns of fatigue vary and a J-shaped curve with levels decreasing in the morning and worsening in the evening has been reported in RA [13].

In qualitative studies of individuals with RA, patients distinguish between systemic fatigue, related to their arthritis, and general tiredness [14]. Fatigue frequently manifests not only as physical fatigue, but also as an inability to think clearly, to concentrate or to motivate oneself [7]. Fatigue is experienced as variable and largely unpredictable, often with sudden onset [15]. Occasionally, an abrupt onset of overwhelming tiredness can occur, which forces people to stop what they are doing and lie down [16]. This characteristic aspect of fatigue has been described in RA, AS and OA [16–18].

Prevalence & severity of fatigue

The reported prevalence of fatigue in RA varies widely depending on the criteria used, but the prevalence of clinically relevant fatigue is commonly given as between 40 and 80% [19–22], with 40% experiencing persistent severe fatigue [23]. Around a third of patients with AS suffer severe fatigue [24], with an overall prevalence of 53–76% [9,24,25]. In OA, the prevalence of fatigue varies between 41 [19] and 56%, with 10% experiencing severe fatigue [8].

Comparison between the levels of fatigue experienced by individuals with different rheumatic diseases is also complicated by patient selection and particularly by the assessment tools used. Comparison of fatigue using one multidimensional tool, the Multidimensional Assessment of Fatigue (MAF; scored 1–50 with higher numbers indicative of worse fatigue) [26], across three forms of arthritis, has demonstrated similar levels of fatigue amongst people with RA (mean: 24.6–29.2; standard deviation [SD]: 9.9–11.1), AS (mean: 28.3; SD: 14.2) and OA (mean 27.7; SD: 10.8) [8,20,25]. Using such measures, fatigue levels are similar to those observed in HIV-positive individuals and mothers nursing newborn infants [27,28].

Impact of fatigue

Fatigue has a major social and economic cost in rheumatic disease. Qualitative studies show that social activities and household chores are commonly affected by fatigue among people with RA [12,15] or OA [18]. In one study of people with RA, up to half the respondents questioned had given up sports specifically owing to tiredness [15]. Fatigue and well-being were ranked as the most important issues after pain and independence, and above joint symptoms, in a questionnaire (based on issues raised in focus groups) completed by 323 people with RA [29].

Rheumatic disease often impacts on the ability of an individual to maintain employment for diverse reasons. In one study of patients with RA, 45% of participants cited fatigue as a persistent threat to employment [30]. These patients had made a number of adaptations in order to continue working, including changing jobs, altering their career path, changing working hours and sleeping more [30]. Fatigue may be a more important threat to employment than other factors, such as pain or psychological stress [31]. In an inception cohort of patients with RA (with a disease duration of <3 years) 27% of patients were found to be work-disabled. In this work-disabled subgroup, there was a strong association between loss of employment and an indicator of fatigue [32].

Work is an important element of health-related quality of life. Loss of employment and subsequent detrimental effects on quality of life are greater in RA than AS. Fatigue has been shown to have some contribution to this [33]. Employment is less indicative of quality of life in OA, since patients tend to be older and the prevalence of OA increases with advancing age. However, OA is associated with significant loss of earnings in those below retirement age [34]. For people with OA, fatigue is described as debilitating and occasionally restricting activity [32]. Some individuals link fatigue to pain, noting difficulties falling asleep or staying asleep and noting fatigue as a very negative aspect of their lives [35]. For people with AS, fatigue is an important and often under-recognized

symptom, which impacts on many different aspects of an individual's life, including physical functioning and relationships [36]. It can also impact on daily working lives and on sport and leisure activities [17]. Fatigue is a strong predictor of work dysfunction and overall health status in a variety of rheumatic diseases including OA and RA [19].

Assessment of fatigue

The prevalence of fatigue is dependent on both how it is defined and how it is measured [19]. Since there are no definitive physiological or biochemical markers of fatigue, accurate assessment relies on validated self-reporting measures [7]. Instruments for measuring fatigue can be divided into single-item fatigue scales, generic multi-item fatigue scales and disease-specific fatigue scales. There are advantages and disadvantages to each of these three approaches to measurement. Neuberger [37] and Hewlett *et al.* [7] reviewed fatigue assessment scales used in a variety of rheumatic diseases. More recent reviews of fatigue measures have tended to focus on generic and specific fatigue measures for individual rheumatic diseases. An extensive review of available fatigue measures used in studies amongst people with RA was carried out by Hewlett *et al.* [38]. A review of fatigue scales has been undertaken in AS by Zochling *et al.* [36], but no systematic review of different measures of fatigue has yet been made in OA. A summary of fatigue assessments that have been used in rheumatic disease is given in Table 1.

Table 1. Summary of validated fatigue measures used in studies of rheumatic diseases

Assessment of fatigue	Study	Number of items	Use in rheumatic diseases	Advantages	Limitations	Ref.
SF-36 Vitality	Ware *et al.* (1992)	4	RA, OA and AS	Widely used and allows direct comparison between many chronic conditions Sensitive to change in RA	Lack of vitality and fatigue are conceptually different May not differentiate depression from fatigue	[24,42,44]
MFI	Smets *et al.* (1995)	5	RA/AS and AS	Used in two large studies in AS	Not developed for use in rheumatic disease Some items confounded by disease activity and disability Limited evidence in RA	[9,33,57]
FACIT-F	Cella *et al.* (2005)	13	RA and OA	Good internal consistency, validity and sensitivity to change in RA Used in OA	Developed for use in cancer patients and some items may not be relevant to rheumatic disease	[18,58,59]
FSS	Krupp *et al.* (1989)	9	AS	Items related to consequences of fatigue Comparable to SF-36 in AS	Developed for systemic lupus erythematosus and multiple sclerosis, with few data for other conditions	[60,61]
MAF-GFI	Belza *et al.* (1993)	16	RA, OA and AS	Developed specifically for RA Large body of published work in a variety of rheumatic conditions Evidence for responsiveness	Layout favors responses in terms of disability not fatigue Lack of cognitive items	[8,20,25,26,65]
VAS	Eg/Wolfe (1996)	1	OA and RA	Easy to administer in clinic situation Valid, reliable and discriminatory Responsive to change	Lack of standardization between various VAS limits comparison between studies Can be time-consuming to score	[19,40,41]
NRS	Nicklin *et al.* (2009)	3	RA	Easy to score and administer Developed specifically for use in RA	Not yet fully validated	[56]
BASDAI-VAS	Garrett *et al.* (1994)	1	AS	Widely used and validated	Abstracted from 6-item disease activity index and not designed for use as a single scale	[24,36,45]

AS: Ankylosing spondylitis; BASDAI-VAS: Bath ankylosing spondylitis disease activity index-abstracted VAS; FACIT-F: Functional assessment of chronic illness therapy; FSS: Fatigue severity scale; MAF-GFI: Multidimensional assessment of fatigue scale (global fatigue index); MFI: Multidimensional fatigue inventory; NRS: Numerical rating fatigue scale; OA: Osteoarthritis; RA: Rheumatoid arthritis; SF-36: Medical Outcomes Short form 36 (vitality scale); VAS: Visual analog fatigue scale.

Visual analog fatigue scales

Visual analog fatigue scales (VAS; commonly a 10-cm horizontal line with two descriptive anchors) have been the most widely used, with a review showing 26 papers using these as a primary fatigue measure in RA [38]. However, of these only three were identical in terms of descriptors, timescale and length [38]. Many studies do not adequately describe the VAS used. This lack of standardization limits comparison between different studies [38,39]. Three longitudinal studies have shown variation in fatigue over time using a VAS, but reliability and sensitivity data are inconsistent [38,40].

VAS have also been used to measure fatigue in OA. Again, there is considerable variation in scales used and the number of studies is fewer [19,41,42]. Levels of fatigue, where directly compared using these scales, are similar to those in patients with RA [19,43].

In AS, a VAS fatigue scale similar to those used in the previously described studies has shown significant correlation with the Medical Outcomes Studies 36 item Short Form Questionnaire (SF-36 [44]) [24]. However, in contrast to other conditions, fatigue data in AS have commonly been abstracted from a component of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [45]. This instrument consists of six VAS questions and is used to assess self-evaluated disease activity. One of the questions comprises a 10-cm VAS fatigue question regarding fatigue. Two large studies have employed this scale to study fatigue in AS, one evaluating 401 patients [46] and the other 812 patients [9].

Visual analog fatigue scales have a number of advantages and have proved to be easy to use, valid, reliable and responsive for measuring a number of subjective experiences such as pain [47] and quality of life [48] as well as fatigue. They have greater discrimination than descriptive terms with numerical values (e.g., 'mild', 'moderate' and 'severe') [47,48]. These properties have permitted the adoption of VAS scales in everyday clinical use [49]. Indeed, VAS scales have been used in different forms for many years in clinical practice [50–53]. However, traditional VAS scales do require some prior patient instruction and this can be time-consuming. As a result, there has been a move towards substituting a numerical rating scale (NRS), which does not appear to compromise the validity of a number of widely used VAS scales and are much easier to score, explain and administer. NRS scales are now available for the component VAS scales within the Western Ontario McMaster Universities' Osteoarthritis Index (WOMAC) and Bath Indices [54,55]. NRS versions of some assessments of fatigue in RA are available [56], with the potential benefit of relative ease of completion compared with VAS, which can be confusing for patients who have not previously completed such scales.

Multi-item fatigue scales

Multi-item scales seek to provide a multidimensional view of fatigue by measuring not only the level of fatigue, but also its impact on areas such as quality of life and activities of daily living. Several such scales have been used to measure fatigue in RA, even though they were originally developed for use in other conditions. Some of these have shown validity, internal consistency and sensitivity to change. However, as they were not designed to measure fatigue specifically in rheumatic disease, they suffer from some limitations. By contrast, one advantage of generic scales is that they allow direct comparisons between levels of fatigue in different conditions.

Perhaps the most widely used generic multi-item fatigue scales is an element of the SF-36. This questionnaire includes a four-item vitality subscale. Zautra *et al.* noted a strong negative correlation between the SF-36 vitality subscale and average levels of fatigue between individuals in both RA (r = -0.60) and OA (r = -0.46) populations [42]. The SF-36 has also been used to asses fatigue in AS, where it has been shown to differentiate between fatigue levels in patients with AS and healthy individuals [24]. Despite its widespread use, controversy surrounds the use of the SF-36 as a fatigue measure, because some authors question whether a lack of vitality is a different conceptual experience to fatigue [38]. Some studies have shown that the SF-36 vitality scale is sensitive to change and has validity in RA [7]. Others, however, have demonstrated that patients with RA have more vitality than healthy individuals [38]. Furthermore, the SF-36 vitality scale may not differentiate depression from fatigue in RA [38].

The Multidimensional Fatigue Inventory was developed to assess fatigue in cancer patients and patients with chronic fatigue [57]. It consists of five subscales. Its use in rheumatic disease has been limited with one study in AS and a comparison of fatigue in RA and AS [9,33]. Some items may be confounded by disability and disease activity (e.g., 'physically I feel only able to do a little')[7].

The Functional Assessment of Chronic Illness Therapy (FACIT-F) is a 13-item fatigue scale. It was also developed to measure fatigue in patients with cancer, but has demonstrated good internal consistency (Cronbach's α = 0.86–0.87), convergent validity and sensitivity to change in RA, where it also correlates with the MAF and SF-36 Vitality scale [58]. Its focus on cancer symptoms, which have not featured in qualitative analyses of patients with rheumatic disease (e.g., 'I feel too tired to eat') is a disadvantage [38]. It was used in a study to evaluate fatigue in a trial of the biologic therapy with tocilizumab, where a reduction in fatigue levels was demonstrated with this therapy [59]. It was recently used in a study of OA, where mean levels of fatigue were comparable to those seen in RA [18].

The Fatigue Severity Scale is a nine-item scale developed for use in multiple sclerosis and systemic lupus erythematosus [60]. It has shown good internal consistency in these diseases. There are also items related to the consequences of fatigue [37]. It has been used in AS and found to be moderately responsive with good discriminative capacity and was comparable to the SF-36 vitality scale [61].

Assessments of fatigue developed specifically for rheumatic diseases

The Assessments of SpondyloArthritis International Society (ASAS) has recommended that fatigue be measured in studies of AS, but has acknowledged that at present no specific tool exists to measure fatigue in AS [62]. For the time-being, without a specific validated measure, ASAS has recommended using the fatigue measure included within the BASDAI [36]. The BASDAI includes a single item (out of six) relating to fatigue. As noted previously, this item has been abstracted to measure fatigue and has validity [24].

Given that there is considerable evidence for fatigue as an important symptom in OA [63], it is perhaps surprising that standard instruments such as the WOMAC, whilst assessing pain and disability, do not include a fatigue measure. No specific measures of fatigue have been developed for OA and it has not been included as a primary outcome measure by OARSI-OMERACT [64].

Multidimensional assessment of fatigue

One of the most widely used fatigue scales in rheumatic disease is the MAF, which is usually expressed as a total Global Fatigue Index (MAF-GFI). The MAF was specifically adapted from the items of the Piper Fatigue Scale for use in RA [26]. The MAF-GFI scale contains 16 items measuring four dimensions of fatigue: severity, distress, degree of interference with activities of daily living and timing. The majority of items are answered on 10-point NRS with various anchors (e.g., 'Not at all' to 'A great deal'). MAF-GFI scores range from 1 (no fatigue) to 50 (severe fatigue) and samples of healthy individuals have recorded scores with a mean between 15.8 and 17.0. The MAF-GFI has been validated in samples of individuals affected by fatigue in a number of circumstances, including mothers nursing young infants and HIV-infected individuals [27,28,65]. The MAF has good internal consistency in both OA and RA (Cronbach's α in RA = 0.91–0.96) [20,65]. The MAF has been used to assess fatigue in OA [8]. It has been used but not validated in AS, where it does, however, correlate with the SF-36 vitality scale [25].

Advantages of the MAF include a large body of published work showing its validity and responsiveness, together with its wide applicability to different rheumatic conditions. The MAF has been criticized for a layout favoring responses in terms of disability rather than fatigue and a lack of cognitive items [7].

Further specific scales for RA would be of value given the limitations of the existing measures previously described. One set of measures, the Bristol Rheumatoid Arthritis Fatigue (BRAF) scales, uses either VAS or NRS to assess fatigue over three independent domains assessed as being relatively independent: level of fatigue, impact of fatigue and coping with fatigue [56]. A multidimensional version of the BRAF has been developed and is currently undergoing further validation [66].

Fatigue diaries & momentary reports

Self-report measures of fatigue typically involve respondents retrospectively averaging their fatigue over a recall period of a number of days or weeks. For example, both the MAF [26] and the BRAF [56] were developed with a 7-day recall period, which has been reported as the maximum length of time preferred by patients, in order to allow them to think back about fatigue over a week's routine structure [39]. Patients with rheumatic disease have, however, expressed the opinion that recalling symptoms like fatigue over a week overlooks the daily variation in their symptoms [67]. Both paper and electronic daily diaries have been shown to be feasible and acceptable to people with RA, with a preference for electronic formats [67].

VAS and NRS measures of fatigue are common in studies using daily diaries. Heiberg *et al.* used a daily fatigue VAS with anchors 'no fatigue' and 'extreme fatigue' in a study of people with RA [67]. Schanberg *et al.* applied a daily fatigue VAS with anchors 'not tired' and 'very tired' in a study of children with juvenile arthritis [68]. The same daily fatigue VAS was asked seven-times a day in the study of juvenile arthritis [69]. In a study by Stone *et al.*, people with RA were also asked how fatigued they felt on seven occasions over the course of a day and recorded this on a seven-point NRS with anchors 'not at all' and 'extremely' [13]. Scores on this scale were worse following nights with poor sleep, indicating predictive validity [13]. Similarly, in a study by Goodchild *et al.*, people with RA or Sjögren's syndrome completed the Profile of Fatigue (ProF [6]) four times a day [70]. The ProF has validated momentary state and recall versions and contains four items addressing mental fatigue and 12 items on somatic fatigue answered on an eight-point NRS with anchors 'No problem at all' and 'As bad as imaginable'. Fatigue increased over the course of the day for these participants, and afternoon fatigue levels on both subscales of the ProF were predicted by discomfort the previous evening mediated by sleep disturbance [70].

Broderick *et al.* have adapted several questions about fatigue (or lack of vitality) [71,72] from the SF-36 [73] and Brief Fatigue Inventory [74]. Questions were posed using a VAS answer format for momentary state and end-of-day ratings of fatigue (in addition to various periods of recalled ratings using the original NRSs). They found that end-of-day ratings or 1-day recall are an acceptable estimate of momentary state rating, particularly when the desired outcome measure is an average level of fatigue, but they conclude that "patients have increasing difficulty actually remembering symptom levels beyond the past several days," reiterating the need for daily assessment in studies of fatigue [72].

Physiological measures of fatigue

Fatigue can be defined as an increase in the physiological cost necessary to realize a given task [75]. For instance, there may be a higher perceived exertion or increased energy cost in walking. Loss of strength and the inability to sustain a given level of submaximal resistance is another potential measure of fatigue [75].

There have been few studies aimed at developing measures to test physiological fatigue in rheumatic disease. Neuberger *et al.* used tests of grip strength (using a syphgnomanometer), a bicycle ergonometer test and a timed 50-ft walk test in a study comparing fatigue and aerobic fitness after an exercise intervention [76].

In a community-based elderly population, tests of physical performance have been adapted and shown to be reliable and achievable measures. These include the 'timed-up-and-go test', 'sit-to-stand test' and gait speed. As yet these have not been used in studies of patients with rheumatic disease or compared with questionnaire measures [77].

Activity analysis may provide information on physiological fatigue. Spontaneous ambulatory activity has been measured using an accelerometer worn by the participant and has been shown to be a valid and reproducible measure that could be used to assess efficacy of an intervention [78]. Studies comparing activity with recalled or momentary reports of fatigue in rheumatic disease have not been published to date, but as a proof of concept, fatigue diaries have been compared with activity, measured by a pedometer, in breast cancer survivors [79].

Which factors influence fatigue?

In the past, the complexity of the experience and the difficulty in developing objective measures for fatigue led to the conclusion that studies into the causes and severity of fatigue were not possible [80]. In the previous section, the variety of validated fatigue measures has been outlined. The use of these various measurement tools has allowed the investigation of factors that may contribute to the experience of fatigue. Several variables appear to predict the severity of fatigue in rheumatic disease. These include disease activity/severity, disability, pain, sleep disturbance, mood, self-efficacy, illness perceptions and coping, as summarized in Table 2.

Physiological fatigue

As previously mentioned, the concept of fatigue encompasses physiological muscle fatigue, which can manifest as a decline in performance that occurs in any prolonged or repeated task, but can occur earlier or be more severe or persistent in chronic illness. A reduction in activity measured by accelerometer has been demonstrated in patients with fibromyalgia and chronic fatigue [81], but has yet to be compared with fatigue in RA or OA.

In RA, fatigue, as measured by the MAF and physiological measures (e.g., grip strength and timed walk), improved following an exercise program; however, these aspects of fatigue were not directly compared [76].

Table 2. Summary of example evidence for predictors of fatigue in rheumatic diseases in longitudinal observation of routine care or following intervention.

Type of study	Study (year)	Rheumatic disease(s)	Sample size	Assessment of fatigue	Number of items	Follow-up	Predictors of lower/decreased fatigue	Ref.
Longitudinal	Treharne *et al.* (2008)	RA	114	VAS	1	1 year	Higher baseline inflammation (ESR) Perceiving their RA to have fewer consequences (IPQ) at baseline	[10]
Longitudinal	Brekke *et al.* (2001)	RA	815	VAS	1	2 years	Greater self-efficacy for pain (ASES) Greater self-efficacy for mood/fatigue (ASES)	[107]
Longitudinal	Scharloo *et al.* (1999)	RA	71	VAS	1	1 year	Perceiving their RA to have fewer consequences (IPQ) at baseline Less use of avoidant coping (UCL)	[98]
Daily	Schanberg *et al.* (2005)	JRD	51	VAS (once daily)	1	2 months	Better mood (FAS) on the same day Lower stress (DEI) on the same day	[68]
Daily	Schanberg *et al.* (2000)	JRD	12	VAS (seven times daily)	1	7 days	Better mood (FAS) on the same day	[69]
Daily	Stone *et al.* (1997)	RA	35	Seven-point NRS (seven times daily)	1	7 days	Better sleep quality (diary) the preceding night	[13]
Daily	Goodchild *et al.* (2010)	RA or PSS	25 with RA 13 with PSS	ProF (four times daily; used in the afternoon)	16	35 days	Less discomfort (ProD) the previous evening Less sleep disturbance (sleep diary and actigraphy) the previous night	[70]
Interventional (non-randomized)	Pollard *et al.* (2006)	RA	54 (starting DMARDs) or 30 (starting TNF inhibitors)	VAS	1	6 months (DMARDs) or 3 months (TNF inhibitors)	Starting DMARDs or TNF inhibitor therapy Greater decrease in disease activity (DAS) Greater decrease in pain (VAS)	[22]
Interventional (randomized)	Strand *et al.* (2005)	RA	482 (starting DMARDs or placebo)	SF-36 vitality	4	1 year	Starting DMARDs	[83]
Interventional (non-randomized)	Minnock *et al.* (2009)	RA	49 (starting TNF inhibitors)	11-point NRS	1	3 months	Starting TNF inhibitor therapy Greater increase in patient global health (VAS) Greater decrease in pain (TJC)	[84]
Interventional (non-randomized)	Weinblatt *et al.* (2003)	RA	271 (starting TNF inhibitors)	FACIT-F or SF-36 vitality	13 or 4	24 weeks	Starting TNF inhibitor therapy	[85]
Interventional (randomized)	Barlow *et al.* (2000)	Physician diagnosis of arthritis	423 (starting self-management or waiting list)	VAS	1	12 months	Attending group self-management (one session per week for 6 weeks)	[105]

ASES: Arthritis Self-Efficacy Scale; CBT: Cognitive behavioral therapy; CIS: Checklist Individual Strength; DAS: Disease Activity Score; DEI: Daily Events Inventory; DMARD: Disease-modifying antirheumatic drug; ESR: Erythrocyte sedimentation rate; FACIT-F: Functional Assessment of Chronic Illness Therapy–Fatigue scale; FAS: Facial Affective Scale; IPQ: Illness Perception Questionnaire; JRD: Juvenile rheumatic disease; MAF: Multidimensional Assessment of Fatigue; NRS: Numerical rating scale; OA: Osteoarthritis; POMS: Profile of Moods Scale; ProD: Profile of Discomfort; ProF: Profile of Fatigue; PSS: Primary Sjögren's syndrome; RA: Rheumatoid arthritis; SF-36: Medical Outcomes Study Short Form 36 (vitality scale); TJC: Tender joint count; UCL: Utrecht Coping List; VAS: Visual analog scale.

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Interventional (randomized)	Barlow *et al.* (1998)	Physician diagnosis of arthritis (RA: 46%; OA: 44%)	112 (starting self-management or waiting list)	VAS	1	4 months	Attending group self-management (one session per week for 6 weeks)	[106]
Interventional (randomized)	Evers *et al.* (2002)	RA	59 (receiving CBT or control)	CIS	8	6 months	Attending all ten sessions of one-on-one CBT (two sessions per week for 5 weeks)	[110]
Interventional (randomized)	Hewlett *et al.* (2010)	RA	127 (receiving CBT or control)	MAF or VAS (impact, severity and coping with fatigue)	16 or 3	6 weeks	Attending group CBT (one session per week for 6 weeks)	[111]
Interventional (non-randomized)	Neuberger *et al.* (1997)	RA	25 (starting aerobic exercise classes)	MAF or POMS	16 or 5	12 weeks	Attending 25 or more out of 36 exercise classes (three sessions per week for 12 weeks)	[76]
Interventional (mostly randomized)	Callahan *et al.* (2008)	Self-reported arthritis	346 (starting exercise classes or control)	VAS	1	6 months	Attending at least one out of 16 exercise classes (two sessions per week for 8 weeks)	[116]

ASES: Arthritis Self-Efficacy Scale; CBT: Cognitive behavioral therapy; CIS: Checklist Individual Strength; DAS: Disease Activity Score; DEI: Daily Events Inventory; DMARD: Disease-modifying antirheumatic drug; ESR: Erythrocyte sedimentation rate; FACIT-F: Functional Assessment of Chronic Illness Therapy–Fatigue scale; FAS: Facial Affective Scale; IPQ: Illness Perception Questionnaire; JRD: Juvenile rheumatic disease; MAF: Multidimensional Assessment of Fatigue; NRS: Numerical rating scale; OA: Osteoarthritis; POMS: Profile of Moods Scale; ProD: Profile of Discomfort; ProF: Profile of Fatigue; PSS: Primary Sjögren's syndrome; RA: Rheumatoid arthritis; SF-36: Medical Outcomes Study Short Form 36 (vitality scale); TJC: Tender joint count; UCL: Utrecht Coping List; VAS: Visual analog scale.

There is an absence of studies in rheumatic disease investigating the correlation of physiological fatigue and self-reported 'experiential' fatigue, and this is an area where more research is required, especially as both aspects are important to patients in qualitative studies [14,18].

Disease activity & severity

It has been suggested that disease activity may be a factor determining the severity of fatigue [22]. Since many systemic illnesses, such as infectious mononucleosis, are associated with chronic fatigue and demonstrate elevated inflammatory markers, it would seem reasonable to extrapolate this finding to RA. One standard measure of disease activity in RA, the Disease Activity Score-28 (DAS-28), has failed to demonstrate a significant correlation with fatigue in RA [8,22], and a recent a study of over 2000 patients with RA showed that inflammatory components of the DAS-28 correlated minimally with fatigue [43]. Standard markers of systemic inflammation include C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR). Although several studies have used inflammatory markers (especially the ESR) to assess disease activity in RA [19,22,82], a direct association between raised inflammatory markers and fatigue has not been demonstrated [8,19,20,22]. In one longitudinal study of patients with RA, higher ESR levels at baseline and follow-up were associated with lower levels of fatigue between baseline and 12-month review [10]; this may relate to the increased probability of sampling consecutive patients at the time of an emergency appointment for a flare of their RA, which demonstrates the importance of sampling approach. Given these conflicting data, it is not possible to draw firm conclusions about the relationship between fatigue and disease activity in RA. However, treatment with standard disease-modifying drugs [83], and in particular with biologic drugs, has shown improvement in fatigue [22,84,85], mirroring the falls in CRP/ESR. The association between systemic inflammation and fatigue in RA is thus complex and far from clear-cut.

In AS, there is a poor correlation between CRP/ESR and disease activity measured by the BASDAI, which includes a fatigue scale as mentioned earlier [86]. Other studies have demonstrated an association between disease activity measured by the BASDAI and the SF-36 vitality subscale [9], but not between ESR/CRP [24] and the BASDAI and the Multidimensional Fatigue Inventory [9].

Some studies have suggested that further evidence against inflammation playing a major role in fatigue is that noninflammatory arthritis,

OA in particular, is associated with similar levels of fatigue as RA [8,43], although this assumes that the causes of fatigue are similar across different conditions.

In OA, the standard tool for assessing severity is the WOMAC [50], with three subscales assessing pain, stiffness and disability. In a study using a VAS scale to measure fatigue, a strong correlation between all three subscales of the WOMAC and fatigue was noted [41]. Interestingly, in another study using the MAF, no such correlation was found [8].

In conclusion, fatigue can be present regardless of disease activity or severity and inflammatory markers do not appear to correlate well with fatigue levels.

Sleep disturbance

An association between poor sleep and fatigue would seem a logical proposition. In RA, sleep disturbance is linked to pain, low mood and disease activity [87]. Although the association between poor sleep and fatigue does not appear to be strong in RA in cross-sectional studies [87], daily studies have shown fatigue to follow nights of poor sleep [13,70]. Symptomatic knee OA is strongly associated with sleep disturbance [88], and although some studies have shown a weak association with fatigue [8,19], others have not supported any association [42]. In AS, nocturnal pain and stiffness strongly affect sleep, but the relationship with daytime fatigue is not strong [89]. Overall, evidence concerning the relationship between sleep disturbance and daytime fatigue is mixed in rheumatic disease.

Pain

Pain is consistently cited as a major symptom by patients with rheumatic disease [14,36]. Studies in RA have shown pain to be significantly associated with fatigue [19,22,41,90]. Similarly, both qualitative and quantitative studies in OA suggest an association between pain and fatigue [18,19,42]. This finding, however, has not been entirely consistent, and some studies have failed to demonstrate such an association [8]. In AS, pain is associated with higher levels of fatigue [9,25].

Disability & anatomical damage

Disability is a feature of chronic rheumatic disease that may influence fatigue by increasing the level of effort and the difficulty in performing everyday tasks, although other factors such as pain, mood and motivation may be important.

A number of studies of fatigue have used self-rating questionnaires to assess disability. Several studies have shown an association between disability and fatigue in RA [19,23,82]. In OA, disability also correlates with fatigue [8,19,41]. In AS, studies have used a measure of functional impairment, the Bath Ankylosing Spondylitis Functional Index (BASFI) [91] and have shown a strong correlation with fatigue [24,25,46].

Given the strong association between self-rated disability and fatigue, it might be expected that this would also be reflected in anatomical joint damage, demonstrated radiographically. The only study to investigate this showed no correlation between radiographic joint damage and fatigue in either OA or RA [8]. No published studies have investigated this in AS.

Mood disturbance

Perhaps the most consistent finding across studies is the strong correlation between depression and fatigue. Again, this is usually assessed on a self-rating scale. In RA, a strong association has been documented between depression and fatigue by several authors [8,10,19,22,23,42,92]. Depression is a well-recognized aspect of AS [93]; however, no studies have attempted to specifically investigate the contribution of mood to fatigue, although two have used the SF-36 mental health subscale in their analyses [24,46].

Anxiety has been less widely studied, except in RA where a strong correlation with fatigue is consistently seen [8,82,92]. It has been suggested that fatigue may elicit anxiety regarding underlying pathology or uncompleted tasks or that ongoing anxiety might be fatiguing [94]. No studies exist in AS, but two studies in OA show conflicting results, with one showing a correlation between fatigue and anxiety [19] and one showing none [8]. Different questionnaires were used in these studies, which raises issues of ease of comparison that are particularly problematic for evidence from cross-sectional studies.

Illness perceptions, self-efficacy & coping

The beliefs that people with rheumatic diseases hold about their illness and their level of confidence in their ability to achieve desired outcomes (i.e., self-efficacy) have been found to predict fatigue. Individuals with RA who have low scores as assessed by the Arthritis Self-Efficacy Scale [95], demonstrate greater VAS fatigue scores after 2 years of follow-up [96]. Perceptions that one's RA has serious consequences (one element of the Illness Perception Questionnaire; [97])

also predicts greater VAS fatigue after 1 year in two studies [10,98]. The effects of coping with RA fatigue have mixed evidence: Scharloo *et al.* found that greater use of avoidance as a coping mechanism predicted greater fatigue [98], but Treharne *et al.* found no effect of praying/hoping as an emotion-focused avoidant method of coping [10]. Further longitudinal studies are required to investigate the many and varied ways of coping and illness perceptions, with a focus on fatigue related to rheumatic disease. In particular, no studies to date have been published examining long-term psychosocial predictors of fatigue for people with AS or OA. The results of such studies provide useful insights into the importance of self-efficacy as a determinant of fatigue. Interventions to improve self-efficacy and reframe illness perceptions have the potential to ameliorate fatigue and should be the focus of future studies.

In summary, a wide variety of predictors of fatigue are recognized, with a growing body of evidence developing from an increasing number of studies involving large numbers of patients with rheumatic diseases. This accumulating evidence indicates that generalizing the experience of fatigue is probably not appropriate, since disparity between correlates of fatigue have been demonstrated; for instance, between OA and RA [8]. Such disparities may also exist between different cultures, even where they share a common language [99]. Furthermore, cause and effect have not been established, so for example it is not possible to ascertain whether depression influences fatigue or *vice versa*. Another difficulty with drawing conclusions is that the comparison between studies is hindered by the wide variety of self-assessment tools that have been used, thus direct comparisons are often inappropriate. Although there is much left to learn about the influences on fatigue, evidence to date does suggest some possible avenues for intervention, which should be the ultimate goal in the study of fatigue.

Managing fatigue in rheumatic disease

Pharmacological treatments

Antirheumatic drugs

As previously mentioned, controlling disease activity has been considered as a means of improving fatigue. In RA, both conventional disease-modifying drugs [22,83] and biologic agents including TNF inhibitors such as adalimumab [85] and the IL-6 inhibitor tocilizumab [59] appear to improve fatigue. There is also evidence that TNF inhibitors improve fatigue in AS [100]. It would appear that the mechanism by which these drugs improve fatigue may be independent of their action in reducing systemic inflammation, which is intriguing [43]. One suggestion is that the effect is mediated through reducing pain in RA [22]. Control of pain and stiffness through the use of NSAIDs has been studied in AS; however, results suggested minimal benefit from these drugs in improving fatigue [46].

Antidepressants & antiepileptic drugs

Tricyclic antidepressants have been widely used to manage fatigue and pain in fibromyalgia, and a systematic review provides some support for their use [101]. Similarly, pregabalin, an antiepileptic drug, has shown significant benefit in terms of fatigue and pain in fibromyalgia [102]. To date, no studies have examined the effects of these drugs on fatigue in other rheumatic diseases, such as AS or RA, but such studies would be of interest, particularly in subgroups of patients with severe fatigue.

Nonpharmacological management

Patient education & self-management programs

Patient education has been defined as a set of planned educational activities designed to improve an individual's health behavior and to maintain or improve health [103]. The focus of arthritis patient education programs is to teach patients to adjust their daily activities in order to control or reduce the impact of their arthritis and to deal with the psychosocial problems generated or worsened by their disease [104].

One community-based study where participants had a broad GP diagnosis of 'arthritis' showed improvement in fatigue and anxiety following an arthritis self-management program, with these benefits apparent at 12 months [105]. Another study showed improvement in fatigue after a self-management program where the majority of patients had a diagnosis of OA or RA [106].

Fatigue is predicted by poor self-efficacy [107], as previously discussed, and it has been found that self-management programs that enhance self-efficacy lead to improvements in fatigue for people with OA or RA lasting as long as 8 years [108]. Such self-management programs often use a number of psychological intervention techniques and also benefit from having course leaders who have the rheumatic disease in question, which facilitates modeling and helps patients support their own community.

Psychological interventions

More directly targeted psychological interventions that address fatigue management for people with rheumatic disease have also been evaluated. There are a number of approaches to psychological intervention for people with rheumatic disease and one set of frequently researched and applied approaches are the cognitive behavioral therapy (CBT) techniques. CBT focuses on facilitating individuals in monitoring and overcoming unhelpful thoughts and behaviors that form a perpetuating problematic pattern [109]. Two randomized controlled trials have investigated CBT specifically addressing fatigue for people with RA. In the first of these, tailored CBT was delivered over ten twice-weekly sessions of 1 h with a psychologist to people with RA of less than 8 years duration who were experiencing psychological problems such as anxiety, stress, helplessness and poor social support [110]. Participants selected two of four CBT modules that they wished to follow: pain/disability, fatigue, negative mood or social relationships. Fatigue, mood and helplessness were all significantly reduced up to 6 months postintervention. In the second trial, a psychologist-led group CBT was delivered in eight weekly sessions each of 2 h duration in a group of patients with RA who had notable fatigue (VAS > 6/10). Initial findings have revealed significantly improved fatigue, mood, quality of life and sleep 6 weeks postintervention [111].

No trials of CBT for fatigue among people with AS or OA have been published to date, but one trial of psychologist-led group CBT delivered in eight weekly sessions of 2 h, has focused on structured management of severe insomnia for people with OA [96]. Sleep and pain were significantly improved 1 year post-intervention, but fatigue was not measured. However, given the improvements in sleep it is likely that this intervention would ameliorate fatigue. It remains to be seen whether such CBT would be beneficial for people with OA with relatively good sleep who are experiencing fatigue, given that fatigue can be present in the absence of severe insomnia.

Exercise interventions

Exercise appears to ameliorate fatigue in many situations, supporting an association between physiological fatigue and cognitive fatigue. A substantial reduction in intensity, frequency and duration of exercise can lead to physiological deconditioning [112]. In a recent study of people with RA, high-intensity resistance training improved muscle mass and strength, although the effects on cognitive fatigue were not explored [113].

An excellent review relating to fatigue in cardiovascular disease suggests an approach to differentiate physical and psychological influences on fatigue and reduced physiological performance during reconditioning programs [114].

Mayoux-Behamou also sets out the evidence for the effectiveness of high-intensity exercise in RA [115]. Muscle function, aerobic capacity and functional ability all improve with high-intensity exercise, which must be comparable in intensity to a cardiovascular prevention program for the general population. This review also notes that the psychological benefits of such programs have been sparsely studied [115].

A Cochrane review of the effectiveness of physiotherapy interventions in AS did not include any studies assessing changes in fatigue in response to exercise therapy [24]. In RA, evaluation of an 8-week aerobic exercise program in 346 patients demonstrated improvement in fatigue from baseline which was maintained at 6 months [116]. In a small study, which was uncontrolled, improvements from exercise intervention were noted in fatigue self-assessment in aerobic fitness and muscle strength. The benefit of exercise was related to frequency of participation [76].

Despite some preliminary evidence for improvements in fatigue following exercise interventions, this approach has not been widely studied in RA and specific studies are lacking in AS and OA.

Assessing fatigue in clinical practice

In general, fatigue is not regularly assessed or addressed in clinical practice [117]. Patients with RA have reported a perceived lack of support from health professionals with respect to fatigue because the emphasis tends to be placed on physical problems and disease activity [16,117].

Incorporating fatigue assessments into the routine clinical care of patients with rheumatic diseases is a challenge. One possible method for examining how this could be achieved is to consider the Specific, Measurable, Achievable Relevant and Time-limited (SMART) criteria [118]. This acronym was originally derived for project management in business, but has been used to develop clinical care pathways [119]. In relation to the feasibility of incorporating fatigue measures into care pathways the following should be addressed:

- Specificity of fatigue. Fatigue is a distinct experience separate from pain, disease activity and depression and therefore warrants exploration in the clinical context;
- Measuring fatigue. A number of validated tools are now available to measure fatigue and some of these were specifically designed to evaluate fatigue in rheumatic disease. A simple, easily applied measure covering different concepts within fatigue is needed for use in the clinic;
- Achievable/treatable. Evidence is lacking at present on the best approach to managing fatigue. It is unlikely that a one-size-fits-all approach will ever be suitable for a complex symptom such as fatigue. However, there is promising evidence for a number of interventions, including exercise therapy, patient education/self-management programs, drug therapy and psychological therapies;
- Relevance of fatigue. Fatigue is frequently rated as one of the most significant and troubling symptoms faced by patients with rheumatic disease, and there is considerable evidence to support the negative effects it has on quality of life and employment;
- Time-limited application in the clinic. If suitably robust and easy to administer questionnaires were available, given the importance of fatigue, incorporation of such measures into routine practice may be time efficient; especially if self-completed prior to the consultation.

In summary, it can be seen that the incorporation of a fatigue measure into routine clinical assessment in the rheumatology clinic could be supported and bring benefits that could result in better patient outcomes.

Conclusion

The importance and relevance of fatigue as an outcome measure in clinical trials in RA has been highlighted in the OMERACT consensus [12] and in AS by ASAS [36]. Extensive evidence from qualitative studies and ranking studies (wherein patients rank the outcomes that they prioritize) has demonstrated the importance of this symptom to patients [14,29].

A number of validated questionnaires are now available for measuring fatigue, which show sensitivity to change with treatment, and some of these are specific to rheumatic disease. An increasing body of evidence has shown that fatigue is a distinct symptom, but that it is predicted by a variety of other factors, including pain and depression, which are the most consistent associations across a number of rheumatic diseases. These associations may differ in their importance between different forms of arthritis or at different stages in the disease process, and thus generalizing the experience of fatigue is not appropriate.

Comparatively little evidence exists in relation to managing fatigue in rheumatic disease, and although self-management programs, psychological interventions and treatment with disease-modifying drugs or biologic agents in RA improves fatigue, the mechanisms by which they do so is unclear. Further research into managing fatigue should be a priority in the future.

Future perspective

Over the next 5–10 years it is hoped that our understanding of fatigue will improve. Central to this will be the development of validated fatigue measures over the range of rheumatic diseases, which can be easily administered in the busy clinic situation. Establishing the relative importance of the different factors that affect fatigue in OA, RA and AS will be essential, together with an understanding of cross-cultural influences on fatigue. Development and validation of measures of physiological fatigue and comparison with self-reported measures will also be helpful in determining the best ways to manage fatigue. At present, our understanding of fatigue and its importance in OA and AS is much less developed than in RA. Over the next few years, studies in these common arthropathies should address this. Through a better understanding of fatigue, evidence regarding the best treatment for fatigue and, ultimately, development of patient care pathways for clinical use should be a goal. Finally, improving our understanding of how biologic therapies improve fatigue in RA and AS and whether this is independent of their action on inflammation or patients' general sense of well-being will be of relevance for understanding the nature of fatigue.

The importance and relevance of fatigue as an outcome measure in clinical trials in RA and AS has been established. Improved standardized assessments of fatigue and comprehensive studies across a range of rheumatic diseases are needed. In future, evidence for the best way of managing fatigue in rheumatic diseases will contribute to improving patient outcomes.

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Executive summary

Fatigue in rheumatic disease: definition & prevalence

- Fatigue in rheumatic disease is a complex symptom with both physical and psychological aspects, which negatively impacts on quality of life and can be overwhelming.
- Fatigue is prevalent with 40–80% of patients with rheumatoid arthritis (RA), 40–55% with osteoarthritis (OA) and 50–75% with ankylosing spondylitis (AS) experiencing a level of fatigue sufficient to impact negatively on their quality of life.

Nature of fatigue in rheumatic disease

- Fatigue in rheumatoid arthritis (RA) occurs on most days and varies in intensity and frequency, ranging from heaviness and weariness to exhaustion.
- Individuals distinguish between systemic fatigue, related to their arthritis and general tiredness.
- Abrupt onset of overwhelming tiredness, where people are forced to stop what they are doing, is common to OA, RA and AS.

Impact of fatigue

- Fatigue has a major social and economic cost in rheumatic disease. It is a strong predictor of work dysfunction and overall health status in a variety of rheumatic diseases.
- Fatigue and well-being were ranked as the most important issues after pain and independence and above joint symptoms.

Measuring fatigue

- Fatigue is most commonly assessed using self-reporting questionnaires. Visual analog scales have been used most widely, but several validated multidimensional questionnaires are available.
- The Multidimensional Assessment of Fatigue (MAF) scale, the SF-36 vitality subscale and the FACIT-F have been most widely used to date.

Factors that affect fatigue in rheumatic disease

- Fatigue is a complex experience and a number of factors determine its severity and persistence.
- Physiological muscle fatigue, systemic inflammation, sleep disturbance, pain, disability, anxiety, depression, self-efficacy, illness perceptions and coping mechanisms have all been demonstrated to have an influence on fatigue.
- The relative influence of co-factors on fatigue varies between different rheumatic conditions, individuals and cultures.

Managing fatigue

- There have been few studies specifically addressing the management of fatigue in rheumatic disease.
- Biologic drug therapy improves fatigue in AS and RA, but the mechanism by which it does so is not clear.
- Patient education programs, exercise regimes and cognitive behavioral therapy all have some evidence for effectiveness in rheumatic disease.

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