Fatigue in rheumatoid arthritis: from apathy to action

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‘…fatigue will become nonexistent as it becomes routinely managed, in the same way that pain is routinely addressed.’

Fatigue is a common problem in rheumatoid arthritis (RA), experienced by the majority of patients, with fatigue scores that are often higher than pain scores [1,2]. Despite this, patients feel fatigue has been largely ignored by clinicians. This article provides a personal overview of the journey of RA fatigue from ‘nonexistence’ to ‘hot topic’ and looks toward a time when fatigue might return to nonexistence because it is routinely and effectively managed.

Importance of fatigue
The journey for fatigue from nonexistence to hot topic was largely prompted by patients. In 2002, patients attended a meeting of the international group Outcome Measurement in Rheumatology Clinical Trials (OMERACT) and were invited to discuss the ACR Core set for RA clinical trials [3]. They said it was unimpressive as it omitted symptoms important to them. This led to qualitative research in the UK and Sweden, exploring what were the important outcomes for patients [4,5]. Fatigue was spontaneously generated and subsequent research revealed that patients rate it as more important than joint swelling or pain [6,7]. Patients said fatigue was important because of its impact on their lives and research confirms that fatigue distinguishes between quality-of-life profiles [8]. A greater understanding of the way in which fatigue affects quality of life was therefore needed.

Meaning of fatigue
Qualitative research exploring RA fatigue revealed three major themes [9]. First, fatigue in RA is overwhelming and different from normal tiredness, being experienced as extreme weariness, weight or heaviness, and complete ‘wipe-out’ (when the patient has to stop altogether). Patients describe cognitive and emotional components, such as an inability to think straight and tearfulness, and say fatigue is unearned, unpredictable and unresolved. Second, the consequences of fatigue permeate every sphere of life, with far-reaching effects on physical activities, emotions, relationships and roles. Third, patients report that their ability to manage fatigue is limited but that they rarely receive professional support. Most patients were not asked by their rheumatologist about fatigue, and when they raised the issue, patients felt it was dismissed. Anecdotally, rheumatologists tell patients fatigue is just part of their disease – perhaps assuming the mechanism to be inflammation.

Mechanisms of fatigue
Mechanisms driving fatigue in RA may be biochemical (inflammation and anemia), physiological (muscle deconditioning, excess effort expended due to disability and poor sleep) or psychosocial (stress, anxiety, depression and low social support). However, evidence for associations between these single variables and RA fatigue yields contradictory results, apart from some consistency in the lack of association with C-reactive protein, anemia and age. It is probable that a combination of variables provides the driving mechanism for RA fatigue, and here there is more consistency, with various explanatory models usually including pain, function and psychosocial variables [1,10,11]. There are several problems with establishing a clear explanatory model for RA fatigue. First, there are many candidate variables to be explored and it appears that no study has measured all of these in a prospective study. Second, the explanatory model is likely to be a complex, multicausal pathway that is cyclical, with events fuelling each other (e.g., pain causing stress, leading to fatigue, which increases sensitivity to pain and stress). It is likely that this pathway will comprise different components for different patients at different points in their disease trajectory (with implications for interventions). Finally, we must be able to measure RA fatigue accurately.
Measurement of fatigue
A systematic search of the literature revealed 23 different fatigue scales used to measure RA fatigue between 1980 and 2004 [12]. However, a review of the published evidence for their validity, reliability and sensitivity suggested only six scales had reasonable evidence of validation in an RA population. Only one was designed for RA patients, and even the frequently used fatigue visual analogue scale (VAS) was neither standardized nor validated for use in RA (only three of the 26 VAS used were identical). Researchers in the UK and The Netherlands are currently developing and validating VAS and multidimensional fatigue scales specific to RA, and will hopefully include validation in the USA and Europe [13]. The development of multi-dimensional scales will allow the identification of different end points following fatigue interventions.

'It is probable that a combination of variables provides the driving mechanism for RA fatigue …' [14]

Multiple end points for fatigue interventions
As fatigue has multidimensional effects on people with RA [9], there is the potential to alter these differentially with different interventions. For example, many patients have low self-efficacy for managing fatigue [11], and enhancing self-efficacy might therefore form the focus of an intervention. Other patients may report a lessening of the effects of fatigue in their lives, even if their global fatigue score remains unchanged. For example, they might be more physically active despite the same level of fatigue, or they may be able to stay awake in company rather than fall asleep. Although medication to reduce RA fatigue would be helpful, it may not be desired or appropriate for all patients, therefore multiple approaches to managing fatigue should be developed.

Management of fatigue
There is increasing evidence that the use of biologic agents and DMARDs can give significant improvements in RA fatigue [14,15] and it is suggested this is through an association with changes in pain and mood, rather than inflammatory activity [2]. These medications have potentially serious side effects, are expensive and patients may have limited access; therefore, if fatigue is present in a patient whose RA is otherwise well controlled, medication changes might not be the appropriate intervention.

In a systematic review of nonpharmacological interventions for fatigue, only two randomized controlled trials were identified in RA [16]. A randomized, controlled trial of home aerobic training demonstrated a trend toward fatigue improvement. However, a randomized, controlled trial of cognitive–behavioral therapy (CBT) in early RA patients at risk of psychological distress demonstrated significant improvement in fatigue [17]. CBT addresses the thoughts (or beliefs) and feelings that influence behaviors and uses individualized problem-solving, goal-setting and cognitive restructuring to help patients change behavior. Such an approach is currently being tested in the UK in patients with high fatigue levels but who are otherwise unselected.

Clearly there are other interventions that still need testing. For example, what are the effects of single components of self-management such as pacing and planning, or joint protection? Can self-management interventions using CBT approaches be delivered by members of the rheumatology team (with suitable training) rather than by specialized clinical psychologists? High-quality studies on reversing deconditioning or to enhance exercise should be carried out, as well as studies that address depression, social support or nonrestorative sleep.

Since patients raised the issue at OMERACT in 2002, RA fatigue has received a great deal of interest and has become something of a hot topic, which demonstrates the power of the patient voice. Research grants have been awarded and studies are under way internationally in a range of areas. After reviewing the available evidence at OMERACT 2006, an international consensus was reached that fatigue should now be measured in all RA clinical trials whenever possible [18]. This will help to further drive the efforts to develop and test useful interventions.

In the clinic situation
Meanwhile, what should the busy clinician do, when a patient with RA reports fatigue? Simply acknowledging and discussing the problems that fatigue causes may validate fatigue as a genuine symptom for patients. Exploring biochemical, physiological and psychosocial causes might help guide thoughts on potential interventions. For example, one patient complained of fatigue...
affecting her ability to work in the office, but eventually it was revealed that she did not eat until the evening – persuading her to eat some breakfast and lunch had a dramatic effect on her fatigue. Referral to members of the multidisciplinary team to assist in managing this distressing symptom is almost certain to be welcomed by the patient.

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Conclusion
Fatigue is a common problem that distresses patients with RA and impacts on their quality of life. Many research avenues are being explored, including issues around mechanisms, measurement and management. Although the search for effective pharmacological and non-pharmacological interventions is under way, there is currently only evidence for DMARDs, biologic agents and CBT. These may not be appropriate or available to all patients; therefore until more evidence on effective interventions appears, busy clinicians should consider referring patients to any member of their multidisciplinary team who has, or would be willing to develop, a special interest in the self-management of fatigue.

Future perspective
Over the next 5–10 years, given the current level of patient, clinician and researcher interest in RA fatigue, evidence on measurement, mechanisms and management should steadily accumulate, facilitating the development of an evidence-based treatment algorithm. Within the next decade, fatigue will be routinely discussed and assessed during clinic consultations, the driving mechanism for the individual patient identified, and the patient offered an appropriate intervention using the treatment algorithm. The intervention might be pharmacological or nonpharmacological but will automatically include referral to a member of the multidisciplinary team with a special interest in enhancing fatigue self-management. Then, once again, fatigue will become nonexistent as it becomes routinely managed, in the same way that pain is routinely addressed.

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Executive summary
Importance of rheumatoid arthritis fatigue
• Fatigue is common and may be more severe than pain.

Meaning of rheumatoid arthritis fatigue
• Fatigue is overwhelming, uncontrolled and ignored by clinicians.

Mechanisms of fatigue
• Biochemical, physiological and psychosocial elements may contribute different amounts at different times for individual patients.

Measurement of fatigue
• Scales should be selected carefully – few are validated for rheumatoid arthritis, new scales are being developed.

Multiple end points for fatigue interventions
• If severity cannot be changed, other outcomes might include improved quality of life, more physical activity but no increase in fatigue, or greater self-efficacy for managing fatigue.

Management of fatigue
• There is evidence for biologic agents, DMARDs and cognitive–behavioral therapy at present.

In the clinic situation
• Acknowledge, discuss, assess, investigate, treat and arrange support with self-management.
Bibliography

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.


• Provides evidence that fatigue is linked to pain and associations with disease activity are secondary.


• Demonstrates the nature and consequences of fatigue for patients, using their own words.


• Provides evidence for a non-pharmacological approach to rheumatoid arthritis fatigue.


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