

Editorial

Fatigue in rheumatoid arthritis: time for a conceptual model*An under-acknowledged patient concern requires a new approach*

In recent years, formal collaboration with RA patients has explored what treatment outcomes are important to them. Patients repeatedly raise concerns about the major impact of RA fatigue. Qualitative research, replicated internationally, shows that patients with RA experience fatigue as uncontrollable and overwhelming yet find it largely ignored by clinicians [1]. Fatigue is highly prevalent in RA (up to 70% of patients), is as severe and frequent as pain [2] and is consistently prioritized by patients within their top outcome priorities, often as high or higher than pain [3]. Fatigue data also provide information about disease activity that is additional to that measured by the current ACR core set variables [4]. All these findings led to an international consensus at OMERACT in 2006 that fatigue should be measured in all clinical trials in addition to the core set [4]. Fatigue measurement is now recommended for other core data sets in Europe [RA Impact of Disease (RAID)], the UK [RA Patient Priorities for Pharmacological Interventions (RAPP-PI)] and the USA (ACR/EULAR recommendation for assessing remission).

However, evidence on the causality of fatigue in RA is conflicting and derived mainly from cross-sectional studies using generic or less-robust fatigue patient-reported outcome measures [5]. In order to clarify which research questions will be most informative in identifying causal pathways for fatigue in RA, and to develop potential interventions, a conceptual framework of RA fatigue is now essential. We propose a conceptual model for RA fatigue (Fig. 1) that suggests interactions between three factors: disease processes (RA), thoughts, feelings and behaviours (cognitive, behavioural) and personal life issues (personal).

RA disease factors (Fig. 1) that might drive fatigue include de-conditioning and actual or perceived increased muscle effort (resulting from joint damage, disability and reduced physical activity), anaemia, RA medication and sleep that is disturbed by RA pain [1, 5]. Joint damage, disability and pain emanate from the inflammatory processes of RA. Inflammatory processes may be associated with an abnormal cortisol response via the hypothalamic–pituitary–adrenal (HPA) axis [6], which might explain the sudden, dramatic and unpredictable wipe-out episodes reported by many RA patients [1].

The cognitive and behavioural factor (Fig. 1) is a recognized dynamic model that demonstrates interactions between thoughts (e.g. I should be able to do all the activities

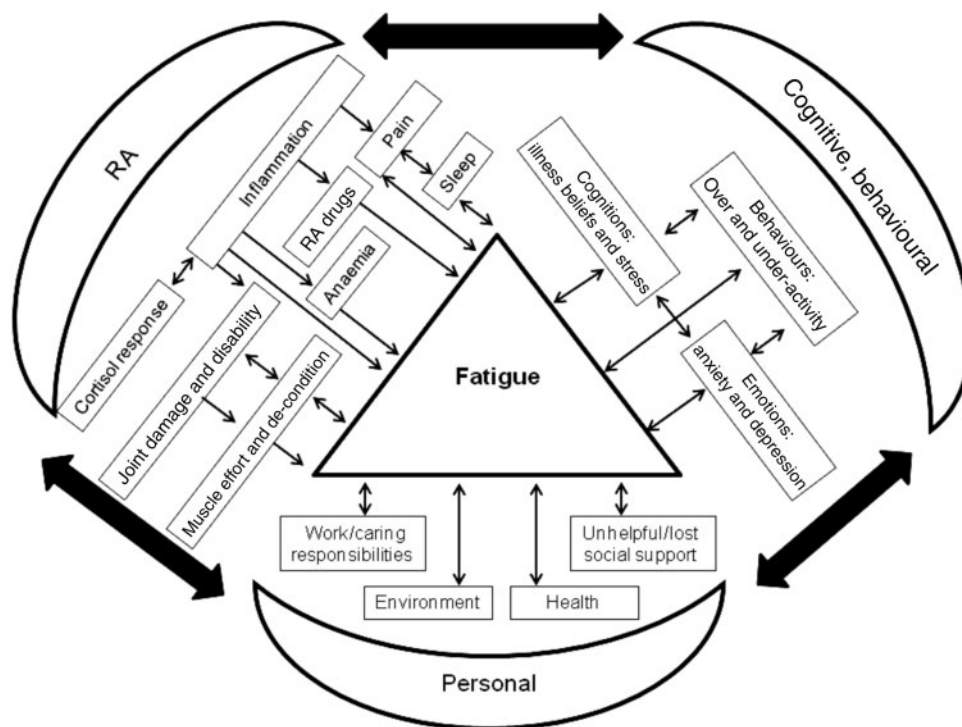
I used to do), feelings (e.g. sad that I am struggling to keep up activities), behaviours (e.g. keep going until I finish this activity) and symptoms (I kept going until completely wiped out with fatigue) [7]. RA studies show that illness beliefs that RA has serious consequences, low self-efficacy and low mood all predict future RA fatigue [8]. Behavioural issues such as persisting with prolonged physical activity until exhaustion supervenes (boom and bust) or resting excessively may also influence fatigue.

Personal factors that potentially influence RA fatigue (Fig. 1) include personal responsibilities that are important for an individual (e.g. going to work to earn income, caring for family members), unhelpful personal environments (e.g. stairs, lack of assistive devices) and social support that is either unhelpful or has been lost. Health issues such as comorbidities (e.g. diabetes, cardiac disease), dietary patterns (poor nutrition, gaps between meals) and age or gender, may be influential.

These variables may either predispose to fatigue (e.g. diagnosis of RA), precipitate a specific fatigue episode (e.g. a poor night's sleep) [5] or perpetuate existing fatigue (e.g. accepting social invitations despite knowing you are too fatigued). However, many may do all three—for example, previous depression predisposes to future RA fatigue and current depression is related to or precipitates current fatigue [5], but depression may also affect behaviours that perpetuate fatigue (e.g. withdrawal from physical activities, leading to de-conditioning). Our proposed model is therefore dynamic, with bi-directional arrows suggesting inter-relationships between and within the three factors (RA, cognitions and behaviours, and personal). For example, it is clear that the thoughts, behaviours and emotions associated with fatigue are related (at least in part) to the consequences of having RA in the first place, and all elements must be set within the context of personal life (e.g. an inflammatory flare is fatiguing because an individual has to work to provide an income, and cannot accept fatigue as a valid reason to take sick leave).

There are few published trials that specifically aimed to improve RA fatigue. However, some interventions that are primarily aimed at improving other variables in the model, also reduce fatigue: pharmacological interventions to reduce inflammation, exercise interventions to improve physical activity and cognitive-behavioural therapy (CBT)

Fig. 1 Conceptual model of RA fatigue.



to improve psychological distress, have all also reduced fatigue in RA [5, 9]. The success of these varied interventions supports the concept of varied causality (Fig. 1). Further, it is likely that not only are there multiple causes for fatigue in RA but these may vary between individuals, and occur in different combinations and strengths within individuals at different times.

Conceptualizing a model for a symptom clarifies thoughts about causation, measurement and intervention. It allows a variety of causal hypotheses to be defined, and refines the research necessary to inform treatment and self-management. For example, the potential link between muscle effort and fatigue (Fig. 1) could be tested to see if it is mediated through actual increased muscle effort (due to de-conditioning, joint damage or disability) or through a neuro-physiological perception of increased effort [10]. Similarly, the potential link between anxiety or depression and fatigue could be tested in a longitudinal study, which would clarify which is cause and which is effect. Studies such as these need to be designed as well-powered, longitudinal studies, using fatigue outcome measures developed specifically for RA that demonstrate its different dimensions (physical severity, emotional fatigue, cognitive fatigue, living with fatigue and coping) [11].

Clarifying such causal pathways would imply a range of potential interventions, targeted to each fatigue dimension, which could then be tested. In the longer term, an algorithm could then be developed to guide assessment and target pharmacological, non-pharmacological and self-management interventions. This would help to

contribute to a journey that started with patients identifying fatigue as a key symptom and continues in an ongoing collaboration with patients aimed at improving health outcomes that are important to them. This conceptual model is a crucial step in this process.

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