Furthering Our Understanding of Fatigue in Rheumatoid Arthritis

SARAH HEWLETT, ERNEST CHOY and JOHN KIRWAN

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*The Journal of Rheumatology* is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
Fatigue is a common problem in people with rheumatoid arthritis (RA), with 42%–69% reporting severe fatigue. RA fatigue can have as much impact as and be as difficult to cope with as pain. Indeed, some studies report fatigue severity levels in RA similar to those seen in chronic fatigue syndrome, and higher than in cancer.

Fatigue has risen higher on the research agenda in the past 6 to 8 years primarily in response to patient involvement in outcome measurement through collaboration in the OMERACT conferences (Outcome Measures in Rheumatology), which led to international consensus that fatigue must be measured alongside the core set of domains for RA. In addition, further research from multiple sources has demonstrated the high prioritization of fatigue by patients in patient-generated core sets such as the RA Patient Priorities for Pharmacological Intervention and the RA Impact of Disease Scale. While there is increasing information about the efficacy of pharmacological and nonpharmacological interventions for RA fatigue, interventions can best be designed and tested if the causal pathway is understood.

Information on the causal pathway of RA fatigue to date has been largely based on cross-sectional studies of single variables. These studies show conflicting results, with (for example) correlation between fatigue and pain ranging from nonsignificant to very strong. It is difficult to draw evidence of causal relationships from cross-sectional studies, but longitudinal studies that explore multivariate modeling to identify characteristics that predict future fatigue (rather than show associations at a single timepoint) have usually not controlled for baseline fatigue. A thorough systematic review of existing studies that examined potential predictors of RA fatigue concluded it is currently not possible to perform a metaanalysis on predictors because of the gaps in data.

The study by Nicassio, et al in this issue of The Journal represents an important step forward in understanding a potential causal pathway for RA fatigue. The investigators are to be applauded for using a logical and hypothesis-driven approach. They have applied, perhaps for the first time in RA fatigue, the technique of sequential equation modeling to test an hypothesized model (current disease activity, mood disturbance, and sleep) as a predictor of current RA fatigue. While we would suggest using the term “correlate” when seeking to explain current fatigue, and applying the term “predictive” only to inferences about future fatigue, their analysis clearly suggests that a model of increased disease activity, low mood, and poor sleep explains 62% of variance in RA fatigue. Further, they used the technique to examine the relationship between the elements of this model and test the indirect effects of disease activity on fatigue. The data show that the main influence of disease activity on fatigue is mediated by its effect on mood, which in turn is related to poor sleep. The effect of mood on fatigue was also mediated by its effects on sleep. As this is a cross-sectional study, negative findings could have disproved their hypothesis, which would have also been an important finding, but the strongest evidence of a causal link, as the authors acknowledge, comes from longitudinal studies.

The causal link between disease activity and RA fatigue has always been the subject of conflicting evidence, with many studies suggesting there is no strong evidence. More recent studies have suggested the link is there, with fatigue being an independent contributor to assessments of disease activity, or that the link exists indirectly through pain. Unfortunately, pain was not included in the model by Nicassio, et al. It would have been interesting to examine whether disease activity leads to pain that results in changes in mood. Nevertheless, a longitudinal study (or stronger still, an intervention study) incorporating pain in the model could now be used to provide more conclusive evidence.
proof of this potentially causative pathway. Nicassio, et al’s study of their hypothesized multidimensional model also provides data to support the recently proposed more general theoretical multidimensional conceptual model of RA fatigue\(^\text{15}\). This model contains 3 main components: inflammatory activity, cognitive/behavioral issues, and personal context. It suggests that at any one time in any one individual, some elements of each component are present, but that the combinations differ between patients and over time. For example pain might disturb sleep (2 elements of inflammatory activity), fueled further by anxiety (element of cognitive/behavioral issues) about not sleeping, and anxiety may be underpinned by the need to be at work early the next morning (element of contextual factors). This complex interaction of fatigue drivers is clearly supported by the novel data provided by Nicassio, et al, opening up the possibility of using their technique to explore other combinations.

The assessment of variables within a causal pathway will always be dependent on the ability to measure those variables with accuracy. In the Nicassio study, a surrogate measure of disease activity rather than an objective laboratory evaluation was used, which might have introduced additional noise into the analysis. Fatigue was measured by 2 different patient-reported outcome measures or PROM (Multi-dimensional Assessment of Fatigue, Short-Form 36 Vitality Subscale). Both give a global score of severity, despite being multi-item PROM. More recently, different types of fatigue such as physical, emotional, and cognitive fatigue have been identified that can now be measured using the Bristol RA Fatigue Multi-Dimensional Questionnaire (BRAF-MDQ)\(^\text{16}\). The BRAF-MDQ would enable an exploration of causal pathways for different types of fatigue, which in turn might help tailor more personalized interventions in clinical practice. Further, components of disease activity such as pain, swollen joint, and acute-phase reactants should also be assessed as these will provide important data on the role of pain, and articular and systemic inflammation, on fatigue.

This well-conducted study has provided important evidence to support the multidimensional causal pathway of RA fatigue — in the Popperian tradition of science it could have proven the hypothesis wrong, but did not do so. A complex causal pathway such as this may explain why simply having the variables will not prove the hypothesis wrong, but did not do so. A complex causal pathway such as this may explain why simply addressing one component, such as disease activity, by using biologic agents reduces but does not resolve fatigue\(^\text{5}\). It has implications for developing multimodal interventions that combine nonpharmacological self-management approaches\(^\text{9,17,18,19,20}\) with pharmacological approaches. Unpicking the unique combination of drivers for each patient’s fatigue will be hard, but if we can continue to accrue evidence around causation and intervention, then the pot at the end of the rainbow could be an evidence-based RA fatigue treatment algorithm.

SARAH HEWLETT, FRCPN, PhD, MA, RN,
Professor of Rheumatology Nursing, Academic Rheumatology,
Department of Nursing and Midwifery,
University of the West of England,
Bristol;
ERNEST CHOY, MD.
Section of Rheumatology,
Institute of Infection and Immunity,
Cardiff University,
Cardiff;
JOHN KIRWAN, MD.
School of Clinical Sciences,
University of Bristol,
Bristol, UK

Address correspondence to Dr. S. Hewlett, Arthritis Research UK,
Bristol Royal Infirmary, Bristol BS2 8HW, UK.
E-mail: Sarah.Hewlett@uwe.ac.uk

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