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1 **Fatigue in Rheumatoid Arthritis**

2 Ernest H Choy<sup>1</sup>, Emma Dures<sup>2</sup>.

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4 <sup>1</sup>CREATE Centre, Section of Rheumatology, Division of Infection and Immunity, Cardiff  
5 University, Cardiff, UK. <sup>2</sup>Centre for Health and Clinical Research, University of the West of England,  
6 Bristol and Academic Rheumatology, Bristol Royal Infirmary, Bristol.

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9 Correspondence: Professor Ernest Choy, CREATE Centre, Section of Rheumatology, Division  
10 of Infection and Immunity, Cardiff University School of Medicine, Cardiff University, Cardiff,  
11 UK CF14 4XN. Email: [choyeh@cardiff.ac.uk](mailto:choyeh@cardiff.ac.uk)

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1 Fatigue is a common symptom in many rheumatic diseases, including Rheumatoid Arthritis  
2 (RA). However, until recently healthcare professionals and researchers had not recognised  
3 its clinical significance and its impact on patients' lives. A turning point came in 2002, at the  
4 Patient Perspective Workshop of the Outcome Measure in Rheumatology (OMERACT)  
5 meeting, when patients highlighted the importance of fatigue.<sup>1</sup> This led to the  
6 recommendation by OMERACT in 2006 that fatigue is included as a core outcome measure  
7 in clinical trials of RA treatments.<sup>2</sup> The process by which the rheumatology community has  
8 come to recognise and focus on fatigue is an example of the value of patient involvement in  
9 setting research priorities. This awareness of fatigue as a patient priority has led many  
10 researchers over the last decade to work on better understanding the causes, assessment  
11 and management of fatigue.

12  
13 Qualitative research has provided insight into the nature of RA-related fatigue. Patients  
14 have described it as a complex and multidimensional symptom that can be overwhelming,  
15 unearned and unpredictable.<sup>3</sup> It can include physical fatigue (e.g. levels of physical energy),  
16 cognitive fatigue (e.g. concentration and clarity of thought), living with fatigue (e.g. ability to  
17 carry out activities of daily living and social activities), and emotional fatigue (e.g. feelings of  
18 distress or upset).<sup>4</sup> Quantitative research has established that it is highly prevalent, with  
19 levels similar to chronic fatigue syndrome.<sup>5</sup>

20  
21 In relation to impact, fatigue has been identified as the consequence of RA that best  
22 differentiates between levels of health-related quality of life.<sup>6</sup> Patients have reported the  
23 negative effects of fatigue on their well-being, physical activities, emotions, mood,  
24 relationships, and social and family roles. From a societal perspective, fatigue is a significant  
25 predictor of high health care costs and the main reason for work disability and loss.<sup>7</sup> The  
26 detrimental effects of fatigue are exacerbated by patients' perceptions that the symptom is  
27 a challenge to manage and that it is not routinely addressed in clinical practice. This  
28 reluctance to discuss fatigue may reflect the lack of information and available treatments.  
29 Consequently, fatigue is widely recognised as important to patients, but how to manage and  
30 improve the symptom remains a major unmet need.

31  
32 A challenge in providing support for RA-related fatigue is that the causes are still unknown.  
33 Cross-sectional studies have found that fatigue is associated with pain severity and  
34 psychosocial factors including depression, but not disease activity.<sup>8</sup> Overall, the current  
35 evidence suggests that fatigue is likely to be caused and maintained by the complex  
36 interaction of clinical factors (e.g. inflammation, pain, and disability), psychosocial issues  
37 (e.g. coping, mood, beliefs and behaviours) and personal factors (e.g. working, caring  
38 responsibilities and comorbidities) that may vary both between and within individuals over  
39 time.<sup>9</sup> This is reflected in evidence from systematic reviews of non-pharmacological and  
40 pharmacological treatments for fatigue, which have identified the potential benefit of  
41 physical activity, psychosocial interventions and some biologic disease modifying anti-  
42 rheumatic drugs (bDMARDs).<sup>10,11</sup> The beneficial effect of bDMARDs suggests that  
43 inflammation has a significant pathobiological role although fatigue does not completely  
44 resolved. Experimental models found that systemic inflammation leads to increase in  
45 intracerebral interferon and TNF $\alpha$  activity.<sup>12</sup> Furthermore, in collagen-induced arthritis, an  
46 animal-model of RA, the blood brain barrier (BBB) is porous to cytokines.<sup>13</sup> In patients with

1 RA, a magnetic resonance spectroscopy study suggested that systemic inflammation may  
2 affect the neurochemical status of the CNS with high levels of choline to creatine ratio.<sup>14</sup>

3  
4 Possibly due to the lack of clarity around causal pathways, there is an increasing focus on  
5 the self-management of fatigue rather than the resolution or cure of the symptom. Recent  
6 evidence includes a multicentre randomised control trial using cognitive behavioural  
7 approaches. This study found that the impact of fatigue was reduced, with the positive  
8 effects maintained at two years.<sup>15</sup> Self-management interventions are typically  
9 hypothesised to work through the therapeutic mechanisms of enhancing patients' self-  
10 efficacy (the belief in their ability to achieve a desired outcome or goal). This is achieved by  
11 addressing patients' illness beliefs, their coping strategies, and their acceptance of fatigue as  
12 a symptom of their RA. In this study, the intervention included the use of daily activity  
13 diaries and goal setting to promote a shift in beliefs and progressive adaptations in how  
14 patients cope with fatigue, leading to better knowledge, confidence, and reactivation in  
15 everyday activities.

16  
17 Measurement is key to evaluating the usefulness of fatigue interventions, whether the focus  
18 is on reducing severity or managing the impact of the symptom. Although OMERACT  
19 included fatigue as a core outcome measure in RA, the lack of an RA specific validated  
20 outcome measure led to researchers adopting instruments developed for other conditions  
21 to assess fatigue. However, this was resolved in 2013 with the development, testing and  
22 publication of the Bristol Rheumatoid Arthritis Fatigue Scale.<sup>16</sup> Designed in collaboration  
23 with patients, this multi-dimensional measure captures physical, cognitive, emotional and  
24 social aspects of fatigue. In addition, three numerical ratings scales enable researchers and  
25 healthcare professionals to measure fatigue severity, impact and coping. As the factors  
26 driving and maintaining RA-related fatigue are likely to vary between patients, insight into  
27 how individuals experience and perceive their fatigue could be an important step in  
28 providing tailored support.

29  
30 Patients have identified fatigue as a priority and a challenge to manage. In this supplement,  
31 authors have provided updates on the pathobiology, clinical assessment and management  
32 of fatigue. Clarifying our current understanding and identifying the gaps in our knowledge is  
33 an important step as we continue to look at ways of supporting patients with this common  
34 and difficult symptom.

35  
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37 and/or served as member of advisory boards and speaker bureaus of Abbvie, Allergan,  
38 Amgen, AstraZeneca, Bio-Cancer, Biogen, BMS, Boehringer Ingelheim, Celgene, Chugai  
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40 Pharmaceuticals, Janssen, MedImmune, Merrimack Pharmaceutical, MSD, Napp,  
41 Novimmune, Novartis, ObsEva, Pfizer, Regeneron, Roche, R-Pharm, Sanofi, SynAct Pharma,  
42 Synovate, Tonix and UCB.

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