Fatigue and Quality of Sleep in Patients with Immune-Mediated Inflammatory Disease

LESLEY A. GRAFF, JOHN R. WALKER, ANTHONY S. RUSSELL, ROBERT BISSONNETTE, and CHARLES N. BERNSTEIN

ABSTRACT. Fatigue, a systemic feeling of exhaustion, is a common symptom of many chronic illnesses, including immune-mediated inflammatory diseases (IMID). IMID-related fatigue is associated with disease activity and pain and has detrimental effects on patient quality of life and overall well-being. Thus, routine assessment and management of fatigue in clinical practice is important. This article provides an overview of the prevalence, correlates, and predictors of fatigue in IMID. There is also discussion of the effects of different treatments on fatigue outcomes, as well as management recommendations. (J Rheumatol 2011;38 Suppl 88;36–42; doi:10.3899/jrheum.110902)

Key Indexing Terms:
INFLAMMATION FATIGUE SLEEP QUALITY OF LIFE

Fatigue, a common symptom for patients with IMID[1,2,3], is a poorly understood phenomenon[4]. It appears to be multifactorial and multidimensional, as different psychological, biological, social, and behavioral factors influence the presence and experience of fatigue[5,6,7]. Patients have identified that the nature of the fatigue they experience in the context of IMID differs both qualitatively and quantitatively from acute fatigue or tiredness that one may feel after a period of physical or mental activity[8]. While tiredness is considered a normal occurrence of daily living that is temporary, responds to rest, and protects from overexertion, IMID-related fatigue usually influences patients' physical and cognitive well-being negatively. This form of fatigue, often described as "overwhelming weariness" and "exhaustion," is also one of the most prevalent concerns of patients with IMID[1,2,3]. In a study of patient concerns related to inflammatory bowel disease (IBD), comparing cross-cultural responses of 2000 participants from 8 different countries, fatigue ranked fourth, even before pain and bowel control[2]. Similarly, fatigue was identified as 1 of the top 5 items on a list of 23 important disease-related outcomes generated by patients with rheumatoid arthritis (RA), the other 4 being pain, independence, mobility, and feeling well[3].

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CURRENT CHALLENGES FACING FATIGUE-RELATED RESEARCH

The lack of objective markers and standard measures is considered the key obstacle in fatigue-related research. There are no consistent biological correlates with the patient experience of fatigue. As well, despite a plethora of fatigue scales, there is no consensus regarding the most appropriate scale(s) for assessment of fatigue in different diseases[9]. Even measures that are frequently used in clinical trials and practice are poorly validated and are often based on arbitrary cutoffs[9]. For example, while some studies in RA and ankylosing spondylitis (AS) define significant or problematic fatigue as ≥ 70 points on the 0–100 visual analog scale (VAS), others use ≥ 50 or only ≥ 20[10].

Recently, Hjollund, *et al*[11] comprehensively catalogued the use of fatigue scales in studies of disease-related fatigue over the past 30 years (Figure 1). The authors pointed out that 80% of the 2285 articles they reviewed with measures of fatigue in chronic diseases were published during the past decade, reflecting the recent explosion of efforts to quantify fatigue. They identified 252 different ways that fatigue was measured, with more than half of the measurement approaches used only once. The more recently developed scales have tended to adopt a multidimensional approach to

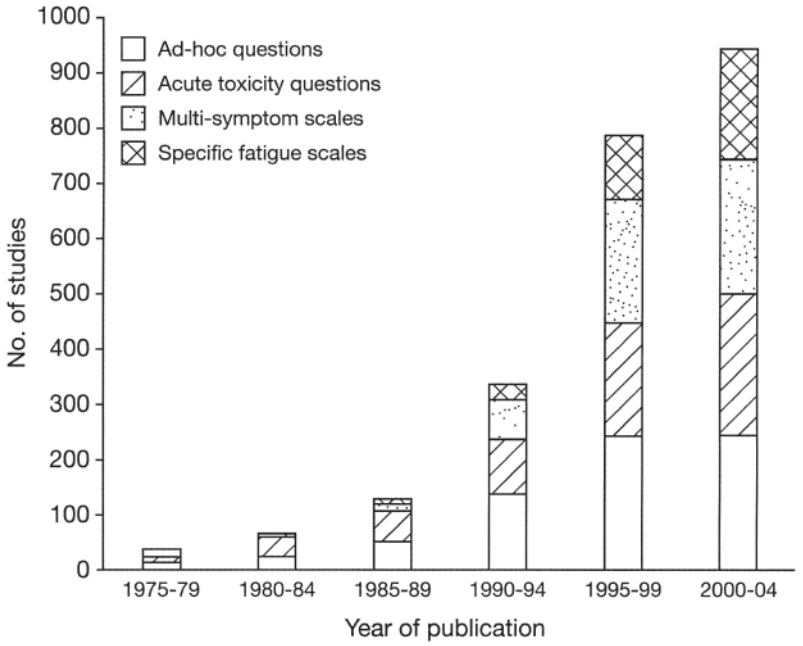

Figure 1. Studies of disease-related fatigue by year of publication by method of fatigue assessment (2285 studies, 252 measures). Reproduced with permission from Hjollund, *et al*. Health Qual Life Outcomes 2007;5:12. Copyright© 2007 Hjollund et al (licensee BioMed Central Ltd.) under Open Access.

fatigue, although many of them were disease-specific or applicable only to a narrow range of diseases. The authors argued that disease-specific scales are unnecessary since fatigue is a nonspecific symptom. The wide variety of approaches to operationalize fatigue has been a barrier to research as it impedes cross-study and cross-disease comparisons. Generic fatigue scales are needed to facilitate documentation of differences in characteristics of fatigue across various diseases. If fatigue-management strategies are to be developed and tested, there needs to be greater consensus regarding optimal and consistent measurement. Certainly, fatigue needs to be accurately assessed using multidimensional generic scales with adequate validation properties, comprehensiveness, accuracy, reliability, and sensitivity to treatment change.

Even as some of the measurement challenges are addressed, an additional difficulty is that fatigue has not been routinely identified or assessed as an outcome in clinical trials[12]. It is only recently that fatigue has been included as a patient-reported outcome in RA studies, and it is still rarely identified as an important outcome in other IMID research. Indeed, in a recent systematic review of fatigue in IBD, fewer than 12 empirical studies that assessed fatigue were identified, and in the majority of these studies fatigue was a secondary, not a primary, outcome[13].

PREVALENCE OF IMID-RELATED FATIGUE

Given the methodological concerns, prevalence of fatigue can be difficult to determine. However, more consistent use of validated fatigue measures, and some overlap of scale use within disease types, has started to provide more reliable estimates. The prevalence of problematic fatigue in healthy adults has been found to vary from 9% to 25%[14,15,16]. Individuals with IMID have a significantly higher prevalence of fatigue compared to the general population (Table 1)[10,17,18,19,20,21,22,23,24]. This group of patients also reports higher fatigue scores than age- and sex-matched controls[25,26].

Clinically relevant fatigue is reported in about 50% of patients with RA. Using a multidimensional measure of

Table 1. Prevalence of fatigue in patients with immune mediated inflammatory diseases.

Condition	Disease Status	Rates, %	Measures
General community[14,15]	—	9 22	Interview, CIS-F
Rheumatoid arthritis[10,18,19]	Active	50 42–52	VAS, CIS-F
Ankylosing spondylitis[20,21]	Active	53–63	VAS
Inflammatory bowel disease[17,23]	Inactive Active	30 72	FIS, MFI-20
Psoriasis[24]		19	Survey question
Psoriatic arthritis[22]		49 moderate 28 severe	mFSS

CIS-F: Checklist Individual Strength - Fatigue; VAS: visual analog scale; FIS: Fatigue Impact Scale; MFI: Multidimensional Fatigue Inventory; mFSS: modified Fatigue Severity Scale.

fatigue, the Checklist Individual Strength (CIS), van Hoogmoed, *et al*[18] confirmed the presence of severe fatigue (CIS ≥ 35) in 42% of RA patients with active disease. In another study of RA patients attending outpatient clinics in the UK, just over 50% were found to have significant fatigue, based on a unidimensional VAS[10]. Using the same scale and cutoff, significant fatigue was reported by 63% of patients with AS[20]. In a Dutch study conducted by van Tubergen, *et al*[21], a single-item measure of fatigue embedded in the Bath Ankylosing Spondylitis Disease Activity Index was validated using a multidimensional fatigue scale, and identified 53% of AS patients as experiencing fatigue.

For those with psoriatic arthritis (PsA), moderate fatigue was found to occur in 49% and severe fatigue in 29% of patients, according to the modified Fatigue Severity Scale[22]. These rates are significantly higher than those reported for psoriasis, based on a national survey of 17,000 members of a psoriasis organization. In that community-based sample, only 19% were identified as being affected by fatigue[24]. The latter results may be an underestimate, however, given the nature of the sample and the use of a single, nonvalidated question to determine fatigue.

Finally, a recent population-based study of fatigue and sleep disturbances in IBD demonstrated that 72% of patients with active disease and 30% of patients with inactive disease have pronounced fatigue, using a conservative cutoff of the 95th percentile score for a healthy sample on the Multidimensional Fatigue Inventory[23]. Parallel results were reported in another study of 70 outpatients with IBD in remission attending a specialty gastrointestinal clinic, in which 41% experienced significant fatigue, based on the same scale and threshold[17]. The high levels of fatigue even among those in remission suggest that fatigue may still be a significant concern even when the disease is thought to be under control.

PHYSICAL AND PSYCHOSOCIAL CORRELATES OF FATIGUE IN IMID

The etiology of IMID-related fatigue is multidimensional, involving physical, psychological, cognitive, social, and behavioral aspects[7]. Fatigue affecting the IMID population is often linked to inflammation, anemia, sleep difficulties, and psychiatric comorbidities. More specifically, data from several studies in patients with RA[10,18], AS[20,21], and IBD[23,27] demonstrated that fatigue in these patient populations is associated with increased disease activity, pain, poor sleep quality, depression, and perceived stress (Figure 2). Of the disease-related factors in RA, fatigue was most strongly associated with pain[28], and moderately associated with disease activity and tender joint count[18], consistent with findings that fatigued RA patients experience significantly more pain[29]. Similarly, more than half of the AS patients reported that fatigue was aggravated by pain and stiffness[30].

Fatigue linked to pain may be explained by several mechanisms[31]. Pain is often a manifestation of disease flare, signaling inflammation, which may give rise to fatigue more directly through exposure to proinflammatory cytokines[32]. Dealing with pain may require more expenditure of energy (both mental and physical) to perform daily tasks without escalating the pain. Finally, pain may indirectly affect fatigue by interfering with sleep, resulting in consequent daytime fatigue.

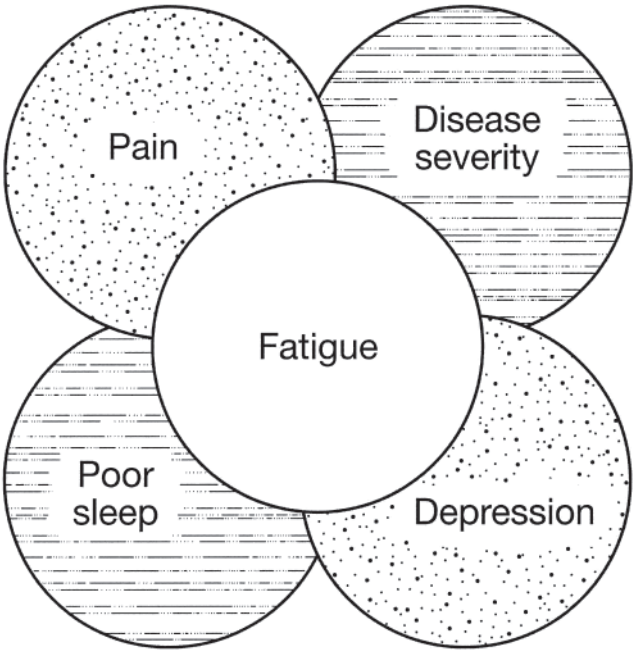

Figure 2. Common fatigue-associated factors in IMID.

Interestingly, the association between fatigue and inflammatory markers in IMID appears to be modest. In a study conducted by van Hoogmoed, *et al*[18], swollen joint count, erythrocyte sedimentation rate, C-reactive protein (CRP), and hemoglobin levels did not correlate closely with fatigue severity. Further, these markers of inflammation and anemia did not differentiate the fatigued and the nonfatigued patients with RA. Similarly, while there was a modest association of fatigue with CRP and hemoglobin in IBD, those correlations were not strong compared to the relationships with other variables, including disease activity, stress, and poor sleep quality[23,27]. A weak association between markers of inflammation and fatigue in AS has also been reported[20,33].

PREDICTORS OF FATIGUE OVER TIME

There have been few longitudinal studies of fatigue in IMID, and of those, most have focused on RA. Mancuso, *et al*[34] found that mean fatigue scores were significantly worse for patients with RA than for controls, both at baseline and 1 year later, although there was little within-patient change across that time. According to Wolfe, *et al*[28], change in fatigue, measured at 2 timepoints 6 months apart, was sig-

nificantly associated with change in health status. Treharne, *et al*[35] reported minimal mean change in fatigue over 1 year, but noted wide individual variability, with almost equal numbers decreasing or increasing fatigue levels. Recent longitudinal studies in IBD[36] and PsA[37] also reported changes in fatigue over time. Modest increases in fatigue levels across 2 years were noted in IBD regardless of disease activity, and in PsA, about half of the sample transitioned across fatigue severity levels (i.e., mild, moderate, severe) over 1 year.

Predictors of subsequent fatigue levels have also been examined in these longitudinal studies. Baseline fatigue, physical disability, pain levels, psychological distress, and disease beliefs related to lack of control were all associated with greater fatigue at followup, with some overlap of factors across studies[19,34,35,37].

SLEEP DISTURBANCES IN IMID POPULATIONS: CAUSES AND CONSEQUENCES

Sleep disturbances are common in IMID, with prevalence estimates of 50%–75%[23,38], in contrast to an estimated one-third of the general population. Epidemiological studies have consistently found correlations among fatigue, pain, mood disturbances, and sleep difficulties. In individuals with IMID, rates of sleep disorders are substantially elevated[23,38,39,40,41,42,43]. For example, the prevalence of insomnia was significantly higher in patients with arthritis compared to the general population (23% vs 16%, respectively)[43], and restless leg syndrome has been reported at high rates for patients with RA (25%–30%) and IBD (9%–30%)[44,45]. It has been shown that poor quality of sleep adversely affects the course of many inflammatory diseases, resulting in increased disease activity, and intensified symptoms of pain and fatigue[40]. The mechanism underlying these effects has been hypothesized to involve dysregulation of the immune system, as mediators of inflammation are altered by sleep loss[46]. Patients with psoriasis and PsA further illustrate the complexity of the etiology of sleep disturbance in those with IMID. In addition to a high general inflammation state, joint pain and pruritus, patients with psoriasis and PsA are more likely to be obese[47]. Obesity is associated with sleep apnea, which in turn has an important effect on sleep disturbance and fatigue. An association between sleep apnea and psoriasis has been reported[48].

In one of the few studies assessing sleep in IBD[39], patients reported significantly greater delay in sleep onset, greater sleep fragmentation, and more use of sleeping pills compared to healthy controls. Poor sleep quality was also strongly associated with lower disease-specific quality of life. A large study of community-based patients with IBD reported high rates of poor sleep when the disease was active (72%–82%)[23]. However, sleep problems were also quite frequent among those with inactive disease (47%–51%), compared to community norms. Similar correlations between sleep quality and disease activity were observed in patients with RA[38,41] and psoriasis[42]. These results suggest that fatigue in IMID is not entirely explained by active inflammation or disrupted sleep, but both processes may be contributing. That is, there is a potential feedback loop such that inflammation worsens sleep and sleep disruption worsens inflammation, with both resulting in fatigue. The findings indicate that managing sleep disturbances should be considered an important factor both to address fatigue specifically, and in the overall management of patients with IMID.

CURRENT APPROACHES TO FATIGUE MANAGEMENT IN CLINICAL PRACTICE

Recent qualitative research has highlighted the challenges faced by patients in dealing with disease-related fatigue. In a United Kingdom study, patients with RA described fatigue as an untreatable part of the disease that they have to struggle to manage on their own or with the help of family and friends[8]. Fatigue was rarely discussed with the clinician, and patients felt that health practitioners were not receptive when concerns about fatigue were expressed. On the other hand, a recent survey of Dutch rheumatologists illustrated their view that fatigue is a multifaceted problem and as such requires a multidisciplinary approach[49]. Although the majority of rheumatologists were willing to assess and manage fatigue, they assumed that the patient would raise it if it were an issue. Most of the rheumatologists reported that they assessed fatigue in the initial consult, but did not typically inquire in followup. Thus, it appears that in routine practice, patients are often left on their own to cope with fatigue-related problems. They may apply trial-and-error self-management approaches, including rest, exercise, assistance, acceptance, and energy rationing for valued activities[8,50].

Fatigue outcomes with pharmacological therapies. Several clinical trials have suggested positive effects of biologic therapies on fatigue in patients with RA[51,52,53,54,55], IBD[56,57], and psoriasis[58]. None of these studies assessed sleep outcomes. Observational studies in routine practice show that fatigue is reduced when active RA is treated with an anti-tumor necrosis factor agent and, to a lesser extent, with disease-modifying antirheumatic drugs. These reductions in fatigue mirror decreases in disease activity and pain.

Two randomized, controlled trials demonstrated significant reduction in fatigue in RA patients with longstanding and/or severe disease treated with adalimumab[51,52]. Treatment with etanercept has also been shown to reduce fatigue in patients with recent-onset RA as well as in those with established disease[53]. Further, the fatigue responded more quickly for the patients with recent-onset RA who received etanercept compared to those receiving methotrexate. Reduction in fatigue in RA patients has also been observed with the newer biologics abatacept[54] and ritux-

imab[55]. There have been fewer studies with other IMID in which fatigue outcomes have been assessed. However, both adalimumab[56] and infliximab[57] were found to reduce fatigue in patients with IBD, and etanercept has been shown to be effective in reducing fatigue in patients with psoriasis[58].

Nonpharmacological treatment. Psychological interventions such as cognitive behavioral therapy (CBT) are well established as effective treatments for pain, depression, and insomnia, including when they occur in the context of IMID, but there has been little evaluation of fatigue outcomes in IMID with these approaches. A systematic review of the literature examining the efficacy of psychological interventions including relaxation training, biofeedback, and CBT in the treatment of RA suggested that these interventions may be important adjunctive therapies in the medical management of RA[59].

Evers, *et al*[60] conducted a randomized, controlled trial of tailored CBT modules with RA patients earlier in their disease (duration < 8 yrs), who had been identified as having psychosocial risk profiles. In addition to standard medical care, the participants received 2 out of 4 possible standardized treatment modules, each of which targeted a common RA-related symptom such as pain, fatigue, or negative mood, depending on the patient's need. The study revealed beneficial effects of CBT on physical, psychological, and social functioning. Both fatigue and depression were significantly reduced at post-treatment ($p < 0.01$), and these treatment gains were maintained at the 6-month followup. There was also improved coping with stress following treatment (Figure 3). These results provide promising support of the utility of targeted CBT in RA patients at risk for psychosocial comorbidities. Exercise as an intervention has also received some attention in RA, with regular exercise being linked to decreased fatigue and disability for patients with RA[61].

Potential management algorithm. Several trials have demonstrated the benefits of managing fatigue in patients with IMID, both pharmacologically and with nonpharmacological treatment options. A fatigue management algorithm originally proposed by van Langenberg, *et al*[13] for patients with IBD could be readily adapted and used in the daily management of IMID-related fatigue (Figure 4). Routine screening for fatigue and sleep disturbance is encouraged, with attention to medical treatment of disease or comorbid factors that can contribute to fatigue, a focus on medical or behavioral treatment targeting sleep quality and psychological symptoms, and optimization of health habits.

CONCLUSION

Chronic fatigue is prevalent among patients with IMID. Further, IMID-related fatigue is intrusive and overwhelming and has the potential to negatively influence disease outcomes and patient well-being. Thus, there is an urgent need to understand and manage fatigue better in routine practice. While descriptive studies can provide additional information on prevalence, severity, and correlates of fatigue, there is also a need for better understanding of pathological pathways to guide therapeutic approaches.

The clinician's goal in treating patients with IMID is often to reduce inflammation, pain, and disability. However,

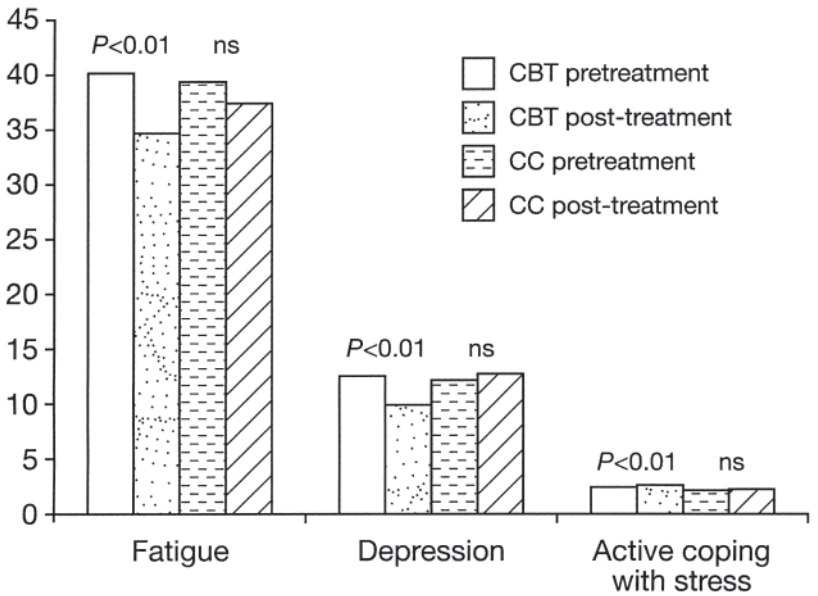

Figure 3. Cognitive-behavioral therapy (CBT) and fatigue in rheumatoid arthritis[60]. Means of fatigue, depression, and active coping with stress in the CBT condition and control condition (CC) at pre- and post-treatment assessments, measured by the Fatigue Scale from the Checklist Individual Strength, a Dutch version of the Beck Depression Inventory, and the Problem Focusing Scale of the Utrechtse Coping List, respectively. ns: nonsignificant.

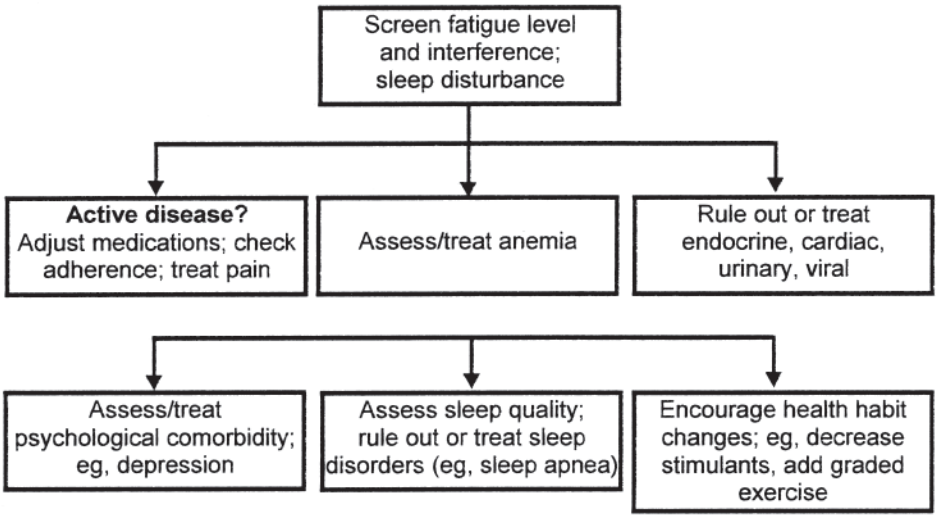

Figure 4. Fatigue management algorithm[62].

fatigue in this patient population should not be ignored. Addressing fatigue in the clinic can begin with clinician awareness of this problem and routine review of the patient's fatigue experience.

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