REVIEW ARTICLE

BJD
British Journal of Dermatology

Fatigue in psoriasis: a phenomenon to be explored*

I.M. Skoie,[1] T. Ternowitz,[1] G. Jonsson,[2] K. Norheim[3] and R. Omdal[3,4]

[1]Department of Dermatology, [2]Department of Medical Biochemistry and [3]Clinical Immunology Unit, Department of Internal Medicine, Stavanger University Hospital, Stavanger, Norway

[4]Department of Clinical Science, Faculty of Medicine and Dentistry, University of Bergen, Bergen, Norway

Summary

Fatigue is a prevalent and substantial phenomenon in many patients with chronic inflammatory diseases, often rated by patients as the most troublesome symptom and aspect of their disease. It frequently interferes with physical and social functions and may lead to social withdrawal, long-standing sick leave and disability. Although psychological and somatic factors such as depression, sleep disorders, pain and anaemia influence fatigue, the underlying pathophysiological mechanisms by which fatigue is generated and regulated are largely unknown. Increasing evidence points towards a genetic and molecular basis for fatigue as part of the innate immune system and cellular stress responses. Few studies have focused on fatigue in dermatological diseases. Most of these studies describe fatigue as a phenomenon related to psoriatic arthritis and describe the beneficial effects of biological agents on fatigue observed in clinical studies. It is therefore possible that this problem has been underestimated and deserves more attention in the dermatological community. In this review, we provide a definition and explanation for chronic fatigue, describe some commonly used instruments for measuring fatigue, and present hypothetical biological mechanisms with an emphasis on activation of the innate immune system and oxidative stress. An overview of relevant clinical studies covering the theme 'psoriasis and fatigue' is given.

Correspondence
Roald Omdal.
E-mail: roald.omdal@lyse.net

Accepted for publication
23 December 2014

Funding sources
I.M.S. was funded by a grant provided by Stavanger Health Research.

Conflicts of interest
None declared.

*Plain language summary available online.

DOI 10.1111/bjd.13647

What's already known about this topic?

- Fatigue is prevalent in patients with chronic inflammatory diseases, cancer and some neurological diseases.
- Depression, sleep disorders and pain influence fatigue.
- Genes and molecular signalling pathways are increasingly recognized as important contributors to fatigue.

What does this study add?

- The relationship of fatigue with psoriasis disease activity is unclear.
- Biological drugs have a beneficial effect on fatigue in patients with psoriasis.
- More knowledge regarding the prevalence, severity and impact of fatigue in patients with psoriasis is needed.
- Future therapeutic studies should include fatigue as an outcome variable.

Chronic fatigue is a frequent and often disabling phenomenon that occurs in patients with chronic inflammatory and autoimmune diseases, cancer, neurological diseases and a number of other conditions in which inflammation and/or cellular stress occurs. Fatigue may be defined as 'an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion'.[1] For the individual, as well as for society, it is important to gain knowledge of the mechanisms through which fatigue is generated, and to develop effective treatment strategies.

Chronic fatigue syndrome (CFS)/myalgia encephalomyelitis (ME) is a condition characterized by chronic fatigue and in which no underlying disease or condition can be identified.

© 2014 The Authors. British Journal of Dermatology published by John Wiley & Sons Ltd on behalf of British Association of Dermatologists.
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

However, in contrast to popular media reports and beliefs, most people with chronic fatigue have an underlying primary disease other than CFS/ME, with the latter reported in 0·2–0·4% of subjects in community-based studies, and 2·6% of patients in primary care.[2,3]

There is a complex inter-relationship between mental depression, pain and fatigue. Also, sleep disorders in general, and disrupted sleep in dermatological disorders such as atopic dermatitis, have been linked to daytime sleepiness.[4] However, it is outside the scope of this review to cover these important psychosocial aspects of fatigue in depth.

Fatigue varies in intensity between patients, and may be so profound that it severely interferes with activities of daily living, leading to long-standing sick leave and disability. Many patients with chronic diseases consider fatigue their most troublesome challenge.[5]

The frequently reported lack of an association between fatigue and disease activity in many studies is a paradox, and apparently goes against common beliefs and conceptions.[6] It is clear that social and psychological factors play a role, but the paradox may have a foundation in genetic and molecular mechanisms that are crucial for the generation and regulation of fatigue.[7] Emerging evidence points to the innate immune system as an important 'fatigue generator', brought on by invading pathogens, autoimmune diseases, cancer or other 'danger-signals', as well as cellular stress responses.[8]

Many dermatological diseases and conditions demonstrate inflammatory or autoimmune features, suggesting that fatigue would be an accompanying phenomenon in a number of chronic skin diseases. Also, psoriasis shares common pathways of immune signalling with other inflammatory diseases including psoriatic arthritis and rheumatoid arthritis (RA), such as the interleukin (IL)-23/T helper cell (Th)17 axis.[9–12] The proinflammatory cytokine IL-23 orchestrates T-cell-dependent pathways of inflammation, and of special importance is activation of the T-cell subtype Th17, which produces IL-17 and other proinflammatory cytokines.[13,14]

From this perspective, one would expect fatigue to be common in dermatological diseases, but the literature on this matter is sparse and deals mainly with the effect of biological agents on fatigue reported as quality-of-life measures. It is therefore both important and challenging to explore the extent of this problem and identify how – and if – this phenomenon interferes with the lives of patients with such diseases.

What is fatigue?

Fatigue is a poorly understood phenomenon. It is abstract in nature and has been described as 'like water it slips away and cannot be grasped'.[15] Although everyone seems to recognize it, fatigue is often less focused on, overlooked or underestimated by clinicians,[5,16] which may reflect there being no specific treatment for chronic fatigue.[17]

While fatigue is difficult to define and treat, it is also a challenge to measure. Making it even more complex, there is conceptual disagreement about whether chronic fatigue can be consider a unidimensional phenomenon, or whether several dimensions or subscales of fatigue exist, such as physical fatigue, muscular fatigue, mental fatigue, cognitive fatigue etc. Arguments for the first view are that fatigue is a universal and global experience that to varying degrees interferes with – or has an impact on – different aspects of human life, including traits or attributes associated with the disease. Arguments for the latter comprehension of fatigue are that fatigue is a phenomenon that more or less specifically influences the muscles, brain, mood, initiative, physical activity etc., and should therefore be considered a separate feature.[18]

Fatigue interferes with several aspects of life including emotional, physical and social functioning. The burden of chronic fatigue on society is high, primarily due to medical expenses, sick leave and loss of work.[19,20] In a qualitative study of patients with primary Sjögren syndrome (pSS) where the effects of medications on fatigue were examined, two themes emerged after individual interviews.[21] Patients clearly differentiated fatigue from normal tiredness and described 'a heavy resistant body and ever present lack of vitality' and 'an unpredictable, uncontrollable fluctuation in fatigue'. This differs from the normal tiredness everyone feels after being exposed to mental and physical stress, and fatigue does not respond to rest as in a healthy individual. Chronic fatigue is therefore not to be confused with tiredness.

Biological mechanisms of fatigue

A highly relevant model for fatigue may be sought in the so-called 'sickness behaviour', which represents an adaptive and complex response in humans and animals during the course of an infection.[22–24] Sick individuals demonstrate loss of appetite, initiative, grooming and interest in other individuals. They develop sleepiness and withdraw from normal social activities.[25] Fatigue is a prominent and dominant feature of this response. Sickness behaviour seems to be deeply conserved throughout evolution and, as such, it is not a maladaptive response but a subconscious strategy for the survival of the individual and the species (the genome) during viral and bacterial infections.

Activation of the innate immune system, which is found in all plant and animal life and which provides the immediate host immune response to infection and other immunological 'danger', may be a key regulator of fatigue in both acute and chronic conditions. A number of studies show that sickness behaviour is associated with proinflammatory cytokines such as IL-1β, IL-6 and tumour necrosis factor (TNF)-α.[23,26] Among these cytokines, IL-1β seems to have a pivotal role.[27] IL-1β possesses an early and strong proinflammatory effect and is secreted mainly by activated monocytes, macrophages and dendritic cells.[28–30] IL-1β also reaches neuronal cells in the brain where it binds to specific IL-1 receptors not causing inflammation, but instead triggering the behavioural response.[22,31]

There is substantial experimental evidence from animal models for an essential role of IL-1β in promoting sickness

© 2014 The Authors. *British Journal of Dermatology* published by John Wiley & Sons Ltd on behalf of British Association of Dermatologists.

behaviour. IL-1β is rapidly transported through the blood–brain barrier in injected animals, followed by rapid upregulation of both IL-1 receptor antagonist and IL-1RI in the brain.[32–35] Also, injection of lipopolysaccharide into the abdominal cavity activates lipopolysaccharide receptors on the vagal nerve. Through neuronal signalling, this leads to production of IL-1β in the brain, which is followed by the animal exhibiting sickness behaviour.[36] IL-1RI knockout mice are resistant to the sickness-inducing effects of IL-1β.[31] All these observations point strongly to IL-1β as a key factor for sickness behaviour and fatigue.

In humans, blockade of IL-1 in both RA and pSS results in reduced fatigue.[37] Also, a number of studies in different diseases have demonstrated beneficial effects on fatigue by all biologics given (i.e. anti-TNF-α, anti-IL-6, anti-CD20 and the cytotoxic T-lymphocyte-associated protein 4 Ig fusion protein, abatacept).[38–41]

Oxidative stress is observed in acute and chronic inflammatory diseases, and an association between chronic fatigue and measures of oxidative stress has been demonstrated in CFS/ME and systemic lupus erythematosus (SLE).[42,43] There are no such studies in dermatological disorders. Oxidative stress results from an imbalance in which reactive oxygen species (ROS) dominate over antioxidant defences.[44–46] ROS are important in the first line of defence against infections, as they kill pathogens engulfed in cellular phagolysosomes.[47] Chronic inflammation causes a prolonged state of increased oxidative stress, as reported in several diseases including psoriasis.[48–51]

Oxidative stress is part of the innate immune response and is triggered by activation of pattern-recognition receptors on innate immune cells such as macrophages and granulocytes. To protect against the harmful effects of free radicals, cells have developed a highly efficient system for combating the cellular stress imposed by these reactive intermediates.[8] The exact mechanism for how oxidative stress is associated with fatigue is unknown, but could involve activation of genes important for cellular viability and protection. These genes might also be responsible for development of fatigue across different disease groups such as chronic inflammatory, neurodegenerative and neoplastic diseases.[7]

How to measure fatigue

Objective markers of fatigue do not exist, and all fatigue instruments are based on self-reporting. Some tests attempt to measure multiple aspects of fatigue, whereas others use a single unidimensional approach.[52] Also, some fatigue instruments are designed to be used in specific diseases and thus include disease-specific variables, for example the Parkinson Fatigue Scale,[53] Fatigue Impact Scale for multiple sclerosis[54] and Profile of Fatigue for pSS.[55] Other instruments are generic and may be used across different disease entities, for example the Fatigue Severity Scale (FSS)[56] and the Functional Assessment of Chronic Illness Therapy Fatigue subscale (FACIT-F).[57] An overview of selected fatigue instruments is given in Table 1.

In patients with psoriasis, studies of fatigue have been assessed mainly by the use of the medical outcomes study short form 36-item (SF-36) health survey.[58] Only three studies have used FACIT-F.[59–61] The SF-36 health survey is a 36-item general health status instrument. It contains subscales for eight domains, where the Vitality subscale is supposed to cover energy and fatigue.[58] A change of 3 or more points in the SF-36 Vitality subscale score is considered clinically meaningful.[62] The FACIT-F self-administered questionnaire, originally developed to assess fatigue associated with anaemia in patients with cancer, includes 13 questions regarding the impact of fatigue on patients' activities over the past 7 days.[57] The FACIT-F scores ranges from 0 to 52, with lower scores indicating more fatigue. A change in score of at least 3 points is considered to be a minimally clinically important difference.[63]

Fatigue in chronic diseases

Fatigue is the defining feature of CFS/ME. The syndrome is diagnosed when no other disease or underlying condition can be identified.[64] No main causes of the syndrome have been agreed upon, but a dominant hypothesis is that CFS is a condition caused by the interaction between a common viral infection and individual susceptibility factors such as genetic and immune system dysfunction.[65]

Table 1 Selected generic self-reported fatigue instruments

Name of scale	Dimension	What is assessed	No. of scale items	No. of subscales	Scale type
Fatigue Severity Scale[56]	Unidimensional	Impact and functional outcomes	9	1	7-point Likert
Fatigue Visual Analogue Scale[110]	Unidimensional	Severity	1	1	Visual analogue
Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F)[57]	Unidimensional	Severity and impact	13	1	5-point Likert
Medical Outcomes Study Short Form 36-item scale (SF-36)[58]	Multidimensional	Severity	36	8	3–6-point Likert, yes/no
Multidimensional Fatigue Inventory (MFI-20) scale[111]	Multidimensional	Severity and impact	20	5	7-point Likert
Multidimensional Assessment of Fatigue (MAF)[112]	Multidimensional	Severity and impact	16	4	4–10-point Likert

© 2014 The Authors. *British Journal of Dermatology* published by John Wiley & Sons Ltd on behalf of British Association of Dermatologists.

Fatigue accompanies inflammation and is frequently reported among patients with a wide range of chronic inflammatory conditions. The prevalence of fatigue in patients with RA, defined as a score of > 20 on the fatigue visual analogue scale, was reported to be 41% in one study,[66] and fatigue is among the most commonly reported phenomena in multiple sclerosis, pSS and SLE.[67–70] In inflammatory diseases, as well as in cancer-related fatigue, the fatigue has sometimes been related to altered or increased proinflammatory cytokine production.[71,72] However, in general there seems to be a poor correlation between disease activity and the severity of fatigue.[6,73–75] Lee *et al.*[76] postulated that among patients with RA there is a large subgroup with low levels of systemic inflammation and low disease activity, yet high levels of fatigue and pain. This could be consistent with a chronic noninflammatory central pain syndrome as seen in fibromyalgia, which is a condition also associated with high levels of fatigue, pain and sleep problems.[77] The underlying pathogenic mechanism, as compared with those with high disease activity inflammatory burden and high fatigue scores, could therefore be somewhat different.

Cancer-related fatigue affects both patients with cancer and cancer survivors.[78] There are no major differences in fatigue depending on cancer type, origin and disease stage.[79] Interestingly, cancer-related fatigue worsens during treatment with cytostatic agents and radiation therapy, and may persist for years in some cancer survivors after the cancer has been eradicated.[80]

Parkinson disease and cerebral stroke are examples of neurological conditions with no clear inflammatory component, and in which fatigue is common and may be debilitating.[81] In cerebral stroke, it is possible that there is a disturbance of neuronal circuits within the basal ganglia, thalamus and cerebral cortex, while the fatigue mechanisms in neurodegenerative diseases are less clear, but might well be due to cellular stress responses.[82,83]

Confounding factors

Depression, sleep disorders and pain are confounding factors to fatigue. Fatigue is strongly associated with depression and vice versa.[84–86] There is an overlap in symptomatology between fatigue and depression, but fatigue also appears without depression.[68] Both depression and fatigue in chronic inflammatory disorders, as well as in depressive diseases, have been associated with proinflammatory cytokines.[87] Intriguingly, patients with chronic fatigue are less responsive to antidepressant drugs than depressed patients.[88] Notably, several biological agents used in chronic inflammatory disorders have shown improvement in both depression and fatigue scores.[89–91] Some evidence indicates that IL-1 and TNF-α may play a role in the regulation of sleep.[92] The clinically interesting question is why these behavioural alterations present more easily and are more severe in some individuals than in others.

Fatigue in psoriasis

Psoriasis vulgaris (plaque psoriasis) is an immune-mediated chronic inflammatory disease affecting about 2% of the world's population.[93] The inflammation is thought to be a consequence of a T-cell-mediated immune response to an as-yet unidentified autoantigen. Several lines of evidence suggest an important role for IL-17 in the pathogenesis of psoriasis, as well as in psoriatic arthritis and other chronic inflammatory disorders.[94] Psoriasis may have a major impact on a patient's life, especially when the disease is moderate to severe.[95]

While psychosocial aspects have been widely studied in dermatological diseases, less is known about fatigue.[96] For an overview of genuine studies of fatigue in psoriasis, see Table 2. The majority of data regarding this phenomenon are derived from the Vitality subscale of the SF-36, a general measure of health-related quality of life. This subscale consists of only four questions, providing some indications of fatigue (Table 1). One study using the SF-36 in dermatological outpatient clinics in Norway reported significantly lower scores than the general norms on eight subscales of the SF-36, and higher levels of psoriasis-specific symptoms (itching, burning, scaling, suppuration, stinging and joint pain) were significantly related to all of the SF-36 subscales.[97] It was not stated whether some patients also had psoriatic arthritis.

Table 2 Genuine studies on fatigue in psoriasis

Study	Design	Fatigue instrument	Outcome (mean)
Rapp (1999)[113]	Postal questionnaire study where scores of 317 patients with psoriasis were compared with those from 10 different health conditions	SF-36 VS	Vitality subscale 45·4
Wahl (2000)[97]	283 patients with psoriasis were included and scores compared with general populations norms	SF-36 VS	Vitality subscale 48·2
Evers (2005)[96]	Questionnaires administered to 128 outpatients with psoriasis	VAS-Fatigue	VAS-Fatigue 3·8
Verhoeven (2007)[114]	Postal questionnaire study where scores of 112 patients with psoriasis registered in general practice were compared with those from nine other skin conditions	VAS-Fatigue	VAS-Fatigue 3·2, 28% reported severe fatigue (VAS > 5)
Jankovic (2011)[115]	Questionnaires administered to 110 outpatients with psoriasis	SF-36 VS	Vitality subscale 48·9

SF-36 VS, Medical Outcomes Study Short Form 36-item scale (SF-36) Vitality subscale; VAS, visual analogue scale.

© 2014 The Authors. *British Journal of Dermatology* published by John Wiley & Sons Ltd on behalf of British Association of Dermatologists.

Table 3 Effect of biological agents on fatigue in patients with psoriasis

Study	Design	Study duration (weeks)	No. of patients	Concomitant arthritis (%)	Drug	Fatigue instrument	Improvement (scores)
Krueger (2005)[101]	R, DB, PC, MC,OL	24	583	26–28	ETN	SF-36 VS	($P < 0{\cdot}001$)[a]
Reich (2006)[102]	R, DB, PC, MC	50	378	NA	IFX	SF-36 VS	4·7
Krishnan (2007)[59]	OL, MC	84	591	33–35	ETN	FACIT- F	> 5
Shikiar (2007)[103]	R, DB, PC, MC	12	147	NA	ADA	SF-36 VS	12·5
Revicki (2007)[104]	R, DB, PC, MC	52	1212	28	ADA	SF-36 VS	6·7
Feldman (2008)[105]	R, DB, PC, MC	50	835	26–28	IFX	SF-36 VS	4·2
Revicki (2008)[106]	R, DB, PC, MC	52	1205	28	ADA	SF-36 VS	3·3
Dauden (2009)[107]	R, OL, MC	54	711	NA	ETN	SF-36 VS	5·8
Reich (2009)[60]	R, DB, PC, MC	24	142	11–16	ETN	FACIT- F	3·7
Lebwohl (2010)[108]	R, DB, PC, MC	76	766	29–37	UST	SF-36 VS	2·6
Papp (2011)[61]	R, OL, C, MC	308	1468	26	ADA	FACIT- F	3·2
Nakagawa (2012)[109]	R, DB, PC, MC	64	158	9	UST	SF-36 VS	> 5
Kalb (2013)[38]	OL, P, MC	26	215	NA	IFX	SF-36 VS	5·4

R, randomized; DB, double blind; PC, placebo controlled; MC, multicentre; OL, open label; C, continuation study; P, prospective study; NA, not applicable; ETN, etanercept; IFX, infliximab; ADA, adalimumab; UST, ustekinumab; SF-36 VS, Short Form-36 Vitality subscale; FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue subscale. [a]Scores not given.

The prevalence of psoriatic arthritis in patients with psoriasis is estimated to be as high as 30%.[98] Few comparative studies of health-related quality-of-life measures between patients with psoriasis with and without arthritis have been performed. In one study, patients with psoriasis without arthritis were found to have less fatigue, as measured by the FSS and the Vitality subscale of the SF-36, compared with patients with arthritis.[99] In this study, the mean Dermatology Life Quality Index of patients with psoriasis was 7·7, indicating a moderate effect on patients' lives. These findings are in contrast to the 2005 Spring US National Psoriasis Foundation Quality of Life study, where no differences were found in overall health-related quality of life between these groups.[100] This study was conducted by telephone interviews, which might affect the quality of the data collected. To what degree arthritis influences fatigue in patients with psoriasis is therefore difficult to assess.

The majority of data on fatigue in patients with psoriasis arises from therapeutic clinical trials in which patients with arthritis have frequently been included, and these studies often lack information on the number of subjects with arthritis (for an overview see Table 3).[38,59–61,101–109] Patients who were included generally had moderate-to-severe psoriasis with a mean Psoriasis Area and Severity Index (PASI) > 14. All therapeutic studies in psoriasis employing biological agents have demonstrated a beneficial effect on the Vitality subscale of the SF-36. Only three studies used the FACIT-F, but revealed a clinically meaningful reduction of fatigue with the TNF-α inhibitors adalimumab or etanercept.[59–61] Tyring *et al.* reported less fatigue as measured with the FACIT-F, which was associated with improvements in joint and skin pain with the use of etanercept. In this study, up to 35% of the patients included had arthritis, and it was debated whether the effect of etanercept on fatigue could be attributed to an effect on psoriatic arthritis.[91]

To the best of our knowledge, no studies have investigated fatigue in relation to disease activity in patients with psoriasis who did not have arthritis. Also, because most patients with psoriasis have low C-reactive protein or erythrocyte sedimentation rate, it is difficult to evaluate the influence that psoriatic inflammation might have on fatigue. Finally, the prevalence and the degree of fatigue in a general population with psoriasis compared with a healthy control group remains to be studied.

Conclusions

Fatigue is an important feature of all inflammatory diseases. In psoriasis and other dermatological diseases, knowledge of fatigue is sparse and could represent a major but hidden problem in a considerable number of patients with psoriasis. Moreover, is it not known whether fatigue in patients with psoriasis is related to the extent of the disease (PASI scores) or other disease characteristics. It is therefore important to determine the prevalence, severity and impact of fatigue because this will add to the clinician's understanding and management of patients with psoriasis. Also, future therapeutic studies should include fatigue as an outcome variable.

The psychological and social factors that influence fatigue are outside the scope of this review. These issues need to be reviewed and synthesized as part of future research projects.

References

1 Krupp LB, Pollina DA. Mechanisms and management of fatigue in progressive neurological disorders. *Curr Opin Neurol* 1996; **9**:456–60.

2 Jason LA, Richman JA, Rademaker AW *et al.* A community-based study of chronic fatigue syndrome. *Arch Intern Med* 1999; **159**:2129–37.

© 2014 The Authors. *British Journal of Dermatology* published by John Wiley & Sons Ltd on behalf of British Association of Dermatologists.

3 Wessely S, Chalder T, Hirsch S *et al.* The prevalence and morbidity of chronic fatigue and chronic fatigue syndrome: a prospective primary care study. *Am J Public Health* 1997; **87**:1449–55.
4 Bender BG, Leung SB, Leung DY. Actigraphy assessment of sleep disturbance in patients with atopic dermatitis: an objective life quality measure. *J Allergy Clin Immunol* 2003; **111**:598–602.
5 Hewlett S, Cockshott Z, Byron M *et al.* Patients' perceptions of fatigue in rheumatoid arthritis: overwhelming, uncontrollable, ignored. *Arthritis Rheum* 2005; **53**:697–702.
6 Wang B, Gladman DD, Urowitz MB. Fatigue in lupus is not correlated with disease activity. *J Rheumatol* 1998; **25**:892–5.
7 Thomson CA, McColl A, Cavanagh J, Graham GJ. Peripheral inflammation is associated with remote global gene expression changes in the brain. *J Neuroinflammation* 2014; **11**:73.
8 Singh S, Vrishni S, Singh BK *et al.* Nrf2-ARE stress response mechanism: a control point in oxidative stress-mediated dysfunctions and chronic inflammatory diseases. *Free Radic Res* 2010; **44**:1267–88.
9 Kikly K, Liu L, Na S, Sedgwick JD. The IL-23/Th_{17} axis: therapeutic targets for autoimmune inflammation. *Curr Opin Immunol* 2006; **18**:670–5.
10 Arican O, Aral M, Sasmaz S, Ciragil P. Serum levels of TNF-α, IFN-γ, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. *Mediators Inflamm* 2005; **2005**:273–9.
11 Li J, Chen X, Liu Z *et al.* Expression of Th17 cytokines in skin lesions of patients with psoriasis. *J Huazhong Univ Sci Technolog Med Sci* 2007; **27**:330–2.
12 Fitzgerald O, Winchester R. Editorial: emerging evidence for critical involvement of the interleukin-17 pathway in both psoriasis and psoriatic arthritis. *Arthritis Rheumatol* 2014; **66**:1077–80.
13 Steinman L. A brief history of T_H17, the first major revision in the T_H1/T_H2 hypothesis of T cell-mediated tissue damage. *Nat Med* 2007; **13**:139–45.
14 Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med* 2009; **361**:496–509.
15 Rasker JJ. The enigma of fatigue. *J Rheumatol* 2009; **36**:2630–2.
16 Swain MG. Fatigue in liver disease: pathophysiology and clinical management. *Can J Gastroenterol* 2006; **20**:181–8.
17 Swain MG. Fatigue in chronic disease. *Clin Sci (Lond)* 2000; **99**:1–8.
18 Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. *J Psychosom Res* 2004; **56**:157–70.
19 Boehncke WH, Kirby B, Thaci D. GRAPPA Fellows Symposium Adjacent to the European Academy of Dermatology and Venereology (EADV) Congress, Istanbul, 2013: a meeting report. *J Rheumatol* 2014; **41**:1197–9.
20 Cohen BL, Zoega H, Shah SA *et al.* Fatigue is highly associated with poor health-related quality of life, disability and depression in newly-diagnosed patients with inflammatory bowel disease, independent of disease activity. *Aliment Pharmacol Ther* 2014; **39**:811–22.
21 Mengshoel AM, Norheim KB, Omdal R. Primary Sjögren's syndrome – fatigue is an ever-present, fluctuating and uncontrollable lack of energy. *Arthritis Care Res (Hoboken)* 2014; **66**:1227–32.
22 Dantzer R, O'Connor JC, Freund GG *et al.* From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 2008; **9**:46–56.
23 Kelley KW, Bluthe RM, Dantzer R *et al.* Cytokine-induced sickness behavior. *Brain Behav Immun* 2003; **17**(Suppl. 1):S112–18.
24 Dantzer R. Cytokine, sickness behavior, and depression. *Immunol Allergy Clin North Am* 2009; **29**:247–64.
25 Hart BL. Biological basis of the behavior of sick animals. *Neurosci Biobehav Rev* 1988; **12**:123–37.
26 Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. *Brain Behav Immun* 2007; **21**:153–60.
27 Kent S, Bluthe RM, Dantzer R *et al.* Different receptor mechanisms mediate the pyrogenic and behavioral effects of interleukin 1. *Proc Natl Acad Sci USA* 1992; **89**:9117–20.
28 Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. *Blood* 2011; **117**:3720–32.
29 Garlanda C, Dinarello CA, Mantovani A. The interleukin-1 family: back to the future. *Immunity* 2013; **39**:1003–18.
30 Dinarello CA. Overview of the interleukin-1 family of ligands and receptors. *Semin Immunol* 2013; **25**:389–93.
31 Bluthé RM, Layé S, Michaud B *et al.* Role of interleukin-1β and tumour necrosis factor-α in lipopolysaccharide-induced sickness behaviour: a study with interleukin-1 type I receptor-deficient mice. *Eur J Neurosci* 2000; **12**:4447–56.
32 Kent S, Bret-Dibat JL, Kelley KW, Dantzer R. Mechanisms of sickness-induced decreases in food-motivated behavior. *Neurosci Biobehav Rev* 1996; **20**:171–5.
33 Crestani F, Seguy F, Dantzer R. Behavioural effects of peripherally injected interleukin-1: role of prostaglandins. *Brain Res* 1991; **542**:330–5.
34 Gabay C, Smith MF, Eidlen D, Arend WP. Interleukin 1 receptor antagonist (IL-1Ra) is an acute-phase protein. *J Clin Invest* 1997; **99**:2930–40.
35 Dantzer R. Cytokine-induced sickness behavior: where do we stand? *Brain Behav Immun* 2001; **15**:7–24.
36 Quan N, Banks WA. Brain-immune communication pathways. *Brain Behav Immun* 2007; **21**:727–35.
37 Norheim KB, Harboe E, Gøransson LG, Omdal R. Interleukin-1 inhibition and fatigue in primary Sjögren's syndrome – a double blind, randomised clinical trial. *PLoS ONE* 2012; **7**:e30123.
38 Kalb RE, Blauvelt A, Sofen HL *et al.* Effect of infliximab on health-related quality of life and disease activity by body region in patients with moderate-to-severe psoriasis and inadequate response to etanercept: results from the PSUNRISE trial. *J Drugs Dermatol* 2013; **12**:874–80.
39 Fragiadaki K, Tektonidou MG, Konsta M *et al.* Sleep disturbances and interleukin 6 receptor inhibition in rheumatoid arthritis. *J Rheumatol* 2012; **39**:60–2.
40 Devauchelle-Pensec V, Mariette X, Jousse-Joulin S *et al.* Treatment of primary Sjögren syndrome with rituximab: a randomized trial. *Ann Intern Med* 2014; **160**:233–42.
41 Meiners PM, Vissink A, Kroese FG *et al.* Abatacept treatment reduces disease activity in early primary Sjögren's syndrome (open-label proof of concept ASAP study). *Ann Rheum Dis* 2014; **73**:1393–6.
42 Kennedy G, Spence VA, McLaren M *et al.* Oxidative stress levels are raised in chronic fatigue syndrome and are associated with clinical symptoms. *Free Radic Biol Med* 2005; **39**:584–9.
43 Avalos I, Chung CP, Oeser A *et al.* Oxidative stress in systemic lupus erythematosus: relationship to disease activity and symptoms. *Lupus* 2007; **16**:195–200.
44 Apel K, Hirt H. Reactive oxygen species: metabolism, oxidative stress, and signal transduction. *Annu Rev Plant Biol* 2004; **55**:373–99.
45 Perricone C, De Carolis C, Perricone R. Glutathione: a key player in autoimmunity. *Autoimmun Rev* 2009; **8**:697–701.
46 Jones DP. Radical-free biology of oxidative stress. *Am J Physiol Cell Physiol* 2008; **295**:C849–68.

© 2014 The Authors. *British Journal of Dermatology* published by John Wiley & Sons Ltd on behalf of British Association of Dermatologists.

47 Valko M, Leibfritz D, Moncol J *et al.* Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol* 2007; **39**:44–84.
48 Ahsan H, Ali A, Ali R. Oxygen free radicals and systemic autoimmunity. *Clin Exp Immunol* 2003; **131**:398–404.
49 Datta S, Kundu S, Ghosh P *et al.* Correlation of oxidant status with oxidative tissue damage in patients with rheumatoid arthritis. *Clin Rheumatol* 2014; **33**:1557–64.
50 Gilgun-Sherki Y, Melamed E, Offen D. The role of oxidative stress in the pathogenesis of multiple sclerosis: the need for effective antioxidant therapy. *J Neurol* 2004; **251**:261–8.
51 Zhou Q, Mrowietz U, Rostami-Yazdi M. Oxidative stress in the pathogenesis of psoriasis. *Free Radic Biol Med* 2009; **47**:891–905.
52 Hewlett S, Dures E, Almeida C. Measures of fatigue: Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF MDQ), Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales (BRAF NRS) for severity, effect, and coping, Chalder Fatigue Questionnaire (CFQ), Checklist Individual Strength (CIS20R and CIS8R), Fatigue Severity Scale (FSS), Functional Assessment Chronic Illness Therapy (Fatigue) (FACIT-F), Multi-Dimensional Assessment of Fatigue (MAF), Multi-Dimensional Fatigue Inventory (MFI), Pediatric Quality Of Life (PedsQL) Multi-Dimensional Fatigue Scale, Profile of Fatigue (ProF), Short Form 36 Vitality Subscale (SF-36 VT), and Visual Analog Scales (VAS). *Arthritis Care Res (Hoboken)* 2011; **63**(Suppl. 11):S263–86.
53 Brown RG, Dittner A, Findley L, Wessely SC. The Parkinson fatigue scale. *Parkinsonism Relat Disord* 2005; **11**:49–55.
54 Fisk JD, Ritvo PG, Ross L *et al.* Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clin Infect Dis* 1994; **18**(Suppl. 1):S79–83.
55 Bowman SJ, Booth DA, Platts RG. Measurement of fatigue and discomfort in primary Sjögren's syndrome using a new questionnaire tool. *Rheumatology (Oxford)* 2004; **43**:758–64.
56 Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989; **46**:1121–3.
57 Yellen SB, Cella DF, Webster K *et al.* Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage* 1997; **13**:63–74.
58 Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; **30**:473–83.
59 Krishnan R, Cella D, Leonardi C *et al.* Effects of etanercept therapy on fatigue and symptoms of depression in subjects treated for moderate to severe plaque psoriasis for up to 96 weeks. *Br J Dermatol* 2007; **157**:1275–7.
60 Reich K, Segaert S, Van de Kerkhof P *et al.* Once-weekly administration of etanercept 50 mg improves patient-reported outcomes in patients with moderate-to-severe plaque psoriasis. *Dermatology* 2009; **219**:239–49.
61 Papp K, Crowley J, Ortonne JP *et al.* Adalimumab for moderate to severe chronic plaque psoriasis: efficacy and safety of retreatment and disease recurrence following withdrawal from therapy. *Br J Dermatol* 2011; **164**:434–41.
62 Samsa G, Edelman D, Rothman ML *et al.* Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. *Pharmacoeconomics* 1999; **15**:141–55.
63 Cella D, Eton DT, Lai JS, *et al.* Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *J Pain Symptom Manage* 2002; **24**:547–61.
64 Fukuda K, Straus SE, Hickie I *et al.* The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med* 1994; **121**:953–9.
65 Prins JB, van der Meer JW, Bleijenberg G. Chronic fatigue syndrome. *Lancet* 2006; **367**:346–55.
66 Wolfe F, Hawley DJ, Wilson K. The prevalence and meaning of fatigue in rheumatic disease. *J Rheumatol* 1996; **23**:1407–17.
67 Krupp L. Fatigue is intrinsic to multiple sclerosis (MS) and is the most commonly reported symptom of the disease. *Mult Scler* 2006; **12**:367–8.
68 Segal B, Thomas W, Rogers T *et al.* Prevalence, severity, and predictors of fatigue in subjects with primary Sjögren's syndrome. *Arthritis Rheum* 2008; **59**:1780–7.
69 Cleanthous S, Tyagi M, Isenberg DA, Newman SP. What do we know about self-reported fatigue in systemic lupus erythematosus? *Lupus* 2012; **21**:465–76.
70 Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC. Fatigue in multiple sclerosis. *Arch Neurol* 1988; **45**:435–7.
71 Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in breast cancer survivors. *Psychosom Med* 2002; **64**:604–11.
72 Harboe E, Tjensvoll AB, Vefring HK *et al.* Fatigue in primary Sjögren's syndrome – a link to sickness behaviour in animals? *Brain Behav Immun* 2009; **23**:1104–8.
73 Pollard LC, Choy EH, Gonzalez J *et al.* Fatigue in rheumatoid arthritis reflects pain, not disease activity. *Rheumatology (Oxford)* 2006; **45**:885–9.
74 van Hoogmoed D, Fransen J, Bleijenberg G, van Riel P. Physical and psychosocial correlates of severe fatigue in rheumatoid arthritis. *Rheumatology (Oxford)* 2010; **49**:1294–302.
75 Bergman MJ, Shahouri SH, Shaver TS *et al.* Is fatigue an inflammatory variable in rheumatoid arthritis (RA)? Analyses of fatigue in RA, osteoarthritis, and fibromyalgia. *J Rheumatol* 2009; **36**:2788–94.
76 Lee YC, Frits ML, Iannaccone CK *et al.* Subgrouping of patients with rheumatoid arthritis based on pain, fatigue, inflammation, and psychosocial factors. *Arthritis Rheumatol* 2014; **66**:2006–14.
77 Ulus Y, Akyol Y, Tander B *et al.* Sleep quality in fibromyalgia and rheumatoid arthritis: associations with pain, fatigue, depression, and disease activity. *Clin Exp Rheumatol* 2011; **29**(6 Suppl. 69): S92–6.
78 Bower JE. Behavioral symptoms in patients with breast cancer and survivors. *J Clin Oncol* 2008; **26**:768–77.
79 Prue G, Rankin J, Allen J *et al.* Cancer-related fatigue: a critical appraisal. *Eur J Cancer* 2006; **42**:846–63.
80 Hofman M, Ryan JL, Figueroa-Moseley CD *et al.* Cancer-related fatigue: the scale of the problem. *Oncologist* 2007; **12**(Suppl. 1): 4–10.
81 Chaudhuri A, Behan PO. Fatigue in neurological disorders. *Lancet* 2004; **363**:978–88.
82 Pavese N, Metta V, Bose SK *et al.* Fatigue in Parkinson's disease is linked to striatal and limbic serotonergic dysfunction. *Brain* 2010; **133**:3434–43.
83 Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. *Neurology* 2013; **80**:409–16.
84 Arnold LM. Understanding fatigue in major depressive disorder and other medical disorders. *Psychosomatics* 2008; **49**:185–90.
85 Choi ST, Kang JI, Park IH *et al.* Subscale analysis of quality of life in patients with systemic lupus erythematosus: association with depression, fatigue, disease activity and damage. *Clin Exp Rheumatol* 2012; **30**:665–72.

© 2014 The Authors. *British Journal of Dermatology* published by John Wiley & Sons Ltd on behalf of British Association of Dermatologists.

86 Omdal R, Waterloo K, Koldingsnes W *et al.* Fatigue in patients with systemic lupus erythematosus: the psychosocial aspects. *J Rheumatol* 2003; **30**:283–7.

87 Lang UE, Borgwardt S. Molecular mechanisms of depression: perspectives on new treatment strategies. *Cell Physiol Biochem* 2013; **31**:761–77.

88 Vercoulen JH, Swanink CM, Zitman FG *et al.* Randomised, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome. *Lancet* 1996; **347**:858–61.

89 Loftus EV, Feagan BG, Colombel JF *et al.* Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial. *Am J Gastroenterol* 2008; **103**:3132–41.

90 Ertenli I, Ozer S, Kiraz S *et al.* Infliximab, a TNF-α antagonist treatment in patients with ankylosing spondylitis: the impact on depression, anxiety and quality of life level. *Rheumatol Int* 2012; **32**:323–30.

91 Tyring S, Gottlieb A, Papp K *et al.* Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet* 2006; **367**:29–35.

92 Kapsimalis F, Richardson G, Opp MR, Kryger M. Cytokines and normal sleep. *Curr Opin Pulm Med* 2005; **11**:481–4.

93 Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. *Ann Rheum Dis* 2005; **64** (Suppl. 2):ii18–23.

94 Fitch E, Harper E, Skorcheva I *et al.* Pathophysiology of psoriasis: recent advances on IL-23 and Th17 cytokines. *Curr Rheumatol Rep* 2007; **9**:461–7.

95 Meyer N, Paul C, Feneron D *et al.* Psoriasis: an epidemiological evaluation of disease burden in 590 patients. *J Eur Acad Dermatol Venereol* 2010; **24**:1075–82.

96 Evers AW, Lu Y, Duller P *et al.* Common burden of chronic skin diseases? Contributors to psychological distress in adults with psoriasis and atopic dermatitis. *Br J Dermatol* 2005; **152**:1275–81.

97 Wahl A, Loge JH, Wiklund I, Hanestad BR. The burden of psoriasis: a study concerning health-related quality of life among Norwegian adult patients with psoriasis compared with general population norms. *J Am Acad Dermatol* 2000; **43**:803–8.

98 Mease PJ, Gladman DD, Papp KA *et al.* Prevalence of rheumatologist-diagnosed psoriatic arthritis in patients with psoriasis in European/North American dermatology clinics. *J Am Acad Dermatol* 2013; **69**:729–35.

99 Rosen CF, Mussani F, Chandran V *et al.* Patients with psoriatic arthritis have worse quality of life than those with psoriasis alone. *Rheumatology (Oxford)* 2012; **51**:571–6.

100 Ciocon DH, Horn EJ, Kimball AB. Quality of life and treatment satisfaction among patients with psoriasis and psoriatic arthritis and patients with psoriasis only: results of the 2005 Spring US National Psoriasis Foundation Survey. *Am J Clin Dermatol* 2008; **9**:111–17.

101 Krueger GG, Langley RG, Finlay AY *et al.* Patient-reported outcomes of psoriasis improvement with etanercept therapy: results of a randomized phase III trial. *Br J Dermatol* 2005; **153**:1192–9.

102 Reich K, Nestle FO, Papp K *et al.* Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate-to-severe psoriasis: a randomized controlled trial. *Br J Dermatol* 2006; **154**:1161–8.

103 Shikiar R, Heffernan M, Langley RG *et al.* Adalimumab treatment is associated with improvement in health-related quality of life in psoriasis: patient-reported outcomes from a phase II randomized controlled trial. *J Dermatolog Treat* 2007; **18**:25–31.

104 Revicki DA, Willian MK, Menter A *et al.* Impact of adalimumab treatment on patient-reported outcomes: results from a Phase III clinical trial in patients with moderate to severe plaque psoriasis. *J Dermatolog Treat* 2007; **18**:341–50.

105 Feldman SR, Gottlieb AB, Bala M *et al.* Infliximab improves health-related quality of life in the presence of comorbidities among patients with moderate-to-severe psoriasis. *Br J Dermatol* 2008; **159**:704–10.

106 Revicki DA, Menter A, Feldman S *et al.* Adalimumab improves health-related quality of life in patients with moderate to severe plaque psoriasis compared with the United States general population norms: results from a randomized, controlled Phase III study. *Health Qual Life Outcomes* 2008; **6**:75.

107 Dauden E, Griffiths CE, Ortonne JP *et al.* Improvements in patient-reported outcomes in moderate-to-severe psoriasis patients receiving continuous or paused etanercept treatment over 54 weeks: the CRYSTEL study. *J Eur Acad Dermatol Venereol* 2009; **23**:1374–82.

108 Lebwohl M, Papp K, Han C *et al.* Ustekinumab improves health-related quality of life in patients with moderate-to-severe psoriasis: results from the PHOENIX 1 trial. *Br J Dermatol* 2010; **162**:137–46.

109 Nakagawa H, Schenkel B, Kato M *et al.* Impact of ustekinumab on health-related quality of life in Japanese patients with moderate-to-severe plaque psoriasis: results from a randomized, double-blind, placebo-controlled phase 2/3 trial. *J Dermatol* 2012; **39**:761–9.

110 Wolfe F, Michaud K, Pincus T. Preliminary evaluation of a visual analog function scale for use in rheumatoid arthritis. *J Rheumatol* 2005; **32**:1261–6.

111 Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995; **39**:315–25.

112 Belza BL. Comparison of self-reported fatigue in rheumatoid arthritis and controls. *J Rheumatol* 1995; **22**:639–43.

113 Rapp SR, Feldman SR, Exum ML *et al.* Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol* 1999; **41**:401–7.

114 Verhoeven EW, Kraaimaat FW, van de Kerkhof PC *et al.* Prevalence of physical symptoms of itch, pain and fatigue in patients with skin diseases in general practice. *Br J Dermatol* 2007; **156**:1346–9.

115 Jankovic S, Raznatovic M, Marinkovic J *et al.* Health-related quality of life in patients with psoriasis. *J Cutan Med Surg* 2011; **15**:29–36.

© 2014 The Authors. *British Journal of Dermatology* published by John Wiley & Sons Ltd on behalf of British Association of Dermatologists.