



SERIES “SARCOIDOSIS FROM BENCH TO BEDSIDE”
Edited by V. Cottin and J. Müller-Quernheim
Number 2 in this Series

Sarcoidosis-associated fatigue

Marjolein Drent^{*,#}, Elyse E. Lower^{†,+} and Jolanda De Vries[§]

ABSTRACT: Sarcoidosis-associated fatigue is globally recognised as a disabling symptom. Fatigue has been reported in up to 50–70% of sarcoidosis patients, causing impaired quality of life. The aetiology of this troublesome problem remains elusive and is usually multifactorial. Fatigue can be a consequence of treatment itself, including as a complication of corticosteroid therapy. The diagnosis of sarcoidosis-associated fatigue requires an extensive evaluation to identify and treat potentially reversible causes. Granuloma formation and cytokine release may be involved in its aetiology. However, despite adequate sarcoidosis treatment, many patients continue to experience fatigue. Comorbidities associated with sarcoidosis, including depression, anxiety, hypothyroidism and altered sleep patterns, may all contribute to fatigue. Despite an exhaustive search for treatable clinical causes of fatigue, most patients' complaints of fatigue are not correlated with clinical parameters of disease activity. Recent studies have demonstrated the effectiveness of various neurostimulants, including methylphenidate, for the treatment of sarcoidosis-associated fatigue. These and other agents may be useful adjuncts for the treatment of sarcoidosis-associated fatigue. Obviously, there is a need for studies evaluating the causes and new therapeutic options of sarcoidosis-associated fatigue. Psychological interventions should also be examined.

KEYWORDS: Fatigue, Fatigue Assessment Scale, quality of life, sarcoidosis

Sarcoidosis is a disseminated granulomatous disease of unknown aetiology. The clinical manifestations are highly variable and often nonspecific, depending on the intensity of the inflammation and the organ systems affected. Virtually every organ can be involved, but most patients present with pulmonary, ocular or cutaneous involvement. Pulmonary sarcoidosis is the second most common respiratory disease in young adults (<40 yrs of age) after asthma [1–3].

Sarcoidosis patients may present with symptoms directly related to the organ(s) involved. Remission occurs for more than half of the patients within 3 yrs of diagnosis, and within 10 yrs for two-thirds with few or no consequences [4]. Unfortunately, up to one-third of patients have persistent disease, leading to significant impairment of quality of life (QoL) [5]. Apart from lung-related symptoms (e.g. coughing, breathlessness, and dyspnoea on exertion), patients may suffer from a wide spectrum of rather nonspecific disabling symptoms. These

symptoms, such as fatigue, fever, anorexia, arthralgia, muscle pain, general weakness, muscle weakness, exercise limitation and cognitive failure, do not correspond with objective physical evidence of disease [5–9]. Several studies have reported that neither lung function test results nor chest radiographs correlate with these nonspecific health complaints or with QoL [5, 10]. Sarcoidosis-related complaints, including fatigue, may become chronic and affect the patients' QoL even after all other signs of disease activity have disappeared [11–13]. There is a positive association between symptoms of suspected small fibre neuropathy (SFN) and fatigue, as well as dyspnoea and fatigue [11, 14, 15].

Hence, fatigue is a common complaint among sarcoidosis patients [6, 10, 16–18]. Sarcoidosis patients report higher fatigue scores compared with healthy controls [8, 10, 19, 20]. Furthermore, compared with healthy controls, sarcoidosis patients suffer more from fatigue even in the absence of other symptoms [14]. In general, tools currently accepted in clinical practice to detect

AFFILIATIONS

*Dept of Interstitial Lung Diseases, Hospital Gelderse Vallei, Ede,
#Faculty of Health, Medicine and Life Sciences, University of Maastricht, Maastricht,
§CoRPS, Dept of Medical Psychology, Tilburg University, Tilburg, The Netherlands,
†Dept of Medicine, University of Cincinnati, and
*Oncology Hematology Care, Inc., Cincinnati, OH, USA.

CORRESPONDENCE

M. Drent
Faculty of Health, Medicine and Life Sciences
University of Maastricht
UNS 40 room 4.550
PO Box 3100
6202 NC Maastricht
The Netherlands
E-mail: m.drent@maastrichtuniversity.nl

Received:

Jan 06 2012

Accepted after revision:

Feb 24 2012

First published online:

March 22 2012

Previous articles in this series: No. 1: Schlobin OA, Nathan SD. Management of end-stage sarcoidosis: pulmonary hypertension and lung transplantation. *Eur Respir J* 2012; 39: 1521–1534.

For editorial comments see page 14.

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

and monitor fatigue are limited. This review provides an overview of the currently published data on the assessment, prevalence, aetiology and treatment of sarcoidosis-associated fatigue, as well as its impact on patients' QoL.

METHODS

A computerised search of the literature from January 1971 until October 2011 was performed using the search terms "sarcoidosis" and "fatigue". Results were identified in PubMed (n=144), PsycINFO (n=5), the Cochrane Library (n=4) and Web of Science (n=107). Reference lists of relevant studies were checked to identify any additional published research not identified by computerised database searches.

Selection criteria

Studies included for evaluation met the following criteria: 1) the study objective was to describe fatigue in sarcoidosis; 2) the study population consisted of only sarcoidosis patients or included an identifiable and separately analysed subgroup of patients with sarcoidosis; 3) the article was a full report (no case reports, editorials, poster texts, letters or reviews); 4) the study was published in English; and 5) the study was published in peer-reviewed journal.

The described inclusion criteria [21, 22] were applied to the initial 260 results, with 71 identified as duplicates. Based on titles, abstracts and references, 30 articles met the inclusion criteria. Of the articles that were excluded, 14 did not meet criterion 1 and 31 did not meet criterion 2. Criteria 3 and 4 were reasons for excluding 101 and 13 articles, respectively. One article was found through reference list inspection. After full article inspection, 29 articles met our selection criteria and were included in this review [5–11, 13–20, 23–36]. Figure 1 presents a flow chart of the study selection.

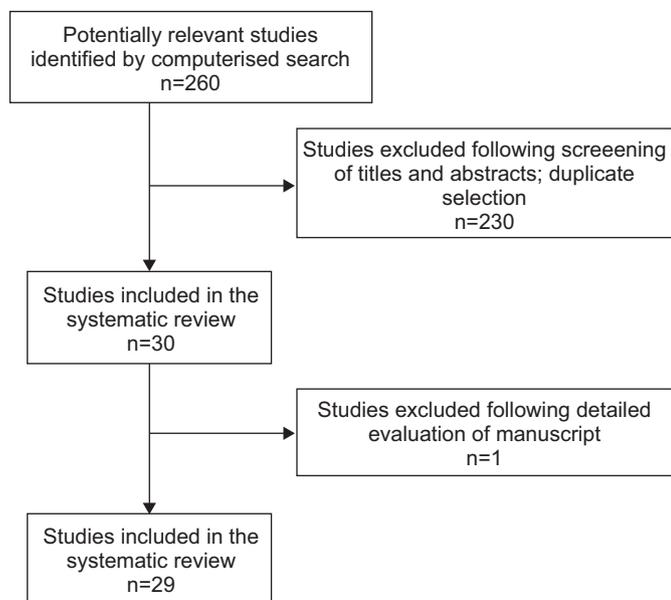


FIGURE 1. Flow chart of included studies.

RESULTS

Fatigue

Currently, no general agreement exists on the definition of fatigue. Fatigue can be seen and measured as a uni- or multidimensional concept. The multidimensional concept of fatigue can be divided into at least two categories: physical and mental [14] or passive and active fatigue [15]. Several studies have reported that neither lung function tests nor chest radiographs correlate with nonspecific health complaints, including fatigue or QoL. Some sarcoidosis patients are debilitated by the symptoms of their disease and are unable to work; others are underemployed and incapable of reaching their full potential due to health-related issues [21]. Individuals affected by the disease usually appear completely healthy, so their symptoms are often not taken seriously by family, friends and healthcare professionals. Consequently, some patients lose their desire and ability to effectively socialise with others, causing relationships and family dynamics to ultimately suffer. These combined factors have an impact on an individual's economic status, interpersonal relationships and family dynamics, and increase their stress levels, and induce depression in patients [21].

Self-reported measures used to assess fatigue

As presented in table 1, a variety of measures can be used to assess fatigue in sarcoidosis patients. Some instruments include only one general indirect fatigue question, such as the Borg score, or only one specific fatigue question, as in the Sarcoidosis Health Questionnaire. Only one instrument, the Fatigue Assessment Scale (FAS), contains 10 specific fatigue questions that have been validated in sarcoidosis patients (table 2). Several studies have confirmed the reliability and validity of the FAS instrument in sarcoidosis [5, 7, 10, 16–18, 25, 27–29, 35]. In addition, the minimal clinical important difference (MCID) score was established and found to be a four-point difference over time [37]. A change in FAS score of four points or more indicates a clinically significant change in fatigue. The FAS score ranges from 10 to 50. Consequently, the percentage of a four-point difference in case of a baseline score of 24 is higher (16.7%) than the percentage of four points change in a patient with a baseline score of 48 (8.3%). Hence, the percentage of the MCID change in FAS score was established more recently. The cut-off value of the percentage-based MCID in the FAS is -10%, which corresponded to a sensitivity of 92% and a specificity of 100% (a personal communication from the authors). As this MCID was only available recently, until now, no studies are published in which the MCID of the FAS were used in analysing the data. Therefore, only the mean scores were compared to evaluate whether there was a significant improvement of fatigue in the studied populations.

Fatigue and QoL

Only seven of the fatigue studies reported a relationship between fatigue and QoL or health status (HS), as shown in table 3 [5, 13, 14, 16, 20, 26, 31]. These studies all had a cross-sectional design. Regardless of the method of assessment for fatigue and QoL or HS, fatigue appeared to be negatively related to QoL and HS in sarcoidosis patients. However, fatigue levels, and not depressive symptoms, appeared to be the best predictor of patients' overall QoL. This indicates that

TABLE 1 Self-report fatigue measurements used in existing sarcoidosis studies and the psychometric properties in sarcoidosis

Measures used to assess fatigue	Reliability in sarcoidosis	Validity in sarcoidosis	Studies using the measures
Borg fatigue score			[20]
CIS		Construct validity examined using one scale [13]	[9, 13]
CRDQ fatigue domain			[20]
FACIT-F			[35]
FAS	Cronbach's α is good [25, 28] Test-retest reliability is good [7, 28] Sensitivity to change appears good [7]	Content validity shows one underlying factor [25, 28] Construct validity is good [16, 17, 28] MCID (four-point change) [37] No floor and ceiling effects [25] Discriminant validity is good [25]	[5, 7, 10, 16–18, 25, 27–29, 31, 35]
Fatigue Scale Interview			[23]
Multidimensional fatigue inventory		Construct validity (examined using a single item) seems good [17]	[6, 15, 24, 33] [8, 17]
SF-36 vitality scale		Construct validity examined using one scale [13]	[13, 34, 36]
Symptom inventory questionnaire			[6, 15, 19, 26, 30]
WHOQOL-100 energy and fatigue facet		Construct validity examined using one scale [19]	[14, 15, 19, 26, 28]

CIS: Checklist Individual Strength; CRDQ: Chronic Respiratory Disease Questionnaire; FACIT-F: Functional Assessment of the Chronic Illness Therapy – Fatigue; FAS: Fatigue Assessment Scale; SF: Short Form; WHOQOL: World Health Organization questionnaire of Quality of Life; MCID: minimal clinically important difference.

although depression plays a role in the reporting of fatigue, the symptom fatigue itself has a more incremental effect on patients' overall QoL [39].

Fatigue and depressive symptoms

American and Dutch studies have emphasised the important role depression plays in sarcoidosis [18, 31, 40]. It has been determined that depressive symptoms are negatively associated with

and affect patients' fatigue scores [11, 14, 15]. In addition, the relationship between fatigue and depressive symptoms parallels the findings of other chronic illness, such as diabetes, chronic obstructive lung disease, cardiac disease and rheumatoid arthritis [41]. Research suggests that the relationship between depressive symptoms and severity of medical illness is bidirectional. Depression may indirectly lead to increased symptoms, because depressive symptoms are associated with poor self-care

TABLE 2 Fatigue Assessment Scale (FAS) with instructions

	Never	Sometimes	Regularly	Often	Always
1) I am bothered by fatigue	1	2	3	4	5
2) I get tired very quickly	1	2	3	4	5
3) I don't do much during the day	1	2	3	4	5
4) I have enough energy for everyday life	1	2	3	4	5
5) Physically, I feel exhausted	1	2	3	4	5
6) I have problems to start things	1	2	3	4	5
7) I have problems to think clearly	1	2	3	4	5
8) I feel no desire to do anything	1	2	3	4	5
9) Mentally, I feel exhausted	1	2	3	4	5
10) When I am doing something, I can concentrate quite well	1	2	3	4	5

Per statement, one out of five answer categories can be chosen, from never to always. 1: never; 2: sometimes (about monthly or less); 3: regularly (about a few times a month); 4: often (about weekly); 5: always (about every day). An answer to each question has to be given, even if the person does not have any complaints at the moment. Scores on questions 4 and 10 should be recoded (1=5, 2=4, 3=3, 4=2, 5=1). Subsequently, the total FAS score can be calculated by summing the scores on all questions (the recoded scores for question 4 and 10). The sum of questions 3 and 6–9 indicates mental fatigue, and the sum of the questions 1, 2, 4, 5 and 10 indicates physical fatigue. The minimal score is 10 the maximal score is 50. Based on large representative samples of the Dutch population, the cut-off score of the FAS is 21, i.e. scores of ≥ 22 are considered to represent substantial fatigue. A change in the FAS score of four points is considered to be clinically relevant (minimal clinically important different) [37]. The FAS has been validated in Croatian, Danish, Dutch, English, French, German, Italian, Japanese, Norwegian, Romanian, Russian and Spanish. A PDF and digital version of the English FAS can be found at the website of the ild care foundation [38]. More information can be provided by the corresponding author. Reproduced and modified from [38] with the permission of the ild care foundation (www.ildcare.eu).

TABLE 3 The relationship between quality of life (QoL) or health status (HS) and fatigue

Study	Sample size	Study design	Questionnaires used	Results
[5]	145 patients	Cross-sectional	Fatigue: FAS QoL: WHOQOL-100	Fatigue was negatively related to all WHOQOL domains and the general facet Females were more tired and had worse QoL on all domains compared with males
[14]	64 patients and 64 matched controls	Cross-sectional	Fatigue: WHOQOL-100 QoL: WHOQOL-100	The energy and fatigue facet was unrelated to the QoL domain on psychological health
[20]	22 patients and 21 matched controls	Cross-sectional	Fatigue: CRDQ fatigue domain HS: SF-36	Fatigue correlated highly with all HS scales
[16]	142 patients	Cross-sectional	Fatigue: FAS HS: SGRQ	Fatigue correlated highly with all HS scales
[26]	150 patients	Cross-sectional	Fatigue: Symptom Inventory Questionnaire QoL: WHOQOL-100	Fatigue was a negative predictor of the QoL domains physical health, psychological health and level of independence
[31]	441 patients	Cross-sectional	Fatigue: FAS QoL: WHOQOL-BREF	Fatigue (together with depressive symptoms) predicted overall QoL (p<0.001)
[13]	75 patients	Cross-sectional	Fatigue: CIS HS: SF-36	Fatigued patients scored lower on all HS scales (all p<0.001)

FAS: Fatigue Assessment Scale; WHOQOL: World Health Organization questionnaire of Quality of Life; CRDQ: Chronic Respiratory Disease Questionnaire; SGRQ: St George's Respiratory Questionnaire; CIS: Checklist Individual Strength; SF: Short Form.

(diet, exercise, cessation of smoking and medication regimens) in patients with chronic diseases. However, physical symptoms and resulting functional impairment caused by complications of medical illness also are likely to pose a burden on the patient's life and provoke depression [41].

Fatigue: role of inflammation and cytokine release

Symptoms such as fatigue can be nonspecific and difficult to objectify. Moreover, an absence of evidence does not mean evidence of absence [7, 12, 13, 15]. Assessment of inflammatory activity in sarcoidosis patients without lung function or radiological deterioration but with unexplained persistent disabling symptoms is an important and often problematic issue. Historically, evaluation of the value of the various available tools for assessment of inflammatory activity has been hampered by the lack of a gold standard. The serological markers used are C-reactive protein, serum angiotensin-converting enzyme, soluble interleukin (IL)-2 receptor and neopterin [4, 15, 42-44].

In the past few years, ¹⁸F-2-fluoro-2-deoxy-D-glucose (¹⁸FDG) positron emission tomography (PET)/computed tomography (CT) has been shown to be a very sensitive technique to assess inflammatory activity in sarcoidosis by detecting and quantifying the degree of inflammatory and granulomatous reactions that occur in the lungs and elsewhere in the body [4, 43, 45-49]. ¹⁸FDG-PET/CT is used more and more in sarcoidosis, and hypermetabolism detected by ¹⁸FDG-PET/CT indicates activity in patients with no other indication of disease activity assessed by other available inflammatory parameters. MOSTARD *et al.* [42] showed that negative serological test results do not exclude the presence of inflammatory activity. Therefore, the added value of ¹⁸FDG-PET/CT for assessment of inflammatory activity is in the group of symptomatic

sarcoidosis patients without serological signs of inflammatory activity. Moreover, in the study by MOSTARD *et al.* [42], the value of whole-body evaluation was demonstrated by the fact that 80% of extrathoracic lesions were found. In that study, five patients with obstructive sleep apnoea (OSA) syndrome who were adequately treated still suffered from disabling symptoms, including fatigue [42]. Hypermetabolism detected by ¹⁸FDG-PET/CT appeared to be present in all these patients, supporting the assumption that inflammatory activity was still present and probably explained the persistent fatigue. In a case series described by KEIJERS *et al.* [48], 12 patients were treated by infliximab. Nine of these patients also suffered from fatigue. All of them showed an improvement on their post-infliximab ¹⁸FDG-PET/CT scan, illustrated by an overall decrease in maximal standardised uptake rate and a reported reduction of fatigue.

Currently, the most widely held view is that chronic inflammatory disorders, including sarcoidosis, cause changes in the central nervous system. Tumour necrosis factor (TNF)-α is increased in the serum of sarcoidosis patients and is related to disease severity. Moreover, TNF-α induces a range of neurological, haematological, metabolic and endocrine changes, and is probably involved in the regulation of sleep [50]. Studies in inflammatory vascular disease suggest that increases in TNF-α, oxidative stress and inflammation-induced changes can alter neurotransmitter metabolism [51, 52] and lead to cognitive impairment. There is evidence that TNF-α regulates synaptic transmission in the brain and that this cytokine is involved in spatial memory impairment in mice [53]. Neuroinflammation with overexpression of cytokines is a characteristic of the brain pathology present in Alzheimer's disease [54]. Recent evidence also suggests that TNF-α may induce the expression of inducible nitric oxide synthase (iNOS). Because overexpression of iNOS was found in the brain of some

Alzheimer's disease patients, antioxidants may be recommended to decrease oxidative damage, leading to disease progression [51, 55]. More recently, the TNF- α inhibitor thalidomide was effective in reducing iNOS/peroxynitrite-related pathology by restraining TNF- α increases without harming the physiological function of iNOS [55]. Involvement of excess TNF- α in the pathogenesis of cognitive impairment and fatigue in patients with sarcoidosis would explain the favourable effect of anti-TNF- α drugs in some studies.

Fatigue and autonomic dysfunction are both dominant symptoms and risk factors for depression [56]. The symptoms may share several neurobiological abnormalities, for example an increase in TNF- α [56]. The relationship between depressive symptoms and fatigue may also be explained by a cytokine imbalance, initiated by an inflammatory immune response in sarcoidosis [9, 41]. The cytokine balance of patients suffering from depression also appears to be disturbed [57].

Sarcoidosis patients treated with immunomodulating drugs exhibited a relationship between fatigue and plasma IL-1 β concentrations [8]. In addition, HEESSEN *et al.* [58] showed that fatigue in multiple sclerosis patients was associated with activation of pro-inflammatory cytokines.

Fatigue in sarcoidosis: multifactorial causes

Fatigue is a global problem experienced by most sarcoidosis patients. Little data are currently available regarding the specific treatment of fatigue associated with sarcoidosis. Because the causes of this symptom are often multifactorial, treatment requires investigation into many reversible and irreversible causes. Initial "reversible" fatigue treatment strategies focus on four areas: metabolic abnormalities, psychosocial conditions, disease-related fatigue and treatment-induced fatigue. Proper identification and treatment of anaemia, diabetes mellitus and thyroid disorders can improve altered QoL secondary to fatigue. Depression, anxiety and stress are closely intertwined with fatigue [27]. Careful assessment and treatment of these underlying triggers are necessary before seeking other fatigue treatment strategies. For many patients, this may include psychological treatment or therapeutic interventions specifically targeted to anxiety, stress and depression.

Sleep disturbances

Secondary organ-related fatigue can occur in many forms, including neurologic manifestations and sleep disturbances. The relationship between fatigue and sleep in sarcoidosis has been studied previously. DRENT *et al.* [59] reported a case in which symptoms of fatigue disappeared after treating sleep apnoea and sarcoidosis. Sleep issues, including OSA and restless leg syndrome, commonly afflict sarcoidosis patients [60, 61]. These disorders are frequently reported in European and US populations. Sleep apnoea is six to eight times more common in the sarcoid population compared to the general population [61]. In addition, in a study by VERBRAECKEN *et al.* [60], OSA, periodic leg movement or restless legs were found in more than half of the sarcoidosis patients. Moreover, sleep disturbances are often related to SFN and autonomic dysfunction, which may, in part, explain the fatigue [60]. However, sleep problems may be caused by anatomical dysfunction as well. For instance, involvement of the tongue, tonsils, infiltration

of the upper airway and larynx can provoke sleep apnoea [62]. In one prospective study of sleep apnoea risk in sarcoidosis patients, increased OSA was identified in male patients along with patients with lupus pernio, upper airway involvement and increased body mass index (BMI). Interestingly, this study revealed no increased risk for OSA in patients receiving corticosteroids, despite the fact that increased BMI often accompanies prednisone usage [61].

It is very important and clinically relevant to differentiate sleep disorders from fatigue symptoms, especially with regard to treatment options. Recognition and treatment of OSA can greatly improve symptoms of fatigue and lethargy. Follow-up studies aiming to identify the most appropriate treatment option(s) for fatigue will require more careful evaluation of sleeping disorders, including sleep questionnaires such as the Epworth Sleepiness Scale, as fatigue appears to be, at least partially, caused by sleep disturbances. Because fatigue and sleep disorders frequently occur in patients with sarcoidosis, future studies should focus on the relationship between autonomic dysfunction, sleep disorders and fatigue in sarcoidosis, in order to include appropriate treatment strategies in the management of sarcoidosis.

Small fibre neuropathy

SFN, a frequently bothersome symptom in a substantial number of sarcoidosis patients, can be linked to fatigue [11, 56]. Although SFN may be difficult to diagnose, its identification can lead to possible targeted treatments, including TNF inhibitors [7, 63] or intravenous immunoglobulin [64].

Patients with high TNF levels have been characterised as having increased fatigue and myalgia. For many patients, successful treatment of active sarcoidosis will also improve the symptoms of fatigue. Some studies suggest that reversal of sarcoid activity with TNF- α inhibitors can be efficacious in eradicating fatigue [7, 63]. Others have demonstrated that some patients on anti-TNF- α therapy still suffer from persistent fatigue, although some improvement has been reported [18, 65]. In a meta-analysis of fatigue in rheumatoid arthritis patients, the use of anti-TNF- α therapy was associated with only a small improvement in fatigue [66].

Drug-induced fatigue

Finally, can the drugs used to treat the granulomatous reaction in sarcoidosis cause fatigue? This remains a controversial area. Systemic corticosteroids frequently cause weight gain, diabetes, hypertension, and sleep disturbances including OSA and insomnia. Although many patients report an initial euphoria with institution of corticosteroid therapy, prolonged usage may actually lead to depression and lethargy [67]. One epidemiological study comparing fatigue in US *versus* European patients reported a negative correlation between fatigue and use of hydroxychloroquine [18]. It remains unclear if the drug hydroxychloroquine successfully treated the fatigue symptoms or whether it was acting as a surrogate marker for less severe disease. Patients receiving hydroxychloroquine tend to have less multiorgan disease, which has been associated with less fatigue. The anti-inflammatory effects of this less toxic drug may more successfully treat fatigue.

Treatment options for sarcoidosis-associated fatigue

Unfortunately, despite careful evaluation and treatment for the reversible metabolic, psychosocial, and organ- and treatment-related causes of fatigue, many patients continue to experience debilitating fatigue. Frequently, successful treatment of active sarcoidosis fails to eradicate the disabling symptoms of continued fatigue [8, 35]. This persistent malady, sarcoidosis-associated fatigue, may require nontargeted, generalised fatigue strategies. Virtually all chronic diseases, including cancer, autoimmune disorders or neurological conditions, have been associated with fatigue. To date, the most frequently employed pharmacological fatigue strategies have focused on the use of neurostimulants, neurostimulant-like drugs and anti-TNF- α drugs (table 4) [7, 47, 71, 72]. These studies were very small and, therefore, are not included in the earlier parts of this review.

Treatment of fatigue with neurostimulants

For treating sarcoidosis-associated fatigue, the original report consisted of an open-label trial of five persistently fatigued chronic sarcoidosis patients treated with methylphenidate hydrochloride [69]. Four out of the five patients self-reported improved fatigue for ≤ 2 yrs. However, this report used no objective measurements of fatigue.

The use of D-methylphenidate (D-MPH) and methylphenidate have been reported to be efficacious in the treatment of fatigue and memory loss in some cancer patients with “chemotherapy brain” [72]. In a large double-blind placebo-controlled trial, it was concluded that D-MPH-treated patients experienced significant fatigue improvement [73]. This effect was observed after 4 weeks of treatment and persisted throughout the 8 weeks of the intervention. For some patients, improved memory was also detected.

In a double-blind placebo-controlled trial of D-MPH for sarcoidosis, study participants received either D-MPH or placebo for 8 weeks followed by a 2-week washout period [35]. These patients were subsequently crossed over to the opposite study arm for an additional 8 weeks of therapy. Most of the 10 chronic sarcoidosis patients in this trial had multiorgan involvement and all patients had persistent fatigue despite adequate sarcoidosis therapy. All patients were receiving concurrent therapy, including systemic corticosteroids in eight patients. By 4 weeks of therapy, significant improvement in fatigue was detected in the D-MPH-treated

group [35]. This statistically significant improvement in fatigue persisted throughout the 8-week treatment period. Based on those data, the approximated mean change scores on the FAS was 4.5 points, indicating a change in fatigue that exceeded the MCID of the FAS [37].

The exact mechanism for improved fatigue in this population remains unclear. These agents have been beneficial for sleep disturbances, such as narcolepsy and aeroplane pilot fatigue disorders. Hence, neurostimulants may relieve fatigue by reversing sleep disorders, including daytime somnolence and sleep apnoea [74–77].

Armodafinil, the R-isomer of modafinil, has been shown to be effective against daytime somnolence [78], and both modafinil and armodafinil have been used to treat fatigue [67, 73, 79]. To better evaluate this possible mechanism of action, a follow-up study was performed using the agent armodafinil in sarcoidosis-associated fatigue patients [70]. In this trial, the underlying sleep disorders were evaluated in all patients with an initial sleep study. A normal sleep study, defined as an apnoea-hypopnoea index < 6 events·h⁻¹, was required for all patients prior to study enrolment. Subsequently, patients were randomised in a double-blind, crossover fashion to receive armodafinil or placebo. A significant improvement in fatigue was detected for those patients receiving armodafinil compared with placebo. Additionally, compared with placebo, armodafinil was associated with an improved mean sleep latency time by approximately 1 min. Although this suggests that the drug was associated with less daytime sleepiness, there was no difference in drug efficacy. In fact, patients with a normal mean sleep latency time of > 8 min reported significantly greater improvement in fatigue compared with those with excessive daytime sleepiness. Overall, the drug was associated with significant improvement in overall symptoms. These studies suggest that neurostimulant drugs can provide effective treatment for some cases of sarcoidosis-associated fatigue. The mechanism of action seems independent of their effectiveness on sleepiness. This improvement in fatigue with armodafinil mirrors that reported for fatigue associated with other chronic disorders, including multiple sclerosis and cancer-associated fatigue.

Treatment of fatigue with TNF- α inhibitors

In sarcoidosis, inflammation results in an increase in TNF- α [4, 80]. Small case series suggest that improvement in fatigue

TABLE 4 Pharmacological treatment of sarcoidosis-associated fatigue

Treatment categories	Specific agents	Comments
Anti-inflammatory therapies for disease		
Antimalarial agents	Hydroxychloroquine	Use of agent associated with less fatigue [18]
Anti-TNF monoclonal antibodies	Infliximab	Case report and series [7, 48, 68]
	Adalimumab	Case series [7, 63]
Neurostimulants	Methylphenidate	Case series [69]
	D-Methylphenidate	Double-blind crossover trial [35]
	Armodafinil	Double-blind crossover trial [70]

TNF: tumour necrosis factor.

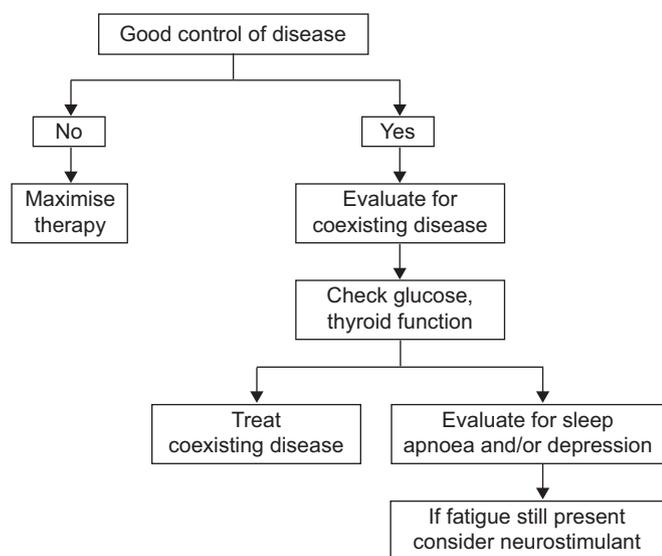


FIGURE 2. A step-wise approach to the management of sarcoidosis-associated fatigue.

can occur with the administration of anti-TNF- α therapies. KEIJERS *et al.* [48] evaluated the effect of infliximab treatment by ^{18}F FDG-PET/CT. In addition to other clinical parameters, fatigue improved in all 12 studied patients. In a subsequent investigation by ELFFERICH *et al.* [7], anti-TNF- α treatment also appeared beneficial in reducing disease activity, cognitive failure and fatigue. In this study, patients who received anti-TNF- α therapy with either infliximab (5 mg·kg $^{-1}$ every 4 weeks, n=31) or adalimumab (40 mg subcutaneously once a week, n=11) experienced substantial improvement in both subjective cognitive functioning and fatigue during the 6-month follow-up. The improvement in FAS scores was significantly higher compared with a reference group of untreated patients as well as patients who received prednisone with or without methotrexate. Based on their data, the approximated mean change scores on the FAS indicated a change in fatigue that exceeded the MCID of the FAS.

More recently, ERCKENS *et al.* [63] demonstrated in 26 refractory chronic noninfectious posterior uveitis sarcoidosis patients that adalimumab successfully improved intraocular inflammation and fatigue. Fatigue, as assessed by FAS, was identified in 21 (81%) out of 26 patients prior to treatment. During treatment with adalimumab, 14 (67%) out of 21 patients became less fatigued, four (19%) remained unchanged and three (14%) reported increase in fatigue. Eight out of these 14 cases reached the MCID (personal communication from the authors).

The evaluation and treatment of sarcoidosis-associated fatigue requires a stepwise evaluation, as shown in figure 2. The initial assessment must include identification of reversible causes of fatigue related to metabolic disorders such as diabetes, anaemia or thyroid dysfunction, psychological conditions such as depression or anxiety, and organ-related conditions such as SFN or sleep disturbances. Additional assessment should include optimal treatment for active inflammation as well as complications from therapeutic drugs such as corticosteroids. Too few interventions studies have been performed to examine the contribution of treatment to the reduction of fatigue scores

in sarcoidosis patients. Even with appropriate identification and treatment of these reversible causes, many sarcoidosis patients may continue to experience persistent fatigue, *i.e.* sarcoidosis-associated fatigue. For these patients, neurostimulant therapy may be helpful. In addition to pharmaceutical treatments, rehabilitation and cognitive behavioural therapy should also be considered as treatment strategies for sarcoidosis-associated fatigue. Cognitive behavioural therapy and graded exercise programmes have proven effective in treating fatigue in patients with chronic fatigue syndrome [81].

In conclusion, sarcoidosis-associated fatigue has a great impact on patients' lives. Although a number of reversible causes of fatigue in sarcoidosis patients are known, the cause of sarcoidosis-associated fatigue is still unknown. Management should focus on appropriate treatment of sarcoidosis and the nature of sarcoidosis-associated fatigue. Successful treatment of active sarcoidosis fails to eradicate the disabling symptoms of continued fatigue. Obviously, longitudinal prospective studies are needed to better define sarcoidosis fatigue, explore its impact on QoL, define aggravating or alleviating factors, and evaluate new potential treatment strategies.

STATEMENT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

The authors wish to thank P. Wijnen (Dept of Clinical Chemistry, Maastricht University Medical Center, Maastricht, The Netherlands) for helping to prepare the manuscript.

REFERENCES

- Morgenthau AS, Iannuzzi MC. Recent advances in sarcoidosis. *Chest* 2011; 139: 174–182.
- Hunninghake GW, Costabel U, Ando M, *et al.* ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. *Sarcoidosis Vasc Diffuse Lung Dis* 1999; 16: 149–173.
- Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *N Engl J Med* 2007; 357: 2153–2165.
- Iannuzzi MC, Fontana JR. Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics. *JAMA* 2011; 305: 391–399.
- Michielsen HJ, Drent M, Peros-Golubicic T, *et al.* Fatigue is associated with quality of life in sarcoidosis patients. *Chest* 2006; 130: 989–994.
- Wirnsberger RM, de Vries J, Wouters EF, *et al.* Clinical presentation of sarcoidosis in the Netherlands an epidemiological study. *Neth J Med* 1998; 53: 53–60.
- Elfferich MD, Nelemans PJ, Ponds RW, *et al.* Everyday cognitive failure in sarcoidosis: the prevalence and the effect of anti-TNF- α treatment. *Respiration* 2010; 80: 212–219.
- Baydur A, Alavy B, Nawathe A, *et al.* Fatigue and plasma cytokine concentrations at rest and during exercise in patients with sarcoidosis. *Clin Respir J* 2011; 5: 156–164.
- Korenromp IH, Grutters JC, van den Bosch JM, *et al.* Reduced Th2 cytokine production by sarcoidosis patients in clinical remission with chronic fatigue. *Brain Behav Immun* 2011; 25: 1498–1502.
- Marcellis RG, Lenssen AF, Elfferich MD, *et al.* Exercise capacity, muscle strength and fatigue in sarcoidosis. *Eur Respir J* 2011; 38: 628–634.
- de Kleijn WP, Drent M, Vermunt JK, *et al.* Types of fatigue in sarcoidosis patients. *J Psychosom Res* 2011; 71: 416–422.
- Sharma OP. Fatigue and sarcoidosis. *Eur Respir J* 1999; 13: 713–714.

- 13 Korenromp IH, Heijnen CJ, Vogels OJ, *et al.* Characterization of chronic fatigue in patients with sarcoidosis in clinical remission. *Chest* 2011; 140: 441–447.
- 14 Wirnsberger RM, de Vries J, Breteler MH, *et al.* Evaluation of quality of life in sarcoidosis patients. *Respir Med* 1998; 92: 750–756.
- 15 Drent M, Wirnsberger RM, de Vries J, *et al.* Association of fatigue with an acute phase response in sarcoidosis. *Eur Respir J* 1999; 13: 718–722.
- 16 Baughman RP, Sparkman BK, Lower EE. Six-minute walk test and health status assessment in sarcoidosis. *Chest* 2007; 132: 207–213.
- 17 Hinz A, Fleischer M, Braehler E, *et al.* Fatigue in patients with sarcoidosis, compared with the general population. *Gen Hosp Psychiatry* 2011; 33: 462–468.
- 18 de Kleijn WP, Elfferich MD, De Vries J, *et al.* Fatigue in sarcoidosis: American versus Dutch patients. *Sarcoidosis Vasc Diffuse Lung Dis* 2009; 26: 92–97.
- 19 Hoitsma E, De Vries J, van Santen-Hoeufft M, *et al.* Impact of pain in a Dutch sarcoidosis patient population. *Sarcoidosis Vasc Diffuse Lung Dis* 2003; 20: 33–39.
- 20 Spruijt MA, Thomeer MJ, Gosselink R, *et al.* Skeletal muscle weakness in patients with sarcoidosis and its relationship with exercise intolerance and reduced health status. *Thorax* 2005; 60: 32–38.
- 21 De Vries J, Drent M. Quality of life and health status in sarcoidosis: a review of the literature. *Clin Chest Med* 2008; 29: 525–532.
- 22 Den Oudsten BL, Van Heck GL, De Vries J. Quality of life and related concepts in Parkinson's disease: a systematic review. *Mov Disord* 2007; 22: 1528–1537.
- 23 Gvozdenovic BS, Mihailovic-Vucinic V, Ilic-Dudvarski A, *et al.* Differences in symptom severity and health status impairment between patients with pulmonary and pulmonary plus extrapulmonary sarcoidosis. *Respir Med* 2008; 102: 1636–1642.
- 24 Wirnsberger RM, Drent M, Hekelaar N, *et al.* Relationship between respiratory muscle function and quality of life in sarcoidosis. *Eur Respir J* 1997; 10: 1450–1455.
- 25 Michielsen HJ, De Vries J, Drent M, *et al.* Psychometric qualities of the Fatigue Assessment Scale in Croatian sarcoidosis patients. *Sarcoidosis Vasc Diffuse Lung Dis* 2005; 22: 133–138.
- 26 Michielsen HJ, Peros-Golubcic T, Drent M, *et al.* Relationship between symptoms and quality of life in a sarcoidosis population. *Respiration* 2007; 74: 401–405.
- 27 De Vries J, Drent M. Relationship between perceived stress and sarcoidosis in a Dutch patient population. *Sarcoidosis Vasc Diffuse Lung Dis* 2004; 21: 57–63.
- 28 De Vries J, Michielsen H, Van Heck GL, *et al.* Measuring fatigue in sarcoidosis: the Fatigue Assessment Scale (FAS). *Br J Health Psychol* 2004; 9: 279–291.
- 29 De Vries J, Rothkrantz-Kos S, van Diejen-Visser MP, *et al.* The relationship between fatigue and clinical parameters in pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2004; 21: 127–136.
- 30 De Vries J, Van Heck GL, Drent M. Gender differences in sarcoidosis: symptoms, quality of life, and medical consumption. *Women Health* 1999; 30: 99–114.
- 31 Elfferich MD, De Vries J, Drent M. Type D or “distressed” personality in sarcoidosis and idiopathic pulmonary fibrosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2011; 28: 65–71.
- 32 Drent M, Wirnsberger RM, Breteler MH, *et al.* Quality of life and depressive symptoms in patients suffering from sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 1998; 15: 59–66.
- 33 Wirnsberger RM, De Vries J, Jansen TL, *et al.* Impairment of quality of life: rheumatoid arthritis versus sarcoidosis. *Neth J Med* 1999; 54: 86–95.
- 34 Spruijt MA, Thomeer MJ, Gosselink R, *et al.* Hypogonadism in male outpatients with sarcoidosis. *Respir Med* 2007; 101: 2502–2510.
- 35 Lower EE, Harman S, Baughman RP. Double-blind, randomized trial of dexamethylphenidate hydrochloride for the treatment of sarcoidosis-associated fatigue. *Chest* 2008; 133: 1189–1195.
- 36 Brancaleone P, Perez T, Robin S, *et al.* Clinical impact of inspiratory muscle impairment in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2004; 21: 219–227.
- 37 de Kleijn WP, De Vries J, Wijnen PA, *et al.* Minimal (clinically) important differences for the Fatigue Assessment Scale in sarcoidosis. *Respir Med* 2011; 105: 1388–1395.
- 38 Ild care foundation. Questionnaires. www.ildcare.nl/index.php?id=100
- 39 de Kleijn WP, De Vries J, Lower EE, *et al.* Fatigue in sarcoidosis: a systematic review. *Curr Opin Pulm Med* 2009; 15: 499–506.
- 40 Chang B, Steimel J, Moller DR, *et al.* Depression in sarcoidosis. *Am J Respir Crit Care Med* 2001; 163: 329–334.
- 41 Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *Gen Hosp Psychiatry* 2007; 29: 147–155.
- 42 Mostard RL, Voo S, van Kroonenburgh MJ, *et al.* Inflammatory activity assessment by F18 FDG-PET/CT in persistent symptomatic sarcoidosis. *Respir Med* 2011; 105: 1917–1924.
- 43 Rothkrantz-Kos S, van Diejen-Visser MP, Mulder PG, *et al.* Potential usefulness of inflammatory markers to monitor respiratory functional impairment in sarcoidosis. *Clin Chem* 2003; 49: 1510–1517.
- 44 Ziegenhagen MW, Rothe ME, Schlaak M, *et al.* Bronchoalveolar and serological parameters reflecting the severity of sarcoidosis. *Eur Respir J* 2003; 21: 407–413.
- 45 Keijsers RG, Verzijlbergen FJ, Oyen WJ, *et al.* ¹⁸F-FDG PET, genotype-corrected ACE and sIL-2R in newly diagnosed sarcoidosis. *Eur J Nucl Med Mol Imaging* 2009; 36: 1131–1137.
- 46 Teirstein AS, Machac J, Almeida O, *et al.* Results of 188 whole-body fluorodeoxyglucose positron emission tomography scans in 137 patients with sarcoidosis. *Chest* 2007; 132: 1949–1953.
- 47 Braun JJ, Kessler R, Constantinesco A, *et al.* ¹⁸F-FDG PET/CT in sarcoidosis management: review and report of 20 cases. *Eur J Nucl Med Mol Imaging* 2008; 35: 1537–1543.
- 48 Keijsers RG, Verzijlbergen FJ, van Diepen DM, *et al.* ¹⁸F-FDG PET in sarcoidosis: an observational study in 12 patients treated with infliximab. *Sarcoidosis Vasc Diffuse Lung Dis* 2008; 25: 143–149.
- 49 Keijsers RG, Verzijlbergen EJ, van den Bosch JM, *et al.* ¹⁸F-FDG PET as a predictor of pulmonary function in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2011; 28: 123–129.
- 50 Darko DF, Miller JC, Gallen C, *et al.* Sleep electroencephalogram delta-frequency amplitude, night plasma levels of tumor necrosis factor α , and human immunodeficiency virus infection. *Proc Natl Acad Sci USA* 1995; 92: 12080–12084.
- 51 McAfoose J, Baune BT. Evidence for a cytokine model of cognitive function. *Neurosci Biobehav Rev* 2009; 33: 355–366.
- 52 Hoitsma E, Faber CG, Drent M, *et al.* Neurosarcoidosis: a clinical dilemma. *Lancet Neurol* 2004; 3: 397–407.
- 53 Baune BT, Wiede F, Braun A, *et al.* Cognitive dysfunction in mice deficient for TNF- α and its receptors. *Am J Med Genet B Neuropsychiatr Genet* 2008; 147B: 1056–1064.
- 54 Tobinick EL, Gross H. Rapid cognitive improvement in Alzheimer's disease following perispinal etanercept administration. *J Neuroinflammation* 2008; 5: 2.
- 55 Alkam T, Nitta A, Mizoguchi H, *et al.* Restraining tumor necrosis factor- α by thalidomide prevents the amyloid β -induced impairment of recognition memory in mice. *Behav Brain Res* 2008; 189: 100–106.
- 56 Freeman R, Komaroff AL. Does the chronic fatigue syndrome involve the autonomic nervous system? *Am J Med* 1997; 102: 357–364.
- 57 Kim YK, Na KS, Shin KH, *et al.* Cytokine imbalance in the pathophysiology of major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; 31: 1044–1053.
- 58 Heesen C, Nawrath L, Reich C, *et al.* Fatigue in multiple sclerosis: an example of cytokine mediated sickness behaviour? *J Neurol Neurosurg Psychiatry* 2006; 77: 34–39.

- 59 Drent M, Verbraecken J, van der Grinten C, *et al.* Fatigue associated with obstructive sleep apnea in a patient with sarcoidosis. *Respiration* 2000; 67: 337–340.
- 60 Verbraecken J, Hoitsma E, van der Grinten CP, *et al.* Sleep disturbances associated with periodic leg movements in chronic sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2004; 21: 137–146.
- 61 Turner GA, Lower EE, Corser BC, *et al.* Sleep apnea in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 1997; 14: 61–64.
- 62 Abad VC, Sarinas PS, Guilleminault C. Sleep and rheumatologic disorders. *Sleep Med Rev* 2008; 12: 211–228.
- 63 Erckens RJ, Mostard RL, Wijnen PA, *et al.* Adalimumab successful in sarcoidosis patients with refractory chronic non-infectious uveitis. *Graefes Arch Clin Exp Ophthalmol* 2012; 250: 713–720.
- 64 Parambil JG, Tavee JO, Zhou L, *et al.* Efficacy of intravenous immunoglobulin for small fiber neuropathy associated with sarcoidosis. *Respir Med* 2011; 105: 101–105.
- 65 Baughman RP, Lower EE. Six-minute walk test in managing and monitoring sarcoidosis patients. *Curr Opin Pulm Med* 2007; 13: 439–444.
- 66 Chauffier K, Salliot C, Berenbaum F, *et al.* Effect of biotherapies on fatigue in rheumatoid arthritis: a systematic review of the literature and meta-analysis. *Rheumatology (Oxford)* 2012; 51: 60–68.
- 67 Baughman RP, Iannuzzi MC, Lower EE, *et al.* Use of fluticasone in acute symptomatic pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2002; 19: 198–204.
- 68 Hoitsma E, Faber CG, van Santen-Hoeufft M, *et al.* Improvement of small fiber neuropathy in a sarcoidosis patient after treatment with infliximab. *Sarcoidosis Vasc Diffuse Lung Dis* 2006; 23: 73–77.
- 69 Wagner MT, Marion SD, Judson MA. The effects of fatigue and treatment with methylphenidate on sustained attention in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2005; 22: 235.
- 70 Baughman RP, Malhorta A, Surdulescu V, *et al.* Armodafinil (R-modafinil) for fatigue in sarcoidosis: not just for treating hypersomnolence. *Chest* 2009; 136: 128s.
- 71 Brown JN, Howard CA, Kemp DW. Modafinil for the treatment of multiple sclerosis-related fatigue. *Ann Pharmacother* 2010; 44: 1098–1103.
- 72 Minton O, Richardson A, Sharpe M, *et al.* Drug therapy for the management of cancer-related fatigue. *Cochrane Database Syst Rev* 2010; 7: CD006704.
- 73 Lower EE, Fleishman S, Cooper A, *et al.* Efficacy of dexmethylphenidate for the treatment of fatigue after cancer chemotherapy: a randomized clinical trial. *J Pain Symptom Manage* 2009; 38: 650–662.
- 74 Boulos MI, Murray BJ. Current evaluation and management of excessive daytime sleepiness. *Can J Neurol Sci* 2010; 37: 167–176.
- 75 Golicki D, Bala MM, Niewada M, *et al.* Modafinil for narcolepsy: systematic review and meta-analysis. *Med Sci Monit* 2010; 16: RA177–186.
- 76 Hirshkowitz M, Black JE, Wesnes K, *et al.* Adjunct armodafinil improves wakefulness and memory in obstructive sleep apnea/hypopnea syndrome. *Respir Med* 2007; 101: 616–627.
- 77 Roth T, Rippon GA, Arora S. Armodafinil improves wakefulness and long-term episodic memory in nCPAP-adherent patients with excessive sleepiness associated with obstructive sleep apnea. *Sleep Breath* 2008; 12: 53–62.
- 78 Bogan RK. Armodafinil in the treatment of excessive sleepiness. *Expert Opin Pharmacother* 2010; 11: 993–1002.
- 79 Czeisler CA, Walsh JK, Wesnes KA, *et al.* Armodafinil for treatment of excessive sleepiness associated with shift work disorder: a randomized controlled study. *Mayo Clin Proc* 2009; 84: 958–972.
- 80 Baughman RP, Lower EE, Drent M. Inhibitors of tumor necrosis factor (TNF) in sarcoidosis: who, what, and how to use them. *Sarcoidosis Vasc Diffuse Lung Dis* 2008; 25: 76–89.
- 81 White PD, Goldsmith KA, Johnson AL, *et al.* Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet* 2011; 377: 823–836.