Managing fatigue in patients with interstitial lung disease

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ABSTRACT

Fatigue is one of the most burdensome symptoms in interstitial lung disease (ILD), and can have a major impact on quality of life of patients, social interactions and work capacity. The etiology of fatigue is complex, and it is caused or aggravated by a combination of different predisposing, precipitating and perpetuating factors. There is no uniform definition of fatigue, but it is often divided in a physical and mental component. Several validated questionnaires can be used for structural assessment of fatigue in daily care. Although the high burden of fatigue in ILD is increasingly recognized, studies investigating pharmacological and non-pharmacological treatment options are scarce. As fatigue in ILD is often a multifactorial problem, therapeutic interventions should ideally be aimed at different domains. One of the first steps is to optimize treatment of the underlying disease. Subsequently, treatable causes of fatigue should be identified and treated. Recently, an increasing number of studies showed that supportive measures have the potential to improve fatigue. However, evidence-based treatment guidelines are lacking, and more research is highly needed in this field. In clinical practice, a comprehensive, multidisciplinary, and individually-tailored approach seems best fit to optimize treatment of fatigue in ILDs.

INTRODUCTION

Interstitial lung disease (ILD) is a broad term for a group of more than 200 rare lung diseases. Some of these diseases are mainly inflammatory, while others are more fibrotic from the start and many are a combination of both. This diversity in underlying pathobiology is also reflected in the variable clinical disease behavior: some ILDs are reversible, some have the potential to stabilize, and some have a progressive fatal course (1). ILDs often have a major impact on patients' quality of life (QOL), daily living, work capacity, and social interactions (2). Most frequently reported symptoms are cough, dyspnea, and fatigue (3-5). Although the impact of fatigue is widely acknowledged, there is limited information about the etiology and management of fatigue in ILDs. Most studies are conducted in patients with sarcoidosis, and, more recently, some small studies have been published in other ILDs. In this review, we will give an overview of the most recent insights of fatigue in ILD.

Case report

A 37-year old man presented at our outpatient clinic with sarcoidosis. His most burdensome symptoms were a dry cough and fatigue. The x-ray showed bilateral lymphadenopathy, and discrete nodular abnormalities in the upper lobes. Pulmonary function tests were normal. Blood testing showed normal blood count, liver and kidney tests. Calcium and thyroid-stimulating hormone levels were also normal, while the soluble interleukin 2 receptor (sIL-2R) level was slightly elevated. Additional examination revealed obstructive sleep apnea (OSA), for which he was successfully treated with continuous positive airway pressure (CPAP), resulting in his apnea-hypopnea index (AHI) becoming normalized. However, fatigue did not improve. On follow up, his x-ray spontaneously improved, pulmonary function tests remained normal, and his sIL-2R normalized. Consultation at the cardiologist revealed no abnormalities. Subsequently, treatment with methylphenidate was initiated without success. Considering the major negative impact of fatigue on his quality of life, we referred him to a psychologist for cognitive behavioral therapy.

Prevalence of fatigue in ILD

In the general population, fatigue is reported in 5-20% (6). Although fatigue is often reported as a common symptom in ILD, data about prevalence in different ILDs are scarce (**Figure 1**). In idiopathic pulmonary fibrosis (IPF), fatigue is reported in up to 95% of patients (4, 7). In the European IPF registry, prevalence of fatigue was similar for IPF patients (69.2%) compared with non-IPF ILDs (70.6%). In systemic sclerosis studies, fatigue was present in up to 89% of the patients (8). In chronic hypersensitivity pneumonitis, fatigue has been reported in up to 87% of patients (9). A recent multinational survey

showed that fatigue was present in 90% of patients with sarcoidosis, with up to 48% of patients mentioning extreme fatigue (5). Fatigue mostly occurs at disease onset and during the active phase of sarcoidosis. Nevertheless, even up to 56% of the patients with complete remission report fatigue (10). The prevalence of fatigue in different ILDs is difficult to compare, because different questionnaires were used. It also depends on whether fatigue is patient- or physician-reported. For instance, in a sarcoidosis registry study physicians only reported fatigue in 30% of the patients, which is much lower than patient-reported fatigue in other studies (5, 11). This emphasizes the importance of regularly asking patients whether fatigue is present.

Etiology of fatigue in ILD

One of the complicating factors in studying fatigue is that there is no uniform definition of fatigue, although it is often divided into a physical and a mental component (6, 12). Mental fatigue (perceived fatigability) can be described as a subjective symptom of malaise, tiredness, lack of energy, and aversion to activity (6, 12, 13). Physical fatigue (performance fatigability) refers to impaired physical performance (6, 12). The etiology of fatigue is poorly understood; however, physiological, psychological, and behavioral factors seem to play a role in the onset and persistence of fatigue (6, 13). In most sarcoidosis studies fatigue is poorly correlated with clinical parameters. However, in IPF and systemic sclerosis, there seems to be an association with disease severity (7, 14-16). Many uncertainties still exist about the etiology of fatigue, which is likely not ILD specific.

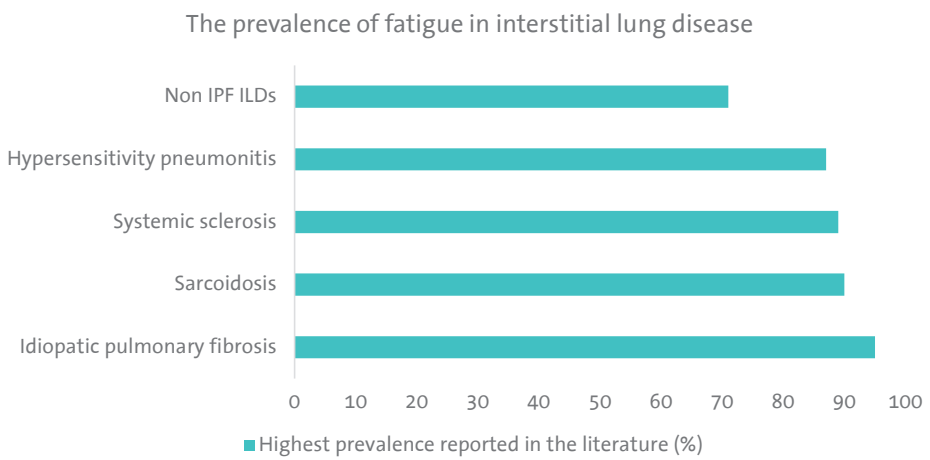

Figure 1. Reported prevalence of fatigue in interstitial lung diseases.

Fatigue is a prevalent symptom in many chronic disorders (17). A recent study demonstrated that only 11% of the variation in fatigue could be explained by the specific diagnosis. In this study, fatigue was mainly explained by transdiagnostic factors, such as reduced motivation, pain, limitations in physical functioning, concentration problems, reduced activity levels, poor sleep quality, and the ability to cope with fatigue (17).

From other areas outside ILD, we have learned that factors influencing fatigue can be divided into predisposing factors, precipitating factors, and perpetuating factors (6, 13). For a large part, many of these factors also hold true for ILD (**Figure 2**). Patients with predisposing factors such as biological vulnerability, vulnerable personality, and

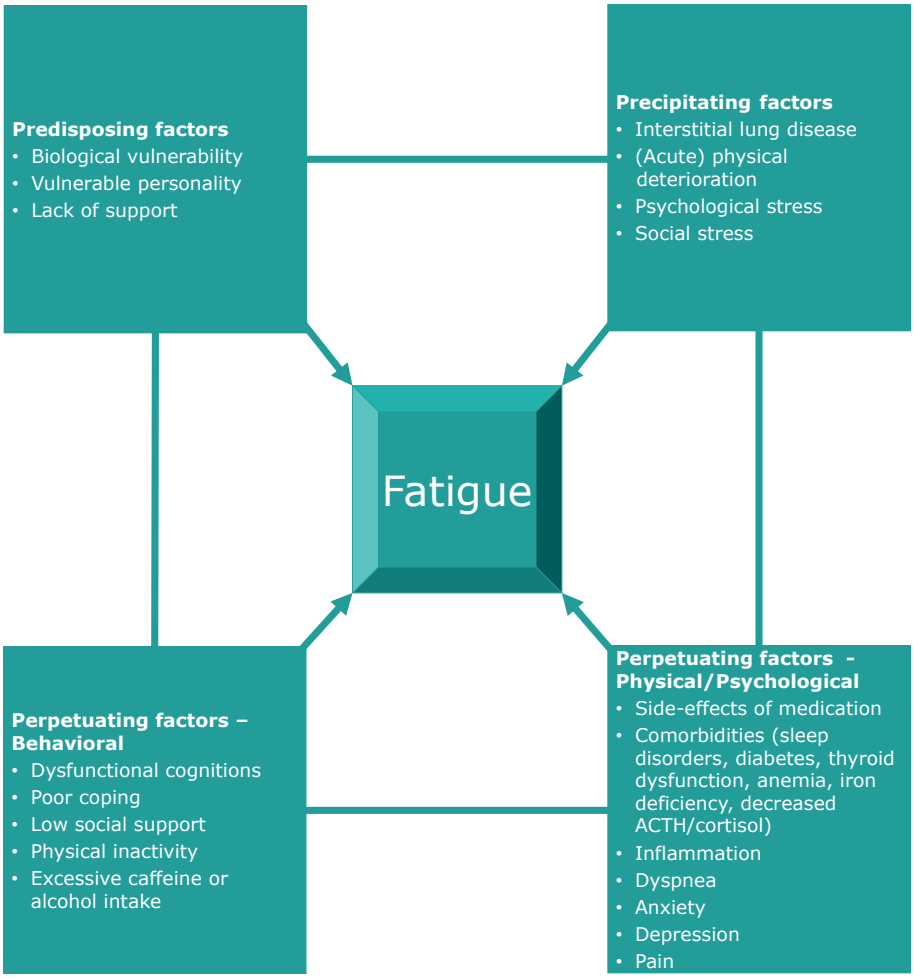

Figure 2. Predisposing, precipitating and perpetuating factors that can cause or aggravate fatigue in ILDs. Most of these factors are interrelated, and some are related in a bidirectional way.

lack of support are at increased risk of developing fatigue (6, 18). In different forms of ILD, physical deterioration, psychological stress, and social stress have been described as precipitating factors that can cause fatigue (2, 7, 8, 16). Furthermore, there is a wide range of physical, psychological, and behavioral factors that may further perpetuate fatigue and are described in more detail below.

Perpetuating factors - physical and psychological factors

Poor sleep quality is reported more frequently in ILD patients as in the general population (16, 19, 20). Sleep architecture is often disrupted, with a decrease of rapid eye movement sleep, increase of sleep fragmentation, and more nocturnal desaturations compared with the general population (20, 21). In a study on sleep quality in 15 IPF patients, a significant correlation was found between nocturnal saturation and fatigue scores (22). Whether nocturnal oxygen suppletion has an effect on sleep quality and fatigue has not yet been studied. Other ILD-related factors that may alter the sleep architecture are cough, periodic limb movement, restless legs syndrome and the side-effects of medication such as corticosteroids (19, 20). Another reason for fatigue may be OSA, with a reported prevalence of up to 88% in ILD (20, 21). The high prevalence of OSA could be partly explained by comorbidities, such as obesity or upper airway pathologies. However, one study showed that even when these comorbidities were excluded, OSA was found in 68% of the ILD patients (82.3% in IPF, 66.6% in sarcoidosis, and 55.5% in systemic sclerosis). Another explanation proposed for the high prevalence of OSA, is the upper airway collapse caused by the restrictive lung disease (20).

It has been suggested that low-grade inflammation may play a role in fatigue; however, not much data for this exist in ILD. A study in patients with sarcoidosis in clinical remission demonstrated that a decrease in Th2 cytokine production was associated with fatigue (23). However, most studies have not found a relation between serological markers, such as angiotensin-converting enzyme, sIL-2R and C-reactive protein, and fatigue (24). Furthermore, fatigue often persists in sarcoidosis patients who are in clinical remission and have no signs of active inflammatory response (10).

Medication is another factor that may cause or aggravate fatigue. Different studies have shown that corticosteroids are associated with fatigue and impaired QoL in sarcoidosis (25). As fatigue is a registered common side-effect of corticosteroids, this may also play a role in other ILDs. Overall, corticosteroids often lead to side-effects such as weight gain, sleep disturbance, psychological disturbance and diabetes mellitus, which are also independently associated with fatigue (20, 24). Current treatment of IPF consists of the anti-fibrotic drugs nintedanib and pirfenidone (26). Fatigue is one of the registered side-effects of pirfenidone (26). Pooled data of the pirfenidone trials showed fatigue occurred

as an adverse event in 26% of the pirfenidone group and 19% of the placebo group (27). In an observational study on the long-term safety of pirfenidone in IPF, fatigue was reported as one of the most common adverse drug reactions in 18.5% of patients (28).

Other comorbidities that are associated with fatigue are diabetes mellitus, thyroid dysfunction, anemia, iron deficiency, and decreased ACTH/cortisol levels (2, 24, 29). Evaluation of the presence of these comorbidities is important, as many are found to be more prevalent in ILDs and may not only impact fatigue but also influence the disease course. For instance, in patients with IPF, hypothyroidism and diabetes mellitus are more prevalent and are also associated with worse prognosis (16, 29-31). Some small observational studies have found an association between physical activity, measured with wrist worn activity trackers, and fatigue in patients with ILD (10, 32, 33). Patients who were less active seemed to be more tired. The association between activity and fatigue seemed stronger in patients with IPF, than in patients with sarcoidosis(32, 33). Most patients with IPF report fatigue as physical exhaustion, while patients with sarcoidosis mainly report mental fatigue (7). This may explain why fatigue is more strongly correlated with physical activity in IPF than in sarcoidosis. Other physical factors associated with fatigue in ILD are dyspnea, muscle strength, and pain (10, 13, 15).

Anxiety, depressive symptoms, memory loss and concentration problems (cognitive failure) are related to fatigue in a bidirectional way (34). Psychological symptoms are not only more prevalent in ILDs but also in other chronic diseases (7, 8, 16, 17). Uncertainty about prognosis, and a decrease in social and work participation are some of the factors that lead to increased stress and anxiety in ILD (2, 35). In patients with (self-reported) cognitive impairment, normal daily tasks require more cognitive effort, which in turn might lead to higher fatigue levels (34). In sarcoidosis, small fiber neuropathy is frequently reported and strongly associated with fatigue (5, 34).

Perpetuating factors - Behavioral

In general, behavioral factors, such as dysfunctional cognitions, poor coping, inactivity, excessive caffeine or alcohol intake, and low social support, can perpetuate fatigue (13). These factors have not been specifically evaluated in ILD in relation to fatigue. However, some of the abovementioned factors could potentially be managed by simple interventions and support from a social worker or psychologist. Therefore, we believe that behavioral factors should not be overlooked in the assessment and treatment of fatigue in ILD.

The impact of fatigue

Fatigue has a huge impact on many aspects of the lives of patients including social relationships, work participation, and quality of life. Many patients consider fatigue as a very burdensome symptom (5, 16). The impact of fatigue may be difficult to understand for family, friends, employers and healthcare professionals because it is a nonspecific symptom and patients often look completely healthy. Consequently, some patients feel that they are not taken seriously, which may lead to further social isolation (2, 6, 34). Fatigue has been reported as an important negative predictor of QOL in ILD patients and was found to be associated with depression and anxiety, both in patients with sarcoidosis as well as with other ILDs (16, 34). Furthermore, fatigue is associated with decreased work participation, loss of income, and social isolation (36-38). In turn, a low income has also been associated with the development of sarcoidosis-related comorbidities, such as fatigue (39). In a study on work performance in sarcoidosis, 43% of 755 patients underwent disability evaluation. In these patients, fatigue levels were significantly higher than in the group who had not undergone work capacity assessments.

Measurement of fatigue

Although highly prevalent, fatigue is often not structurally assessed in patients with ILD. Evaluating fatigue can be challenging due to the different determinants of fatigue and the lack of a uniform approach(12). Obviously, active evaluation of fatigue, and other burdensome symptoms, should take place during every visit. Extensive history taking is needed to assess the severity and impact of fatigue on patients' lives, and to identify possible perpetuating factors. In addition to this, different questionnaires can be used for a more structured evaluation of fatigue. The fatigue assessment scale (FAS) and Sarcoidosis Assessment Tool (SAT) fatigue subscale are developed to asses fatigue in sarcoidosis patients. The FAS is most commonly used, also in other ILDs. It consists of ten questions on a 5-point response scale; five questions about physical fatigue and five questions about mental fatigue. The total score ranges from 10-50 points; a score of ≥ 22 points indicates fatigue and ≥ 34 points severe fatigue. The minimal clinical importance difference is 4 points (40). The SAT fatigue subscale consist of five questions and is incorporated in a QOL questionnaire. Other questionnaires that have been used to measure fatigue in ILD are the Functional assessment of chronic illness Therapy-Fatigue (FACIT-F) and the Patient Reported Outcomes Measurement Information Systems (PROMIS) Fatigue Instrument (PFI) (41). These questionnaires may be used to quantify fatigue in clinical trials, but also to assess the effect of treatment for individual patients in clinical practice.

Treatment of fatigue in ILD

Even though the high burden of fatigue in ILD is well recognized, studies investigating treatment options are limited. As fatigue in ILD is often a multidimensional problem, therapeutic interventions should ideally be aimed at the different domains involved. **Figure 3** shows a decision making flowchart on how to handle fatigue in ILD. One of the first steps is to optimize treatment of the underlying disease, and to exclude that fatigue is a side-effect of prescribed medication. The side-effects of corticosteroid use, especially, should be thoroughly monitored, and the prescribed dosage should be regularly re-assessed and down-titrated if possible. Subsequently, treatable causes of fatigue should be excluded. As mentioned before, one of the treatable causes of fatigue in ILD is OSA. Two studies in IPF concluded that effective CPAP treatment improved daily living activities, quality of sleep, QOL, and daytime fatigue (21, 42). Currently, a trial is ongoing to assess the prevalence and the effect of CPAP treatment in sarcoidosis patients with OSA (NCT03926832). Comorbidities, such as hypothyroidism, should be optimally treated, although no studies have reported on the effect of treatment of comorbidities on fatigue (30). In patients with depression, anxiety or stress referral to a psychologist could be considered. As a high symptom burden of the underlying disease may also directly or indirectly lead to fatigue, treatment should also be directed at symptom relief. At the moment, a randomized controlled trial is assessing the effect of advancing symptom alleviation with palliative treatment (ADAPT) in ILD. In this study, the intervention group is supported by a nurse and social worker with the aim of relieving burdensome symptoms, such as fatigue (NCT02713347).

When all systemic treatable causes have been excluded, the focus should be on the other domains. As far as possible, behavioral, precipitating, and perpetuating factors should be identified and, where possible, targeted. There is increasing evidence that exercise therapy or pulmonary rehabilitation (PR) could be beneficial in ILD patients with fatigue. PR is a comprehensive intervention consisting of exercise training, education and self-management strategies (43). One study showed a positive effect of a 6-week PR program on fatigue in IPF (43). The treatment guideline of IPF also recommends PR to alleviate symptoms (26). A randomized trial in patients with different ILDs demonstrated that an 8-week supervised exercise program improved fatigue scores, exercise capacity and QOL (44). Similar positive results were found in sarcoidosis studies (45). Next to pulmonary rehabilitation, cognitive behavioral therapy has been proposed as a potential treatment option for patients with sarcoidosis-associated fatigue (2). A pilot study in sarcoidosis showed that a 45-minute mindfulness-based workshop improved fatigue and other symptom scores directly after the intervention (46). Long-term effects of this mindfulness workshop have not yet been evaluated. At the moment, a randomized controlled study to evaluate the effects of a 12-week online cognitive behavioral therapy in

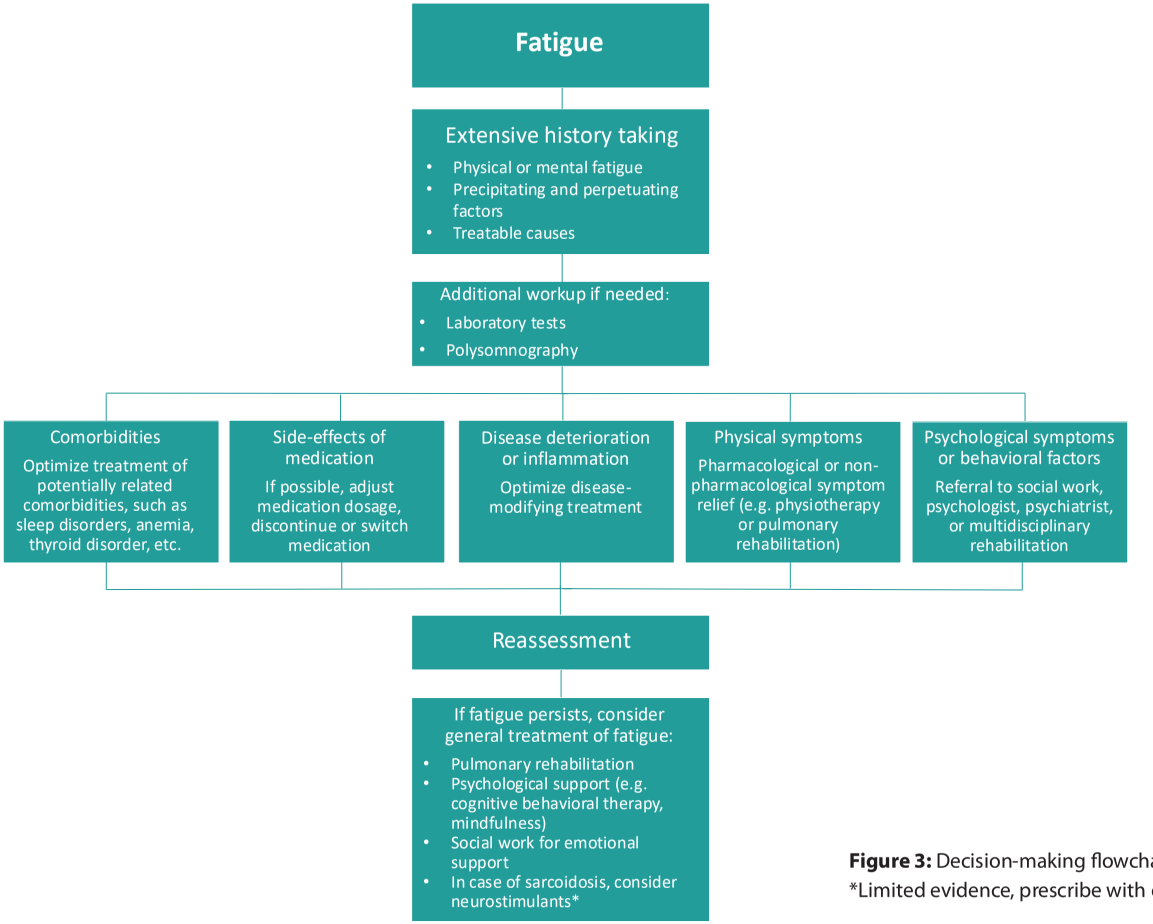

Figure 3: Decision-making flowchart on how to manage fatigue in ILD.
*Limited evidence, prescribe with caution

patients with sarcoidosis-associated fatigue (FAS score ≥22 points) is ongoing (https://www.trialregister.nl/trial/7816). Although cognitive behavioral therapy has also been suggested in IPF, no studies have been conducted to date. As fatigue is also perpetuated by inactivity, low social support and psychological wellbeing, tailored interventions by physiotherapists, psychologists or social workers may sometimes improve symptoms.

Neurostimulants have been suggested as potential treatment options for fatigue in sarcoidosis. The effect of dexmethylphenidate hydrochloride (d-MPH) and armodafinil on sarcoidosis-associated fatigue was first described in 2008 (47, 48). D-MPH, which inhibits dopamine and noradrenaline in the brain, was studied in 10 patients. Armodafinil, which increases extracellular dopamine levels in the brain and is mainly used in narcolepsy, was studied in 15 patients. Both of these neurostimulants led to a significant improvement in fatigue scores and appeared to be safe. While the results of these studies were promising, only a small number of patients were included. Currently, a new study on the effect and side-effects of methylphenidate in sarcoidosis-associated fatigue is being conducted. This trial was mainly initiated to determine the feasibility and design of a future large-scale RCT. Hopefully, these results will enable larger scale future studies to provide better evidence for the use of neurostimulants for fatigue in sarcoidosis (49). The use of these agents has not been investigated and their use cannot be recommended in other ILDs. It has been suggested that anti-TNF-alpha treatment may have positive effects on sarcoidosis-associated fatigue; however, this finding has not been replicated in a randomized trial (50). At present, no studies have evaluated the effects of pharmacological interventions in other ILDs.

Most of the data on how to deal with fatigue in ILD currently stem from sarcoidosis (41). Although we believe that there are many similarities between fatigue in chronic diseases and ILD, and between sarcoidosis and other ILDs, also important differences exist (2, 7, 16). Stable chronic diseases may have more general approaches, while in progressive fatal diseases as IPF, disease course and prognosis will also dictate treatment choices (51). In diseases with more rapid disease progression and worse prognosis, treatment of fatigue should be a part of integrated palliative care programs. To further advance insights into fatigue and develop better treatment strategies, more research is obviously needed. On one hand, the multifactorial etiology in often heterogeneous populations increases the complexity of the research, on the other hand, collaboration with partners outside the ILD research area could help to generate progress in the field, as fatigue is a universal problem in many chronic diseases.

CONCLUSION

Fatigue is a major problem for both patients with ILD and for treating physicians. The etiology of fatigue in ILD is likely multifactorial, but many aspects are still unknown. Different predisposing, precipitating and perpetuating factors contribute to fatigue, of which many also play a role in other chronic diseases. Unfortunately, specific guidelines and evidence-based treatment recommendations for fatigue are still lacking. In clinical practice, a comprehensive, multidisciplinary, and individually-tailored approach seems the best fit to optimize treatment of fatigue in ILDs. Hopefully, new studies will lead to better treatment options for fatigue and ultimately improve quality of life for patients with ILD.

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