Sleep in the chronic fatigue syndrome

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Summary

Chronic fatigue syndrome (CFS) is a disabling condition characterized by severe fatigue lasting for more than six months and the presence of at least four out of eight minor criteria. Sleep disturbance presenting as unrefreshing or nonrestorative sleep is one of these criteria and is very common in CFS patients. Biologically disturbed sleep is a known cause of fatigue and could play a role in the pathogenesis of CFS. However, the nature of presumed sleep impairment in CFS remains unclear. Whilst complaints of NRS persist over time, there is no demonstrable neurophysiological correlate to substantiate a basic deficit in sleep function in CFS. Polysomnographic findings have not shown to be significantly different between subjects with CFS and normal controls. Discrepancies between subjectively poor and objectively normal sleep suggest a role for psychosocial factors negatively affecting perception of sleep quality. Primary sleep disorders are often detected in patients who otherwise qualify for a CFS diagnosis. These disorders could contribute to the presence of daytime dysfunctioning. There is currently insufficient evidence to indicate that treatment of primary sleep disorders sufficiently improves the fatigue associated with CFS. Therefore, primary sleep disorders may be a comorbid rather than an exclusionary condition with respect to CFS.

Introduction

Recurring complaints of disturbed sleep and fatigue are very common among the general population. Patients who present with a combination of these symptoms may perceive malfunction of sleep as the prime cause of tiredness and other impairments in daily life. Because of this attribution, dissatisfaction with daytime functioning may be an incentive to seek medical help for a presumed disturbance of sleep.

Fatigue is a common denominator referring to various aspects of impaired physical, mental, emotional and neurocognitive functioning. Lack of energy, weakness, attention deficits, memory problems and irritability are typically associated with the construct of fatigue. It is a frequent manifestation of a variety of medical, neurological and psychiatric diseases. It may also appear as a side effect of pharmacological treatment.

Presently, there is ample evidence to confirm that sleep curtailment, whether experimentally induced or self-imposed, is causally associated with fatigue. Likewise, primary sleep disorders (PSD) are a known cause of fatigue and excessive daytime sleepiness (EDS). Clinical improvement of these symptoms can be expected from adequate treatment of the underlying sleep disorder.

Finally, fatigue often remains unexplained, leading to the construct of chronic fatigue syndrome (CFS), in which unrefreshing sleep is a prominent (but ill-defined) feature.

The aim of the present review is to:
- give an overview of definitions, health impact and epidemiology of CFS;
- explore current insights into restorative and nonrestorative aspects of sleep;
- assess the relations between sleep and CFS.
more affected in CFS as compared with serious chronic illness such as multiple sclerosis, end stage renal disease and cardiac failure.13–15

While the pathogenesis of CFS remains essentially unknown, it is best conceptualized as a biopsychosocial model. From a biological perspective, it has been contended that abnormalities of the central and autonomic nervous systems may be present and that infectious agents may be involved.16,17 However, there is currently no compelling evidence to accept that these conditions would play a significant role in patients with established CFS.

There is theoretical standing and empirical evidence for the cognitive behavioral model of medically unexplained symptoms in general and for CFS in particular.18 In this construct, predisposing, precipitating and perpetuating factors play a role in the ontogenesis of the disorder. Whilst a biological agent may be related to the onset, the chronicity of CFS may rather be determined by psychosocial factors such as maladaptive behavior, negative conditioning and obtaining a socially accepted label of ‘medical illness’.18

The persistent absence of any clear pathophysiological substrate, biological marker or diagnostic test challenges the construct of CFS. Accordingly, the clinical methods for case finding and the acceptance of CFS as a disease entity remain problematic in both society and amongst the medical community. An overview of the actual controversies in CFS was recently presented by Holgate et al.19

CFS may overlap with other chronic functional syndromes such as fibromyalgia syndrome (FMS), temporomandibular joint pain and irritable bowel disorder.20,21 Diffuse muscular pain, fatigue and sleep disturbances are part of the syndromal definitions of both CFS and FMS, which is a condition characterized by local tender points and chronic diffuse body pain.22 Taking into account the respective case definitions, 20–70% of patients with FMS meet the criteria for CFS,23–25 and conversely, 35–70% of those with CFS have coexistent FMS.24,26 Obviously, this similarity in clinical picture may be confusing and incite semantic discussions on fundamental themes such as pathogenesis and nosological classification. As these conditions may constitute different spectra of the same biomedical and psychosocial processes, a unifying concept should be developed to integrate the various functional somatic syndromes characterized by different degrees of pain, fatigue and disturbed sleep.27

The restorative function of sleep

Because unrefreshing or nonrestorative sleep (NRS) is a hallmark of CFS, insights into the restorative function of sleep are mandatory. The present section gives an overview of our current understanding of this feature, while the next section expands on the construct of nonrestorative sleep.

Sleep is a universal phenomenon in living creatures. While sleep is conceived essential for normal life, its functions are as yet incompletely understood. Regarding non-rapid eye movement (NREM) sleep, most theories suggest a role in energy conservation and nervous system recuperation, whereas rapid eye movement (REM) sleep is thought to be implicated in localized recuperative processes and emotional regulation.28 Yet, how sleep could serve the need for regaining bodily energy remains largely unexplained.

That sleep is for rest and restoration of body and mind is above all an intuitive notion. The feeling of recuperation after a good night of sleep is so fundamental that a restorative function is attributed to sleep from mere subjective experience. Presumably, it is a time of quiescence when the body seems to be able to generally reverse the

### Definitions, health impact and epidemiology of CFS

CFS is characterized by long lasting pathologic fatigue with a disabling impact on professional, social and daily functioning. The absence of any obvious underlying disease, and the presence of a number of associated clinical features are fundamental to this disorder. The term CFS was coined in 1988 by Holmes et al. in a publication of the US Centers for Disease Control and Prevention (CDC).1 Since then, several new case definitions have been introduced. In 1994, revised CDC criteria were published by Fukuda et al.2 These are standard guidelines in the US and are widely used in other countries as well.

To establish the diagnosis of CFS, the Fukuda et al. guidelines require a major criterion of pathological, incapacitating fatigue of at least six months duration, in combination with at least four out of eight minor criteria. These minor criteria include postexertional fatigue lasting for at least 24 h, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain without swelling or redness, headache of a new type, pattern or severity, memory and concentration impairment and unrefreshing sleep. The key features of the different case definitions (Holmes et al., 19881; Lloyd et al., 19903; Sharpe et al., 19914; Fukuda et al., 19945; Carruthers et al., 20036) were recently reviewed by Christley et al.6 All existing guidelines are founded on expert-based consensus and lack robust medical evidence.

Depending on the case definitions and the characteristics of the population screened, a wide prevalence range is reported: between 100 and 2100 per 100,000 patients in primary care,78 and between 0 and 4800 per 100,000 individuals in community-based samples.1,19 As the prevalence of CFS in the community may be quite high, epidemiologic studies relying on referrals to outpatient clinics may lead to an underestimation of the burden of CFS in the general population.

Chronic fatigue and CFS negatively affect socioeconomic status and health-related quality of life. The substantial economic impact of these disorders was shown in earlier investigations. In the UK, the estimated three-month costs per patient with chronic fatigue or CFS were £1906,16 whereas in the US, the annual cost per CFS patient amounted to $20,000.11 CFS has a significant adverse impact on quality of life. When validated instruments such as the medical outcomes study short form 36 item (MOS SF-36) are used,12 physical and mental health scores seem equally or even

### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CAP</td>
<td>cyclic alternating pattern</td>
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<td>CDC</td>
<td>Centers for Disease Control and Prevention (USA)</td>
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<td>CFS</td>
<td>chronic fatigue syndrome</td>
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<td>CPAP</td>
<td>continuous positive airway pressure</td>
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<td>DIS</td>
<td>difficulty with initiating sleep</td>
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<td>DMS</td>
<td>difficulty with maintaining sleep</td>
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<td>EDS</td>
<td>excessive daytime sleepiness</td>
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<td>EEG</td>
<td>electro-encephalography</td>
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<td>FFT</td>
<td>fast Fourier transformation</td>
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<td>FMS</td>
<td>fibromyalgia syndrome</td>
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<td>MOS SF-36</td>
<td>medical outcomes study short form 36-item</td>
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<td>NREM</td>
<td>non-rapid eye movement</td>
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<td>NRS</td>
<td>nonrestorative sleep</td>
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<td>OSA</td>
<td>obstructive sleep apnea</td>
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<td>PSD</td>
<td>primary sleep disorders</td>
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<tr>
<td>PSG</td>
<td>polysomnography</td>
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<td>REM</td>
<td>rapid eye movement</td>
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wear and tear accumulated during wakefulness. Conversely, when night-time sleep is curtailed or interrupted, people may experience a lack of replenishment that expectedly would have occurred if their sleep had been normal.

It is surprising that scientific evidence for a psychophysiological recovery process during sleep is still lacking. Shortage of sleep, however, unveils a lack of restoration. All kinds of sleep deprivation, whether acute complete sleep loss, chronic partial sleep restriction, or sleep fragmentation, result in increased daytime sleepiness, various aspects of mental fatigue and in demonstrable neurocognitive impairment. Therefore, the emergence of psychophysiological ‘nonrestoration’ after loss of sleep could be accepted as a proof by contradiction that sleep has a role to replenish the body and mind for daily functioning. In addition, sleep curtailment increases sleep propensity and subsequent sleep is characterized by a rebound of slow wave activity, which could tentatively signify an intensified recovery process in the brain.

Nonrestorative sleep

While adverse effects of sleep loss on daytime performance were already substantiated more than a century ago, medical attention for insomnia-like daytime symptoms in the presence of normal sleep duration is of a more recent date. The clinical phenomenon of interest is a subjective experience of unrefreshing sleep. Typically, patients report awakening unrefreshed or unrefreshed after a preceding night with sufficient sleep duration. From the 1970s on, unrefreshing sleep was observed as a frequent complaint in unexplained chronic pain and fatigue. Borrowing from the theory that sleep serves a restorative function, the construct of NRS was introduced as a possible lead to the etiologies of CFS and fibromyalgia syndrome (FMS). NRS was first mentioned as a symptom of insomnia in the Diagnostic and statistical manual - third edition- revised (DSM-III-R) of the American Psychiatric Association in 1987 and subsequently embraced by other coding systems, including the International classification of sleep disorders - second edition (ICSD-2) and research diagnostic criteria (RDC).

In a recent review, it was pointed out that the construct of NRS is highly complex, and suffers from conceptual inconsistencies. NRS currently lacks a uniform working definition, known causal agents, and empirically validated assessment and treatment strategies. While different descriptions of NRS have been used in the past, the following definition is currently proposed: 'a feeling of being unrefreshed upon awakening that occurs at least three times a week for at least one month'. To conceptualize NRS as a distinct condition, that is not a symptom of another disorder, two additional criteria are appended, i.e., normal sleep duration, and the absence of an organic sleep disorder. This construct remains a theoretical model and requires further empirical validation. Finally, current evaluation
of NRS is based on a dichotomous approach (i.e., present or not), whereas its severity may vary among patients. No self-report questionnaires are currently available to assess different degrees of NRS.

As a consequence of variant definitions, methods and target populations, disparate figures on the prevalence of NRS have been reported in the general population, varying from 1.4% to 35%.39 Interestingly, NRS is not invariably associated with subjective daytime dysfunction. In the general population, only one fifth of individuals with NRS reported fatigue or irritable mood.41

As waking up unrefreshed is a frequent manifestation of insomnia or organic sleep disorders,37 it has long been debated whether NRS may exist in the absence of known sleep or health problems. To clarify this matter, Roth and colleagues investigated a cohort of subjects selected on a self-report of awakening unrestored or unrefreshed at least three times weekly over a period of three months.32 Impaired daytime functioning was an obligatory inclusion criterion. Individuals with evidence of any medical, neurological, or psychiatric condition were excluded. Polysomnography (PSG) was used to rule out organic sleep disorders. Out of 226 patients, 115 (50.9%) had NRS with normal sleep architecture, and had no difficulties with initiating sleep (DID) or maintaining sleep (DMS). In these NRS-only patients, PSG showed no relevant differences regarding sleep architecture or indices of sleep disturbance in comparison with healthy controls. Whilst this is the first study to show that NRS may exist outside the context of classical insomnia, organic sleep disorders, and comorbid diseases, no inferences could be drawn on any underlying pathophysiological mechanism. PSG did not provide a “diagnostic marker” for NRS and the pathophysiological construct of ‘nonrefreshing sleep’ could not be validated. Furthermore, as the trial was limited to subjects with significant daytime dysfunction, the correlation between NRS and impaired daytime function could not be addressed.

The absence of any objective indicators that corroborate the subjective report of ‘feeling unrefreshed upon awakening’ is a salient weakness of the NRS construct.

**Sleep complaints and assessment of sleep in chronic fatigue and CFS**

In all available case definition guidelines of CFS, sleep problems are described as a minor criterion (Table 1). The terms used vary substantially from (aspecific) sleep disturbance, to unrefreshing or nonrestorative sleep, to various aspects of sleep quality, sleep duration and elements of insomnia and/or hypersomnia. Evidently, the lack of uniformity in working definition mirrors the gap in our understanding of the pathophysiological role of sleep in CFS.

Sleep disturbance is reported by the vast majority of individuals who receive a final diagnosis of CFS (Table 1).43–47 This complaint persists over a time course of several years after diagnosis.48

A complaint of NRS is present in 87–95% of CFS cases identified in community surveys48–51 (Table 1). Subjects with CFS have a very high co-occurrence of NRS and daytime dysfunction. In a study by Unger et al., the adjusted odds ratio for NRS in CFS in comparison with non-fatigued controls was estimated to be 28.1 (95% confidence interval = 7.4–107.0).47 Insomnia patients with NRS have more frequent daytime sequelae than those without NRS.31,52 Sarsour et al. found that NRS vs. no NRS insomnia groups had a different prevalence of decreased daytime physical function (73% vs. 33%), cognitive function (51% vs. 20%) and emotional function (53% vs. 22%).52 In the study by Ohayon, all measures of impaired daytime functioning were at least twice as frequent in NRS subjects compared to those without NRS.41 These studies indicate a potential relationship between NRS and the various aspects of daytime fatigue, but the fundamentals of this connection remain to be further explored. Clearly, CFS and insomnia share features with respect to NRS and daytime dysfunction, and could actually be manifestations of one and the same underlying disorder. For semantic reasons, different diagnostic labels are being used in current clinical practice.

PSG is the standard clinical tool to objectively assess sleep complaints and to establish their neurophysiological correlates. Sleep recording has been performed in subjects with CFS with two purposes: 1) to elucidate as yet undisclosed mechanisms that would explain the impaired restorative function of sleep, and 2) to identify PSD that would exclude the diagnosis of CFS. Obviously, treatable PSD must be excluded if investigation is aimed at finding the very nature of unrefreshing sleep. On the other hand, if PSD are believed to account for the CFS symptoms, their treatment should remediate the complaint of fatigue. If not, PSD are not exclusionary, but unrelated or at the most—comorbid conditions. In the subsequent paragraphs, these two aspects will be expounded separately.

**Structural and dynamic aspects of sleep in chronic fatigue and CFS**

PSG has been performed in CFS patients using different outcomes, including classical sleep architecture, spectral analysis, sleep stage dynamics and the study of cyclic alternating patterns (CAP) in the sleep electro-encephalography (EEG).

Regarding **sleep architecture**, i.e., the structural and temporal features of sleep with respect to wakefulness and the different sleep stages, data are available from a twin study and from a survey in the general population.

Investigators from the University of Washington have conducted a monozygotic co-twin control study of 22 pairs discordant for the phenotype of CFS. In this sample, they explored subjective and objective measures of insomnia,33 as well as objective measures of sleep.34 Compared with their healthy co-twins, the subjects with CFS had more subjective complaints of insomnia and poor sleep. However, no relevant differences were found between CFS and healthy co-twins in the objective polysomnographic measures. Only percent NREM stage 3 and percent stage REM sleep were slightly increased in the individuals with CFS, as compared with their healthy controls (NREM stage 3: 10.7% vs. 8.6%; REM: 27.7% vs. 24.4%, P ≤ 0.05). There was no convincing evidence to support a major role for abnormalities in sleep architecture in CFS. Although the subtle differences in the PSG outcomes did not sufficiently account for the prominence of sleep complaints in the CFS group, there was an indication that individuals with CFS may suffer from an element of sleep-state misperception.

PSG has been performed in a subset of cases and non-fatigued controls from a population based survey, i.e., the Wichita CFS surveillance study.35,56 Approximately 18% of persons with CFS and 7% of asymptomatic controls were diagnosed with severe PSD and were excluded from further analysis. The final assessment of PSG data comprised 35 individuals with CFS and 40 controls. Despite the fact that sleep problems were significantly more often reported by people with CFS as compared with healthy subjects, common characteristics of sleep architecture did essentially not differ between these groups.

Thus, the hypnogram does not seem to discriminate individuals with CFS from healthy controls. Whilst methodological issues including limited montage and only single night recordings57 may
have an influence on these results, the methods used are identical for individuals with CFS and healthy controls. Therefore, the lack of difference between the two groups may not be due to technical limitations in the first place, but rather to limitations inherent to the very method of assessing sleep architecture. Defining sleep stages by conventional scoring methods is a crude and arbitrary approach to the physiological process of sleep, and subtle anomalies may go unnoticed.

Early reports have drawn attention to the appearance of prominent alpha activity in NREM sleep, also known as ‘alpha–delta sleep’. This EEG abnormality has been conceptualized as an intrusion of wakefulness into sleep, that could be a neurophysiological correlate of NRS.58 Alpha–delta sleep has been observed in heterogeneous groups of patients presenting with chronic daytime dysfunctioning, especially in FMS.59–62 Meanwhile, it has become evident that alpha–delta sleep is not an essential feature of NRS,39 nor a consistent marker of FMS or CFS.63 Moreover, alpha–delta sleep may be observed in subjects with other disorders or who do not complain about fatigue.64

Measurement techniques that analyze sleep EEG on a continuous basis may be more suitable to detect delicate neurophysiological intrusions of sleep. Power spectrum analysis of the EEG has been utilized in different groups of subjects with CFS and has failed to corroborate intrusion of alpha activity in NREM sleep as a clinically relevant issue. Armitage et al. reassessed 13 pairs of female twins out of the original 22 pairs from the Washington CFS twin registry.65 PSG was repeated and power spectral analysis using fast Fourier transformation (FFT) was applied on the EEG recordings. No significant differences in spectral power in any frequency band were found between co-twins with or without CFS. Phasic alpha activity, coupled with delta was noted in five subjects with CFS but was also present in four out of five healthy co-twins, indicating that this finding rather reflects genetic influences on the sleep EEG. PSG recordings from the individuals that were included in the Wichita CFS surveillance study were reassessed using FFT.66 The spectral power of each frequency domain for each sleep state was compared between persons with CFS and matched controls. Surprisingly, alpha power was reduced during NREM stages 2 and 3, and REM sleep in the CFS group. In a clinical population, Guilleminault et al. compared 14 consecutive patients with chronic fatigue to 14 controls. Using FFT, they also found decrements in the power of the alpha bands in the patient group.67 In conclusion, power spectrum analysis of the EEG does not seem to provide strong evidence for abnormal alpha intrusion in NREM sleep in subjects with chronic fatigue. Analysis of other spectral bands (theta, delta, beta) shows inconsistent results. For instance, delta power has been reported increased,67 decreased,66 or to be similar65 in CFS groups as compared with normal controls.

Increased CAP rates in NREM are presumed to be an index of sleep instability.66 Guilleminault et al. also looked at CAP rates in their sample of clinical CFS patients versus controls,67 to find significantly higher values in subjects with chronic fatigue as compared with controls (50.9 ± 32.0 vs. 27.0 ± 26.2, P = 0.04). They speculated that this mechanism may be associated with a complaint of unrefreshing sleep. An investigation of sleep stage dynamics70 showed different profiles regarding probabilities of transitions from waking to sleep and between different sleep stages, when comparing CFS and FMS patients with controls. In addition, the rates of these transitions were also significantly increased in subjects with CFS and FMS. Evidently, these results are preliminary, as the new paradigms on which they are based must be reassessed by independent research groups. If these findings can be replicated, their relevance in respect of hypothetical models of sleep dysfunction should be determined.

In conclusion, an undisclosed disturbance of the neurobiological sleep process may still be a plausible explanation for NRS and daytime dysfunction in CFS. However, no robust pathophysiological correlate has been identified as yet to demonstrate that a deficit in sleep function is accountable for these symptoms. The concept of nonrestorative sleep is contentious as it carries the attribution that the problem lies intrinsically within sleep. By the same token, sleep may be normal. It is conceivable that chronic fatigue may persist throughout the entire 24-h period, and is already noticed by the individual after the period of nocturnal sleep. The timing of the first experience of fatigue, i.e., upon awakening in the morning, may falsely raise the individual’s perception that something is wrong with sleep. Until a specific neurophysiological impairment is demonstrated, the claim that NRS is part of the domain of CFS — or insomnia — will remain speculative.

Primary sleep disorders in chronic fatigue and CFS

PSD, including primary insomnia, obstructive sleep apnea (OSA), periodic limb movement disorder and narcolepsy, are not infrequently diagnosed in patients who otherwise meet the Fukuda et al. criteria for chronic fatigue or CFS.43,44,55,71–74 Taking an appropriate sleep history and performing PSG are key to detecting these disorders. Due to different criteria, diagnostic methods, as well as different target populations, the prevalence rates of PSD vary substantially among studies (Table 1). The Wichita CFS surveillance study revealed the presence of severe PSD in 18% of subjects with CFS in the general population.55 In clinical settings, the prevalences of PSD vary between 46 and 81%.43,44,71,73

Two issues stand out in the clinical differentiation between PSD and CFS. First, the constructs of primary insomnia and CFS overlap considerably. Psychophysiological insomnia, more than any other sleep disorder, is associated with high scores on daytime fatigue.75 As discussed earlier, NRS is a hallmark in the contemporary nosological definitions of both insomnia and CFS. Patients with CFS tend to increase the duration of staying in bed, leading to decreased sleep efficiency.46,76 They also may suffer from DIS, DMS or both.71,77 All these findings are also characteristic of insomnia.78 Therefore, the concepts of insomnia and CFS should be further clarified with respect to mutual differences and similarities. Second, organic sleep disorders, especially sleep apnea and narcolepsy, are regarded conditions that exclude CFS.7 This concept has recently been challenged. In a comparative study, Libman et al. found no significant differences between CFS patients with and without associated OSA regarding subjective sleep variables, CFS symptoms, indexes of anxiety and depression, and MOS SF-36 quality of life parameters.79 Neither was there a difference in fatigue scores between subgroups who were and who were not compliant for treatment with nasal continuous positive airway pressure (CPAP).80 From these findings, the authors concluded that OSA should not be an exclusion criterion for CFS. On the other hand, there is preliminary evidence to indicate that treatment of PSD may reduce scores of daytime fatigue. In moderate to severe OSA, a recent placebo-controlled trial with nasal CPAP demonstrated a significant reduction in fatigue and increase in vigor (P values < 0.05) in a group of 29 subjects treated with active CPAP, but not in a group of 30 subjects receiving placebo treatment.81

The beneficial effect of CPAP treatment was most pronounced in patients with high levels of fatigue at onset. In contrast, EDS was reduced only in a subset of patients who were excessively sleepy at onset. Clearly, more studies are needed to trace these results, especially in patients whose presenting complaint is severe chronic fatigue. It is not yet clear whether primary severe fatigue is sufficiently responsive to adequate treatment of comorbid sleep disorders.
Practice points

1) The concept of NRS implies that fatigue is the consequence of dysfunctional sleep, whilst evidence for such cause–effect relationship has not yet been provided. Preferably, this complaint should be referred to as ‘waking up unrefreshed’. Moreover, a uniform working definition should be validated, based on an empirical approach involving experts, clinicians and patients.

2) Patients who report NRS are not necessarily functionally impaired during the daytime. The combined presence of unrefreshing sleep and daytime impairment is found in patients with more severe symptom scores.

3) Patients in whom CFS is suspected should be routinely assessed on appropriate questionnaires and semi-structured history. PSG should be carried out in individuals with high pre-test probability for PSD. CFS can be excluded, not by the mere presence of PSD, but by satisfactory symptomatic relief obtained by causal treatment.

4) CFS overlaps with FMS and other functional disorders. Because of the lack of a solid pathophysiological basis, they do not fit well into currently used nosological catalogs, or explicit names in different classification systems. To avoid using stigmatized syndromal names, a descriptive approach may be employed. Such procedure would consist of scoring the various aspects and the degree of severity of the constituent symptoms, fatigue, sleep disturbance and pain. Thus, a multidimensional functional disorder may be configured. This construct would fit a biopsychosocial impairment model rather than a labeled disease. This approach may hold promise to avoid excessive somatization and to tailor symptomatic treatment to the individual patient’s needs.

References


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The most important references are denoted by an asterisk.


