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Clinical complaints of daytime sleepiness and fatigue: How to distinguish and treat them, especially when they become 'excessive' or 'chronic'?

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Abstract

Chronic daytime fatigue and excessive daytime sleepiness (EDS) are potentially invalidating and also common complaints in primary care and general neurological practice. The lack of distinction in the clinical use of terms like fatigue and sleepiness is an important issue. Although these semiological concepts present fundamental differences from physiological and pathological points of view, general medical literature still often confuses both symptoms. The objective of the present review is to contribute to the clinical distinction between fatigue and sleepiness and describe available measurement tools and respective treatment options.

We found that sleepiness and fatigue both present with semiological multidimensionality and clinical complexity. Although relating to different underlying concepts, they can show overlapping features and several clinical conditions can present with both complaints simultaneously. Existing specific assessment tools are sometimes underutilised, causing EDS and fatigue to continue to be confounded. The blurring contributions of several studies are mainly due to the fact that typically only one of these two clinical dimensions is investigated. Despite consensus on objective sleepiness measures, simple and validated objective fatigue assessments are generally lacking and seem elusive. Causal and symptomatic treatment options exist predominantly for sleepiness-associated conditions.

Although comprehension of sleepiness and its underlying physiology has seemed to improve over time, descriptions of common pathways of fatigue remain relatively incomplete. Clinical research and practice should systematically investigate both conditions with adequate measurement tools. Behavioural medicine is certainly underestimated, especially in the management of chronic daytime fatigue.

Key words: Fatigue; excessive daytime sleepiness; semiology; review; treatment.

Introduction

Persisting invalidating fatigue is a very common and not only potentially invalidating but also a frequently resisting symptom in many clinical conditions primarily related directly or indirectly to the central nervous system (CNS). Like pain, fatigue deserves guidelines addressing specific therapeutic approaches (Pigeon *et al.*, 2003). Nevertheless, fatigue is often neglected because of under-diagnosis, potential confusion with sleepiness, lack of recognition and because of a general lack of clear treatment approaches (Shen *et al.*, 2006).

The semantic and semiological ambiguities arising out of conceptualisations of fatigue and sleepiness are considered by some authors to be a major clinical issue (Pigeon *et al.*, 2003; Shen *et al.*, 2006), particularly for both general medical practice and neurological disciplines (Guilleminault & Brooks, 2001).

Complaints of both fatigue and sleepiness are very common in both the general population (Pawlikowska *et al.*, 1994; Ohayon 2005) and in primary care (Hossain *et al.*, 2005). Excessive daytime sleepiness is often reported in community samples and both fatigue and sleepiness can present heavy burdens for public health care (Kim, 2005; Young, 2004; Pigeon, 2003; Leger, 1995).

Sleepiness is generally described as a trigger signal for an upcoming spontaneous onset of sleep. It is a physiological phenomenon that depends on previous sleep occurring at regular intervals following a circadian rhythm as described by Borbély's 'two process model' (Borbély, 1982; Lavie, 1986). However, in pathological conditions, excessive daytime sleepiness (EDS) can be irrepressible when

associated with, for instance, narcolepsy or sleep apnea-hypopnea syndrome (SAHS). EDS is also linked to other primary sleep disorders, such as periodic limb movement disorder (PLMD), idiopathic hypersomnia and sleep deprivation (Young, 2004).

On the other hand, fatigue is generally described as a condition in which maintaining motor or mental energy levels gets more difficult with an increasing duration of exercise. Recovery from fatigue usually requires rest rather than sleep. Chronic severe daytime fatigue is, for instance, the core symptom in clinical conditions like the chronic fatigue syndrome (CFS). Nevertheless, even in CFS, a significantly overlapping subjective sleepiness has recently been described (Neu *et al.*, 2008).

In contrast to sleepiness, it is generally accepted that if there are any relationships between fatigue and sleep, they are undoubtedly less obvious. However, there have been previous reports linking both fatigue and sleepiness to complaints of non-restorative sleep (NRS) (Ohayon, 2005; Neu *et al.*, 2007). The relationships between fatigue and sleepiness themselves also remain insufficiently understood. While classical structured evaluation scales and psychometric assessment tools are available for both subjective fatigue and sleepiness complaints, the definitions and semiological distinctions between fatigue and sleepiness are often difficult for both patients and clinicians to discern (Bailes, 2006; Pigeon, 2003). Reports suggest that affective symptoms such as mood disturbances and anxiety are frequently associated with daytime conditions related to both sleepiness (Andrews, 2004; Schroeder, 2005) and fatigue (Moss-Morris, 2006; Neu, 2007).

These are important issues, since the aetiopathogenesis of related clinical conditions and the implications for therapeutic orientation can be very different (Leibowitz, 2006; Pigeon, 2003). Potentially overlapping descriptive features can also lead to imprecise diagnoses and subsequently to inadequate or insufficient treatment strategies (Leibowitz, 2006; Young, 2004; Pigeon, 2003). Shen and colleagues have suggested a possible co-existence of both phenomena, along with the fact that both can potentially be related to sleep deprivation (Shen *et al.*, 2006). In an effort to disentangle fatigue and sleepiness, Bailes *et al.* (2006) have proposed two empirical scales measuring either fatigue or sleepiness and reported the ability of those scales to identify "sleepiness which is not fatigue". Indeed, objective para-clinical measurements, if available, are often limited to one dimension of these complex concepts. While there is a certain consensus on 'what and how' we measure when we assess objective sleepiness, resolution of this endeavour has been quite elusive when speaking about fatigue as a global and unique entity.

We will review the available phenomenological definitions, clinical assessments, relationships to sleep and the associated diurnal impairments of both concepts. Considering that fatigue and sleepiness are related to different underlying mechanisms, we will also point out that they mainly relate to very different clinical conditions. The possible co-existence of sleepiness and fatigue complaints and their respective clinical impact will also be discussed. Finally, the objective of the present review is to contribute to an improvement of the clinical distinction between fatigue and sleepiness and describe available measurement tools, related conditions of both concepts and their respective treatment options.

Sleepiness

Definition

Terms like drowsiness, somnolence, somnificity (Johns, 2002) and general sleep propensity are related to sleepiness. Drowsiness and somnolence relate more specifically to an intermediate state between wake and sleep or a near-sleep state. Somnolence also relates to pathological sleepiness. Hence, sleepiness is first of all a physiological phenomenon mainly governed by the sleep drive interaction of processes S (homeostatic) and C (circadian) according to Borbély's 'two-process model' (Borbély, 1982). Moreover, sleepiness can be considered as a function of competing forces, sleep drive (C & S) and wake drive (Johns, 1998 & 2002). The term of somnificity (Johns, 2002) describes the implications of multiple behavioural and environmental factors that influence sleepiness in addition to processes C and S (e.g., the likelihood of falling asleep when lying down in a bed in contrast to standing upright). Excessive daytime sleepiness (EDS) is a clinical symptom and sign closely related to several sleep disorders, depending on values measured on psychometric scales or on objective testing.

Relationships to sleep

EDS can be encountered in numerous clinical conditions, and is particularly evident in primary sleep disorders (e.g., narcolepsy, sleep apnea syndromes). EDS can be linked to sleep fragmentation in general and to sleep deprivation. Even if somnolence does indeed relate to excessive sleepiness and

a near-sleep state, we would tend to use the term of somnolence rather than EDS, in certain metabolic or toxic conditions affecting the CNS, such as hyperammonemia, hypoglycaemia or alcohol intoxication as well as neuropharmacological drug-induced iatrogenic sleepiness. In a rodent model of EDS, adenosine levels in the basal forebrain were increased due to induced sleep fragmentation. The authors concluded that EDS might be mediated by mechanisms involving adenosine in the basal forebrain (McKenna *et al.*, 2007).

In sleep medicine, the standard clinical interview typically assesses its own contributing factors to EDS or to the main sleep complaint as follows (Pigeon *et al.*, 2003): (1) sleep quantity (insufficient sleep); (2) sleep quality (sleep continuity disrupted by a primary sleep disorder or by pain); (3) sleep-wake schedule (e.g., shiftwork, circadian disturbance, excessive napping, etc.); (4) medical or neurological conditions or a general clinical status that could impact sleep; (5) substance use adversely impacting sleep; (6) primary hypersomnolence (e.g., narcolepsy or idiopathic hypersomnia). Finally, we suggest that sleep propensity is the most unifying underlying concept of sleepiness.

Measurement

Sleepiness measurements are generally referred to as subjective (as measured by scales) or objective (as measured by electrophysiological testing) sleepiness.

One of the most widely used self-reporting tools in sleep research is the *Epworth Sleepiness Scale (ESS)*. The ESS consists of 8 items describing situations that may or may not induce sleep, which are arranged on a 4-point Likert scale ranging from 0 (never doze) to 3 (high chance of dozing during daytime). The summed scores range from 0 to 24 and scores above 10 are commonly interpreted as an increased global sleep propensity (Johns, 1991). Johns described the ESS as also measuring the average sleep propensity in daily life of a given subject (Johns, 1998).

The *Stanford Sleepiness Scale (SSS)* contains seven statements describing different levels of current alertness ranging from 1 "feeling alert and vital" to 7 "almost in reverie, lost struggle to remain awake" (Hoddes *et al.*, 1972). Patients have to choose the most appropriate description of their sleepiness level for several time points (0900, 1300, 1700, 2100 hours) during the day.

Like the SSS, *The Karolinska Sleepiness Scale (KSS)* is also a state marker of subjective sleepiness. The KSS measures sleepiness using a 9-point scale based on five states, ranging from "extremely alert" to "extremely sleepy/fighting sleep." There are four intermediate states that are not designated with words (Akerstedt & Gillberg, 1990). Like other state assessments, the KSS also fits for multiple or prospective measurement designs. High scores on the KSS have been shown to be associated with physiological changes in daytime EEGs like slow roving eye movements and elevated alpha and theta power (Akerstedt & Gillberg, 1990).

Visual Analogue Scales (VAS) are also commonly used for the assessment of sleepiness/alertness and may be more sensitive to sleepiness states than ordinal scales like the SSS or the KSS (Monk, 1987). Subjects are asked to place a mark on a 100-mm line to indicate their subjective perception between two extremes usually going from 'alert to drowsy' or 'very alert to very sleepy/drowsy.' The VAS usually needs semantic explanations in order to show accurate results. This type of test is particularly interesting in multiple measurement designs (stimuli or circadian factors) or for prospective study designs (treatment effect or progression of the clinical condition over a given time period) in clinical trials or longitudinal intra- or inter-subject comparisons (Shen *et al.*, 2006).

The multiple sleep latency test (MSLT) is not only the most widely accepted and extensively used measure of objective sleepiness, it is also the best validated test (Thorpy, 1992). The MSLT consists of 4 to 5 daytime naps (MSLT-sessions) separated by two-hour intervals. The beginning of the MSLT is generally initiated about 1.5-3 h after morning wake up. Each MSLT-session includes 20 min of EEG and Electrooculogram (EOG) recordings. Subjects are asked to lie down in a quiet darkened room and are encouraged to fall asleep. Sleep latency is being defined as the time from the recording start (lights out) to the first 30-second epoch scored as sleep. EOG recordings also allow the detection of sleep onset rapid eye movement periods (SOREMPs). The mean sleep latency (SL) over the 4-5 MSLTs is generally calculated to indicate the global objective sleepiness or sleep propensity of a given subject. In research settings, MSLTs are usually stopped at least after one minute of continuous sleep in order to avoid 'power-napping' and interference with successive MSLTs or polysomnographic (PSG) follow-up recordings. Formerly, the International Classification of Sleep Disorders (ICSD) suggested that a mean SL less than 10 minutes on the MSLT indicates moderate to severe sleepiness and a mean SL above 10 indicates mild or normal sleepiness. Current cut-offs, according to the ICSD, suggest a mean SL above 10 minutes as normal sleepiness and below 8 as pathological.

The maintenance of wakefulness test (MWT) was designed in part to provide a measure of the ability to maintain wakefulness (i.e., "resistance to sleepiness") when called upon to do so, as opposed to allowing oneself to fall asleep (Mitler, 1982). Subjects are asked at two-hour intervals to sit upright in bed or in a comfortable armchair in a quiet, darkened room and are instructed to 'remain awake' for a specified period of time in a 20, 30 or 40 minute protocol. The MWT is primarily a measure of 'wakefulness' or 'wake drive' traits. Globally, the MWT presents similar limitations to the MSLT, particularly the fact that it measures only short-term wakefulness (e.g., the day of the study), in only one, fairly soporific situation. Importantly, this renders it incompletely distinct from the sleep drive, and limits its generalization to other situations (e.g., driving). Nevertheless, the MWT provides a standardised measure of a subject's ability to remain awake under maximally soporific conditions (Shen *et al.*, 2006).

The Oxford Sleep Resistance test (OSLER) has been proposed as a behavioural alternative to standard sleep resistance measurements like the MWT (Bennet *et al.*, 1997). The test procedure follows that of the MWT closely. Participants are installed in semi-recumbent position in a dark, quiet room and are instructed to resist falling asleep for the duration of the test. The OSLER adds a monotone signal detection task to the procedure. The individual is required to react to a red Light-Emitting Diode (LED) using a wireless response device with minimal debounce time. The LED is illuminated for 1 s every 3 s, during a maximum of 40 min. Failing to respond within the allocated time is regarded as an error. After 7 consecutive errors, which corresponds to 21 s or ± 1 sleep epoch, the participant is considered to have dozed off and the test is aborted. The sleep onset latency (SOL) and the number of missed events are recorded and displayed. The OSLER has repeatedly shown to discriminate well between normal sleepers and patients with EDS and offers excellent conformity with simultaneous EEG-based definitions of sleep onset latency (Mairesse *et al.*, 2009). Despite evident advantages of the OSLER regarding, including its simplicity and portability, it requires the purchase of a relatively expensive device. In a recent paper, a free software-based valid, sensitive and easy-to-use screening instrument has been proposed as a potential alternative to the OSLER (Mairesse *et al.*, 2009).

The Behavioural Sleep Resistance Task (BSRT), which follows the same procedure as the OSLER, but includes both sleep onset latency (SOL) and error profile analyses as a standard feature and is executable on virtually any low-specification personal computer (Mairesse *et al.*, 2009). The BSRT was highly correlated with actual situational subjective sleepiness measures (KSS, VAS) and EEG activity (Mairesse *et al.*, 2009). Hit ratios, error profiles and SOL variables from the BSRT were also significantly correlated with subjective sleepiness (Mairesse *et al.*, 2009).

The Psychomotor Vigilance Test (PVT), another widespread attention-related indirect measure of sleepiness, has also shown to be highly sensitive to various forms of sleep restriction in different environments (Balkin *et al.*, 2004). Participants subjected to the PVT are required to respond to a visual stimulus (a four-digit LED incrementing from 0 to 60 seconds at 1-millisecond intervals) presented at variable inter-stimulus intervals by pressing a button. A feedback system allows the participant to read his response time (RT) for 1 second, before the counter is restarted. RTs over 500 ms are considered as attentional lapses.

Daytime EEG measures: It is known that the alpha frequency of EEG power changes when individuals move from alertness toward sleepiness; more specifically, when eyes are closed the alpha frequency range decreases and when eyes are open it increases. The *alpha attenuation test (AAT)* is based on these findings. During the AAT, individuals are arranged in a normally illuminated room and instructed to open and close their eyes repeatedly about 8 times, with each opening and closing lasting for 1 minute. The AAT showed significant correlations with the MSLT and subjective sleepiness measurements (Stampi *et al.*, 1995). The AAT also showed significantly different eyes-open / eyes-closed alpha power ratios in drug-free narcolepsy patients compared to controls (Alloway *et al.*, 1997).

Event related potentials (ERP) such as the P300, are known to be related to sleep deprivation. A recent study showed healthy control subjects to have a significantly shorter P300 latency than SAHS patients (Gosselin *et al.*, 2006). Although they contribute to comprehensive and phenomenological approaches, ERPs do not provide specific measurement tools for sleepiness.

In an exploratory study, we compared psychomotor and cognitive functions between chronic fatigue syndrome (as a fatigue-related model) and sleep apnea patients (as a sleepiness-related model) with healthy control subjects. The results showed that cognitive impairment and psychomotor performance were worse when associated with sleepiness rather than with fatigue alone (Neu *et al.*, 2008). In the same sample, P300 latencies did not significantly differ between groups (unpublished data).

Treatment

When confronted with EDS, clinicians should always first seek the causal treatment of any underlying disorders after a careful differential diagnostic evaluation. These treatments would include nasal CPAP for sleep apnea, dopamine agonists for restless leg syndrome associated with periodic limb movement disorder and stimulants such as modafinil in hypersomnia disorders like narcolepsy. Clinical investigations of EDS may, in most cases, require polysomnography to rule out aetiopathogenic primary sleep disorders. Augmentation strategies with different stimulants, such as methylphenidate or modafinil, have been reported as possible secondary treatment options in several conditions of residual invalidating EDS (Banerjee *et al.*, 2004). For example, causally treated SAHS patients have already benefited from treatment with a correctly titrated nasal CPAP (Black & Hirshkowitz, 2005). Modafinil in particular seems to show an overall higher safety and better tolerance profile in secondary treatment approaches addressing EDS-related conditions (Banerjee *et al.*, 2004). Despite evidence of superior outcomes with active stimulant treatments, high rates of placebo responses reporting EDS-improvements in clinical trials may suggest the potential effectiveness of interventions based on Cognitive Behavioural Therapy (CBT). Although clear evidence is lacking, psychoeducational modalities on general sleep hygiene could be of interest in some clinical conditions.

Fatigue

Definition

Descriptive terms that are related to fatigue include exhaustion, lethargy, languidness, languor, lassitude, listlessness, 'tiredness,' and asthenia. Fatigue is weariness; it is only a symptom (not a sign) because of the lack of gold standard objective measures.

Nevertheless, fatigue has also first of all a physiological counterpart before being a significant complaint and a medical symptom. Physical or mental exertion leads to a time-limited sensation of exhaustion. Symptomatic pathology arises when fatigue becomes invalidating and chronic as well as when recovery is incomplete or absent. Fatigue is often divided into time frames (duration and chronicity) and is also described in terms of mental or physical fatigue. Some authors also refer to peripheral fatigue as seen in myasthenia gravis, or to central fatigue like in multiple sclerosis (MS), CFS or stroke-related fatigue.

Chronic severe daytime fatigue is the core symptom of CFS (Kasatkin & Spirin, 2007), but it is also associated with several systemic conditions as anaemia, rheumatoid arthritis, cancer (Stone *et al.*, 2000), MS (Kasatkin & Spirin, 2007; Leocani *et al.*, 2008) or hypothyrosis.

Mitochondrial dysfunction and impaired intracellular energy metabolism has often been suspected in chronic fatigue conditions. A very recent study described an "ATP profile test" designed for CFS and other fatigue conditions (Myhill *et al.*, 2009). This test proposed five factors about the availability of ATP in neutrophils, the fraction complexed with magnesium, the efficiency of oxidative phosphorylation, and the transfer efficiencies of ADP into the mitochondria and ATP into the cytosol. The authors concluded that the "ATP profile test" is a powerful diagnostic tool that can differentiate patients with fatigue as a result of dysfunctional energy management by stress and psychological factors from those who have insufficient energy due to dysmetabolic cellular respiration function. Higher levels of circulating cortisol and pro-inflammatory cytokines as IL-6 or IL-2 have also been associated to chronic daytime fatigue (Vgontzas *et al.*, 2007).

Globally, we can affirm that chronic and invalidating fatigue is associated with many autoimmune disorders, certain infectious diseases and other general inflammatory states as well as with treatments such as radiation or chemotherapy. However, despite intense research on the pathophysiology and treatment-associated issues of cancer-related fatigue through major scientific societies like the American Society of Clinical Oncology (ASCO), it remains surprising that in the practice guidelines for cancer-related fatigue, the US National Comprehensive Cancer Network (NCCN) only suggests a simple 0-10 fatigue intensity scale as a screen for fatigue (Mock *et al.*, 2000). When fatigue is assessed in such modalities, EDS cannot be ruled out or identified in the absence of a specific EDS assessment (Pigeon *et al.*, 2003). However, the NCCN recommends a more detailed assessment of possible primary contributing factors when the patient-rated intensity of fatigue is moderate (4-6) or high (7- 10). These possible contributing factors include (1) pain; (2) emotional disturbance; (3) sleep disturbance; (4) anaemia and (5) hypothyroidism. Fatigue is also frequently a residual symptom of major depression (Baldwin and Papakostas, 2006), associated with treatment resistance (Nutt *et al.*, 2006) and linked to higher relapse rates (Fava, 2006).

Relationships to sleep

The relationships between fatigue and sleep, if any, seem less obvious than those between sleepiness and sleep. As quoted previously, fatigue "needs rest not (necessarily) sleep to recover from." Hence, there is no global regulation model for daytime fatigue like there is for sleepiness. Furthermore, it seems as if chronic daytime fatigue conditions seen in CFS patients present with very a different sleep structure than patients with primary sleep disorders (Neu *et al.*, 2009). Nevertheless, fatigue has, like sleepiness, been related to sleep deprivation in the past (Shen *et al.*, 2006) while fatigue, but not sleepiness, is a core daytime symptom of insomnia.

Measurement

Global levels of fatigue are often measured by means of self-report questionnaires like the *Fatigue Severity Scale (FSS)*. The FSS is used to assess levels of fatigue and its effect on daily functioning. The FSS was initially used on individuals with multiple sclerosis (MS) and systemic lupus erythematosus (Krupp, 1989), but it has since been used in studies examining such factors as obstructive sleep apnea and aerobic exercise. By extension, FSS has been used in many studies investigating fatigue in other chronic conditions like obesity, Parkinson disease, hepatitis C infection, CFS (Olson, 2003) and also in samples of the general population (Lerdal *et al.*, 2005; Stone *et al.*, 2000). The FSS is a 9-item questionnaire with a 7-point Likert scale. Scores are usually reported as 'mean scores' (ranging from 1 to 7) obtained by dividing the total score (ranging from 7 to 63) by 9. The most often proposed cut-off point, for abnormal fatigue, is a mean score of 4 (Flachenecker *et al.*, 2002; Kos *et al.*, 2006), while other authors have proposed a cut-off of 5 (Lerdal *et al.*, 2005). Currently, the FSS is one of the most widely used fatigue scales in clinical research and general internal medicine.

Other global fatigue scales include the fatigue assessment instrument (FAI), the fatigue impact scale (FIS), the brief fatigue inventory (BFI), the multidimensional fatigue inventory (MFI-20) and the fatigue questionnaire (FQ). Most have been used in MS or cancer-related fatigue and showed good correlations with the FSS and high internal consistency (Shen *et al.*, 2006).

The *Fatigue impact scale (FIS)* is a 40-item questionnaire that is used to assess the diurnal impact of fatigue on daytime impairment regarding cognitive, physical and psychosocial functioning. The FIS has been used in studies on MS, hypertension and CFS with high internal consistency and good discrimination abilities. It has also shown to be a useful tool in assessing the impact of fatigue on patients' every-day lives (Fisk *et al.*, 1994).

The *Fatigue questionnaire (FQ)* is an 11-item questionnaire that measures two fatigue dimensions: physical and mental fatigue. It was originally developed for research purposes for studying CFS in hospital and community population samples. Due to its high degrees of internal consistency and validity, it has since then been used in a variety of different medical disorders, such as cancer and HIV (Shen *et al.*, 2006).

The *multidimensional fatigue inventory (MFI-20)* is a 20-item self-report instrument that rates the severity of fatigue over the past week. The MFI-20 investigates five different dimensions: global or general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity. It was tested for its psychometric properties in cancer patients receiving radiotherapy, patients with CFS, psychology and medical students, army recruits and junior physicians. It has been used to discriminate patients with Parkinson's disease (PD) from those without PD. The convergent validity of the MFI-20 was investigated by correlating the MFI subscales with a Visual Analogue Scale measuring fatigue with a correlation coefficient between 0.22 and 0.79 (Shen *et al.*, 2006).

As for state sleepiness, *VAS scales* can also address state fatigue (from "fatigued/exhausted" to "energetic/perfect shape"). Psychometric properties of these VAS scales are useful for testing given stimuli and time points as well as for prospective studies and repeated assessments regarding clinical progression or subjective treatment response.

Unlike objective sleepiness, there is no description of a common underlying pathway or mechanism for fatigue, and there is consequently no objective test for global fatigue. Rather, objective parameters in the assessment of fatigue complaints focus on a specific aspect of fatigue (mental or physical) or more specifically on 'fatigability' (kinetic and dynamic aspects of energy levels as a function of elapsed time during a given task).

Other motor performance-associated methods have been used to assess fatigability in mitochondrial disorders (Meulemans *et al.*, 2007).

A functional neuroimaging study using single photon emission computed tomography (SPECT) scans in a between-group region-of-interest analysis compared CFS patients with healthy controls (HC) during mental tasks. The data showed reduced perfusion in the anterior cingulate region of CFS individuals, although activation changes in these subjects were greater than in the HC during the cognitive

task. CFS patients also reported the perception of higher mental effort requirements when performing the given tasks (Schmaling *et al.*, 2003). Another functional imaging study, using 18-fluorodeoxyglucose positron emission tomography (FDG-PET), showed decreased FDG metabolism (mainly in the cingulate gyrus) in only half of the patients (Siessmaier *et al.*, 2003).

ERP measures have also been shown to differ from HCs in certain studies (Polich *et al.*, 1995) with a large variability with respect to population samples and study conditions. As for sleepiness, ERPs do not currently provide an objective and unified measure of fatigue.

Effort measures and respiratory parameters (VO2max) have also been proposed to be useful under certain clinical conditions, such as fatigability in congestive heart failure or pulmonary obstructive syndromes.

Most objective assessments in studies of fatigue-related conditions mainly rely on fatigability (i.e., kinetics of the decline in performance) during mental tasks (e.g., arithmetic), simple motor tasks (e.g., hand-grip dynamometry) or more complex psychomotor paradigms.

Treatment

Ideally, as for EDS, should causal treatments, in chronic fatigue-related daytime conditions, have a preferred consideration too. Although the latter seems sometimes still to be a more elusive task in fatigue. Despite inconsistent findings, there is evidence that CBT-based interventions can be effective in subgroups of CFS patients (Price *et al.*, 2008). Graded-exercise programs have also been shown to be effective in CFS (Moss-Morris *et al.*, 2005).

Antidepressants should be used in the event of a co-morbid diagnosis of major depression (MDD) or anxiety disorder in chronic fatigue patients. Despite reports of the use of stimulants, such as modafinil, in several fatigue-related conditions including MS, cancer and post-poliomyelitis (Lange *et al.*, 2009; Cooper *et al.*, 2009; Vasconcelos *et al.*, 2007), there is no consistent evidence available that validates the overall clinical utility and wide usage of these treatments for fatigue in general. Donepezil, a cholinesterase inhibitor, and noradrenaline-dopamine reuptake inhibitors (NDRIs) like bupropion, have also been considered as secondary pharmacological treatment strategies in addressing fatigue in cancer (Caroll *et al.*, 2007) or other conditions, such as MS or MDD (Foley *et al.*, 2006). NDRIs in particular need further investigation to better clarify their therapeutic roles.

Discussion

We found that both sleepiness and fatigue present with semiological multidimensionality and clinical complexity. Hence, the common use of undifferentiated terms like “tiredness” in clinical and research settings contributes to the ongoing confusion about sleepiness and fatigue. Along with the underutilization of existing specific assessment tools, the blurring contributions of several studies are mainly because only one of these two clinical dimensions is investigated.

Chronic fatigue is indeed mainly related to systemic conditions. Although the altered perception of sleep quality can be associated with daytime fatigue, its relationship to sleep seems to be of a more indirect nature (Neu *et al.*, 2007). Insomnia (a hyperarousal condition), however, is generally related to fatigue and not to sleepiness. Nevertheless, polysomnographic recordings are unlikely to play a significant role in aetiopathogenic investigations or specific treatment regimes regarding chronic daytime fatigue-related conditions in most cases.

On the other hand, sleepiness is mainly related to sleep and wake drives or to disordered sleep. Excessive daytime sleepiness is primarily related to sleep fragmentation or to primary sleep disorders (excepted insomnia disorders). Polysomnography is indicated, as a para-clinical investigation, in most cases of EDS, to identify eventually underlying primary sleep disorders. We showed that an overlap of the clinical symptoms of both fatigue and sleepiness can be observed in total sleep deprivation. Additionally, both clinical conditions are associated with cognitive and psychomotor impairment and to some extent with altered affective states, such as impaired mood.

Therefore, we suggest that study paradigms for investigating the relationship between sleep and both fatigue and sleepiness (Neu *et al.*, 2007 & 2009) – studies that measure sleepiness levels in fatigue-related conditions (Neu *et al.*, 2008) and fatigue levels in sleepiness-associated conditions – can potentially contribute to a better understanding of both phenomena.

Despite a relative consensus on objective sleepiness measures, simple and validated objective fatigue assessments are generally lacking and seem elusive. Unlike sleepiness, fatigue cannot be reduced to a unifying and underlying process in most cases, even though sleepiness is also a complex, potentially heterogeneous concept with various environemental and behavioural influences. This apparently larger complexity of the ‘fatigue-phenomenon’ leads to the fact that objective assessments of fatigue focus on a

specific aspect of fatigue (mental or physical), on specific tasks or on fatigability.

As mentioned above, although fatigue and sleepiness relate to different concepts and to different underlying processes, they have overlapping features and some clinical conditions present with both symptoms simultaneously. Altered vigilance and psychomotor function are probably the most consistent overlapping features linked to both concepts. Cognitive impairment has been associated with both sleepiness (Schulz *et al.*, 1997; Sallinen *et al.*, 2005) and fatigue (Mahurin *et al.*, 2004; Capuron *et al.*, 2006; Cook *et al.*, 2007; Bailey *et al.*, 2007). This intersection between sleepiness and fatigue warrants more intense research efforts in the future.

Adenosine and related intracellular energy metabolism could also play potential roles in both EDS (McKenna *et al.*, 2007) and chronic fatigue states (Myhill *et al.*, 2009); however, it is likely that they would be associated with different profiles and different regions of the CNS or systemic alterations.

Furthermore, we showed that despite the fundamental differences and theoretically different treatment approaches, arousal promoting and stimulating neuropharmacological treatments have been shown to potentially address both fatigue and sleepiness under certain conditions. However, stimulating treatments have greatly contributed to the confusion about fatigue and sleepiness. Moreover, it seems that specific approaches in behavioural medicine could also be effective for each respective condition, albeit with exercise and educational components unlike treatment with stimulants. Although they are seemingly underutilised, the currently available behavioural medicine and interventions show encouraging results, especially in chronic conditions.

Pigeon and colleagues, along with others, have asserted that fatigue is as clinically significant as pain, and as such, it warrants a similar level of awareness in the broader medical community. Furthermore, they emphasise the fact that although pain has already been called the "fifth vital sign," it is questionable how many vital signs we can effectively take care of and manage.

Finally, we would propose the following state definitions:

1) Fatigue is a clinical symptom associated with a faster decrease of performance levels following a given motor or mental activity task. It leads more rapidly to a state of exhaustion and needs higher (increased) amounts of rest to recover from. Furthermore, it is associated with many systemic medical conditions (including MDD) and, in all cases, it is directly or indirectly related to the CNS. Altered sleep quality, for whatever definition we may use, seems to worsen fatigue states or contribute to its maintenance. Sleep disorders such as insomnia also classically present with daytime complaints of fatigue. Invalidating fatigue, which interferes significantly with major daytime functions, must be chronic by nature and definition.

2) Sleepiness, on the other hand, is a physiological phenomenon regulated by the sleep/wake drives as described by Borbély's two-process model (Borbély, 1982) or by Johns' extensions (Johns, 2002). Excessive daytime sleepiness (EDS) mainly occurs in clinical conditions associated with sleep fragmentation or sleep loss whether due to a PSD (excepted insomnia) or external factors. EDS is best described as a higher sleep propensity and, unlike chronic fatigue, usually resolves with sleep. EDS can be a severe symptom, for instance it has been linked to higher road traffic accidents.

Although chronic daytime fatigue showed a higher incidence of significant co-morbid affective symptom intensity, both chronic fatigue and EDS seem to be related to impaired vigilance and attentional abilities and to altered mood. Presently, the higher impact on vigilance and cognitive functioning in EDS-related conditions remains open to speculation.

In conclusion, we find that although comprehension of sleepiness and its underlying physiology has improved over time, descriptions of common pathways of fatigue remain rather incomplete. Therefore, we believe that functional neuroimaging holds great promise for improving the global assessment of fatigue in the future (Cook *et al.*, 2007), considering the latter as a potentially modified state and altered dynamic functioning of the brain during or after a given mental or physical exercise or task.

Clinical research and practice should systematically investigate both fatigue and sleepiness with adequate measurement tools. Furthermore, behavioural medicine-based treatment approaches are currently underestimated, and should be taken into further consideration for the management of chronic daytime fatigue.

REFERENCES

Alloway CED, Ogilvie RD, Shapiro CM. The alpha attenuation test: assessing excessive daytime sleepiness in narcolepsy-cataplexy. Sleep. 1997;20:258-66.

Akerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. Int J Neurosci. 1990;52(1-2):29-37.

Anderson C, Platten CR, Horne JA. Self-reported 'sleep deficit' is unrelated to daytime sleepiness. Physiol Behav. 2009;96(4-5):513-7.

Bailey A, Channon S, Beaumont JG. The relationship between subjective fatigue and cognitive fatigue in advanced multiple sclerosis. Mult Scler. 2007; 13(1):73-80.

Balkin TJ, Bliese PD, Belenky G, Sing H, Thorne DR. *et al.* Comparative utility of instruments for monitoring sleepiness related performance decrements in the operational environment. J Sleep Res. 2004;13: 219-27.

Banerjee D, Vitiello MV, Grunstein RR. Pharmacotherapy for excessive daytime sleepiness. Sleep Med Rev. 2004;8(5):339-54.

Bennett LS, Stradling JR, Davies RJO. A behavioural test to assess daytime sleepiness in obstructive sleep apnoea. J Sleep Res. 1997;6:142-5.

Baldwin DS, Papakostas GI. Symptoms of fatigue and sleepiness in major depressive disorder. J Clin Psychiatry. 2006 ;67(6):9-15.

Black JE, Hirshkowitz M. Modafinil for treatment of residual excessive sleepiness in nasal continuous positive airway pressure-treated obstructive sleep apnea/hypopnea syndrome. Sleep. 2005;28(4): 464-71.

Borbély AA. A two process model of sleep regulation. Hum Neurobiol. 1982;1(3):195-204.

Capuron L, Welberg L, Heim C, Wagner D, Solomon L. *et al.* Cognitive dysfunction relates to subjective report of mental fatigue in patients with chronic fatigue syndrome. Neuropsychopharmacology. 2006;31(8):1777-84.

Carroll JK, Kohli S, Mustian KM, Roscoe JA, Morrow GR. Pharmacologic treatment of cancer-related fatigue. Oncologist. 2007;12(1): 43-51.

Chaumet G, Quera-Salva MA, Macleod A, Hartley S, Taillard J. *et al.* Is there a link between alertness and fatigue in patients with traumatic brain injury? Neurology, 2008;71(20):1609-13.

Cook DB, O'Connor PJ, Lange G, Steffener J. Functional neuroimaging correlates of mental fatigue induced by cognition among chronic fatigue syndrome patients and controls. Neuroimage. 2007;36(1): 108-22.

Cooper MR, Bird HM, Steinberg M. Efficacy and safety of modafinil in the treatment of cancer-related fatigue. Ann Pharmacother. 2009;43(4):721-5.

Fava M. Pharmacological approaches to the treatment of residual symptoms. J Psychopharmacol. 2006; 20(3 Suppl):29-34.

Fisk JD, Ritvo PG, Ross L. *et al.* Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. J Clin Infect Dis. 1994;18(suppl. 1): S79-S83.

Flachenecker P, Kümpfel T, Kallmann B, Gottschalk M, Grauer O. *et al.* Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. Mult Scler. 2002; 8(6):523-6.

Foley KF, DeSanty KP, Kast RE. Bupropion: pharmacology and therapeutic applications. Expert Rev Neurother. 2006;6(9):1249-65.

Gosselin N, Mathieu A, Mazza S, Petit D, Malo J. *et al.* Attentional deficits in patients with obstructive sleep apnea syndrome: an event-related potential study. Clin Neurophysiol. 2006;117(10): 2228-35.

Guilleminault C, Brooks SN. Excessive daytime sleepiness: a challenge for the practising neurologist. Brain. 2001;124(Pt 8):1482-91.

Hoddes E, Dement WC, Zarcone V. The development and use of the Stanford Sleepiness Scale. Psychophysiology. 1972;9:150.

Hossain JL, Ahmad P, Reinish LW, Kayumov L, Hossain NK, Shapiro CM. Subjective fatigue and subjective sleepiness: two independent consequences of sleep disorders? J Sleep Res. 2005; 14(3):245-53.

Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14:540-545.

Johns MW. Rethinking the assessment of sleepiness. Sleep Med Rev. 1998;2:3-15.

Johns MW. Sleep propensity varies with behaviour and the situation in which it is measured: the concept of somnificity. J Sleep Res. 2002;11(1):61-7.

Kaida K, Takahashi M, Akerstedt T, Nakata A, Otsuka Y. *et al.* Validation of the Karolinska sleepiness scale against performance and EEG variables. Clin Neurophysiol. 2006;117(7):1574-81.

Kasatkin DS, Spirin NN. Possible mechanisms of the formation of chronic fatigue syndrome in the clinical picture of multiple sclerosis. Neurosci Behav Physiol. 2007;37(3):215-9.

Kim H, Young T. Subjective daytime sleepiness: dimensions and correlates in the general population. Sleep. 2005;28(5):625-34.

Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989;46(10):1121-3.

Lange R, Volkmer M, Heesen C, Liepert J. Modafinil effects in multiple sclerosis patients with fatigue. J Neurol. 2009;256(4):645-50.

Leger D. The cost of sleepiness. Sleep. 1995;18(4):281-4.

Leibowitz SM, Brooks SN, Black JE. Excessive daytime sleepiness: considerations for the psychiatrist. Psychiatr Clin North Am. 2006;29(4):921-45.

Leocani L, Colombo B, Comi G. Physiopathology of fatigue in multiple sclerosis. Neurol Sci. 2008; 29(Suppl 2):S241-3.

Lerdal A, Wahl A, Rustøen T, Hanestad BR, Moum T. Fatigue in the general population: a translation and test of the psychometric properties of the Norwegian version of the fatigue severity scale. Scand J Public Health. 2005;33(2):123-30.

Mairesse O, Neu D, Rosseel Y, Van Acker F, Cluydts R, Theuns P. Comparative sensitivity of outcome variables of a software-based Behavioral Sleep Resistance Task. Ind Health. 2009;47(1):80-8.

McKenna JT, Tartar JL, Ward CP, Thakkar MM, Cordeira JW. *et al.* Sleep fragmentation elevates behavioral, electrographic and neurochemical

measures of sleepiness. Neuroscience. 2007; 146(4):1462-73.
Meulemans A, Gerlo E, Seneca S, Lissens W, Smet J. *et al.* The aerobic forearm exercise test, a non-invasive tool to screen for mitochondrial disorders. Acta Neurol Belg. 2007;107(3):78-83.
Mitler MM, Gujavarty KS, Browman CP. Maitenance of wakefulness test: a polysomnographic technique for evaluating treatment efficacy in patients with excessive somnolence. Electorencephalogr Clin Neurophysiol. 1982;53:658-61.
Mock V, Atkinson A, Barsevick A, Cella D, Cimprich B. *et al.* NCCN Practice Guidelines for Cancer-Related Fatigue. Oncology. 2000;14(11A):151-61.
Monk TH. Subjective ratings of sleepiness – the underlying circadian mechanisms. Sleep. 1987;10:343-53.
Moss-Morris R, Sharon C, Tobin R, Baldi JC. A randomized controlled graded exercise trial for chronic fatigue syndrome: outcomes and mechanisms of change. J Health Psychol. 2005;10(2):245-59.
Myhill S, Booth NE, McLaren-Howard J. Chronic fatigue syndrome and mitochondrial dysfunction. Int J Clin Exp Med. 2009;2(1):1-16.
Neu D, Mairesse O, Hoffmann G, Dris A, Lambrecht LJ, Linkowski P, Verbanck P, Le Bon O. Sleep quality perception in the chronic fatigue syndrome. Correlations with sleep efficiency, affective symptoms and intensity of fatigue. Neuropsychobiology. 2007;56(1):40-46.
Neu D, Hoffmann G, Verbanck P, Linkowski P, Le Bon O. Are patients with chronic fatigue syndrome just 'tired' or also 'sleepy'? J Sleep Res. 2008;17(4): 427-31.
Neu D, Pouchkina A, Peigneux P, Hoffmann G, Verbanck P, Linkowski P, Le Bon O. Cognitive impairment in fatigue and sleepiness associated conditions. Sleep. 2008;31(Suppl):18.
Neu D, Cappeliez B, Hoffmann G, Verbanck P, Linkowski P, Le Bon O. High slow wave sleep and low light sleep: the Chronic Fatigue Syndrome is not likely to be a primary sleep disorder. J Clin Neurophysiol. 2009;26(3):207-212.
Nutt DJ, Baldwin DS, Clayton AH, Elgie R, Lecrubier Y. *et al.* Consensus statement and research needs: the role of dopamine and norepinephrine in depression and antidepressant treatment. J Clin Psychiatry. 2006;67(Suppl 6):46-9.
Ohayon MM. Prevalence and correlates of nonrestorative sleep complaints. Arch Intern Med. 2005;165(1): 35-41.
Olson LG, Ambrogetti A, Sutherland DC. A pilot randomized controlled trial of dexamphetamine in patients with chronic fatigue syndrome. Psychosomatics. 2003;44(1):38-43.
Pawlikowska T, Chalder T, Hirsch SR, Wallace P, Wright DJ, Wessely SC. Population based study of fatigue and psychological distress. BMJ. 1994; 308(6931):763-6.
Pigeon WR, Sateia MJ, Ferguson RJ. Distinguishing between excessive daytime sleepiness and fatigue: toward improved detection and treatment. J Psychosom Res. 2003;54(1):61-9.
Price JR, Mitchell E, Tidy E, Hunot V. Cognitive behaviour therapy for chronic fatigue syndrome in adults. Cochrane Database Syst Rev. 2008;(3): CD001027.
Sallinen M, Härmä M, Mutanen P, Ranta R, Virkkala J, Müller K. Sleepiness in various shift combinations of irregular shift systems. Ind Health. 2005;43(1): 114-22.
Schmaling KB, Lewis DH, Fiedelak JI, Mahurin R, Buchwald DS. Single-photon emission computerized tomography and neurocognitive function in patients with chronic fatigue syndrome. Psychosom Med. 2003;65(1):129-36.
Schulz H, Wilde-Frenz J, Grabietz-Kurfürst U. Cognitive deficits in patients with daytime sleepiness. Acta Neurol Belg. 1997;97(2):108-12.
Shen J, Barbera J, Shapiro CM. Distinguishing sleepiness and fatigue: focus on definition and measurement. Sleep Med Rev. 2006;10(1):63-76.
Siessmeier T, Nix WA, Hardt J, Schreckenberger M, Egle UT, Bartenstein P. Observer independent analysis of cerebral glucose metabolism in patients with chronic fatigue syndrome. J Neurol Neurosurg Psychiatry. 2003;74(7):922-8.
Stampi C, Stone P, Michimori A. A new quantitative method for assessing sleepiness: the alpha attenuation test. Work & Stress, 1995;9:368-76.
Stone P, Richards M, A'Hern R, Hardy J. A study to investigate the prevalence, severity and correlates of fatigue among patients with cancer in comparison with a control group of volunteers without cancer. Ann Oncol. 2000;11(5):561-7.
Thorpy MJ. The clinical use of the multiple sleep latency test. Sleep. 1992;15:268-76.
Vasconcelos OM, Prokhorenko OA, Salajegheh MK, Kelley KF, Livornese K. *et al.* Modafinil for treatment of fatigue in post-polio syndrome: a randomized controlled trial. Neurology. 2007; 68(20):1680-6.
Vgontzas AN, Pejovic S, Zoumakis E, Lin HM, Bixler EO, Basta M, Fang J, Sarrigiannidis A, Chrousos GP. Daytime napping after a night of sleep loss decreases sleepiness, improves performance, and causes benificial changes in cortisol and interleukin-6 secretion. AM J Physiol Endocrinol Metab. 2007;292:253-261.

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Appendix

A1: The Epworth Sleepiness Scale (ESS)
A2: The Fatigue Severity Scale (FSS)

A1. The Epworth Sleepiness Scale

Item / Situation	**Probability of dozing** *Use the following scale to choose the most appropriate number for each situation:* **0** = would never doze; **1** = slight chance of dozing; **2** = moderate chance of dozing; **3** = high chance of dozing
1. Sitting and reading	
2. Watching TV	
3. Sitting, inactive in a public place (*e.g.,* a theatre or meeting)	
4. As a Passenger in a car for an hour without a break	
5. Lying down to rest in the afternoon when circumstances permit	
6. Sitting and talking to someone	
7. Sitting quietly after a lunch without alcohol	
8. In a car, while stopped for a few minutes in traffic	
Total Score:	

Legend: The subject is given the following written instructions: "How likely are you to doze off or fall asleep in the following situations, in contrast to feeling 'just tired'? This refers to your usual way of life at present and in the recent past. Even if you have not done some of these things recently, try to work out how they would have affected you."

A2. The Fatigue Severity Scale

	Disagree ←						→ Agree
1. My motivation is lower when I am fatigued	1	2	3	4	5	6	7
2. Exercise brings on my fatigue	1	2	3	4	5	6	7
3. I am easily fatigued	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out responsibilities	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms	1	2	3	4	5	6	7
9. Fatigue interferes with work, family, or social life	1	2	3	4	5	6	7
Total score:							

Comment: Usually a mean score is calculated by dividing the total score by the number of items (9).

Legend: The subject is given the following written instructions: "Circle the number that best represents your response to each question. Scoring range: 1 = strongly disagree with the statement to 7 = strongly agree with the statement. During the past week I have found that."