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The role of sleep in the chronic fatigue syndrome

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AASM	American Academy of Sleep Medicine
ACR	American College of Rheumatology
ACTH	Adreno-corticotrophin hormone
AGFI	Adjusted goodness-of-fit index
AHI	Apnea-hypopnea index
ANOVA	Analysis of variance
BMI	Body mass index
CAIC	Consistent Akaike information criterion
CAP	Cyclic alternating pattern
CBT	Cognitive behaviour therapy
CDC	Centers for Disease Control and Prevention (USA)
CFA	Confirmatory factor analysis
CFI	Comparative fit index
CFIDS	Chronic fatigue immune dysfunction syndrome
CFS	Chronic fatigue syndrome
CIS	Checklist individual strength
CNS	Central nervous system
CO2	Carbon dioxide
CPAP	Continuous positive airway pressure
CRF	Corticotrophin-releasing hormone
CSA	Central sleep apnoea
DADT	Divided attention driving task
DIS	Difficulty with initiating sleep
DMS	Difficulty with maintaining sleep
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders 3rd Edition Revised
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision
EDS	Excessive daytime sleepiness
EEG	Electro-encephalography
EFA	Exploratory factor analysis

ESS	Epworth sleepiness scale
FAI	Fatigue assessment instrument
FFT	Fast Fourrier transformation
FM	Fibromyalgia
FMS	Fibromyalgia syndrome
FQ	Fatigue questionnaire
FSS	Fatigue severity scale
GET	Graded exercise therapy
GFI	Goodness-of-fit index
HIV	Human immunodeficiency virus
HPA	Hypothalamic-pituitary-adrenal
HVS	Hyperventilation syndrome
IBS	Irritable bowel syndrome
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th edition
ICSD-2	International Classification of Sleep Disorders 2nd edition
IL	Interleukin
KSS	Karolinska Sleepiness Scale
ME	Myalgic encephalomyelitis
MFI	Multidimensional fatigue
MOS SF-36	Medical outcomes study short form 36-item
MSLT	Multiple sleep latency test
MUS	Medically unexplained symptoms
MWT	Maintenance of wakefulness test
NREM	non-rapid eye movement
NRS	Nonrestorative sleep
NSAIDs	Non-steroidal anti-inflammatory drugs
OSA	Obstructive sleep apnea
PaCO2	Arterial partial pressure of carbon dioxide
PaO2	Partial Pressure of Oxygen in Arterial Blood
PFRS	Profile of fatigue-related symptoms
PLM	Periodic limb movements
PLMD	Periodic limb movement disorder
PSD	Primary sleep disorders

PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
PVFS	Post-viral fatigue syndrome
PVT	Psychomotor vigilance test
REM	Rapid eye movement
RMSEA	Root mean square error of approximation
Rnase	Ribonuclease
SAS	Sleep apnoea syndrome
SD	Standard deviation
SE	Sleep efficiency
SL	Sleep latency
SpO2	Saturation of peripheral Oxygen
SPSS	Superior Performing Software Systems
SS	Symptom severity
SSS	Stanford sleepiness scale
TNF	Tumour necrosis factor
TST	Total sleep time
UCF	Unexplained chronic fatigue
VAS	Visual analogue scale
VAS-F	Visual analogue scale for fatigue
WASO	Wakefulness after sleep onset
WPI	Widespread pain index
XMRV	Xenotropic murine leukaemia virus-related virus

CHAPTER 1: INTRODUCTION

1. Fatigue

1.1. Dimensions of fatigue

Recurring complaints of disturbed sleep and fatigue are very common among the general population and frequently co-occur. Sleep disturbances lasting at least several nights per month have been reported by 30% of the population [1]. One-third to 50% of the adult population has been found to complain of fatigue [2].

Fatigue is a heterogeneous and multidimensional condition that is essentially subjective. No pathognomonic signs or diagnostic tests are available to assess this complaint. Reported fatigue may represent a difficult diagnostic and therapeutic problem to the medical practitioner, and its management should take into account different dimensions and contexts. The multidimensional aspects and the various types of fatigue are described below.

1.1.1. Physical fatigue versus mental fatigue

Fatigue is generally associated with physical and/or mental weakness, varying from the inability to exert force at the level of an individual's normal physical ability to the exhausted feeling after or during periods of cognitive activity. With respect to physical fatigue, muscular and central mechanisms are thought to determine physical performance [3]. Depletion of physical energy sources including glycogen and phosphocreatine, decrease in resting membrane potential and dysfunctions of the calcium pump in sarcoplasmic reticulum, and failure of neuromuscular transmission have been reported to be associated with muscular mechanisms. Central mechanisms refer to a progressive decline in the ability to activate muscles voluntary and is attributable to impairment at sites proximal to the neuromuscular junction. Supraspinal fatigue is a primary component in the central mechanism of physical fatigue [3].

Mental fatigue is a much more complex phenomenon that has been associated with impaired cognitive and behavioural performance [4]. In this context, continued performance has been proposed to be associated with expected rewards and energetical costs. Adequate evaluation of predicted rewards and potential risks of actions is essential for successful adaptive behaviour. However, while both rewards and punishments can motivate to engage in activities, both types of motivated behaviour are associated with energetical costs. Boksem and Tops [4] suggested that the nucleus accumbens, orbitofrontal cortex, amygdala, insula and anterior cingulate cortex are involved in evaluating both the potential rewards associated with performing a task, as well as assessing the energetical demands involved in task performance. Behaviour will only proceed if this evaluation turns out favourably towards spending

(additional) energy. This evaluation of predicted rewards and energetical costs is proposed to be central to the phenomenon of mental fatigue: people will no longer be motivated to engage in task performance when energetical costs are perceived to outweigh predicted rewards [4].

1.1.2. Fatigue in medical disease, organ failure

Fatigue is a common symptom in medical diseases such as cancer, HIV and other infectious diseases, sleep disorders and organ failure. The cause of fatigue in these conditions is multifactorial and may be associated with disease-related factors such as the stage of the disease, cachexia, pro-inflammatory cytokines, treatment, as well as sociodemographic and psychological factors [5, 6].

1.1.3. Fatigue in psychiatric disease

Fatigue and psychiatric disorders are highly correlated and covary across time [7, 8]. Up to two thirds of subjects with chronic fatigue lasting for at least 6 months can be given a diagnosis of a comorbid psychiatric disorder, and the presence of a psychiatric disorder increases the risk of developing chronic fatigue [7]. Nevertheless, a substantial proportion of individuals with persistent fatigue do not suffer from psychiatric comorbidity. This condition has been supported by some authors as evidence for a separate diagnosis of neurasthenia [7, 8]. The latter term is a nosological item listed in the ICD-10 classification to denote persistent and distressing complaints of fatigue, weakness and exhaustion in the absence of a depressive illness or anxiety disorder [5].

1.1.4. Neuromuscular fatigue

In physiology, fatigue is defined as a loss in force or voluntary force-producing capacity during exercise [9]. Physiological fatigue may originate in both the peripheral and central nervous system (CNS). Peripheral fatigue results from neuromuscular dysfunction outside the CNS and relates to impaired neurotransmission in peripheral nerves and/or defects in muscular contraction. Central fatigue results from alterations or abnormalities in neurotransmitter pathways within the CNS. The prevalence of fatigue in neuromuscular disorders such as multiple sclerosis and its assessment, which involves clinical neurophysiological techniques and psychological measurements, has recently been reviewed by Zwarts et al. [10].

1.1.5. Occupational aspects: time-on-duty fatigue

The shift in the industrialized world from demanding physical effort to demanding mental tasks has led to increasing complaints of mental fatigue, which are common in the working population. Mental fatigue related to workload is dissimilar from mental fatigue in chronic illness, as different mechanisms are involved. It is directly linked with motivation, which in turn relates to obtaining rewards and avoiding harm and punishment [4]. Mentally fatigued subjects estimate perceived effort during exercise higher and reach a level of perceived maximal exertion earlier as compared with normal controls. This seems to indicate that mental fatigue limits exercise tolerance in humans through higher perception of effort rather than cardiorespiratory and musculo-energetic mechanisms [11]. In addition, sleep deprivation may aggravate ratings of perceived exertion during prolonged exercise [12]. To improve the control of fatigue-related incidents, not only hours of duty are important but also the amount of sleep individuals have acquired before starting service [13].

1.2. Measuring fatigue

It is not feasible to objectively assess the severity of reported fatigue, and to discriminate fatigue levels between and within subjects. The fatigue experience can only be measured using subjective self-report questionnaires. The information obtained from these instruments depends on the questions asked and on the interpretation by the responders. Therefore, a given fatigue rating scale may be limited to a specific situation and may fail to validly represent the fatigue experience in other conditions or samples. Taking into account the heterogeneous nature and various dimensions of fatigue, a rating scale should fundamentally measure different aspects of the fatigue experience. In recent years, a range of validated questionnaires has been published. Table 1 gives a comparative overview of the characteristics of the most frequently used fatigue questionnaires in CFS [14-16].

Table 1. Comparative overview of the characteristics of the most frequently used fatigue questionnaires in CFS

Scale name	VAS-F	FQ	FSS	CIS	FAI	MFI	PFRS
What is assessed	Severity	Severity	Impact and functional outcomes related to fatigue	Phenomenology and severity	Phenomenology, severity, impact and possible triggers	Phenomenology, severity and impact	Phenomenology and severity
Number of scale items	18	11	9	20	29	20	54
Scale type	Visual analogue	Yes/no response or 4-point Likert	7-point Likert	7-point Likert	7-point Likert	7-point Likert	7-point Likert
Target sample	General medical	CFS	Chronic medical	CFS	General medical	General medical	CFS
Internal consistency	0.91 - 0.96	0.88 - 0.90	0.88	0.90	0.70 - 0.91	0.84	0.96
Test-retest reliability	-	-	0.84	-	0.29 - 0.69	-	0.97
Cutoff score	-	-	3/4	-	-	-	-
Sensitivity to change	Yes	-	Yes	Yes	-	-	-

CIS, Checklist Individual Strength; FAI, Fatigue Assessment Instrument; FQ, Fatigue Questionnaire; FSS, Fatigue Severity Scale; MFI, Multidimensional Fatigue Inventory; PFRS, Profile of Fatigue-Related Symptoms; VAS-F, Visual Analogue Scale for Fatigue

2. Excessive daytime sleepiness

Fatigue is a complex and heterogeneous symptom that is often confused with sleepiness by patients and medical practitioners due to overlap or coexistence in many psychological and pathological conditions [17, 18]. Moreover, it has been hypothesized that patients with CFS may be unable to distinguish fatigue and sleepiness due to their severe underlying fatigue [19]. A weak association was, however, found between both daytime complaints in sleep-disordered patients [20, 21] as well as in CFS [18, 22].

Fatigue and excessive daytime sleepiness (EDS) have some common characteristics such as tiredness and feeling the need to lay down and rest, but other features clearly differentiate them from each other. Their discrimination is relevant for clinical practice and research purposes. Fatigue is usually described as weariness, weakness, depleted energy and feelings of exhaustion, whereas sleepiness is related to drowsiness, an increased propensity to fall asleep and decreased alertness [15, 17, 20, 23, 24].

A number of tools have been developed for the assessment of EDS. A precise history is often obtained by means of a sleep diary, whereas different rating scales query the patient's perception of sleepiness. The widely used Stanford sleepiness scale (SSS) [25], Karolinska sleepiness scale (KSS) [26] and visual analogue scales (VAS) measure short term changes in sleepiness, whereas other tests, such as the Epworth sleepiness scale (ESS) [27], evaluate a global level of sleepiness. Nevertheless, subjective measures have limitations since individuals are not always aware of their degree of sleepiness or their susceptibility to impairment. In contrast to fatigue, EDS can also be studied objectively. The multiple sleep latency test (MSLT) [28] has been endorsed as the gold standard objective measure for EDS by the American Academy of Sleep Medicine (AASM). Subjects are given multiple nap opportunities following nocturnal polysomnography (PSG) under standardized test conditions, in which the average time to fall asleep or the mean sleep latency is recorded. The results, however, have not consistently reflected subjective sleep outcomes [18, 19]. Other objective measures include the maintenance of wakefulness test (MWT) which records the ability to stay awake [29]. The psychomotor vigilance test (PVT) [30] and divided attention driving task (DADT) [31] focus more on neurocognitive function. This is especially relevant among commercial drivers, but these are not direct tests of physiological sleepiness.

3. Chronic fatigue and chronic fatigue syndrome

Often, fatigue cannot be attributed to a diagnosis of a well defined medical condition, psychiatric illness or primary sleep disorder and seemingly remains unexplained. If fatigue persists for more than six months, the term 'chronic fatigue' is used. If, in addition, a set of minor diagnostic criteria is fulfilled, the disorder is diagnosed as CFS.

3.1. Case definitions

Several case definitions have been developed for CFS as an illness characterized by long lasting unexplained chronic fatigue with a disabling impact on professional, social and daily functioning. The absence of another plausible explanatory disease and the presence of a number of associated clinical features are fundamental to this syndrome.

The term CFS was introduced in the medical lexicon in 1988 by Holmes et al. in a publication of the US Centers for Disease Control and Prevention (CDC) [32]. Since then, several new case definitions have been introduced. In 1994, revised CDC criteria were published by Fukuda et al. [33]. These are standard guidelines in the United States and are most widely used in other countries as well. To establish the diagnosis of CFS, the Fukuda definition require the presence of the major criterion of chronic, incapacitating fatigue of at least six months duration in combination with at least four out of eight minor criteria. These minor criteria include short-term memory or concentration impairment, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain without swelling or redness, headaches of a new type, pattern or severity, unrefreshing sleep and postexertional malaise lasting for more than 24 hours. These revised CDC criteria allow inclusion of a larger number of patients than the previous Holmes guidelines. Additionally, all physical signs, such as palpable lymph nodes and documented fever, were dropped from the inclusion criteria, through which the list of symptoms was diminished from eleven to eight and the required number of secondary symptoms was decreased from eight to four.

The key features of the different case definitions [32-36] are summarized in Table 2a and b. All existing guidelines are founded on expert-based consensus and are not supported by robust medical evidence.

3.2. Epidemiology

Epidemiological data on the prevalence of CFS are quite diverse. Both the case definition used and the characteristics of the screened samples explain the wide ranges observed (Table 2).

The estimated crude point prevalence was 0 to 300 per 100.000 persons when the more restrictive Holmes criteria were used and 190 to 2540 per 100.000 medical patients based on the Fukuda criteria (Table 2). The Holmes case definition considers any psychiatric disease as an exclusion for the diagnosis of CFS, whereas the Fukuda criteria only retain a bipolar disorder and a major depressive disorder with psychotic characteristics (and hence not an unipolar depression) as exclusionary disorders. Furthermore, eating disorders may be either a life long or a five year exclusion criterion.

The prevalence of CFS reported varies between 100 and 2100 per 100.000 patients in primary care and between 0 and 4800 per 100.000 individuals in community-based samples (Table 2). As the prevalence of CFS in the community may be quite high, epidemiological studies relying on referrals to outpatient clinics may lead to an underestimation of the burden of CFS in the general population.

A point prevalence study of CFS in a large random sample of an ethnically diverse community in the US indicated a prevalence of 0.42% (95% confidence intervals 0.29-0.56%) with highest scores in women and minority groups [46]. This finding was reproducible across ethnic groups and did not confirm the previously presumed predominance in white middle class patients, which may be due to bias attributable to accessibility and utilization of health care facilities [52].

3.3. Aetiology and pathogenesis

Among other terms, CFS is also referred to as myalgic encephalomyelitis (ME), post-viral fatigue syndrome (PVFS), and chronic fatigue immune dysfunction syndrome (CFIDS). The terminology of these alternative labels might implicate the existence of a systemic inflammatory condition, however, no such mechanism has been irrefutably demonstrated.

The aetiology and pathogenesis of CFS remain essentially unknown, but are generally believed to be multifactorial. Infections often seem to trigger CFS, although other factors including toxic substances, sleep disturbances and psychological trauma may be involved. Moreover, dysregulation of the immune or the neuroendocrine system may determine the pathophysiology of the illness, leading to a loss of capacity to adapt to all kind of stressors.

Table 2a. Key features of CFS according to different definitions

Holmes et al. 1988 (CDC) USA [32]	Lloyd et al. 1988 Australia [34]	Sharpe et al. 1991 (Oxford) UK [35]	Fukuda et al. 1994 (CDC)* USA [33]
MAJOR AND MINOR CRITERIA			

Major criteria:
- new onset of persistent or relapsing, debilitating fatigue,
does not resolve with bedrest, reduction or impairment of daily activity, duration ≥6 months
- exclusionary clinical conditions that may produce similar symptoms
 	
Minor symptom criteria:
- mild fever
- sore throat
- painful lymph nodes in the anterior or posterior cervical or axillary distribution
- generalized muscle weakness
- myalgia
- prolonged, generalized fatigue after exercise
- generalized headaches
- migratory arthralgia without joint swelling or redness
- neuropsychologic complaints
- sleep disturbance
- acute onset (over a few hours to a few days)
 	
Minor physical criteria:
- low-grade fever
- nonexudative pharyngitis
- cervical or axillary lymphadenopathy
	Major criteria:
	- generalized, chronic persisting or relapsing fatigue, exacerbated by minor exercise, significant disruption of usual daily activities, duration >6 months
	- neuropsychiatric dysfunction
	- and/or: abnormal cell-mediated immunity
	
	Supportive symptoms:
	- myalgia
	- arthralgia
	- headaches
	- depression
	- tinnitus
	- paraesthesiae
	- sleep disturbance
	- lymphadenopathy
	- localized muscle tenderness
	- pharyngitis
		Characteristics:
		- fatigue is the principal symptom
		- syndrome of definite onset
		- disabling fatigue that affects physical and mental functioning
		- duration ≥6 months
		- possible symptoms: myalgia, mood and sleep disturbance
		- exclusions:
		  (i) medical conditions producing chronic fatigue
		  (ii) certain psychiatric disorders (manic depressive illness, substance abuse, eating disorder, organic brain disease)
			Major criterion:
			unexplained, persistent or relapsing chronic fatigue,
			new or definite onset,
			not result of ongoing exertion,
			not substantially alleviated by rest,
			substantial reduction in previous occupational, social or personal activities
			
			Minor criteria:
			- impaired short-term memory or concentration
			- sore throat
			- tender cervical or axillary lymph nodes
			- muscle pain
			- multijoint pain without joint swelling or redness
			- headaches of a new type, pattern or severity
			- unrefreshing sleep
			- post-exertional malaise >24 h
			
			Exclusions:
			- active, unresolved or suspected disease likely to cause fatigue
			- primary sleep disorders
			- psychotic, melancholic or bipolar depression
			- anorexia or bulimia nervosa
			- alcohol or other substance misuse
			- severe obesity

DIAGNOSTIC CRITERIA			
Presence of: 2 major criteria + ≥ 6 out of 11 minor symptom criteria + ≥ 2 out of 3 minor physical criteria **OR** 2 major criteria + ≥ 8 out of 11 minor symptom criteria	**Presence of:** 2 or 3 major criteria + possible presence of supportive symptoms	**Presence of:** 6 characteristics, including the possible presence of other symptoms (different from fatigue) particularly myalgia, mood and sleep disturbance	**Presence of:** major criterion + ≥ 4 out of 8 minor criteria during ≥ 6 months
PREVALENCE			
Primary care 300 / 100.000 [37] 100 / 100.000 [38]	1000 / 100.000 [37] 200 / 100.000 [38]	400 / 100.000 [37] 700 / 100.000 [38]	500 / 100.000 [38] 1600-2100 / 100.000 [43] 190 / 100.000 [44]
Community-based sample 37 / 100.000 [34] 7 / 100.000 [39] 75-267 / 100.000 [40] 4-10 / 100.000 [41] 0 / 100.000 [42]	4800 / 100.000 [42]	2400 / 100.000 [42]	194 / 100.000 [45] 420 / 100.000 [46] 1400 / 100.000 [42] 235 / 100.000 [47] 2540 / 100.000 [48] 1000 / 100.000 [49]

*The Fukuda et al. 1994 definition was used in the present thesis as diagnostic criteria for clinical and research purposes

h, hours; ND, no data

Table 2b. Key features of CFS: comparison of the original and revised Canadian criteria

Carruthers et al. 2003 [36]	Carruthers et al. 2011 [50]
MAJOR AND MINOR CRITERIA	

Symptom clusters:
- fatigue: new onset, unexplained, persistent or recurrent physical and mental fatigue, reduced activity level
- post-exertional malaise and/or fatigue
- sleep dysfunction
- pain
- neurological/cognitive manifestations
- ≥1 symptom from 2 of the following categories:
  (i) autonomic manifestations
  (ii) neuroendocrine manifestations
  (iii) immune manifestations
- duration ≥6 months, usually acute onset, may be gradual
	Major criterion:
	- post-exertional neuroimmune exhaustion
	
	Neurological impairments:
	- neurocognitive impairments
	- pain
	- sleep disturbance
	- neurosensory, perceptual and motor disturbances
	
	Immune, gastro-intestinal and genitourinary impairments:
	- flu-like symptoms may be recurrent or chronic and typically activate or worsen with exertion
	- susceptibility to viral infections with prolonged recovery periods
	- gastro-intestinal tract
	- genitourinary
	- sensitivities to food, medications, odours or chemicals
	
	Energy production/transportation impairments
	- cardiovascular
	- respiratory
	- loss of thermostatic stability
	- intolerance of extremes of temperature

DIAGNOSTIC CRITERIA	
Presence of: 7 criteria (symptom clusters)	**Presence of:** major criterion + ≥ 1 symptom from 3 out of 4 neurological impairments + ≥ 1 symptom from 3 out of 5 immune, gastro-intestinal and genitourinary impairments + ≥ 1 symptom from energy production/transportation impairments
PREVALENCE	
Primary care 110 / 100.000[4] **Community-based sample** ND	**Primary care** ND **Community-based sample** ND

Comments on the consensus criteria of Carruthers et al. 2011 [51] :
  1) No credible substantiated recommendations given for clinical and research application of the criteria
  2) No true consensus represented of the spectrum of credible scientific views
  3) Reversion to the term 'myalgic encephalomyelitis' and abolishing 'CFS'
  4) Criticizing the currently accepted international diagnostic criteria (Fukuda et al. 1994) as 'too broad' and search to discard published findings that have applied these criteria
  5) Cited literature biased towards positive findings
  6) Use of labels which highly suggest a notional pathophysiology	

Some authors, however, heavily rely on one or multiple biological explanations that may co-exist or occur in a sequential fashion [53]. Nevertheless, most hypotheses generated have not reached a high level of evidence, lacking prospective assessment with control groups. This is illustrated in table 3.

3.3.1. Biologic findings in CFS
3.3.1.1. Immunological dysfunction

Regarding the nature of the symptoms and the finding of abnormalities in the immune system, it has been suggested that immunological changes play a role in CFS. Slightly increased parameters of inflammation and circulating pro-inflammatory cytokines such as interleukin (IL) 1, IL-6 and tumour necrosis factor (TNF) α have been found [71]. Ribonuclease (RNase) L, which plays a role in the elimination of viral mRNAs, was shown to be degraded in white blood cells of CFS patients [72]. The literature also suggests a skewing towards impaired cellular immunity including diminished natural killer cell cytotoxicity [73]. Alterations in T cell numbers have been described, but were not consistently found [71].

The analysis of the immune function is a major challenge in a heterogeneous condition as CFS in which the cause is unknown and the variability in symptom severity fluctuates from day to day. Further complications exist in the analysis of immune cells which can vary in number depending on time and day and even mild exertion. Moreover, it is currently well known that the immune system is significantly influenced by stress, mood and sleep disturbances, which are common in CFS. In combination with the fragile nature of most cytokines demanding immediate blood separation and the marked variation in assay sensitivity and reproducibility, it is not surprising that there is little consensus on the presence, the nature and the degree of immune dysfunction and it is still unclear whether these defects are the cause or the effect of the disorder.

Table 3: Illustration of robustness of evidence of a number of etiologic hypotheses on CFS

Etiologic factor	Comparison CFS versus controls		Methods	Treatment	Outcome	Duration of follow-up	Study type	Level of evidence	Study
	CFS (% positive)	Controls (% positive)							
Amalgam	CFS n=132; Relative risk estimate for an exposure unit of 100 amalgam-filled surface-years: HR 0.89 (95% CI: 0.94-1.03)	No healthy controls	• Disease codes • Dental records	Not applicable	Presence of conditions associated with dental amalgam	Mean: • Initial cohort: 12.5y • Final cohort: 11.2y	Retrospective, cohort study	2	Bates 2004 [54]
XMRV	68/101 (67%)	8/218 (3.7%)	PCR	Not applicable	Presence of XMRV	ND	Retrospective, cohort study (not blinded PCR operator)	2	Lombardi et al. 2009 [55]
XMRV	32/37 (86.5%)	3/44 (6.8%)	RT-PCR	Not applicable	Presence of XMRV	ND	Retrospective, cohort study	2	Lo et al. 2010 [56]
XMRV	0/186 (0%)	No healthy controls	PCR	Not applicable	Presence of XMRV	ND	Prospective, cohort study, (blinded PCR operator)	2	Erlwein et al. 2010 [57]
XMRV	0/142 (0%)	0/157 (0%)	PCR Serology	Not applicable	Presence of XMRV	ND	Retrospective, multicentre, case-control	2	Groom et al. 2010 [58]
XMRV	0/32 (0%)	• HIV: 0/43 (0%) • Rheumatoid arthritis (RA): 0/97 (0%) • Hematopoietic stem-cell or solid organ transplant: 0/26 (0%) • General cohort of patients presenting for medical care (matched with RA): 0/95 (0%)	PCR	Not applicable	Presence of XMRV	ND	Prospective, cohort study, monocentric	2	Henrich et al. 2010 [59]

Etiologic factor	Comparison CFS versus controls		Methods	Treatment	Outcome	Duration of follow-up	Study type	Level of evidence	Study
	CFS (% positive)	Controls (% positive)							
XMRV	0/65 (0%)	0/65 (0%) healthy controls	RT-PCR	Not applicable	Presence of XMRV	ND	Retrospective, case-control, matched, monocentric	2	Hong et al. 2010 [60]
XMRV	0/50 (0%) (PCR) 0/51 (0%) (WB) 0/51 (0%) (ELISA)	0/56 (0%) (PCR) 0/53 (0%) (WB) 0/53 (0%) (ELISA) 0/41 (0%) blood donors	PCR Serology	Not applicable	Presence of XMRV	ND	Retrospective, case-control, matched, monocentric	2	Switzer et al. 2010 [61]
XMRV	0/32 (0%)	0/43 (0%)	RT-PCR	Not applicable	Presence of XMRV	ND	Retrospective, Case-control, Matched, monocentric		Van Kuppeveld et a. 2010 [62]
XMRV	0/61 (0%) (43 patients had previously been identified as XMRV+)	ND	PCR RT-PCR	Not applicable	Presence of XMRV	ND	Retrospective, cohort study, monocentric	2	Knox et al. 2011 [63]
XMRV	0/147 (0%) 0/121 (0%) 0/121 (0%) 0/117 (0%) 9/147 (6.1%)	0/146 (0%) 0/110 (0%) 0/111 (0%) 0/126 (0%) 0/146(0%)	RT-PCR RT-PCR PCR PCR Serology	Not applicable	Presence of XMRV	ND	Prospective, blinded, multicentre, case-control	2	Alter et al. 2012 [64]
EBV	3/22 (14%) OR:0.4 (95% CI: (0-2.4)	6/22 (27%)	PCR	Not applicable	Presence of Epstein-Barr virus	ND	Prospective, (co-twin/matched pair design) case-control study	2	Koelle et al. 2002 [65]

Etiologic factor	Comparison CFS versus controls		Methods	Treatment	Outcome	Duration of follow-up	Study type	Level of evidence	Study
	CFS (% positive)	Controls (% positive)							
EBV	*Group 1:* 27 CFS patients, EBV positive • Improvement of EI: Valacyclovir: +1.12 units Placebo: +0.42 units • Decreased serum IgM antibody titer to viral capsid antigen of EBV • Improved or disappearance of abnormal cardiac wall motion • Decreased resting tachycardias • Decrease/absence of symptoms		• Energy Index (EI) point score • Holter monitor • Multigated (radionuclide) MUGA rest/stress ventriculographic examination • EBV serum IgM viral capsid antibodies (VCA) • EBV early antigen diffuse (EA)	*Group 1:* • Valacyclovir 1.0g/6h (n=14) • Placebo (n=13)	• Physical functional capacity • EBV serum antibodies • ECG • Functional activity appraisal	ND	Prospective, blinded, random placebo-controlled trial	1	Lerner et al. 2007[66]
	Group 2: 27 CFS patients, EBV positive • Improvement of EI: +3.2 • Decreased serum IgM antibody titer to viral capsid antigen of EBV • Improved or disappearance of abnormal cardiac wall motion • Decreased resting tachycardias decrease/absence of symptoms		• Energy Index (EI) point score • Holter monitor • Multigated (radionuclide) MUGA rest/stress ventriculographic examination • EBV serum IgM viral capsid antibodies • EBV early antigen diffuse (EA)	*Group 2:* • 3 months Valacyclovir 1.0g/6h • After 3 months (if EI had not improved): + oral cimetidine (500mg bid) or probenecid (500mg bid) • In case of valacyclovir-associated diarrheas: famciclovir (14.3 mg/kg/6h)	• EI • EBV serum antibodies • ECG • Functional activity appraisal	36 months	Prospective, open trial	2	
EBV	Subjects: • 5 fatigued patients, acute EBV infection • 5 fatigued patients, with acute infection not due to EBV, but seropostive for EBV Results: • Antibody levels: no difference between patient groups • Immunoblot confirmed ELISA results • EBV DNA-levels : similar to healthy controls	Subjects: • 10 non-fatigued controls	• ELISA • Immunoblot • PCR	Not applicable	Activity and host response to herpesviruses	12 months	Prospective, case-control, pilot study	2	Cameron et al. 2010 [67]

Etiologic factor	Comparison CFS versus controls		Methods	Treatment	Outcome	Duration of follow-up	Study type	Level of evidence	Study
	CFS (% positive)	Controls (% positive)							
EBV	6 CFS patients: • EBV EA: 93.9% • Neutralizing antibodies against the EBV-encoded dUTPase: 44.2% • DNA polymerase: 78.8%	19 unknown persons: • 31.6% postive for EBV EA • neutralizing antibodies against the EBV-encoded dUTPase: 0% • DNA polymerase: 0%	• ELISA • Neutralization assays	Valacyclovir (14.3mg/kg) ≥ 12 months	• Antibody to EBV viral capsid antigen (VCA) IgM • EBV Diffuse Early Antigen EA(D) • Neutralizing antibodies against EBV-encoded DNA polymerase and EBV encoded dUTPase	16 months	Prospective, matched	2	Lerner et al. 2012 [68]
EBV	32/61 (52% responders) CFS patients • Baseline antibody titers: no significant association with response • After treatment: average change in physical and cognitive functioning levels: +19% and +23% (P<0.0001) • Longer treatment was associated with improved response (P=0.0002) • No significant difference was found between responders and non-responders among other variables analyzed	No controls	• Cognitive and physical functioning levels • Antibody titers EBV VCA IgG, EBV NA IgG, and EBV EA IgG	Valganciclovir 900mg/2 x daily (3 weeks) – 900mg/daily (maintenance dose)	• Physical functioning • Cognitive functioning	6 months after treatment	Uncontrolled, unblinded, retrospective study	2	Watt et al. 2012 [69]

HR: Hazard ratio, PCR: polymerase chain reaction, RT-PCR: real-time PCR, WB: Western blot, ELISA: Enyme-linked immune sorbent assay; EI: Energy Index, EBV: Epstein-Barr virus, XMRV: xenotropic murine leukaemia virus-related virus

Note: Grading system for rating recommendations according to the Infectious Diseases Society of America–United States Public Health Service [70]
1 Evidence from ≥ 1 properly randomized, controlled trial
2 Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from > 1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
3 Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

3.3.1.2. Endocrinology

Interest in investigating the hypothalamic-pituitary-adrenal (HPA) axis in CFS arose from clinical similarities between CFS and states of glucocorticoid deficiencies as well as from early observations of reduced adrenocortical activity in chronically fatigued patients. HPA axis-related research in CFS is, however, hampered by the influence of various factors such as the presence of major depression or other comorbid conditions, early-life stress, the length of illness and the day time of testing. Nevertheless, about half of the basal hormone and challenge studies in literature indicate a mild HPA axis suppression and hypocortisolism, whereas no significant differences in HPA axis function between CFS patients and controls were apparent in other studies [74]. It is thought that physical or psychological stress is a predisposing and/or maintaining factor in CFS, which may be associated with HPA axis hypofunction.

Corticotropin-releasing factor (CRF) is a hypothalamic neuropeptide driving adrenocortico-tropic hormone (ACTH) release and having a key role in the regulation of metabolic, neuro-endocrine and autonomic adaptations to stress. Additionally, there is evidence that CRF itself has analgesic properties and that the reduction in the availability of CRF in the CNS may contribute to complaints of pain and fatigue [75].

Furthermore, the HPA axis dysfunction is possibly linked with immune disturbances in CFS. Inflammatory cytokines such as IL-1 can modulate release of CRF and stimulate the production of cortisol which in his turn exerts immunosuppressive effects. This negative feedback loop prevents the immune response from overshooting. However, if hypothalamic CRF containing neurons fail to response adequately to cytokine stimulation, the immune system may come in a hyper-immune state leading to excessive inflammation [74-76].

Neuroendocrine factors such as CRF have been shown to affect sleep regulation [77]. In major depression, a causal relationship seems to exist between CRF hyperactivity and polysomnographic disturbances such as a decrease in non-rapid eye movement (NREM) sleep and REM disinhibition [77]. Polysomnographic findings in CFS patients show a decrease in slow wave sleep, an increase in sleep onset latency and a higher number of stage shifts per hour, however, the association with neuroendocrine changes has not yet been established [78]. Despite a fairly consistent pattern of findings for HPA axis disturbances has found, it is still a matter of debate whether they have a primary role in the pathogenesis of CFS. Therefore, future work should focus on improving the understanding of the cause and the relevance of these observed changes.

3.3.1.3. Infections

3.3.1.3.1. Microbial infections

Numerous studies have investigated the role of infections in the pathogenesis of CFS and various viruses and virus groups have been implicated in CFS at some time, including Epstein-Barr virus, cytomegalovirus, parvovirus B19, human herpes virus-6, group B cox-sackievirus, human T cell leukaemia virus II-like virus, spumavirus, hepatitis C virus, human lentiviruses and herpes virus-7 [78]. The detection of several viruses has, however, provided conflicting results and various values of seroprevalence have been published. This may, at least, be due to the use of different diagnostic criteria of CFS and to different viral antigens used throughout serological studies. In addition to viruses, several other microorganisms have been considered to be associated with chronic fatigue. These include several types of bacteria such as mycoplasma species in particular but also *Borrelia* [71].

3.3.1.3.2. Xenotropic murine leukemia virus-related virus (XMRV)

Recently, a novel virus, named xenotropic murine leukaemia virus-related virus (XMRV), was described as possible aetiological agent of CFS, however, this hypothesis is currently definitely disproved.

In 2006, researchers identified a novel retrovirus in samples from patients with prostate cancer who had a deficiency in RNase L function [79]. This virus got the name XMRV, because of its similarity with the known murine leukaemia viruses. Although there is no evidence to suggest an increase in prostate cancer among CFS patients, scientists at the Whittemore Peterson Institute and collaborators [55] looked for the virus in their CFS cohort since many of these patients display immunological abnormalities including RNase L deficiencies. In late 2009, they were able to find XMRV nucleic acid in white blood cells from 67% CFS patients compared to only 4% controls, although they did not find a link to RNase L deficiency [55]. This study generated great excitement and has a great impact in the CFS community, especially as the authors claimed to have cultured virus from these patient samples. Some patients started taking antiretroviral medications without waiting for the association to be confirmed [80]. This story was, however, soon mired in confusion as three other teams quickly published contrary reports that they could find little evidence of this virus in their CFS cohorts [57, 58, 62]. Additional negative reports soon followed and to date, no other research groups have published similar positive findings of XMRV in CFS patients. The discussion has been spurred by reports of other murine leukaemia virus-like viruses in CFS patients [81] and sample contamination [64, 82-85]. The increasing and unequivocal evidence

that XMRV has little to do with CFS has nowadays led to the insight that the association between this virus and CFS is very uncertain.

This story shows that research results can have important consequences for public health and that it may raise hope for patients desperate to know the cause of their illness in hope of a possible therapy. Therefore, these data warrants for caution when interpreting research results.

3.3.1.4.Exposure to toxic substances
3.3.1.4.1.   Toxic agents used in war

CFS has been linked to the Gulf War Syndrome because of its similarity and overlap in symptoms. Gulf War veterans were exposed to a wide range of exogenous toxic agents and up to now, they appear to suffer more frequently from a variety of complaints, including depression, fatigue, headache, joint pain, muscle pain, concentration problems and memory loss, than non-Gulf War participants [86].

In their study to correlate exposure to a variety of substances with health damage in Gulf War veterans, Haley and Kurt [87] described three syndromes using factor analysis. In subsequent years, several other groups have tried to replicate this work with different groups of Gulf War veterans, but none of them has found the same clusters of symptoms [88]. Instead, they hypothesized that Gulf War veterans suffered from the same symptoms as also seen in the general population where they have the names CFS and fibromyalgia (FM) [88].

It remains unclear if this set of symptoms, whether they are in accordance with the criteria for CFS or not, are the effect of exposure to toxic agents used in the Gulf War such as nerve gas, pyridostigmine bromide tablets, depleted uranium, pesticides, anthrax and botulism vaccines or smoke from oil wells. The association between CFS and the exposure to toxins has also been studied in other contexts. The bioaccumulation of dioxins for instance has been known to be associated with a wide range of health problems. Older literature suggests higher serum levels of chlorinated hydrocarbons in CFS patients compared to non-CFS control subjects and comparable levels to that of patients with CFS symptoms with known chemical exposure [89]. Nevertheless, some scientists believe that the health complaints of veterans may have little to do with anything specific in the Gulf War and everything to do with war itself, since after almost every major armed conflict, formerly healthy soldiers have come back sick [88].

3.3.1.4.2. Amalgam

In the field of dentistry, CFS has been linked to amalgam fillings. Mercury amalgam restorations have been used since 1818 and although more esthetic dental materials have become readily available, amalgam remains popular due to its relative low cost, durability and ease of use [90]. Nevertheless, dental amalgam contains about 50% mercury and sensitive analytical chemistry techniques showed continuous release of mercury, making its use in dentistry controversial [90]. Inorganic mercury primarily affects the nervous and renal systems, although it may also have effects on immune, respiratory, cardiovascular, gastrointestinal, hematologic and reproductive systems. Additionally, there is a widespread popular belief that CFS is associated with dental amalgams, but little epidemiological investigation. In a retrospective study of 20.000 New Zealand military personnel, no association was found between cumulative amalgam exposure and CFS. The relative risk estimate for an exposure unit of 100 amalgam-filled surface-years was 0.98 (95% CI: 0.94 - 1.03) [54].

3.3.2. Biopsychosocial model

Harvey and Wessely [91] proposed a biopsychosocial model with predisposing, precipitating and perpetuating factors rather than a purely biologic model for all manifestations of CFS (Figure 1). This model is the rationale for behaviourally oriented interventions, such as cognitive behaviour therapy (CBT) and graded exercise therapy (GET). The authors suggest that a trigger instigates fatigue in predisposed individuals, which, mediated by maintaining factors, result in CFS [91]. In this model, the initial cause of fatigue has a limited impact on the eventual course of the syndrome and the perpetuating factors, which are principally behavioural ones, need to be addressed if recovery is to occur. The biological component of this model is restricted to the possible triggers and the biological responses to the initial fatigue. A multitude of aetiological triggers has been postulated, including infectious agents, stress, exposure to toxic substances, abnormalities in the CNS, immune or neuroendocrine systems [91]. However, no unequivocal cause-consequence relationships have been demonstrated for each of these supposed aetiological models.
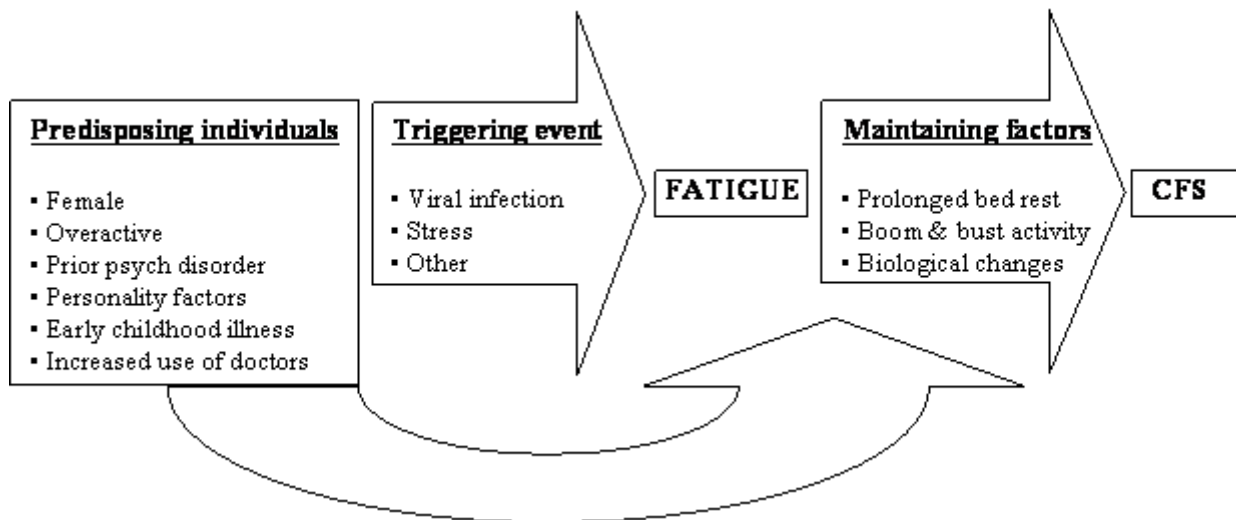
Figure 1. The biopsychosocial model for chronic fatigue syndrome (CFS) of Harvey and Wessely [91].

3.3.3. CFS: a complex illness

CFS has been marred by controversy. The situation became confused when the term 'myalgic encephalomyelitis' was introduced and used besides 'CFS'. A 2002 commentary in the *Lancet* noticed that "the fact that both names for the illness were used, symbolizes respect for different viewpoints whilst acknowledging the continuing lack of consensus on a universally acceptable name" [92]. Major disagreements over the aetiology and the pathophysiology of CFS and the wide range of treatments further compounds the confusion.

Possibly, some medical practitioners do not acknowledge the disease as a 'real' condition and still believe that the syndrome is 'all in the mind'. According to Holgate et al. [93], many patients feel that the medical profession attributes CFS to psychiatric or psychological disorders in the absence of other mechanisms. Nevertheless, these patients often resist the idea of having a psychiatric disorder, because psychiatric illnesses generally remain a stigma and are often seen as hysterical, non-existent or imaginary. This view has been strengthened by the only proven effective interventions being those based on symptom relief rather than on a specific set of underlying aetiological causes. Some CFS patients also report a moderately beneficial effect of graded exercise with an initial worsening of their symptoms. The frustration expressed by patients may reflect the scepticism of medical practitioners about the existence of CFS as a 'real' disease.

The five current case definitions for CFS all attempt to capture critical aspects of the illness in order to differentiate from similar symptom clusters that are associated with other diseases. The existence of such criteria is important prior to make a diagnosis as well as for research purposes. Nevertheless, as long as a validated biomarker for CFS is not discovered, the

definition remains symptom-based and the existence and use of different criteria reflect the complexity of the syndrome. Sometimes the criteria are modified to be more restrictive, to concentrate on severe disease, or less restrictive, to include the wide variety of patients with this syndrome. This hampers making meaningful comparisons across studies and asks for an improved description of enrolment characteristics of both patients and controls.

Holgate et al. [93] emphasize a lack of research capacity in the field and the importance of engaging scientists to undertake research into the condition. An interdisciplinary UK Research Advisory Group, that includes experts from a wide range of disciplines, highlight that more research should be done into autonomic dysfunction, cognitive symptoms, fatigue, immune dysregulation, pain and sleep disorders in patients with CFS [93]. They believe that new research perspectives are essential in the better understanding of the illness and its determinants and identifying preventive and/or therapeutic targets.

3.4. Subgroups within CFS

Chronic fatigue and CFS are likely to be heterogeneous conditions in which different subgroups have been proposed, depending e.g. on the mode of onset, the severity of symptoms, the presence or absence of psychiatric comorbidity and the ways of coping. To seek clusters of patients who share underlying indicators, factor analysis as well as latent class analysis have been used [94-97]. In this way, two to five subphenotypes have been defined in CFS, however, no work has looked into the validity of these empirically defined clusters.

The attempts in defining subgroups have relied on symptoms and demographic measures, without taking into account possibly associated biological abnormalities, such as the down-regulated HPA axis activity. It has been suggested that such biomarkers should be added to reveal subphenotypes that are defined by the underlying biological processes, which are called endophenotypes [98, 99].

Vollmer-Conna et al. [98] defined discrete subject groups within patients with unexplained chronic fatigue using measures of symptoms, demographics, clinical measures and laboratory tests that have been reported to be abnormal in studies of CFS patients. The latter included endocrine and immune tests and PSG. Principal component analyses were performed to reduce the large number of variables and to look for the most explanatory ones, followed by latent class analyses. The resulting classes were differentiated by obesity, sleep hypopnea, depression, psychological stress response, objective and subjective sleep disturbance, interoception and menopausal status [98]. These findings were partially replicated by the same research group in order to validate the existence of a latent class structure of CFS [100].

New insights could originate from functional CNS imaging. Different studies have shown evidence of reduced grey matter in CFS patients which may be suggestive for patient's common complaint of impaired memory [101-104]. It should be emphasized, however, that a number of biological abnormalities have not irrefutably been demonstrated in CFS, implying caution in including biomarkers when looking for subgroups. Nevertheless, it is now generally believed that CFS is a heterogeneous entity comprised of several conditions with different underlying pathophysiological mechanisms.

3.5. Overlapping and comorbid clinical conditions

According to the 1994 CDC criteria, the diagnosis of CFS requires the absence of medical and psychiatric disorders that could explain the chronic fatigue, such as OSA, narcolepsy, past or current diagnosis of a major depressive disorder with psychotic or melancholic features, bipolar affective disorders, schizophrenia, dementia, lifetime eating disorders and alcohol or other substance abuse within 2 years before the onset of the chronic fatigue [33]. Nevertheless, patients with chronic fatigue and CFS often present with additional medical and psychiatric diseases that are not regarded as part of the exclusion criteria and that are considered as comorbid disorders. These exclusionary conditions are, however, not well defined in the Fukuda criteria, leading to different prevalences of comorbid conditions described in literature. Many of these entities also show overlap in symptoms with the syndromal definition of CFS. Although the relationship between these overlapping conditions is poorly understood, it has been the focus of recent research in order to require better understanding and improved management.

3.5.1. Fibromyalgia

In the context of overlapping somatic syndromes, the relationship between CFS and FM has received the most attention in literature. The American College of Rheumatology (ACR) FM classification criteria were introduced more than 20 years ago [105]. For diagnosis, these require the presence of widespread pain for at least three months and tenderness on pressure in at least 11 of 18 specified sites on digital palpation, performed with an approximate force of 4 kg [105]. However, some problems have been recognized in the diagnosis of FM using these strict criteria. On the one hand, the tender point count was not always performed in primary care and FM diagnosis has often been a symptom-based diagnosis in practice. On the other hand, patients who improved or whose symptoms and tender points decreased could fail to satisfy the ACR 1990 classification criteria. Taken these considerations into account, a

broad-based severity scale that could differentiate among patients according to the level of FM symptoms was recently developed [106]. The most important diagnostic variables are the widespread pain index (WPI), a measure of the number of painful body regions, and the symptom severity (SS) scale, a measure of FM symptom severity. A combination of both parameters has given a newly proposed case definition for FM: (WPI $\geq$7 and SS $\geq$5) or (WPI 3-6 and SS $\geq$9) [106]. Remarkably, the SS scale score is based on symptoms which are often seen in CFS patients, namely fatigue, unrefreshing sleep, cognitive problems and a number of somatic symptoms such as muscle pain, headache and thinking or remembering problems. Between 35 and 70% of CFS patients experience myalgia, headache and other local or diffuse pain and up to 90% of adults with FM report significant fatigue. The large overlap in symptomatic features is reflected in a considerable overlap between both syndromes: it has been estimated that in referral clinics, 35% to 70% of CFS patients meet criteria for FM and, conversely, 20% to 70% of those with FM have CFS [107].

It has been hypothesised that the apparent overlap between CFS and FM results from shared underlying mechanisms or coexisting psychiatric disorders. Aaron and colleagues [108] investigated this association in a twin study by examining whether a consistently higher frequency of comorbid conditions among the fatigued twins would be observed when adjusted for the number of lifetime affective and anxiety psychiatric disorders. The odds ratio comparing the frequency of comorbidity between fatigued and non-fatigued twins was greater than 10, even after adjusting for psychiatric status, suggesting that the association was not solely the consequence of psychiatric illness [108]. Possible alternative explanations for the association between CFS and comorbid conditions are the interplay between genes and environmental influences.

3.5.2. Insomnia and other sleep disorders

It is assumed that sleep impairment may provoke daytime dysfunctioning. Obviously, EDS and fatigue may be direct consequences from primary sleep disorders, such as insomnia, sleep-disordered breathing and narcolepsy. Dissatisfaction with daytime functioning may therefore be an incentive to seek medical help for a presumed disturbance of sleep. However, patients without primary sleep disorders may report awakening unrefreshed from nocturnal sleep, commonly known as nonrestorative sleep (NRS). This is a key symptom of chronic unexplained fatigue and CFS.

All CFS case definitions include a minor criterion reflecting on aspects of sleep. The terms used vary substantially from (aspecific) sleep disturbance, to unrefreshing and NRS, to

various aspects of sleep quality, sleep duration and elements of insomnia and/or hypersomnia. Sleep disturbance is, however, reported by the vast majority of patients who receive a final diagnosis of CFS, with 87-95% of CFS cases in community surveys complaining of NRS [46, 49, 95, 109]. The construct of NRS is highly complex and suffers from conceptual inconsistencies. Typically, patients report awakening unrestored or unrefreshed after a preceding night with sufficient sleep duration. NRS was first mentioned as a symptom of insomnia [110]. It has been shown that insomnia patients with NRS have more frequent daytime sequellae than those without NRS [111, 112]. Clearly, CFS and insomnia share features with respect to NRS and daytime dysfunctioning and could be manifestations of one and the same underlying disorder. To reveal if CFS patients suffer from insomnia is predominantly based on their subjective complaints. A thorough study with monozygotic twins revealed that CFS patients mentioned more symptoms being relevant for insomnia, whereas polysomnographic measures of insomnia did not differ between CFS patients and their healthy co-twins [19]. This phenomenon is seen as 'sleep-state misperception insomnia'. Similarly, insomnia patients also report diminished activity levels and a greater number and severity of daytime complaints which seem not to be associated with objective measures of daytime performance [113]. In this manner, a phenomenon of 'daytime performance misperception' is conceptualized as a discrepancy between a patient's self-perceptions of daytime impairment and objective measures of such impairment. It has been proposed that these patients may over attend or selectively attend to the potential consequences of insomnia. The detection of cognitive errors or physical challenges that occur during the day reinforces the tendency to attend to (and interpret such events as being related to) insomnia [113]. In contrast, good sleepers pay little attention to 'deficits' and to the extent that these phenomena are noticed, they are not interpreted as being the result of poor sleep. Insomnia patients have shown to display greater 'attentional bias' for sleep related stimuli than good sleepers [113].

Primary sleep disorders, especially OSA and narcolepsy, are regarded conditions that exclude CFS according to the Fukuda criteria [33], however, they are frequently diagnosed in patients with chronic fatigue and CFS. If these conditions should be seen as diagnostic exclusion criteria or as comorbidities of CFS is discussed further on in this thesis [114].

3.5.3. Psychiatric comorbidity
3.5.3.1.Prevalence

A variety of psychiatric conditions, particularly anxiety and depressive disorders, do not exclude a patient from the diagnosis of unexplained fatigue and are often seen in comorbidity

with chronic fatigue and CFS. In research studies, this comorbidity has especially been investigated in patients from primary and tertiary clinical settings [115-117]. Only a handful of researchers examined the prevalence of psychiatric conditions in patients with chronically unexplained fatigue identified from the general population [118-120]. Variances in prevalence amongst studies may be influenced by the application of different methodologies in assessing psychiatric disorders and by the use of different definitions for chronic fatigue and CFS. Nevertheless, in studies performed in clinical as well as in community-based samples, high prevalence rates of psychiatric comorbidity were observed in CFS patients and slightly lower, but still high in chronic fatigue patients who do not fulfil the criteria for CFS. Up to 90% of CFS patients have been found to show at least one lifetime psychiatric condition and about 60% have been found to fulfil the criteria for at least one current psychiatric diagnosis [117, 118]. Up to 80% and 45% of chronic fatigue patients have been shown to suffer from a lifetime or current comorbid psychiatric disorder, respectively [118].

3.5.3.2.Differential diagnosis

The comorbidity between states of chronic fatigue and psychiatric disorders does not specify a cause-effect relationship. Moreover, it is thought that there is merely a coincidental overlap of symptoms between chronic fatigue/CFS and specific psychiatric conditions. In this context, it needs to be considered that chronic fatigue/CFS and psychiatric disorders, such as depression and anxiety, share characteristic symptoms including fatigue, sleep disturbances, concentration problems, low mood and worry.

The differential diagnosis between CFS and psychiatric disorders is preferably made by a psychiatrist. Psychiatric diagnoses in CFS patients, made by non-specialists, often differ from diagnoses established according to research diagnostic criteria. Deale and Wessely [121] showed that up to 68% of CFS patients were misdiagnosed by general practitioners and hospital doctors when psychopathology of psychiatric disorders was concerned. Not only the overlap in symptoms complicate the diagnostic process, diagnosis may also be affected by the views of doctors (care provider bias) and patients (e.g. social acceptability bias). Some doctors tends to make a psychiatric diagnosis instead of CFS when physical symptoms arise in the absence of any identifiable disease. In contrast, CFS patients are often fiercely resistant to psychiatric diagnoses and complain that they are wrongly given a psychiatric label [121]. These findings highlight the difficulties of evaluating psychiatric disorder in patients presenting with medically unexplained fatigue. Misdiagnosis or inappropriate diagnosis may

have serious consequences. Indeed, treatable conditions may be overlooked as well as the doctor-patient relationship may be irretrievably damaged.

Assessing CFS versus psychiatric conditions lies in the subtle features that discriminate between disorders. The most important difference between CFS and major depression is seen in the core symptomatology, being anergy and anhedonia respectively [122]. Furthermore, low self-esteem, hopelessness and suicidal ideation are frequently seen in depression and are not characteristic of CFS. CFS is more often associated with anergy, frustration and stress, as patients do not feel up to their daily activities. Avoidance behaviour or activity reduction is present in CFS as well as in depression and anxiety disorders, however, in CFS it may be driven by lack of energy rather than fear or loss of interest [121, 122]. In a comparative study of patients complaining of chronic fatigue, CFS patients did not differ from those who were chronically fatigued but did not meet the CDC criteria for CFS with regard to the prevalence of psychopathology [123].

3.5.4. Functional somatic syndromes: one or many?

It has been postulated that the existence of specific somatic syndromes is largely the consequence of medical specialisation [124]. Specialists seem to focus on those symptoms pertinent to their specialty which explains the differentiation of specific functional syndromes rather than real differences between patients. This suggests that the primary diagnosis will depend on the portal of entry for assessment with a care provider bias towards CFS in general internal medicine, FM in physiotherapy and insomnia in sleep medicine.

Literature demonstrates that remarkable overlap exists between individual syndromes with regard to case definitions, reported symptoms and non-symptom characteristics such as patients' sex, outlook and response to treatment between the individual syndromes [124]. This raises the question if one should rather explore a new model in which different symptoms are clustered which may influence each other instead of further differentiating between separated disorders. Clusters of symptoms have also been found within functional somatic syndromes, suggesting a heterogeneous nature of these disorders [125-127]. This additionally indicates a shortcoming in the actual division of syndromes and may encourage the development of a new model in order to facilitate treatment-oriented diagnosis. To develop such a model, there is need to further understand the commonalities across functional somatic syndromes as well as the factors that differentiate between and within these syndromes. Therefore, future research should include symptomatic, demographic and biological variables that may explain patients' complaints [99].

4. Treatment

Shorter duration of the chronic fatigue has been observed to be associated with higher rates of improvement and recovery [128], however, recovery rates are generally low.

In the management of CFS, patients should first be helped to accept their illness and its functional limitations since a short-term treatment is hitherto not available. Indeed, a lack of knowledge about factors that could account for and predict successful treatment in CFS complicates the therapeutic process. To date, therapeutic strategies for CFS include psychological, physical and pharmacological interventions. Randomised controlled trials have been carried out to assess the effectiveness of treatments including self-help treatment [129], antidepressants [130-132] and dietary supplementation with fatty acids [133] and folic acid [134]. However, no definitive proof of favourable effects for any of these therapies has been given until now. There is more evidence for positive effects of cognitive-behavioural approaches [135] and exercise therapy [136].

4.1. Cognitive-behavioural therapy (CBT) and graded exercise therapy (GET)

CBT is a psychological therapy model, delivered mainly by clinical psychologists, that facilitates the identification of unhelpful, anxiety-provoking thoughts. The aim of the treatment is to change the cognitive and behavioural factors assumed to be responsible for perpetuation of the patient's symptoms and disability. Negative thoughts, including fears about symptoms or activity, are addressed using behavioural tasks and skills training. These consist of establishing a baseline of activity and rest and a regular sleep pattern, followed by collaboratively planned gradual increases in both mental and physical activity. Furthermore, CBT helps participants to address social and emotional obstacles through problem-solving [136].

GET in CFS is delivered mainly by physiotherapists and based on the assumption that the syndrome is perpetuated by reversible physiological changes of deconditioning and avoidance of activity. The aim of the treatment is to help the patient gradually return to appropriate physical activities, reverse the deconditioning and thereby reduce fatigue and disability. In practice, a baseline of achievable exercise or physical activity is established, followed by a negotiated, incremental increase in the duration of time spent physically active. Walking is the most commonly chosen exercise [136].

4.1.1. Response to CBT and GET

There is substantial evidence that CBT and GET are efficacious in the treatment of CFS. Patients were more likely to have reduced fatigue symptoms at the end of the CBT treatment compared with usual care and other physiological therapies, including relaxation techniques, counselling and support [135, 137, 138]. GET seems to produce similar effects as CBT in CFS with regard to overall outcome as well as fatigue, functional impairment, depression and anxiety [138]. However, point estimates, as used for a small number of studies with relatively small sample sizes, suggested that CBT might be a more effective treatment for CFS patients with comorbid depression or anxiety [138]. This finding may reflect the greater emphasis on the role of emotional factors in the perpetuating of fatigue.

Promising outcomes at short to medium term follow-up have been resulted from randomized controlled trials, however, there are only limited data on the long-term response of CBT for CFS [139] in contrast to the proven positive long-term effects of CBT in insomnia [140]. More studies are needed to get more insight in the characteristics of patients who show relapses and who could potentially benefit from more sessions or additional intervention strategies.

There is a remarkable variation in the response to CBT and GET among CFS patients [135, 137, 138, 141]. Some of them fully recover, others only show a modest reduction in symptoms and a considerable number of patients do not profit from the therapy. It is supposed that some patients believe that a gradual increase in mental and physical activity may lead to an increase in symptoms. Many patients also feel that CBT implies that their symptoms are 'psychological' although the biopsychosocial model of CFS underlying CBT does not state that there is an absence of a somatic cause for CFS symptoms but only assumes that cognitive and behavioural factors contribute to its maintenance [139]. Such thoughts might hamper efficient treatment. The variation in effect sizes could also be linked to the heterogeneity of CFS. Several subgroups of patients have been identified, however, these subgroups could hitherto not unequivocally be linked to the response to CBT and GET [139, 142]. It should be interesting to get more knowledge about patient's characteristics in order to improve the outcome of behavioural interventions by selecting those patients who have a reasonable chance of improving from CBT and/or GET or by developing additional treatment strategies.

4.2. Pharmacotherapy

CFS patients usually use a wide range of conventional and alternative medicines, since they are often desperate to try anything and hope to find some relief for their disabling symptoms. An Australian study with 94 CFS patients found that the most commonly used conventional medicines where those acting on the CNS [143]. Antidepressants were taken most frequently by 41% of the patients, followed by simple analgesia such as paracetamol, aspirin and NSAIDs (37%), sedative and hypnotics (27%) and opioids (13%). Alternative medicines and supplements were often used by the same study subjects: 47% reported to take B vitamins, 24% used magnesium and 7% were taking a co-enzyme Q10 supplement [143]. The literature shows that application of different medicinal therapies and the frequent concomitant use of multiple drugs in CFS patients. Nevertheless, none of these medicines has been proven to be uniformly effective [143-145]. E.g., CFS patients may be thought to benefit from antidepressants, since CFS and depression show similarities in symptomatology and possible etiology and pathogenesis. Moreover, there is significant overlap between CFS and FM for which antidepressants have shown consistent efficacy [145]. Nevertheless, the number of randomised controlled trials, evaluating the efficacy of pharmacological treatments in CFS patients, is scarce in contrast with the widely studied nonpharmacological interventions. Methodological shortcomings, such as the lack of control groups and not randomised or blinded studies, also lead to a high risk of bias. Additionally, the severity of symptoms fluctuates in CFS and temporary improvements may mistakenly be attributed to the treatments used. It is clear that more evidence from randomised and blinded clinical trial is needed to get insight in the long-term effects of antidepressants in particular and pharmacotherapy in general on CFS to get better guidance for the management of this condition. To date, pharmacotherapy can not be considered first-line treatment in CFS and should rather be used in the context of self-management and rehabilitation.

4.3. From perpetuating factors to individualized-oriented therapy

There is a remarkable variation in the response to CBT and GET among CFS patients, which may be influenced by factors concerning the treatment protocol, the treating therapist and the patient himself. Higher effect sizes seems to be observed for individual therapeutic assessments than for group programs [146, 147]. This may, at least partly, reflect the individual differences between CFS patients and the heterogeneity of perpetuating factors. Together with the fact that therapeutic effects are not always maintained in the long-term and that drop-out rates are fairly high, may insist a more individualized therapy approach [148].

Nevertheless, factors that could account for and predict successful treatment in CFS are not well known and should be studied via process-outcome studies that focus on putative mechanisms of change. Such studies are scarce, although in CFS, some perpetuating factors such as membership of a self-help group, receipt of sickness-benefits low sense of control, strong focus on symptoms, emotional problems and passivity have been found to predict negative treatment-outcome of CBT [149], whereas a decrease in symptom-focussing predicted a positive outcome for CBT [150].

Van Houdenhove and colleague [148] propose that individualized treatment should consist of three components. First, comorbid illnesses including depression, anxiety and sleep disorders should be treated adequately in order to minimize patients' emotional and physical distress. It is not yet clear, however, if treatment of these comorbid disorders may diminish fatigue complaints.

Second, the patient should be offered a plausible illness theory that can be the starting point for translating the therapeutic rationale into concrete practice. The attitude of the therapist towards the treatment goals has shown to affect the expectations and perceptions of the patient. If the therapist says that recovery is possible, the patients expectations raise, which may lead to a change in the perception of symptoms as well as disability.

Third, the perpetuating factors that will be concretely targeted during the therapy should be discussed with the patient. Patients should be encouraged to correct unhelpful thoughts and attitudes and to gradually increase activities in accordance with their personal objectives. They should learn how to pace their activities instead of periodically exceeding their limits and provoking repeated setbacks manifesting as post-exertional malaise.

5. Care path for unexplained chronic fatigue

In view of these observations, the significant overlap of the different entities and functional somatic syndromes as well as the significant prevalences of comorbidity both in the field of sleep disorders as psychiatric disease, it is postulated that patients that are labeled with one of these syndromes should be systematically and thoroughly assessed (and often reassessed). Hence patients referred to our multidisciplinary tertiary care referral center (Department of General Internal Medicine, Infectious Diseases and Psychosomatic Medicine, University Hospital Ghent) for assessment of longstanding chronic fatigue, are invited to systematically enter an integrated path of care (Figure 2). This includes an internal medicine assessment, a psychodiagnostic screening, a physiotherapeutic assessment and a PSG in combination with a MSLT. The internal medicine assessment consists of a physical examination and integrates

the results of previous investigations. The psychodiagnostic screening includes an evaluation by a psychologist and psychological testing using validated questionnaires. The physiotherapeutic evaluation focuses on a screening for musculoskeletal comorbidity such as FM, according to the ACR criteria, and other impairments that are suitable for physical rehabilitation. If psychopathology is suspected, further psychiatric diagnosis is started. The multidisciplinary discussion yields either a final diagnosis or a tentative diagnosis in selected patients, in whom response to treatment is considered an additional diagnostic criterion.
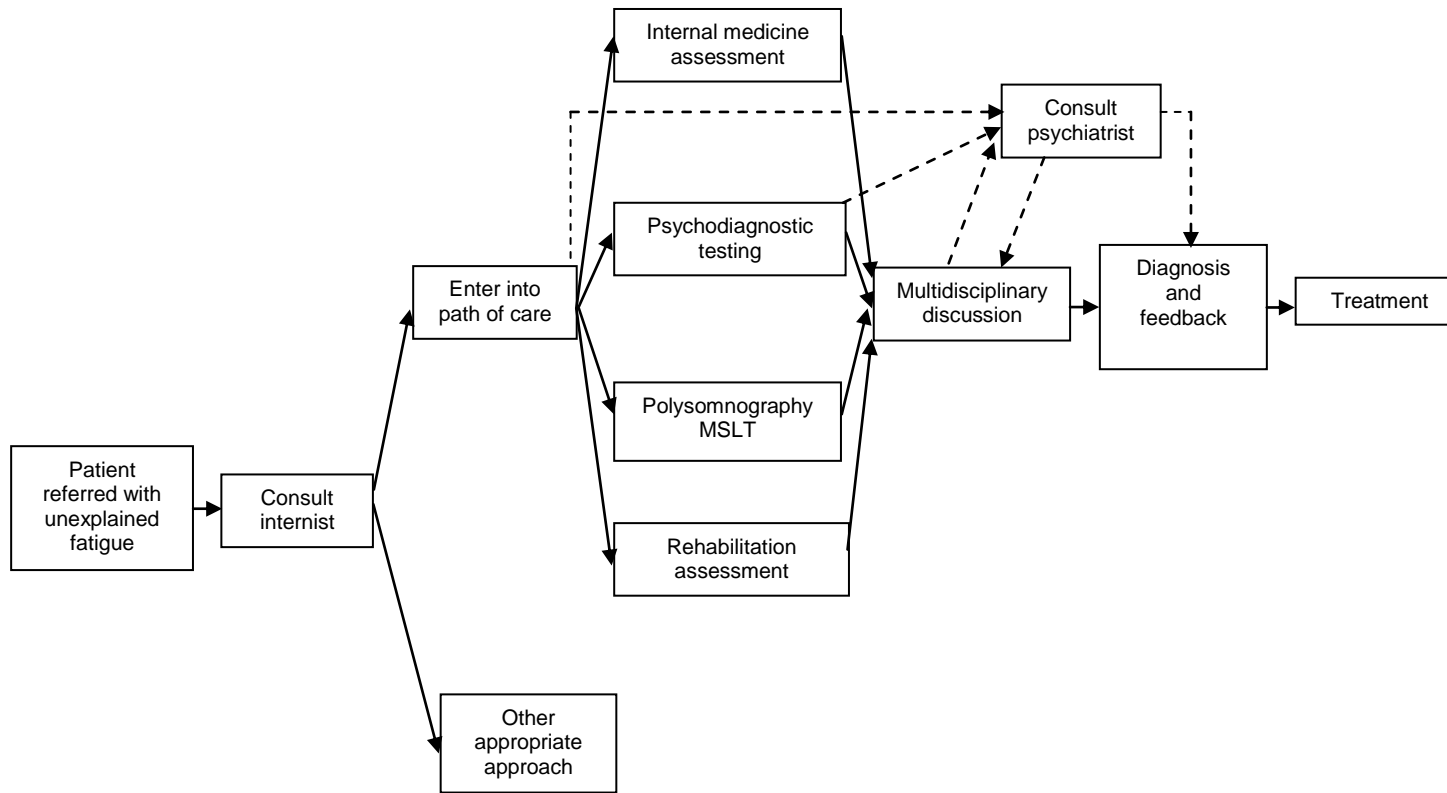
Internal medicine
assessment

Consult
psychiatrist

Psychodiagnostic
testing

Enter into
path of care

Multidisciplinary
discussion

Diagnosis
and
feedback

Treatment

Polysomnography
MSLT

Patient
referred with
unexplained
fatigue

Consult
internist

Rehabilitation
assessment

Other
appropriate
approach

Figure 2. Path of care for unexplained fatigue. Full lines indicate systematic, interrupted lines additional steps.

6. Research aims

Because of the relative lack of objective and subjective data on sleep in CFS, we aimed to build a large patient sample fitting the prevailing Fukuda et al. definition of CFS. In order to assess further research questions, important gaps in objective data needed to be filled in through descriptive research.

In view of the complexity and lack of robustness of both the syndromal definitions and the different aetiological hypotheses, approached in the introduction, we hypothesize that the syndromal constellation of CFS actually erroneously groups together a larger spectrum of underlying pathology, that needs to be differentiated. Furthermore, we wish to explore the causal relationship between sleep and daytime dysfunction (fatigue) in this patient population, in which we challenge the commonly held unidirectional paradigm of adequate sleep as a prerequisite for daytime functioning.

To encounter the first hypothesis, we aim:

- To explore the diagnostic categories of patients with unexplained chronic fatigue through systematic clinical analysis

    - To explore the prevalence of final diagnostic categories of patients with presumed CFS
    - To assess primary sleep disorders in CFS through systematic polysomnography and multiple sleep latency test

For the second hypothesis, we aim:

- To assess the existing literature on sleep in CFS

- To explore subjective sleep parameters and sleep quality in CFS patients

    - To assess subjective sleep quality and daytime sleepiness in a large sample of CFS patients
    - To validate a previously reported three-factor scoring model of the Pittsburgh Sleep Quality Index in a large sample of CFS patients

- To assess objective sleep measures and subjective sleep parameters in a large sample of patients with unexplained chronic fatigue and their mutual correlation

- To explore the interrelationship of self-report questionnaires on different dimensions in the construct of chronic fatigue and CFS

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CHAPTER 2: UNDIAGNOSED AND COMORBID DISORDERS IN PATIENTS WITH PRESUMED CHRONIC FATIGUE SYNDROME

Undiagnosed and comorbid disorders in patients with presumed chronic fatigue syndrome

(Submitted to Journal of Psychosomatic Research, under revision)

Running title: Final diagnoses in presumed CFS

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Abstract

Objective

To assess undiagnosed and comorbid disorders in patients referred to a tertiary care center with a presumed diagnosis of chronic fatigue syndrome (CFS).

Methods

Patients referred for chronic unexplained fatigue entered in an integrated path of care, including internal medicine assessment, psychodiagnostic screening, physiotherapeutic assessment and polysomnography + multiple sleep latency test. Final diagnosis resulted from a multidisciplinary team discussion. Fukuda criteria were used for the diagnosis of CFS, DSM-IV-TR criteria for psychiatric disorders, ICSD criteria for sleep disorders.

Results

Out of 377 patients referred, 279 (74.0%) were included in the study [84.9% female; mean age 38.8 years (SD 10.3)].

23.3% had a diagnosis of unequivocal CFS. In 21.1%, CFS was associated with a sleep disorder and/or psychiatric disorder, not invalidating the diagnosis of CFS. 9.7% had a predominant sleep disorder, 19.0% a psychiatric disorder and 20.8% a combination of both. Only 2.2% was diagnosed with a classical internal disease.

In the total sample, a sleep disorder was found in 49.8%, especially obstructive sleep apnea syndrome, followed by psychophysiologic insomnia and periodic limb movement disorder. A psychiatric disorder was diagnosed in 45.2%; mood and anxiety disorder were most frequently observed.

Conclusions

A multidisciplinary approach to presumed CFS yields unequivocal CFS in only a minority of patients, and reveals a broad spectrum of exclusionary or comorbid conditions within the domains of sleep medicine and psychiatry. These findings favor a systematic diagnostic approach to CFS, suitable to identify a wide range of diagnostic categories that may be subject to dedicated care.

Key words

Chronic fatigue syndrome, comorbidity, prevalence, psychiatric disorders, sleep disorders

Abbreviations

AASM	American Academy of Sleep Medicine
AHI	apnea-hypopnea index
BMI	body mass index
CFS	chronic fatigue syndrome
DSM-IV-TR	Diagnostic and Statistical Manual of mental disorders, 4th edition – text revision
ICSD-2	International Classification of Sleep Disorders, 2nd edition
MSLT	multiple sleep latency test
OSA	obstructive sleep apnea
PLMD	periodic limb movement disorder
PLM	periodic limb movements
PSG	polysomnography
REM	rapid eye movements
SD	standard deviation

Introduction

Chronic fatigue syndrome (CFS) is characterized by long lasting, unexplained 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. Several case definitions have been introduced, including the revised CDC (Centers for Disease Control and Prevention) criteria published by Fukuda et al. in 1994 (1). These are now the standard guidelines in the US and are widely used in other countries as well. To establish the diagnosis of CFS, the Fukuda definition require a major criterion of unexplained, incapacitating fatigue of at least six months duration, in combination with at least four out of eight minor criteria. These minor criteria include postexertional malaise lasting for at least 24 hours, 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.

Fatigue, the main feature of CFS, is a complex, heterogeneous and multidimensional phenomenon. It is a common denominator referring to various aspects of impaired physical, mental, emotional and neurocognitive functioning (2-4). Fatigue is a frequent manifestation of a variety of medical, neurological and psychiatric conditions but it may also appear as a side effect of pharmacological treatment.

With regard to fatigue and associated symptoms, the syndromal definition of CFS overlaps with other entities such as insomnia (5;6), obstructive sleep apnea (OSA) (7), fibromyalgia (8) and mood disorders (9). The Fukuda criteria stipulate limited exclusion criteria within the primary psychiatric disorders, such as past or present diagnosis of a major depression with psychotic features, bipolar affective disorders, schizophrenia of any subtype, delusional disorders of any subtype, dementia of any subtype, anorexia nervosa or bulimia nervosa (1). As a result, the Fukuda criteria allow a diagnosis of CFS, even in the presence of a mood disorder, without specification to which extent this disorder needs to be treated. Within the primary sleep disorders, sleep apnea, without indication of severity, and narcolepsy are conditions that exclude a diagnosis of CFS (1). Primary and secondary insomnia (DSM-IV-TR) (10) do not feature within the Fukuda exclusions, although insomnia can explain the somatic symptoms in a number of presumed CFS patients (5;11).

Chronic unexplained fatigue is best approached from a biopsychosocial perspective (12) within a multidisciplinary setting. A monodisciplinary approach may lead to a spurious diagnosis of CFS as treatable psychiatric or sleep disorders may go unnoticed.

Patients with unexplained chronic fatigue are referred to our tertiary care center to confirm or exclude a presumed diagnosis of CFS. Appropriate medical and psychodiagnostic investigation may reveal some specific nosological entities that are either exclusionary or comorbid to CFS. The aim of the current study was to assess the prevalence of these disorders in the group of patients referred to our center.

Methods

Patient recruitment took place between June 2010 and February 2011. Typically, patients were referred for confirmation of a presumed diagnosis of CFS. Criteria to be enrolled in the present study were unexplained fatigue persisting for at least six months, and a minimum age of 18 years. Participants gave written informed consent. The study was approved by the institutional Ethical Review Board of the University Hospital Ghent, Belgium.

Multidisciplinary assessment

Assessment of chronic fatigue at our center follows a holistic approach that is based on the biopsychosocial model by Wessely et al. (12). The initial diagnostic part of the integrated path of care (Figure 1) involves internal medicine assessment, psychodiagnostic screening, rehabilitation assessment, and polysomnography (PSG) combined with a multiple sleep latency test (MSLT). The internal medicine assessment consists of comprehensive history taking, also considering any previous medical diagnoses or investigations, and a physical examination. If indicated, routine lab tests, chest radiography and echography of the abdomen are carried out. A rehabilitation physician evaluates whether any musculoskeletal comorbidity is present that is potentially suitable for physiotherapeutic management. Psychodiagnostic screening, performed by a medical psychologist, includes history taking, the administration of validated questionnaires (Table 1) and psychological tests. Psychiatric consultation is scheduled when the history is remarkable for a past or present psychiatric disorder, and whenever hints for the presence of a psychiatric disorder emerge from the psychodiagnostic evaluation or from the multidisciplinary discussion (Figure 1). Psychiatric diagnosis complies with DSM-IV-TR criteria (10).

Sleep assessment

Sleep history is based on an interview that integrates the results of relevant sleep questionnaires (Table 1). Sleep diagnosis is in keeping with the ICSD-2 nosology (13).

PSG and MSLT are recorded and scored according to the American Academy of Sleep Medicine (AASM) manual (14). Sleep parameters derived from PSG include time in bed, total sleep time, sleep efficiency, sleep latency, REM sleep latency, time spent in the different sleep stages, wakefulness after sleep onset, arousal index, apnea-hypopnea index (AHI) and presence of periodic limb movements (PLM). MSLT includes assessment of mean sleep latency and presence of sleep onset REM-sleep.

OSA is defined by an AHI ≥5/h in combination with associated symptoms (e.g. excessive daytime sleepiness, fatigue, or impaired cognition). Severity of OSA is classified as mild (5≤ AHI <15), moderate (15≤ AHI <30) or severe (AHI ≥30).

Patients were asked to withdraw from hypnotics (benzodiazepines and z-drugs) at least three weeks before PSG was performed.

Diagnostic decision making and categories

The outcome of the multidisciplinary discussion is a diagnostic decision regarding unequivocal CFS, CFS with comorbidity, or a condition that excludes CFS.

In unequivocal CFS, no symptoms or signs of coexisting sleep or psychiatric disorders are observed. CFS with comorbidity is defined as a combination of chronic unexplained fatigue meeting the major and minor Fukuda criteria, with a comorbid condition that may contribute to, but does not sufficiently explain the degree of reported impairment. Typically, coexisting mood disorder or sleep disorders (e.g. OSA, insomnia, or periodic limb movement disorder (PLMD)) are being considered 'comorbid' in a number of patients. Predominant sleep and/or psychiatric disorders are judged exclusionary to CFS, as they tentatively explain the full clinical picture, including fatigue. In this case, the diagnosis of CFS is not assumed in the first instance, but may be reconsidered in a subsequent stage, pending insufficient symptomatic relief following adequate treatment of the primary disorder.

Diagnostic categories include: 1) CFS without comorbidity (unequivocal CFS), 2) CFS with comorbidity, 3) a predominant sleep disorder, 4) a predominant psychiatric disorder, 5) a combination of a sleep and psychiatric disorder, 6) a classical internal medicine disease (with or without associated psychiatric or sleep disorders), 7) no final diagnosis (complaints of chronic fatigue remaining unresolved).

Statistical analysis

Descriptive statistics were performed with SPSS Statistics version 19.

Results

Inclusion and demographics

Three hundred seventy-seven patients were referred for evaluation of chronic fatigue (Figure 2). Seven patients (1.9%) were excluded because of the age requirement. Fifty-eight patients (15.4%) did not give informed consent and in 17 patients (4.5%) data were incomplete, mostly due to cancellation of appointments. In sixteen patients (4.2%) complaints of fatigue had been present for less than six months. Two hundred seventy-nine patients (74.0%) who met the inclusion criteria were enrolled in the study.

The majority of the patients was female (n = 237; 84.9%). The mean age was 38.8 years (SD 10.44); mean body mass index (BMI) was 25.0 kg/m² (SD 5.19). A minority (n = 104; 37.2%) had a certificate of higher education.

Final diagnoses

An overview of the final diagnoses is presented in Figure 2 and Figure 3a.

Of the 279 included patients, 224 (80.3%) met at least four of the minor Fukuda criteria. Of these, 65 subjects (23.3%) had a final diagnosis of unequivocal CFS. In 59 patients (21.1%), CFS was associated with psychiatric disorders (n = 7; 2.5%), sleep disorders (n = 45; 16.1%) or both (n = 7; 2.5%) that were judged comorbid and did not exclude the diagnosis of CFS. One hundred patients (35.8%), in spite of fulfilling the major and minor criteria of CFS, were diagnosed with another predominant condition, i.e. a psychiatric disorder (n = 35; 12.5%), a sleep disorder (n = 18; 6.5%), a combination of both (n = 41; 14.7%), an internal disease with or without sleep or psychiatric comorbidity (n = 4; 1.4%), and other conditions (n = 2; 0.7%). Fifty-five patients (19.7%) did not meet the minor Fukuda criteria. Eighteen (6.5%) of these patients had a diagnosis of a predominant psychiatric disorder, 9 (3.2%) a predominant sleep disorder, 17 (6.1%) a combination of both, and 11 (4.0%) other conditions.

Only 6 patients (2.2%) of the total sample had a final diagnosis pertaining to the domain of classical internal medicine. Internal disorders consisted of post viral asthenia (4 patients) and diabetes mellitus (2 patients). In one patient the diabetes was associated with severe obesity, liver steatosis and hemochromatosis. Moreover, a psychiatric comorbidity was present in 1 and a sleep disorder in 2 patients of this subgroup.

Sleep disorders

In 242 out of 279 patients (86.7%) the minor criterion of 'unrefreshing sleep' was positive. Objective sleep assessment revealed (predominant or comorbid) sleep disorders in 139 patients (49.8%) of the total sample. Ninety patients (32.0%) had a single sleep disorder, whereas a combination of two and three sleep disorders was present in 46 (16.4%) and 3 patients (1.1%), respectively.

A wide range of sleep disorders was observed (Figure 3b), OSA being the most prevalent (n=80; 28.7%). Mild, moderate and severe OSA were diagnosed in 61 (21.9%), 14 (5.0%) and 5 patients (1.8%), respectively. Other prevalent diagnoses were psychophysiologic insomnia (n=43; 15.4%), PLMD (n=34; 12.2%) and hypnotic dependent sleep disorder (n=14; 5.0%).

Psychiatric disorders

In the total sample, a (predominant or comorbid) psychiatric disorder was diagnosed in 126 patients (45.2%). The majority of these patients (n = 86; 30.8%) had an axis I diagnosis, 14 (5.0%) an axis II diagnosis and 26 (9.3%) a combination of both.

Mood disorder was most prevalent (n = 74; 26.5%), followed by anxiety disorder in 39 patients (14.0%) (Figure 3c). Sixteen patients (5.7%) had a diagnosis of undifferentiated somatoform disorder.

Discussion

The present study is remarkable for the finding that multidisciplinary assessment of presumed CFS confirms unequivocal CFS in only a minority of patients, and reveals a broad spectrum of exclusionary or comorbid conditions within the domains of sleep medicine and psychiatry. In the total group of patients referred to our tertiary care center, different diagnostic categories were identified including unequivocal CFS (23.3%), CFS with significant comorbidity that does not invalidate the diagnosis of CFS (21.1%), predominant sleep disorders (9.7%) and predominant psychiatric disorders (19.0%).

OSA, being the most prevalent sleep disorder in the recruted patient sample, was observed in 28.7%. In other CFS referral centers, prevalence rates of ±45% have been reported (15;16). Obviously, OSA is a salient comorbid, or even an exclusionary disorder that is to be considered in the differential diagnosis of CFS. The prevalence of OSA is estimated 4% in men and 2% in women in the general population (17). Patients with chronic unexplained fatigue are often sedentary and even bedridden (18), which might predispose them to obesity and sleep-disordered breathing (19). However, the weight status of the present patient sample

approximates normalcy (mean BMI 25.0 kg/m²) and is similar to that of the overall Belgian adult population (mean BMI 25.3 kg/m²) (20). This finding is in accordance with limited published data which suggest that patients with chronic unexplained fatigue and CFS are not excessively overweight or obese (21). Interestingly, the high prevalence of OSA in our patient group is in parallel with the rates of unrelated clinical samples, such as arterial hypertension (30-85%), congestive heart failure (20-50%), and metabolic syndrome (82%) (22). The use of PSG to identify OSA has been advocated in clinical populations at risk for OSA (23), and seems from the present data also recommendable in CFS patients.

Insomnia was observed in a relatively small number of enrolled patients (15.4%) which is in contrast with data from the general population that demonstrate a higher prevalence (27.2%) (24). This may be due to selection bias, because patients with a clear history of insomnia are directly being referred for dedicated insomnia-treatment in our hospital. Similarly, hypnotic-dependent sleep disorders (5.0%) may also be underrepresented because patients were asked to withdraw from sleeping pills before PSG was carried out.

Hitherto, a strong connection between CFS and psychiatric disorders has been reported. In a community-based study, Nater et al. found that 57% of individuals with CFS had at least one current and 89% one lifetime psychiatric diagnosis (25). In clinical CFS patients, significant coexistence with psychiatric disease was found (26-29). However, in our patient sample, we mostly observed predominant diagnoses of mood disorder and anxiety disorder, that actually exclude CFS (40.2%), whereas psychiatric disturbances that do not invalidate the diagnosis of CFS were less frequent (5.0%). The predominance of exclusionary over comorbid psychiatric disorders probably resulted from the formal psychodiagnostic evaluation, psychiatric diagnostic work-up and multidisciplinary discussion. As a consequence, we contend that insufficiently recognized psychiatric morbidity should be addressed prior to labelling chronic fatigue as CFS.

Data on prevalence rates of personality disorder in CFS patients are inconsistent. Previously reported figures ranging between 28 and 39% (26-28;30) were not confirmed by Courjaret et al. (31) and by Kempke et al. (32) who found that, respectively, in only 12% and 16% of female CFS patients a personality disorder could be identified. In the present sample, the prevalence of personality disorder (especially cluster B and C) amounted to 14.3%, which approximates the latter figures. Differences in methodology, including sample size, selection bias and the use of different self-report questionnaires, may explain the variety in prevalences among different studies.

Diagnoses pertaining to classical internal medicine are scarce in our sample, probably because they already had been detected at the level of primary or secondary care. This finding would imply that, at the tertiary care level, there is no need for repeating extensive medical tests to detect underlying internal diseases. With respect to health policies pertaining to CFS, it is recommended to limit laboratory and imaging tests in terms of number and reiteration. Obviously, the present reclassification of presumed CFS into categories of unequivocal CFS, comorbid CFS and exclusionary conditions is the result of a systematic and integrated multidisciplinary approach, including internal medicine, medical psychology, psychiatry and rehabilitation medicine. As such, this approach differs from monodisciplinary case management, that tends to label medically unexplained symptoms (MUS) into organ- or specialty driven syndromal definitions, e.g. irritable bowel syndrome, fibromyalgia, and myalgic encephalomyelitis. Unraveling the intricacies of MUS is not a focus of interest for many general practitioners and organ specialists. Often, the characteristics of precipitating and perpetuating factors that are operational in MUS are insufficiently documented. Moreover, salient comorbidity in the domains of psychopathology and sleep medicine may go unnoticed. From our data, it is clear that a tendency to prematurely establish a diagnosis of CFS, carries a risk of underdiagnosis of other treatable disorders. Dedicated methods for differentiated assessment of chronic fatigue, such as ours, may provide means to reorient patients towards integrated care programs based on multimodal therapy, taking into account previously undetected psychiatric and/or sleep disorders. At the same time, this approach may serve as a corrective tool against overlabelling with non-validated syndromal definitions. The wide range of treatable disorders that is found in the present sample may serve as a justification for the need to systematically assess clinical CFS patients in a multidisciplinary setting.

A limitation of this study is the lack of follow-up of patients after treatment. Assessment in our center is part of a regional network of care. Our intervention focuses primarily on the diagnostic pathway, and a number of patients is subsequently referred back to the treating physician. Therefore, systematic follow-up data on the effect of recommended treatment regimens are not available. The report hence focuses on the initial diagnostic classification, which could be subject to adjustment following reassessment after the therapeutic phase.

In conclusion, a multidisciplinary approach to patients with presumed CFS referred to a tertiary care center seems necessary in order to identify a wide range of diagnostic categories relevant to appropriate care. A high prevalence of predominant sleep and psychiatric disorders

is found. These findings favor thorough screening including psychodiagnostic testing, formal psychiatric diagnosis and objective assessment of sleep parameters in patients with presumed CFS.

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Table 1. Overview of psychodiagnostic and other questionnaires

| Questionnaire	Dimension explored
Symptom Checklist-90-Revised (33)	Psychological distress
Chalder Fatigue Scale (34)	Severity of fatigue
Medical Outcomes Study 36-item Short Form Health Survey (35)	Global mental and physical health
Epworth Sleepiness Scale (36)	Excessive daytime sleepiness
Pittsburgh Sleep Quality Index (37)	Global sleep quality
NEO-Five Factor Inventory (38)	Personality assessment
Checklist Individual Strength (39)	Phenomenology and severity of fatigue
Millon Clinical Multiaxial Inventory (40)	Psychopathology
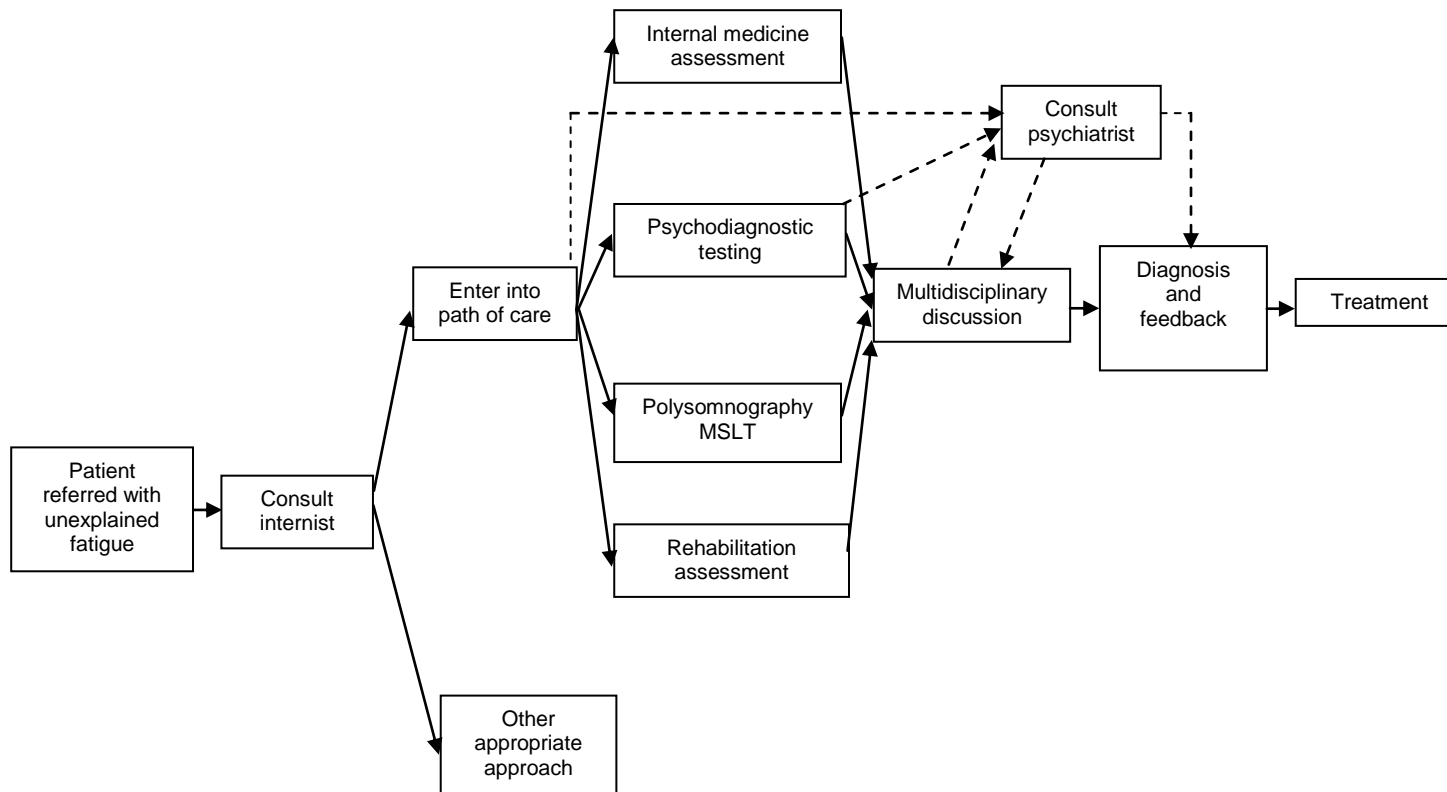
Figure 1. Path of care for unexplained fatigue. Full lines indicate systematic, interrupted lines optional steps.
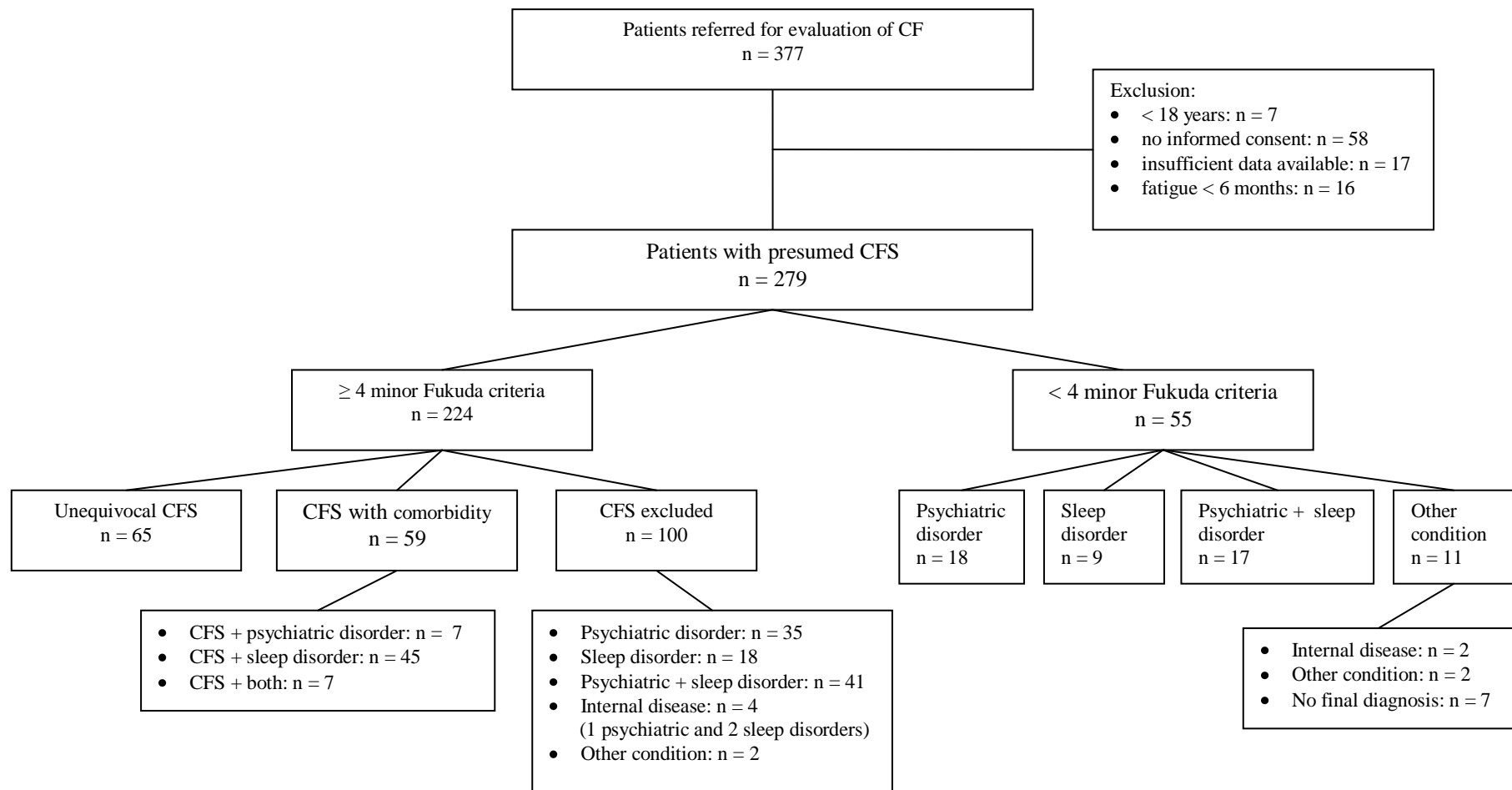
Figure 2. Flow chart of patients referred for evaluation of unexplained chronic fatigue, and final diagnoses in patients with presumed CFS

a.
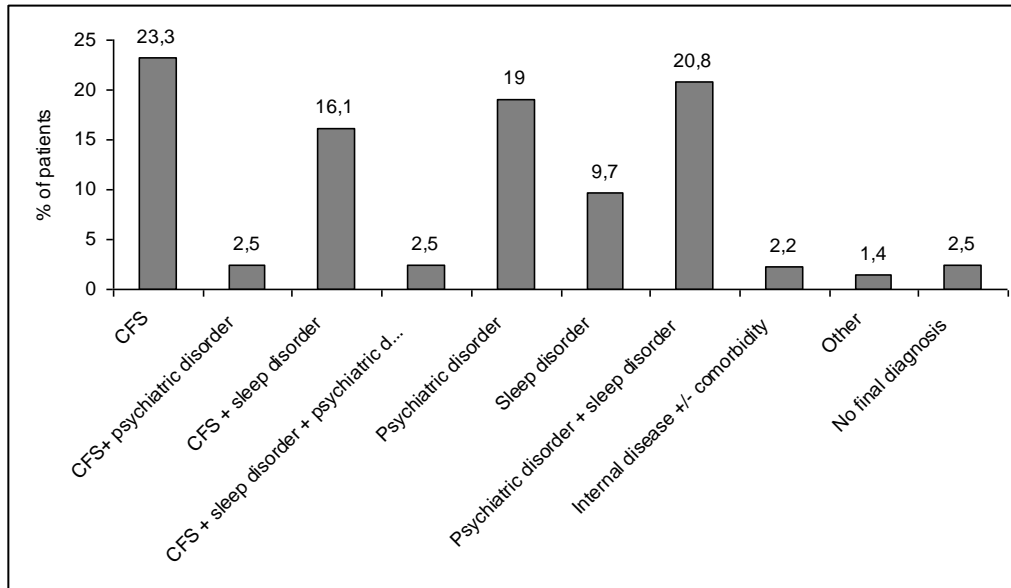
b.
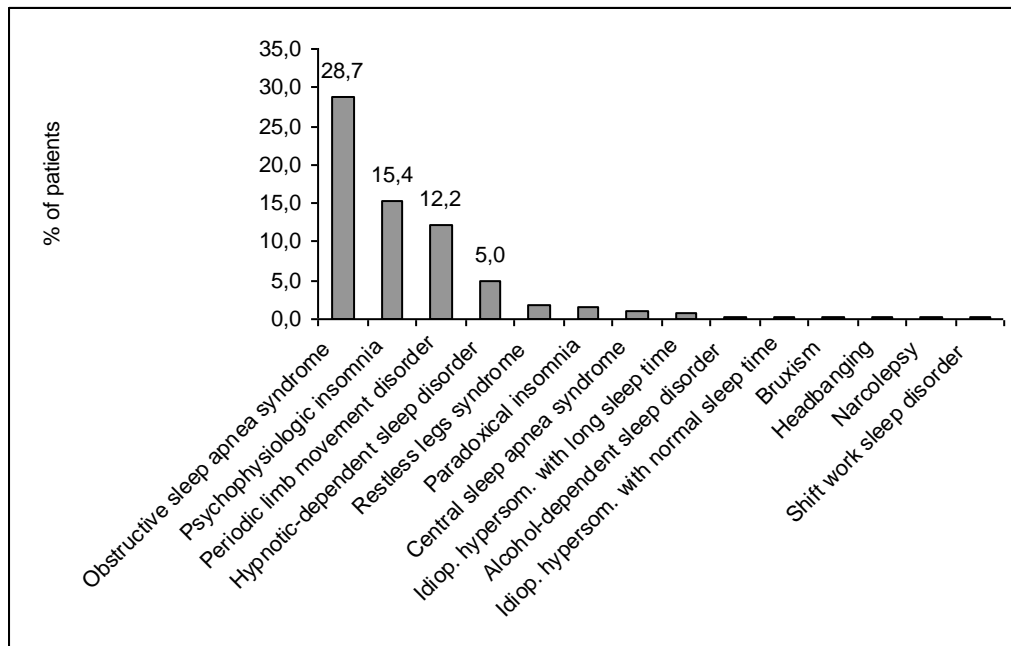
Figure 3. Relative prevalence of (a) final diagnosis; (b) sleep disorders, (c) psychiatric disorders in patients with presumed CFS

Idiop. hypersom.: Idiopathic hypersomnia

c.

Figure 3. Relative prevalence of (a) final diagnosis; (b) sleep disorders, (c) psychiatric disorders in patients with presumed CFS

Idiop. hypersom.: Idiopathic hypersomnia

CHAPTER 3: SLEEP IN THE CHRONIC FATIGUE SYNDROME

Sleep in the chronic fatigue syndrome

CLINICAL REVIEW

Sleep in the chronic fatigue syndrome

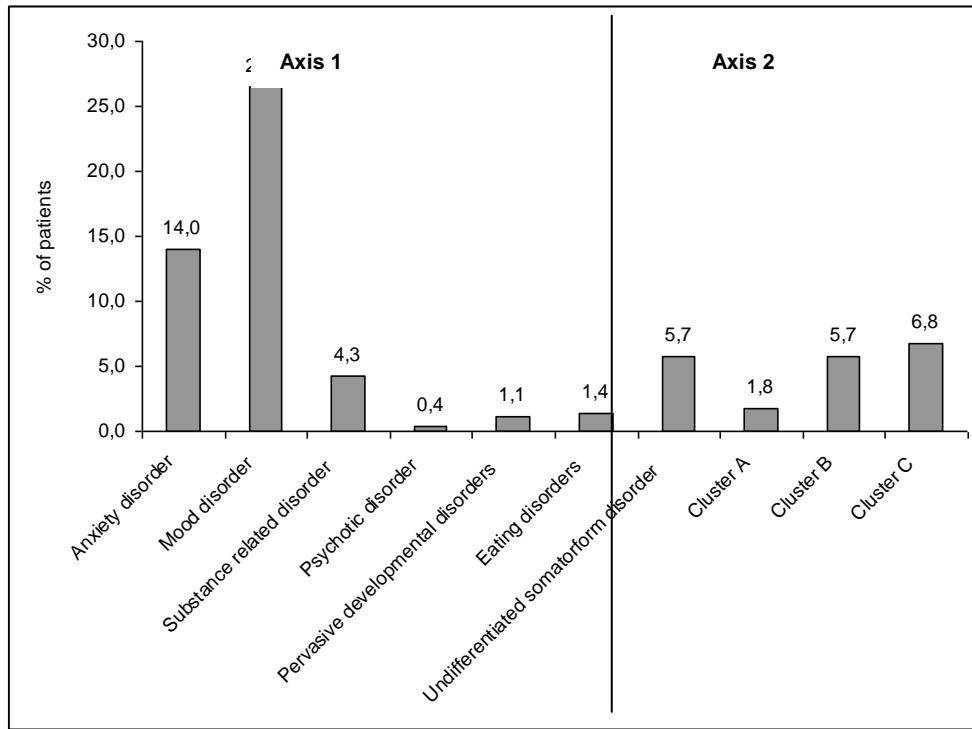An N. Mariman [a,*], Dirk P. Vogelaers [a,b], Els Tobback [a], Liesbeth M. Delesie [a], Ignace P. Hanoulle [a], Dirk A. Pevernagie [b,c]

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ARTICLE INFO

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.

Abbreviations

CAP	cyclic alternating pattern
CDC	Centers for Disease Control and Prevention (USA)
CFS	chronic fatigue syndrome
CPAP	continuous positive airway pressure
DIS	difficulty with initiating sleep
DMS	difficulty with maintaining sleep
EDS	excessive daytime sleepiness
EEG	electro-encephalography
FFT	fast Fourrier transformation
FMS	fibromyalgia syndrome
MOS SF-36	medical outcomes study short form 36-item
NREM	non-rapid eye movement
NRS	nonrestorative sleep
OSA	obstructive sleep apnea
PSD	primary sleep disorder
PSG	polysomnography
REM	rapid eye movement

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:

1. give an overview of definitions, health impact and epidemiology of CFS;
2. explore current insights into restorative and nonrestorative aspects of sleep;
3. assess the relations between sleep and CFS

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., 1988 [1]; Lloyd et al., 1990 [3]; Sharpe et al., 1991 [4]; Fukuda et al., 1994 [2]; Carruthers et al., 2003 [5]) 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 [7,8], and between 0 and 4800 per 100,000 individuals in community-based samples [3,9]. 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 socio-economic 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 [10], 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 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 wear and tear accumulated during wakefulness [29]. 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 [30]. 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 [31] and subsequent sleep is characterized by a rebound of slow wave activity [32], which could tentatively signify an intensified recovery process in the brain [33].

Nonrestorative sleep

While adverse effects of sleep loss on daytime performance were already substantiated more than a century ago [34], 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 unrestored 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 purpose, the construct of NRS was introduced as a possible lead to the etiologies of CFS and fibromyalgia syndrome (FMS) [35]. 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 [36], and subsequently embraced by other coding systems, including the International classification of sleep disorders - second edition (ICSD-2) [37] and research diagnostic criteria (RDC) [38].

In a recent review, it was pointed out that the construct of NRS is highly complex, and suffers from conceptual inconsistencies [39]. 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' [39]. 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 [39]. This construct remains a theoretical model and requires further empirical validation [40]. 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 [42]. 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 duration, and had no difficulties with initiating sleep (DIS) 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 surveys [48-51] (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 [41,52]. 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 dysfunctioning, 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 [53], as well as objective measures of sleep [54]. 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%, $P \leq 0.05$). 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 [55,56]. 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 recordings[57] 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 intricacies 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 [67,68], decreased [66], or to be similar [65] in CFS groups as compared with normal controls.

Increased CAP rates in NREM are presumed to be an index of sleep instability [69]. 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

dynamics [70] 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 [2]. 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) [79]. 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 [80]. 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 brace 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 screened for the presence of PSD. Assessment is based 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 may receive different names in different classification systems. To avoid using stereotypical 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 somatisation and to tailor symptomatic treatment to the individual patient's needs.

Research agenda

1) Gaining insight into the nature of psychophysiological recovery during sleep, and the subjective experience of unrefreshing sleep, will require clarification of relevant neurobiological processes that are as yet elusive.

2) To study sleep as a functional process, future studies should replicate analyses of EEG power spectrum and dynamic sleep stage shifts. Non-EEG techniques such as functional brain imaging may also prove relevant in the exploration of sleep in CFS patients.

3) Further investigations should focus on the relation between alleged NRS and daytime dysfunction. The null-hypothesis would postulate that sleep is basically intact in NRS. According to this concept, fatigue is a 24-h occurrence and is already perceived upon awakening in the morning, leaving sleep as an 'innocent bystander'.

4) Since the role of PSD in CFS is unclear, interventions are needed to assess the symptomatic effects of causal therapy on fatigue as a primary outcome. Randomized controlled trials may clarify whether PSD are to be considered an exclusion criterion vs. a comorbidity to CFS.

5) The diagnostic criteria of primary insomnia and CFS overlap considerably, NRS being a prominent common denominator. The disease characteristics of both conditions should be assessed simultaneously in patient cohorts, to investigate a potential common pathophysiological background.

Acknowledgments

Table 1: Sleep complaints as a criterion for case finding in CFS

Holmes et al. 1988 (CDC) USA	Lloyd et al. 1988 Australia	Sharpe et al. 1991 (Oxford) UK	Fukuda et al. 1994 (CDC) USA	Carruthers et al. 2003 Canada
SLEEP PARAMETERS				
Minor symptom criterion: sleep disturbance (hypersomnia or insomnia)	**Possible symptom:** sleep disturbance, persistent > 6 months with no other cause	**Possible symptom:** sleep disturbance: *(i)* subjective report of a change in duration or quality of sleep *(ii)* distinguished from feelings of daytime fatigue or tiredness *(iii)* should: *(a)* be complained of *(b)* not be a response to external disturbance *(c)* be a change from the previous state *(d)* be persistant *(iv)* should be described as *(a)* type: hypersomnia or increased sleep;insomnia or reduced sleep (either difficulty getting off to sleep, early waking or subjectively disturbed or unrefreshing sleep) *(b)* severity:amount of change in duration of sleep (hours)	**Minor criterion:** unrefreshing sleep **Exclusions:** primary sleep disorders such as sleep apnea and narcolepsy	**Cluster 'Sleep dysfunction':** unrefreshing sleep, poor sleep quality or rhythm disturbances (such as early, middle or late insomnia, with reversed or irregularly irregular insomnia, hypersomnia, abnormal diurnal variation of energy levels, including reversed or chaotic diurnal rest and sleep rhythms) **Remark:** Small number of patients do not have sleep dysfunction, but no other diagnosis fits. A diagnosis of ME/CFS can be maintained if infectious illness type onset. **Exclusions:** treatable sleep disorders (such as UARS, OSA/CSA, RLS)
PREVALENCE OF NON-RESTORATIVE SLEEP / UNREFRESHING SLEEP				
Community-based sample ND	ND	ND	87.5% [49] 95.4% [48] 93.0% [50] 92.2% [51]	ND
Clinical setting			95.0% [46]	

PREVALENCE OF PRIMARY SLEEP DISORDERS				
Community-based sample				
ND	ND	ND	18.6%[55]	ND
Clinical setting				
62.5%[43]	ND	58.3%[71]	ND	ND
81.0%[44]		46.0%[73]		

ND, no data

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CHAPTER 4: SUBJECTIVE SLEEP PARAMETERS AND SLEEP QUALITY IN THE CHRONIC FATIGUE SYNDROME

1. **Subjective sleep quality and daytime sleepiness in a large sample of patients with chronic fatigue syndrome (CFS)**

SUBJECTIVE SLEEP QUALITY AND DAYTIME SLEEPINESS IN A LARGE SAMPLE OF PATIENTS WITH CHRONIC FATIGUE SYNDROME (CFS)

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ABSTRACT

Chronic fatigue syndrome (CFS) is characterised by incapacitating fatigue in combination with a number of minor criteria, including unrefreshing sleep without further specifications, in the absence of psychiatric and internal disease. As little data exist on subjective sleep quality and daytime sleepiness, these parameters were assessed in a large sample of CFS patients.

Consecutive patients with a diagnosis of CFS in a tertiary referral centre filled out the Fatigue Questionnaire (FQ), Medical Outcomes Study 36-Item Short Form Health Survey (MOS SF-36), Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI).

Inclusion comprised 415 individuals (mean age 40.5 yr, SD 7.9, range 18-64; 86% female). Mean FQ (26.90; SD 4.04), mean Global Physical Health from the MOS SF-36 (29.30; SD 12.25) and Global Mental Health from the MOS SF-36 (49.62; SD 18.31) scores corresponded with literature data for similar CFS samples. High mean ESS (10.51; SD 5.52) and global PSQI (10.17; SD 4.02) were observed. No significant relationship was found between ESS and global PSQI. In contrast, regression analysis demonstrated a significant cubic relation between ESS and 'PSQI without daytime dysfunction'. A subgroup (n = 69) with an insomnia-like phenotype low ESS (<5), high PSQI (mean 11.51; SD 3.86) was observed.

The assessment of subjective sleep quality and daytime sleepiness in a large sample of CFS patients indicated high mean PSQI and ESS values. ESS and 'PSQI without daytime dysfunction' were inversely related at the spectral ends of ESS. A distinct subgroup with clinical features of insomnia was identified.

INTRODUCTION

Chronic fatigue syndrome (CFS) is a disabling condition characterized by mental and physical exhaustion that is not relieved by rest and that lasts for more than 6 months in the absence of nosologically defined internal or psychiatric diseases (1). As the pathogenesis of CFS is unknown, no pathognomonic signs or specific tests are available to establish a formal diagnosis. Therefore, the case definition of CFS is based on a syndromal concept, combining chronic unexplained fatigue with at least four out of eight accompanying symptoms: unusual post-exertional malaise, impaired memory or concentration, unrefreshing sleep, headaches, muscle pain, joint pain, sore throat and tender cervical nodes (2). These criteria, published by Fukuda et al. in 1994, prevail as a standard in current clinical practice and scientific research.

Complaints of disturbed or unrefreshing sleep are very common in CFS patients. While this symptom is listed as one of the concurrent criteria in the case definition (2), the guideline provides no instruction as how to assess the nature of the CFS-related sleep disturbances, and offers no clarification on its pathological relevance. This is problematic because fatigue and unrefreshing sleep are also a hallmark of nosologically defined sleep disorders, e.g. insomnia, narcolepsy and the sleep apnoea syndromes (SAS) (3, 4). Without proper clinical assessment of sleep complaints, a primary sleep disorder may go unnoticed in patients complaining of chronic fatigue (5, 6).

The role of sleep disturbances in the pathogenesis and severity of CFS remains speculative. Conceptually, poor sleep quality may contribute to daytime fatigue and impaired performance. Inversely, too much rest and napping during the daytime may compromise nocturnal sleep quality. Assessments

Abstract

Chronic fatigue syndrome (CFS) is characterised by incapacitating fatigue in combination with a number of minor criteria, including unrefreshing sleep without further specifications, in the absence of psychiatric and internal disease. As little data exist on subjective sleep quality and daytime sleepiness, these parameters were assessed in a large sample of CFS patients. Consecutive patients with a diagnosis of CFS in a tertiary referral centre filled out the Fatigue Questionnaire (FQ), Medical Outcomes Study 36-Item Short Form Health Survey (MOS SF-36), Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI). Inclusion comprised 415 individuals (mean age 40.5 yr, SD 7.9, range 18-64; 86% female). Mean FQ (26.90; SD 4.04), mean Global Physical Health from the MOS SF-36 (29.30; SD 12.25) and Global Mental Health from the MOS SF-36 (49.62; SD 18.31) scores corresponded with literature data for similar CFS samples. High mean ESS (10.51; SD 5.52) and global PSQI (10.17; SD 4.02) were observed. No significant relationship was found between ESS and global PSQI. In contrast, regression analysis demonstrated a significant cubic relation between ESS and 'PSQI without daytime dysfunction'. A subgroup (n = 69) with an insomnia-like phenotype low ESS (< 5), high PSQI (mean 11.51; SD 3.86) was observed. The assessment of subjective sleep quality and daytime sleepiness in a large sample of CFS patients indicated high mean PSQI and ESS values. ESS and 'PSQI without daytime dysfunction' were inversely related at the spectral ends of ESS. A distinct subgroup with clinical features of insomnia was identified.

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Methods

Subjects and procedures

Consecutive patients with a final diagnosis of CFS according to the Fukuda criteria (2) in a multidisciplinary tertiary care reference centre were included in this study, which was approved by the institutional Ethical Review Board. All patients filled out the ESS (11), the PSQI (12), the Medical Outcomes Study 36-Item Short Form Health Survey (MOS SF-36) (17) and the Fatigue Questionnaire (FQ) (18). Daytime sleepiness was assessed by the ESS on a scale ranging from 0 to 24 with a cut-off score of > 10 indicating excessive daytime sleepiness. Sleep quality was evaluated by the PSQI. The PSQI generates 7 component scores ranging from 0 to 3 each, defining different aspects of sleep quality and daytime functioning. A global PSQI score > 5 has been validated as an indication of subjectively perceived severe sleep difficulty in at least 2 component scores, or moderate difficulty in more than 3 component scores (12). The correlation between PSQI and ESS was explored in our patient sample. The seventh component score of the PSQI probes daytime dysfunction, which consists in part of daytime sleepiness. This component overlaps with the ESS, confounding the relation between the two scales (19). Consequently, we used the global PSQI without the seventh component score, which was labelled "night-time PSQI", to assess the relation between sleep quality and daytime sleepiness. Global mental and physical health was assessed with the MOS SF-36, generating 8 health dimensions each scored on a scale from 0-100. Normative data are available for healthy reference populations (20, 21) and many illnesses, including CFS (22-24). Severity of fatigue was measured by the 11-item FQ (18), using the Likert method, resulting in a score ranging from 0-33.

Statistical analysis

The data were analysed with SPSS (PASW 17.0). First, we report a number of descriptive statistics, Spearman correlations between age, gender, ESS, the PSQI scales, MOS SF-36 scales and the FQ, and Welch t-tests between the group of men and the group of women for all these variables. The MOS SF-36 component values were compared with published data of a reference sample (22) and samples of CFS patients (23, 24) using Welch-Satterthwaite t-tests. Significance testing was two-tailed; the cut-off level was set at 0.05. Second, we examined the relationship between ESS and "night-time PSQI". The residuals of the linear regression between these variables demonstrated strong curvature, so polynomial (third order) regression was performed between "night-time PSQI" as a dependent variable in function of centered ESS and its square and cubic as independent variables. Centering was done to reduce

collinearity. The plot of the resulting cubic equation revealed the possibility of distinct subgroups, at the spectral ends of ESS. We divided the patients in 5 groups according to their ESS values, with a nearly equal number of patients in each group, and did a one-way ANOVA variance analysis with Tukey's tests to analyse the "night-time PSQI" differences between the groups.

Results

The study sample consisted of 415 patients with a confirmed diagnosis of CFS. The mean age was 40.53 (SD = 7.91), range 18-64 years, and 86% was female. The mean score of the FQ was 26.90 (SD = 4.04; Cronbach's alpha = 0.78). The MOS SF-36 scores indicated poor health-related quality of life in comparison with published data of a reference population, and comparable results with respect to other studies in CFS patients (Table 1). The mean score on the ESS was 10.51 (SD = 5.52; Cronbach's alpha = 0.86). Excessive sleepiness was observed in 53% (Fig 1A). The mean global PSQI score was 10.17 (SD = 4.02; Cronbach's alpha = 0.64). Poor sleep quality was found in 86% (Fig 1B). The mean values and the Spearman correlations between all variables of the study are shown in Table 2. For the discrete variable gender, Welch t-tests between the group of men and the group of women revealed no statistical significance for all variables, except for age: mean 42.36 (SD = 7.41) for men, mean 40.23 (SD = 7.96) for women (p = 0.048). No significant relationship was found between ESS and global PSQI. In contrast, a significant negative correlation was observed between ESS and "night-time PSQI". Further regression analysis demonstrated a significant cubic relation between ESS and "night-time PSQI" (Table 3), yielding an S-shaped curve (Fig 2). This shape suggests three subgroups based on ESS values: a low ESS / high "night-time" PSQI group, a middle group with intermediate values of both scores, and a high ESS / low "night-time" PSQI group. Division of the patients in 5 groups according to their ESS values, with a nearly equal number of patients in each group, revealed that the subgroup with the lowest ESS values (ESS < 5) had significantly higher levels of "night-time PSQI" than each of the other groups (p < 0.001, by one-way ANOVA, p < 0.05 by Tukey's test). The "night-time PSQI" values of the other groups did not differ significantly from each other. Specifically, this means that statistical significance could be demonstrated in the low ESS subgroup (ESS < 5), but not in the high ESS subgroup (ESS > 15).

Discussion

This study describes the hitherto largest sample of CFS patients in respect of subjective sleep and sleepiness characteristics. High scores were found on the subjective measures of both poor sleep quality and daytime sleepiness. The demographic characteristics of the present sample of CFS patients are in keeping with previous reports (25). The low MOS SF-36 dimension scores in our patient group indicated significant impact on both global mental and physical health. These scores are similar to previously reported figures in CFS outpatients treated in specialised referral settings (23, 24), and indicate comparable severity of illness. The mean FQ score approximates the recently reported mean FQ score of 24.4 (SD = 5.8) in a clinical cohort of CFS patients (26), and is clearly larger than values reported at baseline in a large drug intervention trial in CFS patients (15). Hence, the present sample can be considered as representative and congruent with previously reported CFS cohorts. Published data on measures of somnolence are scarce in CFS patients. A small study compared a standard objective measure of sleepiness (i.e. a 4-nap multiple sleep latency test, MSLT) and two subjective measures (i.e. the ESS and the Stanford Sleepiness Scale) of sleepiness in twenty monozygotic twin pairs discordant for CFS (13). CFS twins reported significantly more subjective sleepiness than their healthy co-twins despite similar non-pathological mean sleep latencies on MSLT. It was suggested that patients with CFS may mistake their chronic disabling fatigue for sleepiness. Another limited study evaluated the relationship between fatigue and sleepiness in CFS patients not co-morbid for primary sleep or psychiatric disorders (14). Sixteen untreated CFS patients were compared with 13 untreated SAS patients and 12 healthy controls. Whilst higher than the control group on all measures, compared to SAS, the CFS group had higher subjective fatigue and lower subjective and objective sleepiness. These findings seemed to support the clinical distinction between fatigue and sleepiness, despite possible overlap in symptoms of both daytime conditions. Both studies are restricted by small sample size. The present investigation demonstrates a broad range of ESS values in a large CFS cohort, corresponding to a normal-like distribution between the delimiting values of 0 and 24. More than half of the patients reported an ESS score above 10, indicative of perceived excessive daytime sleepiness. As MSLT was not performed in the present study, no statement on subjective vs. objective sleepiness can be made. PSQI as a measure of disturbed sleep has been investigated in a few trials dealing with CFS patients. Neu et al. assessed different subjective measures (PSQI, Fatigue Severity Scale scores and intensity of affective symptoms by the Hamilton Depression and Anxiety scales) and objective findings using polysomnography (PSG) in 28 "pure" CFS patients after exclusion of

primary sleep and psychiatric disorders (16). Compared to age- and gender-matched healthy controls, CFS patients had significantly higher PSQI scores (9.54 ± 4.0 vs. 2.42 ± 1.2 in controls), without any evidence of PSG abnormalities, suggesting sleep quality misperception. Subjective sleep quality showed a correlation trend with severity of fatigue. Baseline measurements in a large multicenter randomized controlled drug intervention trial showed high PSQI scores, ranging between 8.87 and 9.42 (15). In the present investigation, a mean PSQI score of 10.17 was found, whilst 86% of the subjects had a PSQI > 5 as an indication of poor sleep quality. PSG, however, was not carried out in our sample, leaving the question of potential inappropriate perception of sleep quality unanswered. High PSQI values in the vast majority of our patients, however, confirm that poor subjective sleep quality is indeed an issue in CFS. This observation corroborates the relevance of disturbed sleep as a diagnostic criterion for CFS. The 'daytime dysfunction' subscale has the weakest correlation with the global PSQI (Table 2). Hence, PSQI omitting 'daytime dysfunction' (i.e. "night-time PSQI") seems a better probe for subjective sleep quality than the global scale and avoids overlap with the ESS. No correlation was found between ESS and global PSQI, in contrast with a significant negative correlation between ESS and "night-time PSQI". This is explained by the PSQI item 'daytime sleepiness' that is part of the seventh component score 'daytime dysfunction'. A positive correlation between ESS and the 'daytime dysfunction' component counterbalances the negative correlation with the other PSQI components. Whilst no significant relation between ESS and global PSQI emerged, regression analysis demonstrated a significant cubic relation between ESS and "night-time PSQI" (Fig 2). From the corresponding curve, the existence of three subgroups was postulated: a low ESS / high "night-time PSQI" group, a middle group with intermediate values of both scores, and a high ESS / low "night-time PSQI" group. Only in the middle group with intermediate ESS and PSQI values no significant correlation between ESS and "night-time PSQI" was observed. Such orthogonal relationship between ESS and PSQI after subtraction of the 'daytime dysfunction' component has recently been reported by Buysse et al. in a survey of a community sample (19). In the current sample of CFS patients, however, an inverse relation between ESS and "night-time PSQI" becomes evident at the spectral ends of ESS. Significant differences in "night-time PSQI" were observed in the ESS < 5 vs. ESS $\geq$ 5 but not in the ESS < 16 vs. ESS $\geq$ 16 subgroups (the latter probably due to insufficient statistical power). This suggests that very low sleepiness and high levels of sleep disturbance cluster together, as well as high sleepiness and low sleep disturbance. These associations at both ends of the ESS spectrum may correspond to a clinical profile of insomnia and hypersomnia, respectively. In

primary insomnia, complaints of substantial sleep disturbance are often associated with increased alertness (9, 27), whereas in idiopathic hypersomnia excessive daytime sleepiness persists despite normal nocturnal sleep (28). The hypothesis that clinical profiles of insomnia and hypersomnia may be discerned among CFS patients creates new perspectives for the nosological approach. As a consequence of the inadequate definition of sleep disturbances in the minor CFS criteria, patients with primary sleep disorders may still qualify for the diagnosis of CFS. While narcolepsy and SAS are explicitly mentioned as exclusionary conditions in the Fukuda criteria, primary insomnia and idiopathic hypersomnia – that would be diagnosed as such by sleep medicine physicians – may still go unnoticed in the clinical assessment at CFS referral centres. As a potential pitfall in medical diagnosis, the minor criterion of nonrestorative sleep or sleep disturbance needs to be detailed in future revisions of the CFS definition. Meanwhile, it is recommended to carefully assess the sleep disturbances in individual patients who present with a primary complaint of chronic unexplained fatigue. Finally, some limitations of the present investigation need to be acknowledged. Only subjective sleep quality and sleepiness measures were evaluated. No PSG or MSLT assessments were performed, leaving the potential influence of subjective perception on the outcome variables unexplored. Furthermore, the study has a cross-sectional design and, therefore, conclusions are beyond the scope of probing cause-effect relationships, but are limited to association of factors. A major strength of the study is the large sample of Fukuda criteria confirmed CFS patients.

In conclusion, the subjective assessment of daytime sleepiness and sleep quality in a large sample of CFS patients revealed high mean ESS and PSQI values. ESS and "night-time PSQI" were inversely related at the spectral ends of ESS. Evidence was shown for a distinct subgroup with an insomnialike phenotype, and possibly for an additional subgroup with a hypersomnia-like phenotype. This observation invokes the necessity to transcend prevailing semantics and syndromal definitions in the approach of this as yet insufficiently understood disorder.

Table 1. Mean, standard deviation, Cronbach's alpha of the MOS SF-36 scales, and Welch-Satterthwaite t-test values (our sample compared with other samples). The Welch-Satterthwaite t-test is used to adjust for the inequality of the variances.

	Physical Functioning	Role Physical	Role Emotional	Vitality	Mental health	Social Functioning	Bodily Pain	General Health
CFS sample of this study								
Mean	42.67	10.23	65.76	27.45	60.02	44.93	34.52	29.80
Stand. deviation	19.66	21.20	42.93	13.68	18.05	21.90	19.71	14.13
N	413	409	403	413	412	412	413	413
Cronbach's alpha	0.86	0.68	0.89	0.63	0.83	0.79	0.87	0.64
Reference sample of Picavet et al. (22)								
Mean	82.50	77.70	80.20	69.40	65.90	84.20	87.20	77.30
Stand. deviation	24.80	37.80	23.60	19.60	20.00	23.10	30.60	17.10
N	3664	3664	3664	3664	3664	3664	3664	3664
Cronbach's alpha	0.92	0.90	0.86	0.81	0.77	0.64	0.87	0.80
Significance of difference with our sample	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CFS sample of Myers and Wilks (23)								
Mean	52.40	21.20	60.00	27.20	61.80	49.30	50.90	39.80
Stand. deviation	31.00	34.40	43.90	22.30	21.80	28.10	29.50	21.90
N	85	85	85	85	85	85	85	85
Significance of difference with our sample	< 0.01	< 0.01	ns	ns	ns	ns	< 0.0001	< 0.0001
CFS sample of Rakib et al. (24)								
Mean	41.10	8.20	52.50	22.40	60.10	42.60	38.10	30.20
Stand. deviation	21.30	20.40	45.10	16.60	20.00	24.70	20.30	16.00
N	73	73	73	73	73	73	73	73
Significance of difference with our sample	ns	ns	ns	< 0.05	ns	ns	ns	ns

**Table 2.** Mean, standard deviation and Spearman correlations of the variables used in this study.

	Mean (SD)	2	3	4	5	6	7	8	9	10	11	12	13	14
1.Age	40.53 (7.91)	-.03	-.01	-.14**	.09	.07	-.01	.08	.03	.03	.03	-.00	-.05	-.04
2.ESS	10.51 (5.52)		-.07	-.19**	-.08	-.10*	.15**	-.16**	.45**	-.06	-.15**	-.20**	-.15**	.23**
3.PSQI subj. sleep quality	1.63 (0.84)			.49**	.47**	.40**	.36**	.17**	.15**	.72**	.72**	-.24**	-.23**	.17**
4.PSQI sleep latency	1.69 (1.10)				.34**	.36**	.22**	.16*	.01	.64**	.66**	-.09	-.10*	.15**
5.PSQI sleep duration	0.64 (0.88)					.71**	.24**	.05	.16*	.69**	.70**	-.12*	-.14**	.01
6.PSQI sleep efficiency	1.25 (1.27)						.22**	.07	.07	.72**	.74**	-.07	-.10*	.04
7.PSQI sleep disturbances	1.60 (0.61)							.06	.22**	.47**	.45**	-.28**	-.29**	.20**
8.PSQI use of sleep medication	1.37 (1.40)								.02	.46**	.48**	-.06	-.09	.02
9.PSQI daytime dysfunction	1.99 (0.75)									.30**	.13**	-.37**	-.34**	.32**
10.Global PSQI	10.17 (4.02)										.98**	-.25**	-.28**	.18**
11.Nighttime PSQI	8.18 (3.85)											-.20**	-.23**	.13*
12.SF36 global physical health	29.30 (12.25)												.41**	-.40**
13.SF36 global mental health	49.62 (18.31)													-.38**
14.FQ fatigue	26.90 (4.04)													

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Figure 1. Frequency distribution of ESS (A) and PSQI scores (B)
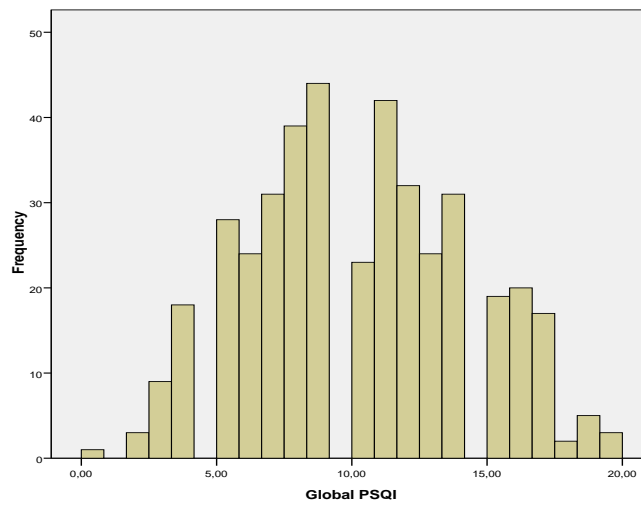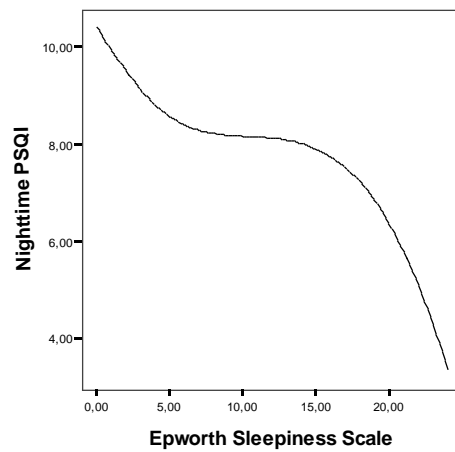
A
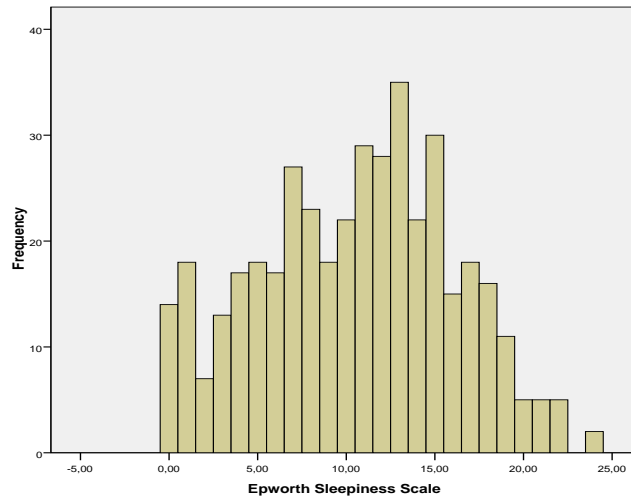
B

Figure 2. Plot of the Cubic Regression Equation of Night-time PSQI in function of ESS.

Equation: Estimated Night-time PSQI = $8.161 - 0.0017976 * (ESS - 10.5060)^3$

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2. Validation of the three-factor model of the PSQI in a large sample of chronic fatigue syndrome (CFS) patients

Validation of the three-factor model of the PSQI in a large sample of chronic fatigue syndrome (CFS) patients

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A R T I C L E   I N F O

A B S T R A C T

Objective: To evaluate whether a 3-factor model of the Pittsburgh Sleep Quality Index (PSQI) scale would fit the constellation of sleep disturbances in patients with a diagnosis of chronic fatigue syndrome (CFS).

Methods: Consecutive CFS patients filled out the PSQI. Scores from this self-report questionnaire were examined with exploratory and confirmatory factor analysis (CFA).

Results: 413 CFS patients were included for analysis in this study. CFA showed that the 7 PSQI component scores clustered into the 3 factors reported by Cole et al. (2006), i.e. Sleep Efficiency, Perceived Sleep Quality and Daily Disturbances. In contrast with the single-factor and all 2-factor models, all factor loadings were significant, and all goodness-of-fit values were acceptable.

Conclusion: In CFS, the PSQI operates as a 3-factor scoring model as initially seen in healthy and depressed older adults. The separation into 3 discrete factors suggests the limited usefulness of the global PSQI as a single factor for the assessment of subjective sleep quality, as also evidenced by a low Cronbach's alpha (0.64) in this patient sample.

Abstract

Objective:

To evaluate whether a 3-factor model of the Pittsburgh Sleep Quality Index (PSQI) scale would fit the constellation of sleep disturbances in patients with a diagnosis of chronic fatigue syndrome (CFS).

Methods:

Consecutive CFS patients filled out the PSQI. Scores from this self-report questionnaire were examined with exploratory and confirmatory factor analysis (CFA).

Results:

Four hundred thirteen CFS patients were included for analysis in this study. CFA showed that the 7 PSQI component scores clustered into the 3 factors reported by Cole et al. (2006), i.e. Sleep Efficiency, Perceived Sleep Quality and Daily Disturbances. In contrast with the single-factor and all 2-factor models, all factor loadings were significant, and all goodness-of-fit values were acceptable.

Conclusion:

In CFS, the PSQI operates as a 3-factor scoring model as initially seen in healthy and depressed older adults. The separation into 3 discrete factors suggests the limited usefulness of the global PSQI as a single factor for the assessment of subjective sleep quality, as also evidenced by a low Cronbach's alpha (0.64) in this patient sample.

Introduction

Chronic fatigue syndrome (CFS) is a disabling condition characterized by chronic fatigue of a new or definite onset that lasts for at least 6 months and that is not explained by medical or psychiatric causes[1]. Next to this major criterion, the 1994 case definition requires the co-occurrence of at least four out of eight minor criteria: unusual postexertional malaise, impaired memory or concentration, unrefreshing sleep, headaches, muscle pain, joint pain, sore throat and tender cervical nodes [1]. These 1994 CDC diagnostic criteria prevail as a standard in current clinical practice and scientific research. Complaints of unrefreshing sleep and poor sleep quality are common in CFS patients. The Pittsburgh Sleep Quality Index (PSQI) is one of the most used and validated questionnaires to measure sleep quality and disturbances during the past month [2]. The self-report questions are divided into 7 clinically derived components of sleep difficulties: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications and daytime dysfunction. Individual component scores are summed to yield one global score or a single factor, with higher scores indicating poorer sleep quality. Psychometric properties of the PSQI have been examined and found to be appropriate in relation to internal consistency [2,3], concurrent validity [3,4] and discriminative validity [3,4] in a range of clinical and healthy populations.

Using a cross-validation approach in healthy and depressed elderly US adults, Cole et al.[5] found that a single summed global score did not best capture the multidimensional nature of sleep disturbances. An exploratory factor analysis (EFA) followed by a confirmatory factor analysis (CFA) on the 7 quality components revealed that a 3-factor scoring model significantly better fitted than either the original single-factor or a 2-factor model. This model documents sleep disturbances in the separated factors Sleep Efficiency, Perceived Sleep Quality and Daily Disturbances.

Three other studies provided evidence that a multiple factor scoring method of the PSQI could be more appropriate to assess sleep problems compared to the originally proposed single-factor method. In a sample of Nigerian university students, a 3-factor model of the PSQI was identified performing EFA, however, the factors differed from Cole's findings [6]. EFA and subsequent CFA on the PSQI results deriving from a sample of Australian adults determined a 2- and 3-factor scoring model with slight differences in the optimal factor structures compared to the model of Cole et al. [7]. Conducting CFA, the original 3-factor model [5] was also found to better fit than a single-factor model in renal transplant recipients [8]. Although the fit

indices noticed were not as good as those found by Cole et al. [5], an additional pathway significantly improved its fit [8].

Differences in sample characteristics may account for the different factor structures identified in various studies since sleep patterns, sleep quality and perception of sleep are influenced by a range of factors related to age, health and culture [9–11]. As a consequence, there is a need for further studies examining the factor structure of the PSQI.

The aim of this study was to evaluate whether the 3-factor model of the PSQI reported by Cole et al. [5] would fit the constellation of sleep disturbances in a large sample of patients with CFS.

Methods

Patient recruitment

Consecutive patients with a final diagnosis of CFS according to the Fukuda criteria in a multidisciplinary tertiary care referral center were included in this study [12]. The sample was approved by the Ethical Review Board of the Ghent University Hospital.

Questionnaire

All patients filled out the PSQI and scores were calculated according to the scoring guidelines provided by Buysse et al. [2].

Statistical analysis

To investigate the validity of the 3-factor model of the PSQI proposed by Cole et al. [5], CFA was performed using SPSS (PASW 17.0) and the AMOS module (5.0). An EFA was performed to investigate the validity of the single-factor and all 2-factor models. The fit of the models was estimated with the Maximum Likelihood Algorithm.

In line with published recommendations, several indices were used to assess the model fit [13,14]. These include χ^2 and its related degrees of freedom (d.f.) and probability (p), goodness-of-fit index (GFI), adjusted goodness-of-fit index (AGFI), comparative fit index (CFI), root mean square error of approximation (RMSEA) and the consistent Akaike information criterion (CAIC). Chi-square assesses whether a significant amount of observed covariance between items remains unexplained by the model. A significant χ^2 (pb0.05) indicates a bad model fit. The RMSEA is a fit measure based on population error of approximation [15]. It is unreasonable to assume that the model will hold exactly in the

population. Therefore the RMSEA takes into account the error of approximation in the population. A RMSEA value b0.05 indicates a close fit and values up to 0.08 represent reasonable errors of approximation in the population. The GFI and the AGFI assess the extent to which the model provides a better fit compared to no model at all [16]. These indices have a range between 0 and 1, with higher values indicating a better fit. A GFI >0.90 and an AGFI >0.85 indicate a good fit of the model. The CFI is an incremental fit index [17]. It represents the proportionate improvement in model fit by comparing the target model with a baseline model (usually a null model in which all the observed variables are uncorrelated). The CFI ranges between 0 and 1, with values >0.90 indicating an adequate fit. The CAIC is a goodness-of-fit measure which adjusts the model's chi-square to penalize for model complexity and sample size [18]. This measure can be used to compare non-hierarchical as well as hierarchical (nested) models. Lower values on the CAIC measure indicate better fit [18].

Results

The study sample included 415 CFS patients (mean age 40.53 years, SD 7.91; 86% female) [12] from which 413 completely filled out all PSQI items, allowing analysis with the AMOS module.

Table 1 provides the descriptive statistics for the global PSQI, the 7 PSQI components and the Spearman's intercorrelations. Generally, high PSQI scores were found with a mean global score of 10.17 (SD 4.02, Cronbach's alpha 0.64). Poor sleep quality was observed in 86% of the patients using the recommended cut-off point of 5 [12].

Several inter-component correlations were not significant; the highest correlation was found between 'sleep duration' and 'habitual sleep efficiency' (r=0.71).

Fig. 1 shows the results of the CFA performed on the 3-factor model proposed by Cole et al. [5]. All factor loadings were significant and all goodness-of-fit values were acceptable ($\chi2$=14.70, d.f.=11, p=0.20; GFI=0.99; AGFI=0.97; CFI=0. 99; RMSEA=0.03; CAIC=134.10). In contrast, the single-factor model proposed by Buysse et al. [2] indicated a poor fit with the data ($\chi2$=109.90, d.f.=14, pb0.001; GFI=0.92; AGFI=0.85; CFI=0.84; RMSEA=0.13; CAIC=208.23) as was also the case for all 2-factor models (significant $\chi2$ values; results not shown).

Discussion

This is the first time that the PSQI factor structure was examined in a large sample of CFS patients. CFA demonstrated that the PSQI

operated as a multiple factor scoring model in CFS, which is consistent with previous findings in different subject groups [5–8]. Moreover, the 3-factor model proposed by Cole et al. [5] showed good fit criteria and the 7 PSQI component scores clustered into the factors Sleep Efficiency, Sleep Quality and Daily Disturbances. Therefore, the 3-factor model could improve the sensitivity of the PSQI in assessing sleep problems in CFS compared to the global PSQI as a single factor.

This limitation of the single-factor global PSQI is further evidenced by the low Cronbach's alpha in our sample (0.64) as an indicator of internal consistency, in contrast with the Cronbach's alpha (0.83) of the original PSQI description [2].

In conclusion, CFA confirmed that the PSQI operates as a 3-factor scoring model in CFS. The separation of the PSQI into 3 discrete factors suggests the limited usefulness of the global PSQI as a single factor for the assessment of subjective sleep quality in CFS patients.

Conflict of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Acknowledgments

We wish to acknowledge the role of Walter Michielsen, MD PhD, who has pioneered the rehabilitation program for CFS patients at the Department of General Internal Medicine, Infectious Diseases and Psychosomatic Medicine of the University Hospital Ghent, Belgium.

Table 1 Pittsburgh Sleep Quality Index (PSQI) component correlations and descriptive statistics

	Mean (SD)	1	2	3	4	5	6	7	8
1. Subjective sleep quality	1.63 (0.84)	—	.49**	.47**	.40**	.36**	.17**	.15**	.72**
2. Sleep latency	1.69 (1.10)		—	.34**	.36**	.22**	.16*	.01	.64**
3. Sleep duration	0.64 (0.88)			—	.71**	.24**	.05	.16*	.69**
4. Habitual sleep efficiency	1.25 (1.27)				—	.22**	.07	.07	.72**
5. Sleep disturbances	1.60 (0.61)					—	.06	.22**	.47**
6. Use of sleep medication	1.37 (1.40)						—	.02	.46**
7. Daytime dysfunction	1.99 (0.75)							—	.30**
8. Global PSQI	10.17 (4.02)								—

*Correlation is significant at the 0.05 level (2-tailed), **Correlation is significant at the 0.01 level (2-tailed)

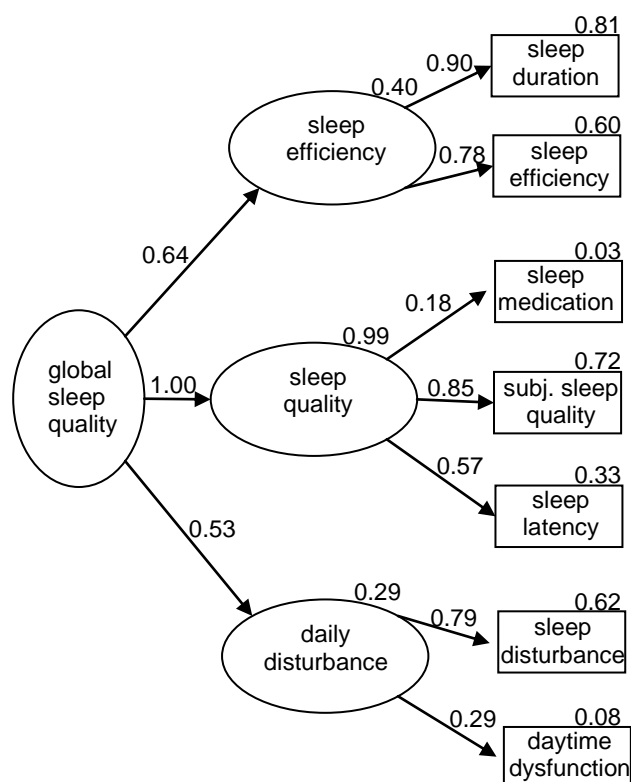**Figure 1** Confirmatory factor analysis (CFA) of the 3-factor model for the PSQI in CFS. Standardized β-coefficients (factor loadings, all significant) and R² values are shown (R² values shown above each variable).

GFI, Goodness-of-fit index; AGFI, Adjusted goodness-of-fit index; CFI, Comparative fit index; RMSEA, Root mean square error of approximation; CAIC, Consistent Akaike information criterion.

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CHAPTER 5: POLYSOMNOGRAPHIC AND MSLT DATA IN A LARGE SAMPLE OF PATIENTS WITH UNEXPLAINED CHRONIC FATIGUE: COMPARISON WITH A REFERENCE SAMPLE AND RELATION WITH SUBJECTIVE SCORES

Polysomnographic and MSLT data in a large sample of patients with unexplained chronic fatigue: comparison with a reference sample and relation with subjective scores

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Abstract

Objectives

This study aimed to assess objective parameters of sleep and sleepiness in a large sample of patients with unexplained chronic fatigue and to compare the results with data from a reference population. Furthermore, the relation was assessed between these objective results and subjective scores derived from questionnaires probing mental and physical health, sleep quality, daytime sleepiness and fatigue.

Methods

Objective sleep parameters derived from polysomnography (PSG) and multiple sleep latency testing (MSLT). Subjective assessment comprised history taking, psychological tests and the administration of validated questionnaires.

Results

Out of 377 eligible patients, 245 subjects were included (mean age 38.6 years, SD 10.69, 86.1% female). Significant differences in several objective sleep parameters were observed between the unexplained chronic fatigue and reference groups (i.e. decreased total sleep time, sleep efficiency and %REM; increased sleep latency, %NREM1, wake after sleep onset and arousal index). This sleep profile suggests an insomnia phenotype in patients with unexplained chronic fatigue. Neither PSG nor MSLT data were correlated with fatigue, and were only weakly correlated with mental health and subjective sleepiness. The latter was not substantiated by objective data from the MSLT.

Conclusions

The overall lack of correlation between subjective scores and objective indices derived from PSG and MSLT may suggest that these tests are inappropriate to explain symptoms of daytime sleepiness and fatigue in patients with unexplained chronic fatigue. However, their application remains justified for the demonstration of comorbid primary sleep disorders in this patient group.

Key words

Introduction

Fatigue is a common complaint among the general population. It is a subjective experience with aspects of lack of energy, weakness, attention deficits, memory problems and emotional instability. Whilst fatigue may often be attributed to a well-defined medical condition, psychiatric illness or primary sleep disorder, a definite cause cannot be determined in many patients, even after comprehensive clinical investigations. If unexplained fatigue persists for more than six months, the term 'chronic fatigue' is used. If, in addition, at least four out of eight minor diagnostic criteria are present, a diagnosis of 'chronic fatigue syndrome' (CFS) may be established according to the Fukuda criteria [1].

Fatigue is conceptually different from excessive daytime sleepiness (EDS), as the latter phenomenon refers to an inability to stay awake in normal conditions [2]. EDS is also quite prevalent in patients with CFS, and high scores on self-report questionnaires have been observed [3]. In these patients, however, little information is available on EDS assessed by objective means, such as the multiple sleep latency test (MSLT). A study in co-twins discordant for CFS revealed a discrepancy between scores on self-reported sleepiness that were higher in the CFS group and the results of the MSLT that were normal and quite similar in the CFS and control groups [4]. Evaluation of objective sleepiness has not been carried out in sufficiently large clinical samples of patients with chronic fatigue.

A complaint of disturbed or nonrestorative sleep (NRS) is one of the minor criteria in the prevailing guidelines for case definition [1]. Sleep disturbances are indeed reported by the vast majority of patients with CFS, and may include complaints of insufficient or too little sleep. Literature data on the nature of sleep complaints and impaired sleep quality assessed by PSG are limited and controversial [5].

Because figures from large clinical samples are lacking, the present study was designed to assess objective parameters of sleep and sleepiness in a large sample of patients referred with unexplained chronic fatigue (UCF), in which previous clinical investigations had not revealed any medical or psychiatric disease as an obvious cause of this presenting symptom. These data were compared with published data from a reference population. In addition, it was explored whether self-reported scores of fatigue, daytime sleepiness, sleep quality and quality of life are correlated with or predicted by objective variables derived from polysomnography (PSG) and MSLT.

Methods

Patient recruitment took place between June 2010 and February 2011.

Patients were admitted to our tertiary care referral centre for further clinical investigation of UCF. Prior to referral they had been examined by conventional methods in primary and/or secondary care settings. These previous assessments did not reveal any underlying medical or psychiatric diseases that would obviously explain the severity and duration of the reported chronic fatigue.

Criteria for enrolment were UCF persisting for at least six months, and a minimum age of 18 years. Participants gave written consent. The study was approved by the institutional Ethical Review Board of the University Hospital Ghent, Belgium.

Objective sleep assessment

PSG and MSLT were recorded and scored according to the manual of the American Academy of Sleep Medicine [6]. Sleep parameters derived from PSG included time in bed, total sleep time (TST), sleep efficiency (SE), sleep latency (SL), REM sleep latency (REM SL), percentage of TST spent in the different sleep stages (NREM1, NREM2, NREM3, REM), wakefulness after sleep onset (WASO), arousal index and apnea-hypopnea index (AHI).

MSLT consisted of taking four naps and assessing mean sleep latency and presence of REM sleep at sleep onset.

A mean sleep latency equal to or less than 8 minutes was considered indicative of clinically relevant hypersomnia, as this is the diagnostic cut-off in narcolepsy patients [7].

MSLT could not be performed in a subgroup of patients because of technical issues (environmental noise due to reconstruction works).

Patients were asked to withdraw from hypnotics (benzodiazepines and z-drugs) at least three weeks before PSG was performed.

Subjective assessment

Subjective assessment comprised history taking, psychological tests and the administration of validated questionnaires, i.e. Medical Outcomes Study 36-Item Short Form Health Survey (SF36) [8], Epworth Sleepiness Scale (ESS) [9], Pittsburgh Sleep Quality Index (PSQI) [10], and Fatigue Questionnaire (FQ) [11] (Table 1). Out of these questionnaires, the parameters global mental and global physical health, daytime sleepiness, global sleep quality, and fatigue were considered for further analysis. Clinically relevant daytime sleepiness is considered with an ESS score > 10, whereas poor sleep quality is defined as a PSQI score > 5.

Statistical analysis

The data were analysed with SPSS (PASW 17.0).

Descriptive statistics of the relevant objective (predictor) and subjective (outcome) variables were computed.

Because female patients represented 86.1% of the sample, some comparative analyses were limited to this gender category.

Simple regressions were performed to investigate the relation between predictor variables and age in female patients.

Welch T tests were carried out to assess differences between female patients and matched age subgroups from the general population [12].

Correlations between all study variables were calculated using the method of Spearman. In addition, multiple regression analysis was performed .

Results

Three hundred seventy-seven patients were referred for evaluation of UCF. Seven patients (1.9%) were excluded because of the age criterion. Fifty-eight patients (15.4%) did not give informed consent and in 51 patients (13.5%) data were incomplete, mostly due to cancellation of appointments. In sixteen patients (4.2%), complaints of fatigue had been present for less than six months. Two hundred forty-five patients (65.0%), who met the inclusion criteria, were enrolled in the study. Of these, 169 patients (69.0%) underwent MSLT.

The majority of the patients was female (n=211; 86.1%). The mean age was 38.6 years (median = 38.0; SD = 10.69; range 18-63); mean body mass index was 25.1 kg/m² (median = 24; SD = 5.27; range 15.5-46.4). A minority (n=85; 34.7%) had a certificate of higher education. ESS > 10 was present 113 patients (46.1%), and PSQI > 5 in 189 (77.1%).

A comparison of the objective sleep parameters in female UCF patients versus matched age subgroups from the general population is presented in Table 2.

Linear regression showed that TST, SE and NREM3 significantly decreased with age, whereas NREM2, WASO and AHI increased with age. No changes were observed regarding other sleep parameters.

TST and SE were significantly lower in female UCF patients of the 39-49, and 50-59 age subgroups compared with reference subgroups. REM was significantly decreased in the 39-49

age subgroup. A significant increase was observed with respect to SL, NREM1, WASO and arousal index in female UCF patients in the 39-49, and 50-59 age subgroups. In the oldest age subgroup (60-69) these differences were no longer present, with the exception of WASO. NREM2 and NREM3 were not significantly different between the patient and reference subgroups. Because of missing reference data, no comparative analysis could made in the 18-38 age subgroup.

The mean sleep latency on MSLT was 15.9 minutes and was not statistically different from the results in the reference sample. In only 10 out of 169 patients (5.9%) the mean sleep latency was less than the pre-set cut-off value of 8 minutes.

The mean values of all subjective and objective variables as well as the Spearman correlation coefficients are shown in Table 3. Only few significant correlations were found between objective sleep variables and subjective outcome data. The SF36 global mental health was correlated with TST and SE, and inversely correlated with SL. The ESS was correlated with TST and SE, and inversely correlated with WASO and MSLT mean sleep latency. All these correlations were weak. In addition, a low but statistically significant inverse correlation was found between PSQI and TST. No correlation was observed between SF36 global physical health or FQ with any of the PSG or MSLT parameters.

On the other hand, stronger correlations were found between the different subjective measures with respect to each other (Table 3).

Further regression analyses demonstrated that MSLT mean sleep latency and WASO significantly predicted ESS values. An inverse relation was also found between TST and PSQI. However, for all these items, the explained variance was low, as evidenced by the R^2 values (Table 4). No significant relation was found between any of the PSG or MSLT parameters and FQ values.

Discussion

This study is the first to statistically describe both objective and subjective sleep data in a large sample of clinical patients with UCF. The demographic characteristics of the present sample of 245 patients are in keeping with previously published data on CFS, showing predominance of female patients in the middle-age group, and remarkably low values on

global physical and mental health related quality of life as measured by SF36 [5, 13]. Therefore, the results from this sample can be inferred to the broader population of patients with presumed or confirmed CFS who seek medical attention in specialized care centers.

A salient objective of the present study was to match the objective sleep data in UCF patients with those from a reference population. Since reference data have not been established in our center, data from the literature were accessed. Published data on objective sleep parameters in healthy subjects are rare. Many studies are biased by small sample size or too specific selection criteria. The demographic dataset published by Unruh *et al.* (2008) was selected for the intended comparison as it covers a sample of 5407 community-dwelling adults from the general population. In analogy with the design of this reference study, patients with UCF were partitioned in age groups. Furthermore, the comparative analysis was limited to the female subgroup, given the predominance of this gender category in the patient sample.

Common age related phenomena, including effects on TST, SE, SL and distribution of time spent in different sleep stages were clearly present in both the patient and the reference groups. However, significant differences between patient and reference groups were observed regarding several PSG parameters. TST and SE were decreased, whereas SL, NREM1, WASO and arousal index were increased in patients with UCF. These differences were prominent in the 39-49 and the 50-59 age subgroups. Interestingly, REM was decreased in the 39-49 age subgroup only. Unfortunately, no reference data were available for the 18-38 age group, precluding any inference about sleep quality in this category.

These results would indicate that middle-aged women with UCF have less and more disrupted nocturnal sleep than controls, which would point to the co-existence of an insomnia-phenotype. This finding is at variance with previous studies showing that key characteristics of sleep architecture were not different between control subjects and CFS patients, despite subjective reports of poor sleep quality by the latter [14-17]. The reason for this discrepancy is not entirely clear. However, previous studies in clinical patients that failed to show an altered sleep structure in subjects with CFS may have been hampered by small sample size. An alternative explanation may be offered by the fact that subjects in the present study had to abstain from sleep medication, whereas in other studies the use of hypnotics was not controlled. Since PSG is not recommended for routine assessment of primary insomnia in clinical practice, there is a paucity of published data, which precludes comparison of objective sleep parameters in this diagnostic entity. Despite this limitation, the sleep profiles in different

age subgroups of female patients with UCF seamlessly match the diagnostic criteria of chronic insomnia, defined as an average SL and WASO exceeding 30 minutes, SE of less than 85% or TST of less than 6.5 hours [18, 19]. A relevant insomnia trait in middle-aged women with UCF is certainly a novel finding that requires further investigation and confirmation. Prospective studies on UCF should include diagnostic tools geared to assess insomnia. Moreover, validated treatment approaches to insomnia, e.g. cognitive behavioural therapy, may have a role in the management of UCF.

It is known from the literature that CFS patients experience EDS, at least subjectively [3]. The mean ESS in the present study was 10.0, which is just below the cut-off value for clinical relevance. Moreover, 113 patients (43.1%) had an ESS value > 10. Although a weak correlation between ESS and MSLT was found, the results of MSLT were not indicative of objective hypersomnolence. The mean MSLT sleep latency was 15.9 minutes, a value that substantially surpasses the present cut-off point of 8.0 minutes, and was not significantly different from the results in the reference cohort. A value below this threshold was present in only 5.9% of patients. Altogether, these results underpin the earlier reported discrepancy between objective and subjective accounts of sleepiness in patients with CFS [5].

In the present study, only few significant correlations were found between objective sleep variables and subjective outcome data. The SF36 global mental health was correlated with TST and SE, and inversely correlated with SL, but these correlations were weak. PSQI was inversely correlated with TST. No correlation was observed between SF36 global physical health or FQ with any of the PSG parameters. The lack of correlation between objective and subjective sleep parameters has been reported before in patients with CFS [16]. These authors concluded that sleep quality misperception might exist in CFS, or that potential neurophysiological sleep disturbances are not expressed by sleep PSG variables. Obviously, the lack of correlation between objective and subjective reports of sleep quality is a source of ambiguity in CFS. Our findings would corroborate the contention that PSG parameters are insufficiently capable of explaining symptom scores in CFS patients across the domains of mental or physical health, sleep quality, daytime sleepiness or fatigue. Whether this paradox may be explained by an as yet undisclosed deficit in the neurobiology of sleep or be inherent to the technical limitations of PSG, remains to be determined [5].

Although correlations between subjective scores and objective indices of sleep were few and weak, coefficients of correlation between results from the different questionnaires were more robust. These questionnaires have been validated for the clinical evaluation of sleep, daytime sleepiness and/or fatigue. Given the good reproducibility of results across different studies [3] these scales are still the mainstay for the assessment of patients with UCF. Whilst clinically valid, these instruments do not disclose the causes of disturbed sleep nor the mechanisms of fatigue in these patients.

Some limitations of the present study must be acknowledged. First, no conclusions could be drawn regarding male subjects with UCF, as they represented only 13.9 % of the sample. Given the scarcity of the male gender in this patient group, a multicenter study would probably be required to collect sufficient numbers. Second, the study lacks an original case-control design. Our department has not constructed a PSG database on healthy controls over the years. Therefore, a historical source had to be accessed. The dataset from the Sleep Heart Health Study seemed suitable, as it comprises a large sample from a general population [12]. The reported information was sufficiently detailed to allow age group comparisons of patients versus controls in the female gender category. Third, there was a difference in applied PSG methodology between the present patient sample and the reference cohort. Laboratory sleep recording was carried out in the patient group versus portable monitoring in the reference group. This methodological difference may induce a measurement bias, as sleep is influenced by the environment. However, a study comparing effects of home-based versus laboratory conditions on PSG variables in insomniacs showed that there were no significant main or interaction effects attributable to the settings in which sleep recording was carried out [20]. Certainly, the laboratory environment may have had a limited influence on sleep in the present study. Conversely, some of these effects may have been counterbalanced by a known paradoxical effect, namely the fact that patients with insomnia often sleep better than usual on their first night in the laboratory [21, 22]. Fourth, sleep may vary in consistency and duration across nights. This is especially true in patients with insomnia [21]. As such, a single night study may not be representative and may fail to properly characterize the full extent of the sleep problem. However, this effect may be averaged out when the number of included subjects is sufficiently high, as is the case in the present study. Nevertheless, night-to-night variability may compromise representative sampling, and a potential sampling error could have played a role in the lack of correlation between subjective scores and objective PSG data observed in the present study.

To conclude, it was observed that objective sleep parameters are significantly worse in middle-aged women with UCF as compared to a reference population, suggesting an insomnia phenotype. While subjectively sleepy, most of these patients have normal MSLT values. The overall lack of correlation between subjective scores and objective indices of sleep and daytime sleepiness would imply that the latter do not contribute to explaining the symptoms of fatigue and EDS. As a consequence, conventional single PSG and MSLT investigations do not seem appropriate to authenticate sleep complaints in relation with symptoms of daytime dysfunction in these patients. However, this observation does not invalidate the role of PSG and MSLT in the diagnosis of primary sleep disorders that may be comorbid factors in the clinical picture of UCF.

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Table 1. Overview of psychodiagnostic questionnaires

Screening tool	Item measured	Scale
Medical Outcomes Study 36-item Short Form Health Survey (SF36) [8]	Global mental and physical health	0-100 on 8 health domains: higher score = better health status, no cut-off
Epworth Sleepiness Scale (ESS) [9]	Excessive daytime sleepiness	0-24: higher score = more severe sleepiness, cut-off > 10
Pittsburgh Sleep Quality Index (PSQI) [10]	Global sleep quality	0-3 on 7 components, 0-21 global score: higher score = worse sleep quality, cut-off global score > 5
Fatigue Questionnaire (FQ) [11]	Fatigue severity	0-33: higher score = more severe fatigue, no cut-off

Table 2. Comparison of objective sleep parameters (means, standard deviation) in female patients with chronic fatigue/CFS and reference female controls according to age

	Patients with chronic fatigue/CFS					Reference adults (Unruh et al., 2008)			
	18-38 years	39-49 years	50-59 years	60-69 years	p trend	39-49 years	50-59 years	60-69 years	p trend
Polysomnography	*n = 106*	*n = 65*	*n = 34*	*n = 6*		*n = 314*	*n = 793*	*n = 759*	
TST (min)	372.30 (65.12)	**358.05*** (63.76)**	**325.15*** (75.52)**	352.83 (27.33)	<.001	385.5 (62.9)	374.6 (58.1)	362.2 (60.9)	<.001
SE (%)	76.90 (12.18)	**74.59*** (13.25)**	**68.32*** (15.46)**	73.48 (12.28)	<.001	85.6 (9.8)	84.6 (8.4)	81.7 (10.3)	<.001
SL (min)	36.79 (31.88)	**33.82** (25.53)**	**41.07*** (40.99)**	30.67 (11.80)	.70	24.2 (26.5)	21.9 (21.9)	25.0 (25.4)	.38
REM SL (min)	172.52 (84.09)	170.62 (89.61)	173.77 (103.03)	193.50 (96.76)	.71	ND	ND	ND	
NREM1 (% TST)	5.89 (4.59)	**6.05*** (2.85)**	**5.76** (2.84)**	3.83 (1.95)	.71	4.2 (2.8)	4.3 (3.1)	4.7 (3.3)	.03
NREM2 (% TST)	51.41 (10.95)	53.75 (13.58)	55.31 (8.97)	57.32 (24.91)	.02	54.4 (10.3)	53.0 (10.9)	52.0 (11.7)	.75
NREM3 (% TST)	25.54 (10.00)	21.61 (13.76)	19.72 (8.42)	18.85 (19.77)	<.001	19.7 (9.8)	21.7 (10.9)	23.0 (11.5)	.004
REM (% TST)	17.13 (6.16)	**18.58*** (7.19)**	19.12 (7.50)	19.89 (10.79)	.12	21.7 (6.2)	21.0 (5.8)	20.3 (5.9)	<.001
WASO (min)	73.72 (46.15)	**87.74*** (55.56)**	**110.82*** (56.81)**	**104.33** (72.25)**	<.001	39.0 (30.2)	48.5 (33.5)	57.7 (40.1)	<.001
Arousal index	23.48 (11.44)	**26.91*** (12.82)**	**26.39*** (14.27)**	15.83 (8.12)	.06	13.9 (7.1)	16.0 (8.6)	17.2 (8.3)	<.001
AHI	2.98 (3.85)	5.12 (5.02)	8.64 (12.08)	8.30 (9.36)	<.001	ND	ND	ND	
Multiple sleep latency	*n = 74*	*n = 50*	*n = 18*	*n = 6*					
MSLT mean sleep latency	15.79 (4.89)	15.31 (4.95)	18.58 (5.25)	17.89 (6.58)	.23	ND	ND	ND	

p trend: tests for statistical significance of a linear age effect within sample

Comparison with corresponding age group of reference subjects (Unruh *et al.*, 2008) is given by p-values: p < .05* p < .01** p < .005*** (Welch test)

AHI, apnea hypopnea index; MSLT, multiple sleep latency test; REM SL, REM sleep latency; SE, sleep efficiency; SL, sleep latency; TST, total sleep time; WASO, wake after sleep onset

ND, no data

Table 3. Means, standard deviation (SD) and Spearman correlations of the variables used in this study

	Mean	(SD)	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. SF36 global physical health	34.30	(16.75)	.42**	-.20**	-.46**	-.46**	.02	.03	.02	-.04	-.07	-.01	-.01	.05	-.05	-.07	.13	-.06
2. SF36 global mental health	49.53	(18.44)		-.11	-.32**	-.46**	.14*	.17**	-.14*	-.12	-.10	-.01	-.00	.07	-.13	-.07	.04	-.08
3. ESS	10.00	(5.68)			-.06	.31**	.17**	.19**	-.11	-.08	-.02	.06	-.05	-.00	-.21**	-.02	.03	-.22**
4. PSQI	9.48	(4.37)				.26**	-.14*	-.10	.08	.07	.03	.04	-.06	.05	.10	.06	-.04	.06
5. FQ	22.76	(5.98)					.07	.07	-.07	.07	-.03	-.09	.09	.02	-.08	.03	-.06	-.01
6. TST (min)	359.68	(67.72)						.92**	-.53**	-.27**	-.40**	.01	-.08	.26**	-.79**	-.21**	-.07	-.14
7. SE (%)	74.96	(13.51)							-.57**	-.36**	-.44**	.00	-.06	.28**	-.89**	-.21**	-.03	-.17*
8. SL (min)	35.25	(29.89)								.47**	.12	-.05	.10	-.14*	.23**	-.00	-.06	.18*
9. REM SL (min)	167.96	(87.12)									.19**	.03	.08	-.34**	.23**	.04	-.05	.02
10. NREM1 (% TST)	5.77	(3.64)										.17**	-.17**	-.40**	.48**	.65**	.35**	-.10
11. NREM2 (%TST)	53.41	(12.17)											-.84**	-.32**	.03	.13*	.08	-.05
12. NREM3 (%TST)	22.67	(11.58)												-.11	-.00	-.15*	-.13*	.02
13. REM (%TST)	18.14	(6.71)													-.24**	-.23**	-.05	.06
14. WASO (min)	84.40	(54.51)														.25**	.07	.13
15. Arousal index	24.96	(12.51)															.46**	-.22**
16. AHI	5.44	(7.46)																.06
17. MSLT mean sleep latency	15.90	(5.24)																

$p < 0.05$* $p < 0.01$**

AHI, apnea hypopnea index; ESS, Epworth Sleepiness Scale; FQ, Fatigue Questionnaire; MSLT, multiple sleep latency test; PSQI, Pittsburgh Sleep Quality Index; REM SL, REM sleep latency; SF36, Medical Outcomes Study 36-Item Short Form Health Survey; SE, sleep efficiency; SL, sleep latency; TST, total sleep time; WASO, wake after sleep onset

Table 4. Multiple regressions with ESS sleepiness, PSQI global quality of sleep and FQ fatigue respectively as dependent variables.

Criterion variable	Entry	Predictor	β	ΔR^2	Adj.R^2
ESS: sleepiness	1	MSLT sleep latency	-.19*	.04**	.04
	2	WASO: wakefulness after sleep onset	-.15*	.02*	.06
PSQI: global quality of sleep.	1	TST: total sleep time	-.21**	.05**	.04
FQ fatigue					

$p < 0.05*$ $p < 0.01**$ $p < 0.005***$

In each regression, the following PSG and MSLT variables were entered stepwise: total sleep time, sleep latency, REM sleep latency, time spent in NREM1, NREM2, NREM3, REM, wakefulness after sleep onset, arousal index, apnea-hypapnea index and MSLT sleep latency. The stepwise entry method was used with Prob.-of-F-to-enter <= 0.05, Prob.-of-F-to-remove >0.10. The Variance Inflating Factors did not indicate collinearity problems. All beta values are, for each criterion variable, from the last step.

AHI, apnea hypopnea index; ESS, Epworth Sleepiness Scale; FQ, Fatigue Questionnaire; MSLT, multiple sleep latency test; PSQI, Pittsburgh Sleep Quality Index; TST, total sleep time; WASO, wake after sleep onset

CHAPTER 6: WHAT DOES FATIGUE MEAN IN THE CHRONIC FATIGUE SYNDROME? A PATH ANALYSIS ON A LARGE SAMPLE OF PATIENTS WITH CHRONIC FATIGUE

What does fatigue mean in the chronic fatigue syndrome? A path analysis on a large sample of patients with chronic fatigue

(Manuscript in preparation)

Running title: Interrelationship of different dimensions of chronic unexplained fatigue

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Abstract

Objective

To explore the interrelationship of different dimensions (fatigue, neuroticism, sleep quality, global mental and physical health) as assessed through self-report questionnaires in the construct of chronic fatigue and chronic fatigue syndrome (CFS).

Methods

Patients with chronic unexplained fatigue in a tertiary referral centre filled out the Fatigue Questionnaire (FQ) and Checklist Individual Strength (CIS), respectively, NEO-Five Factor Inventory (NEO-FFI), Pittsburgh Sleep Quality Index (PSQI) and Medical Outcomes Study 36-item Short Form Health Survey (SF36). Path and regression analyses were performed.

Results

Out of 296 patients fulfilling the enrolment criteria, a full dataset allowing statistical analysis was available in 203 patients (mean age 39.0 years, SD 10.37, 89% female). In a first path analysis, using FQ for assessment of fatigue and involving the questionnaires alone, night-time PSQI sleep quality had a direct effect on SF36 physical health quality of life (PHQL) and no effect on FQ fatigue. This was confirmed by a similar path analysis with CIS fatigue for assessment of fatigue and by regression analyses. These unexpected results raised the question whether FQ and CIS fatigue sufficiently operationalises fatigue, as the major complaint in CFS. For both fatigue scales, the introduction of a latent variable, coined as 'intrinsic fatigue', into the model resulted in an indirect effect of PSQI sleep quality on SF36 PHQL via intrinsic fatigue. Furthermore, this latent variable had a direct effect on FQ and CIS fatigue, respectively and on the two SF36 quality of life variables. NEO neuroticism had a direct effect on FQ and CIS fatigue, respectively, but not on intrinsic fatigue, and its positive direct effect on SF36 PHQL, as was seen in the first path analysis, disappeared.

Conclusions

Path analysis on a large sample of patients with presumed CFS led to the introduction of a latent variable, intuitively called 'intrinsic fatigue', as missing link in the relationship between the subjective complaints neuroticism, fatigue, poor sleep quality and outcome measures of mental and physical quality of life. This new variable seems to correspond better with the subjective feelings of fatigue, mentioned by CFS patients, than the FQ and CIS fatigue variables. These findings emphasize the complex and heterogeneous concept of fatigue as well as the need for more appropriate and innovative tools for measuring fatigue in CFS.

Key words

Chronic fatigue syndrome, path analysis**,** FQ, CIS, PSQI, SF36

Introduction

Fatigue is a subjective experience associated with impaired functioning, and refers to a lack of energy, weakness, attention deficits, memory problems and emotional instability. It is a common complaint among the general population that often may be attributed to a diagnosis of a well defined medical condition, psychiatric illness or primary sleep disorder. However, a definite cause of fatigue cannot be determined in many patients, even after comprehensive clinical investigations. If unexplained fatigue persists for more than six months, the term 'chronic fatigue' is used. If, in addition, at least four out of eight minor diagnostic criteria are present, a diagnosis of 'chronic fatigue syndrome' (CFS) may be established [1].

The 1994 CFS case definition stipulates that patients have 1) clinically evaluated, unexplained, persistent or relapsing chronic fatigue of at least six months duration, 2) that is of new or definite onset, 3) that is not the result of ongoing exertion, and 4) that results in substantial reduction in previous levels of occupational, educational, social or personal activities [1]. This description of fatigue is, however, difficult to apply in practice [2]. Furthermore, 'effort tolerance' is considered to be a minor parameter as mirrored by 'post-exertional malaise', which often has been criticized in literature [3-5]. Since fatigue is highly subjective, multidimensional and variable during the course of disease, the specific meaning remains unclear within the 1994 CFS case definition.

A substantial number of patients with a presumed diagnosis of CFS in tertiary care have psychiatric problems [6-8]. Personality, e.g., is regarded as a contributing factor in CFS [9, 10], and one of the most consistent findings is the high level of neuroticism in CFS patients compared to healthy control groups [11, 12]. Sleep disorders as well are frequently observed in patients with chronic fatigue and CFS [13]. Nevertheless, the relation between fatigue, psychiatric and sleep problems remains unclear in this clinical sample.

The aim of the present study is to explore the interrelationship of self-report questionnaires on fatigue, neuroticism, and sleep quality and their effect on the global quality of life of patients with chronic unexplained fatigue, in order to improve insights in the concept of 'fatigue' within the CFS definition.

Methods

Enrolment criteria in the present study were unexplained fatigue for at least six months and a minimum age of 18 years. These patients were recruited from an integrated multidisciplinary diagnostic pathway for chronic unexplained fatigue offered to patients referred with a presumed diagnosis of CFS. Participants gave written informed consent. Patient recruitment

took place between June 2010 and February 2011. The study was approved by the institutional Ethical Review Board of the University Hospital Ghent, Belgium.

All patients filled out a set of validated questionnaires in order to evaluate personality, fatigue, sleep quality and mental and physical quality of life (Table 1). The seventh component score of the Pittsburgh Sleep Quality Index (PSQI) probes daytime dysfunction, which consists in part of daytime sleepiness. This component overlaps with part of the fatigue questionnaire (FQ), containing the question 'do you feel sleepy or drowsy?'. Consequently, we used the global PSQI without the seventh component score, labelled as "night-time PSQI", to assess the relation between sleep quality and the other variables of this study [14, 15].

Statistical analysis

Data were analysed with SPSS (PASW 17.0) and the AMOS module (5.0).

Path and regression analyses were performed in order to assess the relationship between subjectively measured variables NEO neuroticism, FQ and Checklist Individual Strength (CIS) fatigue, respectively, night-time PSQI sleep quality, Medical Outcomes Study 36-item Short Form Health Survey (SF36) mental (MHQL) and physical health quality of life (PHQL). The study protocol allowed the further exploration of the interrelationship between these variables through the introduction of latent variables, in the presence of insufficient explanatory modeling.

The CIS variable was transformed with a classical transformation (New value = - logarithm [maximum value + 1 - value], because it was not normally distributed, and had high kurtosis and negative skewness [16].

The path analyses were estimated and tested with the maximum likelihood algorithm, which is known to be asymptotically efficient and to give correct chi-square estimators if there is not too much multivariate kurtosis [17, 18]. The indices used in the path analyses for goodness-of-fit modelling were chi square (χ^2) and its related degrees of freedom (*df*), probability (*P*), goodness-of-fit index (GFI), adjusted goodness-of-fit index (AGFI), comparative fit index (CFI), and the Consistent Akaike Information Criterion (CAIC). Chi square assesses whether a significant amount of observed covariance between items remains unexplained by the model. A significant chi square (e.g., $P < .05$) indicates a bad model fit.

The GFI and AGFI assess the extent to which the model provides a better fit compared to no model at all. [19]. These indices have a range between 0 and 1, with higher values indicating a

better fit. A GFI larger than 0.90 and an AGFI larger than 0.85 indicate a good fit of the model. The CFI is an incremental fit index [20] and represents the proportionate improvement in a model fit by comparing the target model with a baseline model (usually a null model in which all the observed variables are uncorrelated). The CFI ranges between 0 and 1, with values larger than 0.90 indicating an adequate fit.

The CAIC is a goodness-of-fit measure that adjusts the model's chi square to penalize for model complexity and sample size [21]. This measure can be used to compare non-hierarchical as hierarchical (nested) models. Lower values on the CAIC measure indicate better fit [21].

Results

Three hundred seventy-seven patients were referred for evaluation of chronic unexplained fatigue. Seven patients (1.9%) were excluded because of age requirement. Fifty-eight patients (15.4%) did not give informed consent. In sixteen patients (4.2%), complaints of fatigue had been present for less than six months. Out of 296 patients (78,5%) fulfilling the enrolment criteria, a full dataset was available in 203 patients, which were suitable for further analysis.

The majority of the patients was female (n = 181; 89%). The mean age was 39.0 years (SD 10.37); mean body mass index (BMI) was 24.7 kg/m² (SD 5.18). A minority (n = 73, 36%) had a certificate of higher education.

In a first path analysis, using FQ for assessment of subjective fatigue (Figure 1A) and involving the questionnaires alone, night-time PSQI sleep quality has no direct effect on FQ fatigue, but does have a direct effect on SF36 PHQL. A similar path analysis with CIS fatigue for assessment of fatigue (Figure 1B) demonstrated a moderate effect of night-time PSQI on CIS fatigue and a direct effect on SF36 PHQL as well. These results were confirmed with regression analyses (Table 2 and 3).

The findings raise the question whether fatigue, as operationalised by the FQ and CIS fatigue, respectively, is a rather poor representative of the dimension of fatigue as represented in the 'F' of 'CFS'. To test this hypothesis, a second path analysis was performed for FQ and CIS fatigue, respectively, with an additional latent variable for which the denominator 'intrinsic fatigue' (Figure 2A and B) was coined.

In this modeling, night-time PSQI sleep quality has a direct effect on intrinsic fatigue. This latent variable has a direct effect on the measured fatigue variables FQ and CIS fatigue, respectively, and on the two SF36 quality of life variables. NEO neuroticism has a direct effect on the result of the FQ and CIS fatigue, respectively, but not on intrinsic fatigue.

Furthermore, neuroticism no longer had a positive direct effect on SF36 PHQL, as was the case in the first path analyses.

In each path analysis, the critical ratio given for the multivariate kurtosis by AMOS (-0.47 in the case of the two analyses with FQ, -1.92 in the case of the two analyses with CIS fatigue) was not significant at the 5% level, showing that the maximum likelihood algorithm was appropriate to carry out the estimation and testing for the path analyses.

Discussion

In this study, the relationship between the variables neuroticism, fatigue, night-time sleep quality and mental and physical quality of life as measured by the self-report questionnaires NEO- Five Factor Inventory (NEO-FFI), FQ and CIS, respectively, PSQI and SF36 was assessed in a large sample of patients with chronic unexplained fatigue by means of path and regression analyses.

Path analysis of these variables demonstrated a direct effect of PSQI sleep quality on SF36 PHQL and no or moderate effect on FQ and CIS fatigue, respectively. However, it should be expected that PSQI sleep quality only has an indirect effect on SF36 PHQL via FQ and CIS fatigue, respectively. These findings suggest that these fatigue scales do not sufficiently operationalise fatigue, as the major complaint in CFS.

The introduction of a latent variable into the model, intuitively called 'intrinsic fatigue', resulted in effects that better correspond with complaints of CFS patients in clinical practice: the sleep quality (night-time PSQI) considerably effects intrinsic fatigue, which in turn influences patients' physical quality of life (SF36 PHQL). As such, the new fatigue variable mediates between PSQI sleep quality and SF36 PHQL. Additionally, a substantial effect of intrinsic fatigue on FQ and CIS fatigue results strengthens the hypothesis that these fatigue scales do not fully measure fatigue, as experienced by patients with chronic unexplained fatigue and CFS. Possibly, the FQ and CIS fatigue insufficiently measure the lack of tolerance to mental and/or physical effort, and a new variable may be needed to take into account this dimension. FQ and CIS fatigue may essentially measure the major criterion within the Fukuda definition, but maybe the Fukuda criteria themselves do not correspond well with the subjective feeling of CFS patients. It can be hypothesised that post-exertional physical and mental malaise may play a role, as partially implicated in the Canadian guidelines by

Carruthers et al. [3]. Nevertheless, the nature of this missing link needs to be further explored and may lead to a revision of the Fukuda case definition.

Furthermore, the findings of both path analyses suggest a more complex and heterogeneous concept and hence warrant the search for other measurement tools of fatigue in CFS. Self-report questionnaires, objective measures, as well as a combination of both subjective and objective tools may be considered in order to better estimate the lack of tolerance to effort in this patient sample.

Path analysis showed a direct effect of NEO neuroticism on FQ and CIS fatigue, respectively and SF36 MHQL, whereas its positive direct effect on SF36 PHQL, as was seen in the first path analysis, disappeared. Nater et al. [10] also found that personality dimensions, as measured by the NEO-FFI, were associated with fatigue and functional impairment in CFS. Among the five personality dimensions, the strongest correlations were found between neuroticism and fatigue and both SF36 health quality of life [10].

In conclusion, path analysis on a large sample of patients with presumed CFS led to the introduction of a latent variable, intuitively called 'intrinsic fatigue', as missing link in the relationship between the subjective complaints neuroticism, fatigue, poor sleep quality and outcome measures of mental and physical quality of life. This new variable seems to correspond better with the subjective feelings of fatigue, mentioned by CFS patients, than the FQ and CIS fatigue variables. These findings emphasize the complex and heterogeneous concept of fatigue as well as the need for more appropriate and innovative tools for measuring fatigue in CFS.

Table 1. Overview of psychodiagnostic questionnaires

Screening tool	Item measured	Scale
NEO-Five Factor Inventory [22]	Personality assessment (neuroticism, extraversion, openness, agreeableness, conscientiousness)	0-4 on 12 items for each personality dimension: ranging from 'totally not agree' (score 0) to 'totally agree' (score 4)
Fatigue Questionnaire (FQ) [23]	Fatigue severity	0-33: higher score = more severe fatigue, no cut-off
Checklist Individual Strength (CIS) [24]	Fatigue phenomenology (fatigue, concentration, motivation, physical activity) and severity	0-7 on 20 items, 0-140 global score, cut-off global score > 76
Pittsburgh Sleep Quality Index (PSQI) [25]	Global sleep quality	0-3 on 7 components, 0-21 global score: higher score = worse sleep quality, cut-off global score > 5
Medical Outcomes Study 36-item Short Form Health Survey (SF36) [26]	Global mental and physical health	0-100 on 8 health domains: higher score = better health status, no cut-off

Table 2. Multiple regressions with SF36 Physical Health Quality of Life and SF36 Mental Health Quality of Life respectively as dependent variables. Fatigue was evaluated by the Fatigue Questionnaire (FQ).

Criterion variable	Entry	Predictor	β	ΔR^2	Adj.R^2
SF36 Physical Quality of Life	1	FQ Subjective Fatigue	-.33***	.24***	.24
	2	SF36 Mental Quality of Life	.46***	.09***	.32
	3	Night time PSQI Sleep Quality	-.24***	.04***	.36
	4	NEO Neuroticism	.29***	.05***	.40
SF36 Mental Quality of Life.	1	NEO Neuroticism	-.59***	.46***	.46
	2	FQ Subjective Fatigue	-.26***	.06***	.51

$p < 0.05$* $p < 0.01$** $p < 0.005$***

In each regression, the independent variables were entered stepwise. In the first regression, all independent variables had a significant contribution, and were thus entered by the stepwise entry method. In the second regression, Night time PSQI Sleep Quality did not have a significant contribution. The stepwise entry method was used with Prob.-of-F-to-enter <= 0.05, Prob.-of-F-to-remove >0.10. The Variance Inflating Factors (VIF) did not indicate collinearity problems. All beta values are, for each criterion variable, from the last step

Table 3. Multiple regressions with SF36 Physical Health Quality of Life and SF36 Mental Health Quality of Life respectively as dependent variables. Fatigue was evaluated by the Checklist Individual Strength (CIS) fatigue.

Criterion variable	Entry	Predictor	β	ΔR^2	Adj.R^2
SF36 Physical Quality of Life	1	CIS Subjective Fatigue	-.35***	.31***	.30
	2	SF36 Mental Quality of Life	.39***	.05***	.35
	3	Night time PSQI Sleep Quality	-.19***	.02**	.37
	4	NEO Neuroticism	.21**	.02**	.40
SF36 Mental Quality of Life.	1	NEO Neuroticism	-.57***	.46***	.46
	2	CIS Subjective Fatigue	-.37***	.13***	.58

p < 0.05* p < 0.01** p < 0.005***

In each regression, the independent variables were entered stepwise. In the first regression, all independent variables had a significant contribution, and were thus entered by the stepwise entry method. In the second regression, Night time PSQI Sleep Quality did not have a significant contribution. The stepwise entry method was used with Prob.-of-F-to-enter <= 0.05, Prob.-of-F-to-remove >0.10. The Variance Inflating Factors (VIF) did not indicate collinearity problems. All beta values are, for each criterion variable, from the last step
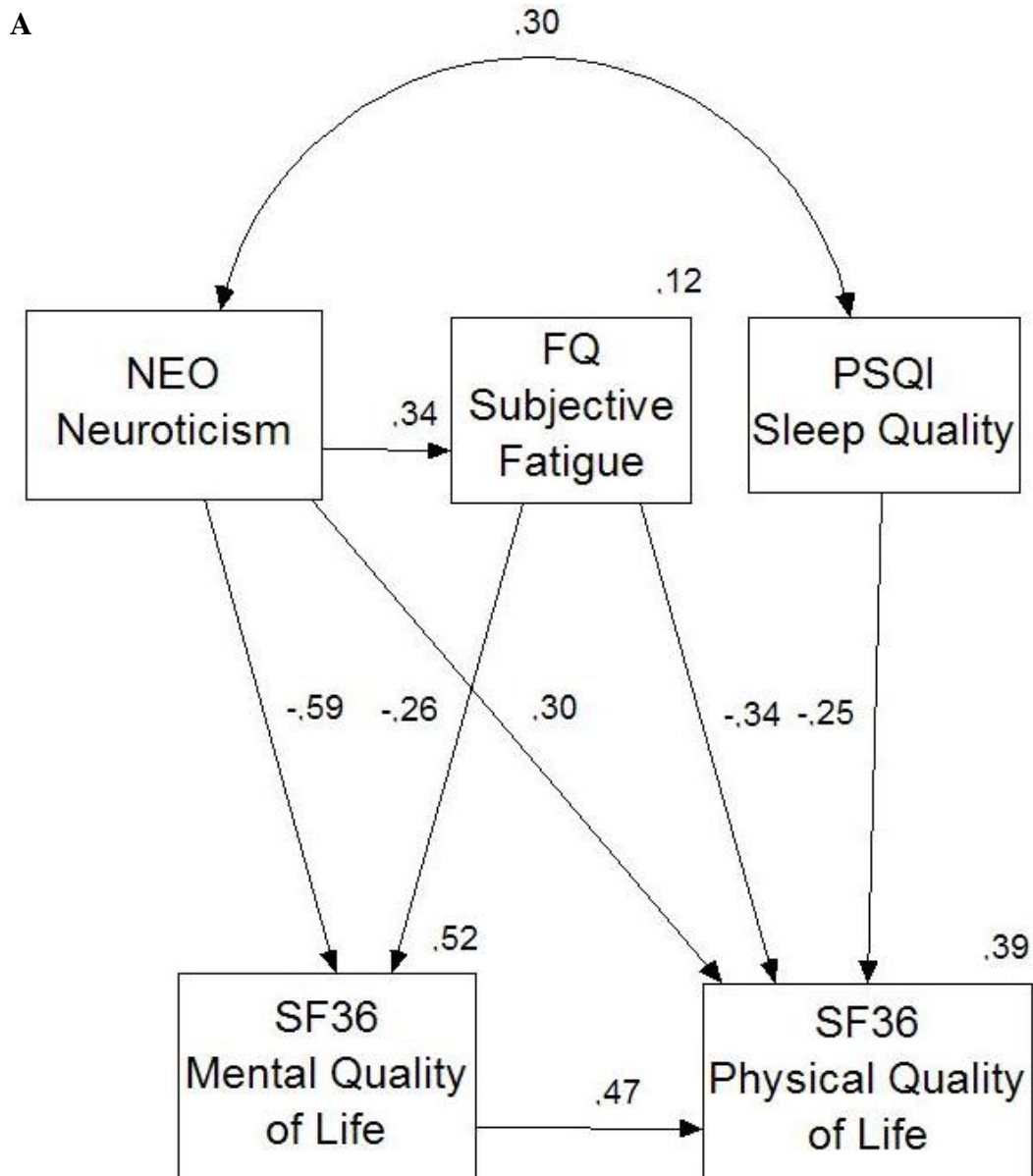
Figure 1A. Path analysis with the measured variables FQ, NEO-FFI neuroticism, night-time PSQI sleep quality and SF36 mental and physical health quality of life

Goodness-of-fit values:

$\chi^2 = 3.98$ (df = 2) (A), n.s. : p = .14, GFI = .99, AGFI = .94, CFI = . 99, CAIC = 86.05 (**A**).

All fit values are acceptable. Standardized β-coefficients (all regression coefficients are significant) and R² values are shown, with R² values shown above each variable.
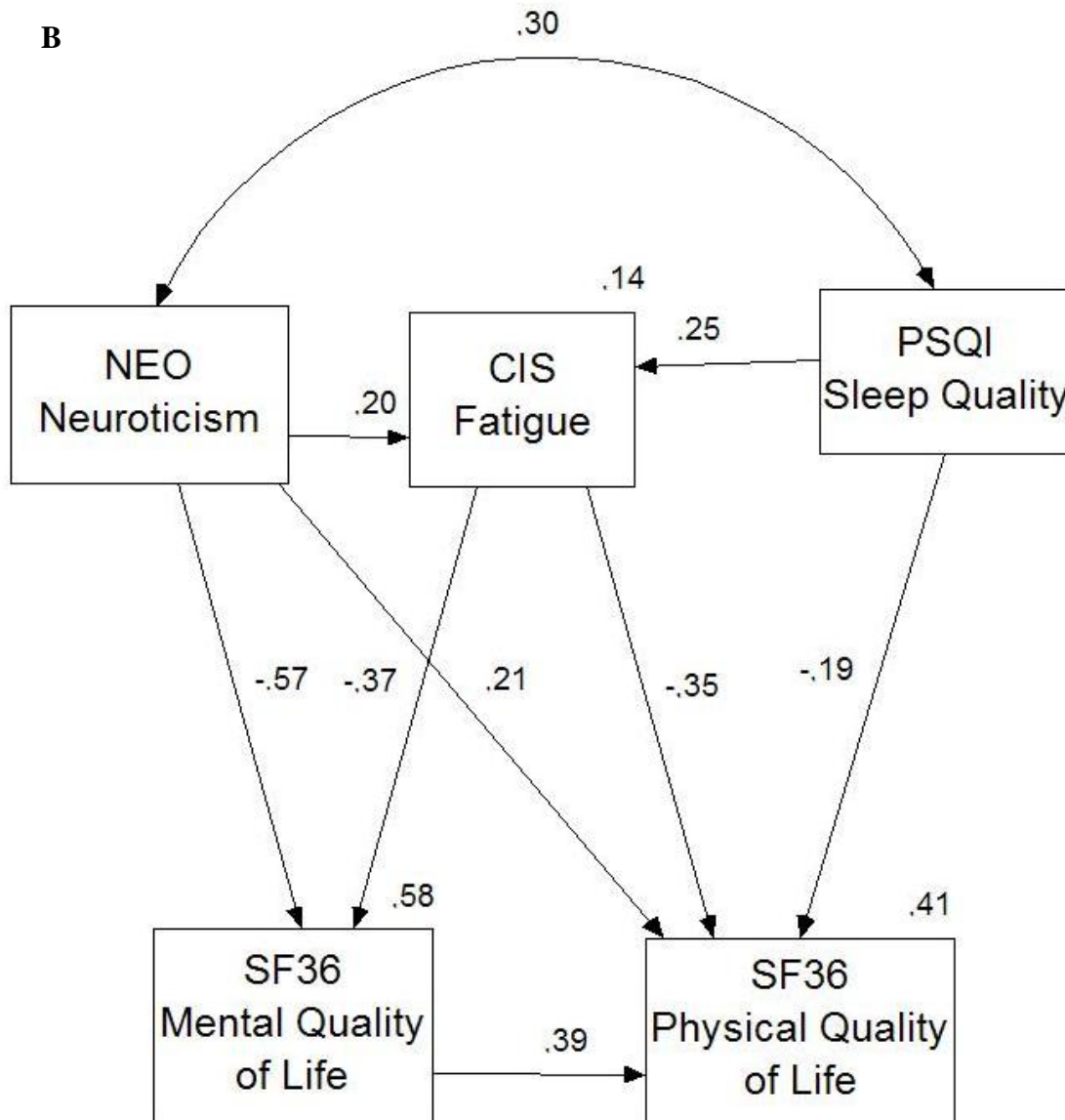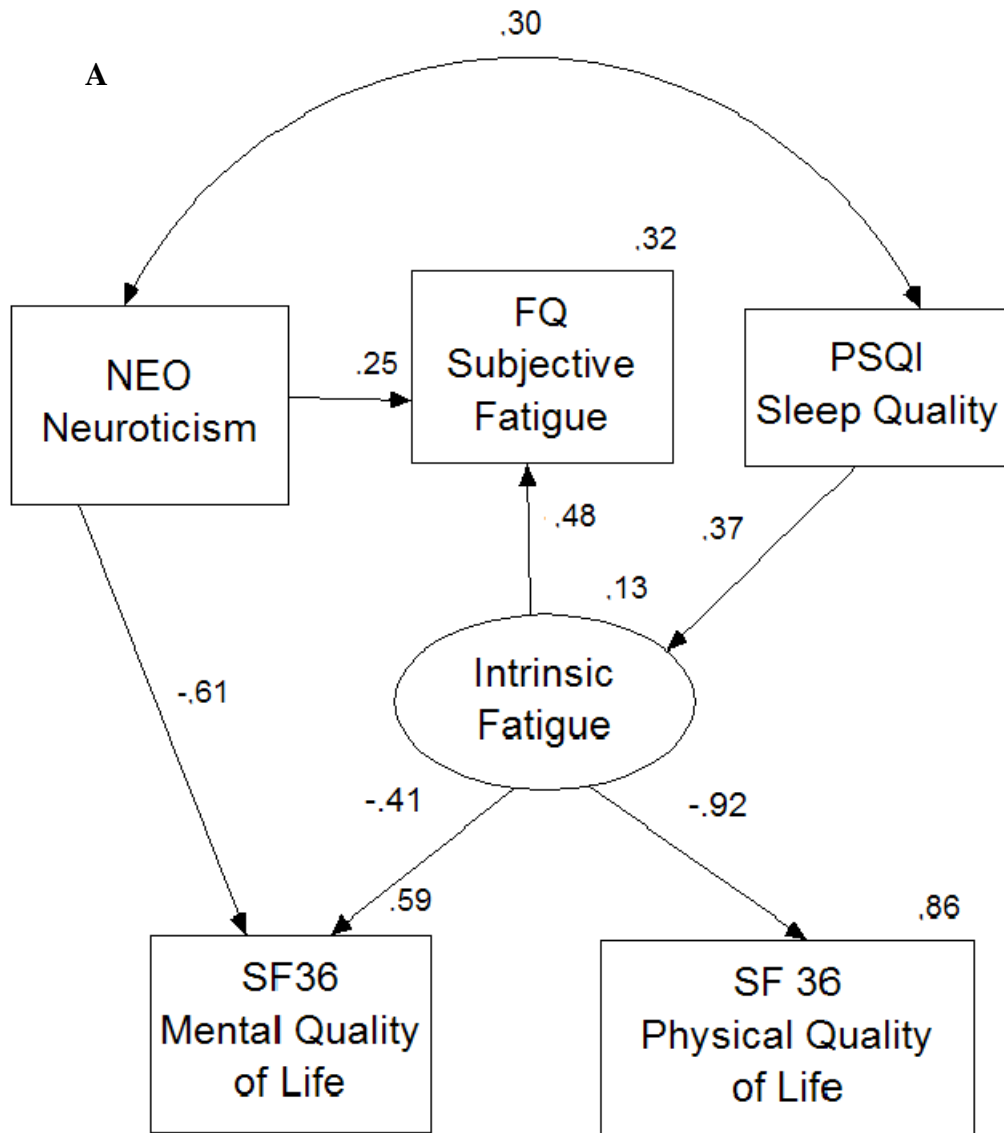
B

Figure 1B. Path analysis with the CIS fatigue, NEO-FFI neuroticism, night-time PSQI sleep quality and SF36 mental and physical health quality of life

Goodness-of-fit values:

$\chi^2 = 0.02$ (df = 1), n.s. : p = .90, GFI = 1., AGFI = 1., CFI = 1., CAIC = 88.40 (**B**).

All fit values are acceptable. Standardized β-coefficients (all regression coefficients are significant) and R^2 values are shown, with R^2 values shown above each variable.

Figure 2A. Path analysis with the measured variables FQ, NEO-FFI neuroticism, night-time PSQI sleep quality and SF36 mental and physical health quality of life and the latent variable intrinsic fatigue

Goodness-of-fit values:

$\chi^2 = 8.51$ (df = 3), n.s. : p = .04, GFI = .98, AGFI = .92, CFI = . 98, CAIC = 84.27. The χ^2 is significant at the 5% value, but not at the 1% value, and all other fit values are acceptable (**A**).

Standardized β-coefficients (all regression coefficients are significant) and R² values are shown, with R² values shown above each variable.

NEO-FFI, NEO-Five Factor Inventory; CIS, Checklist Individual Strength; SF36, Medical Outcomes Study 36-item Short Form Health Survey; PSQI, Pittsburgh Sleep Quality Index; GFI, Goodness-of-fit index; AGFI, Adjusted Goodness-of-fit Index; CFI, Comparative Fit Index; CAIC, Consistent Information Criterion
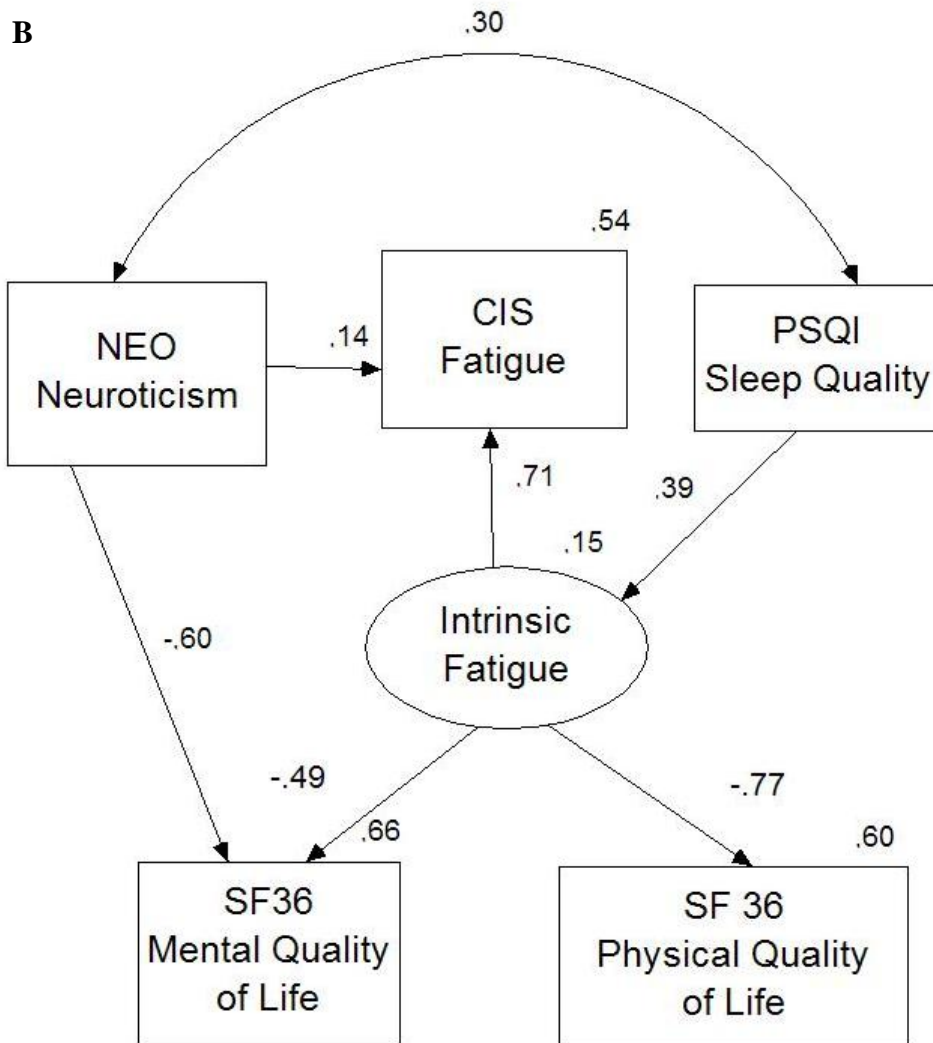
Figure 2B. Path analysis with the CIS fatigue, respectively, NEO-FFI neuroticism, night-time PSQI sleep quality and SF36 mental and physical health quality of life and the latent variable intrinsic fatigue

Goodness-of-fit values:

$\chi^2 = 6.35$ (df = 3), n.s. : p = .10, GFI = .99, AGFI = .94, CFI = . 99, CAIC = 82.11. All fit values are acceptable (**B**).

Standardized β-coefficients (all regression coefficients are significant) and R² values are shown, with R² values shown above each variable.

NEO-FFI, NEO-Five Factor Inventory; CIS, Checklist Individual Strength; SF36, Medical Outcomes Study 36-item Short Form Health Survey; PSQI, Pittsburgh Sleep Quality Index; GFI, Goodness-of-fit index; AGFI, Adjusted Goodness-of-fit Index; CFI, Comparative Fit Index; CAIC, Consistent Information Criterion

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CHAPTER 7: SUMMARY, FUTURE PERSPECTIVES AND CONTRIBUTION TO PATIENT CARE

1. Major findings of the doctoral thesis

The presented research focuses on the role of sleep in patients with hitherto insufficiently explained chronic fatigue or presumed chronic fatigue syndrome (CFS). It aims at exploring:

- the diagnostic categories of patients with unexplained chronic fatigue through systematic clinical analysis
- the existing literature on sleep in CFS
- subjective sleep parameters and sleep quality in CFS patients
- the objective sleep measures and subjective sleep parameters in a large sample of patients with unexplained chronic fatigue and their mutual correlation
- the interrelationship of self-report questionnaires on different dimensions in the construct of chronic fatigue and CFS

Mariman A, Delesie L, Tobback E, Hanoulle I, Sermijn E, Vermeir P, Pevernagie D, Vogelaers D. Undiagnosed and comorbid disorders in patients with presumed chronic fatigue syndrome. Submitted to Journal of Psychosomatic Research, under revisio.

A systematic approach through a diagnostic pathway of a large sample of patients with presumed CFS results into significant diagnostic categorization relevant to appropriate care. This study points to a high prevalence of hitherto under- or unrecognised psychiatric disorders or sleep disorders as either a primary diagnosis or significant comorbidity to CFS. Mood disorder, anxiety disorder, cluster C and cluster B personality disorder were most frequently observed. The prevalence of obstructive sleep apnea (OSA) is similar to that in recognised indications for polysomnographic (PSG) screening such as morbid obesity, atrial fibrillation and heart failure.

This study distinguishes itself from previous reports through a low prevalence of psychiatric comorbidity in CFS. This probably reflects lower validation of psychiatric diagnoses as mere comorbidity and a clearer separation into diagnostic categories. Hence, there was a lower propensity to use the label of a syndromal definition such as CFS, which lacks a pathophysiologic substrate, through a diagnostic pathway and a multidisciplinary assessment.

The recognition of these primary sleep or psychiatric disorders seems essential for an adequate approach of incapacitating fatigue in individual patients. Hence systematic psychodiagnostic testing or, upon indication, psychiatric screening on the one hand, and

objective assessment of sleep through PSG and multiple sleep latency test (MSLT) on the other hand needs to be recommended in this patient sample. This recommendation needs to be at least considered in future evidence-based clinical approaches or algorithms of chronic fatigue and CFS.

Pevernagie D, Mariman A, Vandenbussche N, Tobback E, Overeem S, Delesie L, Janssen H, Vogelaers D. Behavioral hyperventilation as a novel clinical condition associated with central sleep apnea: a report of three cases. Sleep Med 2012;13(10):1317-1320.

The systematic approach through a diagnostic pathway of patients with chronic fatigue allowed the description of a novel entity within the primary sleep disorders, namely central sleep apnea through behavioral hyperventilation.

Mariman A, Vogelaers D, Tobback E, Delesie L, Hanoulle I, Pevernagie D. Sleep in the chronic fatigue syndrome. Sleep Med Rev 2013;17(3):193-199.

This review article is the first analysis in depth of sleep in CFS. It points towards inconsistencies and incomplete descriptions of elements of sleep in the syndromal definition of CFS.

The concept of nonrestorative sleep (NRS), a main minor criterion within the Fukuda-definition, implies that fatigue is the consequence of dysfunctional sleep, whilst evidence for such cause-effect relationship has not yet been provided. The complaint is often described as 'waking up unrefreshed'. However, no uniform working definition is currently available and should be validated, based on an empirical approach involving experts, clinicians and patients. Furthermore, the concept lacks any pathophysiological substrate or quantification tool in order to be reliably used in the clinic.

A significant prevalence of primary sleep disorders is found in different series of patients labelled as CFS, which is in line with our findings. These disorders could contribute to the presence and severity of daytime dysfunctioning. However, a diagnosis of CFS can only be excluded by satisfactory symptomatic relief obtained by causal treatment.

Mariman A, Vogelaers D, Hanoulle I, Delesie L, Pevernagie D. Subjective sleep quality and daytime sleepiness in a large sample of patients with chronic fatigue syndrome (CFS). Acta Clin Belg 2012;67(1):19-24.

A high level of poor sleep quality (high mean Pittsburgh Sleep Quality Index, PSQI) and excessive daytime sleepiness (high mean Epworth Sleepiness Scale, ESS) were observed in a large patient sample of CFS presenting at a tertiary care referral centre. The further analysis of this patient sample allowed the identification of a subgroup with insomnia phenotype. This seems to substantiate a need for differentiation into different subgroups or diagnostic categorisation within a patient sample with a seemingly homogenous presentation based on a mere constellation of aspecific symptoms.

Mariman A, Vogelaers D, Hanoulle I, Delesie L, Tobback E, Pevernagie D. Validation of the three-factor model of the PSQI in a large sample of chronic fatigue syndrome (CFS) patients. J Psychosom Res 2012;72:111-113.

On a large sample of CFS patients, we evaluated whether a three-factor model of the PSQI scale would fit the constellation of sleep disturbances. We found the PSQI to effectively operate as a three-factor scoring model, as initially observed in healthy and depressed older adults. The separation into three discrete factors suggests the limited usefulness of the global PSQI as a single factor for the assessment of subjective sleep quality in this patient sample.

Mariman A*, Tobback E*, Hanoulle I, Delesie L, Vogelaers D, Pevernagie D. Polysomnographic and MSLT data in a large sample of patients with unexplained chronic fatigue: comparison with a reference sample and relation with subjective scores. In preparation. (*: shared first author) Submitted to Sleep Medicine

Data from PSG and MSLT were obtained in a large sample of patients with unexplained chronic fatigue (UCF) and compared with these from a reference group. Decreased total sleep time, sleep efficiency on the one hand and increased SL, wake after sleep onset and arousal index on the other hand were observed in the patient sample, suggesting an insomnia phenotype in patients with UCF. In the assessment of the relation between these objective results and subjective scores derived from validated questionnaires, neither PSG nor MSLT data were correlated with fatigue, and were only weakly correlated with mental health and subjective sleepiness. The latter was not substantiated by objective data from the MSLT.

The overall lack of correlation between subjective scores and objective indices derived from PSG and MSLT may suggest that these tests are inappropriate to explain symptoms of

daytime sleepiness and fatigue in patients with UCF. However, their application remains justified for the demonstration of comorbid primary sleep disorders in this patient group.

Tobback E*, Hanoulle I*, Mariman A, Delesie L, Pevernagie D, Vogelaers D. What does fatigue mean in the chronic fatigue syndrome? A path analysis on a large sample of patients with chronic fatigue. In preparation. (*: shared first author)

Path analysis on a large sample of patients with presumed CFS led to the introduction of the latent variable, intuitively called 'intrinsic fatigue', as missing link in the relationship between the subjective complaints neuroticism, fatigue, poor sleep quality and outcome measures mental and physical quality of life. This new variable seems to correspond better with the subjective feelings of fatigue, mentioned by CFS patients, than the Fatigue Questionnaire (FQ) and Checklist Individual Strength (CIS) fatigue variables. These findings emphasize the complex and heterogeneous concept of fatigue as well as the need for more appropriate and innovative tools for measuring fatigue in this patient sample.

2. Future perspectives

The role of sleep disturbances in the pathogenesis of chronic fatigue and CFS remains speculative. Whilst the Fukuda definition include NRS as one of the minor criteria that define CFS, they do not address the relevance of disturbed sleep in the pathogenesis of CFS.

Generally, a causal relationship between sleep and daytime dysfunction may be inferred from the observation that treatment of the underlying sleep disorder may result in the improvement of daytime symptoms such as fatigue, excessive sleepiness and pain. This implies the need for clinical trials to get more insight in the responsiveness to adequate treatment of comorbid sleep disorders in patients whose presenting complaint is severe chronic fatigue.

a. The effect of nasal CPAP in patients with chronic fatigue and sleep-disordered breathing

A recent randomized placebo-controlled trial in patients with moderate to severe OSA showed evidence that fatigue may be responsive to continuous positive airway pressure (CPAP) treatment. The beneficial effect of CPAP treatment was most pronounced in subjects with high levels of fatigue at onset [1]. In clinical practice, however, it is often observed that complaints of chronic fatigue do not or only transiently respond to CPAP treatment.

To evaluate the effect of improved sleep quality on fatigue, a double-blind, randomized, placebo controlled cross-over trial with nasal CPAP will be carried out in patients who present with a primary complaint of chronic disabling fatigue and who are found to have an apnea-hypopnea index (AHI) $\geq$ 15 on PSG. As secondary outcomes, the CPAP responsiveness regarding sleepiness, sleep quality and general health will be evaluated in the same target sample.

b. The effect of sodium oxybate in patients with chronic fatigue syndrome

Sodium oxybate is a commercial sodium salt of gamma-hydroxybutyrate and is known to increase slow-wave sleep [2]. In patients with narcolepsy, it has been approved to treat cataplexy and a beneficial effect on daytime sleepiness has been shown as well [3]. A number of studies have also been reported on the efficacy of sodium oxybate in the treatment of fibromyalgia (FM) [3-8]. In a small randomized placebo controlled cross-over trial in FMS patients, treatment with sodium oxybate showed significantly improved subjective sleep quality, pain and fatigue. PSG records demonstrated an increase in slow wave sleep and a decrease in the severity of alpha anomaly [4]. Similar improvements in sleep physiology and FM-related symptoms were recently seen in a large cohort of patients with FM [5-7].

Sodium oxybate treatment has hitherto not been studied in CFS patients, although a positive effect may be considered since this disorder shares considerable overlap in symptoms with FMS including sleep-related complaints, pain and fatigue. A preliminary retrospective study recently showed promising results for a role of sodium oxybate treatment in CFS since improvements of fatigue and/or pain after sodium oxybate treatment were observed in the majority of patients with long-standing fatigue in a pattern consistent with CFS [9]. However, some methodological shortcomings such as the inability to distinguish CFS and FMS and the inconsistent use of subjective questionnaires make it difficult to interpret the results.

To evaluate the effect of sodium oxybate on fatigue and to explore the interdependence of sleep quality and fatigue in CFS, a double-blind, randomized, placebo controlled cross-over trial with sodium oxybate will be carried out in CFS patients.

3. Contribution to patient care

a. Development of an integrated path of care

The care for patients with CFS in Belgium has been organized as a pilot project in tertiary care referral centres from 2002 onwards. Patients with a syndromal definition of CFS according to the 1994 Centers for Disease Control and Prevention (CDC) criteria [10] were included in a revalidation program, consisting of a combination of cognitive behavioural therapy (CBT) most often organised as a program of group educational sessions, and progressive aerobic reconditioning or graded exposure/exercise therapy (GET) in different modalities. In 2008, the Belgian Health Care Knowledge Centre performed an assessment of the initial years of this program within the background of updated evidence based knowledge of definitions, epidemiology, therapeutic interventions and their cost-effectiveness, prognosis and organisational models in the care for CFS patients in different countries [11]. The evaluation of the results of the pilot projects mainly focused on the end point of socio-professional reintegration, which proved to be disappointing. Hence, the federal health authorities asked the Committee for Chronic Diseases within the National Institute for Disease and Disability Insurance (RIZIV/INAMI) to elaborate a new and innovative model of stepped care, aiming at improved integration of diagnosis and treatment into primary care and between levels of health care for patients with CFS.

A similar approach is warranted both for the more limited group of patients who fit the syndromal definition of CFS and a larger sample of patients who develop somatic complaints without a classical psychiatric or internal medicine diagnosis. They share common or similar pathogenic mechanisms, including vulnerability, triggering and maintaining factors for somatisation within a biopsychosocial model [12]. The approach should focus on a restriction of a continuous search for a somatic explanation through a simple biologic model, CBT and GET in order to avoid syndromal entrenchment with a poorer prognosis.

To achieve a new model of care for CFS that integrates this broader perspective in a multidisciplinary approach, the reference centre of the University Hospital Ghent developed the initiative recruiting partners through the provinces of East and West Flanders from different professional categories involved in the diagnosis and treatment of patients with medically unexplained symptoms (MUS), in particular unexplained chronic fatigue.

Uniform perceptions of deficits and focus points at different levels of care

The partners within the network agree that different deficits should be addressed to improve appropriate care for patients with unexplained chronic fatigue including CFS. Although the etiology and pathophysiology of chronic fatigue and CFS remain essentially unknown, a clear vision that underlies the current concepts in pathogenesis, focusing on the biopsychosocial model [12], should be offered within the network and towards the patients. Expertise concerning prevention, detection and referral should be shared and reported in guidelines. In Belgium, the current graduate and postgraduate training of medical doctors but also of other health professionals pay insufficient attention to the management of CFS or other forms of aspecific complaints and somatisation. Hence, improvement of these training programs represents a priority in order to better organise care. A prolonged duration of the syndrome should be avoided since this is likely to be associated with a pattern of disease benefits and inflexibility/unresponsiveness to therapeutic improvement. Therefore, early recognition of the patient at risk is essential in order to avoid disease or rather illness progression and should be integrated at primary care. Treatment needs to be initiated at an early stage, preferably within the first two years after disease onset, in order to safeguard significant health improvement opportunities. In the pilot study of the Belgian reference centres, the mean duration of symptoms at the time of initiation of the revalidation program (CBT and GET) averaged eight years, which may explain the disappointing results of socio-professional reintegration. It is within this time frame of the first two years after initiation of symptoms that revalidation (rehabilitation) including assessment of professional reintegration through e.g VDAB/GTB (integrated career coaching), needs to addressed and stimulated, in contestation with controlling instances.

b. Towards a new health care model

Approach in the early stage (< 6 months)

Within this new perspective, primary care physicians will play a central role in the majority of patients with unexplained chronic fatigue and MUS. They need to focus on increased recognition and pre-emptive management of patients at risk, in order to avoid chronic somatisation. Such an attitude is often lacking, resulting in a continued search for a biological explanation and patterns of 'medical shopping'. The development of such patterns, fed by culturing a sense of diagnostic uncertainty and (often sequentially) focusing on different individual symptoms through biological models rather than on the whole syndrome through a biopsychosocial model, needs to be avoided.

Early communication should be of an assertive and reassuring nature, following careful clinical history taking and physical examination for excluding underlying somatic or psychiatric causes. If sufficient factors, such as prolonged or recurrent complaints, argue for the development of unexplained chronic fatigue, the patient may be referred to a program of physical reconditioning and eventually to psychological therapy in the early stage. The physical therapists and clinical psychologists involved need to dispose of a standardized therapy program that still needs to be elaborated.

Timely referral for more extensive specialist assessment (often including synchronous internal medicine and psychodiagnostic screening) is only necessary if the above approach fails within a reasonable time period and/or with suspicion of comorbidity.

Approach in the later stage (≥6 months)

Specialised centres need to evolve into centres of diagnostic expertise, focussing on patients that are referred because of evolution towards chronicity with a tentative cut-off length of symptoms in the range of six months. These patients are generally in need of a more intensive revalidation program, often including individual psychologic coaching and GET. This can be outsourced within a validated network that needs to be visualised into a regularly updated social map. Both social map and standardized therapy program need to be readily accessible, e.g. in a dedicated website of a government agency. From this perspective, it seems logical to continue to build on the expertise of the current CFS reference centres and shifting focus from a revalidation convention agreement towards diagnosis and subsequent referral in a network of identified and validated health care providers.

The evaluation of seemingly unexplained chronic fatigue for more than six months requires an integrated holistic approach based on the biopsychosocial model [12], before allowing an exclusion diagnosis of CFS. Undoubtedly, a large proportion of patients referred to the tertiary CFS reference centres prove to have received prior to referral an unjustified label of CFS. Pathologic fatigue can often be explained through psychiatric comorbidity and/or sleeping disorders and, less frequently, by internal pathology, that had gone under- or unrecognized. This underscores the need for a full diagnostic (re-)assessment. Hence, these referrals have been re-categorized in the department of general internal medicine of the University Hospital Ghent as 'chronic fatigue of yet undetermined origin'. The same under-recognition of psychiatric comorbidity also applies to other entities such as fibromyalgia (FM).

At the CFS referral centre of the University Hospital Ghent, patients in whom fatigue persists for more than six months are eligible to enter an integrated multidisciplinary path of care. This includes administration of standard questionnaires, internal medicine assessment, psychodiagnostic screening, physiotherapeutic assessment and PSG in combination with a MSLT. The internal medicine assessment consists of a thorough history taking and physical examination and integrates the results of previous investigations. The psychodiagnostic screening includes an evaluation by a psychologist and psychological testing using validated questionnaires. Indication for psychiatric disorders from the psychodiagnostic screening are subsequently confirmed (or refuted) by psychiatric evaluation using the DSM-IV-TR criteria. Physiotherapeutic evaluation screens for musculoskeletal comorbidity that is potentially suitable for physical rehabilitation. The multidisciplinary discussion yields either a final diagnosis or a tentative diagnosis in selected patients, in whom response to treatment is considered an additional diagnostic criterion.

Extension of the concept to somatic unexplained complaints

Different case definitions of somatic unexplained syndromes not only share a number of symptom components, but also non-symptom features including sex, outlook and response to treatment [13], as evidenced in CFS, FM and irritable bowel syndrome (IBS) (Figure 2). Although there is disagreement whether these diagnostic labels represent a single disorder or multiple disorder, from the 'lumping' point of view, these syndromes are believed to be an artefact of medical specialization [13]. Indeed in Belgium, patients are not infrequently initiated into either the care path of a Multidisciplinary Pain Centre or that of a CFS Reference Centre, according to whether pain or fatigue represented the dominating symptom within the syndrome at the time of intake. It can not be denied, however, that pain and fatigue undoubtedly interact. Even, if in due course, both syndromes would ultimately be proven to represent separate disease entities, common diagnostic and therapeutic approaches could be bundled into a single holistic model of care. From this point of view, we believe that a well-organised care path, in which different partners collaborate, is necessary in order to require better understanding and improved management of patients with MUS, despite validation and financing is no longer provided by the Belgian authorities.
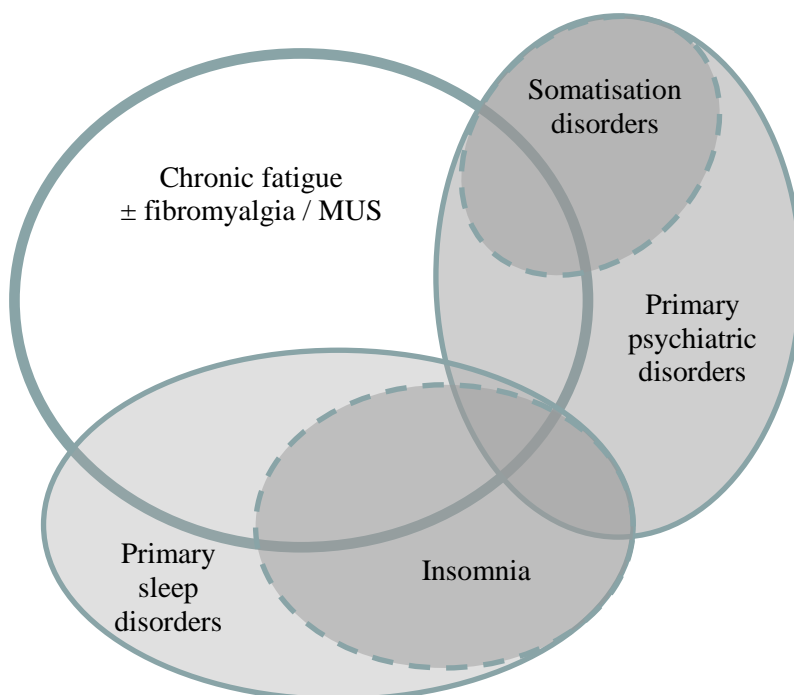

Figure 2. Overlapping conditions sharing chronic fatigue as clinical illness feature. MUS medically unexplained symptoms

Patients with MUS are not always taken seriously by the medical community and the society at large. Dissatisfied patients have described encountering attitudes as dismissive, sceptical or openly disbelieving in a wide variety of social interactions, including families, friends, employers and doctors [14]. Problems in such relationships, loss of unemployment benefit and so on are often stressful and anxious experiences and may contribute to persistent disability and the maintenance of chronic illness. As a result, MUS sufferers continue medical shopping, between medical subspecialties, to seek administrative validation in order to regain social benefits, since objective proof is the generally accepted criterion of professional disability.

The proposed innovative stepped care model for MUS may cope with these problems in emphasizing early detection and correct diagnosing (by better communication and education of doctors) on the one hand and improved socio-professional reintegration on the other hand. We believe that not only patients, but medical practitioners as well may benefit from this improved new care model. Indeed, physicians in primary and specialists care are frequently confronted with MUS patients. Health care providers not seldom feel helpless or frustrated when dealing with patients for whom no objective abnormalities are found in order to explain their subjective complaints. When they frequently have to deal with such patients without a supportive network, they might be at higher risk for physical and mental exhaustion and burn-out. Therefore, it is believed that working in a multidisciplinary care network with integrated team discussions might give support to individual health care providers.

The development of a centre for MUS within a university setting additionally gives the opportunity to educate students, trainees and the medical staff in general how to deal with and treat somatic unexplained symptoms. It is important to make them aware of a biopsychosocial approach in order to diminish the tendency of Cartesian thinking, splitting the body and the mind within medical science.

With the present studies on one of the most important presentations of MUS, namely CFS, we hope to have contributed to the development of these innovative insights.

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SAMENVATTING

Het huidig onderzoek richt zich in hoofdzaak op de rol van slaap bij patiënten met onvoldoende verklaarde vermoeidheid of vermoeden van chronisch vermoeidheidssyndroom (CVS). De doelstellingen van het onderzoek bestaan uit het exploreren van:

de bestaande literatuur omtrent slaap bij CVS

de diagnostische categorieën van patiënten met onverklaarde chronische vermoeidheid op basis van een systematische benadering bestaande uit een klinische evaluatie, psychodiagnostiek en polysomnografie

subjectieve slaapparameters en slaapkwaliteit bij CVS patiënten

de objectieve meting en subjectieve appreciatie van de slaap en hun onderlinge relatie in een grote groep patiënten met onverklaarde chronische vermoeidheid

de onderlinge samenhang van vermoeidheid, slaapkwaliteit en persoonlijkheidskenmerken en hun beïnvloeding van mentale en fysieke levenskwaliteit, geëvalueerd door op zelfrapportage gebaseerde vragenlijsten, bij patiënten met onverklaarde chronische vermoeidheid

Mariman A, Vogelaers D, Tobback E, Delesie L, Hanoulle I, Pevernagie D. Sleep in the chronic fatigue syndrome. Sleep Med Rev 2013;17(3):193-199.
Dit overzichtsartikel is de eerste grondige evaluatie van de bestaande literatuur over slaap bij CVS. In elke syndromale CVS-definitie wordt gestoorde slaap als mineur criterium vermeld. Deze beschrijvingen zijn evenwel sterk uiteenlopend en inconsistent.

Het concept niet-recuperatieve slaap (NRS) is een prevalent mineur criterium van de in de literatuur meest gehanteerde Fukuda-definitie en suggereert dat vermoeidheid mede een gevolg kan zijn van disfunctionele slaap. Nochtans is een dergelijke oorzaak-gevolg relatie nog niet aangetoond. Hoewel de klacht vaak beschreven wordt als 'het niet uitgerust wakker worden', is een uniform gehanteerde definitie niet beschikbaar. Op heden mist dit concept een pathofysiologisch substraat en is er geen bruikbaar meetinstrument in de klinische praktijk.

Zowel bij bevolkingsonderzoek als onderzoek bij CVS-discordante eeneiige tweelingen konden geen duidelijke afwijkingen van de slaaparchitectuur geobjectiveerd worden.

Uit de literatuur blijkt dat bij een aanzienlijk aantal patiënten met een CVS label een primaire slaapstoornis wordt aangetoond. Deze stoornissen kunnen wel degelijk bijdragen tot het disfunctioneren overdag. Het is plausibel dat een diagnose van CVS overeind blijft wanneer symptomen blijven bestaan na adequate behandeling van de primaire slaapstoornis.

Mariman A, Delesie L, Tobback E, Hanoulle I, Sermijn E, Vermeir P, Pevernagie D, Vogelaers D. Undiagnosed and comorbid disorders in patients with presumed chronic fatigue syndrome. Under revision. Journal of Psychosomatic Research.

Een systematische diagnostische evaluatie van patiënten met vermoeden van CVS resulteert in een waaier van diagnostische categorieën. Deze studie toont een hoge prevalentie van psychiatrische aandoeningen en slaapstoornissen aan, die voorheen veelal onder- of niet-gediagnosticeerd gebleven waren. De meest geobserveerde psychiatrische stoornissen zijn stemmingsstoornissen, angststoornissen, cluster C en cluster B persoonlijkheidsstoornissen. Obstructief slaapapneu (OSA) komt in deze groep met een gelijkaardige prevalentie voor als bij aandoeningen zoals obesitas, atriumfibrillatie en hartfalen. Voor deze laatste indicaties wordt polysomnografie (PSG) als standaardonderzoek aanbevolen.

In tegenstelling tot eerdere studies rapporteert het huidig onderzoek een lage prevalentie van psychiatrische comorbiditeit bij CVS. Dit reflecteert waarschijnlijk een affirmatievere indeling in diagnostische categorieën met een specifieke therapeutische benadering. Aldus bestond er minder de neiging om het label van een syndromale definitie zoals CVS te gebruiken, welke niet berust op een duidelijk pathofysiologish substraat.

De herkenning van specifiek behandelbare primaire slaap- en psychiatrische stoornissen is van belang voor een op maat gemaakte therapie bij patiënten met onverklaarbare chronische vermoeidheid. Daarom moet systematische psychodiagnostische testing en psychiatrische screening enerzijds en objectief slaaponderzoek anderzijds sterk aanbevolen worden bij deze patiëntengroep.

Mariman A, Vogelaers D, Hanoulle I, Delesie L, Pevernagie D. Subjective sleep quality and daytime sleepiness in a large sample of patients with chronic fatigue syndrome (CFS). Acta Clin Belg 2012;67(1):19-24.

Slechte slaapkwaliteit (hoge gemiddelde waarde op de Pittsburgh Sleep Quality Index, PSQI) en toegenomen slaperigheid overdag (hoge gemiddelde waarde op de Epworth Sleepiness

Scale, ESS) werden geobserveerd bij een grote groep CVS-patiënten die verwezen werden naar ons tertiair centrum. Verdere analyse van deze patiëntengroep leidde tot de identificatie van een subgroep met een insomnie fenotype. Dit pleit ervoor om een schijnbaar homogene groep patiënten met onverklaarde chronische vermoeidheid nader te onderzoeken met aandacht voor verschillende subgroepen of diagnostische categorieën met betrekking tot de slaapkenmerken.

Mariman A, Vogelaers D, Hanoulle I, Delesie L, Tobback E, Pevernagie D. Validation of the three-factor model of the PSQI in a large sample of chronic fatigue syndrome (CFS) patients. J Psychosom Res 2012;72:111-113.

Bij een grote groep CVS-patiënten werd de scoringsmethodiek van de PSQI geëvalueerd. Traditioneel worden in dit model 7 componenten onderscheiden waarvan het resultaat in 1 globaal cijfer wordt geïntegreerd. Bij CVS bleek de PSQI echter effectief te opereren als een driefactor scoringsmodel, wat in overeenstemming is met vroegere observaties bij gezonde mensen en depressieve ouderen. Deze opdeling in drie factoren suggereert een beperkte bruikbaarheid van de globale PSQI als één globale score of éénfactor scoringsmodel ter evaluatie van subjectieve slaapkwaliteit bij deze patiëntengroep.

Mariman A*, Tobback E*, Hanoulle I, Delesie L, Vogelaers D, Pevernagie D. Polysomnographic and MSLT data in a large sample of patients with unexplained chronic fatigue: comparison with a reference sample and relation with subjective scores. Submitted: Sleep Medicine. (*: shared first author)

Bij een grote groep patiënten met onverklaarde chronische vermoeidheid werden objectieve slaapparameters verzameld door PSG en MSLT. Deze data werden vergeleken met deze van een referentiegroep. In de patiëntengroep werd een afname van de totale slaaptijd en de slaapefficiëntie waargenomen en een toename van de slaaplatentie, wake after sleep onset en de ontwaakindex. Dit komt overeen met een insomnia fenotype. Bij onderzoek naar de relatie tussen deze objectieve data en subjectieve scores, uit gevalideerde vragenlijsten, werd geen correlatie gevonden tussen PSG of MSLT data met vermoeidheid en slechts zwakke correlaties met mentale gezondheid en subjectieve slaperigheid. Subjectieve slaperigheid werd niet geobjectiveerd door MSLT.

Het gebrek aan correlaties tussen subjectieve scores enerzijds en objectieve slaapparameters anderzijds suggereert dat deze objectieve testen niet geschikt zijn voor het verklaren van symptomen zoals slaperigheid overdag en vermoeidheid bij patiënten met onverklaarde

chronische vermoeidheid. Desondanks blijven PSG en MSLT aangewezen voor het aantonen van primaire slaapstoornissen bij deze patiëntengroep.

Tobback E*, Hanoulle I*, Mariman A, Delesie L, Pevernagie D, Vogelaers D. What does fatigue mean in the chronic fatigue syndrome? A path analysis on a large sample of patients with chronic fatigue. In preparation. (*: shared first author)

Padanalyse op een grote groep patiënten met vermoeden van CVS toonde geen duidelijk rechtstreekse beïnvloeding van vermoeidheid op fysieke levenskwaliteit in tegenstelling tot slaapkwaliteit. Er werd ook geen duidelijke beïnvloeding van vermoeidheid door slaapkwaliteit gevonden. De introductie van een latente variabele, tentatief benoemd als 'intrinsieke vermoeidheid', liet toe om de onderlinge relatie tussen deze verschillende dimensies verklaarbaar te maken. Dit leidt tot de werkhypothese dat de klassiek gebruikte vermoeidheidsvragenlijsten, Fatigue Questionnaire (FQ) en de Checklist Individuele Spankracht (Checklist Individual Strength, CIS) de reële dimensie van vermoeidheid bij deze patiëntengroep onvoldoende of slechts partieel peilen.

ADDITIONAL PAPER

Behavioural hyperventilation as a novel clinical condition associated with central sleep apnoea: a report of three cases

Brief Communication

Behavioural hyperventilation as a novel clinical condition associated with central sleep apnoea: A report of three cases

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A R T I C L E   I N F O

S U M M A R Y

Central sleep apnoea (CSA) is a disorder characterised by repetitive episodes of decreased ventilation due to complete or partial reduction in the central neural outflow to the respiratory muscles. Hyperventilation plays a prime role in the pathogenesis of CSA. Chronic heart failure and dwelling at high altitude are classical conditions in which CSA is induced by hyperventilation.

Hyperventilation syndrome (HVS) is a prevalent behavioural condition in which minute ventilation exceeds metabolic demands, resulting in haemodynamic and chemical changes that produce characteristic dysphoric symptoms. HVS is frequently caused by anxiety disorders and panic attacks.

Until now, medical literature has focussed primarily on daytime symptoms of behavioural hyperventilation. It is currently unknown how this condition may affect sleep. Three cases are reported in which behavioural hyperventilation was associated with occurrence of significant central sleep apnoea, which was not present during normal tidal breathing in steady sleep. Therefore, behavioural hyperventilation should be added to the list of known clinical conditions associated with CSA.

Summary

Central sleep apnoea (CSA) is a disorder characterised by repetitive episodes of decreased ventilation due to complete or partial reduction in the central neural outflow to the respiratory muscles. Hyperventilation plays a prime role in the pathogenesis of CSA. Chronic heart failure and dwelling at high altitude are classical conditions in which CSA is induced by hyperventilation.

Hyperventilation syndrome (HVS) is a prevalent behavioural condition in which minute ventilation exceeds metabolic demands, resulting in haemodynamic and chemical changes that produce characteristic dysphoric symptoms. HVS is frequently caused by anxiety disorders and panic attacks.

Until now, medical literature has focussed primarily on daytime symptoms of behavioural hyperventilation. It is currently unknown how this condition may affect sleep. Three cases are reported in which behavioural hyperventilation was associated with occurrence of significant central sleep apnoea, which was not present during normal tidal breathing in steady sleep. Therefore, behavioural hyperventilation should be added to the list of known clinical conditions associated with CSA.

1. Introduction

Central sleep apnoea (CSA) is characterised by a temporary lack of neural drive to breathe during sleep, resulting in a decrease or cessation of airflow. In clinical practice, CSA is diagnosed when the apnoea/hypopnoea index (AHI) exceeds 15 apnoeas and/or hypopnoeas per h of sleep and when more than half of these respiratory events are of central origin [1].

During non-rapid eye movement (NREM) sleep, breathing is metabolically controlled through the arterial partial pressure of carbon dioxide ($PaCO_2$). A fall of $PaCO_2$ below the CO_2 apnoea threshold results in cessation of respiratory effort. This is a robust physiological mechanism that is present in many species [2]. In humans, CSA is often observed by conditions that are associated with hyperventilation, for example, in chronic heart failure and dwelling at high altitude [3]. Transient hyperventilation is the mechanism that drives $PaCO_2$ below the apnoea threshold during NREM sleep.

The term 'hyperventilation syndrome' was first introduced for anxiety-related prolonged excessive breathing without a distinct organic aetiology [4]. Whilst the cause–effect relationship between hyperventilation and anxiety/panic attacks is still a matter of debate, it is presumed that increased ventilation and hypocapnia by themselves contribute to an emotional state of anxiety/panic. In other words, the underlying psychiatric disorder and the inappropriate breathing response may be constituents of a vicious cycle [5].

Evidently, lowering $PaCO_2$ by transiently raising minute ventilation increases proneness to CSA, irrespective of the mechanism that drives the ventilation. This report describes three cases in which polysomnography (PSG) revealed CSA caused by behavioural hyperventilation.

2. Methods

The cases described in this report were individuals admitted for regular medical care. The procedure of the present case reporting complies with the guidelines of the institutional review boards of both institutions (Kempenhaeghe and Ghent University Hospital). None of the three patients were obese (Case 1: L = 1.02 m, W=14 kg, BMI = 13.6 kg m^2; Case 2: L = 1.89 m, W= 90 kg, BMI =25.2 kg m^2; Case 3: L = 1.63 m, W= 59 kg, BMI = 22.2 kg m^2). None had symptoms or signs of cardiac or pulmonary disease.

3. Case Records

3.1. Case 1

A 9 year old girl with Cornelia de Lange syndrome, characterised by multiple congenital abnormalities and mental retardation [6], suffered from severe insomnia with difficulties initiating sleep. These symptoms had developed after she had been admitted to the hospital for a minor intervention. During her stay, she had witnessed the sudden death of a roommate. Ever since, she became frightened around bedtime, and when brought to bed, she became very agitated and was unable to fall asleep.

PSG revealed a significantly prolonged sleep onset. In the initial phase of sustained wakefulness, her respiratory rate was ±40/minutes and baseline SpO_2 was $\pm100\%$. Transitions to stage 1 and 2 NREM sleep were associated with the appearance of protracted CSA events (max 59s) and severe oxygen desaturation ($<70\%$). CSA completely disappeared in the subsequent period of consolidated sleep, during which respiratory rate fell to ±18/minutes and baseline SpO_2 was $\pm96\%$. Relevant PSG data are presented in Fig. 1(a).

3.2. Case 2

A 32 year old man presented with complaints of non-restorative sleep, fatigue and daytime sleepiness. The history was remarkable for insulin-dependent diabetes mellitus and incidental nocturnal migraine attacks. He mentioned that he would voluntarily start hyperventilating during these attacks, as he had experienced that this behaviour was effective in preventing migraine-associated nausea and vomiting.

During the PSG recording, the patient unexpectedly suffered from a migraine attack. Before this event, sleep and breathing had been unremarkable. Respiratory rate was ±16/minutes and SpO_2 was $\pm96\%$ at baseline. The attack triggered a prolonged awakening and a significant increase in respiratory rate up to a maximum of 68/minutes with an associated increase of SpO_2 to 98%. Several CSA events were observed in subsequent episodes where stage 1 NREM sleep was reinitiated (Fig. 1(b)).

3.3. Case 3

A 43 year old woman consulted with recurrent symptoms of daytime hyperventilation, including diffuse paraesthesias, which were diagnosed as HVS. Recently, the patient had developed sudden nighttime awakenings with dyspnoea, chest oppression and paraesthesias. In the past 2 years, she had experienced several stressful life events, and developed a state of anxiety. A neurologic, pulmonary and cardiologic check-up, including echocardiography and

pulmonary function tests, had been unremarkable. Arterial blood gas analysis assessed at the department of pulmonary medicine had confirmed hyperventilation: pH 7.54 ($\uparrow\uparrow$), $PaCO_2$ 25.5 mmHg ($\downarrow\downarrow$), PaO_2 103 mmHg ($\uparrow$) and bicarbonate 21.7 mmol^{-1} ($\downarrow$).

PSG demonstrated cyclic sleep architecture with intermittent prolonged awakenings. The respiratory rate during steady sleep was ±16/minutes. During the wakefulness episodes, the respiratory rate fell to ±8/minutes, but respiratory amplitude increased substantially, resulting in an increase of SpO_2 to $\pm98\%$. Subsequent transitions to stage 1 and 2 NREM sleep were associated with multiple CSA events. This pattern was observed throughout the entire sleep period (Fig. 1(c)).
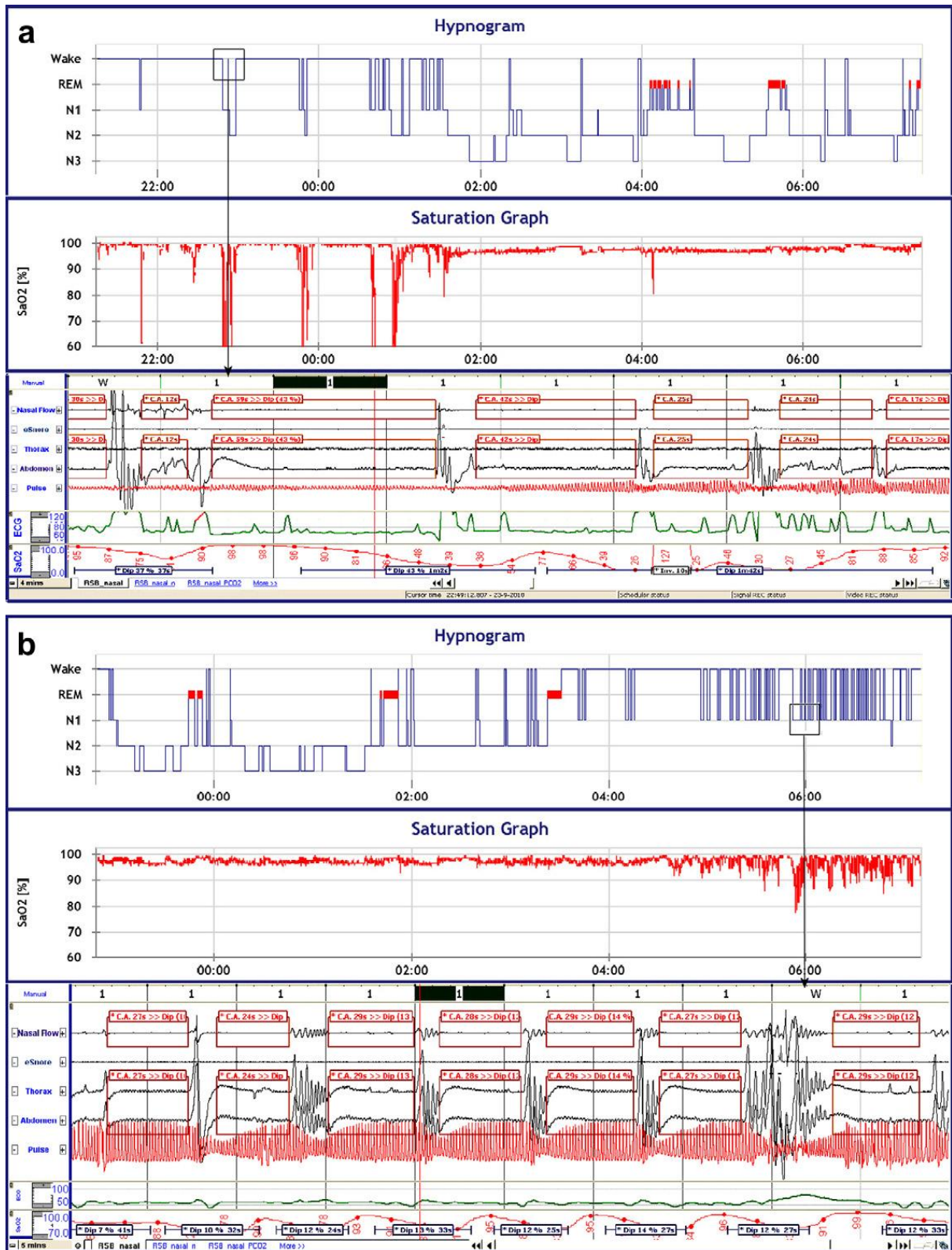
Fig. 1. Hypnogram, all night SpO$_2$ trend and epoch with examples of CSA in case 1 (panel a), 2 (panel b) and 3 (panel c). Increase in baseline oxygen saturation during episodes of hyperventilation and central sleep apnea is seen in the saturation graphs. Epochs are taken from episodes of sleep following a period of wakefulness during which hyperventilation was present. The location of the example epochs is indicated with a (h) on the hypnogram. CA, central apnea; ECG, electro-cardiogram; Wake and A, wakefulness, N1 and 1, non-rapid eye movement stage 1; N2 and 2, non-rapid eye movement stage 2; N3 and 3, non-rapid eye movement stage 3; REM and R, rapid eye movement; SaO$_2$ and SAO$_2$, oxygen saturation.
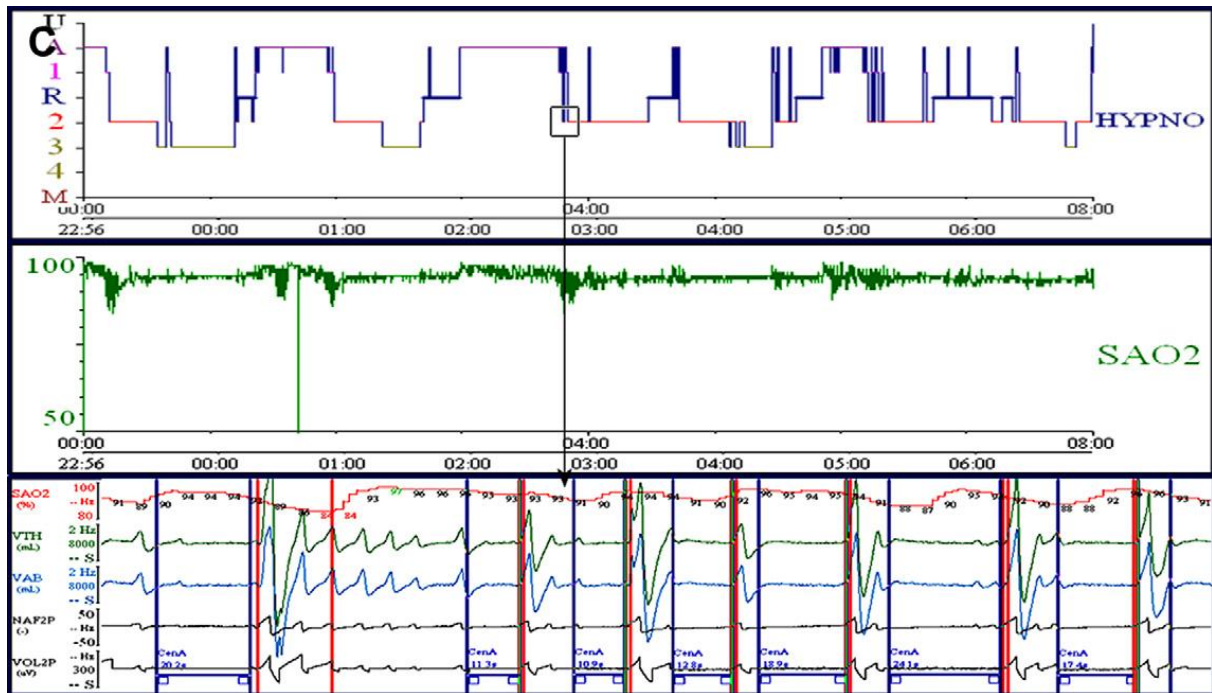
Fig. 1. (continued)

4. Discussion

In the current report, we describe a new clinical condition associated with hyperventilation-mediated CSA, namely behaviourally induced overbreathing in the context of panic attacks or anxiety. None of the patients had evidence of cardiac or pulmonary disease, and hyperventilation appeared to be a behavioural manifestation of incident anxiety or panic attacks.

In all three cases, an increase in baseline oxygen saturation was observed as a hallmark of increased ventilation associated with major episodes of CSA (Fig. 1(a)–(c)). Two patterns of behavioural hyperventilation and associated CSA became evident: an incidental 'panic' phenotype incited by acute triggers (fear and pain) versus a more chronic 'anxiety' pattern maintained by latent stressors. In the former phenotype, CSA emerged during a limited stretch of time, whereas in the latter, CSA appeared in clusters throughout the entire sleep period. In the first two cases, significant CSA emerged in the context of sudden tachypneic hyperventilation due to distinct and transient emotional triggers. The first case was consistent with a panic response conditioned by a previous psychotrauma and elicited by fear for going to bed. Remarkable CSA occurred in the wake-to-sleep transitions, but once the stage of steady sleep was reached, respiratory rate decreased and CSA disappeared. In the second case, behavioural hyperventilation was induced by a migraine attack. Repetitive central apnoeas were present in the subsequent period, while breathing had been normal before this event. In

both cases, hyperventilation had started during an initial phase of wakefulness and continued through the subsequent transitions to superficial NREM sleep, thereby causing sequences of long central apnoeas. The third case is a classical example of HVS in the context of a generalised anxiety disorder including paroxysmal nighttime symptoms. PSG demonstrated clusters of central apnoeas after periods of prolonged awakening during which hyperpneic hyperventilation was present.

Periodic breathing, and sometimes limited clusters of respiratory interruptions, may be observed in healthy subjects in the unstable phase between wakefulness and stage 1 NREM sleep [7]. This is considered a normal physiological phenomenon. Rarely, these physiological apnoeas may prolong the time needed to progress from light to consolidated deeper sleep. The respiratory events that are observed in the present cases are clearly different because of their severity: the central apnoeas persisted during an extended time period, were long in duration (up to 59 s in case 1) and were associated with substantial oxygen desaturations. Because of the obvious clinical relevance, behaviourally induced hyperventilation with CSA qualifies as a breathing disorder.

Whilst chronic hyperventilation and associated hypocapnia are in fact protective against central apnoea, increased chemosensitivity to CO_2 may counterbalance this advantage [2,8]. Indeed, brisk transient surges in minute ventilation may drive the $PaCO_2$ below the apnoeic threshold, even in the presence of steady state hyperventilation. This mechanism has been shown to be a prime pathogenic factor for CSA in altitude-related hypoxia and chronic heart failure. Whether increased chemosensitivity may play a role in behavioural hyperventilation is uncertain. However, the present case records illustrate that behavioural hyperventilation may be sufficiently robust to cause major episodes of CSA.

Patients with nocturnal panic attacks are known to have a greater incidence of insomnia. Phobic avoidance behaviour may impair initiation and/or maintenance of sleep in these patients [9]. Bodily symptoms observed in nocturnal panic include dyspnoea, chest pain and feelings of choking [10]. Mild breathing pattern abnormalities, but not frank sleep apnoea, have been described in patients with panic disorder [11]. Overall, their sleep structure does not seem remarkably abnormal [12]. Based on the current findings, PSG may reveal CSA in some of these patients.

To the best of our knowledge, this is the first report to draw attention to CSA as a significant disturbance of sleep in patients with panic or anxiety disorders and co-morbid behavioural hyperventilation. We believe that the findings in the present paper are pertinent and warrant prospective surveys exploring the incidence and impact of CSA on sleep quality in patients

with anxiety and panic disorders. From a therapeutic point of view, treating the underlying psychiatric disorder would be the preferred approach, rather than starting treatment with positive airway pressure.

In conclusion, these case records illustrate that behavioural hyperventilation is causally associated with sleep-disordered breathing of central origin. From these observations, it is proposed to add behavioural hyperventilation as a distinct aetiological factor to the list of known causes of CSA.

Conflict of interest

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5. Scientific activities

INTERNATIONAL CONGRESSES – INVITED LECTURES

Mariman A. An HIV patient with disturbed sleep. 14th Annual International Clinical Symposium Kempenhaeghe "Epilepsy, Sleep and Neurocognition Update@Kempenhaeghe.nl". Heeze, Netherlands, March 23th 2012.

INTERNATIONAL CONGRESSES – ORAL PRESENTATION (submitted abstract)

Mariman A, Delesie L, Tobback E, Hanoulle I, Sermijn E, Vermeir P, Pevernagie D, Vogelaers D. Prevalence of primary sleep disorders in a large sample of patients with presumed chronic fatigue syndrome referred to a tertiary care referral centre. Journal of Sleep Research 2012; 21(S1):90. European Sleep Research Society-congress 2012.

INTERNATIONAL CONGRESSES – POSTER PRESENTATION (submitted abstract)

A. Mariman, G. Henry, M. Van Moffaert, W. Michielsen. Psychosomatic Outpatients: Underlying Anxiety and its Treatment. 12th World Congress of Psychosomatic Medicine, Bern, Zwitserland, 29/8-2/9/1993 :

W. Michielsen, A. Van Duyse, A. Mariman, M. Van Moffaert. Psychosomatic Consultations in a University Hospital: 10 Years. 15th World Congress of Psychosomatic Medicine, Athene, Greece, 16/4-20/4/1999 :

Mariman A, Vogelaers D, Hanoulle I, Delesie L, Pevernagie D. Sleep quality and daytime sleepiness in a large sample of patients with Chronic Fatigue Syndrome. European Sleep Research Society-congress, Lisbon, Portugal, 2010.

Mariman A, Vogelaers D, Hanoulle I, Delesie L, Pevernagie D. Characteristics of the Pittsburgh Sleep Quality Index in a large sample of patients with Chronic Fatigue Syndrome. European Sleep Research Society-congress, Lisbon, Portugal, 2010.

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NATIONAL CONGRESSES – INVITED LECTURES

Mariman A. Pain and sleep. Symposium Belgian Pain Society. June 4th 2005. University Hospital Leuven, Belgium.

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Mariman A., Vogelaers D., Hanoulle I., Brusselaers N., Delesie L., Pevernagie D. Sleep quality and daytime sleepiness in a large population of patients with chronic fatigue syndrome (CFS). Belgian Association for Sleep Research and Sleep Medicine, 2009. Dinant, Belgium.

Mariman A, Vogelaers D, Hanoulle I, Delesie L, Pevernagie D. Sleep quality and daytime sleepiness in a large sample of patients with Chronic Fatigue Syndrome. Annual congress of the Belgian Society of Internal Medicine, 2010.

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6. Awards

Winner BASS-award : presentation and abstract : Pevernagie D, Boon P, Mariman A, Verhaeghen D, Pauwels R. Vocalization during episodes of prolonged expiration: a parasomnia related to REM-sleep. Sleep Medicine, 2001, 54,pp. 1-12.